CHEST Translating Basic Research Into Clinical Practice

Oxidative Stress in COPD

Paul A. Kirkham, PhD; and Peter J. Barnes, DSc, FCCP

Oxidative stress is now recognized as a major predisposing factor in the pathogenesis of COPD. Existing therapies for COPD are ineffective at halting disease progression, with bronchodilators being the mainstay of pharmacotherapy, providing symptomatic relief only. It is, therefore, important for a better understanding of the underlying mechanisms by which oxidative stress drives disease pathogenesis to develop novel and more effective therapies. Antioxidant capacity in COPD is substantially reduced as a result of cigarette smoking and exacerbations, with oxidative stress persisting long after the cessation of cigarette smoking or exacerbation, due to the continued production of reactive oxygen species from endogenous sources. We discuss (1) how oxidative stress arises in the lung, (2) how it is neutralized, (3) what genetic factors may predispose to the development of COPD, and (4) how this impacts inflammation and autoimmunity in the development of emphysema and small airways disease. Finally, various strategies have been considered to neutralize the increased oxidative burden present in COPD. This review highlights why current antioxidant strategies have so far failed and what promising alternatives are on the horizon. Moreover, a number of studies have shown that there is no single "magic bullet" to combat oxidative stress, but instead a combination therapy, targeting oxidative stress in the various subcellular compartments, may prove to be more effective in COPD. ***CHEST 2013; 144(1):266–273***

Abbreviations: GSH = reduced glutathione; GST = glutathione-S-transferase; HDAC = histone deacetylase; MDA = malondialdehyde; MPO = myeloperoxidase; NF-κB = nuclear factor-κB; NOX = NADPH oxidase; Nrf2 = nuclear erythroid-2-related factor 2; ROS = reactive oxygen species; SOD = superoxide dismutase

COPD is a major and increasing global health problem that is set to become the third leading cause of death worldwide by 2020. It currently affects about 10% of the population over 45 years of age, rising to 50% in heavy smokers.[1] The major etiologic factor driving this disease is likely to be oxidative and carbonyl stress in the lungs following long-term exposure to cigarette smoke or the combustion products of biomass fuels.[2] Oxidative stress arises as a result of endogenous antioxidant defenses being genetically impaired and/or overwhelmed by the presence of reactive oxygen species (ROS). This in turn can lead to carbonyl stress, where oxidative damage to the surrounding tissues leads to the formation of highly reactive organic molecules that can modify proteins nonenzymatically. COPD is characterized by chronic inflammation and remodeling of the small airways and destruction of the lung parenchyma (emphysema).[3] A striking feature of COPD is its failure to resolve when exposure to cigarette smoke has stopped,[4] which has led to the suggestion that other endogenous factors, such as autoimmunity or persistent infection may also be driving the disease.[1,5]

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Affiliations: From the National Heart and Lung Institute, Imperial College London, London, England.
Correspondence to: Paul A. Kirkham, PhD, National Heart and Lung Institute, Imperial College London, Dovehouse St, London, SW3 6LY, England; e-mail: p.kirkham@imperial.ac.uk

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Persistent Lung and Systemic Oxidative Stress in COPD

There is evidence for oxidative and carbonyl stress in COPD, particularly during acute exacerbations. Alveolar macrophages from patients with COPD are more activated and release increased amounts of ROS in the form of the superoxide radical and hydrogen peroxide.[6] Similarly, activated peripheral blood neutrophils from patients with COPD release increased amounts of ROS, particularly during exacerbations. Markers of oxidative stress and carbonyl stress in COPD include elevated concentrations of nitrotyrosine[7]

and lipid peroxidation products, such as 8-isoprostane, 4-hydroxy-2-nonenal, and malondialdehyde (MDA).[8,9] In contrast, concentrations of the endogenous antioxidant glutathione are lower in BAL fluid from patients with COPD with frequent exacerbations compared with those with stable COPD.[10] Although more refined noninvasive methods of assessing oxidative stress have been developed, they are limited due to a lack of standardization.[11]

Despite this, several markers of oxidative stress, for example, hydrogen peroxide, carbon monoxide, myeloperoxidase (MPO),[11,12] and markers of oxidative tissue damage, such as 8-isoprostane[13] and carbonyl stress in the form of MDA,[14] have consistently been shown to be elevated in exhaled breath or exhaled breath condensate from patients with COPD. Moreover, systemic exposure to oxidative stress in COPD is also indicated by increased carbonyl adducts, such as 4-hydroxynonenal in respiratory[8] and skeletal muscle.[15]

Source of ROS in the Lung

The lung is particularly vulnerable to injury from environmental oxidative stress due in part to its anatomic structure. It is constantly exposed to sources of endogenous oxidative stress generated by mitochondrial respiration and inflammatory responses to bacterial and viral infections within the lung. The environmental sources of airborne oxidative stress include oxidant gases and ultrafine particulate material and nanoparticles from industrial pollution and car exhaust fumes. However, the single most important etiologic factor in causing COPD in the western world is cigarette smoking, with inhalation of combustion products from enclosed cooking fires being an important additional etiologic factor in developing countries.[16]

While exposure to cigarette smoke can drive the onset of COPD, once the disease has become established cessation of smoking does not stop the continued presence of oxidative stress and progression of disease.[17] The continued presence of oxidative stress most likely arises from endogenous sources such as mitochondrial respiration. Indeed, airway epithelial cells when exposed to carbonyl stress induce the production of mitochondria-derived ROS,[18] and airway smooth muscle cells from patients with COPD produce greater amounts of mitochondrial-derived ROS when subject to inflammatory stress from IL-1, tumor necrosis factor α, and interferon γ. Pathway analysis has identified mitochondrial dysfunction around complexes I and III as being tightly associated with COPD.[19] In addition, other sources of intracellular ROS include the cytoplasmic ROS-generating enzymes, such as NADPH oxidase (NOX) and the xanthine/xanthine oxidase system as well as the heme peroxidases, levels of which are elevated in broncholavage fluid and inflammatory cells within the airways of patients with COPD.[20,21]

The abundantly produced superoxide radical is a relatively weak oxidizing agent but is the precursor for other more damaging ROS species (Fig 1), such as the hydroxyl radical which is elevated in COPD,[22] or the very powerful and damaging peroxynitrite radical formed by the rapid reaction of superoxide with nitric oxide.[23] Similarly MPO, released from activated neutrophils which accumulate in the lungs of patients with COPD, produces very destructive hypochlorous acid. However, in healthy cells intracellular antioxidant defenses are able to efficiently mop up these ROS species, thus limiting their impact.

Carbonyl Stress in COPD

ROS generation has been directly linked to oxidation of proteins, lipids, carbohydrates, and DNA. The major outcome is the formation of reactive carbonyls and their reaction with proteins, otherwise known as protein carbonylation. This accumulation of reactive carbonyls and subsequent protein carbonylation has been commonly referred to as "carbonyl stress," predominantly associated with chronic disease[24] and aging. Unlike other posttranslational modifications, protein carbonylation is nonenzymatic and targets specific peptide residues, such as lysine, arginine, cysteine, and histidine.

Protein carbonylation is increasingly recognized as a major driver of the underlying pathology associated with many chronic diseases.[25] It is present in both smokers and patients with COPD.[26] Increased levels of free carbonyls, such as MDA, a major product of lipid peroxidation, have also been detected in the lungs of patients with COPD.[9] Levels of carbonyl stress are correlated with disease severity as measured by the decline in FEV_1.[8] Like many posttranslational protein modifications, protein carbonylation can modify protein function, disrupting normal cell function and physiologic mechanisms.[27]

Antioxidant Defenses in the Lung

Because the lung is constantly exposed to both external and endogenous sources of oxidative stress, it has evolved a number of efficient antioxidant defensive strategies, of which reduced glutathione (GSH) plays an important part. Moreover, up to 20% of all glutathione produced is found within the mitochondria to neutralize endogenous ROS production as a by-product of metabolism.[28] Protecting the exposed surface of the lung from the environment is the epithelial lining fluid, which contains several antioxidants that include