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Review Article

COPD and stroke: are systemic inflammation and oxidative stress the missing links?

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Abstract

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation and loss of lung function, and is currently the third largest cause of death in the world. It is now well established that cardiovascular-related comorbidities such as stroke contribute to morbidity and mortality in COPD. The mechanisms linking COPD and stroke remain to be fully defined but are likely to be interconnected. The association between COPD and stroke may be largely dependent on shared risk factors such as aging and smoking, or the association of COPD with traditional stroke risk factors. In addition, we propose that COPD-related systemic inflammation and oxidative stress may play important roles by promoting cerebral vascular dysfunction and platelet hyperactivity. In this review, we briefly discuss the pathogenesis of COPD, acute exacerbations of COPD (AECOPD) and cardiovascular comorbidities associated with COPD, in particular stroke. We also highlight and discuss the potential mechanisms underpinning the link between COPD and stroke, with a particular focus on the roles of systemic inflammation and oxidative stress.

Key words: cardiovascular disease, chronic obstructive pulmonary disease (COPD), comorbidities, oxidative stress, stroke, systemic inflammation.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major incurable global health burden and is currently the third largest cause of death in the world [1–3]. Much of the disease burden and health care utilization in COPD is associated with the management of its comorbidities and infectious (viral and bacterial) exacerbations (acute exacerbation of COPD; AECOPD). In the United States alone, the medical costs attributed to COPD in 2010 were estimated to be in excess of $32 billion [4]. Comorbidities, defined as other chronic medical conditions, in particular cardiovascular disease (CVD) markedly impact on disease morbidity, progression and mortality. Indeed, it is estimated that between 30% and 50% of COPD-related deaths are due to a cardiovascular comorbidity such as coronary artery disease, hypertension and diabetes [5–7]. In addition, patients with COPD are at increased risk for stroke and this is even higher in the weeks following an AECOPD [8,9].

The mechanisms and mediators underlying COPD and its comorbidities are poorly understood. However, there is compelling evidence to suggest that increased oxidative stress and the 'spill over' of lung inflammation into the systemic circulation play an important role in the pathophysiology of COPD and its comorbidities. Therefore, although there are currently no effective therapies for reversing the lung pathology that is the characteristic of COPD [10], targeting oxidative stress and lung/systemic inflammation could prove to be an effective way to improve survival and quality of life in these patients. In this review, we briefly describe the pathogenesis of COPD, AECOPD and cardiovascular comorbidities associated with COPD, in particular stroke. In addition, we discuss the mechanisms common to both COPD and stroke and how these could explain why patients with COPD are at increased risk of stroke.

OVERVIEW OF COPD PATHOPHYSIOLOGY

COPD is a disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and

Abbreviations: AECOPD, acute exacerbations of COPD; BAL, bronchoalveolar lavage; BBB, blood–brain barrier; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVD, cardiovascular disease; EBC, exhaled breath condensate; Gpx, glutathione peroxidase; GSH, glutathione; GM-CSF, granulocyte-macrophage colony-stimulating factor; H_2O_2, hydrogen peroxide; IL-6, interleukin-6; IL-8, interleukin-8; MDA, malondialdehyde; MI, myocardial infarction; NO, nitric oxide; $O_2^{\bullet-}$, superoxide radical; $^{\bullet}OH$, hydroxyl radical; $ONOO^-$, peroxynitrite; PWV, carotid-femoral pulse wave velocity; ROS, reactive oxygen species; SAA, serum amyloid A; SOD, superoxide dismutase; TNF-α, tumour necrosis factor-α.

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associated with an abnormal inflammatory response of lungs to noxious particles and gases [11]. Cigarette smoking is the major cause of COPD and accounts for more than 95% of cases in industrialized countries [12], but other environmental pollutants are important causes in developing countries [13]. COPD encompasses chronic obstructive bronchiolitis with fibrosis and obstruction of small airways, and emphysema with enlargement of airspaces and destruction of lung parenchyma, loss of lung elasticity and closure of small airways. Most patients with COPD have all three pathologic conditions (chronic obstructive bronchiolitis, emphysema and mucus plugging), but the relative extent of emphysema and obstructive bronchiolitis within individual patients can vary [14].

It is well established that a number of inflammatory cell types are involved in the pathophysiology of COPD including macrophages, neutrophils and T-cells (reviewed in [14–17]). These cells release a variety of mediators [e.g. tumour necrosis factor (TNF)-α, monocyte chemotactic protein-1, reactive oxygen species (ROS), leukotriene B_4 (LTB_4), interleukin (IL)-8, granulocyte-macrophage colony- stimulating factor (GM-CSF), elastolytic enzymes such as neutrophil elastase and matrix metalloproteinases] in response to cigarette smoke which orchestrate and perpetuate the inflammatory response in COPD (reviewed in [14–17]). In addition to an increase in the number of macrophages and neutrophils, these cells appear to have an impaired phagocytic function, resulting in impairment in clearance of apoptotic cells and potentially contributing to the chronic inflammatory state in the lungs [14]. The above events promote further inflammation creating a feedback loop that leads to chronic inflammation. Chronic inflammation induces repeated cycles of injury and repair that result in structural remodelling of the airway walls (collagen deposition and mucus hypersecretion), destruction of the parenchyma and alveolar walls and hence alveolar enlargement and emphysema. Once induced, the patient's condition progressively deteriorates with worsening inflammation, emphysema, declining lung function and increased breathlessness. Importantly, the mechanisms and mediators that drive the induction and progression of chronic inflammation, emphysema and altered lung function are not well understood, and this has severely hampered the development of effective treatments for COPD. In addition, current treatments have limited efficacy in inhibiting chronic inflammation, do not reverse the pathology of disease and fail to modify the factors that initiate and drive the long-term progression of disease [17]. Therefore, there is a clear and demonstrated need for new therapies that can prevent the induction and progression of COPD.

ACUTE EXACERBATIONS OF COPD

An AECOPD is defined as 'a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variation, which is acute in onset and necessitates change in regular medication in a patient with underlying COPD' [18]. Exacerbations are a common occurrence in COPD patients and contribute mainly to morbidity, death and health-related quality of life [18]. AECOPD is a major cause of avoidable hospital admissions and often due to viral and bacterial infections with 40%–60% attributed to viral infections alone [18]. The majority of these infections are due to respiratory syncytial virus (22%), influenza A (25%) and picornavirus (36%), with influenza having the potential to be more problematic due to the likelihood of an epidemic [18–20]. Respiratory viruses produce longer and more severe exacerbations and have a major impact on health care utilization [20,21]. Currently, bronchodilator combinations modestly reduce the risk of exacerbation by approximately 30% and are even less effective at preventing severe exacerbations that result in hospitalization [18].

The understanding of the cellular and molecular mechanisms underlying AECOPD are limited, but there is an increase in neutrophils and concentrations of IL-6, IL-8, TNFα and LTB_4 in sputum during an exacerbation [22,23] and patients who have frequent exacerbations have higher levels of IL-6 and lower concentrations of SLPI, even when COPD is stable [24,25]. There is also an increase in the activation of NF-κB in alveolar macrophages during exacerbations of COPD [26] which is indicative of an inflammatory environment.

OXIDATIVE STRESS IN COPD AND AECOPD

There is now extensive evidence to show that oxidative stress plays an important role in COPD given the increased oxidant burden in smokers [27,28]. Oxidative stress is initiated by cigarette smoke which has more than 10^{14} relatively long-lived oxidants/free radicals per puff [29]. These oxidants give rise to secondary ROS by inflammatory and epithelial cells within the lung as part of an inflammatory-immune response towards a pathogen or irritant. Activation of NADPH oxidase 2 (Nox2) on macrophages, neutrophils and epithelium generates superoxide radicals ($O_2^{\bullet -}$), which can then either react with nitric oxide (NO) to form highly reactive peroxynitrite molecules ($ONOO^-$) or alternatively be rapidly converted into damaging hydrogen peroxide (H_2O_2) under the influence of superoxide dismutase (SOD) [30–33]. This in turn can result in the non-enzymatic production of damaging hydroxyl radical ($^{\bullet}OH$) from H_2O_2 in the presence of Fe^{2+}. Polymorphisms in extracellular SOD have been associated with reduced lung function and susceptibility to COPD [34]. Glutathione peroxidases (Gpxs) and catalase serve to catalyse toxic H_2O_2 into water and oxygen. The ROS $O_2^{\bullet -}$, $ONOO^-$, H_2O_2 and $^{\bullet}OH$ then trigger extensive inflammation, DNA damage, protein denaturation and lipid peroxidation [29]. Consequently, smokers and patients with COPD have higher levels of exhaled ROS than non-smokers, and these levels are further increased during exacerbations [35,36]. We have shown that loss of the antioxidant enzyme Gpx-1 resulted in augmented cigarette smoke-induced lung inflammation compared with sham-exposed wild-type mice and that synthetic repletion of Gpx activity with ebselen reduced cigarette smoke-induced lung inflammation and damage [37].

Alveolar macrophages obtained by bronchoalveolar lavage (BAL) from the lungs of smokers are primed to release greater

amounts of ROS compared with those obtained from non-smokers [38]. Exposure to cigarette smoke *in vitro* has also been shown to increase the oxidative metabolism of alveolar macrophages [39]. Subpopulations of alveolar macrophages with a higher granular density appear to be more prevalent in the lungs of smokers and are responsible for the increased $O_2^{\bullet -}$ production associated with macrophages from smokers [39,40]. The generation of ROS in epithelial lining fluid may be further enhanced by the presence of increased amounts of free iron in the pulmonary airspaces in smokers [41]. This is relevant to COPD since the intracellular iron content of alveolar macrophages is increased in cigarette smokers [42]. In addition, macrophages obtained from smokers release more free iron *in vitro* than those from non-smokers [43].

EVIDENCE OF SYSTEMIC INFLAMMATION AND OXIDATIVE STRESS IN COPD

In addition to lung inflammation, a state of chronic systemic inflammation is observed in COPD [44]. Studies have shown increases in the serum levels of C-reactive protein (CRP), fibrinogen, serum amyloid A (SAA) and different pro-inflammatory cytokines including TNFα, IL-6 and IL-8 in COPD patients [45–47]. Importantly, these markers of systemic inflammation are elevated even further during AECOPD [48]. The origin of this systemic inflammation remains unclear. However, one explanation is that the inflammatory cells and pro-inflammatory mediators present in the lungs 'spill over' into the systemic circulation [45,49]. This state of chronic low-grade systemic inflammation is thought to contribute to the development of comorbidities of COPD [45,49].

The contribution of systemic oxidative stress in COPD has also been recognized. There is an increased concentration of H_2O_2 in the exhaled breath condensate (EBC) of smokers and patients with COPD compared with non-smokers, and those are further increased during exacerbations [35,36]. In addition, concentrations of lipid peroxidation products [e.g. 8-isoprostane, 4-hydroxy-2-nonenal and malondialdehyde (MDA)], LTB_4, carbon monoxide and myeloperoxidase (MPO) have consistently been shown to be elevated in exhaled breath or EBC from patients with COPD [47,50]. Systemic exposure to oxidative stress in COPD is also indicated by increased carbonyl adducts, such as 4-hydroxy-2-nonenal in respiratory and skeletal muscle [51–53]. Moreover, systemic markers of oxidative stress such as oxidized low-density lipoprotein, advanced oxidation protein products and MDA are elevated in COPD patients [54,55].

In order to combat and neutralize the deleterious effects of ROS-mediated damage, the normal lung has various endogenous antioxidant strategies, which employ both enzymatic and non-enzymatic mechanisms. Within the lung lining fluid, several non-enzymatic antioxidant species exist, which include glutathione (GSH), vitamin C, uric acid, vitamin E and albumin [56]. Enzymatic antioxidant mechanisms include SOD, catalase and Gpx. However, studies have shown that COPD patients have a systemic antioxidant imbalance, including reduced vitamin C, GSH and Gpx [50,57]. Moreover, polymorphisms in extracellular SOD have been associated with reduced lung function and susceptibility to COPD [34].

COPD AND CARDIOVASCULAR DISEASE

There is evidence showing that patients with COPD have an increased risk of CVD and thus are at greater risk of dying from cardiovascular causes [45,58,59]. Comorbid CVD can manifest itself in one or more various disorders such as angina, stroke, arrhythmia, hypertrophy of the heart and myocardial infarction (MI), and its presence greatly reduces the survivability of COPD patients [60]. Studies have reported that up to 40% of deaths in COPD patients is due to CVD [61–64] and more people with mild to moderate COPD die of cardiovascular causes than of respiratory failure [58]. Specifically, patients with COPD have a significantly higher risk of acute MI, arrhythmia and congestive heart failure [65]. Over 5 years of follow-up and compared with patients without COPD, patients with COPD had higher rates of death, MI, stroke and a higher rate of hospitalization due to heart failure, unstable angina or arterial revascularization [66]. Studies have shown that over 50% of patients hospitalized for AECOPD have a high prevalence of coexisting CVD [67]. It has also been demonstrated that cardiovascular risk is even more pronounced, and has a greater effect, during the peri-exacerbation period due to further increases in pulmonary and systemic inflammation. One to five days after a severe exacerbation, the risk of MI increases 2–3 times [8] and subclinical ischaemia might be even more common during these events, as well as during exacerbations of only moderate severity [68]. A retrospective review examining 24 h mortality following AECOPD hospitalization found that approximately 60% of deaths that occurred resulted from cardiovascular causes [69]. It has also recently been shown that patients with COPD are at increased risk for stroke and this is even higher (approximately 7-fold) in the weeks following an acute severe exacerbation [9].

OVERVIEW OF STROKE PATHOPHYSIOLOGY

In 2013, stroke was the second-leading global cause of death behind heart disease, accounting for 11.8% of total deaths worldwide [70]. Moreover, stroke is a leading cause of disability. Indeed, it is estimated that up to 30% of stroke survivors do not recover full independence, and thus require assistance with self-care for the rest of their lives [70]. In 2012, the estimated cost for stroke was $33 billion (U.S.A.) and is projected to be $1.52 trillion by 2050 for non-Hispanic whites, $313 billion for Hispanics and $379 billion for blacks (in 2005 dollars) [70]. Thus, the personal and economic burden of stroke is staggering.

Ischaemic stroke is the most common subtype, accounting for approximately 80% of all strokes. This type of stroke typically occurs as a result of a blockage of a cerebral blood vessel

by a thrombotic (usually on an atherosclerotic plaque) or embolic clot, or as a result of cerebral vascular insufficiency due to structural (e.g. atherosclerosis) and/or functional abnormalities of cerebral blood vessels. Ischaemic stroke can be further classified depending on the aetiology such as large-artery atherothrombosis, cerebral small vessel disease resulting in lacunar stroke and cardioembolism. Less frequently, stroke can occur as a result of haemorrhage (intracerebral approximately 10% or subarachnoid approximately 3%) or cardiac arrest. There are number of traditional risk factors for stroke. Some stroke risk factors cannot be modified, for example age, genetic predisposition, gender (male) and race, whereas others are potentially modifiable. These include hypertension, hypercholesterolaemia, atrial fibrillation, diabetes and smoking, which account for >60% of stroke risk and often coexist [71]. Moreover, as discussed above, lung diseases including COPD are emerging as 'novel' stroke risk factors.

The pathogenesis of ischaemic stroke is very complex. In brain tissue of the ischaemic core, which is a region characterized by a severe reduction in cerebral blood flow, cell death occurs rapidly and largely as a result of energy failure and subsequent necrotic death [72]. Injury to brain tissue surrounding the infarct core (the ischaemic penumbra), however, occurs over hours to days and multiple mechanisms are involved. These include excitotoxicity, calcium dysregulation, mitochondrial dysfunction, spreading depolarization and apoptotic cell death [72,73]. Oxidative and nitrosative stress also play a key role in injury development in this region [74]. Compelling evidence implicates the ROS-generating NADPH oxidases as key drivers of oxidative stress-induced brain and vascular injury following cerebral ischaemia [75–79]. Substantial evidence also supports the importance of inflammation and immune system activation in injury development and expansion after stroke [80,81]. Moreover, there is a growing appreciation of the vascular contribution, particularly at the level of the neurovascular unit [82]. The neurovascular unit is a collective term for the structural and functional association between neurons, perivascular astrocytes, vascular smooth muscle cells (pericytes/astrocytes), endothelial cells and the basal lamina [83]. Together, the components of the neurovascular unit act to regulate and maintain cerebral perfusion, preserve homoeostatic balance in the brain and control immune regulation. Furthermore, it represents the primary site of the blood–brain barrier (BBB). Cerebral ischaemia has devastating effects on both the structure and functioning of the neurovascular unit. It impairs endothelial function and thus brain perfusion, disrupts the BBB by increasing its permeability and enhances inflammatory cell infiltration [82]. Collectively, these mechanisms contribute to and exacerbate brain injury [82].

During intracerebral haemorrhage, the most common type of haemorrhage stroke, the accumulation of blood within the brain leads to rapid damage as a result of mechanical injury and increased pressure [84]. Secondary damage can also occur due to the presence of intraparenchymal blood. Similar to ischaemic stroke, multiple pathological pathways are involved including excitotoxicity, oxidative stress, inflammation, cytotoxicity of blood, hypermetabolism and disruption of the neurovascular unit and BBB [85].

EVIDENCE LINKING LUNG FUNCTION, COPD AND STROKE

Link between poor lung function and risk of cerebral events

Studies have shown that impairment in lung function is related to an increased risk of stroke [86–90]. Previous studies have shown that reduced FEV_1 is associated with an increased incidence of both ischaemic and haemorrhagic stroke, and this association is independent of smoking status [86–90]. Similar associations have been observed linking reduced pulmonary function and higher risk of subclinical cerebrovascular abnormalities, including in individuals who have never smoked [91,92]. These asymptomatic lesions, such as silent lacunar infarcts, white matter lesions and cerebral microbleeds are considered to be precursors of clinical stroke and manifestations of cerebral small vessel disease [93–95]. Additionally, associations between lower FEV_1 and markers of subclinical atherosclerosis have been reported, although the relevance of this to the presence of subclinical infarcts and white matter lesions is unclear [96]. The explanations for these observations are unclear, although impairments in lung function and lung volume may reflect impairments in cardiac function [97,98].

COPD and risk of clinical stroke

Previous studies have shown that strokes are more prevalent in COPD compared with the general population [99–101]. COPD patients are reported to have an increased risk of approximately 20% for both ischaemic and haemorrhagic strokes [9,65,102]. This risk is estimated to be up to 7-fold higher following an AE-COPD compared with stable COPD [9], suggesting that COPD itself is contributing to an increase in stroke risk, as opposed to the risk being solely due to shared risk factors. Despite an increased risk of stroke in COPD, no association between the presence of COPD and stroke severity or short-term mortality has yet been shown to exist. However, given that COPD results in systemic inflammation and oxidative stress, which are key mechanisms of stroke-related brain injury, one might predict that COPD also results in a worsening of stroke severity. Consistent with this, studies have shown that chronic inflammatory airway disease (CIAD) is an independent risk factor for long-term mortality post-stroke [103]. It is also known that stroke causes lung injury/dysfunction *per se* as evidenced by impaired cough, weakness of respiratory muscles and increase in the propensity of pneumonia [104–107]. Therefore, it is plausible that worsening of lung function due to stroke could contribute to the increased in long-term mortality after stroke.

POTENTIAL MECHANISMS LINKING COPD AND STROKE RISK

Contribution of shared risk factors

The factors linking COPD and stroke risk are currently not fully understood and are likely to be interconnected. It is well known that two of the most important risk factors for COPD, chronic cigarette smoking and aging, are also established risk factors

for stroke [108,109]. Thus, the association between COPD and stroke may be largely dependent on these shared risk factors [9]. Like other traditional stroke risk factors, aging and chronic smoking increase the propensity to stroke by impairing the ability of the cerebral circulation to meet the brain's high-energy demands. This largely occurs as a result of structural and functional changes to cerebral blood vessels, resulting in vascular insufficiency and ultimately brain injury. For example, both risk factors often alter the structure of intracranial and extracranial blood vessels by promoting atherosclerosis, vascular atrophy and remodelling and vascular stiffness [110–114]. Moreover, these structural abnormalities are typically accompanied by functional impairments of cerebral blood vessels resulting in alterations in cerebral blood flow regulation. Indeed, it is well documented that smoking (and nicotine) and aging cause endothelial dysfunction [115–121], which in turn, is associated with an increased risk of stroke [122,123]. Also, they impair neurovascular coupling [124–127], which is an essential adaptive mechanism that matches cerebral blood flow to neuronal activity. Lastly, aging and smoking can disrupt the BBB [128–130], which may contribute to the increased risk of intracerebral haemorrhage and microbleeds in COPD.

Evidence indicates that aging and smoking produce vascular impairments, at least in part, by promoting oxidative stress, which is driven primarily by the NADPH oxidases [119,120,124]. Perhaps the best characterized mechanism by which oxidative stress can cause vascular dysfunction is via the inactivation of endothelial-derived NO by $O_2^{\bullet-}$ [131]. This reaction reduces the bioavailability of NO and thus nullifies its vasodilator, anti-platelet, anti-proliferative and anti-inflammatory properties. In addition, ROS can directly promote inflammation in the vessel wall by inducing the production of cytokines and pro-inflammatory genes through the activation of NF-κB [132]. Importantly, whereas oxidative stress may set the stage for inflammation, it in turn accentuates ROS production, creating a vicious cycle that worsens vascular dysfunction [73]. Indeed, pro-inflammatory cytokines such as TNF-α and IL-6 alter the functioning of cerebral vessels by increasing ROS production via the NADPH oxidases [133,134]. Moreover, studies of systemic arteries infer that T-cells and macrophages also contribute [135,136]. Oxidative stress and inflammation can also alter the structure of cerebral vessels by promoting vascular remodelling, stiffness, atherosclerosis and BBB disruption [73,137–139].

In addition to producing vascular insufficiency, it is likely that aging and chronic smoking modulate stroke risk by increasing the propensity for atherosclerotic plaque rupture [140]. The prothrombotic effects of smoking are well documented. For example, smoking increases platelet activation and triggers the coagulation cascade [141,142]. Similarly, aging is associated with increased platelet aggregation and enhanced thrombosis [143,144]. Thus, aging and smoking increase the risk of thrombotic/embolic events.

Association with traditional stroke risk factors

Some but not all studies have shown that an association between COPD and stroke still exists after adjusting for age and smoking status [9,95,102]. Thus, although it is difficult to correct for the total amount of smoking or environmental smoke exposure [7,145], stroke risk in COPD might not be wholly explained by the contribution of shared risk factors. As discussed, multiple studies have shown a link between COPD and the development of CVD. Moreover, vascular/stroke risk factors are common in COPD patients including hypertension, diabetes and hypercholesterolaemia [146,147]. Similar to aging and smoking, these traditional risk factors increase the propensity to stroke by altering the structure (e.g. atherosclerosis and vascular remodelling) and functioning of vessels, and by increasing the propensity for atherosclerotic plaque rupture and thrombus formation [131,137]. Moreover, oxidative (via the NADPH oxidases) and inflammatory mechanisms play vital roles in disease progression [148–156]. Thus, although the potential contributions of aging and smoking cannot be ignored [7], it is conceivable that the systemic inflammation and oxidative stress in COPD may initiate and/or accelerate the development of traditional stroke risk factors, thereby leading to increased stroke risk.

COPD-specific systemic inflammation and oxidative stress

Systemic inflammation is emerging as a non-traditional risk factor for stroke [157,158]. For example, systemic markers of inflammation such as CRP and total leucocyte counts, which are both elevated in COPD, are predictive markers of ischaemic stroke risk [159]. As discussed, inflammation and oxidative stress are major drivers of cerebral vascular dysfunction. Thus, although definitive proof is lacking, it is conceivable that the systemic inflammation and increased oxidative stress in COPD may independently increase stroke risk by directly promoting cerebral vascular dysfunction and thus vascular insufficiency. Consistent with this concept, COPD is associated with increased carotid-femoral pulse wave velocity (PWV; the 'gold standard' measurement of arterial stiffness) independent of cigarette smoke exposure [7,160,161]. Treatment of COPD patients with an antioxidant cocktail (vitamin C, vitamin E and α-lipoic acid) improves PWV implicating a role for oxidative stress. In COPD patients with frequent exacerbations, arterial stiffness increases and this is associated with inflammation [68]. Importantly, PWV is closely associated with lacunar stroke and white matter lesions [162], which as mentioned are key manifestations of cerebral small vessel disease. Functional abnormalities of systemic arteries have also been reported in COPD patients compared with control subjects and smokers with normal lung function. These include impaired flow-mediated dilation [161,163], a mechanism that is largely dependent on the production of NO by the endothelium. Moreover, evidence suggests that impairments in flow-mediated dilation are related to CRP levels but not pack-years of smoking protein levels are an independent predictor of flow-mediated dilation suggesting a role for inflammation [163]. Moreover, an antioxidant cocktail improves flow-mediated dilation in COPD patients, implicating a role for oxidative stress [161].

Our knowledge of cerebral artery function in COPD lags behind those studies of systemic arteries. However, evidence thus far suggests that COPD is associated with cerebral vascular disturbances. For example, in an experimental model of COPD, activation of endothelial-dependent dilator pathways

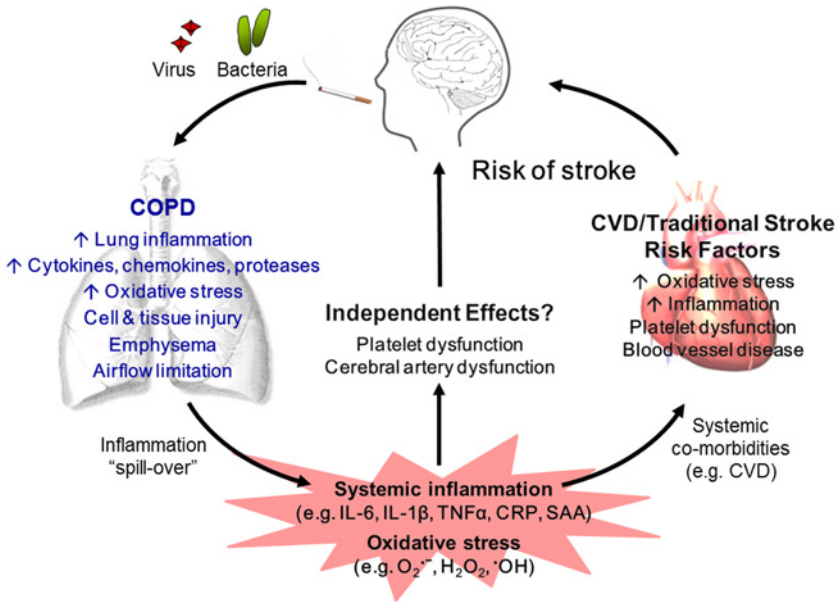

Figure 1 Increased oxidative stress and lung inflammation in response to cigarette smoke causes a spill over of cytokines (e.g. IL-6, TNF-α and SAA) into the systemic circulation

Systemic inflammation in COPD initiates and/or worsens comorbid conditions such as CVD/traditional stroke risk factors and stroke. Viral and bacterial pathogens markedly increase ROS production and systemic inflammation and hence exacerbate COPD and its comorbidities. Targeted co-inhibition of mechanisms underlying both COPD and stroke (e.g. oxidative stress, local and systemic inflammation) may lead to increased survival and improvements in quality of life of patients.

paradoxically leads to constriction of cerebral vessels (e.g. middle cerebral artery), indicative of endothelial dysfunction [164]. However, the roles of inflammation and oxidative stress in this dysfunction were not examined. Studies measuring cerebral blood flow in COPD patients have revealed contradictory findings [165–168]. Indeed, some investigators have revealed that cerebral blood flow is reduced in COPD patients [165,166], whereas other report that it is increased [167,168]. Other studies have focused on examining acute responses to hypercapnia in COPD patients [54,165,169]. It is well documented that in a healthy subjects, increased $PaCO_2$ results in cerebral vascular dilation and increased cerebral blood flow. Several mechanisms are responsible including a dilatory response of cerebral arteries, which is largely dependent on NO production. Some but not all studies report that COPD patients show decreased sensitivity to hypercapnia [54,165,169], inferring that NO-dependent cerebral vasodilator responses might be impaired. Consistent with this, one study found that these abnormalities were eliminated after adjustments were made for markers of oxidative stress, which might suggest a role for oxidative inactivation of NO [54]. However, it is important to remember that central chemoreceptors and the ventilatory response are also involved in hypercapnia cerebral vascular responses. Thus, it is conceivable that impairments of these mechanisms might also contribute. Clearly, more research is needed to fully investigate the impact of COPD (independent of smoking and aging) on the functioning of cerebral vessels, and how any such abnormalities relate to stroke risk.

Previous evidence suggests that patients with COPD have increased platelet activation, with further activation occurring during AECOPD [170]. CRP levels positively correlate with activation of the coagulation/fibrinolysis system after stroke, suggesting a link between coagulation and inflammation [171]. Also, excess levels of ROS such as H_2O_2 may lead to platelet hyperactivity and pro-thrombotic phenotype [143]. Thus, COPD-specific inflammation and oxidative stress may also influence stroke risk by increasing susceptibility to thrombotic or embolic events.

The link between acute infections and stroke is well documented. Indeed, numerous studies have shown that acute/chronic viral and bacterial infections are independent risk factors [158,172]. Moreover, this mainly relates to acute respiratory infections [173]. Multiple links between inflammation and coagulation may explain the link between infections and stroke *per se* [158,172]. Thus, given that systemic inflammation is elevated even further during an acute exacerbation, it is likely that such mechanisms may also underpin the increased stroke risk in COPD patients in the weeks following AECOPD.

Considerable evidence supports a relationship between systemic inflammation and poor outcome in stroke patients and in models of experimental stroke. Indeed, experimental models of comorbidities and stroke have shown that various systemic inflammatory mechanisms exacerbate brain damage and worsen functional deficits by augmenting cerebral vascular inflammation, BBB disruption, brain oedema and excitotoxicity [174–176]. Moreover, systemic inflammation activates microglia (the brain's resident immune cells) to induce cyclooxygenase-dependent neuroinflammation and increased $O_2^{\bullet-}$ production [177]. Thus, although future research is needed, it is

conceivable that in addition to increasing stroke risk, COPD-specific systemic inflammation and oxidative stress may worsen stroke severity and functional outcomes.

CONCLUSIONS

COPD is a major incurable global health burden and is currently the third largest cause of death in the world. Much of the disease burden and health care utilization in COPD is associated with the management of acute exacerbations and comorbidities including CVD. Current treatments have limited efficacy and fail to modify the long-term progression of COPD, its exacerbations and its comorbidities. No pharmacological treatment has been shown to reduce the risk of death in COPD in prospective clinical trials. It is now evident that increased oxidative stress within the local lung microenvironment is a major driving mechanism in the pathophysiology of COPD and that it may directly influence other organ (e.g. heart, brain and blood vessels) behaviour in a 'COPD-specific manner'. Moreover, as discussed in this review, patients with COPD are at increased risk for stroke and this is even higher in the weeks following an acute exacerbation. The mechanisms linking COPD and stroke are not fully understood and are likely to be interconnected. Shared risk factors (aging and smoking) and associations with the development of traditional stroke risk factors are likely to be important. Moreover, we propose systemic inflammation and oxidative stress may independently increase stroke risk by promoting cerebral artery dysfunction and thus vascular insufficiency, and by increasing susceptibility to thrombotic events due to excessive platelet activation (Figure 1). Thus, targeting these pathways may be the way of preventing stroke in COPD.

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