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REVIEW

Hypoxemia in patients with COPD: cause, effects, and disease progression

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Abstract: Chronic obstructive pulmonary disease (COPD) is a leading cause of death and disability internationally. Alveolar hypoxia and consequent hypoxemia increase in prevalence as disease severity increases. Ventilation/perfusion mismatch resulting from progressive airflow limitation and emphysema is the key driver of this hypoxia, which may be exacerbated by sleep and exercise. Uncorrected chronic hypoxemia is associated with the development of adverse sequelae of COPD, including pulmonary hypertension, secondary polycythemia, systemic inflammation, and skeletal muscle dysfunction. A combination of these factors leads to diminished quality of life, reduced exercise tolerance, increased risk of cardiovascular morbidity, and greater risk of death. Concomitant sleep-disordered breathing may place a small but significant subset of COPD patients at increased risk of these complications. Long-term oxygen therapy has been shown to improve pulmonary hemodynamics, reduce erythrocytosis, and improve survival in selected patients with severe hypoxemic respiratory failure. However, the optimal treatment for patients with exertional oxyhemoglobin desaturation, isolated nocturnal hypoxemia, or mild-to-moderate resting daytime hypoxemia remains uncertain.

Keywords: COPD, hypoxia, sleep, inflammation, pulmonary hypertension

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of global morbidity and disability, and by 2020 is predicted to become the third greatest cause of death worldwide.[1] As pulmonary function deteriorates, and as the disease progresses, the risk of alveolar hypoxia and consequent hypoxemia increases.[2] A mounting body of evidence suggests that hypoxemia is more than a signifier of advanced disease. Rather, it now seems clear that tissue hypoxia is a key player in many of the maladaptive processes and extrapulmonary comorbidities that characterize COPD.

The prevalence of hypoxemia among COPD patients remains somewhat uncertain. In large general COPD populations, severe hypoxemia is relatively uncommon, with only 2% of the 5993 participants in the UPLIFT® trial being prescribed supplemental oxygen.[3] Conversely, over 80% of the patients with advanced disease enrolled in the National Emphysema Treatment Trial were using some form of oxygen therapy.[4]

Hypoxemia associated with COPD contributes to reduced quality of life, diminished exercise tolerance, reduced skeletal muscle function, and ultimately increased risk of death.[5] On the other hand, treatment of severe hypoxemia with long-term oxygen therapy (LTOT) is one of the few interventions shown to prolong life in hypoxemic COPD patients.[5] This review will examine how alveolar hypoxia and hypoxemia arise in COPD patients, the adverse consequences of chronic hypoxemia in COPD patients,

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and some of the benefits and drawbacks of supplemental oxygen therapy in COPD.

Pathophysiology of alveolar hypoxia and hypoxemia in COPD

The principal contributor to hypoxemia in COPD patients is ventilation/perfusion (V/Q) mismatch resulting from progressive airflow limitation and emphysematous destruction of the pulmonary capillary bed.[6] In studies utilizing the multiple inert gas elimination technique, COPD patients with a predominantly emphysematous phenotype have increased ventilation of poorly perfused lung units (ie, high V/Q ratio), and hence increased physiological dead space.[7] Conversely, subjects with a significant degree of airway disease are more likely to have a low V/Q ratio, with heterogeneous alveolar hypoventilation, substantial perfusion of under-ventilated areas, and consequent physiological shunt. V/Q mismatch due to pulmonary emphysema and small airways disease is measurable even in subjects with mild COPD,[8] but appears to increase with disease progression.[9]

Exacerbations of COPD are frequently associated with deterioration in gas exchange and associated hypoxemia. Unsurprisingly, increased inequality in V/Q relationships appears to be the major determinant of these changes.[10] Increased tissue consumption of oxygen, with resultant decreased mixed venous oxygen tension also appears to contribute to increased hypoxemia during exacerbations, but is at least partially offset by a concomitant increase in cardiac output.

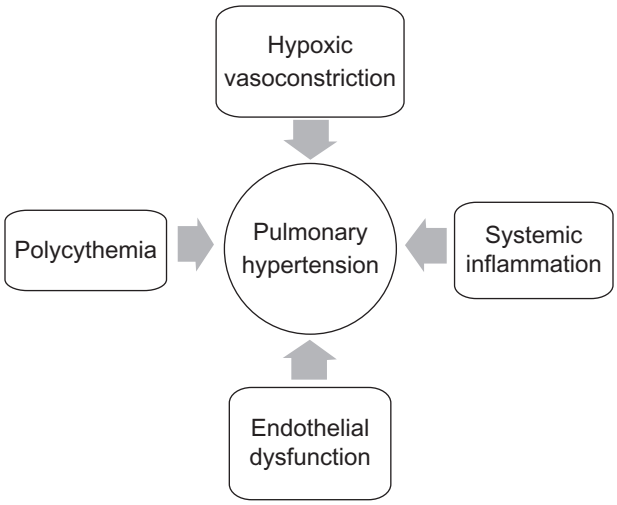

Figure 1 Hypoxia-related factors contributing to the development of pulmonary hypertension in chronic obstructive pulmonary disease.

Obesity is increasingly prevalent in modern COPD cohorts, and may contribute to abnormalities in gas exchange.[11] Even in the absence of COPD, obesity is associated with small airways dysfunction, decreased chest wall compliance, V/Q mismatch, and increased peripheral oxygen consumption, all potentially leading to relative hypoxemia. Risk of sleep-disordered breathing and consequent nocturnal hypoxemia correlates with the degree of obesity,[12] and in extreme cases, morbid obesity can lead to profound alveolar hypoventilation, with chronic hypercapnic respiratory failure.[13]

Dysregulated ventilatory control is another factor contributing to the occurrence and persistence of hypoxemia in COPD patients. Subjects with chronic airflow obstruction have blunted ventilatory responses to hypoxia,[14] and this is particularly the case in those with chronic hypoxemia.[15] In the majority of cases, this is not driven by diminished central nervous system output, with COPD patients often exhibiting increased neural drive to the respiratory muscles as the disease progresses.[16] Rather, peripheral mechanisms related to disordered inspiratory muscle function and associated hyperinflation appear to be the key.[6] Nonetheless, reduction in central ventilatory drive may be of relevance in cases of nocturnal hypoxemia, in bronchial type ("blue bloater") patients, and with use of sedatives, hypnotics, and alcohol.

Exercise, COPD, and hypoxemia

Exercise may actually improve gas exchange in subjects with mild COPD, largely due to an improvement in V/Q relationships resulting from more even distribution of ventilation.[17] However, in more severe disease, V/Q mismatching and peripheral oxygen extraction are increased,[18] and dynamic hyperinflation contributes to alveolar hypoventilation,[19] with resultant exertional hypoxemia.

Desaturation with exercise appears to predict increased risk of mortality,[20] but the role of supplemental oxygen in this area is uncertain. A number of studies have shown it to provide short-term symptom relief and exercise performance, but longer-term data are lacking.[21] Similarly, there is little evidence in the published literature to support a role for ambulatory oxygen therapy in prolonging survival. While often viewed as an attractive therapeutic option, the use of supplemental oxygen is not free of risk or adverse consequences, and this will be discussed in greater detail later in this review. The ongoing Long-term Oxygen Treatment Trial is a large-scale, multicenter attempt to address knowledge deficits in this field.[21]

Sleep, COPD, and hypoxemia

Sleep has significant effects on respiration, even in healthy subjects. Chemoreceptor sensitivity decreases, respiratory motor output, and muscle contraction diminish, ventilation/perfusion relationships alter, and airflow resistance increases. The net effect of these changes is relative alveolar hypoventilation, which is particularly pronounced in rapid-eye-movement sleep. While clinically unimportant in otherwise healthy individuals, these changes can lead to significant nocturnal hypoxemia in patients with COPD.[22]

While diaphragmatic function is maintained during rapid-eye-movement sleep, contraction of the accessory muscles is markedly reduced. In the presence of pulmonary hyperinflation and consequent reduced diaphragmatic efficiency, this can lead to pronounced hypoventilation. Furthermore, subjects with COPD and mild daytime hypoxemia may be particularly vulnerable to oxyhemoglobin desaturation during sleep, because they will often reside on the steep portion of the oxyhemoglobin dissociation curve.[22] Interestingly, COPD patients may be relatively protected from the potential detrimental effects of rapid-eye-movement sleep, because they have reduced sleep quality, with sleep fragmentation and consequent reduction in slow-wave and rapid-eye-movement sleep duration.[23]

Respiration during sleep is of particular relevance to a subset of COPD patients with coexisting obstructive sleep apnea syndrome, the so-called overlap syndrome. Community-based population studies would suggest the overlap syndrome occurs in at least 1% of adults, with the prevalence of obstructive sleep apnea syndrome in COPD patients approximating that in the general population.[23,24] Overlap patients have more pronounced nocturnal hypoxemia, are more likely to develop pulmonary hypertension, and appear to be at increased risk of death compared with COPD patients matched for Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage.[25,26] At a molecular level, the systemic inflammation associated with COPD and obstructive sleep apnea syndrome may act synergistically to promote the development of atherosclerosis and subsequent overt cardiovascular disease, although further studies in this area are needed.[25]

A number of interventions may be of benefit in COPD patients with significant nocturnal hypoxemia. The available evidence does not suggest supplemental oxygen provides a survival benefit in COPD patients with isolated nocturnal desaturation,[27] but its prescription may be appropriate in such cases if complicated by pulmonary hypertension or polycythemia. Care should be taken to avoid the development of hypercapnia as a result of abolition of hypoxic respiratory drive, although the available evidence indicates that the degree of elevation in arterial carbon dioxide tension during sleep with supplemental oxygen therapy in COPD patients is mild and nonprogressive.[28] Theophylline acts as a central respiratory stimulant and improves diaphragmatic contractility, thus improving gas exchange during sleep in COPD,[29] and has the added benefit of reducing the level of sleep-disordered breathing in obstructive sleep apnea syndrome.[30] Furthermore, bronchodilatation with long-acting anticholinergic agents and long-acting β-agonists may also be beneficial.[31,32] Meanwhile, administration of nocturnal continuous positive airway pressure therapy appears to abrogate the increase in mortality seen in patients with the overlap syndrome.[26]

Consequences of hypoxemia in COPD

Pulmonary hypertension

Alveolar hypoxia is an important contributory factor to the development of pulmonary hypertension in patients with COPD.[33] The exact prevalence of pulmonary hypertension in COPD remains uncertain, but it appears to be relatively common in moderate–severe disease,[34] and increases in prevalence with disease severity. In a series of 120 patients with severe emphysema enrolled in the National Emphysema Treatment Trial who underwent right heart catheterization, 90.8% had pulmonary artery pressures above the normal range.[35] The degree of pulmonary hypertension in this study correlated with severity of emphysema as measured by forced expiratory volume in one second and diffusion lung capacity for carbon monoxide. Similarly, in a population of 215 French COPD patients listed for lung transplant or lung volume reduction surgery, pulmonary hypertension was present in 50.2% of cases.[36]

A striking feature of modern studies, however, is the preponderance of mild pulmonary hypertension even in severe COPD. Of the patients with advanced disease studied in the National Emphysema Treatment Trial, only 5% had severe pulmonary hypertension (pulmonary artery pressure $>$ 35 mmHg).[35] Similarly, in a large retrospective study of COPD patients undergoing right heart catheterization, only 27 of 998 subjects had a pulmonary artery pressure $>$ 40 mmHg.[34] Thabut et al identified a small subset of "atypical" patients with severe pulmonary hypertension and marked hypoxemia, but only moderately severe COPD.[36] Therefore, the discovery of severe pulmonary hypertension in COPD patients should lead to investigation for contributory

comorbidities, such as obstructive sleep apnea syndrome, obesity-hypoventilation syndrome, and chronic thromboembolic disease.

In the majority of cases, COPD-related pulmonary hypertension will progress slowly, if at all, although pulmonary artery pressure can transiently increase during acute exacerbations.[37] A minority of cases will go on to develop the overt right heart failure and peripheral edema that characterize cor pulmonale. The occurrence of cor pulmonale portends a significantly worse prognosis for the patient.[38] A potential contributory factor to this is worsening of nocturnal hypoxemia, due to rostral shift of peripheral edema leading to compromise of the upper airway and associated alveolar hypoventilation.[39]

Factors contributing to the development of pulmonary hypertension at an anatomic level include emphysematous obliteration of the pulmonary capillary bed, thromboembolic disease, and pulmonary vascular constriction and remodeling.[40] The pulmonary vasculature of COPD patients with pulmonary hypertension is characterized by luminal narrowing due to thickening of the intima, along with arteriolar muscularization. These changes may be observed in mild COPD, and even in otherwise healthy smokers, suggesting pulmonary vascular changes may arise before clinically overt disease.[41]

At a functional level, a key factor contributing to the development of increased pulmonary vascular resistance is hypoxic pulmonary vasoconstriction, driven by alveolar hypoxia.[33] Indeed, the degree of pulmonary vasoconstriction appears contingent on the severity and duration of hypoxia.[42,43] The molecular basis of this response remains uncertain. Hypoxia appears to induce calcium influx with consequent membrane depolarization in pulmonary arterial smooth muscle cells, while hypoxia-driven Rho kinase activation may also contribute to increased vascular tone.[44] However, mitochondrial and NADPH oxidase function, and associated generation of reactive oxygen species, also appear to play a key role.[45]

Hypoxia also appears to contribute to the development of endothelial dysfunction, characterized by loss of the physiological balance between vasodilation and vasoconstriction. The key mediator of endothelium-dependent vasodilation is nitric oxide, the constitutional expression of which is dependent on endothelial nitric oxide synthase activity. Hypoxia has been demonstrated to impair endothelium-dependent pulmonary artery relaxation in subjects with severe COPD, suggesting a diminution of nitric oxide bioavailability.[46] Conversely, hypoxia appears to upregulate production of vasoconstrictive mediators, such as endothelin-1, thus leading to increased vascular tone.[47] Other factors related to hypoxia that may contribute to the development of pulmonary hypertension, such as systemic inflammation and polycythemia, are discussed in detail elsewhere in this review.

A number of studies have suggested a link between defined genetic mutations and the occurrence of pulmonary hypertension in COPD. The largest of these is the National Emphysema Treatment Trial Genetics Ancillary study, which examined candidate gene single nucleotide polymorphisms in 389 subjects with severe COPD.[48] In this cohort, a single nucleotide polymorphism within the surfactant protein-B gene was associated with elevated systolic pulmonary artery pressure. Meanwhile, separate studies by Eddahibi et al show that polymorphisms in the serotonin transporter gene and the interleukin-6 gene confer increased risk of pulmonary hypertension in COPD patients.[49,50] However, conflicting results have been reported in studies evaluating the role of endothelial nitric oxide synthase and angiotensin-converting enzyme polymorphisms.[51–53] To date, no large-scale linkage studies or genome-wide association studies have been published in this field.

LTOT is the treatment of choice for COPD patients with pulmonary hypertension. Subjects receiving continuous oxygen therapy in the Nocturnal Oxygen Therapy Trial showed a reduction in pulmonary vascular resistance and pulmonary artery pressures,[54] while LTOT led to stabilization of pulmonary hemodynamics in the Medical Research Council study.[55] In contrast, there is little evidence to support the use of dedicated pharmacological therapies for pulmonary hypertension, including calcium channel blockers, inhibitors of the renin-angiotensin system, endothelin-receptor antagonists, prostacyclin analogs, or phosphodiesterase-5 inhibitors. While some of these interventions may improve pulmonary hemodynamics, this has been observed to occur at the expense of a deterioration in gas exchange in some patients.[56]

In the pre-LTOT era, the presence of pulmonary hypertension portended a particularly poor prognosis for COPD patients. In 1981, Weitzenblum et al found subjects with a mean pulmonary artery pressure of >20 mmHg at baseline had a seven-year survival of 29.2% versus 55.6% in the group without pulmonary hypertension.[57] Conversely, a normal pulmonary artery pressure was predictive of prolonged survival.[58] Supplemental oxygen therapy appears to stabilize, and occasionally reverse pulmonary hypertension in COPD patients.[33] Despite this, the presence of pulmonary hypertension remains predictive of adverse outcomes even in patients receiving LTOT.[59]

Polycythemia

COPD has long been recognized as an important cause of secondary polycythemia. Early reports include that of Epstein in 1912,[60] which described polycythemia occurring in cases of "respiratory embarrassment", including emphysema, while an association between the presence of polycythemia and increased risk of mortality was observed by Weber in 1913.[61] When present in COPD, polycythemia can contribute to the development of pulmonary hypertension, and leads to pulmonary endothelial dysfunction, reduced cerebral blood flow, hyperuricemia and gout, and increased risk of venous thromboembolic disease.[62–65]

More recent studies suggest polycythemia is less of an issue in modern COPD populations. Analysis of a prospective cohort of 683 stable COPD outpatients by Cote et al revealed a prevalence of only 6%,[66] while only 8.4% of over 2500 French patients with severe COPD receiving LTOT had a hematocrit greater than 55%.[67] This low prevalence may be at least partially attributable to the widespread prescription of LTOT in severe COPD populations.

Strikingly, anemia seems highly prevalent in these populations, and is predictive of increased mortality. Indeed, Chambellan et al found mortality decreased by 14% for every 5% increase in hematocrit.[67] A number of explanations have been advanced to account for these findings. COPD is associated with chronic, low-grade systemic inflammation, which may lead to anemia of chronic disease,[68] and emerging evidence suggests clinically occult chronic kidney disease may be common in elderly patients with COPD, potentially leading to anemia via impaired production of erythropoietin.[69]

The development of polycythemia in response to hypoxemia is critically dependent on the transcription factor hypoxia-inducible factor (HIF)-1, which functions as the master regulator of cellular oxygen homeostasis. HIF-1 is a heterodimeric protein consisting of a constitutively expressed β subunit, and an oxygen-regulated α subunit. In normoxic conditions, the latter is hydroxylated by a family of proline hydroxylases, and subsequently ubiquinated and degraded. The presence of cellular hypoxia allows stable HIF-1 to induce adaptive genes, such as vascular endothelial growth factor and erythropoietin.[70] However, HIF-1 can lead to maladaptive responses. One example of this is the generation of polycythemia in patients with COPD, resulting from HIF-1 upregulation driven by hypoxemia.

A number of interventions have been assessed in polycythemic COPD patients. In the Nocturnal Oxygen Therapy Trial, continuous oxygen therapy had a greater beneficial impact on mortality in patients with a hematocrit of >47.4%,[54] while the Medical Research Council study showed LTOT reduced risk of death in patients with hypoxic cor pulmonale, hypercapnia, and secondary polycythemia.[55] Pharmacological interventions, such as administration of theophylline[71] or antagonism of the renin-angiotensin pathway with losartan, may reduce secondary erythrocytosis in COPD patients.[72] In selected subjects, venesection can ameliorate pulmonary hypertension.[73]

While relatively uncommon in modern COPD populations, historic evidence suggests that, when present, polycythemia can contribute to diminished quality of life, increased morbidity, and excess mortality. As with pulmonary hypertension, its presence in a COPD patient should prompt consideration of supplemental oxygen therapy.

Systemic inflammation

In common with other chronic diseases, subjects with COPD have increased circulating markers of systemic inflammation when compared with healthy controls.[74] Systemic inflammation drives atherosclerosis and promotes cardiovascular disease, and in COPD patients may also contribute to the development of skeletal muscle dysfunction, osteopenia, and depression.[75] Moreover, the degree of systemic inflammation present appears to correlate with clinical outcomes. Elevated C-reactive protein levels are predictive of increased cardiovascular morbidity,[76] increased risk of hospitalization, and, ultimately, increased mortality.[77]

Several factors likely play a role in the genesis of systemic inflammation of COPD. These include tobacco use, airway inflammation, airflow obstruction, and hyperinflation.[75] However, an independent role for tissue hypoxia seems likely.

The transcription factor nuclear factor κB (NFκB) is the master regulator of cellular inflammatory responses, controlling expression of key inflammatory cytokines, such as tumor necrosis factor alpha (TNFα) and interleukin-8.[78] Evidence of a role for hypoxia in the induction of an NFκB response comes from in vitro, in vivo, and clinical studies. Intermittent hypoxia is classically seen in patients with obstructive sleep apnea syndrome, but may arise in COPD, particularly during sleep or exertion. Intermittent hypoxia induces upregulation of NFκB- dependent cytokines in endothelial cells in vitro, while systemic inflammation increases with nocturnal hypoxemia in subjects with obstructive sleep apnea syndrome.[79]

In sustained hypoxia, NFκB appears to interact with HIF-1α to promote the expression of inflammatory genes, such as cyclo-oygenase II.[80] Similarly, in a rodent model, 24 hours of sustained hypoxia has been shown to upregulate NFκB activity in pulmonary and cardiac tissue.[80]

Meanwhile, clinical studies in COPD patients have found that circulating levels of TNFα and soluble TNF receptors increase as arterial oxygen tension decreases.[81]

How systemic inflammation arises in COPD remains somewhat controversial.

A number of studies have suggested it may result from "overspill" of inflammatory mediators from the lungs and pulmonary circulation, while others have failed to find any correlation between measurable pulmonary and circulating inflammatory mediators.[82]

One potentially important source of inflammation in obese patients with COPD is white adipose tissue. In obese subjects, white adipose tissue is dysfunctional and inflamed. A growing body of evidence supports a role for tissue hypoxia in the genesis of this inflammation.[83] Indeed, adipose tissue oxygenation appears to correlate negatively with the degree of obesity present.[84] When exposed to hypoxia in vitro, adipocytes take on a dysfunctional, diabetogenic, and proinflammatory phenotype.[83] Obesity is highly prevalent in modern COPD cohorts, and recent studies would suggest white adipose tissue inflammation is significantly greater in hypoxemic patients with advanced disease.[85]

This systemic inflammation is at least partially reversible. Treatment with inhaled or oral corticosteroids has been shown to reduce the degree of systemic inflammation in COPD patients.[86] However, trials of more targeted anti-inflammatory therapies have been disappointing. Blockade of TNFα with the monoclonal antibody, infliximab, in patients with moderate-severe COPD fails to produce a significant decrease in systemic inflammation, provides no objective clinical benefit, and may be associated with an increased risk of pneumonia.[87,88] The effect of supplemental oxygen therapy in this regard is uncertain, with some authors reporting an increase, and others a decrease, of inflammatory markers following oxygen administration.[89,90]

Skeletal muscle dysfunction

Skeletal muscle dysfunction is an important extrapulmonary consequence of COPD. Particularly affecting the quadriceps, this manifests as decreased muscle strength with reduced endurance capacity. At a microscopic level, muscle fiber atrophy and alteration of fiber type can be seen.[91] The presence of skeletal muscle dysfunction is a key prognostic indicator in patients with severe COPD. Muscle weakness is predictive of reduced exercise capacity, increased health care utilization, and increased risk of readmission following hospitalization for an exacerbation.[92] In patients with moderate-severe disease, reduced quadriceps strength predicts increased mortality, independent of age, nutritional status, or degree of airflow obstruction.[93]

A number of factors appear to interact in the generation of skeletal muscle dysfunction in COPD. These include disuse atrophy, malnutrition, corticosteroid usage, and hormonal dysregulation.[91] However, there is increasing evidence that chronic hypoxemia may significantly contribute to this process. Healthy subjects exposed to chronic hypoxia at altitude undergo a reduction in muscle strength and endurance, with a concomitant alteration in composition.[94] Similarly, chronically hypoxemic COPD patients have accentuated muscle dysfunction, an effect that is partially reversed by supplemental oxygen.[95]

Hypoxia may contribute to skeletal muscle dysfunction in COPD patients by a number of mechanisms. As discussed above, hypoxia helps generate the low-grade chronic systemic inflammation that characterizes COPD. TNFα can provoke muscle cell apoptosis and protein degradation via the ubiquitin/proteasome system.[91] Levels of TNFα, and of other circulating inflammatory cytokines, such as interleukin-8, have been shown to correlate with the degree of muscle dysfunction in COPD,[96] while NFκB activation appears to occur in the skeletal muscle of COPD patients with low body weight.[97] These findings have suggested that systemic inflammation may be a contributory factor in skeletal muscle dysfunction. However, other studies have failed to demonstrate an increase in inflammatory cytokine expression in quadriceps biopsies from patients with severe COPD,[98] and the area remains somewhat controversial.

Another possible contributor to skeletal muscle dysfunction is the generation of oxidative stress. Reactive oxygen species are produced in normal aerobic metabolism, and at physiological levels act in a beneficial manner, participating in cell signaling and host-defense against infection. However, higher concentrations of reactive oxygen species can mediate damage to lipids, proteins, and DNA, and drive inflammatory cascades. Reactive oxygen species generation is usually balanced by enzymatic (eg, superoxide dismutase) and nonenzymatic (eg, glutathione) antioxidant defense mechanisms. Oxidative stress occurs when there is an imbalance between the generation of reactive oxygen species and antioxidant capacity. Oxidative stress impairs skeletal muscle contractility, and subjects with COPD have evidence of increased oxidative stress, particularly following exercise.[93,99] This effect appears particularly marked in chronically hypoxemic subjects, in whom markers of oxidative stress

are significantly increased in peripheral muscle specimens at rest and following exercise.[100]

Chronic hypoxemia may also directly affect smooth muscle function. The AKt/mTOR (mammalian target of rapamycin) pathway regulates skeletal muscle mass and prevents muscle atrophy.[101] Hypoxia has been demonstrated to downregulate this pathway in a rodent model, possibly via overexpression of the hypoxia-induced gene, *REDD1* (regulated in development and DNA damage response 1), thus leading to reduced muscle mass.[102] Comparative analysis of skeletal muscle from hypoxemic and nonhypoxemic COPD patients demonstrates inhibition of mTOR signaling in the former. Furthermore, von Hippel-Lindau protein appears to be overexpressed in the skeletal muscle of patients with COPD, thereby potentially impairing HIF-1α-mediated adaptive pathways in hypoxia.[103]

Thus, chronic hypoxemia may contribute to skeletal muscle dysfunction via both systemic factors, such as systemic inflammation, and local factors, such as direct inhibition of cellular pathways and local induction of oxidative stress.

Neurocognitive dysfunction

Neurocognitive dysfunction appears to be relatively common in COPD populations, and appears to increase in prevalence with impairment in gas exchange.[104] When present, impaired cognitive function is associated with reduced quality in life, and may be predictive of increased morbidity and mortality in COPD patients. A number of factors have been postulated to contribute to this, including concomitant vascular disease and smoking. However, resting hypoxemia appears to be a key risk factor, with markedly increased prevalence among subjects with severe hypoxemia.[104] Suggested mechanisms include systemic inflammation and oxidative stress leading to direct neuronal damage, as well as depletion of neurotransmitters due to dysfunction of oxygen-dependent enzymes. Once again, the potential benefits of oxygen therapy are debated, with some authors failing to demonstrate any effect,[105] while others have found supplemental oxygen to be protective against, or capable of ameliorating, neurocognitive dysfunction.[106,107]

Supplemental oxygen therapy

Although supplemental oxygen had been used in the treatment of patients with emphysema and chronic bronchitis for decades, its ability to prolong survival in selected COPD populations was only conclusively established in the early 1980s. The Nocturnal Oxygen Therapy Trial and Medical Research Council trial, both relatively small by modern standards, demonstrated increased survival in markedly hypoxemic patients receiving more than 18 hours of supplemental oxygen per day when compared either with those receiving oxygen for 12 hours per day, or those receiving no treatment.[54,55] Subsequent studies have shown supplemental oxygen can reduce pulmonary hypertension, improve neurocognitive function, increase exercise tolerance, and reduce frequency of exacerbations.[5]

Its utility in populations with moderate daytime hypoxemia, nocturnal hypoxemia, or exertional oxyhemoglobin desaturation remains less clear. The available evidence suggests that supplemental oxygen does not prolong survival in these patients, but further carefully designed studies investigating its potential to improve survival, function, and well-being are warranted.[108]

The use of supplemental oxygen is not free of risk. When administered in supraphysiological doses, oxygen therapy can lead to diminished ventilatory drive, increased ventilation/perfusion mismatch, and consequent hypercapnia. However, controlled oxygen therapy, targeting an oxygen saturation in the 90%–92% range, is not likely to result in clinically significant hypercapnia.[109] Oxygen administration has been shown to generate oxidative stress and airway inflammation, which could theoretically contribute to further tissue damage and progression of disease.[5]

Finally, the drawbacks of LTOT use are not all medical. Quite apart from significant financial cost, and the perceived societal stigma of LTOT, the combination of cigarette smoking and oxygen use is a potentially lethal one. Although this is generally considered to be an absolute contraindication to the prescription of supplemental oxygen, reports suggest up to 20% of COPD patients receiving LTOT may be active smokers.[110] Whether supplemental oxygen therapy should be withdrawn from such patients remains an underexplored and a rather fraught question.

Conclusion

Alveolar hypoxia and consequent hypoxemia increase in prevalence as COPD severity increases. Chronic hypoxemia contributes to the development of adverse sequelae of COPD, such as pulmonary hypertension, secondary polycythemia, skeletal muscle dysfunction, and systemic inflammation. These comorbidities reduce quality of life in COPD patients, and predispose them to acute exacerbations, cardiovascular morbidity, and increased risk of death.

Supplemental oxygen therapy improves quality of life and survival in selected cases. However, its role in patients with moderate hypoxia, or isolated exertional or nocturnal hypoxia, remains unclear.

Disclosure

The authors report no conflicts of interest in this work.

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