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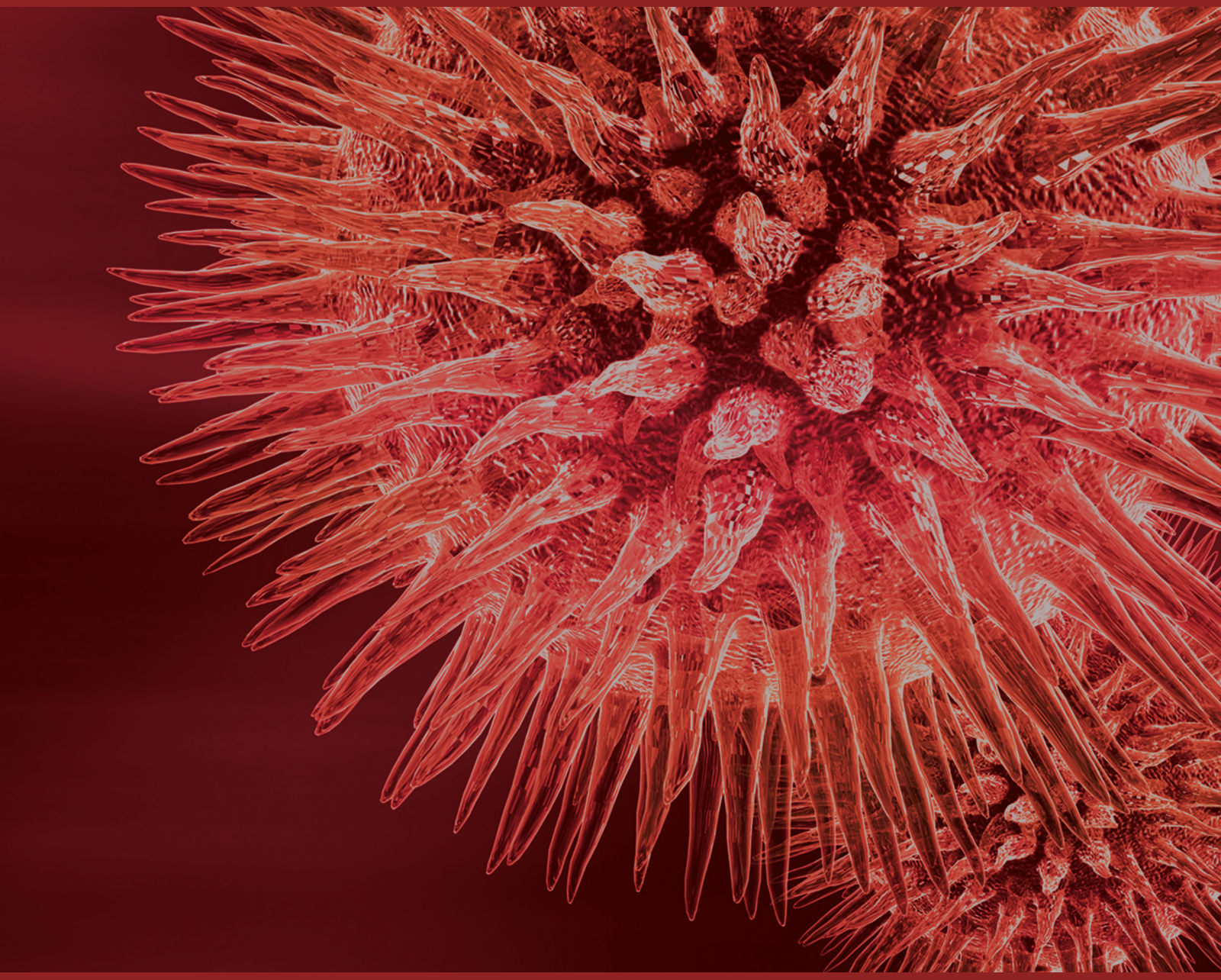
Comorbidities in Chronic Obstructive Pulmonary Disease From Assessment to Treatment

Guest Editors: Enrico M. Clini, Piera Boschetto, Mitja Lainscak, and Wim Janssens



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Editorial

Comorbidities in Chronic Obstructive Pulmonary Disease from Assessment to Treatment

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In recent years several studies in the field of chronic obstructive pulmonary disease (COPD) have addressed the impact of comorbidities on the phenotypic presentation of an individual patient [1]. Epidemiological studies have investigated the prevalence of comorbidities in COPD patients and have reported clear associations between COPD and other chronic diseases, such as cardiovascular, cancer, and metabolic diseases as the most frequent ones. Since then the awareness for coexisting diseases in COPD patients has been steadily growing and their role on increased morbidity, worse prognosis, and higher economic burden has currently been recognized.

Notwithstanding, the clinical and pathophysiological links between COPD and other chronic conditions remain controversial and are largely unknown. Some authors suggest that COPD may favor the development of other diseases via the spilling of inflammatory mediators from the lung to the systemic circulation. They indirectly support the idea of a causal relationship between COPD and its comorbid conditions. Others claim that the association of COPD and coexisting diseases is only based on the presence of common risk factors [2], and there is also cumulating evidence about activation of neurohumoral response [3]. In particular, metabolic abnormalities and physical inactivity on top of smoking may accumulate and intensify as COPD and its coexisting diseases progress. From this point of view, the term "multimorbidity" better reflects the concept of chronic complex patients with COPD rather than that of COPD patients with chronic comorbidities [4]. Moreover, advantageous to the multimorbidity concept is that its recognition in elderly adults also highlights the role of risk factors and premorbid conditions in COPD as unexplored pathways for intervention [5]. A comprehensive and individualized approach is therefore warranted, and rehabilitation in its broadest meaning may appear as best interventional process to assess, care, and manage according to this holistic view [6, 7].

The articles published within the special issue tackle these concepts and review some important areas of both assessing the presence of relevant coexisting conditions in COPD, as well as evaluating the effect of comprehensive care dedicated to these patients. In particular, the analysis of specific phenotypic clusters of these individuals, the presence of specific conditions which may worsen prognosis and quality of life, such as musculoskeletal disorders and dysfunction, the cognitive impairment, and the cardiovascular problems are reported. Moreover, the effectiveness of a rehabilitation course and associated problems, in such complex patients, is also reported in separate contributions.

In conclusion, actual evidence suggests that patients with multimorbidity represent a huge part of the elderly population, being COPD one component, not necessarily the most important, of this clinical phenotype that requires a comprehensive assessment, care, and long-term management. The respiratory community should recognize this complexity of chronic care in patients with COPD, and health care

providers should carefully consider all strategies of primary and secondary prevention in the adult population.

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Review Article

Musculoskeletal Disorders in Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by airway obstruction and inflammation but also accompanied by several extrapulmonary consequences, such as skeletal muscle weakness and osteoporosis. Skeletal muscle weakness is of major concern, since it leads to poor functional capacity, impaired health status, increased healthcare utilization, and even mortality, independently of lung function. Osteoporosis leads to fractures and is associated with increased mortality, functional decline, loss of quality of life, and need for institutionalization. Therefore, the presence of the combination of these comorbidities will have a negative impact on daily life in patients with COPD. In this review, we will focus on these two comorbidities, their prevalence in COPD, combined risk factors, and pathogenesis. We will try to prove the clustering of these comorbidities and discuss possible preventive or therapeutic strategies.

1. Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (COPD) as "a preventable and treatable disease, characterized by a persistent airflow limitation that is progressive and not fully reversible and associated with an abnormal inflammatory response of the lungs to noxious gases or particles. Exacerbations and comorbidities contribute to the overall severity in individual patients" [1]. Currently, COPD is the fourth leading cause of death in the world and will rise to the third leading cause of death by 2030 [2].

COPD is spirometrically diagnosed by the presence of a postbronchodilator $FEV_1/FVC < 0.70$ and is assessed for its severity according to FEV1 level: mild COPD ($FEV_1 \geq 0.80$ predicted), moderate COPD ($0.50 \leq FEV_1 \leq 0.80$ predicted), severe COPD ($0.30 \leq FEV_1 \leq 0.50$ predicted), and very severe COPD ($FEV_1 < 0.30$ predicted) [1]. In 2013, a new classification method has been developed which combines spirometric classification with symptomatic assessment (through the modified British Medical Research Council (mMRC) questionnaire or COPD Assessment Test (CAT)) and/or with exacerbation risk [1]. All the literature discussed in this review is based on the old classification system.

Although COPD is primarily a lung disease, it is associated with comorbidities such as cardiovascular disorders, metabolic diseases (diabetes mellitus, metabolic syndrome, and obesity), chronic kidney disease, sleep apnoea, anemia, depression, lung cancer, weight loss, skeletal muscle weakness, and osteoporosis. These comorbidities contribute to a reduced health status, increased healthcare utilization and hospital admission, and mortality [3].

In this review, we will focus on skeletal muscle weakness and osteoporosis in patients with COPD. Risk factors and pathogenesis contributing to both comorbidities, as well as therapeutic strategies, will be discussed.

2. Skeletal Muscle Weakness and Osteoporosis in COPD

2.1. Definition and Prevalence. Skeletal muscle function is described by muscle strength (the ability to generate force production), muscle endurance (the ability to sustain a given contraction over time), and muscle fatigue (a physiological sense defined as the failure of force generation resulting from activity under load which is reversible by rest). In COPD, skeletal muscle weakness is characterized by reduced

muscle strength, reduced muscle endurance, and the presence of muscle fatigue [4]. The estimated overall prevalence of skeletal muscle weakness in patients with COPD was shown to be 32% [5]. In addition, a trend towards higher prevalence of skeletal muscle weakness with disease severity (GOLD stages) has been reported [5]. Skeletal muscle weakness was shown to contribute to decreased functional capacity, poor quality of life, increased healthcare utilization, and even mortality [3], independently of lung function [6].

The World Health Organization defines osteoporosis as a systemic disease, characterized by a low bone mineral density and/or microarchitectural deterioration of bone tissue, leading to increased bone fragility and fracture risk [7]. The prevalence in patients with COPD varies between 9 and 69%, depending on the population studied, diagnostic methods used, and the definition used to define osteoporosis [8]. Prevalence increases with the severity of COPD [9–11]. Two types of fractures are related to osteoporosis. Peripheral fractures or hip fractures impair mobility, while vertebral fractures lead to back pain and indirectly decline pulmonary function due to decreased rib mobility [12, 13]. Fractures are a substantial cause of morbidity and lead to functional decline, loss of quality of life, need for institutionalization, and mortality [14]. Since osteoporosis is highly common in patients with COPD [15], the impact of these events may be even worse.

2.2. Clinical Evidence for Skeletal Muscle Weakness and Osteoporosis in COPD. Skeletal muscle weakness is reflected by reduced muscle strength (Figure 1) and endurance and increased muscle fatigability [16]. Muscle weakness is mainly observed in the lower limb muscle of patients with COPD [17]. Indeed, quadriceps muscle weakness is a common feature in patients within all stages of COPD [5] in both men and women [18]. Lower limb muscle weakness is found to be more severe in patients with cachexia [19] and worsens during acute exacerbations [20, 21]. The structure and function of the upper limb muscles are found to be relatively preserved [22] (Figure 1), even when patients are in a cachectic state [19], but not during acute exacerbations where strength of upper limb muscles was found to be reduced [21]. Preservation of upper limb muscle in stable COPD is most probably due the fact that those muscles are involved in daily activities [23]. In lower limb muscles, several adaptations develop with COPD; these include muscle fiber type shift from type I towards type IIx muscle fibers resulting in reduced oxidative and increased glycolytic capacity, fiber atrophy, loss of muscle mass (Figure 2), and decreased capillary density [4]. Importantly, reduced quadriceps strength is found to be a useful predictor for mortality in patients with COPD (Figure 3) [24].

Osteoporosis is common in both male and female patients with COPD [15]. Moreover, the risk of developing osteoporosis was found to be associated with airflow obstruction [26]. COPD was also shown to be a significant independent predictor for reduced bone mineral density (Figure 4) and

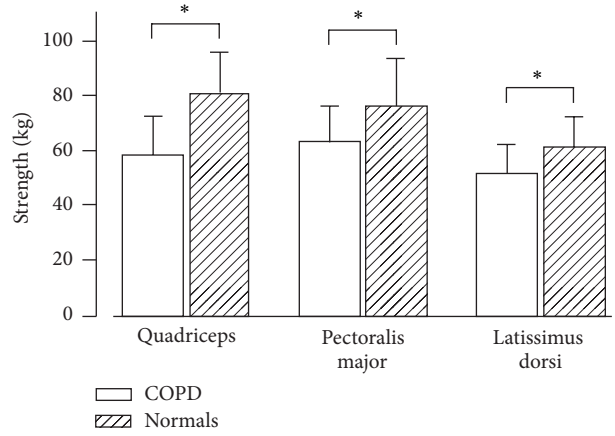


Figure 1: Reduced muscle strength of the quadriceps, pectoralis major, and latissimus dorsi obtained in normal subjects and patients with COPD. All three types of muscles show decreased muscle strength in patients with COPD. $^{*}P < 0.005$ Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society, official journal of the American Thoracic Society [17].

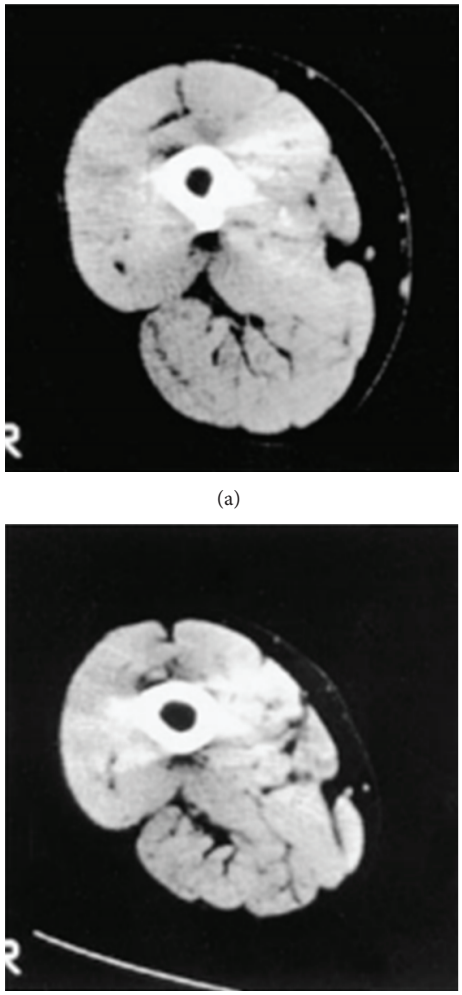
increased fracture risk [27], and both are associated with the severity of the disease [11, 28].

There is evidence of a possible direct mechanistic link between COPD and osteoporosis. This is highlighted in studies using CT-scan, indicating a relationship between pulmonary emphysema and reduced bone mineral density [29, 30], independently of airflow obstruction and other osteoporosis risk factors [31].

2.3. Risk Factors for Skeletal Muscle Weakness and Osteoporosis. There are several risk factors in COPD that may contribute to both skeletal muscle weakness and osteoporosis. These include cigarette smoking, physical inactivity, systemic and local inflammation, oxidative stress, corticosteroid use, hormonal disturbances, and age (Figure 5).

2.3.1. Cigarette Smoke. The most important risk factor for the development of COPD is cigarette smoke. Twenty percent of the world population smokes cigarettes [32] (http://www.tobaccoatlas.org/) and 90% of patients with COPD either have a history of smoking or still smoke.

Cigarette smoke is an important contributor to skeletal muscle weakness and it has been shown to exert negative effects on bone. Cigarette smoke was shown to be related to decreased skeletal muscle strength and physical performance in healthy adults [33, 34]. Compared to controls matched for age and physical activity, healthy young smokers showed a reduced fatigue resistance of the quadriceps muscle [35]. In healthy smokers and patients with COPD, cigarette smoke was shown to induce muscle atrophy, reduce muscle protein synthesis, induce oxidative modifications on muscle proteins [36], and increase the expression of genes involved in muscle catabolism and associated with inhibition of muscle growth



(a)

(b)

Figure 2: Cross-sectional area as well as muscle force of thigh muscle was reduced in patients with COPD (b) compared to normal subject (a). Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society, official journal of the American Thoracic Society [17].

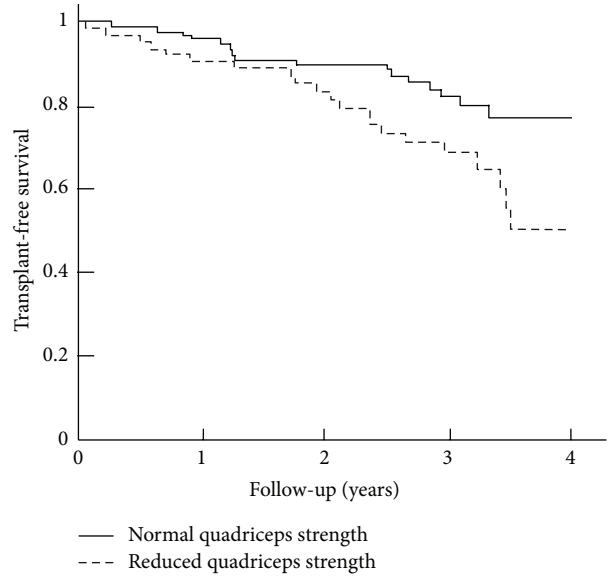


Figure 3: Survival of patients with COPD with normal and reduced quadriceps strength. The curves are significantly different $P = 0.017$ [24].

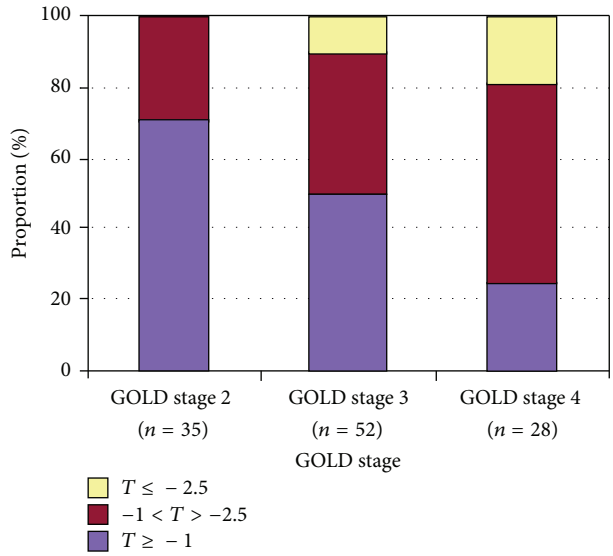


Figure 4: Bone mineral density in different GOLD stages. The T-score is the difference between the patient's results and the mean results obtained in a young population, expressed in units of standard deviation. Osteoporosis is the condition with a T-score below −2.5; osteopenia is the condition of a T-score between −1 and −2.5. The prevalence of low bone mineral density increases with higher GOLD stage [25].

[37]. Also in studies with animals chronically exposed to cigarette smoke, muscle atrophy developed [38].

In healthy smokers, cigarette smoke was found to compromise bone strength [39] and to be associated with reduced bone mineral density [40], increased risk of fractures, and delayed fracture healing at all skeletal sites. The association was present in current as well as former smokers [41] and the risk for osteoporosis was stronger with higher cigarette consumption. The effects of cigarette smoke on bone mineral density and fracture risk were observed in both men and women but were reported to be more deleterious in men [40]. In addition, this effect was found to be independent of age [42]. The effect of cigarette smoke on bone mineral density and bone turnover was confirmed by animal studies [43, 44].

2.3.2. Physical Inactivity. Daily physical activity is significantly reduced in patients with COPD, compared to healthy age-matched controls. Indeed, patients with COPD spent more time sitting and lying and less time walking (<50 minutes daily versus 81 minutes) and standing [45]. Daily physical activity is already reduced in patients with GOLD stage I, and this reduction further worsens with disease severity, with patients with COPD with the GOLD stage IV being very inactive [46–48]. Importantly, patients with COPD with very low physical activity had a higher risk

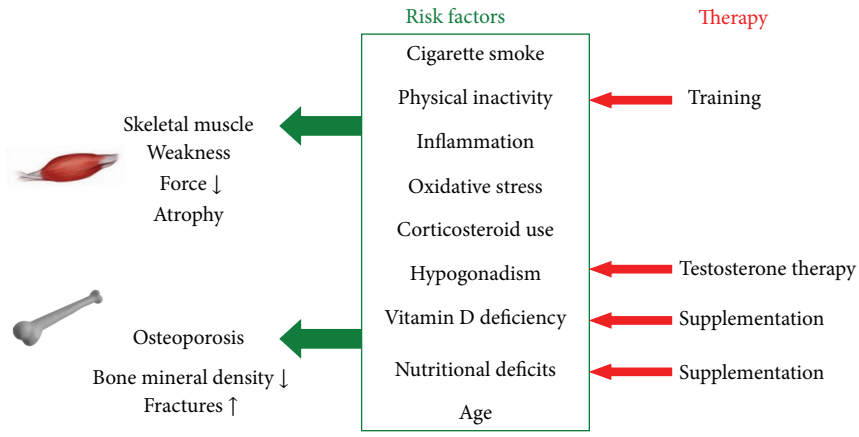


Figure 5: Several risk factors, such as cigarette smoke, physical inactivity, inflammation and oxidative stress, corticosteroid use, hormonal disturbances, nutritional deficits, and age, lead to the development of skeletal muscle weakness and osteoporosis in healthy individuals, as well as patients with COPD. There are several therapy modalities that can be used to treat or inverse the consequences of these risk factors so that the risk of developing skeletal muscle weakness and osteoporosis can be reduced in patients with COPD.

for hospital admission and mortality [49, 50]. Finally, these patients are very inactive during hospitalization for an acute exacerbation (daily walking time becomes <10 minutes) and remained inactive even one month after discharge [51], thereby increasing the risk for readmission [52].

Physical inactivity was found to be crucial in the development of skeletal muscle weakness in patients with COPD. It is believed to result in quadriceps weakness due to mechanical unloading of the muscle and due to muscle wasting [17, 53] and it was shown to be associated with impaired muscle endurance [54]. The reduced lower leg activity observed in patients with COPD was shown to be related to total daily activity [55]. It may contribute to impaired physical balance [56] and to increased risk of falling [57] in patients with COPD. Decreased physical activity has been suggested as a possible link between low body composition and osteoporosis or low bone mineral density in patients with COPD. Alternatively, decreased bone formation due to a reduction in mechanical loading on the bones may play a role too [8]. In elderly healthy individuals, it was shown that physical inactivity was related to a high rate of bone loss and with the risk of fractures [58] but there are no direct studies yet in patients with COPD.

2.3.3. Systemic and Local Inflammation. Systemic inflammation has been reported in patients with severe COPD with muscle wasting. It is characterized by increased serum levels of tumor necrosis factor (TNF)-α, its receptors [59], interleukin (IL)-1β [60], IL-6, IL-8, IL-18 [61], and acute phase reactants [62]. Interestingly, in patients with COPD who are hospitalized for acute exacerbations, increased serum levels of IL-8 were found to be negatively associated with quadriceps weakness, while IL-6 levels remained unaltered and TNFα was not detectable [21].

The presence of local inflammation in the muscle of patients with COPD is still controversial. Some studies reported an upregulation of TNFα [63, 64] in the quadriceps muscle, while other studies did not [20, 61, 65, 66], even during acute exacerbations [20]. Also, IL-6 and IL-8 expression in the muscle remained unaltered during acute exacerbations [20]. In patients with stable COPD, IL-18 was shown to be upregulated in the vastus lateralis muscle [61]. But cytokine profile in the quadriceps of weight stable patients with severe COPD did not show any presence of a proinflammatory environment [65]. Along the same line, a microarray analysis did not reveal any upregulation of inflammatory markers in the muscle of patients with COPD during exacerbations [67].

2.3.4. Oxidative Stress. Oxidative stress occurs when the balance between oxidant production (reactive oxygen species) and antioxidant capacity in the cell is disturbed, causing damage of lipids, proteins, and DNA [68]. The most important triggers for the development of oxidative stress in patients with COPD are cigarette smoke and systemic inflammation [69].

Several markers of oxidative stress were shown to be upregulated in the muscle and plasma of patients with stable COPD [65, 70, 71], and these were further enhanced in plasma during exacerbations [72, 73]. On the other hand, the antioxidant capacity was found to be increased in the muscles of patients with COPD, probably because the defense system was triggered by exposure to reactive oxygen species [74]. Importantly, oxidative stress was found to be associated with decreased quadriceps muscle strength [36, 75] and was shown to cause increased bone resorption during severe COPD exacerbations [76]. But whether oxidative stress directly affects bone mineral density and osteoporotic fractures in these patients is not yet known.

2.3.5. Corticosteroid Use. Corticosteroids are frequently used in patients with COPD to reduce pulmonary symptoms and to treat exacerbations [77]. Steroid-induced myopathy and

steroid-induced osteoporosis represent the well-known side effects of corticosteroid treatment.

Two types of steroid-induced myopathy have been described: acute or chronic. Acute steroid myopathy is rare in COPD. It represents a complication of treatment with systemic corticosteroids [78], leading to proximal as well as distal muscle weakness, occurring after 5–7 days of high dose (hydrocortisone 1–4 g/day or dexamethasone 40 mg/day) intravenous treatment. After treatment cessation, the recovery is prolonged up to 6 months [79, 80]. Chronic steroid myopathy occurs after long-term treatment with low doses of oral corticosteroids and results in proximal muscle weakness and generalized muscle fiber atrophy [81, 82]. This myopathy is more frequently observed with fluorinated corticosteroids. Recovery of this type of myopathy may be spread over weeks to months. On follow-up, survival of patients with steroid-induced myopathy was reduced in comparison to COPD with a similar degree of airflow obstruction [82]. In patients with COPD receiving daily low doses of oral corticosteroids, a negative relationship was found between corticosteroid use and skeletal muscle strength [81]. Oral corticosteroid treatment was found to contribute to loss of fat-free mass [83], which is an independent predictor of mortality in patients with COPD [84].

Oral corticosteroids were found to be inversely correlated with bone mineral density, and the daily dose was correlated with the risk of osteoporotic fractures [85]. The risk of fractures was found to increase within 3 to 6 months after the start of the therapy and decreased after therapy cessation [85]. Bone mineral density was found to be decreased in patients receiving multiple courses of oral or intravenous glucocorticosteroids [86]. In patients with COPD, a long-term treatment with inhaled corticosteroids had no effect on fracture risk [87] at conventional doses [88]. One year of inhaled corticosteroid treatment was shown to exert no effects on bone mineral density [89] while a treatment of 3 years with inhaled triamcinolone was found to reduce bone mineral density [90].

2.3.6. Hormone Disturbances

(1) Hypogonadism. The prevalence of hypogonadism (total testosterone levels <280–300 ng/dL and free testosterone level <5 pg/mL [91, 92]) in men with COPD varies between 22 and 69% [93] and is unknown in women. The most important risk factors to develop hypogonadism are smoking, hypoxia, systemic inflammation, and corticosteroid treatment, risk factors that are also related to COPD [93].

In male individuals without COPD, hypogonadism was shown to be associated with the loss of muscle mass and strength, increased prevalence of osteoporosis, and accelerated bone loss [42, 94]. In patients with COPD, low levels of testosterone are associated with reduced quadriceps strength, but preserved exercise capacity, when compared to healthy age-matched controls [92]. Since low testosterone levels are associated with osteoporosis, and osteoporosis is common in COPD, a potential link might be suggested although this has not yet been investigated.

(2) Vitamin D Deficiency. Vitamin D is essential for bone and muscle health while regulating calcium, phosphate, and bone homeostasis [95]. It was shown to play an important role in the growth of skeletal muscles, muscle contractility, and myogenesis [96] as well as in the development of the growth plate, mineralized bone, and osteoclastogenesis [97].

In humans, vitamin D deficiency, defined as serum levels below 20 ng/mL (50 nmol/L) was found to be associated with poor muscle strength and performance [98] and decreased physical activity [99]. Due to an imbalance in calcium and phosphate homeostasis, vitamin D deficiency is also known to be a risk factor for severe osteoporotic fractures [100]. In addition, an association between a polymorphism of the vitamin D receptor and bone mineral density has been highlighted [101].

The prevalence of vitamin D deficiency in patients with severe and very severe COPD is, respectively, 60% and 77% [102]. Vitamin D deficiency was found to be correlated with disease severity [102, 103] but not with acute exacerbations and mortality [104, 105]. Several reasons could account for vitamin D deficiency in patients with COPD, including a poor diet, reduced capacity of the aging skin to synthesize vitamin D, absence of outdoor activity and sun exposure, increased catabolism by glucocorticosteroids, impaired activation due to renal dysfunction, and lower storage capacity in muscles or fat, due to wasting [106].

In patients with COPD, a relationship was found between variants in the vitamin D receptor gene and skeletal muscle strength [107] but, although an association was observed between vitamin D levels and muscle strength in control patients, this association was not present in patients with COPD [108, 109]. This observation might indicate that some patients with COPD may be resistant to the actions of vitamin D, which was corroborated by elevated levels of PTH in these patients [108]. Plasma concentration of vitamin D was found to be positively correlated with bone mineral density and functional exercise capacity in patients with COPD [109], and with an increased risk of osteoporosis in these patients [110].

2.3.7. Nutritional Deficits. In patients with stable COPD, the prevalence of undernutrition was estimated between 20% and 27% [111, 112], and up to 35% in patients admitted to a pulmonary rehabilitation program [113]. It was found to be more prevalent in female patients with moderate to severe COPD [112].

Undernutrition in patients with COPD can be caused by inadequate dietary intake, which was found to be worse during an acute exacerbation [114], and enhanced energy expenditure. Other causes are a loss of appetite, anorexia, and the effects of humoral factors, such as inflammatory cytokines, adipokines, and hormones [113].

Undernourished patients with stable COPD were found to have lower skeletal muscle strength [111]. Importantly, in patients with COPD who are hospitalized for acute exacerbations, malnutrition was highly prevalent [115] and was found to increase the risk for having new exacerbations [116] and the risk for rehospitalization and mortality [117].

When marked undernutrition occurs, the distortion of the energy balance was found to cause cachexia, the involuntary loss of over 5% of bodyweight [118]. In patients with COPD, loss of body weight correlated with disease severity [83, 119, 120] and skeletal muscle weakness [121] independently of airflow obstruction [6]. Decreased body weight has been identified as a poor prognostic factor in patients with COPD [120, 122]. Similarly, low fat-free mass and low body mass index were found to be related with bone mineral density loss [25, 123] and increased risk for developing osteoporosis [9, 124, 125] in patients with COPD.

2.3.8. Age. In healthy subjects, age is known to negatively impact muscle strength and contraction speed [126]. It also induces a shift from muscle type II to type I fibers and atrophy of type II fibers [127, 128]. As a consequence, limb muscles of elderly are smaller and contain more fat and connective tissue [126]. With age, the incidence of fractures is also found to increase while bone mineral density decreases [129].

In patients with COPD, increasing age was found to reduce quadriceps strength [130] and this loss of strength was more pronounced than that of age-matched healthy individuals [131]. Important to emphasize is that the muscle fiber shift in patients with COPD (from type I to type II fibers) is opposite to the shift induced by age. Increasing age was also found to be associated with an increased risk for osteoporosis in patients with COPD [124].

2.4. Clustering of Skeletal Muscle Weakness and Osteoporosis in a Subgroup of Patients with COPD. COPD is commonly associated with one or more comorbidities [132–134]. Several studies highlighted clustering of some of these comorbidities in subgroup of patients with COPD [3, 134]. As such, skeletal muscle weakness, osteoporosis, and cachexia were described as a cluster in a group of patients with COPD [3]. Similarly, in a study where the frequency and clustering of 13 relevant comorbidities of COPD have been investigated [134], underweighted patients with COPD were found to have a high prevalence of osteoporosis (57%) and muscle wasting (93%). Fifty percent of the patients with COPD with osteoporosis were found to have muscle wasting, while 55% of the patients with muscle wasting also suffered from osteoporosis [134].

Cachexia is a complex metabolic syndrome associated with an underlying illness and characterized by loss of muscle with or without loss of fat mass, often combined with signs of systemic inflammation, and anorexia [118]. Cachexia occurs in 20% to 40% of the patients with COPD [135].

Cachexia was found to be associated with poor functional capacity, reduced quality of life [136], and increased risk for morbidity and mortality in patients with COPD [84, 137–141]. It is independently correlated with osteopenia and osteoporosis in elderly patients [124]. The risk factors for cachexia are multifactorial and include a disturbed energy balance, oxidative stress, systemic inflammation, hypogonadism, and corticosteroid treatment [142]. Because of the similarity in risk factors, as described before, the possibility of the clustering of skeletal muscle weakness, osteoporosis, and cachexia in a subgroup of patients with COPD is emphasized. It is not clear yet whether cachexia is associated with changes in protein synthesis, but several proteolytic markers (Atrogin-1, MuRF1) were found to be increased in muscles of cachectic patients with COPD together with a decreased expression of myogenic differentiation factors [135]. Weight loss is found to cause bone loss [143], but the exact mechanism is unknown. But cachexia is associated with muscle loss, causing decreased mechanical loading on bones, which is a risk factor for osteoporosis. On the other hand, cachexia is also associated with systemic inflammation, which is also found to be a risk factor for osteoporosis.

Interestingly, there is also evidence for associations between muscle strength and bone mineral density in other diseases, such as cystic fibrosis [144], Crohn's disease [145], acute lymphoblastic leukemia [146], and osteoporosis itself [147–150].

2.5. Pathogenesis. Cigarette smoke may affect skeletal muscle and bone through its toxic components, while inducing oxidative stress and systemic inflammation [37]. Nicotine is the major toxic component of cigarette smoke and may interact with the nicotine acetylcholine receptor in many cells. At concentrations of nicotine equivalent to levels found in blood of heavy smokers, nicotine reduced cell proliferation and downregulated genes associated with osteogenesis [151], thereby impairing bone strength and bone mass [152]. Nicotine is also found to induce insulin resistance and to decrease insulin release by pancreatic beta cells. Insulin modulates protein synthesis and degradation in the muscle, and therefore, insulin resistance is found to promote catabolism of the skeletal muscle [37]. Chronic exposure to nicotine also decreases the total Na-K ATPase activity, thereby depolarizing the membrane in the skeletal muscle [153].

Cigarette smoke also contains reactive oxygen and nitrogen-free radicals, causing imbalance between oxidants and antioxidants and leading to oxidative stress. The latter is known to induce modification of proteins, lipids, and DNA. In patients with COPD, levels of protein carbonylation and nitration, lipid peroxidation, and protein oxidation are found to be elevated in blood and limb muscles [154]. Oxidative stress is found to be involved in reduced quadriceps endurance [155] and protein oxidation to contribute to muscle loss and dysfunction [36]. Oxidative stress in skeletal muscle may lead to increased muscle proteolysis, through the upregulation of E3 ligases (MAFbx/Atrogin-1 and MuRF-1), thereby activating the ubiquitin proteasome system [37]. These ligases are both increased in skeletal muscle of patients with COPD [135]. On the other hand, the muscular antioxidant status is found to be altered in patients with COPD as a compensation for increased ROS formation [74]. In patients with COPD, oxidative stress also affects the protease/antiprotease balance, inducing inactivation of antiproteases, and activation of metalloproteinases [156]. Matrix metalloproteinases (MMP) have regulatory functions in bone turnover. MMP9 levels are increased in patients with COPD [76] and are related to osteoporosis, through the activation of osteoclasts [157].

Cigarette smoke also induces systemic inflammation through activation of circulating inflammatory cells and release of inflammatory mediators into the circulation [158]. In patients with stable COPD, enhanced IL-6 and TNFα levels are associated with reduced quadriceps strength and exercise capacity [159, 160] as well as muscle wasting [161–164]. These increased IL-6 and TNFα levels are also stimulating bone resorption [165] and inhibiting bone formation, thereby lowering bone mineral density [166, 167]. Increased CRP serum levels are also associated with reduced quadriceps strength and exercise capacity in patients with stable COPD. CRP also plays an important role in osteoporosis [168]. IL-1 was found to play an important role in osteoclast action by increasing the production of the macrophage colony stimulating factor (a regulator of osteoclastogenesis) and by inhibiting osteoclast apoptosis [169].

Cigarette smoking is also known to be associated with low levels of physical activity [170]. In fact, physical inactivity is common in patients with COPD and starts early in the development of the disease. It might aggravate skeletal muscle weakness and osteoporosis while causing mechanical unloading of muscle and bone. Reduced mechanical loading on bone is found to inhibit osteoblast-mediated bone formation and to accelerate osteoclast-mediated bone resorption, causing disuse osteoporosis [171]. Physical inactivity is also found to lead to increased oxidative stress in the skeletal muscle [172].

Since many patients with COPD have reduced physical activity levels, they will spend less time on outdoor activities, whereby the amount of sun exposure will decline. This could lead to vitamin D deficiency, which is also highly prevalent in patients with COPD.

All these effects combined with the presence of other risk factors worsen skeletal muscle function and bone health in patients with COPD, causing muscle weakness and osteoporosis.

2.6. Possible Preventive and Therapeutic Strategies

2.6.1. Pharmacological Interventions

Testosterone Replacement Therapy. Testosterone therapy (Figure 5) has been shown to increase muscle protein synthesis in elderly men [173], to increase muscle mass [174], and muscle strength in healthy and hypogonadal men [175, 176]. In addition, testosterone therapy was able to enhance bone mineral density in healthy and hypogonadal men [177, 178] by suppressing bone resorption [179, 180] and bone remodeling [181] due to the inhibition of IL-6 expression [182].

In patients with COPD, testosterone therapy (80–100 mg/week, 25–50 mg/2 weeks, or 250 mg/4 weeks) was shown to improve peak muscle strength [183, 184] and to increase body weight and fat-free mass [185, 186]. This increased muscle mass and strength was not necessarily translated into improved functional capacity. There are no studies dealing with the effect of testosterone therapy on osteoporosis, quality of life, or survival in patients with COPD.

Testosterone therapy is found to be accompanied by several deleterious side effects such as increased hemoglobin and hematocrit levels and a small decrease in high-density lipoprotein cholesterol [187]. There is also evidence for potential carcinogenetic effects of testosterone therapy on the prostate gland, although this is still controversial [188].

Vitamin D and Calcium Supplementation. Vitamin D deficiency is highly prevalent in COPD and, as such, supplementation may appear as a treatment option (Figure 5), particularly since such treatment was found to have beneficial effects in deficient individuals. Indeed, vitamin D supplementation has been shown to increase muscle strength in vitamin D deficient adults, to decline the odds of falling, and to reduce the risk of hip and other nonvertebral fractures in elderly [189]. When combined with calcium supplementation, it also improved balance [190], increased bone mineral density, suppressed bone remodeling [191], and improved muscle function [192, 193]. Further, the combination of vitamin D supplementation and exercise training in elderly without COPD improved gait speed, body sway, and muscle strength [194].

In patients with COPD, a few studies have examined the effects of vitamin D supplementation. A 6-week treatment with a daily dose of 2000 IU of vitamin D was found to increase vitamin D levels towards normal levels but was not associated with improved physical performance, as assessed with short physical performance battery, or with health related quality of life [195]. The supplementation of a high dose of vitamin D (100.000 IU per month) during a 3-month rehabilitation program improved maximal oxygen uptake, but not quadriceps strength or six-minute walking distance [196]. Finally, in a randomized controlled trial, although no overall reduction in exacerbations could be found after a one-year treatment with a high dose vitamin D, it was clear that, in a subgroup of patients with COPD very deficient for vitamin D at baseline, supplementation resulted in 43% reduction of exacerbations [197]. Keeping in mind the deleterious direct or indirect effects of exacerbations on skeletal muscle and osteoporosis in COPD, these data should not be neglected.

2.6.2. Nonpharmacological Interventions

(1) Land-Based Exercise. Pulmonary rehabilitation consisting of strength and exercise training is the most effective nonpharmacological and multidisciplinary intervention used to improve symptoms, muscle strength, and exercise capacity and health status in patients with COPD (Figure 5) [198, 199]. In patients with stable COPD, exercise training is found to improve muscle function and exercise capacity and to increase fatigue resistance [198, 200]. It is also associated with improved health status [201] and quality of life [198, 202, 203]. Interestingly, muscle strength was also found to be improved when exercise training was combined with testosterone therapy [204, 205]. In addition, exercise training improved cross-sectional area of all fiber types within the vastus lateralis muscle [206–209] and shifted quadriceps muscles fiber type distribution in favor of type I fibers [206, 207], resulting in

a muscle energy metabolism shifted from glycolytic towards oxidative metabolism [210]. The morphological adaptations in peripheral muscles were similar in GOLD stages II-IV [208].

In patients with COPD hospitalized for acute exacerbations, resistance training, starting from the second day of hospitalization, was found to increase muscle force with 10% and to improve six-minute walking distance after discharge. This was associated with a more favorable anabolic/catabolic balance in the muscle. One month after discharge, functional status and muscle force were better in the group under training during exacerbation [211]. Starting pulmonary rehabilitation immediately after a COPD exacerbation was found to be highly effective and safe. It resulted in reduced hospital admissions and mortality, improved quality of life, and improved exercise capacity in patients with COPD [212].

Maintaining a physical active life is the best remedy for reducing the risk for osteoporosis and improving quality of life [149] since training is found to regulate bone maintenance and stimulate bone formation [213], including accumulation of minerals [214], and is associated with higher bone mineral density [215, 216] in healthy individuals. While there is plenty of evidence of the positive effect of physical activity on bone density and fractures in the general population, studies in patients with COPD are lacking.

(2) Alternative Training. For patients with COPD with severe dyspnea, older age, and physical comorbidities, water-based training is found to be an excellent alternative for land-based training. Although water-based training did not cause extra beneficial effects on walking distance, strength, and well-being in patients with COPD without any physical comorbidities [217], patients with COPD with physical comorbidities were found to be more susceptible to the beneficial effects of water-based exercises, as observed by a greater improvement of endurance exercise capacity and fatigue as well as dyspnea [218]. Water-based exercises also prevent bone loss and improve dynamic standing balance and quality of life in healthy individuals [219] as well as in older women with osteoporosis, although it did not change their fear of falling [220, 221].

Neuromuscular electrical stimulation is another intervention that was found to be very useful for severely deconditioned patients with COPD, since its load on the cardiopulmonary system is low [222], and moreover, it might be considered for home use [223]. Exercise capacity and quality of life were improved, while muscle strength was found to be increased with 20% to 30% in patients with COPD [223–226]. The cross-sectional area of the mid-thigh muscle and type II fibers was found to be enhanced, while that of type I fibers was decreased [227, 228]. A fiber shift in favor of type I muscle fibers as well as reduced muscle oxidative stress [229] was observed along with a more favorable anabolic to catabolic balance [228].

Another alternative training is the use of whole body vibration. It is a neuromuscular intervention whereby a low amplitude and high frequency (35–40 Hz) mechanical vibration is applied to the whole body through a vibrating platform. This training modality is found to improve muscle strength [230, 231], jump height [232, 233], and balance and to reduce bone fragility in healthy individuals [234]. In patients with severe COPD, whole body vibration is a promising training modality as it improves functional capacity [235], muscle force, and quality of life [236]. It is suggested that whole body vibration might even enhance the effects obtained with a conventional pulmonary rehabilitation program [236]. The optimal intensity and duration of the whole body vibration training as well as its long-term effects still need to be optimized.

(3) Nutritional Intervention. Weight loss is highly prevalent in patients with COPD and this worsens during an acute exacerbation [114]. Weight loss is also known to be a negative contributor to survival in these patients [122] and it is also associated with skeletal muscle weakness [111] and osteoporosis [25]. Therefore, nutritional supplementation (Figure 5) might be a useful therapy to increase body weight in these patients. Indeed, body weight gain was found to be associated with improved prognosis of patients with COPD [122] and increased energy intake was found to improve quality of life [237].

In patients with stable COPD, the effect of nutritional supplementation is still controversial. Any caloric supplementation of more than 2 weeks did not improve weight gain, lung function, or functional exercise capacity [238, 239], while, in other studies, oral administration of high calorie/high protein diet for 3 months resulted in increased muscle strength and improved muscle contractility and fatigability [240]. Similarly, dietary counseling, food fortification, and nutritional supplementation were found to have positive effects on weight gain in undernourished patients with COPD [241, 242] but improved weight gain was predominantly due to increased fat mass. In patients with COPD who are hospitalized for an acute exacerbation, nutritional support was found to increase the caloric intake [243]. The integration of a nutritional supplementation therapy in a pulmonary rehabilitation program was found to improve body composition, muscle function, exercise capacity, and health status in undernourished patients with COPD [244].

Since many studies conclude that body mass index and fat-free mass index are related to skeletal muscle weakness and osteoporosis, adequate nutritional support is warranted, especially in patients with an already impaired energy balance.

(4) Fall Prevention and Balance Training. Patients with COPD often exhibit balance problems [56] and are highly susceptible to falls [245, 246]. In healthy individuals, strengthening of the muscles during exercise programs is found to improve muscle strength and stability and to optimize bone mineral density [247] and bone strength [248, 249]. As a consequence, the risk of fall and fractures is reduced [250] and physical balance is improved [219]. Balance training as part of the pulmonary rehabilitation program also improved balance performance,

muscle strength, and physical function in patients with COPD [251].

3. Future Perspectives

Although the literature concerning chronic obstructive pulmonary disease, skeletal muscle weakness, and osteoporosis is already very broad, after writing this review it became clear that much information is still lacking. In particular, the link between risk factors such as physical inactivity, oxidative stress, and hypogonadism and osteoporosis in patients with COPD is indirectly based on data obtained in healthy individuals. Therefore, studies revealing the impact of these risk factors on the development of osteoporosis in patients with COPD are recommended. Further, this review emphasized the importance of systematically assessing skeletal muscle function together with osteoporosis in patients with COPD, keeping in mind their high prevalence in these patients as well as their impact on quality of life and mortality. Finally, therapies and strategies that are directed at improving both comorbidities should be considered, since, for the time being, only exercise training seems to reach this goal.

4. Conclusion

This review emphasized evidence that skeletal muscle weakness and osteoporosis are two comorbidities of chronic obstructive pulmonary disease that most likely coexist together. These comorbidities are highly prevalent in patients with COPD; they share several risk factors, including cigarette smoke, physical inactivity, systemic and local inflammation, oxidative stress, hypogonadism, vitamin D deficiency, nutritional deficits, and age. In addition, a cluster analysis confirmed the cooccurrence of both comorbidities together in a subgroup of patients with COPD. Therefore, several therapies known to improve muscle function can be beneficial for osteoporosis as well. This should be taken into account when treating patients with COPD.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

COgnitive-Pulmonary Disease

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Over the past few decades, chronic obstructive lung disease (COPD) has been considered a disease of the lungs, often caused by smoking. Nowadays, COPD is regarded as a systemic disease. Both physical effects and effects on brains, including impaired psychological and cognitive functioning, have been demonstrated. Patients with COPD may have cognitive impairment, either globally or in single cognitive domains, such as information processing, attention and concentration, memory, executive functioning, and self-control. Possible causes are hypoxemia, hypercapnia, exacerbations, and decreased physical activity. Cognitive impairment in these patients may be related to structural brain abnormalities, such as gray-matter pathologic changes and the loss of white matter integrity which can be induced by smoking. Cognitive impairment can have a negative impact on health and daily life and may be associated with widespread consequences for disease management programs. It is important to assess cognitive functioning in patients with COPD in order to optimize patient-oriented treatment and to reduce personal discomfort, hospital admissions, and mortality. This paper will summarize the current knowledge about cognitive impairment as extrapulmonary feature of COPD. Hereby, the impact of smoking on cognitive functioning and the impact of cognitive impairment on smoking behaviour will be examined.

1. Introduction

The twentieth century spread of tobacco use led to a global epidemic of smoking-related illnesses, resulting in 5.4 million deaths worldwide each year. The yearly toll is expected to surpass 6 million by 2015. By then, approximately 30% of the tobacco-related deaths will be caused by chronic respiratory diseases [1]. Cigarette smoking is the leading cause of chronic obstructive pulmonary disease (COPD). The risk of COPD is 56-fold higher in current smokers than in never-smokers [2]. Passive exposure to smoking, air pollution, and occupational chemical fumes or dust may act synergistically with active smoking to increase the risk of COPD [3]. COPD is defined as a disease characterized by progressive, irreversible airflow limitation and abnormal inflammatory response in the lungs [4]. Extrapulmonary features of COPD include weight loss, decrease in muscle mass, strength, and endurance, osteoporosis, heart failure, anxiety, depression, and cognitive impairment [4]. A recent review article indicates a specific pattern of cognitive impairment in patients with COPD [5]. This suggests that COPD is associated with specific abnormalities in brain structure. Cognitive impairment might have an adverse effect on functional, social, emotional, affective, and communication skills. Nowadays, COPD is increasingly seen as a disorder with both physical effects and effects on brains, including impaired psychological and cognitive functioning. The present narrative review provides an overview of the currently available knowledge about cognitive impairment as extrapulmonary feature of COPD. Hereby, the impact of smoking on cognitive functioning and

the impact of cognitive impairment on smoking behaviour will be examined.

2. Cognitive Functioning

Cognitive functioning refers to a range of brain functions that include the processes by which an individual perceives, registers, stores, retrieves, and uses information by which our behaviour can be adapted to new situations. Cognitive functioning can be divided into several cognitive domains, such as information processing, attention and concentration, memory, executive functioning, and self-control. Each domain contains specific functions, which can be seen as basic capabilities that influence the content and amount of intellectual skills, personal knowledge, and competences (Figure 1). These cognitive functions allow us to read, remember a phone number, recognize a human face, drive, and make decisions [6]. The executive functions can be seen as the "higher" cognitive functions such as complex cognitive activities, purposeful, self-regulatory, and future-oriented behaviour (e.g., planning, initiating, and problem solving), involved in the regulation and control of "lower" cognitive functions [7]. Self-control consists of a subset of self-regulatory processes which aim to prevent yielding to unwanted impulses or urges (such as craving for a cigarette when trying to quit smoking) [8].

3. COPD = COgnitive-Pulmonary Disease?

In 1992, Grant et al. showed that 42% of the patients with COPD had moderate to severe cognitive impairment compared to only 14% in controls [9]. The incidence of cognitive impairment in patients with COPD varies in different studies from 12 to 88% [10]. Cognitive impairment in patients with severe to very severe COPD seems to be associated with the severity of airway obstruction [11]. However, not all studies show a relationship between FEV_1 and cognitive functioning [5]. Dodd et al. showed that patients with COPD and an exacerbation had poor scores on cognitive measures compared to stable patients with COPD. This was independent of the presence of hypoxia, vascular risk factors, the number of pack years, and even the severity of COPD [12]. Incalzi et al. showed that the average performance on cognitive tests of patients with COPD was comparable with the performance of patients with vascular dementia [13]. Unfortunately, this paper did not mention the stage of vascular dementia of these subjects. Villeneuve et al. demonstrated that 36% of patients with COPD, compared with 12% of healthy subjects, had mild cognitive impairment, which refers to significant cognitive decline without major functional impacts on activities of daily living. Cognitive impairment may occur in different domains of cognitive functioning [5]. However, the current literature does not provide a clear picture of the pattern of cognitive impairment in COPD. Discrepancies in the current literature can be explained by several methodological limitations of previous studies, such as unknown or self-reported premorbid cognitive functioning [12], limited neuropsychological assessment [14], a self-reported diagnosis of COPD [15], use of control groups that are not matched on potentially important characteristics, for example, educational level [16], or inclusion of patients with COPD without comorbidities [17].

4. Causes of Cognitive Impairment in COPD

In recent years the literature on cognitive functioning in COPD has postulated several causes for cognitive impairment, including brain damage, reduced physical activity, and exacerbations.

4.1. Atrophy. It is assumed that cognitive impairment in patients with COPD is related to structural brain abnormalities. A voxel-based morphometric study showed that stable patients with COPD in contrast to controls had a lower density of gray matter in the limbic and paralimbic brain regions. This was correlated with a decrease in the arterial oxygen content, deterioration of performance in visual tasks, and an increased duration of illness [18]. Ryu et al. showed that patients with severe COPD showed extensive regions with significantly lower fractional anisotropy (a measure for the quantitative integrity of brain tissue) and higher trace (an index of water movement across cell membrane) in gray and white matter compared to controls. Furthermore, a decrease in fractional anisotropy was demonstrated in prefrontal lobes of persons with moderate COPD compared to normal control subjects [19]. The loss of white matter integrity was associated with the severity of COPD suggesting a correlation with a significant decrease in frontal function in persons with severe COPD and may explain pathophysiological and psychological changes in patients with COPD [18]. Using a Single Photon Emission Computed Tomography (SPECT) scan in patients with COPD without hypoxemia, a decreased perfusion in the left frontal regions of the brain was observed, whereas in patients with COPD and hypoxemia both a decreased perfusion in frontal and parietal areas was found. Reduction of brain perfusion is correlated with impairment in verbal memory, attention, and delayed memory [20]. The brain abnormalities which are seen in patients with COPD are also found in chronic hypoxic diseases such as obstructive sleep apnea syndrome and congenital central hypoventilation syndrome. Possible causes of structural abnormalities in the brains of COPD are cigarette smoke, inflammation, hypoxemia, atherosclerosis, hypercapnia, and nocturnal desaturations.

4.2. Smoking. In 2011, the American rapper ASAP Rocky sang "I smoked away my brain," and in fact, smoke may cause severe brain damage. Smoke from a cigarette, pipe, or cigar consists of many toxic chemicals, including tar, carbon monoxide, and nicotine. Nicotine is believed to be the most active ingredient that modulates brain function and produces addiction [21].

Nicotine inhaled via cigarette smoke enters the bloodstream through the lungs and reaches the brain in 10–20 seconds [22]. Depending on the number, volume, duration, smoke dilution, and depth of inhalation, nicotine can act

as either a stimulant or tranquilizer. This can explain why smokers report that smoking gives them energy, stimulates their mental activity, and helps them to attend and concentrate, while others note that smoking relieves anxiety, leads to feelings of contentment, and relaxes them [23]. Upon entering the bloodstream, nicotine immediately stimulates the release of neurotransmitters, neuromodulators, and hormones, which are responsible for most of nicotine's effects like reducing pain, stress, and anxiety or increasing arousal and enhancing cognitive functions like alertness, concentration, and memory [24]. Additionally, there are a lot of adverse neurocognitive effects of cigarette smoking in humans (vide infra).

4.2.1. Acute Nicotine Exposure. Several studies demonstrated cognitive benefit due to acute nicotine exposure. However, such cognitive enhancement may only be observed in persons with neuropsychiatric disorders (e.g., Alzheimer's disease, attention-deficit hyperactivity disorder, Parkinson's disease, and schizophrenia) who exhibit defined cognitive deficits that are intrinsic to their illness [25]. Improvement in some cognitive domains is mostly seen in vigilance and working memory [26]. Except for the positive gains in alerting attention accuracy and response time, fine motor skills, orienting attention, reaction time, short-term episodic memory accuracy, and working memory reaction time [27], there is no evidence to support nicotinic enhancement of cognitive functioning in healthy adult smokers and nonsmokers. Also under extreme task demands it has been shown that smokers are disadvantaged compared to never-smokers. This suggests that cigarette smoking may work against a person's ability to apply sufficient cognitive resources to achieve maximal performance under progressively more difficult testing conditions [28]. Studies of healthy non- or never-smokers are unlikely to show cognitive performance improvement with nicotinic stimulation by smoking or nicotine patches because they are likely to be operating already at or near optimum levels of cognitive performance. In contrast, studies that tend to show enhancement of cognitive functioning generally utilize persons with impaired cognitive functioning (e.g., neuropsychiatric subjects) or for whom task demands do not match the level of on-going nicotinic stimulation [25]. In these persons nicotinic stimulation brings their cognitive performance to near optimal levels (Figure 2).

4.2.2. Chronic Cigarette Smoking. Chronic cigarette smoking generally does not improve cognitive functioning. Chronicity of smoking is reflected in the number of cigarettes smoked daily, the lifetime duration of smoking, and dose duration (e.g., pack years). A review by Durazzo et al. found poorer domain-specific cognitive skills, including auditory-verbal learning and memory, information processing speed, cognitive flexibility, executive functions, general intelligence, reasoning, sustained attention and impulse control, visual search speeds, and working memory among smokers, compared to nonsmokers [29]. Impairment in specific cognitive domains is found to be positively related to the level of chronicity of smoking [30]. Jacobsen and colleagues observed greater

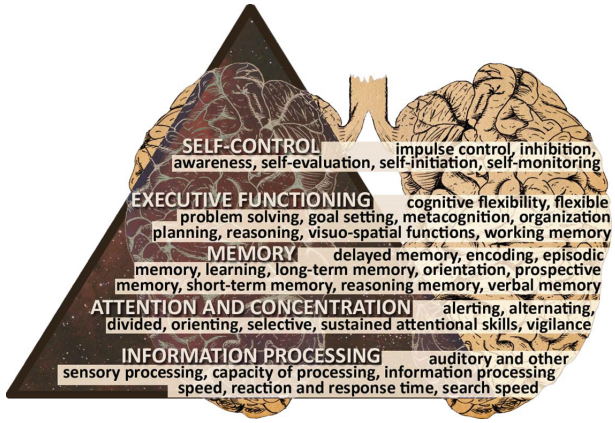

Figure 1: Cognitive domains and specific functions.

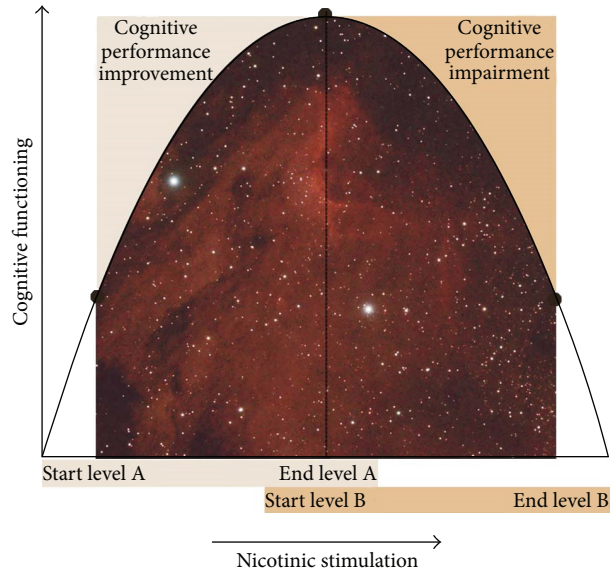

Figure 2: Nicotinic stimulation results are a reflection of baseline cognitive performance level (data from Figure 1 in [25]).

impairment in working memory performance accuracy in adolescents who began smoking at younger age than those who began smoking at older age [31]. These findings implicate a continuum of toxicity, whereby earlier exposure to nicotine is associated with greater brain damage than is exposure occurring at later age. Similarly, in animal models and children, prenatal nicotine exposure causes cognitive impairment [32]. With increasing age, chronic smoking is associated with declined global cognitive functioning [33] and reasoning memory [34] and an increased risk for both vascular dementia and Alzheimer's disease [35]. The risk of dementia is dose dependent and increases with the number of cigarettes smoked [35]. Inconsistencies among studies may be related to the smoking study cohort and the baseline cognitive performance level.

4.2.3. Smoking in COgnitive-Pulmonary Disease. Smoking may promote cerebral atherosclerosis and hypoxemia. It may also affect the microstructural integrity of cerebral white matter due to the stimulating effect of nicotine on nicotine receptors and induction of cerebral small-vessel disease [19]. Consequently, cognitive functioning may be negatively affected. Lung function has been implicated as a potential mediator of the association between smoking and the adverse neurocognitive consequences since research on hypoxemic patients with COPD has documented the presence of mild decrements in cognitive functioning [9]. Because smoking history is a primary risk factor for COPD and other lung disorders, smoking may have an indirect effect on cognitive functioning through its impact on lung function [36]. However, some studies have shown an association between lung function and cognitive function, regardless of smoking status [37].

4.2.4. The Influence of Cognitive Impairment on Smoking Cessation. Common barriers to quitting smoking include concerns regarding weight gain, cost of medicine and classes, discouragement, disruption of relationships, fear of failure, and the loss of perceived psychological benefits of smoking (reward effects, e.g., stress relieve) [38, 39]. After diffusion into brain tissue nicotine binds to nicotinic acetylcholine receptors (nAChRs), for example, the $\alpha_4\beta_2$ receptor subtype [40]. Receptor stimulation results in increased levels of several neurotransmitters, neuromodulators, and hormones in the brain. The neurotransmitter dopamine induces a pleasurable experience and is critical to the reward effects of nicotine [25, 41]. Next to the brain reward effects, craving for cigarettes and withdrawal symptoms (e.g., anxiety, depressed mood, difficulty in concentrating, irritability, restlessness, and sleep/appetite disruption) after quitting serve as a barrier to smoking cessation. Craving may stem from both psychological and physical dependence on nicotine and the associated withdrawal effects can become conditioned cues for smoking. However, conditioning develops only by pairing the pharmacologic actions of nicotine with behaviors. In individuals who are vulnerable to addiction, repeated exposure to nicotine induces neuroadaptation (tolerance) to some of the effects of nicotine. The number of binding sites on the nACHRs in the brain increases, probably in response to nicotine-mediated desensitization of receptors. These neuroadaptive changes are the bases of nicotine tolerance and addiction. Withdrawal symptoms occur in chronic smokers when desensitized $\alpha_4\beta_2$ nAChRs become activated in the absence of nicotine [40]. Taken together, individuals become addicted not only to smoking cigarettes but also to neurotransmitter, neuromodulator, and hormone release in the brain. The desire to quit smoking is not sufficient to accomplish smoking cessation. The ability to guide our behavior according to our long-term goals requires inhibition and monitoring of ongoing behavior [42]. In order to quit smoking, actions should be planned and the determination to implement these actions is crucial. The cognitive domains involved are executive functioning and self-control. These are essential for making a deliberate effort to break habitual and rigid behavioral patterns in order to fulfill the desire to quit smoking. Impairment in executive functioning as seen in older adults has a negative effect on quitting smoking [43].

4.2.5. Genetic Predisposition for Smoking Dependency. The finding that genetic factors account for roughly 70% of the variance in nicotine dependency in adults supports a type of biological vulnerability [44]. Evidence from affected relative or allele sharing methods of analysis demonstrates a number of plausible "candidate genes" for nicotine dependency, which may affect individual's vulnerability to develop nicotine dependency. These candidate genes code for dopamine receptors and transporters, GABA receptors, nAChR-receptor subtypes, and opiate and cannabinoid receptors [45]. In addition, polymorphisms in the CYP2A6 gene are associated with slower nicotine metabolism which reduces the number of cigarettes smoked per day [44]. Furthermore, genes in the chromosomal region that code for brain-derived neurotropic factor (BDNF) are associated with smoking initiation [46]. Genetically based personality traits like impulsivity and risk taking may predispose certain individuals to experiment with drugs, including tobacco [47]. In addition adoption, family, and twin studies converge on the relevance of genetic factors in the use of tobacco and the risk of developing nicotine dependence. Parameter estimates for heritability, shared environmental influences, and unique environmental influences for nicotine dependence are 67%, 2%, and 31%, respectively [48]. Greater concordance in current smoking, experimentation, and cessation has been observed in identical twin pairs compared to fraternal twin pairs [49]. Niu et al. demonstrated that individuals with a nicotine dependent sibling are more likely to be nicotine dependent as well [50]. Adoption studies tried to discriminate between genetic and environmental influences. These studies demonstrated a greater similarity of smoking between adoptive children and their biological parents [51] which suggests a genetic determination of smoking. Although studies confirm the important role of both genetic and environmental influences in nicotine dependence, there is little consistency between studies for the importance of family environment. It is also possible that normative pressure encourages smoking behavior though this might also depend on their particular genetic makeup [52].

4.3. Inflammation. Many inflammatory cells, mediators, and enzymes are involved in the complex pathophysiology of COPD. White blood cell count and levels of C-reactive protein, interleukin (IL)-6, and fibrinogen are elevated and tend to increase with disease progression [53]. Inflammation from the systemic effects of COPD may also damage the white matter integrity [12]. C-reactive protein has a direct neurotoxic effect and contributes to cerebral atherosclerosis. Further, IL-6, IL-1β, tumor necrosis factor-α, and α1-antichymotrypsin have been associated with cognitive impairment [54, 55]. The effects of acute, chronic, and systemic inflammation have been associated with cognitive impairment in patients with COPD [12, 37, 56, 57].

4.4. Alveolar Hypoxia and Consequent Hypoxemia. Hypoxia is characterized by deprivation of oxygen supply to an organ or the total body. Hypoxic episodes or chronic hypoxia in the brain can lead to the generation of free radicals, an inflammatory mediated neurotoxic effect, and oxygen dependent enzyme, which mediate the neuronal damage. [19]. Although some studies found weak or no correlation between cognitive functioning and hypoxia, there are studies that show that patients with COPD and hypoxia have more cognitive impairments than patients with COPD without hypoxia [9, 11]. Likewise, hypoxemia, which is characterized by low levels of dissolved oxygen in the arterial blood, can result in a lack of oxygen supply to the brains and may lead to cognitive impairment in attention, reasoning, memory, and processing speed in patients with COPD [20]. Furthermore, nocturnal desaturations may affect cognitive functioning. It is assumed that the structural abnormalities in the cerebral cortex and white matter result from cerebral hypoperfusion and microemboli, resulting in hypoxia [58]. Thirty years ago it was demonstrated that oxygen supplementation in COPD patients with hypoxemia may have beneficial effects on cognitive functioning [14, 59].

4.5. Hypercapnia. As hypoxia, hypercapnia (characterized by increased carbon dioxide levels in the blood) can also lead to the generation of free radicals and oxygen dependent enzymes which can result in global neuronal injury. However, little is known about the relationship between hypercapnia and cognitive impairment in patients with COPD. Although a correlation has been demonstrated between increased arterial carbon dioxide tension and impaired cognitive functioning in attention and memory [60], not all studies observe a correlation between hypercapnia and cognitive functioning [61].

4.6. Atherosclerosis. Atherosclerosis is a progressive disease process involving both chronic artery wall inflammation and hypoxia. Atherosclerosis can lead to partial or complete obstruction of the vasculature in the brain. This may lead to oxygen deprivation of brain cells situated behind the obstructed vessel wall, resulting in decreased brain function or even brain cell death (stroke) which can impair cognitive functioning. In patients with cardiovascular disease, the thickness of the carotid artery—a measure of atherosclerosis—is associated with reduced results on cognitive tasks related to attention and executive functions [62]. COPD is known to facilitate atherosclerosis in blood vessels throughout the body, for example, via oxidative stress, hypoxia, hypoxemia, and systemic inflammation [63].

4.7. Decreased Physical Activity. Age- and disease-related decline in physical activity is associated with cognitive functioning [64]. Physical activity has a positive effect on cognitive functioning in patients with COPD by influencing mediating factors such as anxiety, depression, nutrition, and sleep quality [65]. Improvement of cognitive functioning after physical activity has been found using a cognitive test of verbal fluency [66]. A vicious circle of deconditioning may occur, whereby cognitive impairment leads to a decrease in physical activity because patients have difficulty with initiating activities or fail to recognize the importance of exercise. Consequently, this could lead to more cognitive deficits.

4.8. Exacerbations. During exacerbations, hypoxemia and systemic inflammation increase which may explain cognitive impairment in COPD. Dodd et al. demonstrated worse performance on cognitive functioning tests concerning episodic memory, executive functions, visuospatial functions, working memory, and processing speed in COPD patients with an exacerbation compared to age-matched controls. They also had worse scores compared to stable patients with COPD, except performance on episodic memory and executive function tests. Furthermore, they had lower scores compared to the normal range of the healthy population [12]. While one study showed that cognitive functioning did not improve three months after the exacerbation, other studies showed that cognitive functioning is reversible after six months [12, 67, 68].

4.9. Discrepancies and Ambiguities. Although evidence has been found for the above described causes of cognitive impairment in patients with COPD, these factors cannot explain all cognitive impairments [37]. To date, it is still unknown which other factors play a role. Previous research has shown that cerebrovascular disease explains part of the variance in cognitive impairments in patients with COPD and an exacerbation [12]. The variance in cognitive impairment in COPD could also be explained by comorbid conditions such as obstructive sleep apnoea syndrome and major depressive disorders which also decrease cognitive performance [69, 70]. Therefore, causes of cognitive impairment in patients with COPD may be multifactorial.

5. Consequences of Cognitive Impairment in COPD

The extent to which a person experiences difficulties in daily life due to cognitive impairment depends on which cognitive functions are affected. In theory, "higher" cognitive functions affect the operation of "lower" cognitive functions. Three consequences of cognitive impairment can be distinguished. First, immediate discomfort for the patient, such as memory problems and problems with attention and concentration, occurs [37]. Second, cognitive impairment affects self-management. Third, cognitive functioning affects the duration and frequency of hospital admissions and mortality [71].

Patients with COPD will be advised to stop smoking, use their medication properly, and maintain an active lifestyle [72]. Furthermore, cognitive impairment is related to limitations in activities of daily living. A study of Antonelli Incalzi et al. demonstrated an association in patients with COPD between low results on cognitive tests and disability in activities of daily life [73]. Physical activity patterns of patients with COPD are usually lower than the ones that

the patient is expected to be capable of [74]. This may be explained by the fact that patients can have a cognitive impairment, which limits the ability to initiate activities and understand the importance of activities such as physical exercise. Executive function deficits in patients with COPD lead to improper use of (inhalation) medication, difficulties in dealing with comorbidities, and difficulty in handling guidelines. In addition, patients with executive function deficits seem unmotivated because they do not follow advised guidelines, while they may not have good self-management skills [75]. Consequently, cognitive impairment in patients with COPD may adversely affect treatment. Reduced verbal memory may reduce medication compliance. Poor adherence to medication increases the risk of an acute exacerbation, which consequently results in poorer health outcomes [12].

5.1. Hospitalizations and Deaths. A prospective study showed over a three-year period that the coexistence of COPD and cognitive impairment has an additive effect on respiratory-related hospital admissions and mortality [71]. A retrospective study showed that patients who were still alive after three years had a better performance on cognitive tests at the start of the study [76]. The cause still remains unknown. A possible explanation is that cognitive impairment may be more common in patients with severe COPD, hypoxia, inflammation, or comorbidities. Another explanation is that patients with cognitive impairment are more often hospitalized due to insufficient self-management compared to COPD patients without cognitive impairment. The length of hospitalization is also correlated with cognitive functioning, such as processing speed, immediate visual recognition, and verbal fluency [12]. However, cognitive functioning is not a part of the current prognostic indices, such as the BODE index [77].

6. Clinical Implications of Cognitive Impairment in Patients with COPD and Conclusions

Cognitive impairment in patients with COPD may affect health and daily functioning. Further research into the degree of cognitive impairment, the origin, and consequences is important to optimize clinical care, treatment, and support of patients with COPD and to reduce exacerbations and hospitalizations, to optimize survival and improve quality of life. In addition, knowledge of deficits in executive functions may lead to insight into continued smoking among persons with respiratory diseases. It also allows clinicians to arrange resources like assistance from a social network and environmental structure in order to enhance the success in quitting smoking. Research on changes in brain morphology, clinical and demographic characteristics of patients with COPD, and comorbid cognitive impairment may give more insight into the risk factors and causes of domain-specific cognitive impairment. By adapting the environment to the personal needs of the patient limitations in daily life can be reduced. Also, education of beneficial health activities and treatment adherence can be provided and the patient can learn to make their own decisions. To maintain the motivation of the patient, it is important to encourage the confidence of the patient and to establish or maintain considerable external support. Hereby it is important to monitor the emotional state of the patient and to have good communication with health care providers, partners, and neighbors. By properly using this system, social support, knowledge of the disease and care, coping, and self-management skills can contribute to improving the care and guidance of these patients. Self-management can be focused on the individual needs and problems in daily practice, knowledge about lung disease, and physical activity. Future studies should focus on interventions with the aim to optimize cognitive functioning of patients with COPD (COgnitive-Pulmonary Disease).

Conflict of Interests

The authors declare that they have no conflict of interests regarding the publication of this paper.

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Review Article

Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Cardiovascular Links

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Chronic obstructive pulmonary disease (COPD) is a chronic, progressive lung disease resulting from exposure to cigarette smoke, noxious gases, particulate matter, and air pollutants. COPD is exacerbated by acute inflammatory insults such as lung infections (viral and bacterial) and air pollutants which further accelerate the steady decline in lung function. The chronic inflammatory process in the lung contributes to the extrapulmonary manifestations of COPD which are predominantly cardiovascular in nature. Here we review the significant burden of cardiovascular disease in COPD and discuss the clinical and pathological links between acute exacerbations of COPD and cardiovascular disease.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by emphysema, small airways disease, and bronchitis, associated with pulmonary hypertension. The chronicity of COPD is well documented, characterized by a progressive decline in lung function associated with airway narrowing due to inflammation, fibrosis and mucus plugging, and parenchymal destruction with a loss of elasticity, gas exchange surface area, and airway support with subsequent early airway closure [1]. Acute insults result in the clinical syndrome of acute exacerbation of COPD (AECOPD) where the classical etiology is either infectious, viral or bacterial, or environmental in nature [1]. Not infrequently, there is a cardiovascular trigger underlying the clinical presentation, and this remains challenging to identify [2]. It is imperative that we further explore our understanding of AECOPD as this clinical diagnosis constitutes a major cause of morbidity and mortality in the COPD population, with a 50% mortality at 3.6 years, a 75% mortality at 7.7 years, and a 96% mortality at 17 years following the index hospitalization for AECOPD [3]. In this review, we will explore what we understand about the relationship between cardiovascular disease and AECOPD. We will also explore how current treatments for AECOPD impact cardiac disease and vice versa in order to improve management for patients with AECOPD.

2. Cardiovascular Disease and COPD: Friend or Foe?

2.1. Epidemiology. The close association between COPD and cardiovascular disease has received significant attention in the last fifteen years in a concerted effort to improve our understanding of the systemic consequences of COPD. It is estimated that the diagnosis of COPD increases the risk of cardiovascular disease by an OR of 2.7 (95% CI 2.3–3.2) [4]. Finkelstein and colleagues report that patients with COPD are at a significantly higher risk of coronary artery disease (OR 2.0, 95% CI 1.5–2.5), angina (OR 2.1, 95% CI 1.6–2.7), myocardial infarction (OR 2.2, 95% CI 1.7–2.8), stroke (OR 1.5, 95% CI 1.1–2.1), and congestive heart failure (OR 3.9, 95% CI 2.8–5.5) [4]. Not unexpectedly, those hospitalized for AECOPD have a high prevalence of coexisting cardiovascular disease, often exceeding 50% [5]. These associations have been documented in a variety of different nationalities and

ethnicities, including those within North America [4, 6–13], Asia [5], South America [14], and Europe [15–19], to list a few.

Mortality from cardiovascular disease is similarly increased in the COPD population. The 45,966 patients with COPD in the Northern California Kaiser Permanente Medical Care Program had an adjusted RR for mortality for all cardiovascular endpoints of 1.68 (95% CI 1.50–1.88), ranging from 1.25 (stroke) to 3.53 (heart failure) [6]. Both the Buffalo Health Study and the Lung Health Study, two well-described prospective studies, found an increased mortality from ischemic heart disease associated with degree of airway obstruction on spirometry [7, 8]. A pooled estimate of large population studies published before 2005 estimates that the RR of cardiovascular mortality is 1.99, 95% CI 1.71–2.29 [9].

COPD patients do not tolerate cardiac injury or intervention as well as those without airways obstruction. Bursi et al. determined that COPD subjects with an acute myocardial infarction have a five-year survival rate of 46% (95% CI 41–52%) as compared to those without COPD (survival rate 68%, 95% CI 66–70%), with an adjusted hazard ratio of 1.30, 95% CI 1.10–1.54 [20]. The VALIANT trial had similar results in their population, with an HR for all-cause mortality of 1.14, 95% CI 1.02–1.28 [21]. Salisbury et al. looked at subjects with obstructive airways disease following index myocardial infarction and document an elevated one-year mortality (HR 2.00; 95% CI 1.44–2.79) and a lower-health related quality of life, as compared to those without obstructive lung disease [11]. Coexisting COPD confers an increased risk for all-cause mortality when undergoing coronary artery bypass grafting as documented by Angouras et al. and Leavitt et al. (HR 1.28, 95% CI 1.11 to 1.47 and 1.8, 95% CI 1.6–2.1, resp.) [22–24].

The difference in mortality after a cardiovascular event may relate to a difference in management of COPD patients with cardiovascular disease. Those with coexisting cardiac disease and COPD are more likely to have less aggressive treatment with cardiac medications and/or coronary angiography [11, 20, 25, 26]. Furthermore, on discharge, patients with obstructive airways disease are less likely to receive percutaneous coronary intervention (50.9% versus 62.9%), to be discharged on aspirin (87.8% versus 94.5%) or a β-blocker (86.2% versus 92.6%), or to be referred for cardiac rehabilitation (37.5% versus 50.4%) following an index myocardial infarction than those without obstructive airways disease [11].

2.2. COPD and Classical Cardiovascular Risk Factors. COPD contributes to cardiovascular risk, so it is important to understand whether other cardiovascular risk factors are associated with COPD as well. There are a multitude of studies linking classical cardiovascular risk factors [27, 28] to COPD, such as hypertension, a family history of coronary artery disease, an abnormal lipid battery, or diabetes [6, 10, 20, 29]; yet other studies demonstrate no independent association but simply a high prevalence of these conditions [30]. Two classical risk factors for coronary artery disease, age and male gender, are associated with increased mortality in COPD [3]. The diagnosis of COPD is associated with a higher prevalence of a 10-year cardiovascular risk assessment >20% in those aged 55–74 than the general population [10]. Notably, though, even the young or female patients with COPD experience significant cardiovascular morbidity [6]. At this time, studies strongly support the association of COPD with smoking and age as the most prominent classical cardiovascular risk factors associated with the COPD population [15, 20], and it is recognized that classical cardiovascular risk factors and COPD commonly coexist.

Interestingly, the metabolic syndrome phenotype is commonly present in COPD patients [31, 32], yet a low body mass index (BMI) carries a worse prognosis [33–35]. A low BMI in COPD patients is linked to increased systemic inflammation [36], and it may be systemic inflammation driving cardiovascular disease rather than the negative health effects of obesity. A surrogate biomarker for systemic inflammation, C-reactive protein (CRP), is independently associated with both all-cause and cardiovascular mortality in this population (RR 1.79 95% CI 1.25–2.56, RR 1.69 95% CI 1.86–3.33, resp. when the highest quintile of CRP is compared to the lowest) [37]. Further work is needed to determine the benefit to an elevated BMI in advanced COPD and the implications to the cardiovascular system in early stages of COPD when obesity is commonly present.

2.3. Nature of Cardiovascular Disease in Subjects with COPD

2.3.1. Systemic Vascular Disease and COPD. The presence of peripheral vascular disease is very common in COPD patients, and there are multiple variables that contribute to this disease process including the systemic inflammatory response induced by the inhalation of cigarette smoke, diesel exhaust particles, and other air pollutants [38]. Peripheral vascular disease has been documented in the upper extremities [39–43] and the large, central vessels, such as the carotid and femoral arteries [44–47]. Multiple methodologies to document increased arterial stiffness are validated, either relating vessel size adjustments to distending pressure, determining pulse wave velocity (PWV), or examining pulse waveforms [48]. Aortic PWV (utilizing carotid-femoral distance in equation or the carotid-femoral distance after subtraction of sternal-femoral distance or carotid-sternal distance) is strongly associated with cardiovascular events, cardiovascular mortality, and all-cause mortality in the general population [49]. It is also a safe and noninvasive tool that has the advantage of being highly reproducible in the COPD population [45, 50]. The frequency of increased intima-media thickness and abnormal PWV increases as FEV1 decreases [44, 46]. There is mounting evidence that endothelial cell dysfunction, as measured through surrogates such as flow-mediated dilation, correlates with severity of COPD [40–42, 51, 52].

Cerebrovascular disease, as a manifestation of severe vascular disease, is increased in the COPD population, both in the presence of acute inflammation and in chronic disease [53]. A cross-sectional analysis of COPD patients identifies that COPD confers the highest increase in risk of stroke to those in the lowest quintile of age (age 35–44, HR 3.44, 95% CI 0.85–13.84), with the oldest quintile of age having the lowest increase in risk (age $\geq$ 75; HR 1.10, 95% CI 0.98–1.23) [54]. The burden of strokes is inversely proportional to FEV1 [53],

although there have been some studies that do not find this association independent of other risk factors [26].

2.3.2. Pulmonary Vasculature and Right Heart Dysfunction in COPD. The emphysematous component of COPD is characterized by destruction of alveolar walls and pulmonary capillaries, hyperinflation with resultant positive alveolar pressure throughout inspiration, hypoxic vasoconstriction, and pulmonary vascular endothelial dysfunction, with subsequent pulmonary hypertension. Depending on the definition used, 25 to 70% of COPD patients have pulmonary hypertension [1, 55–57]. Pathological changes of pulmonary hypertension are present in tissue samples from COPD patients who do not have a diagnosis of pulmonary hypertension [58, 59]. It is estimated that 25% of patients with moderate to severe COPD will develop pulmonary hypertension within 6 years, if they have no disease at baseline [60]. Severe pulmonary hypertension, defined by a mean pulmonary artery pressure (PAP) of greater than 40 mmHg, accounts for <5% of diagnoses and is usually disproportionate to the degree of airflow obstruction [57]. The majority of these patients will have a comorbid disease that is contributing to the degree of pulmonary hypertension [61]. In the right heart, objective findings that have been detected in COPD patients include concentric right ventricular (RV) hypertrophy and elevated end-diastolic RV pressures, one of the first manifestations of adjustment to elevated pulmonary artery pressures, followed by impaired relaxation and systolic dysfunction [57, 62]. RV systolic dysfunction is common in end-stage COPD, with one study documenting an average RV ejection fraction of 45 ± 9% [63]. Both right heart failure and pulmonary hypertension are associated with increased mortality in COPD patients [64].

2.3.3. Left Heart Dysfunction and COPD. Left heart dysfunction in COPD patients can be a challenge to recognize clinically and has recently been shown to be associated with significant morbidity and increased mortality in the COPD population. Many of the early studies looking at cardiac dysfunction and COPD lacked objective parameters defining reproducible echocardiographic measures and spirometric criteria [65]. In those with peripheral vascular disease, mild COPD is associated with subclinical left ventricular (LV) dysfunction (OR 1.6, 95% CI 1.1–2.3), but only moderate-severe COPD is associated with subclinical LV dysfunction and clinical heart failure (OR 1.7, 95% CI 1.2–2.4, and OR 2.0, 95% CI 1.2–3.6, resp.) [18]. In this population, subclinical LV dysfunction increased all-cause mortality in all patients with COPD, with risk the least in those with mild COPD (HR of 1.7, 95% CI 1.2–5.9) and most in those with moderate to severe COPD and overt heart failure (HR of 3.8, 95% CI 1.6–9.1) [18]. Studies have estimated that in patients with moderate COPD, up to 20.5% have unrecognized heart failure with reduced or preserved ejection fraction by their care providers [14, 17]. Similarly, the diagnosis of airflow obstruction is commonly missed in patients with cardiac disease [14, 66], indicating that recognition of these comorbid diseases requires a high index of suspicion.

COPD patients with co-existing heart failure experience similar mortality, hospitalization for cardiovascular events, and frequency of pulmonary events, regardless of whether they have a preserved or reduced ejection fraction [67]. Interestingly, classical examination features that are associated with an acute exacerbation of heart failure in the general population are valid in the COPD population. Physical examination findings associated with heart failure with comorbid obstructive airways disease include presence of rales, leg edema, elevated jugular venous pressure, and an S3 [68].

2.3.4. Arrhythmias and COPD. Arrhythmias associated with airflow obstruction are relatively common and have been a long-standing research interest. Hudson et al. in 1973 report a variety of arrhythmias noted in those with airflow obstruction, as defined by ATS guidelines in the 1970's [69]. More recently, 35.6% of COPD patients who underwent 24-hour Holter monitoring at age 68 had frequent or complex ventricular arrhythmia, as defined by Lown classes 2–5, recorded at baseline [70]. Frequent or complex ventricular arrhythmia on this recording was significantly associated with increased severity of obstructive airways disease, higher mortality (52% versus 41%), and coronary event rates (28% versus 18%) over 14 years of follow-up [70]. This data supports the known association of FEV1 with risk of cardiovascular death, ischemic heart disease, and mortality but also identifies the correlation of these with increased ventricular ectopy and ventricular arrhythmia.

An increased risk of supraventricular arrhythmia has also been reported, most commonly atrial fibrillation and multifocal atrial tachycardia. A higher risk of irregular heartbeats [4] and postoperative supraventricular tachycardia [71] has been reported. Atrial fibrillation occurs in an estimated 8 to 13% of all admissions to hospital for AECOPD [72, 73], with lower prevalence (~2%) of patients with stable disease followed longitudinally [74, 75]. In those with COPD, mean age in the early 50 s, approximately 0.4% will be found to have atrial fibrillation on re-examination at 5-years with an additional 2.2% identified to have atrial fibrillation in the emergency department within that 5 year period [74]. Presence of atrial fibrillation has been found to be inversely associated with FEV1 [74]. Multifocal atrial tachycardia (MAT) is a less common arrhythmia but highly associated with COPD. The estimated in-hospital prevalence of MAT in the general population is 0.05% to 0.32% with 55–66% of these diagnoses associated with comorbid COPD [76, 77]. The estimated in-hospital mortality with MAT is 45% and up to 80% in those with COPD likely due to the severity of acute illness and significant comorbidity in this population [76]. MAT is underdiagnosed on electrocardiogram (ECG) as it is commonly misinterpreted as atrial fibrillation [78].

3. Acute Exacerbations of COPD and Cardiovascular Disease

3.1. Cardiovascular Disease and Mortality in AECOPD. While numerous factors have been associated with poor outcomes from AECOPD, cardiovascular disease is being increasingly recognized as an important predictor of in-hospital mortality.

Cardiovascular risk factors and cardiac comorbidities that correlate with in-hospital mortality include age [73, 79–82] and male gender [79], cerebrovascular disease [73], ischemic heart disease [83, 84], atrial fibrillation [73], and congestive heart failure [84]. Cardiovascular features on admission that aid prognostication are hypotension, tachycardia, arrhythmia, stroke, pulmonary edema, elevated mean PAP > 18 mmHg, and bilateral pedal edema [81, 84–86]. Cardiac biomarkers associated with in-hospital mortality include an elevated serum CRP [73], serum troponin [83–85], NT-pro-brain natriuretic peptide (NT-proBNP) [85], and brain natriuretic peptide (BNP) [55]. Further studies into prediction models that can be utilized in clinical practice for prognostication are necessary to translate this knowledge into clinical care that will improve patient outcomes.

The cardiovascular morbidity of the population admitted with AECOPD is often underappreciated and underdiagnosed at the time of admission, as it is in stable disease. As an example, a high frequency (55%) of those with AECOPD have systolic or diastolic left ventricular dysfunction; more than are accounted for by known comorbid disease [87]. In the TORCH trial, there was a high frequency of sudden death, but disproportionately low prevalence of documented myocardial infarction, leading them to speculate that this was a diagnosis that may have been missed [88]. This is plausible, particularly since COPD patients have an increased risk of acute myocardial infarction (unadjusted HR 3.53, 95% CI 3.02–4.13) [54] and a high frequency of electrocardiographic evidence of previous myocardial infarction with no known ischemic heart disease [89]. A retrospective review of 43 autopsies of patients who died within 24 hours from admission from AECOPD in a university-affiliated tertiary care facility in Serbia revealed that 37.2% had a final cause of death from heart failure and 20.9% from pulmonary emboli [2]. AECOPD proves itself to be a complex clinical scenario that is difficult to separate from the cardiovascular pathology that is so frequent in this population. Lately, due to this diagnostic challenge, there has been recent discourse on the terminology given to these patients, using "acute respiratory symptoms in patients with COPD" or "exacerbation of respiratory symptoms in patients with multimorbidity," rather than "acute exacerbation of COPD" [90].

3.2. Cardiovascular Disease and Readmission to Hospital following AECOPD. There is much interest in the prevention of repeated or prolonged hospitalizations for AECOPD as recurrent admissions are associated with a higher all-cause mortality [3, 80]. Comorbid cardiovascular disease and an elevated troponin at the time of discharge are independently associated with increased risk of readmission for AECOPD [87]. Cardiovascular modifying factors such as physical activity and a higher physical quality of life score are protective and decrease the risk of readmission [91]. A major predictor of readmission for an AECOPD is the severity of airway obstruction, an independent risk factor for cardiovascular disease [81, 84, 92, 93].

Length of stay in hospital for an acute exacerbation of COPD averages between 6 and 9 days [81, 91, 94]. Predictors of an increased length of stay include age ≥65 years, poor performance status, or lowest FEV1 tertile, on a multivariate analysis of COPD patients [81]. Elevated serum troponin has been associated with longer length of stays for AECOPD (Harvey and Hancox report 5 days, 95% CI 1–20 versus 3 days, 95% CI 1–15) [95, 96].

3.3. AECOPD as a Trigger for Cardiovascular Events. There is mounting evidence that associates a higher frequency of acute cardiovascular disease with acute respiratory illness, such as pneumonia or AECOPD. In the general population, subjects with a respiratory tract infection are more likely to get an acute myocardial infarction within 1-2 weeks (OR 2-3) [97–99]. Huiart and colleagues found that current use of oral corticosteroids was associated with an increased risk of an index myocardial infarction (RR 2.01 95% CI 1.13 to 3.58), particularly if the prescription was for 25 mg or greater (RR 3.22, 95% CI 1.42 to 7.34) [100], suggesting that patients were undergoing active treatment for AECOPD at the time of the myocardial infarction. Increased likelihood of cerebrovascular disease is also associated with systemic respiratory tract infection [97, 101]. Some of the literature supports significant reduction in cardiovascular morbidity and mortality with prevention of respiratory tract infections; as an example, Nichol et al. report that influenza vaccinations were associated with a 19% reduction in hospitalization for cardiac disease, 16–23% reduction in cerebrovascular disease, 29–32% reduction in pneumonia or influenza, and 48–50% reduction in all-cause mortality in those ≥65 years of age [102]. Some studies have suggested a decrease in cardiac arrest in the community with vaccination against influenza [103] but a systematic review suggests a nonsignificant protective effect from vaccination against cardiovascular death (RR 0.51, 95% CI 0.15–1.76) [104].

Increased vascular risk associated with infection can be more broadly defined as secondary to an acute inflammatory lung condition, as other inflammatory states within the lung are associated with vascular dysfunction as well. Diesel exhaust has been linked to exercise-induced ST-segment depression and surrogates for vascular endothelial dysfunction [105, 106]. Air pollution has been linked to increased cardiac arrest [107]. Exposure to smoke as a firefighter is associated with significant lung inflammation [108] and an increased frequency of death from coronary artery disease [109]. The association between an acute on chronic inflammatory insult and increased cardiovascular events is explored by Man et al., who describe the possibility that increased systemic inflammation may destabilize vulnerable plaques and induce a prothrombotic state [38]. Such profound endothelial dysfunction occurs during these episodes of acute inflammation that macroscopic surrogates of endothelial and vascular smooth muscle function objectively improve three months following an AECOPD [51], increasing the plausibility of this theory.

4. Markers of Cardiac Disease in AECOPD

4.1. Electrocardiograms. In any disease state, ECG analyses are used to identify predisposing risk for development of ischemia/arrhythmias or signs of underlying cardiac disease.

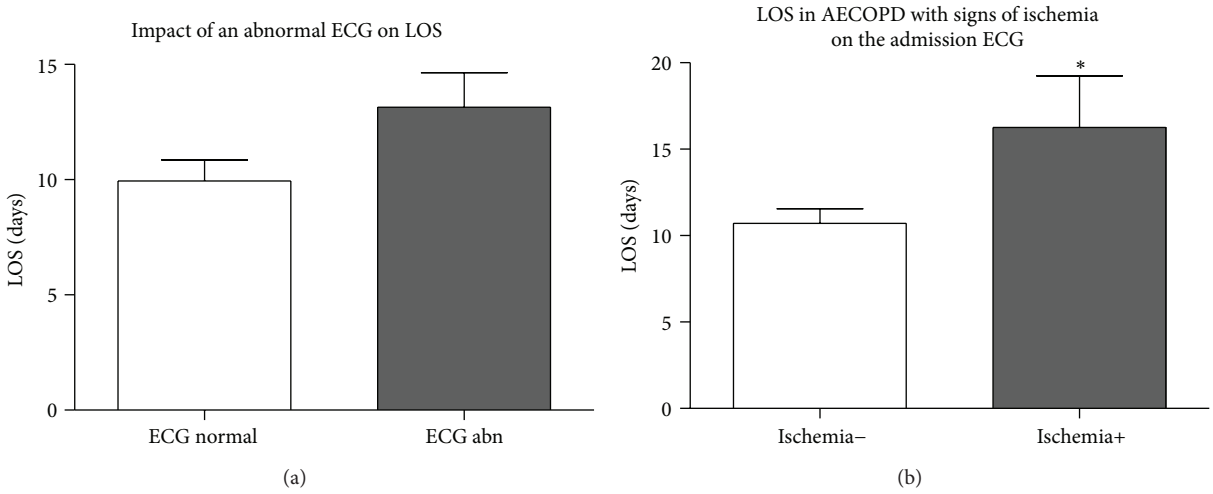

Figure 1: Presence of an electrocardiogram (ECG) abnormality and length of stay (LOS) of subjects admitted with an AECOPD to St. Paul's Hospital or Mount St. Joseph's Hospital between 2007 and 2008. The presence of ECG abnormalities did not influence LOS (11.7 ± 1.4 versus 13.2 ± 1.5, (a) P = NS). Subjects with ischemic changes on ECG had a longer LOS (11.2 ± 1.0 versus 16.6 ± 3.0, (b) $P = 0.031$).

In stable COPD patients, there are subtle changes in the ECG that are not present in the general population. Screening ECGs in patients with COPD have a low coefficient of variation of the RR interval that correlates with degree of hypoxemia [110]. Depressed heart rate variability, of which the variation of the RR interval is a surrogate, is correlated with mortality after a myocardial infarction in the general population [111]. A series of studies suggest COPD is associated with a disturbance of autonomic function manifested by increased sympathetic activation [112–115] and loss of normal circadian variations in heart rate [116]. Finally, vertical P wave axis correlates with a diagnosis of COPD, as measured by P wave amplitude in lead III > lead I and/or a dominantly negative P wave in lead aVL, findings that indicate a P wave axis >60° [117–119]. As such, vertical P wave axis on ECG has been suggested as a screening tool for unrecognized COPD.

Stable COPD patients ($n = 243$) are more likely to have an abnormal ECG than the general population (OR 1.5; 95% CI 1.0–2.1) as summarized: 11% premature ventricular contractions, 7% atrial fibrillation, 9% prolonged corrected QT (QTc) interval, 7% right bundle branch block (RBBB), 2% left bundle branch block (LBBB), 14% left anterior fascicular block, 0.4% left posterior fascicular block, 10% intraventricular block, 8% atrioventricular block, 1% RAE, 7% left ventricular hypertrophy, 1% right ventricular enlargement (RVH), 10% ST segment depression, 0% T wave abnormalities, and 7% inferior and 4% anterior Q-wave myocardial infarctions [120]. In comparison to normal controls, patients with COPD were significantly more likely to have an LBBB, RBBB, a higher resting heart rate, or a prolonged QTc and less likely to have bradycardia [120]. In those referred for pulmonary rehabilitation, 21% of stable COPD patients had an ischemic ECG at rest [121]. Holtzman and colleagues demonstrated that severe COPD patients are more likely to have RAE, RVH, RBBB, marked clockwise rotation, low voltage in limb leads, inferior QS pattern, left axis deviation, premature atrial contraction, supraventricular tachycardia, and an abnormal ECG as compared to mild/moderate COPD [122].

In AECOPD, ECG changes are very common, and studies demonstrate a high frequency of finding a new abnormality on ECG from baseline. In a study by Harvey and Hancox, 8% had ST segment depression, 37% had T wave changes, 17% had conduction block, and 6% had a new change on their ECG from baseline ($n = 182$) [96]. ECG findings of a conduction block, ST segment depression, and T wave changes are more likely if the patient has elevated troponin levels [96]. In the emergency department of tertiary care facilities in Vancouver, BC, Canada, we reviewed the ECGs of 163 admissions for AECOPD from 82 patients. Eighty-seven percent of admissions had an ECG, of which 65% were abnormal and 58% had a new abnormality from baseline. ECG abnormalities were as follows: 24% ischemic changes; 17% evidence of a previous myocardial infarction; 8% arrhythmia (excluding tachycardia); 30% heart block; and 16% chamber enlargement (van Eeden, unpublished data). An abnormal ECG, particularly with ischemic changes, on presentation to the emergency department with AECOPD, is correlated with a prolonged hospital stay (see Figure 1, van Eeden, unpublished data). These findings suggest that ischemic ECG changes are associated with more morbidity from AECOPD. There are few studies on electrographic changes in this high risk population, and very little is known about the prognosis and implications of these changes in the acute setting.

AECOPD is associated with greater prolongation of P wave dispersion than in stable COPD [123]. The association of prolongation of P wave dispersion and right atrial enlargement (RAE) with COPD may explain the increased prevalence of atrial arrhythmias, such as atrial fibrillation and MAT [124, 125]. Increased P wave amplitude is present in 14% of patients presenting to the emergency department with AECOPD [126]. P wave amplitude decreases after acute treatment in patients admitted for AECOPD, possibly reflecting reduced right atrial strain [126].

4.2. BNP/NT-proBNP. The natriuretic peptides have an established role in differentiating amongst the causes of dyspnea in COPD patients presenting with AECOPD [127]. These biomarkers increase the accurate identification of the trigger of the exacerbation and aid in prognostication while in hospital and after discharge. The BNP Multinational Study identified that in the general adult population presenting to the emergency department with dyspnea, of whom 25% had a history of obstructive airways disease, a BNP of 100 pg/mL had a sensitivity (Sn) of 93.1%, specificity (Sp) of 77.3%, positive predictive value (PPV) of 51.9%, negative predictive value (NPV) of 97.7%, positive likelihood ratio (+LR) of 4.10, and negative likelihood ratio (−LR) of 0.09 [68]. Mueller et al. similarly identified that a BNP of 100 pg/mL had a similar predictive value for the detection of congestive heart failure in patients who present to the emergency department dyspneic with a history of COPD, asthma, pneumonia, or PE [128]. In this study, a BNP of >500 pg/mL was considered to be diagnostic of heart failure, <100 pg/mL excluded heart failure, and 100–500 pg/mL had to be combined with clinical judgement [128]. The use of BNP in the initial assessment resulted in earlier initiation of therapy, reduced hospital admissions, shorter length of stays in hospital, and lower costs of treatment [128]. With use of BNP as outlined, 95% of heart failure subjects are correctly diagnosed rather than 35% [128].

Similarly, NT-proBNP levels in patients with AECOPD and left heart failure were significantly higher than those with AECOPD without LV failure or stable controls [129]. An NT-proBNP of 935 pg/mL has a Sn of 94.4%, Sp of 68.2%, accuracy of 74.3%, and NPV of 97.6%, whereas at a level of 584 pg/mL, heart failure was excluded with a NPV of 100% [129]. Abroug and colleagues identified a similar cut-off of 1000 pg/mL being accurate to rule out left-heart involvement in AECOPD (Sn 94%, NPV 94%, and negative likelihood ratio (−LR) 0.08) [130]. In order to rule in LV involvement in AECOPD, an NT-proBNP cut-off of 2500 pg/mL had the best operating characteristics (+LR 5.16) [130]. In subjects admitted to hospital with an AECOPD, increased NT-proBNP was associated with 30-day mortality (OR 9.0, 95% CI 3.1–26.2) [85] and long-term mortality [87, 131]. Rutten et al. compared BNP and NT-proBNP directly and found that they behaved similarly, able to identify systolic LV dysfunction more frequently than diastolic LV dysfunction or RV dysfunction [132].

The utility of BNP and NT-proBNP is well-proven in its ability to document heart failure, but clinicians are still challenged to predict whether the BNP is indicative of right heart dysfunction or left heart dysfunction. Several studies have attempted to correlate BNP and NT-proBNP with right heart and left heart pathology but have as yet not been able to discriminate between the two [55, 129, 133, 134].

4.3. Troponin. Elevated troponin levels are hallmarks of stress or ischemia affecting the myocardium. At baseline, COPD patients have been shown to have higher highly sensitive cTnT than the general population [135]. Patients who present with AECOPD are often found to have elevated serum troponin [136, 137], of which a minority are secondary to an acute coronary syndrome [96, 137–139], often in the absence of chest pain [140]. In those admitted to hospital for an AECOPD, elevated serum troponins are correlated with long-term mortality [83, 95, 138, 139], 30-day mortality [85], in-hospital mortality [142], increased length of stay [95, 96] and risk of readmission [87]. Høiseth et al. found a similar association between mortality and highly sensitive cTnT, most notably in those who were tachycardic (heart rate >100 bpm) [139]. Elevated troponins have been associated with the elderly, comorbid heart failure, chronic renal failure, atrial fibrillation, atrial flutter, increased requirement for NIPPV, and higher BNP levels [95]. Interestingly, elevation in serum troponins in AECOPD has also been associated with presence of neutrophilia, supporting the presence of an inflammatory milieu at the time of troponin elevation [143]. A summary of study associations with an elevation of serum troponin in the context of AECOPD is provided in Table 1.

5. Impact of Respiratory Medications and Interventions for AECOPD on Cardiovascular Disease

5.1. Bronchodilators. Tachycardia has been shown to be an independent risk factor for cardiovascular mortality in the general population [145]; therefore the liberal use of bronchodilators theoretically could exacerbate underlying cardiac disease during AECOPD. Bronchodilators have beneficial effects by relieving airway disease in the acute setting, but concerns regarding the $\beta 2$ agonist properties and cardiac effects in the setting of a population with high prevalence of cardiovascular disease have resulted in numerous studies to investigate this further.

The Lung Health Study is a large prospective randomized control trial that looked at the benefits of intensified smoking cessation regimens and ipratropium. It found no significant difference in mortality or cardiovascular morbidity associated with ipratropium, although this study was not powered to examine this rigorously [146]. A Cochrane review looked at the use of short-acting $\beta 2$ agonists for stable chronic obstructive pulmonary disease in 2002. They highlight the need for better studies looking at adverse effects secondary to treatment and acknowledge there was not enough information to draw a conclusion [147]. Recently, another Cochrane review was performed comparing short-acting $\beta 2$ agonists to short-acting anticholinergics in patients with stable COPD. The only adverse effects investigated were heart rate and blood pressure, both of which were similar between the two treatment groups once statistical heterogeneity was addressed [148]. Bouvy et al. explored any association between readmission for heart failure exacerbated by an arrhythmia and use of oral and inhaled sympathomimetics. This study was limited by small sample size, so although there was a suggestion of an association of heart failure exacerbation by arrhythmia, the results were not significant [149]. Rossinen et al. prospectively studied 24 patients with known or symptomatic coronary artery disease and comorbid asthma or COPD. After observation for 24 hours on cardiac monitoring while receiving escalating doses of salbutamol, there were no episodes of angina, tachycardia, nor arrhythmias [150].

Table 1: Summary of studies analyzing the prognostic and diagnostic importance of serum troponins in patients admitted to hospital for acute exacerbations of COPD.

Author	Study design	Sample size	Controls	Follow-up (months)	Associations with elevated troponin
Fruchter and Yigla [83] Israel	Retrospective	83	953 without troponins and 99 with low cTnI	≤72	Increased long-term mortality
Martins et al. [95] Portugal	Retrospective	121	52 with undetectable cTnI	>18	Age, heart failure, atrial arrhythmia, elevated BNP, need for NIPPV Increased LOS and long-term mortality
Harvey and Hancox [96] New Zealand	Retrospective	47	147 with undetectable cTnI or cTnT	Until discharge	Older age, lower pulse oximetry, acidosis, hypercapnea Longer length of stay in hospital
Brekke et al. [138] Norway	Retrospective	173	897 without troponins and 223 with undetectable cTnT	<66	Increased all-cause mortality (HR 1.64, 95% CI 1.15–2.34)
Brekke et al. [143] Norway	Retrospective	321	120 with undetectable cTnT	Discharge	Neutrophilia, increased creatinine, cardiac infarction injury score, low hemoglobin, and tachycardia
Odigie-Okon et al. [137] USA	Prospective	19	95 without an ischemic ECG and undetectable cTnT	First 24 hours from admission	Presence of acute coronary syndrome or marker of ischemia
Marcun et al. [87] Slovenia	Prospective	32 at admission 15 at discharge	95 admitted with cTnT ≤ 0.012 ng/L and 112 discharged with cTnT ≤ 0.012 ng/L	6	Increased risk of repeat hospitalization (HR 2.89, 95% CI 1.13–7.36)
Høiseth et al. [139] Norway	Prospective	73	26 with a low highly sensitive cTnT	<36	Increased long-term mortality and higher mortality with tachycardia
Høiseth et al. [141] Norway	Prospective	49	50 with a low geometric mean of hs-cTnT	Discharge	Age, arterial hypertension, tachycardia, creatinine
Baillard et al. [142] France	Prospective	13	58 with normal troponins	Discharge	In-hospital mortality
Soyseth et al. [136] Norway	Prospective	50	124 stable COPD patients admitted to a rehabilitation hospital	Until discharge	No association between retrosternal chest pain or T wave inversions on ECG and elevated troponin
Chang et al. [144] New Zealand	Prospective	40	201 with undetectable cTnT	12	Increased 30-day mortality

LOS: length of stay; LVH: left ventricular hypertrophy; cTnI: cardiac troponin I; cTnT: cardiac troponin T; AECOPD: acute exacerbation of COPD; ECG: electrocardiogram.

There are studies that suggest a possible contribution of inhaled bronchodilators to cardiovascular morbidity, but each study has inherent limitations and therefore more studies are needed. The Lung Health Study did not show a statistical difference between supraventricular arrhythmias in patients using ipratropium as compared to those using placebo or with usual care but did find that those with an arrhythmia were very compliant in their usage of ipratropium [146]. A large retrospective case-control study by Wang et al. associates ipratropium use in the preceding thirty days with stroke (OR 2.97; CI 2.27 to 3.88), a risk that diminished if the last prescription was at a longer interval preceding the cerebrovascular event [151]. Dutch citizens with their first nonfatal myocardial infarction were reviewed, finding that patients with ischemic heart disease and a low dose exposure to β2 agonists had an increased risk of acute myocardial infarction (OR 2.47, 95% CI 1.60–3.82) [152]. Overall, studies identifying potential adverse effects of bronchodilator use on cardiac disease in the COPD population are small. The evidence that short-acting bronchodilators have adverse cardiac effects is currently lacking.

5.2. Noninvasive Positive Pressure Ventilation. Noninvasive positive pressure ventilation (NIPPV), in the form of bilevel positive airway pressure, is a commonly used intervention in severely dyspneic or hypercarbic patients with AECOPD. Recently, 7.5 million admissions for AECOPD between 1998 and 2008 were reviewed documenting an increasing usage of NIPPV from 1% to 4.5% in all admissions for an AECOPD and a significant reduction in the number of patients who required mechanical ventilation [153]. Notably, a subset of COPD patients have negative outcomes associated with NIPPV use, and these were the patients who required mechanical ventilation after failing a trial of NIPPV [153]. Bilevel positive pressure ventilation is ideal for use in AECOPD as it improves arterial oxygenation and arterial hypercarbia at 6, 12, and 24–48 hours after intervention and is associated with a lower likelihood of intubation than those utilizing continuous positive airway pressure (CPAP) [154]. Due to the significant respiratory benefits to utilization of this intervention in AECOPD, it is imperative that we explore the cardiovascular impact of this intervention in a population at such high cardiovascular risk.

Bilevel noninvasive ventilation has been shown to be beneficial in heart failure [155]. NIPPV and continuous positive airway pressure (CPAP) have proven mortality benefits when applied to patients with cardiogenic pulmonary edema as shown in a recent meta-analysis (RR 0.73, 95% CI 0.55–0.97, and RR 0.63, 95% CI 0.44–0.89, resp.) [156]. In both AECOPD and acute heart failure, bilevel noninvasive ventilation increases partial pressure of oxygen in arterial blood, arterial pH within 90 minutes, associated with a reduction in blood pressure [155]. There is a higher frequency of myocardial infarction in those on bilevel who had cardiogenic edema as compared to AECOPD (21% versus 0%) [155]. This finding in itself is not surprising, as ischemia may have been the trigger for acute heart failure, but as to whether bilevel positive pressure ventilation is associated with myocardial infarctions remains to be seen. Mehta et al. studied 27 patients, 13 of whom received nasal CPAP (10 cm H_2O) and 14 of whom received nasal bilevel positive airway pressure (inspiratory pressure 15 cm H_2O and expiratory pressure 5 cm H_2O) [157]. In this cohort, more patients achieved an equivalent if not improved ventilator and hemodynamic response to bilevel positive pressure ventilation, as compared to CPAP, but had a higher frequency of chest pain (10 versus 4) and a higher likelihood of being diagnosed with a myocardial infarction (10 versus 4) [157]. Due to the small cohort size and the difference in symptoms at baseline prior to group assignment, further studies are needed to explore whether this association is valid in the acute setting.

The impact that bilevel ventilation has on hemodynamics has been studied in stable COPD. Sin et al. performed a double-blind, parallel randomized control trial in 23 patients with advanced COPD to determine if bilevel noninvasive ventilation improves cardiac functioning by evaluating heart rate variability, functional performance, and serum markers of cardiac dysfunction after three months of treatment. Notably, use of bilevel positive pressure ventilation resulted in increased heart rate variability, which is a good prognostic marker and a surrogate for improved cardiac functioning as outlined previously [158]. In addition, subjects with daily bilevel positive pressure ventilation had lower NTpro-BNP levels at three months of therapy and a longer 6MWT by 30 m (95% CI 2–57 m) [158]. This study raises important questions regarding the utility of NIPPV in this population, but further studies are needed to confirm and validate these findings with hard clinical outcomes [158]. Notably, similar outcomes were assessed by Held and colleagues when they used right heart catheterization to examine the hemodynamic consequences of NIPPV on patients with pulmonary hypertension secondary to hypoventilation [159]. Five of these 18 patients had COPD as the only cause of hypoventilation [159]. Right heart catheterization at time of initiating bilevel positive pressure ventilation and 3 months after utilizing it daily revealed a decrease in mean PAP, systolic PAP, diastolic PAP, and peripheral vascular resistance with a reduction in right atrial volume and improvement in left atrial volume and right ventricular function with no impact on cardiac index or pulmonary artery wedge pressure [159]. Clinical outcomes monitored revealed substantial improvement in 6MWT (+66 m), maximum work rate (+18 W), and a reduction in NT-proBNP (2487 ± 2143 pg/mL versus 377 ± 416 pg/mL) in comparison to baseline values [159]. Hemodynamic changes associated with low-intensity and high-intensity noninvasive positive pressure ventilation were recently analyzed in a hypercapnic COPD population [160]. A high intensity ventilator strategy averaged 27.6 ± 2.1 cm H_2O inspiratory positive airway pressure, 4 ± 0 cm H_2O expiratory positive airway pressure, and respiratory rate of 22 breaths per minute [160]. The high intensity strategy was associated with a reduction in cardiac output, as measured by finometry, which is a possible mechanism that could decrease coronary artery supply in the acute setting [160]. Further work is needed to determine the impact that varying bilevel ventilator protocols have on cardiac physiology and clinically relevant outcomes, so that we optimally manage this high risk population.

6. Impact of Cardiac Medications on the Respiratory System during AECOPD

6.1. β Blockers. The use of β blockers in patients with COPD has been a contentious issue since older generations of β blockers were shown to be intolerable by patients with obstructive airways disease, by precipitating bronchoconstriction [161], reducing FEV1, or lowering the methylcholine challenge threshold [162]. As a result, β blockers have been prescribed less to COPD patients, likely due to a concern that these side effects outweighed any cardiovascular benefit [11, 20, 21, 25]. There is increasing evidence, however, that COPD patients clinically benefit from the use of β blockers and may have adverse effects by not taking one. In the presence of comorbid heart disease, COPD patients tolerate heart rates >70 beats per minute poorly reporting more frequent angina, less satisfaction with medical treatment, and a lower quality of life [163].

COPD patients derive significantly less morbidity from respiratory disease when using β blockers. A review of 5977 COPD patients in the NHS Tayside Respiratory Disease Information System, Scotland, found that use of β blockers was protective for index hospitalization for respiratory disease [164]. For patients taking an inhaled corticosteroid, long acting β agonist, and tiotropium in combination with or without a β blocker, the hazard ratios were 0.32, 95% CI 0.22–0.44, and 0.70, 95% CI 0.61–0.80, respectively, for respiratory disease admission, and 0.31, 95% CI 0.22–0.43, and 0.68, 95% CI 0.61–0.75, respectively, for prescription of oral corticosteroids [164]. Rutten et al. demonstrated a benefit in prevention of readmission for AECOPD in the subgroup of their cohort without overt cardiovascular disease, as the use of β blockers was still protective (HR 0.68, 95% CI 0.46–1.02) [165]. Not all studies have been unanimous in supporting a decrease in respiratory disease admissions. Cochrane and colleagues found an increased annual risk in admission for AECOPD in patients taking β blockers that developed over the 6 years of follow-up (risk per annum of acute worsening of symptoms RR 1.30, 95% CI 1.11–1.53 and risk per annum of requiring treatment for an acute exacerbation RR 1.37, 95% CI 1.09–1.72) [166]. Prospective randomized control trials are needed to determine whether there is truly a reduction in hospitalization for respiratory disease while on β blocker therapy.

β blocker use is associated with a 22% reduction in all-cause mortality (HR 0.78, 95% CI 0.67–0.92) in COPD [164]. A similar association between β blockers and an improvement in all-cause mortality following myocardial infarction in the COPD population was found in the VALIANT trial (HR 0.74, 95% CI 0.68–0.80) [21]. A meta-analysis analyzing the mortality benefit of use of β blockers in the COPD population identified the most homogenous group as gaining significant benefit from the use of β blockers (RR 0.74, 95% CI 0.70–0.79) [167]. The magnitude of reduction is dose dependent, as demonstrated in a Dutch trial of patients undergoing vascular surgery, of whom a third had COPD, where a low dose of cardioselective β blocker regimen was associated with a reduced long-term mortality (median follow-up 5 years), and an intensified dose regimen was associated with a reduced 30-day and long-term mortality (low dose being <25% and intensified dose being ≥25% of the maximum recommended dose) [168].

Recent work has focused on determining if there is an optimal β blocker of choice in this population. A Cochrane review from 2005 suggested that cardioselective β blockers are well-tolerated in COPD patients [169]. A separate meta-analysis looked at studies before May, 2011, and determined that cardioselective β blockers only provoked a 30 mL decrease in FEV1 [170]. Lainscak and colleagues performed an open-label randomized control trial of carvedilol and bisoprolol and determined that bisoprolol is associated with an improvement in FEV1 (1561 ± 414 mL versus 1698 ± 519 mL) as compared to carvedilol (1704 ± 484 mL versus 1734 ± 548 mL) and fewer adverse effects (19% with bisoprolol, and 42% with carvedilol) [171]. Discontinuation of the study drug only occurred in two patients for respiratory symptoms [171]. Another study with an open-label, randomized, triple crossover trial between bisoprolol, metoprolol, and carvedilol showed that FEV1 was lowest in the carvedilol group and highest in the bisoprolol group (1.85 L, 95% CI 1.67–2.03 L versus 2.0 L, 95% CI 1.79–2.22 L) [172]. At this time, no β blocker has been consistently superior amongst the class 2 and class 3 drugs. Cardioselective β blockers are safe to use in COPD patients, initiated at low dose and titrated to effect [173].

6.2. Angiotensin-Converting Enzyme Inhibitors (ACEi) and Angiotensin-Receptor Blockers (ARBs). Several studies have documented a mortality benefit for COPD patients within the first 90 days following discharge from AECOPD who use ACEi and statins [174–176]. Decreased 30-day and 90-day mortality was noted in subjects admitted with AECOPD when taking ACEi (OR 0.58, 95% CI 0.48–0.70, and OR 0.55, 95% CI 0.45–0.66, resp.) [175]. Mancini and colleagues demonstrate a mortality benefit with the use of ARBs after hospitalization for AECOPD and for the combination of ACEi/ARBs and statins [176]. ACEi and ARBs are independently associated with a reduction in myocardial infarction, and both ACEi and ARBs reduced the combined endpoint of MI or death [176]. Further evidence is needed as to whether this mortality benefit is purely due to a decrease in cardiovascular mortality.

There has been an effort to determine whether ACE inhibitors may directly improve morbidity from COPD. The DD genotype of the angiotensin-converting enzyme (ACE) is associated with pulmonary hypertension and tissue oxygenation with exercise, raising questions as to whether it is associated with the phenotype of COPD [177]. Captopril administered to COPD patients resulted in improved mean PAP, peripheral vascular resistance, and lactate production in genotypes other than the DD genotype, as measured by right heart catheterization, suggesting captopril positively influenced exercise performance [178]. Recently, Zhang and colleagues looked at ACE gene polymorphisms and exercise performance in patients with COPD and found no significant differences in resting lung function and cardiopulmonary exercise testing parameters among the three ACE genotype control groups [179]. Di Marco et al., in 2010, performed a

double-blind, placebo-controlled, crossover study looking at 21 patients with moderate to severe COPD by GOLD criteria using enalapril 10 mg daily or placebo for four weeks. The authors showed a significant improvement in work rate at peak and anaerobic threshold and increased cardiac stroke volume. The only spirometric value that was significantly improved was DLCO adjusted for alveolar volume [180]. For clinical outcomes such as reduction in admission for AECOPD, ACEi and ARBs were only correlated with this when combined with statin use [176]. At present time, further studies are needed to define the role that ACEi and ARBs can perform to reduce the morbidity and mortality of respiratory and cardiovascular comorbidity in the COPD population.

6.3. Statins. Originally designed to lower cholesterol, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also called "statins," are recognized as anti-inflammatory agents [181] and have been demonstrated to decrease morbidity from COPD. Experimental observations suggest that these agents have a wide range of pleiotropic anti-inflammatory properties *in vitro* and *in vivo* with the inhibition of isoprenoid synthesis, which leads to the inhibition of small GTPases such as Rho, Rac, and Cdc42, making them potentially useful in COPD [182–185]. Lee et al. in 2008 performed a prospective, double-blind, randomized control trial on 125 stable COPD patients comparing placebo and pravastatin 40 mg daily and demonstrated a significant improvement in lipid levels and hsCRP. Exercise capacity was significantly improved in those taking pravastatin, from 599 ± 323 s to 922 ± 328 s, as compared to stable exercise times in the placebo group (608 ± 273 s to 609 ± 180 s) with no improvement in lung function parameters [186]. These findings suggest that curbing lung and systemic inflammation with the use of a statin may improve quality of life, exercise capacity, and chronic inflammation in stable COPD [186]. Bartziokas and colleagues also looked at morbidity from COPD and demonstrate an association between statin therapy and an improvement in health-related quality of life and fewer AECOPD (2.1 ± 2.7 versus 2.8 ± 3.2 AECOPD/patient, resp.) [187]. This is supported by Mancini and colleagues work that reports a decreased risk of hospitalization for AECOPD when statins are combined with either an ACEi or ARB [176]. A prospective randomized control trial is currently underway with the aim to support these findings.

Statins are associated with improved mortality from COPD. A systematic review performed by Dobler and colleagues supports the mortality benefit of statins in COPD, but the data was predominantly based on observational and retrospective studies, with only the one randomized control trial by Lee et al. [186, 188]. Since this review, Bartziokas et al. have published another prospective study that showed no difference in mortality at 30-days and one year [187]. Two studies retrospectively looked at mortality and statin use, data not incorporated into the review, and found lower mortality from COPD in those on statin therapy [175, 189]. At this time, there is some evidence to support a mortality benefit in COPD with statin use, but further prospective studies are needed.

7. Potential Mechanisms of How AECOPD Could Trigger Cardiovascular Disease/Events

There are strong mechanistic links between acute and chronic lung injury, inflammation, peripheral vascular disease, acute vascular events [97–99], and endothelial dysfunction [51]. COPD is characterized by chronic inflammation in lung tissue and the extent of the inflammatory reaction correlates with the severity of the disease [190]. Chronic inflammation in the lung parenchyma is associated with a downstream systemic inflammatory response [191] characterized by activation of the acute phase response, release of inflammatory mediators in the circulation, stimulation of the bone marrow to release leukocytes and platelets, and priming and activation of circulating leukocytes and vascular endothelium. While this systemic inflammatory response impacts many organ systems, the vascular system is particularly affected. Figure 2 shows how lung inflammation triggers an inflammatory cascade, causing potential downstream effects of this systemic inflammatory response on blood vessels while enhancing the inflammatory response in the lung, thereby initiating a vicious cycle.

Recent experimental evidence has shown that inflammatory mediators produced in the lung (following exposure to either lipopolysaccharide or particulate matter) directly translocate to the blood stream supporting the concept that inflammation in the lung directly contribute to the downstream systemic response [192, 193]. The leakage of inflammatory mediators, such as reactive oxygen species, cytokines, and chemokines generated in the lung airspaces and lung tissues, directly into the peripheral blood, could activate all of the different pathways characteristic of a systemic inflammatory response. Importantly, this includes peripheral blood leukocytes and blood vessel activation resulting in progression of atherosclerosis with downstream cardiovascular events, the predominant reason for COPD morbidity and mortality. Several studies have shown that this systemic inflammatory response in COPD is augmented during an acute exacerbation, leaving the vasculature and atherosclerotic plaques even more vulnerable for activation, rupture, and thrombus formation, resulting in acute cardiac events [191]. Lastly, recent experimental evidence showed that lung inflammation [194] and vascular activation and atherosclerosis induced by airborne particles can be attenuated by statins [195, 196], supporting clinical data that statins improve COPD symptoms and reduce AECOPD. Figure 3 shows potential mechanisms of how acute exacerbation of COPD could trigger systemic inflammation that activate the vasculature and specifically atherosclerotic plaques, inducing endothelial dysfunction, plaque instability, and a prothrombotic state that together could trigger vascular events.

8. Conclusion

COPD is a complex lung and systemic disease that is associated with a variety of cardiovascular diseases including coronary artery disease, peripheral vascular and cerebrovascular disease. COPD patients have frequent right and left

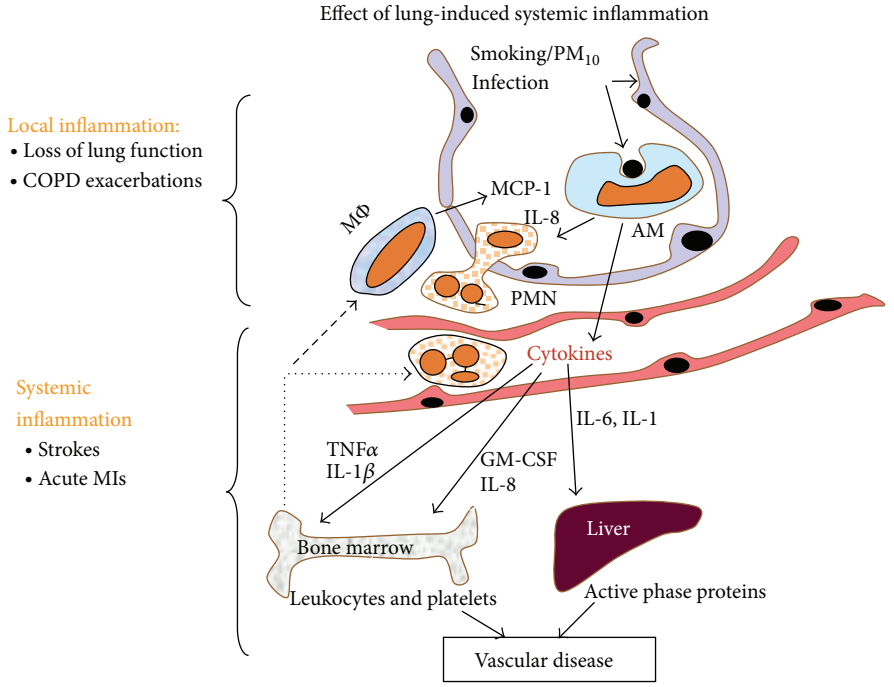

FIGURE 2: Acute inflammatory events in the lungs provoke a cascade of systemic inflammation that starts in the lung, with hematologic spread to other organs, activating the systemic inflammatory response, and thereby promoting the development of atherosclerosis and vascular events.

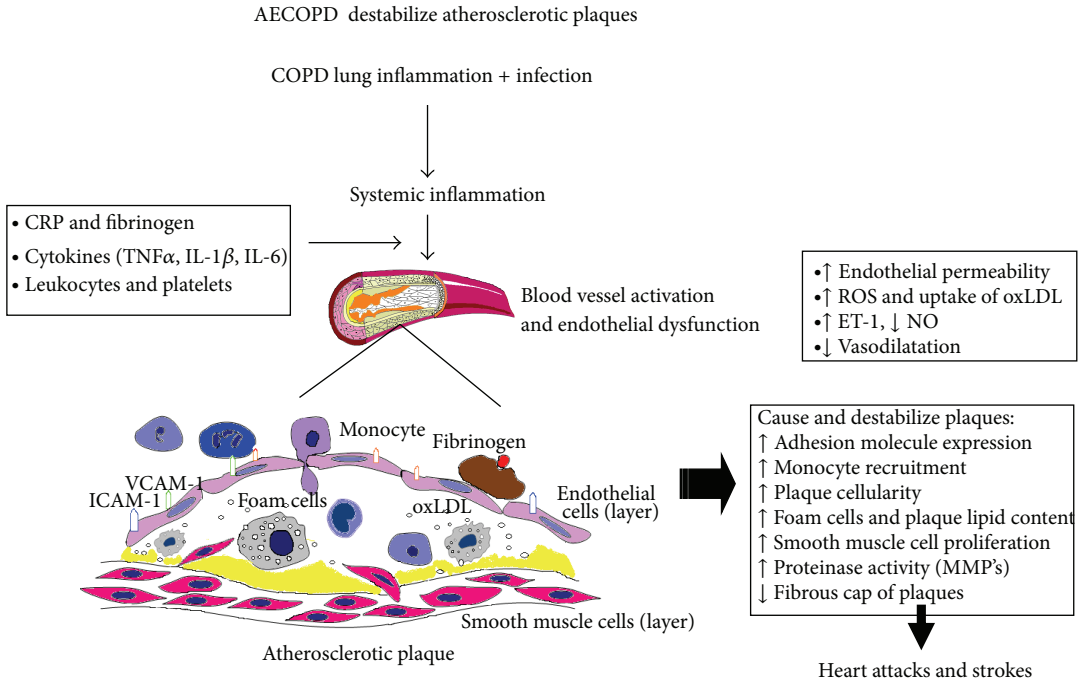

FIGURE 3: AECOPD is associated with an acute lung injury initiating the local and systemic inflammatory pathways that cause endothelial injury and vascular dysfunction, a prothrombotic environment, and instability in vascular plaques that may predispose to coronary and cerebrovascular events.

ventricular dysfunction and an increase in sympathetic activation with high morbidity from arrhythmias. Acute exacerbations of COPD may trigger cardiac events but are also often precipitated by cardiac events. At the present time, many of these events are unrecognized, despite improved tools for diagnosis and assessment. The treatments we utilize for AECOPD have not been rigorously examined as to the effects they have on a vulnerable cardiovascular system and further studies are needed to explore this area. Finally, the association between lung inflammation (including that in COPD and AECOPD) and cardiac events may be due to consequences of the systemic inflammatory response and downstream microvascular changes in plaque stability, hypercoagulability, and endothelial cell dysfunction.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Exhaled Nitric Oxide as a Biomarker in COPD and Related Comorbidities

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Chronic Obstructive Pulmonary Disease (COPD) is defined as a disease characterized by persistent, progressive airflow limitation. Recent studies have underlined that COPD is correlated to many systemic manifestations, probably due to an underlying pattern of systemic inflammation. In COPD fractional exhaled Nitric Oxide (FeNO) levels are related to smoking habits and disease severity, showing a positive relationship with respiratory functional parameters. Moreover FeNO is increased in patients with COPD exacerbation, compared with stable ones. In alpha-1 antitrypsin deficiency, a possible cause of COPD, FeNO levels may be monitored to early detect a disease progression. FeNO measurements may be useful in clinical setting to identify the level of airway inflammation, *per se* and in relation to comorbidities, such as pulmonary arterial hypertension and cardiovascular diseases, either in basal conditions or during treatment. Finally, some systemic inflammatory diseases, such as psoriasis, have been associated with higher FeNO levels and potentially with an increased risk of developing COPD. In these systemic inflammatory diseases, FeNO monitoring may be a useful biomarker for early diagnosis of COPD development.

1. Introduction

As is well known, chronic obstructive pulmonary disease (COPD) is simply considered a lung disease characterised by the presence of fixed and progressive airflow limitation derived from airway inflammation/remodelling associated with parenchymal destruction so-called pulmonary emphysema. However, in most of COPD patients the disease coexists with several other systemic manifestations which can make health-related quality of life worse and increase mortality [1]. Thus, COPD could no longer be defined as a disease restricted to the lung but might be considered part of a complex chronic systemic disease previously defined as "chronic systemic inflammatory syndrome" [2].

The best-recognised comorbidities in COPD include lung cancer, cardiovascular diseases, malnutrition involving primarily the loss and dysfunction of skeletal muscles, osteoporosis, anaemia, diabetes, increased gastroesophageal reflux, metabolic syndrome, obstructive sleep apnoea, depression, and anxiety. Comorbidities can be classified in conditions that share pathogenetic mechanisms with COPD (e.g., smoking-related diseases such as ischemic heart disease and lung cancer), conditions that complicate COPD (such as osteoporosis and sarcopenia), and conditions that are simply associated with COPD for epidemiologic reasons (like glaucoma and obstructive sleep apnoea) [3].

In COPD patients, the high frequency of concurrent diseases may be largely explained by the old age of the majority of patients and by cigarette smoke exposure, the major risk factor for COPD, many other chronic diseases, and certain cancers. Smoking triggers a local inflammatory response throughout the whole tracheobronchial tree, and pathologic changes, a characteristic of COPD, are found in the proximal large airways, peripheral small airways, lung parenchyma, and pulmonary vasculature [4]. Apart from

these local effects, smoking may significantly contribute to or cause systemic inflammation including the stimulation of the hematopoietic system with polymorph nuclear leukocytes release, the generation of systemic oxidative stress, and the endothelial dysfunction of peripheral vessels [4]. These systemic effects due to smoking may account for the frequent concurrent presence of other chronic illnesses such as cardiovascular diseases and metabolic disorders in COPD patients [4].

Furthermore, one-half of all people aging more than 65 years have at least three chronic medical conditions, and aging itself is associated with a chronic low-grade inflammatory status [5]. Thus, the theory that systemic inflammation is the common driver of chronic diseases would explain the high prevalence of chronic diseases with increasing age, so-called "inflammaging" [5]. Concerning the observed associations between COPD and its comorbidities, there are two possible explanations: the systemic "spill-over" of the inflammatory and reparatory events occurring in COPD lungs with a central role of the disease in the process and the "systemic" inflammatory state due to multiple organ compromise which includes also COPD pulmonary manifestations [2, 6]. Patients with COPD show systemic inflammation, especially related to disease severity and exacerbations, that can be measured as increment of circulating cytokines (IL-6, TNF-α), chemokines (IL-8), and acute phase proteins (C-reactive protein (CRP) and surfactant protein D) or abnormalities in circulating cells [7]. One of the most important pathogenetic mechanisms of COPD is oxidative stress associated with inflammatory cellular infiltration (macrophages, neutrophils, and lymphocytes CD8) that in conjunction with an altered release of endogenous nitric oxide (NO) may provoke the formation of "nitrative stress" [6].

2. Nitric Oxide and COPD

Endogenous nitric oxide (NO) is a gaseous signaling molecule produced by residential and inflammatory cells in both large and peripheral airways/alveoli. NO plays an important role in regulating airway and vascular function and is generated by three isoforms of NO synthases (neuronal NOS (nNOS, NOS1), endothelial NOS (eNOS, NOS3), and inducible NOS (iNOS, NOS2)) with different expression and pathophysiologic roles in the airways. In particular, iNOS is not constitutively expressed but is induced by several stimuli including endogenous mediators (chemokines and cytokines) and exogenous factors (bacterial toxins, viral infection, allergens, environmental pollutants, etc.) [8]. NO is generated by the conversion of L-arginine to L-citrulline and during inflammation, due to iNOS induction, large amounts of NO are produced which may exert proinflammatory effects [9].

Corticosteroids directly suppress iNOS in rodent cells but do not directly inhibit iNOS expression in human airway epithelial cells [10]. The increase in NO in exhaled breath in asthma is presumed to originate from increased iNOS expression in the respiratory tract, although cNOS isoforms (nNOS and eNOS) may also contribute. Increased iNOS expression is found in airway epithelial cells of patients with asthma and is reduced by inhaled corticosteroids [11]. Increased iNOS expression is found in central and small airways and in peripheral lung of COPD patients [12, 13]; however, there was no effect of high-dose ICS on exhaled nitric oxide at both airway and alveolar compartments [14] suggesting that probably in COPD iNOS is not the main source of NO. In other studies, selective inhibitors of iNOS reduce FeNO in asthmatic patients and also in normal subjects [15–17] but have less effect on COPD patients. In a recent study, Brindicci et al. showed that nNOS expression and activity are increased in COPD according to disease severity suggesting that in these patients the increased peripheral NO may be derived from nNOS [12].

Oxidative stress generates superoxide anions and in combination with NO may result in the formation of the highly reactive species peroxynitrite, which is increased in exhaled breath condensate and airway mucosa of COPD patients [13–18] and removes NO from the gaseous phase so that its concentration in the airways is reduced when there is a high level of oxidative stress, as in COPD patients [10].

3. FeNO and COPD

FeNO measurements have been considered a surrogate for eosinophilic airway inflammation, especially in asthma. In most mild asthmatics, high FeNO at 50 mL s^{-1} (>45 ppb) has been regarded as a marker for steroid responsiveness [19, 20] including improvement in spirometry and airway hyperresponsiveness [21]. The ATS clinical practice guideline for exhaled nitric oxide in asthma concluded that add-on FeNO monitoring provides potential easier detection of eosinophilic airway inflammation and likelihood of corticosteroid responsiveness [22].

FeNO levels in COPD are conflictual [8], but it seems that smoking habits and disease severity are the most important factors influencing exhaled NO levels in these patients [23]. Current smokers [24] and severe COPD (particularly in combination with *cor pulmonale*) [25] show lower levels of exhaled NO than ex-smokers and mild/moderate COPD (Table 1). Increased exhaled NO levels have been reported in hospitalized patients during an exacerbation of COPD (Table 1) [26]. Interestingly, exhaled NO levels returned to control values only months after discharge of those steroid-treated patients, suggesting different inflammatory mechanisms in COPD compared with the highly steroid-sensitive asthmatics [26].

In COPD patients, the magnitude of the NO signal is considerably less than in asthma and, most importantly, the major causative agent, cigarette smoke, dramatically masks any tendency towards a disease related rise in exhaled NO levels. This may have consequences not only for monitoring patients with COPD, but also for the natural history and prognosis of the disease. The positive relationship between exhaled NO levels and FEV_1 is in keeping with the hypothesis that endogenous NO represents an important protective mechanism. This could be particularly relevant in patients

with COPD who may require local NO release for antimicrobial host defence or preservation of ventilation/perfusion matching within the lung [23].

Several studies [27–31] showed that elevated FeNO in COPD may also be a variable signal for increased spirometric response to ICS. Moreover FeNO is increased in patient with COPD exacerbation, compared to the levels observed in patients with stable COPD [32]. In a recent study, Soter at al. demonstrated that FeNO is a good biomarker of eosinophilic inflammation in COPD patients with exacerbation [33].

In conclusion, in COPD the role of FeNO monitoring to therapeutic intervention is still unclear with respect to clinical relevance in particular because of the absence of randomized, double blind, control studies.

3.1. FeNO in Alpha-1 Antitrypsin (AAT) Deficiency. Alpha-1 antitrypsin (AAT) deficiency is a genetic disorder due to homozygosity or heterozygosity for the protease inhibitor (Pi) Z allele, and these two genetic phenotypes are, respectively, characterized by a severe reduction (PiZZ) and a lower reduction (PiMZ) of plasma levels of AAT than in normal subjects. The homozygotic form of the disease is considered to be an important risk factor for developing COPD [34].

Severe AAT deficiency (PiZZ) is characterized by lower FeNO level (Table 1) compared to healthy nonsmokers and COPD patients, which is correlated to the pulmonary function impairment which is a characteristic of this kind of patients [35, 36]. While, PiMZ subjects show increased FeNO levels (Table 1) compared to COPD patients and healthy controls [37] and FeNO levels are related to the reduced concentration of AAT in plasma [38]. In these patients FeNO measurement may be very important to monitor a possible progression of airways inflammation to COPD.

3.2. FeNO in Pulmonary Arterial Hypertension. Pulmonary arterial hypertension (PAH) is characterized by an elevation of the pulmonary arterial pressure and an increased pulmonary vascular resistance, leading to decline in cardiopulmonary function and premature death [39].

PAH is commonly caused by an underlying pulmonary or systemic disease, whilst idiopathic PAH (IPAH) is referred to PAH when diagnosed in the absence of an identifiable cause or disease.

IPAH is the most studied form of PAH, characterized by endothelial and smooth muscle cell proliferation, medial hypertrophy, and thrombosis in situ [40]. The elevated vascular resistance probably is due to an imbalance between local vasodilators and vasoconstrictors, associated with cellular proliferation and vascular remodeling. NO is one of the important pathophysiologic mediators of pulmonary vascular resistance [41, 42]. NO produced in the upper and lower airways by NOS2 is able to affect the pulmonary vascular tone together with the NO produced by NOS3 in the vascular endothelium [43]. Once produced NO is highly diffusible and activates soluble guanylate/cyclase in pulmonary vascular smooth muscle cells to produce guanosine 39-59-cyclic monophosphate, inducing vascular smooth muscle relaxation and then vasodilation [44]. Patients with PAH show low FeNO values (Table 1) [44, 45]. Patients with PAH also show lower concentrations of NO than normal in the BAL fluid, inversely related to the degree of pulmonary hypertension [46]. Therefore, replacement of NO seems to work well in treating PAH [42]. Phosphodiesterase type 5 inhibitors, preventing the collapse of the NO effector molecule 39,59-cyclic guanosine monophosphate, prolong NO mediated vasodilatation [47, 48]. Prostacyclins and endothelin receptor antagonists also are able to reduce the NO deficiency state in patients with PAH [49]. PAH patients who respond to therapy show higher FeNO levels compared with those who do not change their FeNO levels in response to therapy [47]. The presence of reduced FeNO levels in patients with PAH and the increase after treatment suggest that serial monitoring of FeNO in these patients may be useful.

Table 1: Trend of FeNO levels in COPD and related comorbidities.

Disease/condition	FeNO levels
Smoking habit	↓
Severe COPD	↓
Stable COPD	=
Exacerbation of COPD	↑
AAT deficiency PiZZ	↓
AAT deficiency PiMZ	↑
PAH	↓
Systemic sclerosis	↑
Decompensated HF	↑
After exercise in stable HF	↑
Atherosclerosis	↓
Psoriasis	↑

↑: >20 ppb; =: 10–20 ppb; ↓: <10 ppb.

3.3. FeNO in Systemic Sclerosis (SSC) with Pulmonary Arterial Hypertension. Systemic sclerosis (SSc) is a connective tissue disorder of unknown etiology, characterized by a multisystemic involvement, and that is often complicated by pulmonary involvement [50], especially PAH with or without interstitial lung disease (ILD) [51]. The mechanisms underlying pulmonary involvement of SSc are unknown, but endothelial changes, both morphological and functional, may be pathogenetically important [52]. Moreover, in these patients inflammation probably promotes the development of pulmonary fibrosis [53]. NO can be implicated in the pathogenesis of both PAH and ILD. In fact, NO plays an important role in maintaining the low resistance of the pulmonary circulation [54], so if basal production of NO mediated by eNOS is low, it could promote vasoconstriction and vascular wall thickening, bringing to PAH [55]. Moreover iNOS is stimulated by inflammatory cytokines [56]; the presence of an inflammatory pattern, such as in SSc, is linked to an increase of iNOS activation; and NO proinflammatory and cytotoxic effects could promote ILD [57]. A recent study investigated the value of FeNO in a group of 50 SSc patients, with the diagnosis based on American Rheumatism Association criteria [58], compared with 40 healthy subjects [45]. The FeNO levels were higher in SSc patients than in

control subjects (Table 1), and lower in patient with ILD and/or PAH than in those without PAH, moreover there was an inverse correlation between the severity of pulmonary artery pressure and FeNO levels.

3.4. FeNO in Cardiovascular Diseases

3.4.1. Heart Failure. It has been hypothesized that NO provides an important role in heart failure (HF) in either the pathogenesis or disease progression, although the precise role played by NO is complex [59]. In particular, NO release from the vascular endothelium in patients with heart failure may help to maintain tissue perfusion by reducing the vasoconstriction induced by various neurohumoral factors; moreover NO is able to modulate cardiac contractility [59].

In patients with chronic HF, deregulated systemic NO production due to endogenous inhibitors of NO synthases such as asymmetric dimethylarginine (ADMA) has been related to both systolic and diastolic dysfunction in addition to poor long-term adverse outcomes [60].

Several studies in symptomatic HF patients at rest have reported variable FeNO levels compared with normal control subjects, and the results in literature are conflicting. Higher levels of FeNO were observed in decompensated HF resting (Table 1) compared with compensated and resting FeNO decreased after lowering of left ventricular filling pressures [61]. Higher FeNO levels have been observed after exercise in stable chronic HF patients (Table 1) compared with control subjects [62, 63].

Patients who fail to raise FeNO during exercise have been related to a higher long-term mortality rate [64]. Accordingly a potential role of NO production as a compensatory response to the increased pressure in the pulmonary venous circulation has been hypothesized.

As mentioned above, several FeNO studies have shown conflicting results regarding FeNO levels at rest and exercise. These contradictory reports can probably be explained by the difference in the populations studied and the use of different techniques for FeNO analysis; moreover the type of cardiomyopathy is rarely reported, and it can be hypothesized that ischemic heart disease could be much different in terms of NO production than idiopathic dilatative heart disease. However, more recent reports seem to indicate that FeNO levels increased after exercise in chronic compensated HF patients [63]. This seems to be related to the degree of pulmonary congestion and hypertension; probable increased activity of pulmonary endothelial NO synthases appears in response to improved flow, in the pulmonary vasculature taking place during exercise, as a compensatory mechanism. Consequently, higher FeNO may represent a compensatory mechanism in response to high-flow conditions [65].

3.4.2. FeNO in Atherosclerosis and Cardiovascular Risk Factors. Endothelial NO seems to play a key role in the atherogenic process platelet adhesion and aggregation, expression of adhesion molecule and chemokine production, and inflammatory cell infiltration together with smooth muscle cell migration and proliferation [66, 67].

This central balancing function of NO is hindered during the atherosclerotic process, in which endothelial damage causes the decline in bioactivity of endothelial nitric oxide synthase and consequently impaired release of NO. Furthermore, ischemic heart disease (IHD) is characterized by a low-grade systemic inflammation and associated with increased oxidative stress; these factors enhance the inactivation of NO at endothelial level in the arterial wall and could lead to diminished systemic bioavailability of NO [68]. Therefore, it is possible to hypothesize that, because NO production is reduced and its inactivation increased in dysfunctional atherosclerotic endothelium, atherosclerosis is inversely associated with NO and FeNO (Table 1). Consequently a recent paper [69] observed that two common atherosclerosis risk factors, triglycerides serum levels and hemoglobin/A1c (a marker of hyperglycaemic metabolism), were inversely associated with FeNO levels in patients with IHD. This can be explained by the reduced eNOS and the enhanced NO degradation due to endothelial damage, characteristics of atherosclerosis [69].

3.5. FeNO in Psoriasis. Psoriasis vulgaris is a multisystem common dermatologic disease characterized by chronic inflammatory pathogenesis [70]. The prevalence in adults ranged from 0,91% in USA to 8,5% in Norway, while Italy with the 2% was in the middle [71]. In literature, psoriasis is also related to several comorbidities; these patients were more likely to have diabetes, dyslipidemia, hypertension, a history of myocardial infarction, inflammatory arthritis, obesity, and metabolic syndrome than control groups [72]. Two recent studies evaluated the correlation between COPD and psoriasis, concluding that there is a significant correlation between these two diseases. A large, population-based case-control Israeli study by Dreiher et al. [73], including 12.502 psoriasis cases and 24.287 controls, demonstrated that the prevalence of COPD was significantly higher in patients with psoriasis (5,7% versus 3,6%, $P < 0{,}001$ OR = 1,63). Another study, conducted in Taiwan, on 10.480 patients with psoriasis, underlined that psoriasis patients are at a greater risk of developing COPD, with significantly lower COPD-free survival rates than the comparison cohort [74].

Recent developments described psoriasis pathophysiology as mainly directed by Th1 and Th17 cells which provoke a skin barrier dysfunction [75]. In literature, NO production in skin cells was demonstrated physiologically for several cytotypes such as keratinocytes, fibroblasts, and melanocytes [76]. In psoriasic lesions, an overexpression of iNOS is associated with a compensatory increase of arginase 1 enzyme which may reduce the NO availability [77]. On the other hand, direct measurements of NO production in psoriasic lesions did not find any evidence of a competitive inhibition [78]. However, in psoriasis patient's serum Gabr et al. discovered an increase of NO levels that correlated with the PASI (Psoriasis Area Severity Index) [79]. So this study was performed in order to detect if FeNO measurement is useful in revealing earlier the pulmonary involvement in this disease. The preliminary analysis about FeNO levels in psoriasic patients pointed out the strong correlations between

the active disease and an increased level of FeNO (Table 1), suggesting a lung involvement.

4. Conclusions

New evidence concerning FeNO in relation to COPD and the best-recognized comorbidities collectively highlights the following potential roles of this biomarker in monitoring (1) the stability of COPD; (2) the response to therapy in heart failure and in PAH patients; (3) the possible progression to COPD of other diseases like alpha-1 antitrypsin deficiency and psoriasis. These latter aspects may be useful to integrate the clinical evaluation of patients with COPD and comorbidities.

Since FeNO levels are strongly affected by cigarette smoking and many COPD patients are current smokers, the usefulness of FeNO measurement can be limited. In COPD patients, the role of add-on FeNO monitoring to therapeutic intervention is less clear with respect to clinical benefits, especially in the absence of conclusive double-blind, randomized, control studies. Therefore, routine monitoring of FeNO in COPD is less established than in asthma as noted in the recent ATS Clinical Guidelines.

Abbreviations

NO: Nitric oxide
NOS: Nitric oxide synthase
nNOS: Neuronal NOS
iNOS: Inducible NOS
eNOS: Endothelial NOS
FeNO: Exhaled nitric oxide fraction
ATS: American Thoracic Society
CS: Corticosteroids
COPD: Chronic obstructive pulmonary disease
CF: Cystic fibrosis
AAT: Alpha-1 antitrypsin
SSc: Systemic sclerosis
PAH: Pulmonary arterial hypertension
ILD: Interstitial lung disease
HF: Heart failure
IHD: Ischemic heart disease
PS: Psoriasis
PASI: Psoriasis area severity index
FEV_1: Forced expiratory volume in the 1st second.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Pulmonary Rehabilitation: The Reference Therapy for Undernourished Patients with Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) combines the deleterious effects of chronic hypoxia, chronic inflammation, insulin-resistance, increased energy expenditure, muscle wasting, and exercise deconditioning. As for other chronic disorders, loss of fat-free mass decreased survival. The preservation of muscle mass and function, through the protection of the mitochondrial oxidative metabolism, is an important challenge in the management of COPD patients. As the prevalence of the disease is increasing and the medical advances make COPD patients live longer, the prevalence of COPD-associated nutritional disorders is expected to increase in future decades. Androgenopenia is observed in 40% of COPD patients. Due to the stimulating effects of androgens on muscle anabolism, androgenopenia favors loss of muscle mass. Studies have shown that androgen substitution could improve muscle mass in COPD patients, but alone, was insufficient to improve lung function. Two multicentric randomized clinical trials have shown that the association of androgen therapy with physical exercise and oral nutritional supplements containing omega-3 polyinsaturated fatty acids, during at least three months, is associated with an improved clinical outcome and survival. These approaches are optimized in the field of pulmonary rehabilitation which is the reference therapy of COPD-associated undernutrition.

1. Introduction

The natural history of COPD is poorly understood. It is commonly assumed that chronic bronchial inflammation and small airway narrowing secondary to tobacco smoke take place for many years before any obstructive ventilatory defect could be detected [1]. The main and most serious symptom reported by COPD is dyspnea as a consequence of the mechanical constraints of the obstructive ventilatory defect, which increase during exercise leading to physical inactivity and handicap [2–4]. The combined effects of systemic inflammation and tissue hypoxia partially explain several comorbidities often associated with COPD at a higher frequency than in non-COPD smokers: cardiovascular diseases, osteoporosis, diabetes, and metabolic syndrome [5]. COPD shares similar characteristics with other chronic organ insufficiencies, chronic infections, and cancer: anorexia, inflammation, insulin-resistance, hypogonadism, and anemia [6]. Moreover, increased resting energy expenditure has been reported in COPD patients [7]. These conditions are responsible for fat loss and muscle wasting [8], leading to weight loss [9], muscle weakness, and fatigue (Figure 1). COPD-related weight loss is affecting mostly muscle mass [10, 11] and may be found in almost 40–50% of patients at severe stages of the disease [8]. As muscle wasting is affecting skeletal as well as respiratory muscles, COPD-associated chronic undernutrition and muscle wasting lead to physical inactivity [4, 12], exercise deconditioning [13], and impairment of respiratory function [14], resulting in impaired

quality of life [4, 12], increase in bronchial infections, general practitioner consultations [15], and reduced survival [4, 12, 16–26]. This, in turn, increases COPD-related costs (Figure 1). As the prevalence of COPD is expected to increase in future decades [27], the medicoeconomic burden of COPD-associated undernutrition will increase. The impact of undernutrition and fat-free mass loss on clinical outcome and survival is independent of respiratory parameters [16–19]. Several studies have shown that fat-free mass loss measured by bioimpedance analysis (BIA) or midthigh CT scan is a stronger predictor of mortality than body mass index [16, 20, 21, 24]. Therapies aiming at specifically managing COPD-associated nutritional disorders and improving muscle mass are mandatory to reduce the negative impact of the disease on physical activity, quality of life, and clinical outcome.

2. Physiopathology of Muscle Wasting in COPD

As renal or chronic heart failure, the musculoskeletal system is profoundly altered in COPD patients. Muscle is characterized by decreased capillary density and a shift from the aerobic to the anaerobic glycolytic pathways: decreased diameter and smaller fraction of type I muscular fibers [29, 30] together with an increase in type II nonoxidative muscular fibers [31, 32] and decreased expression of aerobic glycolysis enzymes [33, 34]. These alterations are mainly related to tissue hypoxia and inflammation. Both provoke oxidative stress and stimulate the activity of the ubiquitin-proteasome pathways responsible for protein breakdown [35–38], and, in turn, muscle wasting, physical inactivity, and sedentarity. Increased protein catabolism is observed during COPD acute exacerbations [39] and during the whole course of COPD due to systemic inflammatory reaction. Protein catabolism is driven by the secretion of proinflammatory cytokines: tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and interferon-γ (INF-γ). The conservation of an oxidative muscle phenotype could protect myofibers from pathological insults, as shown in mice with chronic heart failure [29, 40]. Therefore the preservation of muscle mass and function, through the protection of the mitochondrial oxidative metabolism, is an important challenge in the management of COPD patients. Recent evidence suggests that pulmonary rehabilitation including physical exercise, oral nutritional supplements, and androgen therapy could improve muscle mass and function and the outcome of COPD patients [41].

3. Evidence for Androgen Therapy in COPD

In COPD patients, plasma concentrations of anabolic hormones, such as growth hormone (GH) and testosterone, are frequently decreased [38, 42–45]. A prevalence of low plasma testosterone, that is, hypogonadism, of 38% was reported considering a cut-off of free plasma testosterone of 50 pg/mL in a group of men with severe COPD and a mean age of 70 years [43]. Others have reported a prevalence of 22% [44] and 69% [45], which is higher than age-related hypogonadism. Indeed, total testosterone levels less than 320 ng/dL were found in 17% of patients aged between 40 and 79 years [46], and free testosterone levels less than 6.5 ng/dL were found in 32% of patients aged between 73 and 78 years [47]. In contrast to age-related hypogonadism, lower testosterone plasma concentrations in COPD are mostly associated with a decrease in luteinizing hormone (LH) and follicle stimulating hormone (FSH) hypophysis secretion [43, 48]. COPD severity and hypoxia are related to lower plasma concentrations of LH and FSH [49]. In COPD patients, one study showed an improvement in testosterone plasma concentrations after one month of oxygen therapy [50]. Chronic systemic corticosteroid treatment may alter pituitary stimulation by gonadotropin releasing hormone (GnRh) and thus decrease LH and testosterone synthesis and secretion [45]. Moreover, chronic inflammation, through the effects of TNF-α on the hypothalamus-hypophysis-gonadal axis, may participate in reducing testosterone plasma concentrations in COPD [50]. In the general population, low plasma concentrations of testosterone have been related to a decreased muscular mass [51–53] and force [51, 54, 55]. Quadriceps muscle weakness is related to low circulating levels of testosterone in men with COPD [56]. Testosterone increases muscle protein synthesis [57, 58], reduces adipocyte, and increases muscle cells proliferation [57]. Testosterone also inhibits leptin and stimulates ghrelin production which in its turn stimulates GH secretion [11, 57] and appetite. In addition to hypogonadism, reduced protein synthesis and muscle anabolism observed in COPD and in other chronic diseases could also be the consequence of the decrease in IGF-1 plasma concentrations, itself related to reduced GH secretion [11, 42, 59, 60]. In patients with low plasma testosterone, androgen therapy was associated with a decrease in subcutaneous fat and an increase in muscle mass [53, 57, 58, 61, 62], as well as an improvement of muscle force and functional capacities [53, 55, 57, 58, 61–66]. The rationale for androgen therapy in COPD patients is based on its ability to improve muscle mass and function [67], as well as nutritional status and clinical outcome.

4. Androgen Therapy: Clinical Results in COPD Patients

In COPD patients, androgen therapy has been tested alone or together with physical exercise or nutritional supplementation.

4.1. Androgen Therapy Alone. Two studies have evaluated the effect of testosterone alone, that is, not integrated in a rehabilitation program, in COPD patients [68, 69] (Table 1). Oral testosterone analogue oxandrolone was given in a group of 128 outpatients (57 men and 71 women) with GOLD II-III COPD (forced expiratory volume (FEV) < 50%). A significant increase in fat-free mass was observed after four months of treatment [68]. However the 6-minute walking distance and spirometric data remained unchanged [68]. No differences were observed between men and women concerning treatment efficiency. Six women developed androgenic side effects (alopecia, cliteromegaly, hirsutism, and deepening of the voice) causing treatment discontinuation [68].

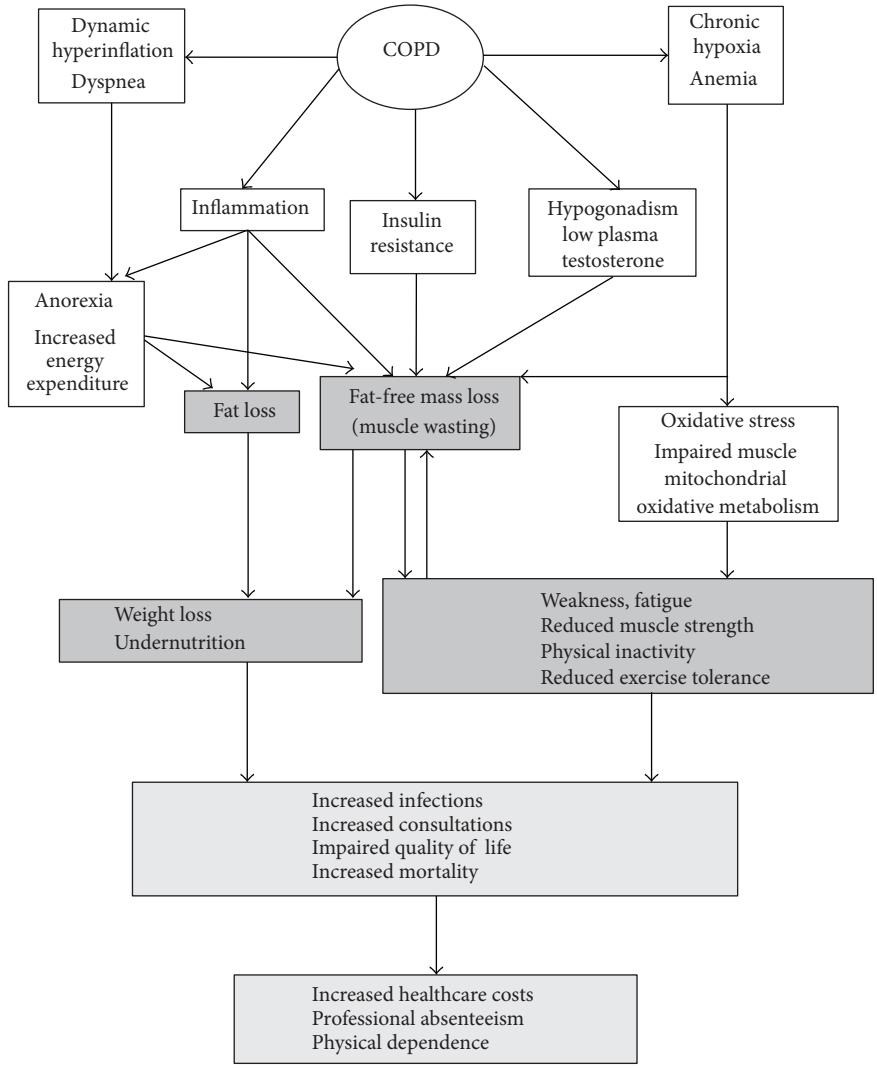

Figure 1: Mechanisms and clinical consequences of undernutrition in COPD patients (from [6]). The white boxes represent the metabolic mechanisms or features, and the grey boxes represent their nutritional clinical consequences. Dyspnoea is mainly attributable to dynamic hyperinflation [2]. Dynamic hyperinflation is the consequence of the loss of lung elastic recoil and increase in airway resistance, thus leading to air trapping, ventilation inefficiency, and increase in work of breathing through increase in inspiratory muscle load [28]. Dyspnoea and inflammation increase in energy expenditure and induce decreased food intake and anorexia. Other features of COPD are insulin resistance, low plasma testosterone, and chronic hypoxia associated with anemia. Altogether these conditions induce undernutrition, characterized by muscle wasting and fat loss. Chronic hypoxia and anemia are responsible for oxidative stress and impaired muscle mitochondrial oxidative metabolism. These results in weakness, fatigue, reduced muscle strength, physical inactivity, and reduced exercise tolerance, which are all favored by muscle wasting. The consequences of undernutrition are increased risk of infections, number of medical consultations, impaired quality of life, and worse survival. This worse clinical outcome has economic consequences: increases in healthcare costs, professional absenteeism, and physical dependence.

Nevertheless, testosterone supplementation was rather well tolerated in men as well as in women. In another group of 29 male outpatients with moderate to severe COPD (FEV < 60%), intramuscular testosterone was administered for 26 weeks with positive effects on body composition: fat-free mass increased by 1.1 kg, and fat mass decreased by 1.5% as compared to baseline. No effect was observed on lung function-associated parameters, such as blood gas analyses, spirometric data, 6-minute walking distance, and nocturnal oxygen saturation [69]. However an improvement in erectile function and sexual quality of life was reported. These two studies indicate that androgen therapy is able to improve muscle mass in COPD patients but, alone, is insufficient to improve lung function-associated parameters.

4.2. Androgen Therapy Combined with Physical Exercise. In two other studies, androgen therapy was combined with physical exercise [25, 71] (Table 1). A one-time 250 mg intramuscular injection of testosterone at baseline, followed by daily intake of 12 mg of oral stanozolol, was administered to ten undernourished (BMI < 20 kg/m^2) male outpatients

Table 1: Clinical studies and trials having tested different protocols of androgen therapy in COPD patients.

Study	Drug/administration route	*N*	GOLD stage	Fat-free mass (FFM) loss	Method of FFM assessment	Dose	Frequency	Duration
Schols et al. [70]	Dandrolone decanoate/IM	217	II, III	FFM < 67% (men)/<63% (women) of ideal weight	BIA	M: 50 mg W: 25 mg	1x/2 weeks	6 weeks
Ferreira et al. [71]	Mixture of testosterone phenylpropionate, isocaproate, propionate, caproate/IM unique dose, and then stanozolol/PO	Total = 23, 17 completed study	II, III	—	DEXA	M: 250 mg M: 12 mg	"Charging dose" 1x/day	Unique dose 27 weeks
Yeh et al. [68]	Oxandrolone/PO	Total = 128 55 included in 4-month analysis	II, III	—	BIA	M: 10 mg W: 10 mg	2x/day 2x/day	16 weeks
Casaburi et al. [25]	Testosterone enanthate/IM	Total = 53 47 completed protocol	II, III, IV	—	DEXA	M: 100 mg	1x/week	10 weeks
Pison et al. [72]	Testosterone undecanoate/ PO	126	II, III, IV	<25th percentile of predicted FFMI: <18 (men) <15 (women)	BIA	M: 80 mg W: 40 mg	2x/day 2x/day	12 weeks
Svartberg et al. [69]	Testosterone enanthate/IM	29	II, III	—	DEXA	M: 250 mg	1x/4 weeks	26 weeks

BIA: bioelectrical impedance analysis; DEXA: dual energy X-ray absorptiometry; FFM: fat-free mass; FFMI: fat-free mass index (=FFM (kg)/height $(m)^2$; IM: intramuscular; M: men; PO: per os; W: women.

with GOLD II-III COPD [71]. The control group consisted of seven patients with similar characteristics who received placebo. All patients were part of an outpatient pulmonary rehabilitation program consisting in inspiratory muscle exercises (weeks 9 to 27) and cycle ergometer exercises (weeks 18 to 27). An increase in body weight was observed in the patients receiving anabolic steroids. On the contrary, in patients receiving placebo, body weight decreased and body mass index was significantly lower at the end of the study than in the intervention group. Fat-free mass (thigh circumference, arm muscle circumference, and dual energy X-ray absorptiometry) was significantly higher in the intervention group. No differences were found in maximal inspiratory pressure or 6-minute walking distance [71]. Casaburi et al. [25] studied the effects of a 10-week intramuscular testosterone administration (100 mg of testosterone enanthate per week) with or without resistance training (45 minutes three times per week) in a group of 47 men with moderate to severe (GOLD II to IV) COPD (mean FEV < 60% predicted) and low testosterone plasma concentrations (<400 ng/dL). The patients were divided in four groups: placebo without training; testosterone without training; placebo and training; testosterone and training. Only patients treated with testosterone (with or without training) reported a significant increase in fat-free mass. The group "testosterone and training" had the highest increase in muscle mass and force. This was also the only group in which significant increases in peak oxygen uptake, peak work rate, and lactic acidosis threshold were observed. A significant and similar increase in muscle force was observed in the groups "placebo and training" and "testosterone without training" [25]. These two studies indicate that the combination of testosterone and training is superior to testosterone or training alone to improve muscle mass and force.

4.3. Androgen Therapy (Testosterone) Combined with Physical Exercise and Nutritional Supplementation: Pulmonary Rehabilitation. Multimodal interventions including androgen therapy, a nutritional intervention, and an exercise program have also been assessed [70, 72] (Table 1). A double blind randomized trial in 217 patients with moderate to severe (GOLD II-III) COPD studied the effects of an 8-week nutritional intervention alone or combined with nandrolone decanoate IM injections every two weeks (50 mg for men and 25 mg for women) [70]. The nutritional intervention consisted in daily adding to the regular meals one oral nutritional supplement (ONS) which was a high caloric drink (200 mL = 420 kcal) administered in the early evening between 7:00 and 9:00 p.m. Nutritional intervention lasted at least until day 57. Patients were all admitted to an intensive inpatient pulmonary rehabilitation program. Both groups (nutrition alone and nutrition + testosterone) presented with a similar weight gain. Nevertheless, those treated with the

testosterone analogue had a significantly higher increase of fat-free mass than the placebo group. Maximal inspiratory pressure, as a measure of respiratory muscle function, significantly increased after 8 weeks only in the group treated with nandrolone [70]. No differences concerning outcomes or side effects were observed between males and females [70]. A multimodal intervention was applied in a clinical trial in a group of moderate to severe COPD outpatients consisting in endurance physical exercises combined with oral nutritional supplements and oral testosterone undecanoate administration (80 mg or 40 mg twice daily for men and women, resp.) [72]. Nutritional intervention consisted ingiving three 120 mL ONS per day containing 180 kcal each. This triple intervention was applied for 90 days in 60 patients with chronic respiratory failure on long-term oxygen therapy and/or noninvasive ventilation. The control group consisted of 62 patients. Patients were undernourished (body mass index < 21 kg/m^2 and low fat-free mass) (Table 1). In the "intervention group," positive effects were reported on muscle mass, peak workload, quadriceps isometric force, and endurance time. No effect was observed on the 6-minute walking distance. Quality of life was improved only in women, independently of respiratory status, nutritional status, or compliance to therapy. Given these results, a stronger effect of hormonal therapy in women was speculated by the authors. One year after the end of the intervention (450 days of follow-up), survival was improved in the patients compliant to the pulmonary rehabilitation. Compliance was defined as having received at least 30% of two of the three treatments (exercise, ONS, and oral testosterone undecanoate) during the 3-month intervention [72]. These two trials clearly indicate the benefits of multimodal pulmonary rehabilitation associating physical exercise, oral nutritional supplementation, and androgen therapy, on muscle mass and force and clinical outcome of COPD patients.

4.4. Pulmonary Rehabilitation: A Pivotal Therapy for COPD. As stated in recent recommendations [41, 73], pulmonary rehabilitation should now be considered as a pivotal treatment, that is, not optional, for COPD patients functionally limited by dyspnea. It has been quoted with a grade A of evidence to improve dyspnea, exercise capacity, and health status [74]. The minimal content of a pulmonary rehabilitation program is to favour the regular practice of physical activity. Physical activity is initiated through at least three-weekly supervised sessions. This has to be followed by encouragements to maintain physical activities five times a week for 30 minutes each time. This training should contain progressive muscle resistance and aerobic endurance exercises to ensure muscle strength and endurance benefits [75, 76]. For more severely disabled patients, neuromuscular electrical stimulation could be helpful to improve muscle function [77]. Multimodal rehabilitation could be also beneficial in other chronic diseases. Specific care programs enclosing exercise training could delay the worsening of muscle atrophy in CHF patients [78, 79]. In patients with lung transplantation for respiratory chronic failure, renal failures, and type 2 diabetes, nutritional rehabilitation is associated with an improvement in the muscular oxidative metabolism [80–82] and a better survival [72]. The clinical trial NUTRICARD (ClinicalTrial.gov NCT01864733) is currently conducted to demonstrate whether nutritional rehabilitation would improve the clinical outcome of patients with CHF.

Table 2: Current contraindications to androgen therapy in COPD patients (from [83]).

Expected survival < 6 months
Previous history or actual hormono-dependent cancer (prostate or breast cancer)
Prostatic nodule without any urological evaluation
International prostate symptom score (IPSS) > 19/35
Prostate-specific antigen (PSA) > 4 ng/mL (>3 ng/mL if familial (1st degree) history of prostate cancer or if black people)
Previous history of psychotic disorders
Acute heart failure
Coronary heart disease in the past 6 months
Sleep apnea in the absence of ventilator support
Hematocrit > 50%
ASAT or ALAT > 3 times of normal values
Pulmonary artery hypertension
Neuromuscular diseases

ALAT: alanine aminotransferase; ASAT: aspartate aminotransferase.

4.5. Safety of Androgen Therapy in COPD Patients. In the trials conducted in COPD patients and described above, androgen therapy has a safety profile. However, in these studies, androgen therapy was given during a short period of time while testosterone adverse effects appear mostly with longer treatment durations. The safety of androgen therapy has to be assessed on the long term. Extrapolating data from hypogonadic patients would be hazardous. Indeed, a significative proportion of COPD patients included in the different trials had no hypogonadism; in these patients, testosterone was used as a drug more than a hormone replacement therapy. Anyhow, physicians prescribing testosterone have to be aware of its potential side effects: cardiovascular, sleep apnea syndrome worsening, prostate cancer, and polycythemia. Androgen therapy has to be specifically monitored [84]. Contraindications to androgen therapy are known (Table 2). Patients should also be informed about adverse effects such as mastodynia, gynecomastia, acne, and infertility. The risk for polycythemia seems particularly high in patients with chronic respiratory failure [84].

5. Perspectives

Three-month pulmonary rehabilitation is associated with an improved survival one year after the end of therapy [72]. However, the questions of the efficacy and the safety of a long-term pulmonary rehabilitation remain. Longer studies are warranted to better judge the safety profile of testosterone

treatment in moderate to severe COPD patients. The success of pulmonary rehabilitation is the compliance of the patients to therapy. After the end of 3-month rehabilitation, patients are strongly encouraged to go on physical activity at home. This is difficult in daily practice since patients could lack willing and encouragement. This point is crucial and deserves improving the number of caregivers specialized in the area of pulmonary rehabilitation: pneumonologists, physiotherapists, nurses, ergotherapists, ... Research is clearly warranted to evaluate the long term effect of pulmonary rehabilitation and to determine the adapted frequency of long term physical exercise. Another important area of future research is the identification of clinical, molecular (myostatin, mitochondrial enzymes (cyclooxygenases, citrate synthase, ATPase, ...), and transcriptional factors involved in protein metabolism (mTOR, Akt, ...)) or related genetic factors involved in the clinical response to pulmonary rehabilitation. Indeed, identifying the patients who will have the best clinical benefits of pulmonary rehabilitation or androgen therapy is a key challenge.

6. Conclusion

Fat-free mass loss and physical inactivity are key features of COPD and are related to impaired muscular oxidative metabolism. The preservation of muscle mass and function, through the protection of the mitochondrial oxidative metabolism, is an important challenge in the management of COPD patients. Androgen therapy improves muscle mass and force but is insufficient, alone, to improve lung function and clinical outcome. Nevertheless, in undernourished COPD patients, in combination with physical training and nutritional supplementations, androgen therapy is associated with increased fat-free mass and muscle force, together with increased peak workload and endurance time, and improved survival at least one year after the end of therapy. Pulmonary rehabilitation, associating physical exercise and nutritional supplements containing omega-3 polyunsaturated fatty acids, during at least three months, is the reference therapy of undernourished COPD patients. A short-term androgen therapy (3 months) could optimize the effects of rehabilitation in selected patients. Longer studies are warranted in order to identify whether mid- or long-term pulmonary rehabilitation could further improve the clinical outcome.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Contribution of Psychological Factors in Dropping out from Chronic Obstructive Pulmonary Disease Rehabilitation Programs

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Significant positive effects, particularly on psychological state in patients who completed the follow-up pulmonary rehabilitation programs, are indicated by a large number of studies. Yet, a remarkable proportion of selected patients drop out from these programs. In this study, we investigated existing differences on psychological variables among COPD patients who complete and those who drop out from pulmonary rehabilitation programs. The study included 144 patients, 43 (29.9%) of whom did not complete the program. SCL-90 was used for the assessment of psychological symptoms. On the SCL-90-R scale 55.6% of patients had abnormal findings. Patients who discontinued the program had higher rates of depression and somatization compared to those who completed it. Regarding the psychopathology scales of SCL-90R, we found that patients who discontinued the program showed higher levels of psychopathology on the scales of somatization, depression, paranoid ideation, and psychotism compared to those who completed the program. The final regression model showed that patients with low educational status and psychotism were more likely to leave the program. In conclusion, psychopathology contributes to patients dropping out from a COPD rehabilitation program; thus, psychological assessment prior to inclusion in rehabilitation programs may reduce dropouts.

1. Introduction

Pulmonary rehabilitation is defined as the evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic obstructive pulmonary disease (COPD) who are symptomatic and often have reduced activity of daily living. Intervention incorporates individualized patient treatment, and aims to reduce symptoms, to optimize patients' functional status, to increase participation in treatment and to reduce health care costs through stabilization or improvement of systemic manifestations of disease [1, 2]. During the last decades pulmonary rehabilitation has emerged as a standard of care for patients with COPD and is included in guidelines and algorithms of care in patients with COPD [3, 4]. The positive effects in patients who completed follow-up in rehabilitation programs have been reported in many studies [5]; among those, a positive effect on the psychological state of patients is prominent [6, 7]. According to the literature COPD is clearly associated with high levels of psychological morbidity and the condition's objective severity alone is insufficient to predict clinical outcomes. Such levels of psychological morbidity detrimentally affect quality of

life [8] in these patients (emotional and social role functioning and activities of daily livings and recreational pastimes [9]). In rehabilitation [10], health-related quality of life (HRQL) measures, such as disease-specific health status (St. George's respiratory questionnaire, SGRQ [11]; chronic respiratory questionnaire, CRQ [12]) and generic health status (medical outcomes short form 36 questionnaire, SF-36 [13]), evaluate both physical and emotional functions and the impact of disease on social function and psychological disturbance [14, 15]. Disease-specific measures have demonstrated greater sensitivity to change from baseline after rehabilitation intervention [16]. However, a significant proportion of eligible patients do not complete the follow-up program and the percentage of patients discontinuing the program in various studies ranges from 20 to 40% [17–20]. Despite the significant percentage of patients discontinuing rehabilitation programs few studies have examined the relevant causes and even fewer studies have focused on psychological factors that differentiate patients who dropped out from those that completed the pulmonary rehabilitation programs. Depression is probably the only psychological factor that has been studied and correlated with dropping out [19]. Depression and depressive symptoms are known to be significantly prevalent in patients with COPD [7, 21–23]. It seems very likely that depressive symptoms are contributing to dropping out. Symptoms include feelings of worthlessness, intense guilt or regret, helplessness or hopelessness, difficulties in concentration and memory, lack of motivation, neglect of personal hygiene, withdrawal from social activities such as family and friendly gatherings, decreased libido, and thoughts of death and suicide [24]. Clinical experience, however, makes us reluctant to fully attribute the phenomenon of dropping out to depressive symptomatology. As a matter of fact, clinicians perceive from the early rehabilitation programs sessions a marked decline in depressive symptomatology that in theory should act in a positive feedback manner by limiting dropout rates. The purpose of this study is to investigate whether there are differences in psychosocial factors among patients with COPD who quit rehabilitation programs and those who complete such programs. We should point out that the study is not intended in any way to exclude patients with COPD from rehabilitation programs due to psychological factors.

2. Subjects and Methods

2.1. Sample. The study lasted for four years and involved all patients with COPD who presented at a pulmonary rehabilitation program and met the criteria for inclusion in the study. Inclusion criteria in the study were as follows: age less than 80 years without other chronic comorbid conditions (cardiovascular disease, major psychiatric disorders, etc.) and the absence of acute exacerbation of COPD during the last two months before the start of the program. Contraindications included angina, myocardial infarction, severe pulmonary hypertension, congestive heart failure, unstable diabetes, restriction to exercise due to orthopedic or other reasons, dementia (already diagnosed severe cognitive dysfunction or psychiatric illness that interferes with memory and compliance), or severe hypoxia caused by exercise and not corrected by O_2 administration [25, 26].

2.2. Physical Measures. In order to determine COPD severity of our sample, a spirometric evaluation before and after bronchodilation (200 μg salbutamol) was performed. We followed the Global Initiative for Chronic Obstructive Lung Disease (GOLD-updated 2010) diagnostic criteria, which classifies COPD severity (in relation to forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio (FEV1%)—percentage of predicted) into four stages: stage I (mild COPD): FEV1 >80% predicted; stage II (moderate COPD): FEV1 50% to 80% of predicted; stage III (severe COPD): FEV1 30% to 50% of predicted; and stage IV (very severe COPD): FEV1 <30% of predicted [27]. The spirometric evaluation of each patient was performed a few days before he/she started the rehabilitation program.

2.3. Psychological Measures. The SCL-90-R is a 90-item self-report symptom inventory designed to reflect psychological symptom patterns of psychiatric and medical patients. Each item of the questionnaire is rated on a 5-point scale of distress from 0 (none) to 4 (extreme). The SCL-90-R consists of the following nine primary symptom dimensions: somatization (SOM, which reflects distress arising from bodily perceptions), obsessive-compulsive (OC, which reflects obsessive-compulsive symptoms), interpersonal sensitivity (IS, which reflects feelings of personal inadequacy and inferiority in comparison with others), depression (DEP, which reflects depressive symptoms, as well as lack of motivation), anxiety (ANX, which reflects anxiety symptoms and tension), hostility (HOS, which reflects symptoms of negative reflects, aggression, and irritability), phobic anxiety (PHO, which reflects symptoms of persistent fears as responses to specific conditions), paranoid ideation (PAR, which reflects symptoms of projective thinking, hostility, suspiciousness, and fear of loss of autonomy), and psychotism (PSY, which reflects a broad of symptoms from mild interpersonal alienation to dramatic evidence of psychosis) [28, 29].

The SCL-90 takes between 12 and 20 min to complete. With regard to its reliability, the internal consistency coefficient α values for the nine symptom dimensions ranged from 0.77 for psychotism to a high of 0.90 for depression. Additionally, the few validity studies of the SCL-90-R demonstrate that this scale has equal validity compared with other self-report inventories. The SCL-90-R has been standardized and used in the Greek population and its reliability (Cronbach's α) for the total of the items is 0.97 [30–32]. The cutoff for the SCL-90-R subscales is 0.99 [32].

The inventory was completed in the presence of psychologists who provided clarifications when necessary.

2.4. Pulmonary Rehabilitation Program. Patients of our study followed a pulmonary rehabilitation program for a period of three months, with three sessions per week, each lasting 50 minutes. The program included respiratory physiotherapy, respiratory muscle training, aerobic exercise on a bicycle ergometer and on a treadmill, and strengthening of muscle groups. The exercise was performed with oxygen

Table 1: Sex, education, FEV1%, and years of diagnosis.

		Age	Education (years)	FEV1%	Years of diagnosis
Male	Mean	65.0179	10.5268	40.7428*	8.9118
	$N = 112$				
	Std. deviation	8.04602	4.02013	20.20831	6.01195
Female	Mean	63.6563	11.9063	52.2203*	8.0588
	$N = 32$				
	Std. deviation	7.74017	4.02700	22.43287	9.28352
Total	Mean	64.7153	10.8333	43.2379	8.6275
	$N = 144$				
	Std. deviation	7.97256	4.04866	21.16720	7.18320

COPD staging per GOLD criteria: mild: $N = 12$, moderate: $N = 27$, severe: $N = 60$, very severe: $N = 45$.
*t-test $P < 0.05$.

Table 2: Percentages of pathological values in SCL-90-R.

($N = 144$)	Total ($N = 144$)	Male ($N = 112$)	Female ($N = 32$)	Dropout ($N = 43$)	Patients who remained in the program ($N = 101$)
Somatization	33.3%	31.3%	40.6%	46.5%*	27.7%*
Obsessive-compulsive	30.6%	26.8%	43.8%	32.6%	29.7%
Interpersonal sensitivity	13.9%	11.6%	21.9%	20.9%	10.9%
Depression	36.1%	30.4%	56.3%	48.8%*	30.7%*
Anxiety	23.7%	18.8%	40.6%	27.9%	21.8%
Hostility	20.8%	17.0%	34.4%	18.6%	21.8%
Phobic anxiety	12.9%	13.4%	9.4%	18.6%	9.9%
Paranoid ideation	16.7%	15.2%	21.9%	27.9%*	11.9%*
Psychoticism	4.9%	3.6%	9.4%	11.6%*	2%*
Without psychopathology	44.4%	50. 0%	25.0%	35.7%	48.5%

*χ^2 $P < 0.05$.

supplementation while simultaneously recording heart rate and hemoglobin saturation. The minimum and maximum number of sessions per patient was 34 and 39, respectively, with an average of 37 per patient.

Dropping out was predefined as being absent from five consecutive sessions or from 20% of all sessions. In fact all dropout patients were patients fulfilling the first definition of dropping out from the program. Dropout patients were given the chance to start again in a subsequent rehabilitation program.

2.5. Statistical Analysis. Statistical analysis was performed using χ^2 test, paired t-test, ANOVA, sample t-test, Pearson correlation, and logistic regression. For regression models, an empirical approach was used after correlation analysis. Statistical significance was set at $P < 0.05$ and all the analyses were done with SPSS 19.

The hospital ethics committee approved the study and all participants provided written informed consent. No financial support was necessary.

3. Results

The study included 144 patients, 43 (29.9%) of whom did not complete the program and without any manifestation of COPD relapse. One hundred twelve men (77.8%) and 32 women (22.2%) were studied. Table 1 shows the years of education, FEV1%, disease duration, and stage per GOLD. The sample is not statistically different compared with the general population of patients with COPD in Greece in terms of gender (χ^2 > 0,05) and age (t-test P > 0,05) [33]. The female population did not differ from males (t-test P > 0,05) in disease duration (8,05 ± 9,02 to 8,91 ± 6,01), years of education (11,9 ± 4,02 versus 10,52 ± 4,02), and age (63,65 ± 7,74 to 65,01 ± 8,04, Table 1). Males had lower FV1% compared to females (40,74 ± 20,21 to 52,22 ± 22,43 t-test P < 0,05, Table 1).

3.1. Psychopathology in Patients with COPD. On the SCL-90-R scale 55.6% of patients had abnormal findings (Table 2). High rates were observed for depression (36.1%), somatization (33.3%), compulsion (30.65%), and anxiety (23.7%), while low levels were noted for psychotism (4.9%), phobic anxiety (12.9%), and paranoid ideation (16.7%). Among the 80 patients (55.6%) with positive findings, 60% were positive in more than two scales, while only 23.8% were positive in only one scale of the SCL-90-R. In the SCL-90-R scale patients with very severe COPD showed higher averages in terms of somatization compared to patients with mild COPD (ANOVA test P < 0.05) but no statistically significant

Table 3: SCL-90-R scores by GOLD stage.

	Mild COPD $N = 12$		Moderate COPD $N = 27$		Severe COPD $N = 60$		Very severe COPD $N = 45$		Total $N = 144$	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Somatization	1.1908*	0.73960	0.8227	0.57141	0.7530	0.47151	0.6912*	0.52627	0.7849	0.54514
Obsessive-compulsive	1.1167	0.74813	0.7423	0.55941	0.7632	0.50661	0.7209	0.56844	0.7768	0.56340
Interpersonal sensitivity	0.6383	0.61962	0.5142	0.54969	0.4698	0.45054	0.3800	0.48991	0.4649	0.49788
Depression	1.1875	0.78261	0.7092	0.53305	0.9196	0.61554	0.8814	0.65194	0.8914	0.63288
Anxiety	0.8925	0.81761	0.6577	0.58663	0.6228	0.55870	0.6674	0.53529	0.6667	0.58068
Hostility	0.8708	0.79086	0.5062	0.66781	0.5771	0.73508	0.4356	0.53662	0.5450	0.67371
Phobic anxiety	0.4267	0.80009	0.4454	0.79923	0.2984	0.51654	0.4321	0.57746	0.3789	0.61958
Paranoid ideation	0.5383	0.72665	0.6592	0.68492	0.4291	0.48233	0.3658	0.57452	0.4622	0.57925
Psychoticism	0.3000	0.59544	0.2000	0.33226	0.1649	0.27742	0.1442	0.39176	0.1768	0.35909

*ANOVA test $P < 0.05$.

Table 4: Means of SCL-90.

	Dropout $N = 43$		Patients who remained in the program $N = 101$	
	Mean	Std. deviation	Mean	Std. deviation
Somatization	1.0056*	0.65567	0.7012*	0.45826
Obsessive-compulsive	0.8488	0.71759	0.7475	0.47741
Interpersonal sensitivity	0.5281	0.64144	0.4376	0.42644
Depression	1.0791*	0.72996	0.8139*	0.55606
Anxiety	0.7863	0.64028	0.6307	0.56351
Hostility	0.6000	0.78412	0.5340	0.61777
Phobic anxiety	0.4921	0.69419	0.3306	0.56846
Paranoid ideation	0.5616	0.77954	0.4269	0.47995
Psychoticism	0.2674	0.54890	0.1505	0.25598

*t-test $P < 0.05$.

differences in the other subscales (ANOVA test $P > 0.05$, Table 3).

3.2. Dropout Patients. Thirty percent of patients ($N = 43$; 32 men and 11 women) discontinued the program before completion. They did not differ in gender (χ^2 $P > 0{,}05$), age (66,05 ± 7,5 years versus 64,15 ± 8,1 years for those who were attentive, t-test $P > 0{,}05$), or disease duration (7,9 ± 8,3 years versus 9,0 ± 6,6 for those who were attentive t-test $P > 0{,}05$) from patients who completed the program. There was no difference in the FV1% (42.6 ± 20,5 for those who discontinued versus 43,5 ± 21,5 of the others, t-test $P > 0{,}05$). Chi-square test revealed no difference concerning disease severity per GOLD criteria (χ^2 $P > 0{,}05$). Patients who completed the program had more advanced education (11,3 ± 4,1 versus 9,8 ± 3,8, t-test $P < 0{,}05$). Patients who discontinued the program had higher rates of depression (1,08 versus 0,81, t-test $P < 0{,}05$) and somatization (1,01 versus 0,70, t-test $P < 0{,}05$) compared to those who completed it (Table 4). Regarding the psychopathology scales of SCL-90-R we found that patients who discontinued the program showed higher levels of psychopathology on the scales of somatization, depression, paranoid ideation, and psychotism compared to those who completed it (χ^2 $P < 0{,}05$, Table 2).

To determine which variable distinguished better patients who discontinued from patients who completed the program, we performed a binomial logistic regression with years of education and (from the SCL-90-R) whether or not there was psychopathology present (somatization, depression, and paranoid ideation) as covariates. The final regression model showed that people with low educational status and psychoticism were more likely to leave the program. However, the adjustment of the resulting model to the data was not satisfactory (Cox & Snell Pseudo-R2 0,077).

4. Discussion

In this study of dropping out from a COPD rehabilitation program, patients who did not complete the program did not differ from those who completed in terms of gender or illness severity. High rates of psychopathology in patients with COPD have been identified in several studies [7, 21–23]. In this study we tried to examine whether this psychopathology contributes to patients dropping out from a COPD rehabilitation program. Dropping out, apart from the financial cost, results in frustration and disappointment to both health professionals and patients. Furthermore it is still unknown what the consequences are for patients remaining in

the rehabilitation program. We know that rehabilitation can enhance the psychological aspects of patients who complete the program [7], but we do not know whether this improvement is negatively or positively associated with dropout rates. Our findings point to psychological factors being involved in quitting the rehabilitation program. More specifically, patients who left the program seemed to have higher rates of depression and somatization and among them we found higher rates of pathological psychotic features. We have indications that behind the abandonment of the program it is possible, in terms of psychological parameters, to find psychotic elements. A link with some incipient organic brain syndrome may be possible, since patients of our sample had no history of mental disorder, while the age of these patients made them highly unlikely to show emerging schizophrenia. On the other hand, COPD patients are particularly vulnerable for dementia syndromes [34]. Systemic inflammation is likely to be the common factor linking the two diseases; acute and chronic effects of inflammation in the brain have been associated with cognitive decline and risk of dementia in older adults [34]. Studies show that depressive symptoms are associated with an increase in proinflammatory cytokines and that the level of cytokines corresponds to the severity of depressive symptoms [35, 36]. Depression, in turn, can negatively affect cognitive function by interfering with working memory, executive function, and processing speed. Additionally, depression and depressive symptoms are associated with increased risk of cognitive impairment and dementia among the elderly [37].

Low educational level is a risk factor for dementia syndromes, while a high level of education is considered to be a protective factor [38]. Patients who left the rehabilitation program appeared to feel more physical symptoms compared to those that did not quit; perhaps this is a separate dropout factor. The close relationship between depression and somatization [39] can explain equally well the high percentages of patients who left the program.

It is very likely that the main elements of a pulmonary rehabilitation program that have a positive effect on patients who complete it are the same that make some patients drop out of it. Being a patient in a pulmonary rehabilitation program, mutatis mutandis works in a way analogous to group function [40]; it is formed by people who share common characteristics; it may act therapeutically while it can expel patients with psychotic elements. The sense of belonging to a group is often beneficial: it gives participants the opportunity to interact and through this process to recognize elements of their personal experiences in others as well as to process these elements [41]. However, this is hardly tolerated by some patients. The feeling of the individual that he/she is acceptable, the sense of belonging to a group, the recognition of elements of personal experience in others, identification with others, and emotional contact with other patients and therapists within the program provide help to most COPD patients [7] and may turn away psychotic patients from the program.

We have to point out that the aim of the study was not, in any case, to exclude patients with COPD from the process of rehabilitation. It is very likely that individual rehabilitation programs can help and be well tolerated by COPD patients who for some reason cannot function well within a group. Further research should examine whether there is a direct relationship between cognitive deficits and dropping out from rehabilitation programs.

5. Conclusion

Psychological factors in patients with COPD potentially contribute to refraining from participation in pulmonary rehabilitation programs. Psychological evaluation of patients during the selection process for rehabilitation programs may reduce dropout rates.

Conflict of Interests

The authors declare that they have no competing interests.

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Review Article

Identification of Clinical Phenotypes Using Cluster Analyses in COPD Patients with Multiple Comorbidities

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Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation, the severity of which is assessed using forced expiratory volume in 1 sec (FEV_1, % predicted). Cohort studies have confirmed that COPD patients with similar levels of airflow limitation showed marked heterogeneity in clinical manifestations and outcomes. Chronic coexisting diseases, also called comorbidities, are highly prevalent in COPD patients and likely contribute to this heterogeneity. In recent years, investigators have used innovative statistical methods (e.g., cluster analyses) to examine the hypothesis that subgroups of COPD patients sharing clinically relevant characteristics (phenotypes) can be identified. The objectives of the present paper are to review recent studies that have used cluster analyses for defining phenotypes in observational cohorts of COPD patients. Strengths and weaknesses of these statistical approaches are briefly described. Description of the phenotypes that were reasonably reproducible across studies and received prospective validation in at least one study is provided, with a special focus on differences in age and comorbidities (including cardiovascular diseases). Finally, gaps in current knowledge are described, leading to proposals for future studies.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by incompletely reversible airflow limitation and its prevalence is strongly associated with ageing and smoking [1]. It has long been noticed that COPD patients constitute a heterogeneous group of patients and a large observational study recently confirmed that subjects with similar range of airflow limitation (as defined by FEV_1% predicted) had marked differences in symptoms (dyspnea, cough, and sputum production), rates of exacerbations, exercise capacity, and health status [2]. Based on these findings, interest has grown on the identification of subgroups of COPD patients sharing clinically meaningful characteristics, also called phenotypes [3].

In the past decade, it has become clear that chronic diseases often coexist [4]. Accordingly, COPD patients often suffer from other chronic diseases (called comorbidities). Cardiovascular diseases, psychological disorders (e.g., anxiety and/or depression), metabolic disorders (e.g., diabetes, dyslipidemia, and metabolic syndrome), and cancer have been found highly prevalent among COPD patients [5, 6]. The association of comorbidities and COPD may merely reflect common risk factors (e.g., age or cigarette smoking). However, chronic low-grade systemic inflammation, which is observed in some COPD patients, could also be involved [7], as well as biological mechanisms related to decreased physical activity, which is often observed with ageing [8]. The importance of coexisting diseases has been underscored by several studies showing that COPD patients with multiple comorbidities have worse prognosis [4, 9–11]. However, it has not been established whether the presence of one or several of these comorbidities represent or contribute to a coherent phenotype per se.

Recently, several groups have reported studies aimed at finding COPD phenotypes using multivariable exploratory analyses (e.g., cluster analysis). The purpose of the present paper is to review recent evidence obtained from studies that have searched for COPD phenotypes using cluster analyses of observational data obtained in COPD cohorts, with a special interest in the contribution of comorbidities to phenotypes.

2. COPD Phenotypes: A Historical Perspective

Historically, the concept of COPD phenotypes probably goes back to the recognition of two major COPD components, that is, emphysema and chronic bronchitis [12]. These components had been described long before the first appearance of the term COPD in 1960 [13], but they had been considered as separate diseases before being unified under the term COPD. Interestingly, as soon as the use of the term COPD began being generalized, the disease was recognized as being markedly heterogeneous [14]. At the 9th Aspen Emphysema Conference, Burrows and Fletcher presented their findings on "the emphysematous and bronchial types of chronic airway obstruction," which were subsequently published in 1968 [15]. The authors defined two distinct aspects (emphysema, type A or "pink puffer" and airways disease, type B or "blue bloater") of a single condition (chronic airflow obstruction), being a precursor of the phenotypes concept in the COPD area. Almost half a century later, the 48th Conference (renamed "Thomas L. Petty Aspen Lung Conference") began with a clinical theme emphasizing clinical COPD phenotypes [16]. In the meantime, reference to A and B types of chronic airway obstruction had disappeared, due to the lack of relation between clinically relevant outcomes and pathologic findings, especially regarding the centri- or panlobular nature of emphysema: the traditional definition of phenotypes (referring to "the observable structural and functional characteristics of an organism determined by its genotype and modulated by its environment" [17]) was already considered insufficient to establish clinically relevant COPD phenotypes. Therefore, Han et al. recently proposed a novel definition of COPD phenotypes, that is, "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death)" [3].

3. Relation of Phenotypes to Prognostic Indices and COPD Classifications

As suggested in a recent editorial [18], it seems important to avoid confusion between phenotypes and markers of disease severity (e.g., prognostic indices) or disease activity. Additionally, the recent update of the Global Initiative for Obstructive Lung Disease (GOLD) has introduced a new multidimensional classification of COPD, with four categories that could correspond to phenotypes.

3.1. Prognostic Indices Do Not Identify Phenotypes. Several multidimensional prognostic indices have been developed in COPD [19], the BODE index being one of the most widely quoted [20]. By definition, these tools were shown to reliably predict the risk of death and/or other outcomes such as the risk of exacerbation or hospitalization, at least in the populations in which they were developed. For many of them, external validity was also demonstrated, even if some adjustments "recalibration" were sometimes advocated. Importantly, patients who share similar prognosis (at least from a statistical, population perspective) based on a similar prognostic score might not necessarily be considered as belonging to a specific phenotype. For example, an 80-year-old patient with a body mass index (BMI) at 20 kg/m^2, medical research council (MRC) dyspnea grade 3, FEV_1 45% predicted, and 6-min walking distance (6MWD) = 340 m will have the same BODE score (i.e., 6) as a 55-year-old patient with FEV_1 28% predicted, BMI 28 kg/m^2, MRC grade 3, and 6MWD = 255 m. Although sharing the same predicted survival, these two patients look very different and will certainly not die at the same age. Thus, it seems difficult to state that they belong to the same phenotype, and prognostic indices are not substitutes for phenotypes.

3.2. COPD Classifications: From Lung Function to Multidimensional Assessment. Until recently, COPD classification was largely based on FEV_1 [21], which was poorly correlated with symptoms [2]. Even if guidelines advocated the need for thorough clinical assessment of symptoms and exacerbations, they did not formalize the way these items had to be accounted for. In 2011, the GOLD classification was profoundly modified. It now comprises four quadrants (A-B-C-D) based on (i) symptoms (dyspnea and health status/global impact) and (ii) risk of exacerbations estimated through the severity of airflow obstruction (with the same grades 1-2-3-4 as previously stated) and previous history of exacerbations/hospitalizations [22]. Descriptions of the four groups look like phenotypes: low symptoms/low risk, high symptoms/low risk, high risk/low symptoms, and high risk/high symptoms. However, it must be outlined that, although associated with several differences in clinical characteristics and prognosis [23], these four categories are the result of expert opinions rather than formal statistical approaches. In addition, how they predict mortality is debated (with some discrepancies between studies, and a discriminant capacity that does not exceed that of FEV_1-based classification), and their relations with response to treatments are unknown. Finally, age and comorbidities were not included in this novel classification, suggesting that they account only partially for the heterogeneity of COPD patients.

4. Statistical Strategies for Identifying COPD Phenotypes

Disease characteristics that could be used to define phenotypes of patients with chronic airway diseases include clinical features (e.g., risk factors, clinical manifestations, and comorbidities), imaging (e.g., emphysema, airway thickening, and bronchiectasis), pulmonary function and exercise tests, and biomarkers. Integrating these various characteristics with

the aim of defining phenotypes is challenging. Historically, investigators have used classical multivariable analyses, but recent studies have highlighted the potential of using cluster analyses for this purpose.

4.1. Classical Multivariable Analysis. The classical approach to the identification of COPD phenotypes seeks associations between phenotypic characteristics (also called phenotypic traits) and outcomes using multivariable analyses (i.e., logistic or multilinear regression analyses). For example, sputum or bronchoalveolar lavage eosinophilic inflammation has been associated with response to systemic corticosteroids in COPD patients [24] and the presence of chronic cough and sputum production has been associated with poorer long-term outcomes in terms of lung function decline [25] and risk of exacerbations and hospitalizations [26]. Further, repeated hospitalizations were independently associated with mortality in COPD patients [27]. All these studies related a single disease attribute, usually identified by physicians based on observation, to a specific outcome. However, classical statistical analyses can also be used for phenotypic characterization using combinations of disease attributes: for example, investigators of the National Emphysema Treatment Trial found that COPD patients with emphysema who have a low FEV_1 and either homogeneous emphysema or a very low carbon monoxide diffusing capacity were at high risk for death after lung volume reduction surgery and also were unlikely to benefit from the surgery [28].

Although this classical statistical approach has produced interesting results, leading to the identification of potential COPD phenotypes including those described above and others (e.g., frequent exacerbators [29]), it is usually based on clinical observation of a limited number of variables and may have missed more complex phenotypes. Because integrating the growing number of information available in clinical medicine only using clinical judgment may be difficult, it was suggested that mathematical models may help in unraveling the complexity of COPD [30].

4.2. Cluster Analyses and Related Exploratory Analyses. The term "cluster analysis" refers to a group of statistical methods that seek to organize information so that data from heterogeneous variables can be classified into relatively homogeneous groups [30]. In recent years, cluster analysis has been used to examine heterogeneity of patients with chronic airway diseases including asthma [31, 32] and COPD [33–40]. Cluster analysis is often presented as an unsupervised and unbiased method. However, important aspects related to the different methods of cluster analysis and to the choice of variables included in the analysis may affect the results.

The two main different cluster analyses methods, which have been used in studies of airway diseases, are hierarchical and nonhierarchical (e.g., K-means) cluster analyses. Hierarchical cluster analysis is based on the idea that patients who share similarities on a set of data can be grouped together. In the agglomerative techniques (the most widely used), the results are shown as a dendrogram in which each horizontal line represents an individual subject and the length of horizontal lines represents the degree of similarity between subjects [30, 41]. The number of clusters is determined according to the results of the analysis (see below). In K-means cluster analysis, the number of clusters (k) is determined before the analysis and the algorithms find the cluster center and assign the objects to the nearest cluster center [30, 41]. Drawbacks of the K-means analysis are the necessity of choosing the k number of clusters and the fact that the algorithms usually prefer clusters of approximately similar size, which may lead to ignoring a smaller, yet important, group of subjects [30, 41]. Self-organizing maps (SOM) are an alternative neural network-based nonhierarchical clustering approach, which has been used for analysis of gene arrays [42] and has also been used recently to examine comorbidities in COPD patients [40].

The choice of variables included in a cluster analysis is a very important aspect of the analysis; cluster analysis detects structures within selected variables, but cannot determine whether some of the selected variables are irrelevant for phenotyping. The choice of variable is dictated by practical considerations (e.g., the type of data available in the cohort), underscoring the need for well-characterized cohorts. Although some investigators performed cluster analysis with as many variables as available in their database [37], we believe that selection of a limited number of variables considered important in defining the disease process may be preferable. For example, when looking for phenotypes associated with different risk of mortality, our cluster analyses were based on data previously associated with death in COPD patients [34, 43]. This strategy is very similar to what has been performed for analysis of multiple genes using gene arrays: although it is possible to set up arrays using very large numbers of gene, it is also possible to use gene sets containing smaller numbers of genes that are defined based on prior biological knowledge, for example, published information about biochemical pathways [44].

The encoding of variables (e.g., using raw data, categorized data, or Z-scores [37]) may also affect the results of a cluster analysis [45], but this aspect has not been formally explored in the COPD literature. Further, the ways to handle missing data, which are present in any large dataset of observational data, have been different among studies; it has resulted in exclusion of patients from the analysis in some studies [34, 35], whereas other investigators suggested the usefulness of multiple imputation for missing data, to avoid excluding patients from the analyses [46]. The impact of patient exclusion versus imputation remains to be established.

Another important aspect relates to the fact that correlations between initially selected variables may add statistical noise and corrupt the cluster structure. To limit this problem, strategies of data transformation using principal component analysis (for numerical variables) and/or multiple correspondence analyses (for categorical variables) have been proposed [26, 43]. An advantage of using these techniques is the ability to combine mathematical axes obtained in these analyses in a single cluster analysis, allowing analyzing of numerical and categorical variables simultaneously [43]. However, when studying a limited number of continuous

or categorical variables that are not closely correlated with each other, these steps of data transformation may not be necessary.

Choosing the appropriate number of clusters among the multiple possibilities generated by the analyses may also be challenging. In hierarchical cluster analysis, the number of clusters can be deducted from visual inspection of the dendrogram, or from statistical measurement of large jumps in the similarity measure at each stage (e.g., pseudo-F and/or pseudo-T2 statistics) [34]. However, the number of clusters can also be deducted from the clinical outcome used for validation of the analysis. For example, in an analysis of the Leuven COPD cohorts, statistical methods based on the dendrogram obtained by hierarchical cluster analysis suggested that data could be optimally grouped in 3 or 5 clusters [43]. When grouping the data into 3 clusters, there was a clear difference in mortality rates among clusters, whereas grouping data into 5 clusters did not improve the ability to predict mortality, leading to the final choice of 3 clusters [43]. When using K-means clusters (or equivalent nonhierarchical cluster analyses), the number of clusters needs to be prespecified [37]. Although there are statistical methods to determine the optimal number of clusters (e.g., performing a hierarchical cluster analysis before the K-means analysis [31]), investigators have also used clinical judgment to determine the optimal numbers of prespecified clusters [37].

In summary, various strategies of data selection, data transformation, and use of various algorithms clearly underscoring that exploratory cluster analyses in airway have been used, diseases cannot be considered as really "unsupervised and unbiased." Thus, cluster analysis should be better viewed as a supervised multivariable exploratory analysis, and its results need to be validated using clinically relevant endpoints in multiple cohorts of patients.

4.3. Limitations of Current Studies Aimed at Finding COPD Phenotypes Using Cluster Analyses. In recent years, several studies have used cluster analyses to examine cohorts of COPD patients aiming at the identification of clinical phenotypes in stable patients [33–40, 43]. In the present paper, we will not examine studies performed in mixed populations of patients with various chronic airway diseases [30, 47], in COPD patients recruited in clinical trials [48] (i.e., who may not be representative of the real-world COPD population), nor studies that aimed at the identification of phenotypes of COPD exacerbations [49].

A summary of studies that have used cluster analyses for identification of COPD phenotypes is presented in Table 1. Several limitations of these approaches should be acknowledged. First, all studies were performed in relatively small numbers of patients recruited either in a single center or in multiple centers in a single country. Their designs have likely resulted in the selection of patients that cannot be considered representative of the COPD population at large and thus may have missed important phenotypes; for example, Altenburg et al. [33] and Vanfleteren et al. [40] recruited patients participating in rehabilitation programs; Garcia-Aymerich et al. recruited patients at the time of their first hospitalization in Spain, and these patients were almost exclusively (93%) men [37]. Burgel et al. recruited patients who were all followed in tertiary care [34] or combined a cohort of patients followed in tertiary care with a cohort of milder COPD patients identified in a lung cancer screening study [35]. Fens et al. also studied patients with mild airflow limitation diagnosed during a lung cancer screening study [36].

Second, there was marked heterogeneity in the data selected for cluster analyses. Some studies selected only clinical data and pulmonary function tests, whereas others also included imaging and/or biological biomarkers; these choices, often based on the availability of data, could have affected the results. Regarding comorbidities, several studies did not report assessment of comorbidities in their patients [33, 38, 39]. Others examined self-reported [36, 37] or physician-diagnosed [34, 35] comorbidities, both of which may have resulted in underestimations due to the high level of undiagnosed comorbidities in COPD patients [50]. Only one study has performed systematic assessment of several comorbidities [40]. Of note, cluster analysis reported in this study was performed using data on the presence of comorbidities (categorical) and the degree of their presence (linear), but not using data characterizing COPD (e.g., pulmonary function tests) [40].

Finally, validation of possible phenotypes using longitudinal outcomes was performed only in a limited number of studies: Burgel et al. performed two studies in two different cohorts of COPD outpatients and validated their findings using all-cause mortality [34, 35, 43]. Garcia-Aymerich et al. studied patients recruited at the time of a first hospitalization for COPD exacerbation and used all-cause mortality and hospitalizations related to COPD and to cardiovascular diseases to validate their findings [37]. Altenburg et al. found two phenotypes in which patients responded differently to pulmonary rehabilitation [33]. Other studies did not report prospective validation of their findings. At the end, although these limitations should be taken into consideration, cluster analyses have resulted in interesting preliminary results that are summarized in the next section.

4.4. Main COPD Phenotypes Identified by Cluster Analyses. Several possible phenotypes were identified in the various studies that have used cluster analyses in observational cohorts of COPD patients (see Table 1). Here we limit the description to the phenotypes (i) that were reasonably reproducible across various studies performed in various countries, using various initial data sets and various types of cluster analyses and (ii) that received prospective validation in at least one study.

Several studies have identified groups of COPD subjects with metabolic and cardiovascular comorbidities. Garcia-Aymerich et al. identified a cluster of COPD patients with "systemic COPD" [37]. These subjects were characterized by a high body mass index and very high rates of diabetes, congestive heart failure and ischemic heart disease; interestingly, they had higher levels of dyspnea and poorer health status than subjects with comparable airflow limitation,

Table 1: Summary of studies exploring possible phenotypes using cluster analyses in stable COPD patients.

Reference	n	Setting	Population characteristics	Data used to build clusters	Multiple comorbidities	Types of analyses	Main results	Outcome for validation
Altenburg et al. [33]	65	Single center, tertiary care, and pulmonary rehabilitation (Groningen, The Netherlands)	Moderate to very severe airflow limitation Referred for rehabilitation	Age, BMI, quadriceps force, body plethysmography, and exercise testing	Not assessed	K-means	2 phenotypes: (i) worse lung function and exercise capacity, worse quadriceps force, and better response to exercise training (ii) better lung function and exercise capacity and less response to exercise training	High or low improvement in endurance exercise capacity rehabilitation
Burgel et al. [34, 35]	322	Multicenter cohort (Initiatives BPCO), and tertiary care (France)	Mild to very severe airflow limitation Outpatients	Age, history, and symptoms, spirometry, BMI, exacerbations, health status, psychological status	Physician-diagnosed Not included in the cluster analysis	PCA, HCA (Ward's)	4 phenotypes: (i) young subjects with severe respiratory disease, cachexia (ii) older subjects with mild airflow limitation and mild comorbidities (iii) young subjects with moderate to severe airflow limitation, but few comorbidities (iv) older subjects with moderate to severe airflow limitation and high rates of cardiovascular comorbidities	All-cause mortality
Burgel et al. [43]	527	Single center, tertiary care (Leuven, Belgium)	Mild to very severe airflow limitation Outpatients and COPD patients identified as part of a lung cancer screening study	Age, history and symptoms, health status, body plethysmography, DL_{CO}, CT-scan, and physician-diagnosed comorbidities	Physician-diagnosed Included in the cluster analysis	PCA, MCA, HCA (Ward's)	3 phenotypes: (i) younger patients with severe respiratory disease, cachexia, and low rates of cardiovascular comorbidities. (ii) older patients with less severe airflow limitation, but often obese and with high rates of cardiovascular comorbidities and diabetes. (iii) mild to moderate airflow limitation, absent or mild emphysema, absent or mild dyspnoea, normal nutritional status, and limited comorbidities	All-cause mortality
Fens et al. [36]	157	Population-based survey (Utrecht, The Netherlands)	Mild to moderate airflow limitation COPD patients identified as part of a lung cancer screening study	History and symptoms, health status, comorbidities, spirometry, DL_{CO}, CT-scan, and breathomics (electronic nose)	Self-reported Included in the cluster analysis	PCA, HCA (Ward's), K-means	4 possible phenotypes: (i) mild COPD (ii) moderate airflow obstruction with chronic bronchitis and emphysema (iii) asymptomatic emphysema with preserved lung function (iv) high symptoms, preserved lung function	None

Table 1: Continued.

Reference	n	Setting	Population characteristics	Data used to build clusters	Multiple comorbidities	Types of analyses	Main results	Outcome for validation
Garcia-Aymerich et al. [37]	342	Multicenter study, tertiary care (Spain)	Mild to very severe airflow limitation COPD patients recruited after a 1st hospitalization	History and symptoms, health status, body composition, body plethysmography, CT-scan, biology (sputum and serum), and exercise testing	Self-reported Included in the cluster analysis	K-means	3 phenotypes: (i) severe respiratory COPD (ii) moderate respiratory COPD (iii) systemic COPD (high rates of cardiovascular comorbidities)	(i) Hospitalizations (COPD or cardiovascular) (ii) all-cause mortality
Paoletti et al. [38]	415	Single center, tertiary care (Florence, Italy)	Mild to very severe airflow limitation Outpatients	History and symptoms, body plethysmography, DL_{CO}, and chest X-ray	Not assessed	MDS, PCA, MCA, K-means	2 phenotypes: (i) predominant airflow obstruction (ii) predominant parenchymal destruction	None
Pistolesi et al. [39]	322	Single center, tertiary care (Florence, Italy)	Mild to very severe airflow limitation Outpatients	History and symptoms, body plethysmography, DL_{CO}, and chest X-ray	Not assessed	MDS, PCA, cluster analysis*	2 phenotypes: (i) predominant airflow obstruction (ii) predominant parenchymal destruction	None
Vanfleteren et al. [40]	213	Single center, tertiary care, pulmonary rehabilitation (Horn, The Netherlands)	Moderate to very severe airflow limitation Referred for rehabilitation	13 comorbidities	Systematically assessed Cluster analysis performed exclusively on comorbidities	SOM, HCA (Ward's)	5 possible comorbid phenotypes: (i) less comorbidity (ii) cardiovascular (iii) cachectic (iv) metabolic (v) psychological with no difference in systemic inflammation	None

*Type of cluster analysis not described; HCA: hierarchical cluster analysis; PCA: principal component analysis; MCA: multiple correspondence analysis; MDS: multidimensional scaling; SOM: self-organizing maps.

but less cardiovascular and metabolic comorbidities [37]. Importantly, these patients were at high risk of hospitalization for cardiovascular events and also had substantial risk of hospitalization for COPD (despite having moderate airflow limitation) and all-cause mortality [37]. These findings were consistent with those of Burgel et al. who reported marked differences between two clusters of subjects with comparable moderate to severe airflow limitation [34]. Subjects with high rates of obesity, diabetes, and cardiovascular comorbidities had more symptoms and higher rates of exacerbations. Interestingly, these subjects were markedly older, a finding consistent with the increasing prevalence of cardiovascular diseases and obesity with age [51]. Vanfleteren et al. also found a group of subjects with cardiovascular comorbidities but mostly normal BMI and suggested that this group differed from another one called "metabolic" in whom subjects showed high rates of obesity, dyslipidemia atherosclerosis, and myocardial infarction [40]. Although it remains unclear whether COPD patients with cardiovascular versus metabolic comorbidities truly represent two different groups of patients, it is concluded that most studies identified these comorbidities in subsets of patients with worse prognosis compared to other COPD subjects.

Burgel et al. have identified subjects with severe airflow limitation occurring at an early age in two different cohorts of COPD patients [34, 43]. These subjects were characterized by nutritional depletion [34, 43], high rates of emphysema and COPD exacerbations [43], muscle weakness, and high rates of osteoporosis [43], but very low rates of cardiovascular comorbidities [34, 43]. In both studies, these subjects were at very high risk of mortality at a relatively young age [34, 43], suggesting that specific therapeutic intervention should be targeted to this group of very severe patients. Interestingly, Vanfleteren et al. also found a cluster of cachectic subjects who were very similar to these latter subjects [40]. These authors suggested that common pathophysiologic pathways may be responsible for the cooccurrence of emphysema, muscle wasting, and osteoporosis. Of note, women appeared most prevalent in the cachectic phenotype in all 3 studies [34, 40, 43], a finding that is consistent with data obtained in the Boston Early-Onset COPD study [52].

Finally, Vanfleteren et al. identified a cluster of subjects with less comorbidity [40]. Interestingly, COPD patients without significant rates of major comorbidities were also found in other studies [34, 35]. Although these data suggest that COPD may occur in the absence of other comorbidities, this absence may be interpreted differently in younger subjects (in whom comorbidities may occur later with ageing, if they survive long enough) and in older subjects (in whom these comorbidities are presumably less likely to occur as they did not in previous years). Nevertheless, at a similar level of FEV_1, patients with less comorbidities were suggested to have less COPD exacerbations [34].

5. Future Studies and Implications

5.1. Future Studies. The studies described in this review paper have produced interesting results by showing the feasibility of using cluster analyses and associated statistical methods for unraveling the heterogeneity of COPD patients. As already explained, all the previously published studies had limitations, largely related to the settings of patient recruitment in these cohorts (see above). Large cohorts, containing detailed information on patients recruited in multiple settings, are costly to establish. One option could be to merge multiple cohorts obtained in different settings, to ensure representation of different subgroups of patients. In this regard, future analyses should consider grouping cohorts that recruited inpatients in tertiary care (which may contain the most severe patients, including those awaiting for lung transplantation) with cohorts of in/outpatients recruited in secondary care and cohorts of patients recruited in primary care. Additionally, inclusion of preclinical COPD patients (e.g., recruited through systematic screening in the community) will ensure that all groups of age, disease severity, gender, and other patients characteristics (e.g., comorbidities, risk factors, social background, ...) will be represented. Further, obtaining data from various areas of the world will provide better representation of patients with various genetic backgrounds and environmental exposures and will account for differences in healthcare systems.

Although there is currently no consensus on which data are required for optimally phenotyping COPD patients, it appears clear that characterization of patients should not be limited to the respiratory system but should include comorbidities. Undiagnosed comorbidities are highly prevalent and may have an important impact on COPD patients, suggesting that systematic assessment of comorbidities may be preferable, although it may be difficult to achieve in large cohorts of patients.

Prospective validation of phenotypes using clinically meaningful endpoints appears mandatory [3]. Longitudinal followup of phenotypes will also be interesting for examining their stability, as all current studies were performed using transversal rather than longitudinal data. Although phenotype stability is a major problem in asthmatic patients [53], a disease characterized by marked variability, it is probably less problematic in COPD, especially in older patients in whom airflow limitation and comorbidities are unlikely to show marked changes with time. However, followup of younger COPD patients with less comorbidity will be interesting to examine whether or not ageing will result in incident comorbidities and in the progression of airflow limitation and COPD-related outcomes. Furthermore, researchers should concentrate on establishing physician-friendly rules for assigning patients to appropriate phenotypes in daily practice. Tree-diagram analysis has proven useful to assign asthmatic patients to cluster-defined phenotypes using easily available clinical data [32] and may provide interesting insight in COPD subjects.

5.2. Future Implications. Identification of clinical COPD phenotypes using cluster analyses may ultimately result in important changes in our conception of COPD. Validation of phenotypes across multiple cohorts of patients in various settings (see above) may result in the development of novel

classifications of COPD patients, better reflecting their heterogeneity. Each phenotype may have different pathophysiology and identification of biological mechanisms specific of some phenotypes (endotypes) may lead to the development of biomarkers aimed at early diagnosis of phenotypes and identification of candidates to specific, more targeted treatments. From a methodological perspective, there are two ways to identify endotypes associated with phenotypes: the first is to identify clinical phenotypes first, then determine which biological mechanisms are associated with them; the second is to mix clinical and biological variables in cluster analyzes. Available data do not allow determining which approach is the most relevant, and they might be complementary.

Finally, we propose that classifying patients based on some of the phenotypes consistently identified in various cluster analyses may provide an interesting alternative to currently used criteria based mostly on FEV_1, symptoms and, exacerbation history for recruiting patients in clinical trials. For example, selecting patients who also share other similar characteristics (e.g., age, presence or absence of comorbidities) and future risks may provide a form of enrichment strategy, allowing for smaller sample size and shorter duration of followup [54].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Determinants of Noninvasive Ventilation Outcomes during an Episode of Acute Hypercapnic Respiratory Failure in Chronic Obstructive Pulmonary Disease: The Effects of Comorbidities and Causes of Respiratory Failure

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Objectives. To investigate the effect of the cause of acute respiratory failure and the role of comorbidities both acute and chronic on the outcome of COPD patients admitted to Respiratory Intensive Care Unit (RICU) with acute respiratory failure and treated with NIV. *Design*. Observational prospective study. *Patients and Methods*. 176 COPD patients consecutively admitted to our RICU over a period of 3 years and treated with NIV were evaluated. In all patients demographic, clinical, and functional parameters were recorded including the cause of acute respiratory failure, SAPS II score, Charlson comorbidity index, and further comorbidities not listed in the Charlson index. NIV success was defined as clinical improvement leading to discharge to regular ward, while exitus or need for endotracheal intubation was considered failure. *Results*. NIV outcome was successful in 134 patients while 42 underwent failure. Univariate analysis showed significantly higher SAP II score, Charlson index, prevalence of pneumonia, and lower serum albumin level in the failure group. Multivariate analysis confirmed a significant predictive value for pneumonia and albumin. *Conclusions*. The most important determinants of NIV outcome in COPD patients are the presence of pneumonia and the level of serum albumin as an indicator of the patient nutritional status.

1. Introduction

Patients with acute respiratory acidosis caused by an exacerbation of chronic obstructive pulmonary disease (COPD) are the group that benefits most from noninvasive ventilation [1]. Its early use in patients with COPD who have mild respiratory acidosis (as low as pH 7.30) and mild-to-moderate acute respiratory failure (ARF) prevents further deterioration and thus avoids endotracheal intubation and improves survival compared with standard medical therapy [2]. "Real life" observational studies, performed outside specific RCTs, have shown on average a higher percentage of NIV failure than those performed in selected population [3, 4]. Most of the RCTs have enrolled, as a matter of fact, very selected population of patients. In particular subjects with some comorbidities like pneumonia, neurological and cardiac diseases, dementia, myocardial infarction, and severe obesity were excluded a priori from those studies [2, 5–7]. A recent study pointed out that COPD is not very often a "stand-alone" disease since comorbidities are frequent and 12 of them negatively influence the 4-year survival [8]. Whether the presence of chronic comorbidities could also influence the short-term mortality and the NIV success during an acute exacerbation of COPD was only partially investigated. Scala et al. in

2004 [9] showed that the presence of acute and chronic comorbidities negatively influences NIV outcome. On the other hand some acute comorbidities," such as pulmonary oedema, may per se cause of ARF [10]. At present little data is available regarding the "individual" effect of comorbidities, since their analysis was mainly performed as a group one (i.e., cardiovascular, noncardiovascular, metabolic, etc). In the present observational study we wanted to investigate the possible effect on NIV outcomes of (1) the etiology of ARF and (2) the overall number and "individual" chronic and acute comorbidities in COPD patients ventilated for an acute exacerbation of their disease.

2. Material and Methods

In an analysis of data collected prospectively and inserted in a database, we evaluated data collected from 176 consecutive patients with COPD exacerbation admitted over 36-month period to our 7-bed Respiratory Intensive Care Unit (RICU). COPD diagnosis was based on pulmonary function tests when available, otherwise on clinical history, physical examination, and imaging data (chest radiograph or HRCT scan) according to the 1987 ATS statement [11].

The protocol of the study was approved by the scientific committee of our institution. The ethical committee commented that the approval was waived since the patients at hospital admission must sign or not the consent that their medical records and "routine" examinations may be used for research proposals. We have analyzed only records of patients who agreed to sign.

Inclusion criteria were pH < 7.35 and a $PaCO_2$ > 45 mmHg with at least one of these three criteria: massive use of accessory muscles, respiratory rate > 20 breaths/min, and severe dyspnoea (Borg ≥ 5).

Exclusion criteria were (a) refusal of NIV; (b) facial deformity sufficient to affect mask fitting; (c) overt gastrointestinal bleeding; (d) upper airway obstruction; (e) acute ischaemic heart disease; (f) need for urgent intubation due to cardiac or respiratory arrest, prolonged respiratory pauses, and psychomotor agitation requiring sedation; (g) ventricular arrhythmia requiring treatment; (h) cerebrovascular accident. Postoperative patients were also excluded. All the patients first underwent standard medical therapy lasting about 45–60 min before initiating a trial of NIV.

2.1. NIV Settings. Patients were ventilated with pressure support ventilation (PSV) or pressure-controlled ventilation (PCV) using a full face mask or the helmet in few cases. The inspiratory pressure was adjusted according to the patient's tolerance to obtain an expired tidal volume of 7-8 mL/kg with external PEEP not exceeding 6 cmH_2O. ICU ventilators using NIV mode or dedicated NIV platforms (all of which allowed exhaled tidal volume to be recorded) were used. Flow and pressure curves were used to detect the possible occurrence of patient/ventilator mismatching. Trigger sensitivity was set usually at 5 L/min or the one imposed by the machine was used if setting was not possible. FiO_2 was set to achieve an SaO_2 of >90% and not >95%.

2.2. Definitions of NIV Success or Failure. Success was defined as the achievement of a clinical and functional condition stable enough to allow patient discharge to the ward.

Failure was defined, at any time during the RICU stay, as a sudden or progressive worsening of arterial blood gas tensions (pH < 20% of the last arterial blood gases with an increase in $PaCO_2$ of >15–20% compared with previous arterial blood gas tensions), dyspnea, and/or sensory deterioration while still on mechanical ventilation for at least 6 hours/day. Death while in the RICU was also considered as NIV failure.

The need of intubation in the failure group was decided by the attending physician, always according to our internal guidelines and/or clinical judgments and upon the criteria of failure above reported.

2.3. Measurements. The following variables were recorded in all patients: age, sex, SAPS II score severity illness defined as the worst value measured within the first 24 hours of RICU admission, Barthel index, blood gases analysis values at the admission, 2 hours after NIV institution, and at the time of RICU discharge (success group) or prior to intubation or death (failure group), and length of hospital stay before RICU admission.

Causes of acute respiratory failure were classified as follows: (1) pneumonia, (2) pulmonary embolism, (3) pneumothorax, (4) congestive heart failure, and (5) cardiogenic pulmonary edema.

Types and number of acute [12] and chronic [13] nonrespiratory comorbidities according to the Charlson index were recorded at hospital admission.

Other causes of chronic disorders, not included in the Charlson index, were also recorded, such as obesity (BMI > 35), diagnosed overlap syndrome, dysfunction of the diaphragm (assessed through imaging methods such as standard chest X rays, CT, and sniffing test, revealing elevation and hypomobility), pneumonectomy, and bedridden syndrome.

The primary end points of the study were to detect differences, if any, in the clinical variables at admission, in the two groups of patients (NIV success or failure), and to eventually depict a priori predictors of the NIV outcome.

2.4. Statistical Analysis. Descriptive statistics are expressed as mean and standard deviation (SD) for continuous variables and percentage for categorical variables. Demographic and comorbidities characteristics were compared among the two groups (NIV success or failure) on continuous variables using t-tests, on ordinal-level variables using the Mann-Whitney test, and on categorical variables using χ^2 tests or Fisher exact test, as appropriate.

Univariate and multivariate analysis and odds ratio (OR) were estimated with logistic regression for identifying the risk factors associated with NIV outcome, using the clinical variables illustrated in the Material and Methods. In particular a set of variables significantly associated with success in univariate analyses were included in a multiple logistic regression analysis. A P value less than 0.05 was considered

Table 1: Differences in the main demographic clinical and functional parameters between the two groups of patients. Values are expressed as mean ± standard deviation. SAPS: simplified acute physiology score, ABG: arterial blood gases, NIV: noninvasive ventilation, RICU: Respiratory Intensive Care Unit, LTOT: long term oxygen therapy, and HMV: home mechanical ventilation.

	42 NIV-failure	134 NIV-success	*P* value
Age (years)	81.05 ± 7.05	77.81 ± 9.27	**0.019**
Albumin (g/dL)	3.07 ± 0.48	3.54 ± 0.46	**0.047**
SAPS score	44.50 ± 10.24	37.28 ± 8.87	**<0.001**
Barthel score	7.95 ± 9.37	15.86 ± 17.77	**<0.001**
ABGs admission			
P/F (PaO_2/FiO_2 ratio)	193 ± 93.05	195 ± 71.07	0.862
$PaCO_2$ (mmHg)	73.60 ± 23.64	79.93 ± 19.27	0.080
pH	7.32 ± 0.09	7.28 ± 0.09	**0.015**
Days in hospital before RICU admission	9.21 ± 13.93	4.59 ± 8.79	**0.047**
LTOT	18/42	55/134	0.83
HMV	6/42	15/134	0.59

Table 2: Causes of acute respiratory failure.

	42 NIV-failure	134 NIV-success	*P* value
Pneumonia	20	29	**0.002**
Congestive heart failure	39	116	0.414
Cardiogenic pulmonary edema	16	48	0.855
Pulmonary embolism	2	3	0.594
Pneumothorax	3	7	0.704

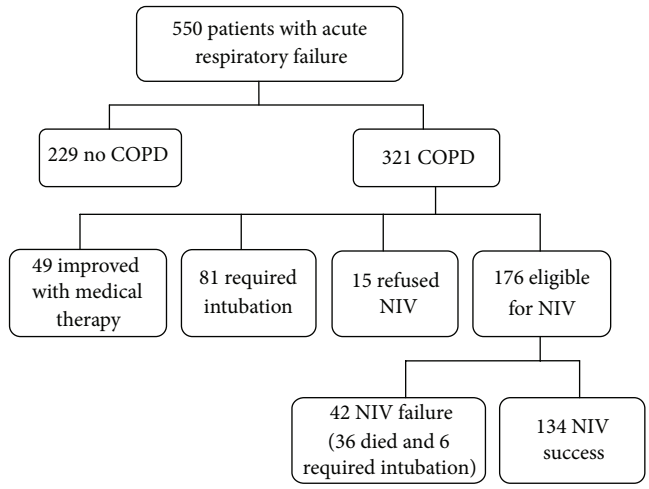
statistically significant. All statistical analyses were carried out using IBM SPSS Statistical Software, version 20.0.

3. Results

Figure 1 illustrates the patients flow through the study. A total of 550 patients were admitted in our RICU during the time period considered. Of these, 321 had COPD with acute or acute on chronic respiratory failure; the remaining 229 cases included patients without COPD and with respiratory failure caused by different conditions; 15 patients intolerant to NIV in the first hour of treatment were excluded from data analysis; 49 patients required oxygen therapy alone, while 81 required invasive ventilation (either via endotracheal tube or tracheostomy). A total of 176 patients were enrolled in the study; 134 were successfully ventilated with NIV and discharged alive, and 42 were considered NIV failure (36 deaths and 6 intubation). Causes of death in those patients (some patients presented more than one cause) were cardiogenic pulmonary edema (7), pneumonia (12), sepsis (8), atrial or ventricular arrhythmia (11), myocardial infarction (2), intestinal occlusion (1), pneumothorax (1), and lung cancer (2).

Overall patients characteristics' at the time of RICU admission are illustrated in Table 1. Patients failing NIV were significantly older, sicker according to the SAPS II score and albumin level, and with a lower degree of independence, as assessed by the Barthel index. Length of hospital stay before admission in RICU was also higher in the failure group.

Interestingly arterial blood gases (ABGs) on admission were not statistically different between the two groups.



COPD: chronic obstructive pulmonary disease
NIV: non-invasive ventilation

Figure 1: Patients flow through the study.

Table 2 shows the causes of ARF. Those patients failing NIV had a significantly higher number of pneumonia than those who succeeded.

Table 3 reports the numbers and types of acute and chronic comorbidities in the two groups of patients. Chronic heart failure was prevalent in both groups.

Dementia was significantly higher in the failure group. The presence of chronic renal failure was also higher in

the failure group, although the difference did not achieve a level of statistical significance ($P = 0.06$).

Overall, the number of chronic comorbidities was significantly higher in the failure group versus the successful one (Charlson score 4.12 ± 2.15 versus 3.46 ± 1.6, resp., $P = 0.035$). Figure 2 shows the ABGs changes after 2 hours of NIV and at the last measurement in the two groups. Interestingly, NIV failure group had a statistically higher pH on admission; they still had a significantly higher pH and also a lower $PaCO_2$ level after 2 hours of ventilatory treatment compared to the patients who succeeded, despite that the percentage changes were similar in the two groups. The level of blood bicarbonates was equally high at the onset in both subgroups (34.9 mMol/L and 34.03 mMol/L in the failure group and in the successful group, resp.; difference is not significant) with no significant changes after 2 hours of NIV; however, at the time of discharge the success group had significantly higher bicarbonates than the failure group (36 mMol/L versus 33.4 mMol/L, $P = 0.03$). The PaO_2/FiO_2 ratio was not different between the two groups. At the time of discharge from the RICU the success group had statistically better gas exchange parameters versus those patients who required intubation or died.

Four variables were significantly associated with NIV success on univariate analysis (SAPS II score, Charlson score, serum albumin, or presence of pneumonia) and were eligible to be entered in the multivariate analysis in addition to age, gender, and renal failure, which were almost statistically significant.

Table 4 shows that serum albumin and pneumonia retained a significant predictive value; in particular, probability of success increases by 5.6 times for every 1 g/dL increase in albumin serum level, while presence of pneumonia decreases the success probability by 61.8%.

4. Discussion

This observational "real life" study showed that the cause of ARF, pneumonia in particular, is the main determinant of NIV success in COPD patients, rather than the presence of comorbidities.

It is well known that many patients dying do so during a severe COPD exacerbation, when they experience acute respiratory failure [14]. There is general agreement that NIV may prevent further deterioration in gas exchange, dyspnoea, respiratory workload, and endotracheal intubation in patients hospitalized for exacerbations of COPD with rapid clinical deterioration [1, 2]. Unfortunately a considerable number of the patients receiving NIV (approximately 30%) still require endotracheal intubation or die [4].

Several studies have assessed possible determinants of NIV failure in COPD patients, and most of them concluded that the severity of gas exchange (i.e., $PaCO_2$ and pH in particular) at admission and its changes after 1 or 2 hours of ventilation are the major predictors of patients' outcome [12, 15].

More comprehensive risk chart for NIV failure has been also proposed including also other clinical parameters such as respiratory rate, severity score, and neurological status [15]. All these parameters are good markers of severity of the episode of ARF, and they may drive for sure the decision

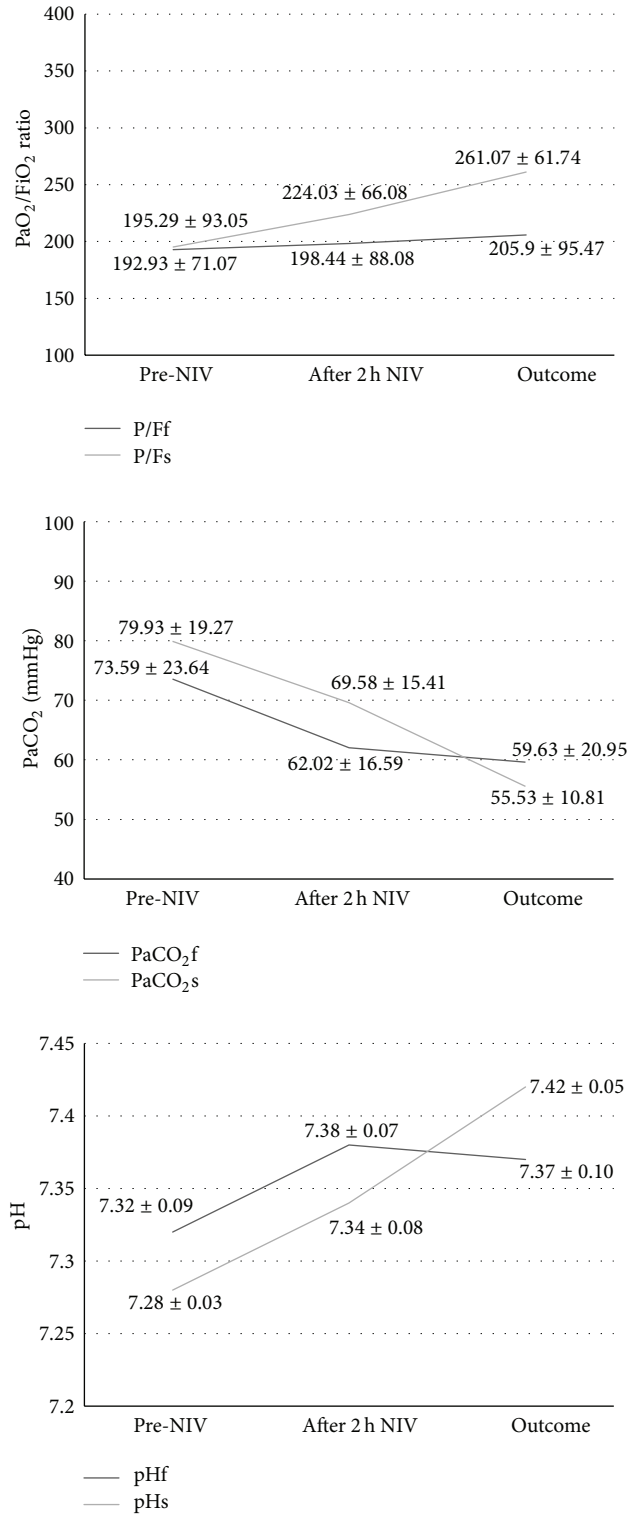


Figure 2: Arterial blood gases (ABGs) changes during the time course of the study. Outcomes mean discharge from the Respiratory Intensive care Unit (RICU) in the success group and death or time of intubation in the failure one.

Table 3: Numbers and types of acute and chronic comorbidities in the two groups of patients. Numbers in bold font represent the acute comorbidities.

	Total patients population (176 pts) *n* (%)	42 NIV-failure	134 NIV-success	*P*-value* (failure versus success)
Charlson comorbidities				
History myocardial infarction	26 (14.8)	2 (0.8)	24 (17.9)	/
Congestive heart failure	155 (88.1)	39 (92.9)	116 (86.6)	0.414
Peripheral vascular disease	20 (11.4)	5 (11.9)	15 (11.2)	1.00
Cerebrovascular disease	17 (9.7)	5 (11.9)	12 (8.9)	0.558
Chronic pulmonary disease	176 (100)	42 (100)	134 (100)	/
Dementia	25 (14.2)	11 (26.2)	14 (9.9)	**0.02**
Connective tissue disease	3 (1.7)	1 (2.4)	2 (1.5)	/
Peptic ulcer disease	8 (4.5)	1 (2.4)	7 (5.2)	/
Mild liver disease	3 (1.7)	2 (4.8)	1 (0.7)	/
Diabetes without end-organ damage	28 (15.9)	5 (11.9)	23 (17.2)	0.479
Hemiplegia	8 (4.5)	2 (4.8)	6 (4.5)	/
Moderate or severe renal disease	32 (18.2)	12 (28.6)	20 (14.9)	0.065
Acute on chronic	*8 (4.5)*	*5 (11.9)*	*3 (2.2)*	
Diabetes with end-organ damage	15 (8.5)	2 (4.8)	13 (9.7)	/
Glycemia > 200 mg/dL			*5 (3.73)*	
Tumor without metastases	11 (6.2)	1 (2.4)	10 (7.5)	/
Leukemia	1 (0.6)	1 (2.4)	0	/
Lymphoma	3 (1.7)	0	3 (2.2)	/
Moderate or severe liver disease	0	0	0	/
Metastatic solid tumor	6 (3.4)	4 (9.5)	2 (1.5)	/
AIDS	0	0	0	/
Others comorbidities				
Pulmonary embolism	5 (2.8)	2 (4.8)	3 (2.2)	0.594
Obstructive sleep apnea	10 (5.7)	1 (2.4)	9 (6.7)	0.455
Diaphragmatic paralysis	7 (4)	5 (11.9)	2 (1.5)	**0.009**
Fibrothorax	10 (5.7)	1 (2.4)	9 (6.7)	0.455
Bed-ridden syndrome	22 (12.5)	5 (11.9)	17 (12.7)	1.000
Obesity	28 (15.9)	2 (4.8)	26 (19.4)	**0.028**
Pneumothorax	10 (5.7)	3 (7.1)	7 (5.2)	0.704
Kyphoscoliosis	5 (2.8)	0	5 (3.7)	0.340
Pneumonectomy	2 (1.1)	0	2 (1.5)	1.000
Acute myasthenia	1 (0.6)	0	1 (0.7)	1.000

of the clinician to go further with NIV or pass directly to invasive ventilation, but they are overall epiphenomena of one or more underlying diseases. Surprisingly only very few studies have included in their analysis the importance of the cause of ARF [3] and/or the potential effect of the chronic comorbidities [9] that very often are present in COPD patients.

Concerning the cause of acute exacerbation, Seneff et al. [10] have demonstrated that they are not only necessarily related to a "simple" respiratory infection, but also to pneumonia, cardiovascular problems, pulmonary embolism, and pneumothorax. Concerning the effect of comorbidities, Divo et al. [8] have recently reported that easily identifiable comorbidities confer an independent risk of death when the patients are still in a phase of clinical stability. A large cross-sectional study performed in the USA has shown that, among other variables, more comorbidities conditions were independent risk factors for in-hospital mortality [16].

Only one study [9] so far investigated to our knowledge the role of comorbidities in determining NIV failure during an exacerbation of COPD. It divided the types of comorbidities into chronic or acute, and their prevalence was significantly higher in the NIV failure group. No study to our knowledge has so far attempted to assess the individual power of single comorbidities. The present study shows clearly that the main independent determinant of NIV failure was

Table 4: Multivariate analysis. OR = odds ratio. Probability of NIV success increases by 5.6 times for every 1 g/dL increase in albumin serum level, while presence of pneumonia decreases the success probability by 61.8%.

	OR	95% CI		*P*-value
		Inf	Sup	
Gender	0.566	0.243	1.318	0.187
Age	0.969	0.917	1.023	0.255
SAPS score	0.962	0.921	1.006	0.090
Albumin (g/dL)	**5.617**	**2.242**	**14.078**	**0.000**
Charlson index	0.938	0.717	1.227	0.639
Pneumonia	**0.382**	**0.161**	**0.902**	**0.028**
Renal disease	0.760	0.251	2.302	0.628

the presence of pneumonia at admission to the hospital, as a cause of ARF, and it accounted for >45% of these patients. Persons with comorbidities, COPD in particular, and elderly persons are at increased risk of pneumonia and of having a more complex illness [17]. The patients failing NIV were in our study on average significantly older and malnourished since their albumin level was lower, and, in this subset of individuals, mortality reached up to 30% [18].

In agreement with our data, the presence of pneumonia has been associated already as a predictor of NIV failure, together with lack of improvement of pH [3]. On the contrary in a randomized controlled trial [19] performed on selected patients with ARF caused by severe community-acquired pneumonia (CAP), NIV was associated when compared to medical treatment with a significant reduction in the rate of endotracheal intubation (zero percent) and duration of ICU stay only in the subgroup of COPD patients. The difference between the studies relies probably not only on the study design (RCT versus observational), but also mostly on the different population of patients; those in Confalonieri's study [19] were much younger and likely less severe. As of interest the presence of pneumonia was considered, in most of the RCTs performed in COPD, an exclusion criterion for the enrolment of patients, and this explains why very little attention has been paid so far to the "negative" predicted role of pneumonia in determining NIV success. In the present paper, due to difficulties in picking up the exact timing of diagnosis (ER stay before admission, etc.) we were unable to discriminate between CAP and HCAP, so we considered in the analysis the overall presence of pneumonia.

Overall the high prevalence of chronic comorbidities found in our population is in line with most of the previous studies performed during an exacerbation of COPD (42–97%) [20–22] but higher than in Scala's study [9], probably once more due to the older age of our sample and also the fact that, in Charlson index, COPD is per se accounted for as one of the comorbidities, and therefore all the enrolled patients scored at least 1 point, while this was not the case of the above mentioned investigation.

In general, as shown in Table 5, comparisons between the different studies are difficult on account of the heterogeneity in the patients populations in terms of age, the setting of the study (RICU [12], respiratory monitoring unit in a respiratory ward [9], ICU [10, 20], both hospital ward and ICU [22]), type of ventilatory treatment (noninvasive [9, 12, 20], invasive [10], no mechanical ventilation [21]), criteria used to assess severity (APACHE II [12, 20], APACHE III [9, 10, 22]), and, not least, the criteria employed to evaluate comorbidities (Charlson score [9], comorbidities included in the APACHE II [20] and III [10] scores, classes of comorbidities, e.g., cardiovascular and noncardiovascular [9], cardiac, pulmonary, metabolic, renal, gastrointestinal [12], etc.).

Among the Charlson comorbidities, the most prevalent in our study (obviously besides the chronic respiratory disease) was congestive heart failure (overall 88%, subgroups 93% and 86%, resp.) followed by renal failure (overall 18,2%, subgroups 28,6% and 15%); the prevalence of the other comorbidities was much lower.

The number of comorbidities was higher in our NIV failure group versus those patients who succeeded, but the predictive value of the Charlson index was very weak in the multivariate analysis and was not accounted for in the multivariate one. This is perfectly in agreement with Seneff et al. who demonstrated that the number of preexisting comorbidities was not a significant predictor of in-hospital mortality among patients admitted to the ICU [10]. In both studies the number of comorbidities itself may not have provided additional predictive power since we have examined a stratum of patients already at an elevated risk of death and not a broader range of disease severity due to the nature of our study performed in a RICU.

Interestingly some variables were statistically different in the two groups of patients. Dementia has a high prevalence in old ICU patients, most often associated with lack of physician awareness [23], and in our study was more prevalent in the failure group. Pisani et al. [23] documented no difference in outcomes from ICU care in older patients with and without dementia. Physical consequences of dementia predispose patients to infection, especially aspiration pneumonia [24, 25] and urinary tract infections [26]. This may have predisposed these patients to develop pneumonia that was therefore the leading cause of ARF. Another possibility of the higher percentage of patients in the NIV failure group is the lack of tolerance to NIV, although those patients intolerant to ventilation were excluded a priori from the analysis. Indeed our nursing team is specialized and trained to offer continuous care and support even for unconscious patients undergoing NIV.

Two rather common comorbidities were not associated with poor outcome of our patients. First obesity was surprisingly more prevalent in the success group. Many epidemiological studies have demonstrated that obesity is associated with higher morbidity and mortality rates in the general population [27, 28], but a more recent study demonstrated that BMI did not have a significant impact on mortality in ICU patients [29]. Obesity has been reported to increase respiratory muscle oxygen demand, with more oxygen being consumed for any given task compared to patients with normal weight, especially when undergoing an episode of

Table 5: Comparison between the different studies concerning COPD and comorbidities, highlighting the main differences in the patients population, methodology, and findings.

	Setting	Age (mean)	Ventilatory treatment	ABG pH $PaCO_2$ (mmHg) P/F	APACHE score (II or III)	Pts with more than 1 comorbidity (%)	Criteria to find comorbidity	Predictors of failure treatment and mortality
Dewan et al. (Chest 2000) [21]	Outpatients	66	No ventilatory treatment	—	—	87	Chronic comorbidities	Home oxygen therapy Rate of exacerbations Number of comorbidities
Connors et al. (AMJRCCM 1996) [22]	Hospital wards and ICUs	70	Generically mechanical ventilation (35% of pts)	7.36 56 211	(III) 39	97	Acute comorbidities (causes of COPD exacerbation) and number of chronic ones	APACHE score PaO_2/FiO_2, ADL, CHF BMI, cor pulmonale Causes of COPD exacerbations
Moretti et al. (Thorax 2000) [12]	RICUs	70	NIMV (100% of pts at admission) IMV (22% of NIMV failed pts)	7.23 85 —	(II) 22	45 (successful group) 70 (failure group)	Cardiac comorbidities and other complications (pulmonary, metabolic, renal, and gastrointestinal)	Haemodynamic variables Number of associated complications on admission ADL, ABG APACHE II, and age
Scala et al. (Intensive Care Medicine 2004) [9]	Respiratory monitoring unit in a respiratory ward	72	NIMV (100% of pts at admission) IMV (6% of NIMV failed pts)	7.28 78 183	(III) 61	40 (acute comorbidities) 20 (chronic comorbidities)	Acute and chronic comorbidities. Cardiovascular and noncardiovascular ones	Acute cardiovascular comorbidities (influence on NIMV failure) Acute comorbidities and chronic noncardiovascular ones (influence on 6-month mortality)
Nevins and Epstein (Chest 2001) [20]	ICUs	67	IMV (100% of pts)	7.27 68 92	(II) 13	42	Chronic comorbidities and those included in APACHE II	Need of mechanical ventilation APACHE II More than 1 comorbidity
Seneff et al. (JAMA 1995) [10]	ICUs	66	IMV (47% of COPD patients)	—	(III) 57	—	Chronic comorbidities included in APACHE III. Respiratory and nonrespiratory	APACHE III Length of stay before ICU admission

ARF, but they are also likely to respond faster to NIV than expected [30].

About 20% of the whole group of patients had complicated or noncomplicated diabetes, but this was not a determinant of success or failure. We have shown [12] previously that "late NIV failure" defined by deteriorating gas exchange was more frequent in patients with an initially raised blood sugar. More recently, in a relatively small study, Chakrabarti et al. [31] found that hyperglycaemia, even when defined at only one time point, was related to the final NIV outcome irrespective of the diagnosis of diabetes, use of insulin, or prior oral corticosteroid use. Unfortunately the timing of our recording of blood glucose was not standardized so that it was impossible to get "unbiased" data, since the level of glycaemia is affected by fasting and actual medical therapy. Indeed, also for the above mentioned reason, hyperglycaemia cannot be considered a comorbidity, but rather an indicator of distress.

Use of domiciliary NIV did not influence the outcome in our patients (among the failure group, 14.3% of patients were on home NIV versus 11.2% cases in the success group; difference is not significant).

Last, surprisingly in this investigation we were unable to demonstrate a predictive effect of ABGs on the NIV outcome. As a matter of fact the patients who successfully responded had a significantly lower pH on admission and retained a lower pH after 2 hours of NIV. At first sight the results are not in line with the findings of previous reports [15]. It is likely that in elderly patients with multiple comorbidities the pathogenesis of acidosis is multifactorial and this may account for the apparent worse initial response to ventilator treatment in the group that in the end fared better. The relatively low degree of acidosis (pH > 7.26 in both groups) may also explain the initial homogeneous improvement in both groups. The level of blood bicarbonates in the two groups was not significantly different at the onset and after 2 hours of NIV and was elevated, likely because in most cases the patients had already an underlying chronic respiratory failure, and also because in ER or even during ambulance transport to the hospital they may have been administered i.v. bicarbonates to buffer the acidosis; however the difference became significant at the last measurement, with the failure group exhibiting lower levels, perhaps indicating an earlier exhaustion of the kidney bicarbonate reabsorption capacity in these patients.

The difference in gas exchange became significant at the time of intubation or death (failure) versus discharge from the RICU (success), and it was particularly true for the PaO_2/FiO_2 ratio. This seems to indicate that the improvement in such complicated patients is not always apparent at the beginning of the ventilator treatment but occurs over a longer period of time during the RICU stay, making it more difficult to predict the outcome after only a few hours.

5. Conclusions

Our study has some important limitations. First, it is a single-center study, and therefore it may reflect a specific reality where the NIV team is skilled and used to managing a large number of patients/year, and therefore these data may not be generalized. Second, only a minority of patients obtained the microbiological origin of their pneumonia, so the different pathogens may have affected the outcome of the patients. Third, for some patients pulmonary function tests data was not available and the diagnosis of COPD was therefore clinical/radiological. Last, the criteria of intubation were not standardized a priori, as for an RCT, but we followed our institutional guidelines about this, and on the other hand we are confident that our data reflect the "real life" scenario, rather than the "selected world" of those mentioned studies.

In conclusion, in this observational study we have shown that, in an unselected group of patients with ARF due to COPD exacerbation, the number of chronic comorbidities is quite elevated, but we were unable to discriminate between those patients who succeed or fail an NIV trial. The cause of ARF, pneumonia in particular, is the major independent discriminant of NIV failure, while ABGs in this study were not initial indicators of success or failure.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Altered Pulmonary Lymphatic Development in Infants with Chronic Lung Disease

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Pulmonary lymphatic development in chronic lung disease (CLD) has not been investigated, and anatomy of lymphatics in human infant lungs is not well defined. *Hypothesis*. Pulmonary lymphatic hypoplasia is present in CLD. *Method*. Autopsy lung tissues of eighteen subjects gestational ages 22 to 40 weeks with and without history of respiratory morbidity were stained with monoclonal antipodoplanin and reviewed under light microscopy. Percentage of parenchyma podoplanin stained at the acinar level was determined using computerized image analysis; 9 CLD and 4 control subjects gestational ages 27 to 36 weeks were suitable for the analysis. *Results*. Distinct, lymphatic-specific staining with respect to other vascular structures was appreciated in all gestations. Infants with and without respiratory morbidity had comparable lymphatic distribution which extended to the alveolar ductal level. Podoplanin staining per parenchyma was increased and statistically significant in the CLD group versus controls at the alveolar ductal level ($0.06\% \pm 0.02\%$ versus $0.04\% \pm 0.01\%$, 95% CI -0.04% to -0.002%, $P < 0.03$). *Conclusion*. Contrary to our hypothesis, the findings show that there is an increase in alveolar lymphatics in CLD. It is suggested that the findings, by expanding current knowledge of CLD pathology, may offer insight into the development of more effective therapies to tackle CLD.

1. Introduction

Chronic lung disease (CLD), a result of combined oxidative and ventilator induced lung injury, is a major cause of respiratory morbidity in very low birthweight (VLBW) infants [1]. The major pathological findings of blood microvascular hypoplasia and arrested alveolarization [2–6] translate clinically into varying degrees of respiratory insufficiency and impaired pulmonary tissue fluid homeostasis [1, 7]. The latter has been attributed to capillary leak from injured vasculature [8–10] and, in the case of established CLD, increased capillary perfusion pressure from decreased vascular load and/or increased arteriolar muscularization [11].

It is known that maintenance of tissue perfusion homeostasis and response to interstitial fluid burdens in pathological states are dependent on an intact lymphatic system. With regard to the neonatal lung at risk for CLD, investigators have reported increased lymphatic congestion in autopsy lungs from human infants dying of respiratory distress syndrome (RDS) [12] and increased lymphatic flow in sheep models of early CLD [13]. While these studies describe increased reliance on the lymphatic system in the face of evolving CLD, lymphatic microvascular development as it relates to CLD is not known. Moreover, knowledge of anatomy of lymphatics in normal human lungs is limited, especially as there are no data from infant lungs based on immunohistochemical detection of lymphatics [14, 15]. A failure of adequate adaptation and/or development of the pulmonary lymphatic microvasculature may contribute to the pathomorbidity and mortality seen in established CLD.

Pulmonary blood microvascular development is linked with alveolar development and both are impaired in CLD [4, 5]. Since it is likely that blood and lymphatic vascular development in the lungs occur in parallel [16], we *hypothesized* that lymphatic hypoplasia would be present in lungs of infants with CLD when compared to that of

Table 1: Clinical variables of controls and infants with CLD.

	Controls		CLD*
	Qualitative	Quantitative	
Number	9	4	9
Gestational age, weeks	31 ± 6[a]	31 ± 4	26 ± 2
Postmenstrual age (PMA)	NA	NA	30 ± 2
Birth weight, kg	1.926 ± 1.2	1.474 ± 0.894	0.819 ± 0.222
Ventilator days	1.6 ± 1.0	1.7 ± 1.3	29.6 ± 19
Days lived	1.6 ± 1.0	1.7 ± 1.3	30 ± 16
% antenatal steroids	11	0	42
% surfactant	33	50	71
% RDS (moderate to severe)	0	0	71
% postnatal steroids	11	0	71
Cause of death			
Respiratory failure	0	0	3
Extreme immaturity (died in DR)	1	0	0
Intracranial hemorrhage, grade IV	1	0	0
NEC	0	0	2
DIC/other hemorrhage	2	1	1
HIE/encephalomalacia	3	2	0
Sepsis/pneumonia	1	1	1
Other	1	0	2

[a]Average ± standard deviation.
*Complete clinical data available for 7 CLD infants.

age-matched controls. The objectives of this study were to examine pulmonary lymphatic distribution in developing human lungs from normal and diseased infant lung tissue, and, importantly, to quantify and compare the abundance of lymphatic microvasculature at the acinar level in infants with CLD versus controls.

2. Materials and Methods

2.1. Subjects. A bank of formalin-fixed paraffin-embedded human infant lung autopsy specimens gestational ages 22 to 40 weeks was accessed. On initial selection, subjects were excluded if there was history of congenital anomalies known to affect the pulmonary system, prolonged rupture of membranes >3 days, severe bronchopneumonia, extensive pulmonary hemorrhage, and extreme intrauterine growth restriction. A sample size of eighteen infants was chosen (Table 1). It consisted of 9 infants who died from nonrespiratory causes within 48 to 72 hours of birth with only brief exposure to oxygen and/or ventilation and 9 infants of similar gestational age or postmenstrual age (PMA) at risk or with evidence of moderate to severe chronic lung disease (CLD) at the time of death. From this group, 13 infants with gestational or PMA of 27 to 36 weeks were chosen for quantitative study of acinar lymphatics. The control group consisted of four infants who died from nonrespiratory causes after 1.7 ± 1.3 days of birth at 31 ± 4-week gestational age with a low respiratory severity score [17]. The chronic lung disease (CLD) group consisted of nine infants with evidence of moderate (1 subject) to severe (8 subjects) CLD or at risk for CLD at the time of death after 30 ± 16 days at 30 ± 2-week PMA. CLD was defined as supplemental oxygen requirement at 28 days and those at risk identified as having an elevated respiratory score determined by multiplying the average daily FiO_2 by the average daily mean airway pressure (MAP) in cm H_2O and integrating the area under the curve, using the trapezoidal rule, for the total number of days lived [17].

This project was reviewed by the University of Missouri-Kansas City Children's Mercy Pediatric Institutional Review Board and received an exempt status.

2.2. Lung Preparation. Lungs were collected from 1988 to 2002. The time from death to autopsy was 15 ± 11 hours. Lungs from five of the subjects used in a previous study in our lab were infused with a heated barium-gelatin mixture at about 70 mm Hg pressure via the pulmonary artery until uniform surface filling of the lungs was appreciated and the pulmonary artery ligated at the infusion pressure. Lungs from the remaining 13 subjects were not barium infused. Both barium and nonbarium filled left lungs were deflated by vacuum, warmed to 38°C, and inflated via the trachea for 72 hours at 24 cm H_2O pressure with 10% formalin. Sections of the left lung were cut horizontally, 2-3 mm thick, from top to bottom of the lung. Ten to fifteen blocks were chosen at random from the slabs and paraffin embedded.

2.3. Immunohistochemical Methods. Three to five 5-μm thick sections of formalin-fixed, paraffin-embedded tissues were mounted on positively charged glass slides and placed in 60°C oven overnight (12 to 18 hours) then subjected to xylene

and graded concentrations of ethanol for dewaxing. Slides from all subjects underwent immune staining with monoclonal mouse anti-human podoplanin (Acris Antibodies, Hiddenhausen, Germany) using a modified avidin-biotin-peroxidase method [18]. Podoplanin was chosen for this study, as it appeared to have superior lymphatic specificity in lung tissue when compared to VEGFR-3, LYVE-1, and Prox-1 in a pilot study performed by our lab. 1 : 800, 1 : 400, and 1 : 200 dilutions of podoplanin antibody were tested first to determine optimal concentration to avoid over or understaining of which a 1 : 200 dilution was chosen. Slides were first deparaffinized with xylene twice for 3–5 minutes per pass, placed in 100% alcohol then 95% alcohol for 1–3 minutes per pass, and then rehydrated in deionized H_2O. Antigen retrieval was enhanced by steaming slides bathed in target retrieval solution (DAKO, Carpinteria, CA) for 20 minutes. After incubation with blocking serum (DAKO, Carpinteria, CA) for 10 minutes, slides were incubated with primary antibody for 1 hour. Endogenous peroxidase was quenched with hydrogen peroxide and slides were then incubated for 30 minutes with biotinylated IgG and avidin-biotin peroxidase complex (Vectastain ABC Elite Kit, Vector Laboratories, Burlingame, CA). Antigenic sites were visualized by the addition of the chromogen 3,3′ diaminobenzidine (DAB), keeping the time in which slides were exposed equal. The slides were then counterstained with Harris hematoxylin (Fisher HealthCare, Houston, TX). Negative control slides were stained using the same procedures omitting the primary antibody.

To confirm podoplanin specificity for lymphatic endothelial cells, slides from all subjects were also immunostained sequentially with a mouse anti-human podoplanin monoclonal antibody (Acris Antibodies GmBH, Herford, Germany) and a mouse anti-human CD31 monoclonal antibody (AbD Serotec, Raleigh, NC) using a polymerized reporter enzyme staining system (Vector Laboratories, Inc., Burlingame, CA). After xylene deparaffinization (2 × 3 minutes) and rehydration in graded alcohols to deionized water, antigen retrieval was performed by steaming slides bathed in target retrieval solution, pH 6.1 (DAKO corporation, Carpinteria, CA) 20 min then cooling 15 minutes at room temperature. Slides were rinsed in deionized water, then were incubated in 3% hydrogen peroxide to block endogenous peroxidase activity, and were blocked with 2.5% normal horse serum for 20 minutes. Sections were incubated with podoplanin antiserum (1 : 200) for 1 hour at room temperature, rinsed in phosphate-buffered saline, pH 7.4 (PBS), and incubated with a micropolymer of active peroxidase coupled to an affinity purified anti-mouse IgG (H + L) secondary antibody for 30 minutes at room temperature. After rinsing with PBS, antigenic sites were visualized by the addition of the chromogen (DAB). Slides were rinsed in tap water and again blocked with 2.5% normal horse serum for 20 minutes. The sections were then incubated with CD31 antiserum (1 : 50) overnight at 4°C. After rinsing with PBS, they were incubated with the same anti-mouse IgG reagent used previously for 30 minutes at room temperature. They were rinsed again with PBS and CD31 antigenic sites were visualized with ImmPACT VIP Substrate (Vector Laboratories, Inc.). Slides were rinsed with tap water and counterstained with methyl green (Vector Laboratories, Inc.).

2.4. Image Analysis. Slides stained with podoplanin alone were viewed under standard light microscopy at 4, 10, 20, and 40x magnification and assessed for quality of staining and histology. Specimens with mild to moderate evidence of lung injury were analyzed but those with extensive pulmonary hemorrhage, bronchopulmonary pneumonia, or poorly expanded or overdistended architecture were excluded. Slides from the thirteen subjects chosen for quantitative study were then viewed via light microscopy by an observer blinded to the gestation and clinical status of the subjects at 40x magnification. Lymphatic vessels associated with arterioles at the respiratory bronchiolar and alveolar ductal levels were identified in well-expanded regions in 40 to 60 consecutive fields per slide. Fields with conducting airways or large blood vessels filling more than 50% of the field were skipped. Lymphatic vessels in CLD samples were studied in regions exhibiting typical histological features of CLD including cystic areas and/or regions with thickened interstitium. Using standard image analysis software (analySIS, Soft Imaging System Corp., Lakewood, CO), images were photographed and converted to grey scale and parenchymal tissues with and without podoplanin staining were assigned different thresholds. As podoplanin had selectivity for type I alveolar epithelial cells in some specimens, any stained tissues other than lymphatic vessels were kept out of the field of interest for analysis. The percentage of parenchyma that was podoplanin stained was then measured. Parenchyma in this study included tertiary arterioles, saccules, alveolar ducts, alveolar walls, septae, and air. Measurements were performed on lymphatic vessels that appeared to be in cross-section and associated with an arteriole for better standardization. An analysis was not performed if vessels appeared to be in a significantly oblique or longitudinal orientation; there was too much background staining, artifact, or other positive staining structures in close proximity that could not be excluded from the area of interest. This approach was used to avoid overestimation of actual lymphatic tissue.

2.5. Statistical Analysis. Statistical analysis was performed using SPSS version 9.2 (SPSS, Inc.). The average percentage parenchyma and interstitial staining for each specimen was calculated. The average mean and 95% CI for difference in means were then determined between infants with CLD and controls. A P value < 0.05 was considered significant.

3. Results

3.1. Pulmonary Lymphatic Distribution in Infants 22- to 40-Week Gestation. Immunostaining of podoplanin in fetal and infant lung tissue displayed distinct lymphatic-specific staining with respect to other vascular structures regardless of gestational age or presence of lung injury. Specificity was confirmed with double immunostaining (Figure 1) with mouse anti-human podoplanin and mouse anti-human CD31 antibody which displayed lymphatic-specific staining

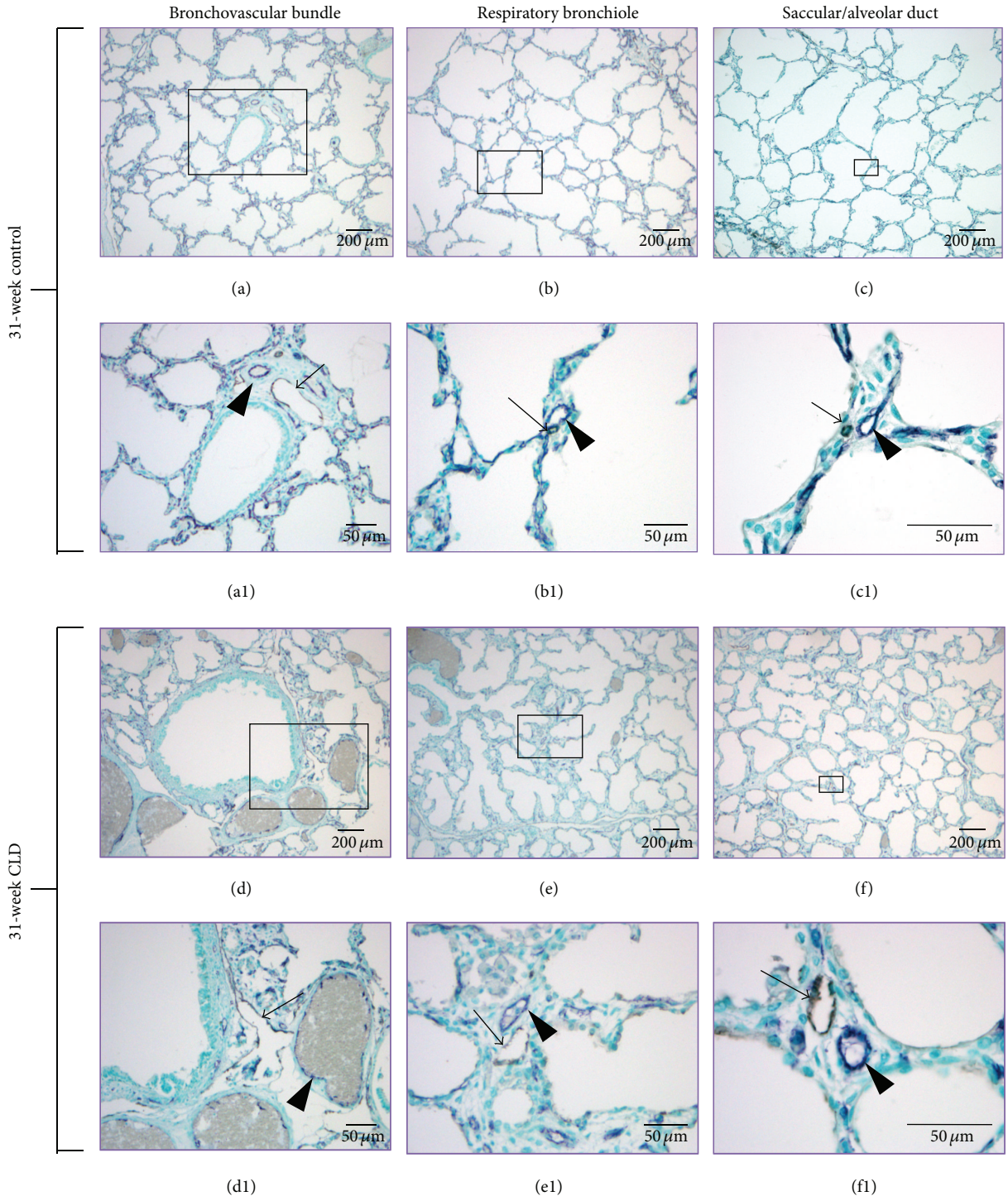

Figure 1: Lung specimens from a 31-week control infant ((a)–(c1)) and 31-week infant with moderate CLD ((d)–(f1)). Bronchovascular bundle ((a), (d) and (a1), (d1)), respiratory bronchiolar ((b), (e) and (b1), (e1)), and alveolar ductal ((c), (f) and (c1), (f1)) levels are displayed. ((a1), (b1), (c1)) and ((d1), (e1),(f1)) are higher magnifications (10x, 20x, 40x, resp.) of regions outlined in ((a), (b), (c)) and ((d), (e), (f)), respectively (magnification 4x). Slides are double immunostained with anti-human podoplanin and anti-human CD31 antibodies. Podoplanin and CD31 stains are selective for lymphatic and blood vasculature, respectively. Lymphatic vessels are stained brown (arrows) and are associated with arteries and arterioles. Arteries and arterioles are stained purple (arrowheads).

with podoplanin while other vascular structures (arteries, arterioles, capillaries, and veins) stained with CD31 only. In connective tissue sheaths supporting bronchovascular bundles (Figures 2(a), (a1), (d), (d1), (g), and (g1)) along with interlobular and pleural regions, lymphatic vessels are extremely dense, usually associated with blood vasculature and most have open lumens. In bronchovascular bundle sheaths, lymphatic vessels have extremely thin, irregular serpentine walls investing conducting airways and blood vasculature extensively (Figures 2(a), (a1), (d), (d1), (g), and (g1)). In interlobular planes, lymphatics investing venous structures are appreciated as well as single lymphatic vessels that traverse great lengths with occasional connections with lymphatic vessels from other regions. Lymphatic communication between bronchovascular bundles and interlobular planes can be appreciated. In addition to lymphatic vessels that are associated with veins, pleural tissue also possesses large, variably shaped lymphatics not associated with blood vasculature that occasionally connect with interlobular lymphatics. Lymphatic vascularization in all of these regions appears to be well developed even in the lowest gestational ages studied of 22 to 25 weeks.

Beyond connective tissue planes, lymphatic vessels are consistently associated with arterioles and extend peripherally from bronchovascular bundles as far as the saccular/alveolar ductal level (Figures 2(c), (c1), (f), (f1), (i), and (i1)). Lymphatic microvasculature at the alveolar ductal level is present in infants with and without a history of respiratory morbidity (Figure 3). Lymphatics become less extensive and their presence more variable moving peripherally from the terminal bronchiole to the alveolar ductal level. Lymphatic vessels at this level usually appear to have closed lumens with occasional communication with interlobular lymphatics. These connections are more apparent past 24- to 25-week gestation. More abundant lymphatic staining in peripheral regions of the lung is noted in advanced gestational ages (>30 weeks). No distinct interstitial staining is present within the alveolar septa with antipodoplanin antibodies at any gestational age or under different pathological conditions.

In addition to lymphatic vasculature, antipodoplanin antibody was found to be selective for bronchial-associated chondrocytes (not shown), mesothelium, and saccular/type I alveolar epithelial cells (Figures 2(b1) and (c1)). Interestingly, staining of the distal airway epithelium again became apparent in infants with gestations greater than 32 weeks with a history of respiratory morbidity. With the exception of the latter, staining of bronchial and mesothelial structures was independent of gestation or lung injury. Bronchial epithelial basement membrane occasionally stained in lower gestations (not shown).

3.2. Quantification of Pulmonary Lymphatics at the Acinar Level in Infants with CLD Compared to Age-Matched Controls. Average parenchyma podoplanin stained at the saccular/alveolar ductal level was increased and statistically significant in the CLD group compared to controls (0.06% ± 0.02% versus 0.04% ± 0.01%, 95% CI −0.04% to −0.002%, $P = 0.03$) (Figure 4). Staining at the respiratory bronchiolar level was also increased but not statistically significant in the CLD group versus controls (0.25% ± 0.03% versus 0.18% ± 0.05% CI −0.15 to 0.01, $P = 0.06$). Because interstitial thickening is seen in CLD and parenchymal measurements included air, the percent interstitium podoplanin stained was also calculated to see if podoplanin staining remained relatively increased in the CLD group. Average interstitium podoplanin stained remained increased at the respiratory bronchiolar and saccular/alveolar ductal regions in the CLD group versus controls but did not reach statistical significance (1.36% ± 0.37% versus 0.93% ± 0.4% CI −1.03 to 0.16, $P = 0.12$ for the respiratory bronchiolar level and 0.39% ± 0.13% versus 0.31% ± 0.17% CI −0.34 to 0.16, $P = 0.4$ for the saccular/alveolar ductal level).

Four of the nine infants with CLD did not receive surfactant (specimens were collected prior to 1990) and arguably may have worse histological abnormalities than those that did receive surfactant. An additional analysis was thus performed comparing only those infants with CLD that had received surfactant and control infants. This analysis continued to show increased parenchymal and interstitial podoplanin staining in the CLD group versus controls at the respiratory bronchiolar and saccular/alveolar ductal levels reaching significance at the alveolar ductal level with percent parenchyma stained (0.07% ± 0.02% versus 0.04% ± 0.01 CI −0.05 to −0.003, $P = 0.03$). Percent parenchyma stained at respiratory bronchiolar level in CLD group versus controls was 0.24% ± 0.3% versus 0.18% ± 0.05% CI −0.14 to 0.01, $P = 0.07$. The percent interstitium podoplanin stained in the postsurfactant CLD group versus controls was again increased in infants with CLD but did not reach significance (1.43% ± 0.31% versus 0.93% ± 0.4% CI −1.11 to 0.11, $P = 0.09$ at the respiratory bronchiolar level and 0.46% ± 0.12% versus 0.31% ± 0.17% CI −0.4 to 0.1, $P = 0.2$ at the alveolar ductal level).

4. Discussion

To our knowledge, this is the first study describing pulmonary lymphatic distribution in human infant lungs using podoplanin as surrogate marker to identify lymphatics. Moreover, we examined pulmonary lymphatic development in the setting of chronic lung disease (CLD) by quantifying podoplanin staining at the acinar level in subjects with and without CLD. In both pre- and postsurfactant era groups of CLD infants, podoplanin staining at the acinar level was increased when compared to age-matched controls. As lymphatic development in the face of CLD has not been previously reported, this finding adds to the current understanding of the pathology in CLD and thus may provide additional insight into the development of effective therapies for the condition.

Qualitative comparison of the infants with and without a history of respiratory morbidity revealed comparable temporospatial distribution of the pulmonary lymphatics into pleural, interlobular, bronchovascular, and acinar vessels at gestational ages 22 to 40 weeks. Those lymphatic networks within the pleura, interlobular septae, and connective tissue sheaths supporting bronchovascular bundles appeared well

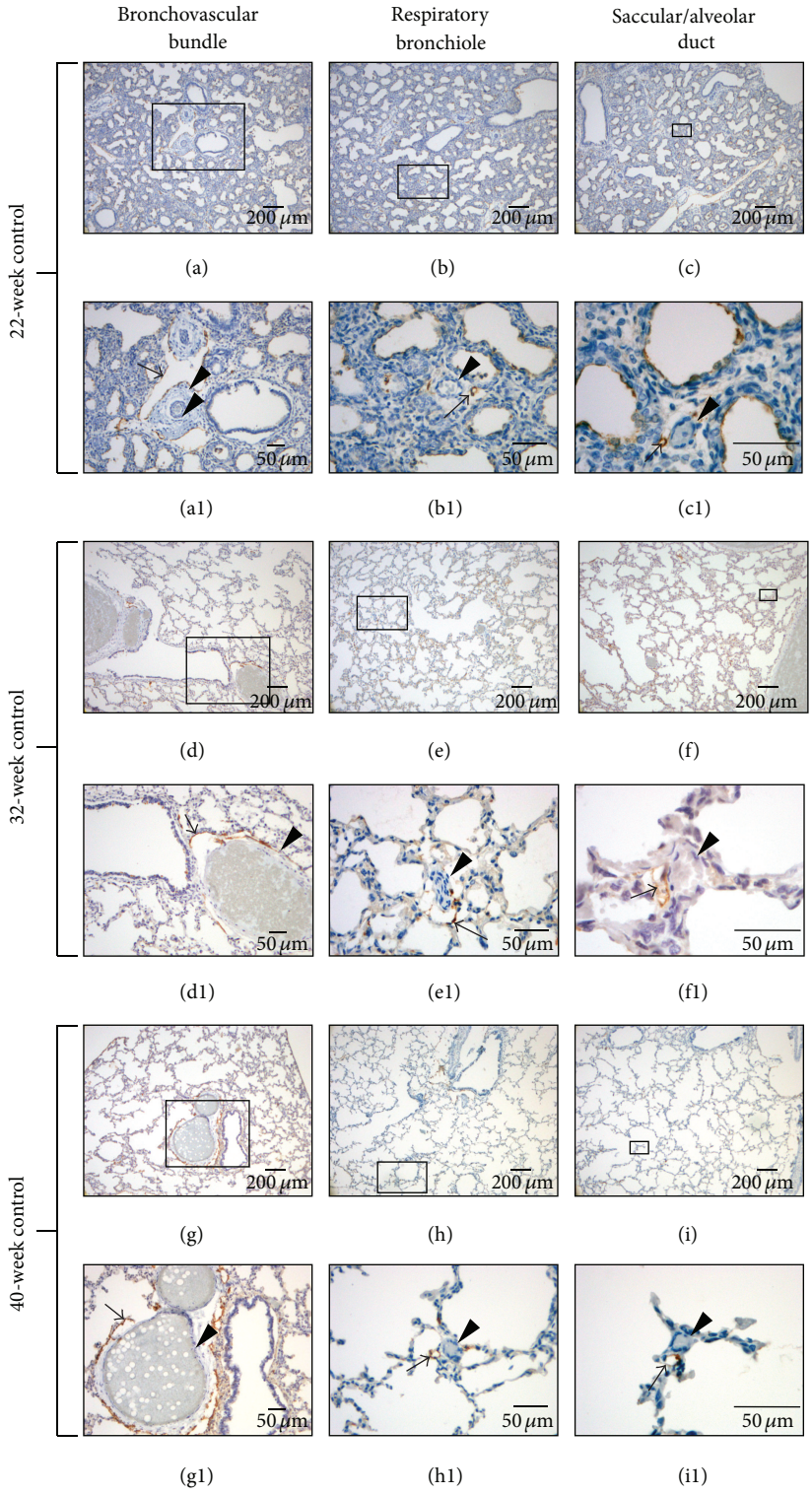

Figure 2: Pulmonary lymphatic distribution at the bronchovascular bundle ((a), (d), (g) and (a1), (d1), (g1)), respiratory bronchiolar ((b), (e), (h) and (b1), (e1), (h1)), and saccular/alveolar ductal ((c), (f), (i) and (c1), (f1), (i1)) levels in 22- ((a)–(c1)), 32- ((d)–(f1)), and 40- ((g)–(i1)) week gestation infants without a history of respiratory morbidity. ((a1), (b1), (c1)), ((d1), (e1) (f1)) and ((g1), (h1), (i1)) are higher magnifications (10x, 20x, 40x, respectively) of regions outlined in ((a), (b), (c)), ((d), (e), (f)), and ((g), (h), (i)), respectively (magnification 4x). Lymphatic vessels are stained with monoclonal mouse anti-human podoplanin antibody (arrows) and are associated with red blood cell or barium-filled arteries and arterioles (arrowheads). Lymphatics are well-developed at the bronchovascular and respiratory bronchiolar levels at all gestations with a paucity of staining in the distal parenchyma in the 22-week subject. Additional selectivity is seen with saccular epithelial staining in the 22-week subject ((b1), (c1)) that is absent in older gestational ages. Lymphatic staining is not appreciated beyond the alveolar ductal level in any gestation.

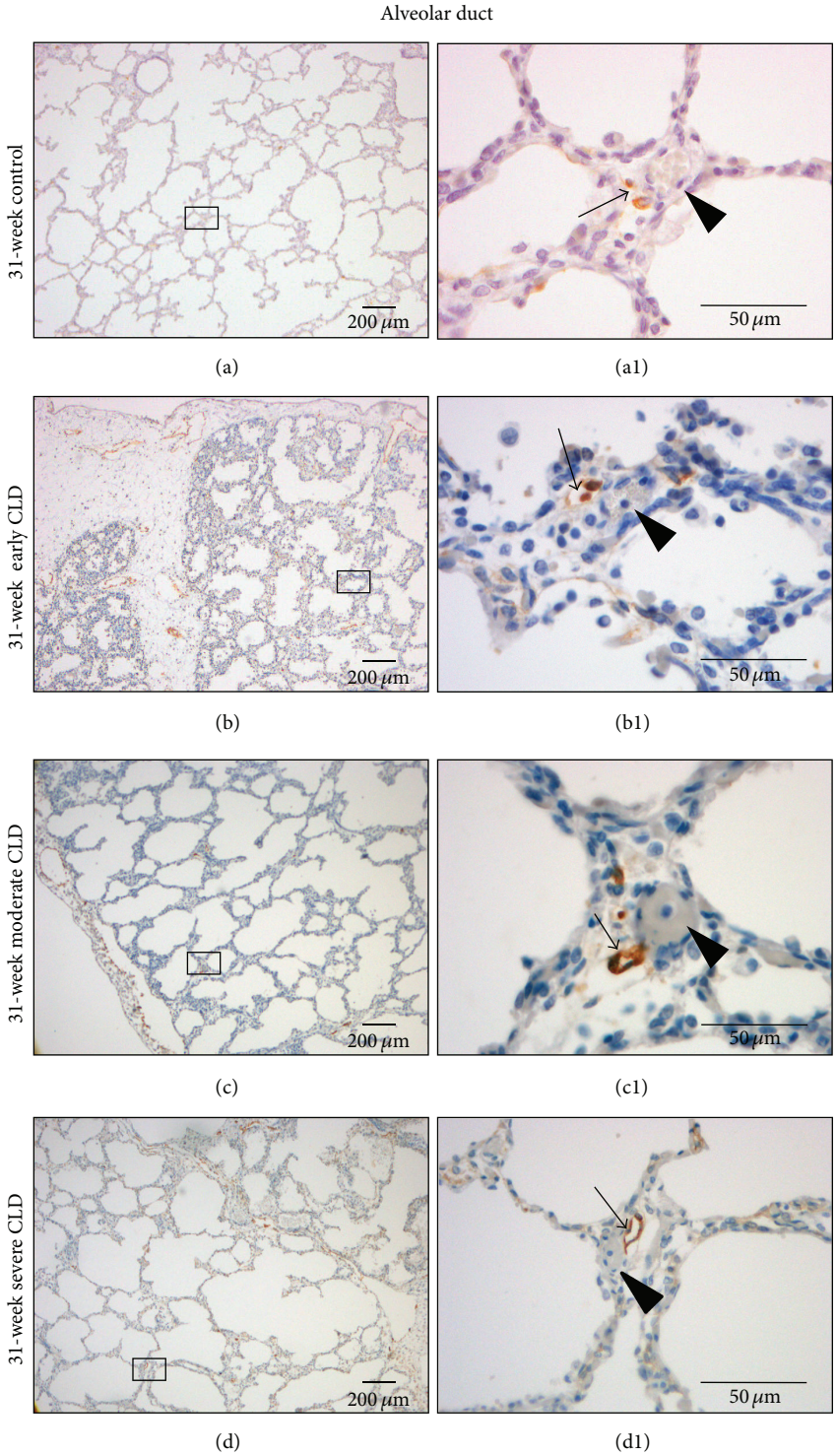

Figure 3: Lymphatic vascular staining with monoclonal antihuman podoplanin antibody at the alveolar ductal level in a 31-week infant without history of respiratory morbidity ((a), (a1)) and 3 infants with a postmenstrual age of 31 weeks with early CLD ((b), (b1)), moderate CLD ((c), (c1)), and severe CLD ((d), (d1)). ((a1), (b1), (c1), (d1)) are higher magnifications (40x) of regions outlined in ((a), (b), (c), (d)), respectively (magnification 4x). Note presence of interstitial thickening and presence of inflammatory cells in ((b), (b1)), decreased alveolarization ((c), (c1)), and cystic distortion ((d), (d1)) as CLD evolves. Lymphatic vessels (arrows) are associated with red blood cell or barium-filled arterioles (arrowheads).

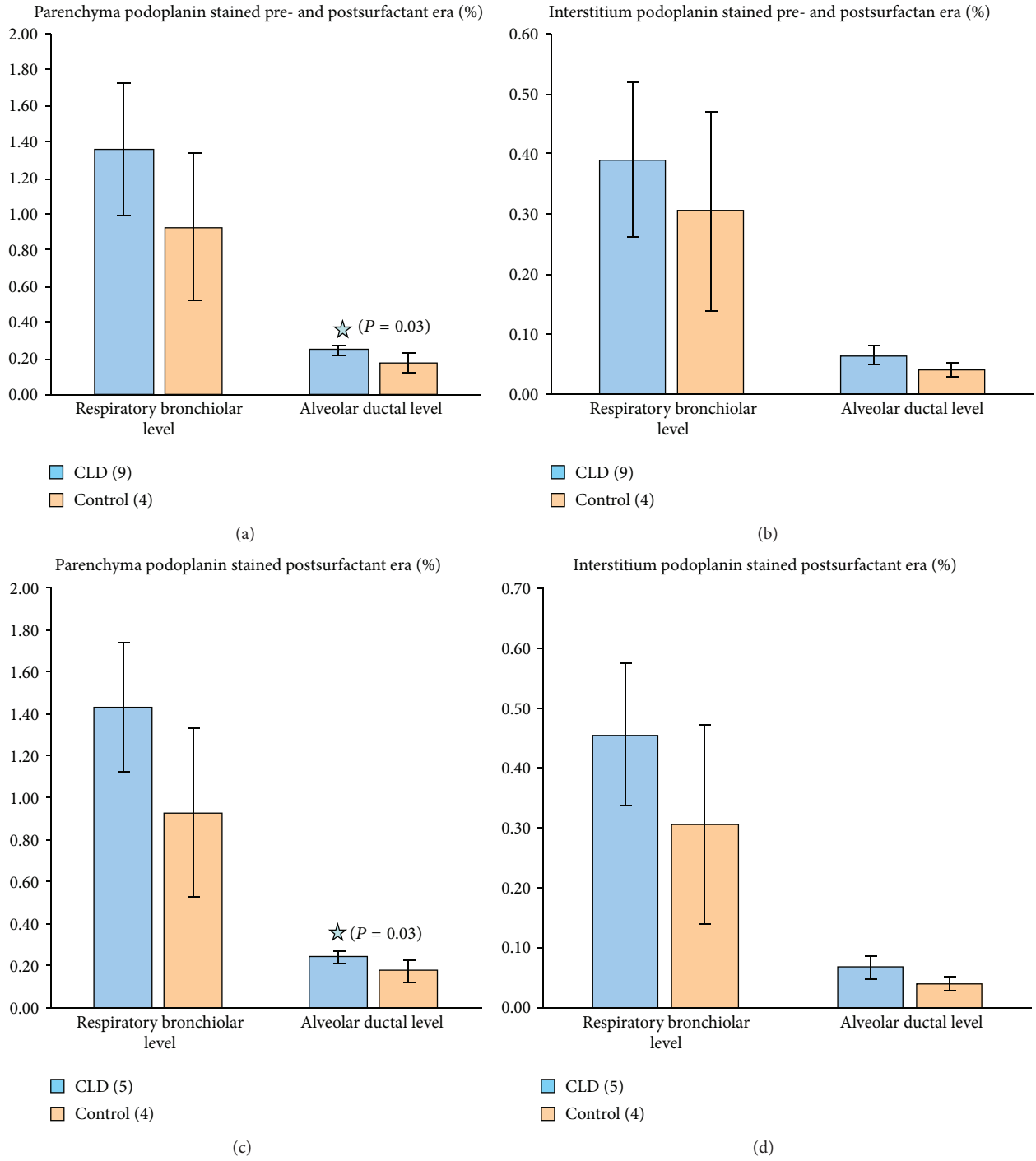

Figure 4: Percent parenchyma and interstitium podoplanin stained (representing lymphatic tissue) at the respiratory bronchiolar and alveolar ductal levels in infants with CLD versus controls. (a) and (b) include CLD infants from both pre- and postsurfactant eras; (c) and (d) include infants from postsurfactant era only. Podoplanin staining is consistently increased at both levels in infants with CLD reaching statistical significance at the alveolar ductal level with percent parenchyma stained ((a) and (c)).

developed even in the lowest gestational age of 22 weeks. This degree of development is not surprising considering that the bronchopulmonary segments are complete by 16 to 18 weeks and there is evidence that airway, vascular, and lymphatic development occur in a coordinated fashion [16, 19]. Consistent with reports from adult lung studies [14, 15, 20–24], we find lymphatic vessels extended no further than the alveolar ductal level with the air blood barrier devoid of lymphatics regardless of age or presence of injury.

Quantitative study of lymphatic vascularization in infants with CLD versus age-matched controls was directed at the acinar level where oxidative and positive pressure-induced injury has the most deleterious effect in preterm lungs. The increased podoplanin staining that we observed at this level in CLD infants compared to controls suggests that increased lymphatics are present. Mechanisms driving this may include either neoproliferation or recruitment of existing lymphatics.

Lymphangiogenesis, or the growth of new lymphatic vessels, is orchestrated by Prox-1, a homeobox transcription factor, and vascular endothelial growth factors (VEGF) C and D [25–27]. Pulmonary lymphangiogenesis outside normal development has been observed as a response to chronic inflammatory processes associated with transplantation, wound healing, and tumor growth/metastasis [28, 29]. Indeed, it was recently reported that COPD patients have increased number of alveolar lymphatics [30, 31]. Increased lymphangiogenesis in the setting of CLD may follow a similar pathway as key inflammatory mediators such as NF-kappaB [32] and elevated numbers of VEGF-C producing alveolar macrophages have been demonstrated in tracheal aspirate fluid from premature infants that later develop CLD [33].

In addition to proliferation, the apparent increase in lymphatics observed in infants with CLD may alternatively be due to the recruitment of existing lymphatic vessels. Functional impairment of fluid homeostasis may be related to the loss of normal architecture and elastic properties of the lung upon which lymphatics rely for effective uptake and removal of fluids. In this case, the capacity of an otherwise normal lymphatic system may be exceeded [22]. Illustrating recruitment of lymphatic reserves in the event of acute or chronic lung injury, scanning electron microscopy (SEM) studies of rat lungs following ventilator-induced injury have displayed identical lymphatic structures in both acute and chronic states of pulmonary edema [34]. In addition, lymphatic vessels in this and other studies have been identified by airway or vascular perfusion with plastic resinous compounds that do not reliably dilate microlymphatics in normal as opposed to the inflamed lung [34, 35]. These observations suggest that only a fraction of the existing lymphatic system's capacity is utilized for routine maintenance of pulmonary fluid homeostasis. If podoplanin expression is linked to the degree of lymphatic function, increased podoplanin staining in infants with CLD could simply signify the number of lymphatic vessels in use.

Despite podoplanin's lymphatic specificity relative to other vascular structures in our study lungs, saccular/type I epithelial cells were also found to stain positively with specific temporal and pathological patterns. T1-alpha, a podoplanin homolog estimated to be 50% identical at the nucleotide level [36], is present exclusively in type I epithelial cells in mice at all levels of development. In our study of human lung, however, staining of saccular/type I alveolar cells was seen consistently in gestations ≤24 weeks or in the presence of severe lung injury with otherwise sparse to no staining after 32-week gestation.

From a developmental standpoint, podoplanin may contribute to the transition and maturation of cuboidal epithelial cells to a more flattened type I phenotype [37–40] and/or contribute to secondary septation in those infants ≤24 weeks. With regard to lung injury, hyperoxia exposure in the rat lung has been associated with an increased expression of the podoplanin homolog T1-alpha [41], and in the mouse lung, increased T1-alpha staining of Type I alveolar cells [42]. If conserved expression of podoplanin exists in human saccular or Type I alveolar cells with exposure to hyperoxia, the staining patterns in this study support upregulation of podoplanin in the presence of lung injury specifically in RDS and CLD.

Although pulmonary vascular hypoplasia is predominately thought to be a major finding in CLD [2–6] other studies suggest that while microvasculature remains dysmorphic, remodeling of the remaining septae may establish a normal capillary load [43, 44] and eventually pulmonary function in infants with CLD. While our study compliments this notion from a lymphatic standpoint, other structural differences in CLD may have influenced our findings. As many of the distal acinar structures have been obliterated or developmentally interrupted in CLD, it is the more proximal structures that are left behind to adapt. In our study, it is possible that the more distal acinar structures in control subjects have been compared to the adapted proximal structures in the CLD subjects potentially making the amount of acinar lymphatic tissue in CLD appear larger. This raises the question as to whether an adaptation has really taken place (by way of proliferation) and may still imply a relative paucity of acinar level lymphatics when considering the lung parenchyma as a whole.

Several other limitations of this study exist which first include the small sample sizes for both control and CLD groups. Obtaining optimally preserved, nonedematous human autopsy specimens is challenging at best making even the control subjects suboptimal representatives of "normal" lung tissue. In addition, a more appropriate control group for the subjects with severe CLD used in our study would be those infants with mild or moderate CLD born at similar gestational ages. There is naturally a paucity of midgestation infants falling in this category however due to improved survival. This study also only represents those infants with CLD that died which makes the finding of increased lymphatics difficult to extrapolate to those that survived.

Podoplanin staining of other lung structures in this study poses a limitation to accurate measurement of lymphatics. Although other stained structures were kept out of the field of interest, this may have affected the relative amount of interstitium included in the measurement especially for the CLD infants as they tended to have increased Type 1 alveolar cell staining. This approach potentially overestimates the amount of podoplanin staining per interstitium.

A larger number of subjects studied under rigorous stereologic techniques will be needed to overcome many of these limitations.

5. Conclusion

This study shows that chronic lung disease is associated with increased lung lymphatics at the alveolar ductal level.

As lung lymphatic vascularization in the face of CLD has not been previously reported, it is suggested that this observation not only adds to the current understanding of the pathology in CLD but may also open insight into new therapeutic approaches to tackle the condition.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

The Influence of Comorbidities on Outcomes of Pulmonary Rehabilitation Programs in Patients with COPD: A Systematic Review

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Introduction. Chronic obstructive pulmonary disease (COPD) is associated with comorbidities such as cardiovascular disease, metabolic disease, osteoporosis, and anxiety and/or depression. Although pulmonary rehabilitation programs are proven to be beneficial in patients with COPD, it is unclear whether comorbidities influence pulmonary rehabilitation outcomes. The aim of the present review was to investigate to what extent the presence of comorbidities can affect pulmonary rehabilitation outcomes. *Methods*. The systematic literature search (Pubmed, EMBASE, and PEDro) resulted in 4 articles meeting the inclusion criteria. The odds ratios (95% confidence intervals) of the logistic regression analyses, with comorbidities as independent variables and pulmonary rehabilitation outcomes (dyspnea, functional exercise capacity, and quality of life) as dependent variables, were used for data extraction. *Results*. Patients with anxiety and/or depression less likely improve in dyspnea. Osteoporosis is associated with less improvements in functional exercise capacity, while cardiovascular disease does not seem to negatively impact on this outcome. Patients with cardiovascular comorbidity will experience less positive changes in quality of life. *Conclusion*. Evidence from literature suggests that comorbidities can have a negative influence on pulmonary rehabilitation outcomes. Screening for comorbidities in pulmonary rehabilitation settings seems useful to readdress the right patients for individually tailored pulmonary rehabilitation.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is often described as a multicomponent syndrome, characterized by pulmonary and extrapulmonary consequences [1–3]. The pulmonary component of the disease is characterized by airflow limitation and chronic inflammation and typically gives rise to symptoms of cough, sputum production, and dyspnea [2]. The origin of the extrapulmonary consequences or comorbidities in COPD, which are prevalent alongside the disease spectrum [3–6], remains unclear. However, a lot of possible mechanisms have been suggested in literature. Systemic inflammation, inactivity, and deconditioning seem to have an important role in the development of these comorbidities [4, 7]. Cardiovascular disease, metabolic disease, osteoporosis, and anxiety and/or depression are the most frequently reported [1, 4, 6, 8, 9]. For all these conditions, rehabilitation and more specifically exercise training are indicated [10]. Pulmonary rehabilitation programs, generally consisting of both exercise training and strength training, are part of nonpharmacological interventions improving dyspnea, exercise capacity, quality of life, the amount of hospitalizations, and the recovery afterwards in patients with COPD [11–13]. Comorbidities increase the complexity of individual patients as evidenced by increased hospital admission rates and mortality [1–3]. It is, hence, plausible that conventional pulmonary rehabilitation may be more difficult in patients with comorbidities. On the other hand, the room for improvement may be larger in patients with COPD and comorbidity [14].

Literature does not provide clarity about the role of comorbidities on the success of pulmonary rehabilitation programs in patients with COPD. The aim of the present systematic review was to summarize the relevant literature on this topic, with the following research question: "Do comorbidities in COPD have an impact on outcomes of pulmonary rehabilitation programs"?

2. Material and Methods

This systematic review adhered where possible to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement on developing a systematic review [15].

2.1. Inclusion Criteria. Studies meeting the following criteria were included. (1) The study included stable patients with COPD (GOLDI-IV). (2) The patients with COPD should be screened in terms of comorbidities before starting pulmonary rehabilitation or comorbidities should be collected from medical records. (3) Comorbidities should include cardiovascular disease (ischemic heart disease, heart failure, and hypertension) and/or metabolic disease (diabetes, dyslipidemia, and obesity) and/or osteoporosis, and/or anxiety and/or depression. (4) The study predicted the outcomes of standard outpatient rehabilitation programs, that is, dyspnea, exercise capacity, or quality of life. Reviews were not selected, but references were hand-searched for relevant literature.

We did not report muscle weakness as a comorbidity in the present review as it can be assumed that muscle weakness is most likely present in those patients referred for pulmonary rehabilitation.

2.2. Search Strategy. A systematic electronic literature search was performed in Pubmed, PEDro (Physiotherapy Evidence Database), and EMBASE (Excerpta Medica dataBASE). The search terms we used included COPD, comorbidities or extrapulmonary comorbidities, and rehabilitation. In PEDro, the search was performed by indicating COPD, fitness training, and cardiothoracics in the proposed key terms. A more detailed description of the search strategies is depicted in Table 1. Reference manager 11 was applied to combine all the records from the three databases, to exclude duplicates and to provide information about the title and abstracts for abstract screening. The review team consisted of two reviewers (MH and HVR), who screened the title and abstract of the retrieved articles. Papers that met all in- and exclusion criteria were labeled as "1," other articles were excluded and labeled as "0." When disagreement occurred, MH and HVR re-evaluated the specific records, discussed them, and gave a final score in consensus. Additional articles were picked up by reviewing the reference list of relevant articles (hand-search). Articles which were labeled as "1," were selected for full text assessment to check if they met the predetermined in- and exclusion criteria.

2.3. Data Extraction. From each article, we extracted the study design, the type of analysis and the disease severity.

Table 1: Search strategy for the three different electronic databases.

Pubmed	(((((COPD) OR Chronic Obstructive Pulmonary Disease) OR Chronic Obstructive Pulmonary Disease [MeSH Terms])) AND (((Comorbidities) OR (Co-morbidities) OR Extrapulmonary comorbidities)) AND ((Rehabilitation) OR Rehabilitation [MeSH Terms]))
PEDro	((COPD) AND (Fitness training) AND (Cardiothoracics))
EMBASE	(("COPD" exp OR COPD) AND (("Comorbidities") OR ("Co-morbidities") OR "extrapulmonary Comorbidities") AND ("Rehabilitation" exp OR Rehabilitation))

The content of the rehabilitation program described in each article was used. The specific comorbidities, their prevalence and the outcomes of pulmonary rehabilitation were extracted and the odds ratio (95% confidence interval (CI)) from each logistic regression analysis was retrieved to investigate the impact of comorbidities on outcomes of pulmonary rehabilitation. If the odds ratio was not calculated, but the author did report the β-coefficient (standard error (SE)) from the logistic regression analysis, we calculated the odds ratio (OR) with the formula: $\text{OR} = e^{\beta}$. The lower limit of the 95% CI of the odds ratio was then found based on $\beta - 1.96 * \text{SE}$ and the upper limit of the 95% CI based on $\beta + 1.96 * \text{SE}$. When only the β-coefficient without SE was presented, the author was contacted to become the 95% CI of the OR. A significant OR < 1 indicates that the presence of the specific comorbidity leads to a lower chance of improving in the outcome investigated. With a significant OR being higher than 1, it is more likely that the presence of the comorbidity leads to improvement in the outcome of pulmonary rehabilitation.

3. Results

The systematic review resulted in 4 articles, involving a total of 3595 stable patients with COPD. The majority of patients ($n = 2962$) came from one study [16]. The flow chart of the results of the search strategies and the study selection are shown in Figure 1. Comorbidities were either retrieved from the medical record of the patients [16, 17] or were identified based on the Charlson Comorbidity Index [16, 18–20]. All articles reported comorbidities to be prevalent among patients with COPD, with a mean percentage of 70% of patients having one or more comorbidities. Pulmonary rehabilitation programs were supervised and involved either strength training or both strength and whole body exercise training. In 2 out of 4 articles, pulmonary rehabilitation programs were multidisciplinary [17, 18]. One article reported patients to be referred to standard outpatient rehabilitation, with no detailed description of the program [20]. None of the articles provided a description of the modifications of the goals of the program or the program content, taking into account the specific comorbidities. The pulmonary rehabilitation programs were beneficial in both patients with and

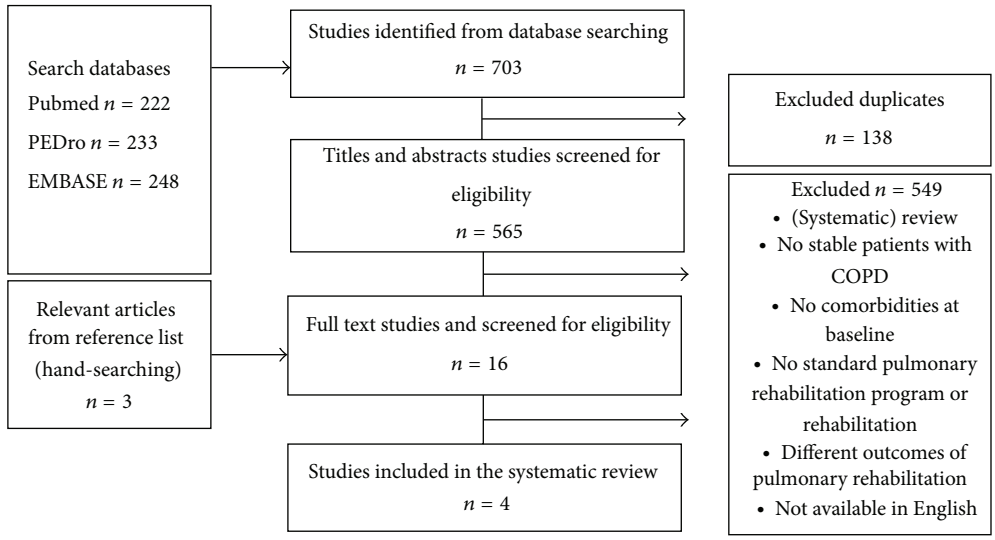

Figure 1: Flow chart of the results of the search strategies and study selection.

without comorbidities. However, the improvements in dyspnea and health status were significantly less in patients with comorbidities, with patients diagnosed with more comorbidities achieving the least improvements [16]. Details about the comorbidities, the content of the pulmonary rehabilitation programs, the specific outcomes, and the response rates of the included articles can be found in Table 2. Table 3 provides an overview of the obtained odds ratios (95% CIs) of the logistic regression analyses. More specifically, we concluded that patients with COPD and anxiety and/or depression have a 10 times higher chance of not reaching the minimal clinically important difference (MCID) in *symptoms of dyspnea* [17]. On the other hand, Crisafulli et al. [16] showed that having metabolic disease is associated with a higher chance of improving the symptoms of dyspnea and that osteoporosis is associated with a lower chance of improving the symptoms of dyspnea. However, these results were not significant. Improvements in *functional exercise capacity* were 4 times lower in patients with osteoporosis [18] and 2 times higher in patients with cardiovascular disease [16]. There was no consistency regarding the association between metabolic disease and functional exercise capacity, since 3 studies showed different results [16, 17, 20]. Patients with cardiovascular and metabolic disease will improve less in terms of *quality of life* [16, 17]. The relation between metabolic disease and quality of life did not show significance, while the association between cardiovascular disease and quality of life was found to be significant in the 2 studies [16, 17].

4. Discussion

The primary aim of our review was to summarize the literature concerning the impact of comorbidities on the outcomes of pulmonary rehabilitation. We found that the presence of comorbidities can have a negative influence on some outcomes of pulmonary rehabilitation. Overall, however, data are scarce. In detail, our review indicated that patients with symptoms of anxiety and/or depression are less likely to improve in dyspnea. In addition, patients with osteoporosis were found to improve less in terms of functional exercise capacity and patients with cardiovascular disease to improve more in functional exercise capacity. The findings on metabolic disease were inconsistent. Lastly, we found less positive changes in quality of life in patients with cardiovascular disease. A formal meta-analysis was not possible due to heterogeneity of the methods and the outcomes.

The present study contains several limitations. First of all, the majority of studies were retrospective, which could have impacted on the accuracy of collecting comorbidities. Another limitation was that we only included studies reporting odds ratios to show associations and studies providing data on improvements in pulmonary rehabilitation outcomes. Therefore, studies looking at comorbidities and outcomes in a different way were not withheld [19, 21–25]. The study of von Leupoldt et al. [25] confirmed our findings that anxiety and/or depression are associated with more symptoms of dyspnea. They showed that anxiety was positively associated with symptoms of dyspnea at rest ($\beta = 0.18$; $P < 0.01$), measured by the Borg scale before performing a 6MWD test. Both anxiety and depression were associated with more symptoms of dyspnea at baseline, measured by the Baseline Dyspnea Index ($\beta_{\text{anxiety}} = -0.25$; $P < 0.001$; $\beta_{\text{depression}} = -0.35$; $P < 0.001$) and after the 6MWD ($\beta_{\text{anxiety}} = 0.15$; $P < 0.05$; $\beta_{\text{depression}} = 0.22$; $P < 0.05$). Vanfleteren and colleagues [19] rejected the fact that cardiovascular disease is associated with higher levels of functional exercise capacity, by showing a negative association between ischemic heart disease and 6MWD ($\beta = -0.11$; $P = 0.007$). Mentz et al. [21] were not able to show significant different associations between either patients suffering from cardiovascular disease, that is, heart failure and COPD, or patients only diagnosed with COPD and outcomes of pulmonary rehabilitation. Trappenburg et al. [24] focused on maximal work rate, functional exercise capacity, and quality of life as dependent variables.

Table 2: Detailed description of each individual article.

Author	Subjects	Analysis (study design)	Disease severity (mean FEV_1 (% predicted))	Comorbidity(ies) investigated	Detailed prescription of pulmonary rehabilitation program	Outcome(s) study	Response rates in patients with comorbidities (% of patients reaching MCID)
Carreiro et al. [17]	$n = 114$	Retrospective (observational cross-sectional study)	46 ± 17	(i) Cardiovascular disease (68%) (ii) Metabolic disease (71%) (iii) Osteoporosis (11%) (iv) Anxiety and depression (21%)	(i) Period: 8 weeks (3*x*/week) (ii) Duration/session: 30–45 minutes (iii) Intensity endurance training: 80% PWR	(i) Dyspnea (MDI) (ii) Functional exercise capacity (6MWD) (iii) Quality of life (SGRQ)	(i) Dyspnea: 49% (ii) Functional exercise capacity: 63% (iii) Quality of life: 63%
Crisafulli et al. [16]	$n = 2962$	Retrospective (observational cohort study)	49 ± 15	(i) Cardiovascular disease (24%) (ii) Metabolic disease (62%) (iii) Osteoporosis (7%)	(i) Period: 20 sessions (3*x*/week) (ii) Duration/session: 3 hours (iii) Intensity endurance training: 70–80% PWR (iv) Strength training upper/lower body	(i) Dyspnea (MRC) (ii) Functional exercise capacity (6MWD) (iii) Quality of life (SGRQ)	(i) Dyspnea: 82% (ii) Functional exercise capacity: 60% (iii) Quality of life: 58%
Crisafulli et al. [18]	$n = 316$	Prospective (observational cohort study)	50 ± 14	(i) Cardiovascular disease (21%) (ii) Metabolic disease (56%) (iii) Osteoporosis (10%)	(i) Period: 21 sessions (3*x*/week) (ii) Duration/session: 3 hours (iii) Intensity endurance training: 70–80% PWR (iv) Strength training upper/lower body	(i) Dyspnea (MRC) (ii) Functional exercise capacity (6MWD) (iii) Quality of life (SGRQ)	(i) Dyspnea: 68% (ii) Functional exercise capacity: 60% (iii) Quality of life: 63%
Walsh et al. [20]	$n = 203$	Retrospective (observational cohort study)	53 ± 22	(i) Cardiovascular disease (32%) (ii) Metabolic disease (28%) (iii) Osteoporosis (12%)	No detailed information	Functional exercise capacity (6MWD)	No detailed information

Cardiovascular disease (ischemic heart disease, heart failure,and hypertension); metabolic disease (diabetes, dyslipidemia,and obesity); bone disease (osteopenia, osteoporosis); MCID: minimal clinically important difference; PWR: peak work rate; MDI: Mahler Dyspnea Index; 6MWD: six-minute walking distance; SGRQ: St George's Respiratory Questionnaire; MRC: Medical Research Council Scale.

Table 3: Overview of the logistic regression analyses performed in each article.

Comorbidity	Author	Outcome variables of PR	Measurement	OR (95% CI)	P value	
Anxiety and/or depression	Carreiro et al. [17]	Improvement in dyspnea (defined as +1 point)	MDI	0.10 (0.02 to 0.58)	0.01	⬇
Osteoporosis	Crisafulli et al. [16]	Improvement in dyspnea (defined as −1 point)	MRC	0.69 (0.66 to 1.48)	0.07	⇩
	Crisafulli et al. [18]	Improvement in functional exercise capacity (defined as +54 meter)	6MWD	0.28 (0.11 to 0.70)	<0.01	⬇
Cardiovascular disease	Crisafulli et al. [16]	Improvement in functional exercise capacity (defined as +54 meter)	6MWD	2.36 (1.85 to 3.01)	0.001	⬆
	Carreiro et al. [17]	Improvement in quality of life (defined as −4 points)	SGRQ	0.20 (0.05 to 0.85)	0.03	⬇
	Crisafulli et al. [16]	Improvement in quality of life (defined as −4 points)	SGRQ	0.67 (0.55 to 0.83)	0.001	⬇
Metabolic disease	Crisafulli et al. [16]	Improvement in dyspnea (defined as −1 point)	MRC	1.17 (0.93 to 1.77)	0.10	⇧
	Carreiro et al. [17]	Improvement in functional exercise capacity (defined as +30 meter)	6MWD	4.57 (0.91 to 23.0)	0.07	⇧
	Crisafulli et al. [16]	Improvement in functional exercise capacity (defined as +54 meter)	6MWD	0.57 (0.49 to 0.67)	0.001	⬇
	Walsh et al. [20]	Improvement in functional exercise capacity (defined as +60.9 meter)	6MWD	2.47 (1.08 to 5.67)	0.03	⬆
	Crisafulli et al. [16]	Improvement in quality of life (defined as −4 points)	SGRQ	0.91 (0.77 to 1.07)	0.25	⇩

Cardiovascular disease (ischemic heart disease, heart failure, and hypertension); metabolic disease (diabetes, dyslipidemia, and obesity); bone disease (osteopenia, osteoporosis); MDI: Mahler Dyspnea Index; MRC: Medical Research Council Scale; 6MWD: six-minute walking distance; SGRQ: St George's Respiratory Questionnaire.

⬆ represents significant positive associations; ⬇ represents significant negative associations; ⇧ represents nonsignificant positive associations; ⇩ represents nonsignificant negative associations.

Only the association between maximal work rate and symptoms of depression was significant, meaning that patients with COPD and depressive symptoms improve less in maximal work rate ($r = -0.34$; $P = 0.008$). The present review could not draw clear conclusions about the influence of metabolic disease on functional exercise capacity. However, Sava et al. [23] focused on obesity (BMI > 30 kg/m^2) as a component of the metabolic disease and looked at its influence on the change in the 6MWD test. More specifically, they concluded that obese patients with COPD significantly improved in functional exercise capacity, but to the same extent as overweight patients and persons with a normal BMI. These findings are in line with the conclusions of Walsh et al. [20]. In another study on obesity, Ramachandran and colleagues [22] revealed that symptoms of dyspnea, investigated by the Chronic Respiratory Disease Questionnaire, were higher after pulmonary rehabilitation in patients with a BMI > 30 kg/m^2. In contrast, Crisafulli et al. [16] found patients with metabolic disease to have a higher chance of improving in symptoms of dyspnea, but these results were not significant. The last limitation was that the rehabilitation programs in the included studies were not adapted to the specific comorbidities. It remains unknown whether better adaptations of the rehabilitation programs to the comorbidities would have resulted in better outcomes.

Focusing on comorbidities in patients with COPD is of importance since they contribute to the overall severity of the disease and have a negative impact on patient's life expectancy [12, 26]. Considering this, there is an urgent need to address the role of comorbidities into the nonpharmacological treatment of patients with COPD. Although pulmonary rehabilitation programs are promoted by international guidelines to

be an integral part of the management of COPD [11, 27], they largely focus on single diseases and do not take into account the comorbidities. Therefore, one must strive to develop guidelines for rehabilitation focusing on patients not on diseases so that treatment is in the individual's best interests [28]. Boyd et al. [29] confirm that comorbidities should receive more attention in patients with chronic diseases. In up to 55% of clinical trials in patients with COPD, patients with comorbidities are excluded [29]. This may explain why we only found 4 articles meeting our in-and exclusion criteria. Our findings can be supported by Patrick et al. [30], who investigated the effects of medical comorbidities on rehabilitation in geriatric patients. The focus of rehabilitation in the elderly addressed restoring functional independence and optimizing quality of life. They concluded that disability and cardiovascular, gastrointestinal, musculoskeletal, and endocrinal disease were significant negative predictors of rehabilitation efficiency in geriatric patients. On the other hand, not referring patients with comorbidities to pulmonary rehabilitation is surely not the way forward. All studies included in the current review demonstrate that patients with comorbidities can be trained with significant benefits. The real question is whether programs specifically tailored on comorbidities can improve these outcomes. Standard outpatient programs normally include exercise training as one of the most important components, which is proven to have a positive effect on cardiovascular disease, metabolic disease, and osteoporosis [26]. In order to achieve these benefits, patients with COPD have to train for 8–12 weeks, four times a week, at an intensity of 60–80% of maximal workload, during 20–30 minutes each session [31–33]. Based on the joint statement of the European Association for Cardiovascular Prevention and Rehabilitation, patients with ischemic heart disease and heart failure benefit from training sessions ranging from light (25–44% peak VO_2, continuous training) to moderate (45–59% peak VO_2, continuous training) to high (60–84% peak VO_2, interval training) to very high intensity (≥85% peak VO_2, interval training) to improve exercise capacity. The chosen intensity depends on the preserved ejection fraction and the exercise capacity of the patient during the pretraining period, measured by a cardiopulmonary exercise test [34]. Patients with arterial hypertension are instructed to train 30 minutes at moderate intensity (40–60% HRR), 5 times a week or 20 minutes at vigorous intensity (60–84% HRR), 3 times a week [35]. The guideline for patients with metabolic disease contains that patients have to perform 150 minutes of aerobic exercise, three times a week at moderate to vigorous intensity (40–60% VO_2max) [35, 36]. Literature is available on the importance of exercise training in patients with osteoporosis. However, there is no clarity about the duration, intensity, or frequency of the training programs [37]. For patients with anxiety and/or depression, the advice is to train 3-4 times a week at moderate intensity (40% VO_2max), during sessions of 20–30 minutes for a period of 8–14 weeks [38]. According to Fischer et al. [39] the intensity of the program being too high is the most often reported reason for drop-out in patients with COPD. In some patients, therefore, the guidance on training for comorbidities can overrule the guidance for training of the COPD related patients. A last point of attention relates to self-management as part of the disease management, which aims at changing the behavior of the patient by improving their problem solving skills. Clearly, these also need to be adapted to the comorbidities [40]. These literature findings defend our statement that comorbidities should be included into the management of patients with COPD, but that there is a need for cross-disease guidelines for rehabilitation. Training programs should be individually tailored and adapted to the specific comorbidity(ies) of the patient.

5. Conclusions

Comorbidities are prevalent in patients with COPD and they potentially have a negative effect on outcomes of standard pulmonary rehabilitation. More specifically, they could reduce the benefits in terms of dyspnea, functional exercise capacity, and quality of life. Based on the present review, we conclude that including patients with comorbidities in pulmonary rehabilitation programs is still reasonable as they improve with training. However, we should be aware that, without altering the program, response rates will be lower. An optimal treatment should therefore include a baseline assessment of comorbidities with a subsequent individually tailored pulmonary rehabilitation program.

Conflict of Interests

The author and coauthors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Six-Minute Walking Distance Improvement after Pulmonary Rehabilitation Is Associated with Baseline Lung Function in Complex COPD Patients: A Retrospective Study

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Introduction. Conflicting results have been so far reported about baseline lung function, as predicting factor of pulmonary rehabilitation (PR) efficacy. *Aim*. To ascertain whether or not baseline lung function could predict a benefit in terms of a significant change in 6-min walk test (6MWT) after PR. *Methods*. Seventy-five stable moderate-to-severe COPD inpatients with comorbidities (complex COPD), allocated to a three-week PR program, were retrospectively evaluated. Pulmonary function, 6MWT, dyspnea (BDI/TDI), and quality of life (EQ-VAS) were assessed before and after PR program. The patients were divided into two groups depending on the change in 6MWT (responders > 30 m and nonresponders ≤ 30 m). Logistic regression analysis was used. *Results*. After PR, 6MWT performance all outcome measures significantly improved ($P < 0.01$). Compared to nonresponders ($N = 38$), the responders ($N = 37$) had lower values in baseline lung function ($P < 0.01$). Logistic regression analysis showed that $FEV_1 < 50\%$ pred and TL, CO < 50% pred were independent predictors of PR efficacy. *Conclusions*. Our study shows that in stable moderate-to-severe complex COPD inpatients, baseline lung function may predict the response to PR in terms of 6MWT. We also found that complex COPD patients with poor lung function get more benefit from PR.

1. Introduction

Pulmonary rehabilitation (PR) is widely used to treat COPD patients with different degrees of severity and prevalence of chronic comorbidities [1], bringing them benefits in terms of improved exercise capacity, symptoms, and quality of life, regardless of whether the setting is inpatient or ambulatory [2, 3]. Several studies have focused on identifying clinical and functional predictors of the beneficial effects of PR in COPD patients [4]. However, determining patients who may benefit from PR remains a debatable issue, with no conclusive data available.

To date, change in exercise performance is still considered one of the most important and easiest outcome measures adopted to evaluate the effects of PR in COPD patients [5]. Since PR is a comprehensive and multidimensional intervention, little is known as yet about the correlation existing between change in exercise capacity after PR and the predictive value of multiple factors potentially associated with this change [4]. Some of the baseline characteristics of COPD patients, such as arterial oxygenation [6], degree of dyspnea [7], body mass index (BMI) arterial partial pressure of oxygen (PaO_2) [8], and health status [9], appear to be considered as predictors of PR, in terms of change in walking distance of 6-minute walking test (6MWT). In these studies [6–9], there has been the general observation that, in COPD patients, a poorer baseline condition, due to a higher magnitude of breathlessness, deconditioning in overweight, hypoxemia, or

health status impairment, can leave greater possibility for improvement in exercise capacity after PR.

Up to now, conflicting results have been reported about the role of baseline lung function, as predicting factor of PR efficacy. According to some reports, the FEV_1 baseline value appears to be irrelevant to predict benefits from PR in COPD patients [6, 7, 10, 11]. Other studies [8, 9] provided evidence that improvements in physiologic training response of PR program were positively associated with the degree of airflow limitation. By contrast, a recent study [12] showed that COPD patients with poor lung function get more benefit from PR in terms of endurance walking capacity.

The aim of this study was to examine in patients with clinically stable complex COPD the relationship between functional baseline parameters and exercise response to PR and to ascertain whether or not baseline lung function could predict a benefit in terms of a significant change in 6MWT after PR. We performed, therefore, a retrospective analysis from a database of inpatients with complex COPD who had undergone PR in a tertiary care center.

2. Methods

2.1. Design of the Study. A retrospective analysis was performed on data from COPD patients admitted to our rehabilitation center from January 1 to December 31, 2011.

Spirometry and blood gas analysis together with walking capacity, dyspnea, and HRQoL were measured in all patients at admission and at the end of the PR program.

Outcome measure was the change in walk distance after completing PR. Correlation between baseline variables and improvement in walk distance were also analyzed.

2.2. Subjects. We examined 151 COPD patients who attended an inpatient PR program. All patients were diagnosed with COPD according to the GOLD criteria [13]. Patients suffering from acute exacerbation over the previous four weeks were excluded, as well as patients who were not able to perform a 6MWT. Patients who did not complete the PR program, for COPD exacerbation, or any unstable medical condition, were also excluded. Contraindications for participation in the PR program included musculoskeletal disorders, malignant diseases, unstable cardiac condition, and lack of compliance to the program. Finally, 75 patients were considered for the study.

Individuals' self-reported comorbidities, as assessed by the Charlson Index [14] which assigns to each disease a score that is proportional to the disease related risk of death, were retrieved by the medical files. The Charlson Index was computed during the hospital stay by the physician in charge of each admitted patient.

All of patients were exsmokers and were receiving regular pharmacologic treatment (inhaled long-acting β2-agonists in 62 patients, tiotropium in 70 patients, and inhaled corticosteroids in 44 patients). Eleven patients were under long-term oxygen therapy and 13 out of 75 had two or more exacerbations in the preceding year and were classified as frequent exacerbators.

In all patients, the clinical and functional assessment had been undertaken for clinical reasons at the request of the patient's clinician and approval to report these data has been given by our ethical review board. All participants' data were analyzed and reported anonymously. No extramural funding was used to support this study.

2.3. Pulmonary Function Tests and Arterial Blood Gas Analysis. VC, FEV_1, TLC, and RV were measured by means of a flow-sensing spirometer and a body plethysmograph connected to a computer for data analysis (Masterlab, Jaeger, Wurzburg, Germany). TL, CO was measured by the single breath method using a mixture of carbon monoxide and methane (Sensor Medics, Yorba Linda, USA). VC, FEV_1, TLC, RV, and TL, CO were expressed as a percentage of the predicted values, which were obtained from regression equations by Quanjer et al. [15] and Cotes et al. [16]. FEV_1/VC and RV/TLC ratios were taken as indices of airway obstruction and lung hyperinflation, respectively.

PaO_2 and $PaCO_2$ were measured immediately after sampling from a puncture of the radial artery at rest (Gas analyzer ABL 330; Radiometer, Copenhagen, Denmark).

2.4. Walking Capacity. Walking capacity was evaluated by means of the distance covered during a 6MWT according to the ATS statement [17]. In all patients, the change in distance covered during 6MWT (Δ6MWD) after PR was recorded. Before and immediately after the 6MWT, patients rated the magnitude of their perceived breathlessness and of their leg fatigue using a 1–10-point Borg scale.

2.5. Dyspnea and Health Status-HRQoL. Dyspnea was assessed by the baseline/transitional dyspnea index (BDI/TDI) [18]. Health status-HRQoL of patients was evaluated by the VAS component of EQ-5D, reflecting their perceived health state, where 0 meant the "worst imaginable health state" and 100 meant the "best imaginable health state" [19].

2.6. Pulmonary Rehabilitation Program. Patients underwent a comprehensive PR program consisting of (a) exercise training, (b) verbal inputs stressing the need for adherence to therapy, (c) educational support, and (d) a nutritional and psychological counseling, if needed. According to the guidelines recommendations, the PR program was completely tailored to suit the needs of the individual [2, 3]. The program consisted of 12 sessions completed over a 3-week period, including (a) aerobic exercise training (cycling, walking, and/or arm exercise), (b) respiratory muscle training, (c) breathing exercise, (d) postural exercises, and (e) upper- and lower-body muscle strength training exercise. Exercises were graded, being their intensity weekly increased as the patient progressed in the PR [20]. The exercise program was supervised by a chest physiotherapist. Patients with chronic respiratory failure were provided with oxygen during the exercise sessions.

Table 1: Subjects' characteristics.

	All patients ($n = 75$)	Responders ($n = 37$)	Nonresponders ($n = 38$)	P value*
Age (yrs)	71 ± 8	69 ± 8	73 ± 7	0.020
Gender (F, M)	11, 64	6, 31	5, 33	0.708
FEV_1 (% pred)	57 ± 18	45 ± 14	68 ± 15	<0.001
VC (% pred)	85 ± 16	78 ± 14	92 ± 15	<0.001
FEV_1/VC (%)	50 ± 12	45 ± 11	55 ± 10	<0.001
RV (% pred)	162 ± 43	178 ± 43	147 ± 37	0.002
TLC (% pred)	113 ± 17	115 ± 18	111 ± 16	0.256
RV/TLC (%)	57 ± 9	61 ± 9	54 ± 7	<0.001
IC (liters)	2.2 ± 0.6	2 ± 0.6	2.4 ± 0.5	<0.001
TL, CO (% pred)	61 ± 20	55 ± 19	67 ± 19	0.007
BMI (Kg/m^2)	29.7 ± 5.3	29 ± 6	30 ± 5	0.419
PaO_2 (mm Hg)	71.2 ± 8.2	69 ± 5	73 ± 10	0.026
$PaCO_2$ (mm Hg)	38.5 ± 4.5	39 ± 5	38 ± 4	0.070
Charlson Index	1.6 ± 0.9	1.8 ± 1	1.4 ± 0.8	0.084

* Responders versus nonresponders.

2.7. Statistical Analysis. Data are reported as mean ± standard deviation (SD), unless otherwise specified. The distribution of variables was assessed by means of Kolmogorov-Smirnov Goodness-of-Fit test. Relationships between variables were assessed by Pearson's correlation coefficient (r) and linear regression analysis. Comparisons between variables were determined by unpaired t-test and χ^2 test, when appropriate.

In order to evaluate the role of baseline lung function parameters to predict the PR benefit, the COPD patients were subdivided into different subgroups according to FEV_1 (≥50% pred, $N = 44$ and <50% pred, $N = 31$), RV (≥160% pred, $N = 36$ and <160% pred, $N = 39$), TL, CO (≥50% pred, $N = 53$ and <50% pred, $N = 22$), and PO2 (≥70 mm Hg, $N = 39$ and <70 mm Hg, $N = 36$). The efficacy of PR was expressed by the significant Δ6MWD, consisting in an increase in walked distance greater than 30 meters after PR, which is considered as a minimal clinically important difference (MCID) [21]. According to whether or not the patients reached a MCID, they were classified as responders (Δ6MWD > 30 m, $N = 37$) and nonresponders (Δ6MWD ≤ 30 m, $N = 38$). Logistic regression analysis was then performed to test the association between the baseline lung function parameters, as binary independent variables, and the significant Δ6MWD, as a binary dependent variable. Odds ratios are presented with 95% confidence intervals.

A P value < 0.05 was considered as significant.

3. Results

Characteristics of COPD patients are reported in Table 1. According to GOLD criteria 9, 35, 27, and 4 out of 75 patients had mild, moderate, severe, and extremely severe airflow obstruction, respectively. After PR, a significant improvement in 6MWT, TDI, and EQ-VAS was found in all patients. The 6MWT improved by 35 ± 39 meters (from 440 ± 102 to 475 ± 91, $P < 0.001$). Dyspnea showed a clinically significant reduction (from BDI 7.1 ± 2.3 to TDI 3.8 ± 2.1), corresponding to a change of ≥1 unit in 94% of the patients. EQ-VAS improved by 15.3 ± 12 (from 57.8 ± 18 to 72.7 ± 15.2, $P < 0.001$).

After PR, there was a very modest, though statistically significant, increase in both FEV_1 and VC ($P < 0.001$ and $P = 0.006$, resp.) in responders and in FEV_1 in nonresponders ($P = 0.02$).

As compared to nonresponders, responders were significantly younger with a worse respiratory function and showed a higher percentage of frequent exacerbators (27% versus 8%, $P = 0.031$). At baseline, responders were more dyspnoeic than nonresponders (BDI, 6.4 ± 2.2 versus 7.7 ± 2.3, $P = 0.021$) and at baseline experienced a higher dyspnea (Borg scale, 4.6 ± 2.3 versus 3.1 ± 1.6, $P = 0.004$) and a higher leg fatigue (Borg scale 4.1 ± 2.4 versus 3.1 ± 1.5, $P = 0.036$) during the 6MWT than nonresponders. No differences were observed in EQ-VAS between the two groups at baseline. Fifty-three out of 75 patients participated at a previous PR (71%). They did not differ in walking distance, as compared to the remaining patients.

In all patients, Δ6MWD was inversely related to baseline values of FEV_1% predicted ($r = -0.50$) (Figure 1), VC% predicted ($r = -0.45$), IC ($r = -0.38$), FEV_1/VC ($r = -0.33$), PaO_2 ($r = -0.30$), and TL, CO% predicted ($r = -0.25$) (Figure 1) and directly related to baseline values of RV/TLC ($r = 0.40$), RV% predicted ($r = 0.33$). Moreover, in all patients and in responders group Δ6MWD was inversely related to baseline values of 6MWD ($r = -0.47$ and $r = -0.46$, resp.).

Logistic regression analysis showed that, in all patients, the significant change in 6MWT was significantly associated with FEV_1 and TL, CO values but not with RV and PaO_2 values (Table 2).

4. Discussion

In this retrospective study, we examined the role of lung function and clinical parameters at baseline in determining

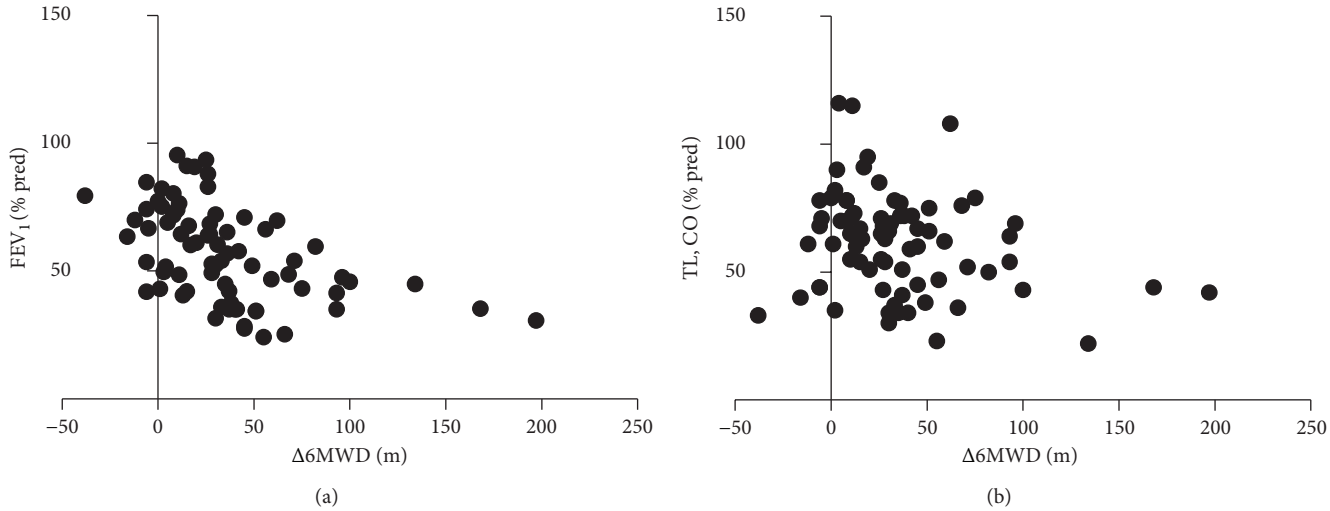

Figure 1: Relationship between the change in six-minute walking distance after pulmonary rehabilitation and FEV_1 (a) and TL, CO (b).

Table 2: Odds ratios (95% confidence intervals) by regression logistic analysis of FEV_1 < 50% pred, TL, CO < 50% pred, RV > 160% pred, and PaO_2 < 70 mm Hg for COPD responder to PR.

	OR (95% CI)	*P* value
FEV_1 < 50% pred	5.740 (1.782–18.491)	0.003
TL, CO < 50% pred	4.001 (1.151–13.906)	0.028
RV > 160% pred	2.255 (0.717–7.090)	0.164
PaO_2 < 70 mm Hg	1.147 (0.383–3.439)	0.806

benefits after a 3-week PR program in 75 moderate-to-severe and stable complex COPD patients. As expected, we found an improvement in PR outcomes in all patients. In addition, we observed that a worse baseline lung function was associated with a better response in walking capacity to PR. Notably, airflow obstruction and lung diffusion were independent predictors of benefit, in terms of the fact that patients with FEV_1 and TL, CO less than 50% of predicted values reached the MCID of 6MWT after PR, as compared to the other subgroups of patients.

The relationship between change in exercise capacity after PR and baseline clinical and functional characteristics of COPD patients has been extensively investigated [6–12]; however, the results are discordant and difficult to interpret. The finding that emerges most frequently from these studies [6, 7, 10, 11] is the negligible value of the baseline lung function in determining benefits after PR. Furthermore, when a relationship between lung function and change in exercise capacity was observed, patients with less severe obstruction showed greater improvements in exercise tolerance [8, 9].

In COPD patients recovering from an acute exacerbation, Cilione et al. retrospectively studied the predictors of change in exercise capacity after comprehensive COPD inpatient rehabilitation [6]. They found that baseline values of 6MWD and arterial oxygenation had the most consistent correlation with change in 6MWD [6]. Garrod et al. [7] studied the predictors of success and failure in pulmonary rehabilitation in a heterogeneous group of COPD patients. They recruited their patients from primary and secondary care, who followed either out-patient or home-based PR with relation to the severity degree of the disease and did not find any relationship between baseline lung function and change in 6MWD [7]. Interestingly, they observed that patients with lower FEV_1 showed greater improvement in quadriceps strength [7]. Vagaggini et al. [8] retrospectively evaluated clinical predictors of the efficacy of a pulmonary rehabilitation program in moderate-to-severe outpatients with complex COPD and by logistic regression analysis only BMI and PaO_2 were positively associated with the improvement in 6MWD [8]. More recently, in a large cohort of moderate-to-severe COPD patients, van Ranst et al. found a weak positive correlation between baseline values of FEV_1 and FEV_1/VC and the improvement in 6MWD [9]. In this study, FEV_1/VC, baseline WD, and peak oxygen uptake at incremental cycle exercise test contributed to explain a modest 19% of the variance of change in 6MWD [9].

In contrast to these data, we found that our complex COPD patients with worse baseline lung function, both in terms of airflow obstruction and in terms of diffusion lung capacity, gained greater improvement in walking capacity. Differences in participants and in PR setting might explain this discrepancy. Our patients were followed in an inpatient PR program in a specialized rehabilitation center. Thus, our patient sample comprised a considerable portion of severe to extremely severe patients (41%), including even oxygen-dependent patients. It is conceivable that patients with poor baseline lung function are at risk to enter a downward spiral of dyspnea, sedentariness, demotivation, and finally deconditioning [22]. On the other hand, these patients may show a larger capacity of improvement after PR, as compared to patients with more preserved lung function and exercise capacity. It is of note that our responder patients had a shorter 6MWD and a greater exertion dyspnea and leg fatigue than nonresponder patients; in addition, the percentage of patients

with two or more exacerbations was significantly higher in the former group of patients than in the latter one.

Interestingly, we observed a significant but very modest clinical impact on dynamic lung volumes in both groups, with a higher magnitude in responders group. Even though the exercise program included a nutritional training as a component, it is difficult to attribute the improvements in ventilator capacity to this aspect per se. A more likely explanation relates to indirectly derived educational benefits in the use of inhaled medications.

Our results are in line with the other studies [12, 23]. Plankeel et al. [23] analyzed the change in exercise capacity after PR in a large population of nonhypoxemic patients with COPD. The patients were classified into subgroups based on the primary limitation seen on exercise testing, such as ventilator limited, cardiovascular limited, mixed ventilatory/cardiovascular limited, and noncardiopulmonary-limited. Interestingly, the authors found that the ventilatory limited group had a marked improvement in walk distance after PR and the degree of improvement was similar to the groups without ventilatory limitation [23]. Recently, by means of the cluster analysis Altenburg et al. [12] have investigated whether or not there is a patient profile among the COPD population, associated with the improvement in endurance walking capacity after PR. They identified a cluster profile of patients characterized by a larger improvement in walking capacity, assessed by endurance shuttle walk test, which was associated with poor baseline lung function consisting in high TLC and RV/TLC and low FEV_1 values [12].

Finally, it is of note that individual comorbidities of our patients did not preclude effectiveness of PR course. These findings confirm the feasibility of our programme, which reproduces the internationally shared standards, and are in line with the results of Crisafulli and colleagues [24], which observed that, among all the individual comorbidities, either alone or in combination, only the presence of osteoporosis was independently associated with poorer rehabilitation outcomes.

In conclusion, our study shows that complex COPD patients with worse lung function, that is, with FEV_1 and TL, CO values less than 50% of predicted, seem to benefit more from pulmonary rehabilitation, in particular reference to change in six-minute walk distance. This finding suggests that complex COPD patients with more severe pulmonary impairment not only should not be excluded from rehabilitation programs but also may have the best results.

Abbreviations

6MWT: Six-minute walking test
6MWD: Six-minute walking distance
Δ6MWD: Six-minute walking distance change
PR: Pulmonary rehabilitation
BMI: Body mass index
FEV_1: Forced respiratory volume in one second
VC: Vital capacity
TLC: Total lung capacity
RV: Residual volume
TL, CO: Transfer factor of the lung for carbon monoxide
PaO_2: Arterial partial pressure of oxygen
$PaCO_2$: Arterial partial pressure of carbon dioxide
HRQoL: Health-related quality of life
BDI/TDI: Baseline dyspnea index/transitional dyspnea index
EQ-VAS: EuroQol-visual analogue scale
MCID: Minimal clinically important difference.

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Review Article

Cardiovascular Function in Pulmonary Emphysema

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Chronic obstructive pulmonary disease (COPD) and chronic cardiovascular disease, such as coronary artery disease, congestive heart failure, and cardiac arrhythmias, have a strong influence on each other, and systemic inflammation has been considered as the main linkage between them. On the other hand, airflow limitation may markedly affect lung mechanics in terms of static and dynamic hyperinflation, especially in pulmonary emphysema, and they can in turn influence cardiac performance as well. Skeletal mass depletion, which is a common feature in COPD especially in pulmonary emphysema patients, may have also a role in cardiovascular function of these patients, irrespective of lung damage. We reviewed the emerging evidence that highlights the role of lung mechanics and muscle mass impairment on ventricular volumes, stroke volume, and stroke work at rest and on exercise in the presence of pulmonary emphysema. Patients with emphysema may differ among COPD population even in terms of cardiovascular function.

1. Introduction

Pulmonary emphysema, a phenotype of chronic obstructive pulmonary disease (COPD), is a pathologic condition characterized by abnormal and permanent enlargement of the airspaces distal to the terminal bronchioles that leads to airspace walls destruction and usually to progressive airflow limitation [1]. In pulmonary emphysema, the loss of elastic recoil leads not only to the irreversible bronchial obstruction, but also to the lung hyperinflation, which implies an increased volume over the normal tidal breathing range and an increase in functional residual capacity (FRC). Furthermore, the more lung function is impaired, the more the airway collapsibility affects lung mechanics, leading to a high intrinsic positive end-expiratory pressure (PEEPi) that increases intrapleural pressure.

The emphysema phenotype defines COPD patients, who complain of dyspnoea and reduced exercise capacity, as predominating symptoms. Skeletal muscle depletion and malnutrition may also characterize emphysema patients. An inverse correlation was found between body mass index (BMI) and degree of emphysema, evaluated by high-resolution computed tomography [2].

There is an increasing body of evidence that, in COPD patients, a chronic cardiovascular disorder, such as coronary artery disease or congestive heart failure, may be a frequent comorbidity because of smoking habit, which is a common risk factor, and that the inflammation associated with COPD is not limited to the lung, but it can also affect nonpulmonary organs, such as the cardiovascular system [3–5]. Interestingly, in pulmonary emphysema changes both in lung mechanics and in skeletal muscle pump may impair *per se* the cardiovascular function. This overview, therefore, is specifically addressed to the cardiovascular system function in patients with pulmonary emphysema.

2. Heart and Pulmonary Hyperinflation

Pulmonary hyperinflation can significantly affect heart size and its function. By means of magnetic resonance technique, Jörgensen et al. [6] studied patients with severe emphysema and found a decrease in intrathoracic blood volume and in left ventricular and right ventricular end-diastolic volumes and an impaired stroke volume and stroke work in hyperinflated lungs, as compared to controls. The authors argued that

there are at least two main explanations of these findings. In presence of hyperinflated lungs, a high PEEPi could cause intrathoracic hypovolemia and small end-diastolic dimensions of both left and right ventricular chambers. The redistribution of pulmonary circulation in emphysema might occur not only because of a direct parenchymal destruction or hypoxia vasoconstriction, but also because of a decreased compliance of pulmonary vascular bed that tends to push blood to the periphery borne down by a high PEEPi. Secondly, right and left ventricular chambers could be mechanically compressed by hyperinflated lungs that could worsen end-diastolic stiffness. According to the Frank-Starling law, a low preload finally reduces ventricular performance in terms of stroke volume (SV) and stroke work.

In a large sample of COPD patients, ranging from GOLD I to IV class, Watz et al. [7] found that the degree of COPD severity was directly correlated to heart dysfunction. Interestingly, in this study, the cardiac chamber sizes and impaired left ventricular diastolic filling pattern correlated more to the degree of static hyperinflation, as assessed by inspiratory capacity-to-total lung capacity ratio (IC/TLC), than to the degree of airway obstruction, expressed as forced expiratory volume in 1st second (FEV_1) % predicted, or to diffusion capacity to carbon monoxide. Furthermore, IC/TLC was an independent predictor of cardiac chamber sizes after adjustment for body surface area [7].

In line with the findings by Watz et al. [7], Malerba et al. [8] reported a frequent subclinical left ventricular filling impairment in COPD patients at the earlier stage of the disease, even in the absence of any other cardiovascular disorder. Furthermore, Smith et al. [9] have recently shown a reduction of pulmonary vein dimension in COPD, which is related to percent emphysema, thereby supporting a mechanism of upstream pulmonary causes for left ventricle underfilling.

Interestingly, as the pulmonary hyperinflation may have negative effects, so the pulmonary deflation has the potential to improve the cardiac function in patients with pulmonary emphysema. In patients severely hyperinflated, Come and coworkers [10] have recently found that the decreased hyperinflation through lung volume reduction surgery (LVRS) was significantly associated with an improvement in oxygen pulse, which may be considered as a noninvasive marker of cardiovascular efficiency and a measure of SV.

It is of note that the extent of emphysema, as detected on computed tomography (CT), may be associated with an impaired cardiac function, even in patients without very severe lung disease [11]. In a recent population-based study, a greater extent of emphysema on CT scanning was linearly related to impaired left ventricular filling, reduced stroke volume, and lower cardiac output without changes in the ejection fraction [11]. The smoking status significantly worsened these associations. Accordingly, the authors [11] hypothesized that the mechanisms of the impaired left ventricular filling in early, mild emphysema might be the subclinical loss of capillary bed due to the apoptotic effect of smoking on pulmonary endothelium.

3. Cardiovascular Response to Exercise and Dynamic Hyperinflation

In healthy subjects at rest, FRC physiologically equals the relaxation volume (V_r), at which all respiratory muscles are relaxed and the outward elastic recoil of the chest wall precisely balances the inward recoil of the lungs. By contrast, in patients with expiratory flow limitation, changes in ventilation, such as an increase in flow and/or in breathing frequency, can elevate FRC above V_r. The condition characterized by FRC which is not equal to but greater than V_r is called "dynamic hyperinflation" and may typically occur during exercise in COPD patients. In addition to the static lung hyperinflation, dynamic hyperinflation is responsible for limitation to exercise in COPD patients and for onset of exertion dyspnoea [12]. Accordingly, it is conceivable that during exercise dynamic hyperinflation can further worsen a poor resting cardiac function in patients with pulmonary emphysema.

Both ventilatory and cardiac responses to exercise can be well studied through cardiopulmonary exercise test (CPET). CPET is a relatively noninvasive method to test tolerance to maximal exercise and gives several pieces of information about how cardiovascular, respiratory, and muscle apparatuses respond to exercise. Notably, the assessment of the dynamic hyperinflation is based on the comparison of the IC performed at rest and during exercise and a positive difference between them is putative of dynamic hyperinflation, assuming that TLC remains constant during exercise.

Dynamic hyperinflation, which impairs the cardiovascular function in COPD patients, may be documented during rapidly incremental CPET. Vassaux et al. [13] first observed that dynamic hyperinflation is negatively associated with oxygen pulse at peak of exercise in patients with severe COPD. These results were confirmed and extended by our group in COPD patients with different degrees of severity, by showing a significant relationship between dynamic hyperinflation and a battery of noninvasive measures of cardiovascular function during exercise [14]. Notably, in these patients, we found that the extent of dynamic hyperinflation was inversely related not only to oxygen pulse, but also to the product of systolic blood pressure and heart rate, the so-called double product (DP). Interestingly, DP reflects myocardial oxygen uptake during exercise because the three major determinants of myocardial oxygen uptake are the tension in the wall of the ventricle, the contractile state of the heart, and the heart rate [15]. Secondly, we observed that the oxygen uptake efficiency slope (OUES), a parameter that integrates the functional capacities of several organ systems (cardiovascular, musculoskeletal, and pulmonary) and that represents the rate of increased O_2 consumption in response to a given ventilation during incremental exercise [16], was negatively associated with dynamic hyperinflation.

Importantly, it has been recently shown that in patients with severe pulmonary emphysema the reduction in dynamic hyperinflation after LVRS was significantly associated with an improvement in cardiac response to exercise, both in terms of oxygen pulse and pulse pressure, which is the difference between systolic and diastolic blood pressure [17]. It is of

note that pulmonary rehabilitation may lower the ventilatory demand during exercise, resulting in the prolongation of the expiration time and, in turn, in the reduction of dynamic hyperinflation [18]. Accordingly, one may hypothesize that, in COPD patients, pulmonary rehabilitation may improve the cardiovascular response to exercise by enhancing the ventilatory function. In line with this assumption, our group has recently reported an improvement in cardiovascular response during exercise at submaximal exercise independent of the external work after a standard pulmonary rehabilitation program [19]. This change was significantly associated with an enhancement in ventilatory function during exercise.

4. Skeletal Muscle Pump and Cardiovascular Function

Skeletal muscle pump is of basic importance both in local and systemic circulatory effects, since it may enhance venous return, central venous pressure, end-diastolic volume, and thus stoke volume and cardiac output, by expulsing the peripheral venous blood volume during exercise [20]. In this way, the muscle pump makes also more blood flow available to be diverted to active muscle and thereby indirectly inducing muscle hyperemia [20]. On the other hand, a skeletal muscle depletion may negatively affect the cardiovascular response to exercise.

In COPD patients, a skeletal muscle depletion may commonly occur, resulting from several factors, such as disuse atrophy, poor nutrition, systemic inflammatory mediators, and oral corticosteroids chronically administered [21]. Importantly, when in a COPD population the characterization of phenotypes was based on the presence and the severity of emphysema, patients with the phenotype in which emphysema predominates have significantly lower BMI [22].

Recently, our group has shown that the muscle mass depletion plays a part *per se* in the reduction of exercise capacity of COPD patients, regardless of lung function impairment, and is strictly associated with poor cardiovascular response to exercise and to leg fatigue [23]. Notably, in our study, both resting and peak oxygen pulse values were significantly lower in depleted patients, as compared to nondepleted, whereas peak oxygen pulse value was strongly related to fat-free mass in the whole population. We also found that depleted and nondepleted patients differed in OUES, which is an objective measure of cardiorespiratory and muscular fitness [24]. Lastly, in our patients, we found that the heart rate recovery after a maximal exercise, a marker of the cardiac autonomic function and a powerful predictor of mortality in the general population [25], was significantly lower in depleted patients.

5. Conclusions

There is growing recognition that COPD and chronic cardiac diseases appear to be linked by an underlying systemic inflammatory status. At the same time, lung mechanics and cardiac performance are deeply dependent on each other and both may be responsible for exercise limitation, exertion dyspnoea, and poor quality of life in the presence of irreversible airflow limitation and lung hyperinflation. Furthermore, muscle mass depletion, which especially characterizes patients with pulmonary emphysema among COPD population, may also contribute to cardiovascular response to exercise.

Clinicians should take into consideration that any therapeutic approach, such as inhaled bronchodilators, lung volume reduction surgery, and pulmonary rehabilitation, that aims to improve lung mechanics may in turn improve cardiac performance as well in COPD patients. Furthermore, all that can increase muscle mass in depleted COPD patients may in turn improve their cardiovascular function.

In conclusion, emphysema and chronic bronchitis are two different phenotypes of COPD not only from a clinical and functional point of view, but also in terms of cardiovascular function. Notably, systemic inflammation, lung mechanics impairment, and muscle mass depletion might play a different role in conditioning cardiovascular function in patients with emphysema and in patients with chronic bronchitis. Further studies are requested to address this matter and to provide solutions.

Abbreviations

BMI: Body mass index
COPD: Chronic obstructive pulmonary disease
CPET: Cardiopulmonary exercise test
CT: Computed tomography
DP: Double product
FEV_1: Forced expiratory volume in 1st second
GOLD: Global initiative for chronic obstructive lung disease
IC: Inspiratory capacity
LVRS: Lung volume reduction surgery
OUES: Oxygen uptake efficiency slope
PEEPi: Intrinsic positive end-expiratory pressure
SV: Stroke volume
TLC: Total lung capacity.

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