Pulmonary Perspective

The Relationship between Lung Inflammation and Cardiovascular Disease

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Acute and chronic lung inflammation is an underrecognized risk factor for cardiovascular disease. Yet, there are compelling epidemiological data to indicate that airway exposures to cigarette smoke, air pollution particles, and viral and bacterial pathogens are strongly related to acute ischemic events. Over the past 10 years, there have been important human and animal studies that have provided experimental evidence to support a causal link. In this article, we review the epidemiological data for the relationship between lung inflammation and cardiovascular disease and provide plausible mechanistic pathways by which acute and chronic inflammation contributes to the development of acute cardiovascular syndromes.

Keywords: lung inflammation; cardiovascular disease; atherosclerosis; COPD

In 2008, 36 million people around the world died of noncommunicable diseases. Nearly 60% of these (representing 21 million deaths) were due to either cardiovascular or chronic respiratory causes (1). If left unchecked, by 2030, these two conditions will kill 33 million people worldwide annually (2). Over the last 30 years, there has been a tremendous improvement in cardiovascular disease (CVD) outcomes. However, the disappointments of torcetrapib (which increased high-density lipoprotein cholesterol) (3), combination therapy with fenofibrate and simvastatin (which reduced low-density lipoprotein cholesterol [4]), and renin–angiotensin system blockers (which reduced blood pressure) (5) in reducing the risk of cardiovascular events beyond standard therapy suggest that the therapeutic limits of these traditional CVD targets may have been reached. This raises an urgent call to find novel pathways and targets to reduce the burden of cardiovascular disease. We believe that lung injury and inflammation is another important and modifiable risk factor for cardiovascular disease (and in particular ischemic heart disease) that could be a source of novel therapeutic and biomarker discoveries. Although traditionally cardiovascular diseases and chronic lung conditions were believed to be distinct and unique entities, emerging epidemiological and experimental data over the past two decades indicate that they are closely linked. In this article, we provide a concise overview of the emerging evidence linking acute and chronic lung inflammation to cardiovascular morbidity and mortality.

EPIDEMIOLOGY

It is well known that cigarette smoking is a leading risk factor for CVD and in particular for ischemic heart disease. In the INTERHEART Study, for instance, smoking was the second leading modifiable risk factor for ischemic heart disease, trailing only hypercholesterolemia, with a population attributable risk of 36% (vs. 49% for dyslipidemia and 10% for diabetes) (6). Similarly, in the Renfrew and Paisley Study, the population attributable risk of cigarette smoking for mortality related to ischemic heart disease was 32% in women and 38% in men (7). Importantly, independent of the effects of smoking, reduced lung function (as assessed by FEV_1) was responsible for 24–26% of deaths from ischemic heart disease (7). Indeed, even among lifetime nonsmokers, there was a dose–response relationship between reduced FEV_1 and mortality from ischemic heart disease and stroke (7). These data have been replicated in multiple other cohorts, suggesting that reduced lung function, independent of cigarette smoking, is a significant risk factor for cardiovascular morbidity and mortality (8).

One major cause of reduced lung function in the community is chronic obstructive pulmonary disease (COPD). The Lung Health Study prospectively evaluated more than 5,800 smokers with mild to moderate COPD. Although close to 50% of the cohort stopped smoking at some point during follow-up, the leading cause of hospitalization of this group of patients was from cardiovascular events, accounting for nearly 50% of all hospital admissions (9). The reverse is also true. The prevalence of COPD is high among patients with ischemic heart disease. For instance, in one study, Soriano and colleagues showed that 34% of patients with angiography-proven coronary artery disease had significant airflow limitation on spirometry compared with only 17% among control individuals, who were representative of the Spanish population over the age of 40 years (10). Interestingly, many with even moderate to severe airflow limitation had never been previously diagnosed with COPD in this study, suggesting that the relationship between COPD and CVD is underrecognized and underappreciated in the cardiovascular community, likely owing to the underuse of spirometry in this group of patients (11). Although the exact mechanism by which COPD induces CVD remains obscure, COPD is characterized by persistent lung and systemic inflammation, which intensifies during acute exacerbations (12, 13). Interestingly, patients with COPD have the highest risk of myocardial infarction and stroke within the first 5 days of an exacerbation episode (which are usually triggered by viral or bacterial infections) (14). The etiology for the chronic inflammatory process in COPD is unknown. Autoimmunity and disturbances in the "normal" microbial flora of the lungs have been implicated as

possible sources for the persistent inflammatory process in patients with COPD who have stopped smoking (15, 16).

Although cigarette smoking and COPD are by far the most important and prevalent respiratory risk factors for cardiovascular disease, there are compelling data to implicate air pollution (especially small particulate matter) (17, 18), second-hand cigarette smoke (19), diesel exhaust fumes (20), acute (viral) respiratory infections (21) and bacterial pneumonia (22), and periodontitis and other oral diseases (23) as acute and chronic triggers for cardiovascular morbidity and mortality. Despite the heterogeneity of these environmental factors, they all lead to lung injury and inflammation. Interestingly, large particles (in air pollution) and noxious gases, which produce an inflammatory response mostly in the upper and central airways, have been less strongly associated with cardiovascular events (17, 24) compared with smaller particles, which penetrate deeper into the peripheral airways and alveoli. Together, these data suggest that the downstream inflammatory process in the small airways or airspaces may play an important role in the pathogenesis of lung-related cardiovascular disease.

CAUSAL RELATIONSHIP OR EPIPHENOMENON?

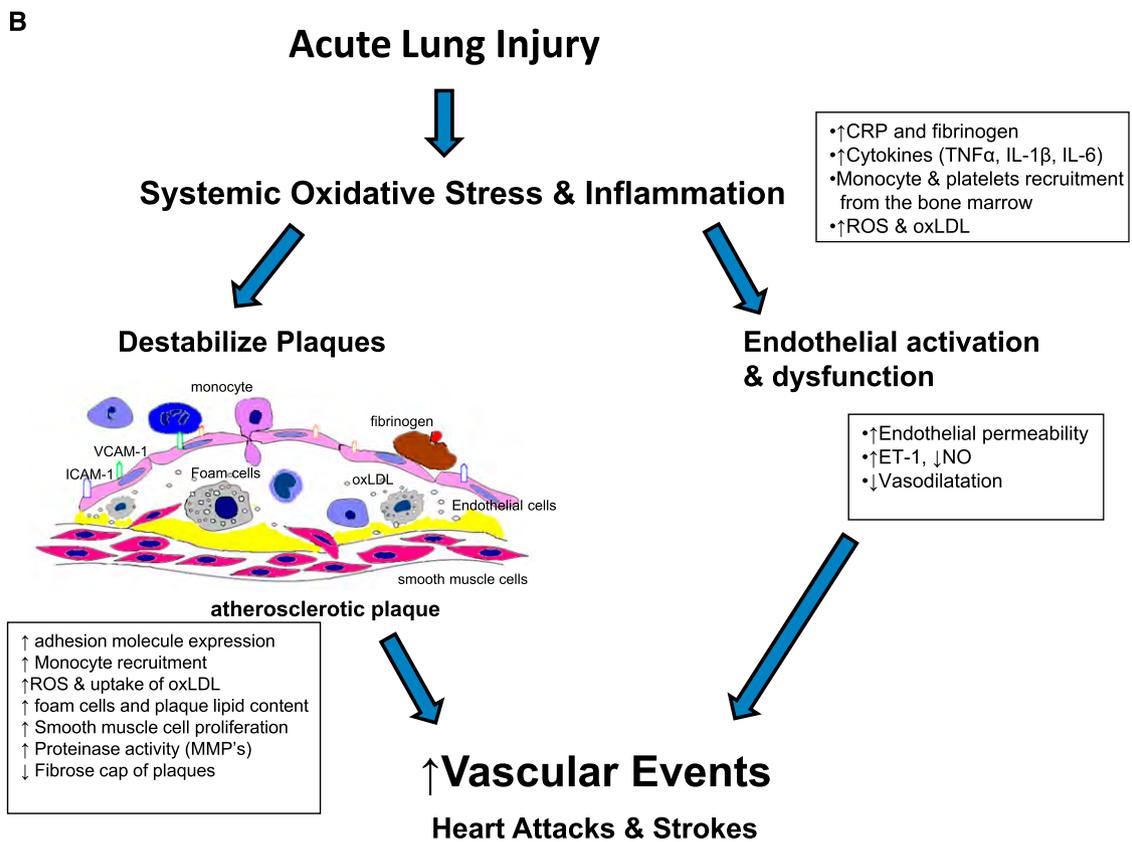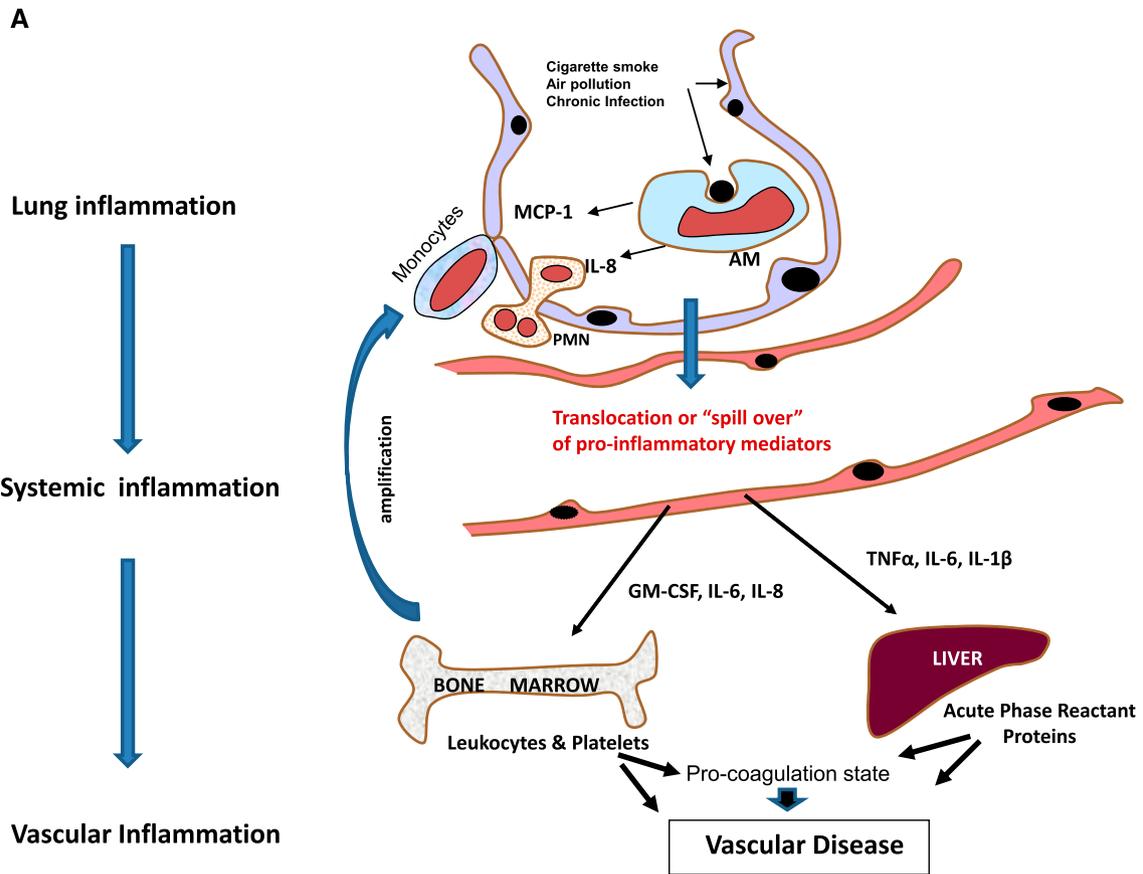### Chronic Exposure Leading to Accelerated Atherosclerosis

Ischemic heart disease is the most common cardiovascular disease and is predominantly caused by atherosclerosis. Postmortem studies have firmly established a causal dose–response relationship between cigarette smoking and the burden of atherosclerosis (25, 26). More recently, epidemiological studies have extended this relationship to chronic environmental exposures to small particulate matter (27, 28). These epidemiological data have been supported by data from elegant animal models. For instance, Suwa and colleagues (29) exposed Watanabe heritable hyperlipidemic rabbits to urban air pollution particles (mean diameter of $0.8 \mu m$) for 4 weeks. Compared with control rabbits (exposed to saline) the rabbits exposed to urban particulate matter demonstrated a marked increase in the burden of atherosclerotic plaques in both the left main and right coronary arteries ($\sim71\%$ increase in the volume of atherosclerosis in the exposed vs. control animals; $P < 0.005$). Importantly, the plaques in the experimental group displayed more features of vulnerability such as a large lipid core, increased number of inflammatory cells, and a thin fibrous cap (29) (see below for definition of vulnerable plaque). These plaque features have been associated with a higher risk of plaque rupture and therefore atherothrombosis. Interestingly, the rabbits that were exposed to particulate matter demonstrated both lung and systemic inflammation, and the atherosclerotic plaque volume in the coronary arteries was directly proportional to this inflammatory response in the lungs. These findings were corroborated and extended by Sun and colleagues (30), who exposed 6-week-old apolipoprotein E–deficient mice for 6 hours/day to air containing 10 times the nominal ambient concentration of PM2.5 (air pollution particles with a mean aerodynamic diameter of less than $2.5 \mu m$) over a 6-month period. They found that although these mice had lower total serum cholesterol, they demonstrated greater atherosclerotic burden in the abdominal aorta and worse endothelial function compared with mice exposed to filtered air. Importantly, the aortas of mice exposed to PM2.5 contained increased expression of inducible nitric oxide synthase and reactive oxygen species. Together, these data indicated that chronic exposure of the lungs to small particles accelerates atherosclerotic plaque progression in susceptible arteries through a process that is independent of dyslipidemia. Although the exact pathways are unknown, these experiments suggest that chronic lung and systemic inflammation (resulting in increased

plaque cell turnover and oxidative stress) are likely to play a pivotal role in this process.

Acute Exposure Leading to Plaque Disruption and Acute Coronary Syndromes

Although accelerated progression of atherosclerosis is an important long-term risk factor for cardiovascular morbidity and mortality, stable atherosclerotic plaques usually do not produce acute coronary syndromes (31). Typically, acute ischemic events are precipitated by rupture of a "vulnerable" plaque, leading to partial or total occlusion of the local artery with thrombus formation. Vulnerable plaques are those that are characterized by a large lipid core (>40% of total lesion area), a thin fibrous cap ($<65 \mu m$), and increased inflammatory cell content (31). An important effector contributing to the rupture of these vulnerable plaques is neutrophilic inflammation in the coronary vessels (32). Interestingly, neutrophil activation involves not only the vessel containing the culprit lesion but also other coronary vessels (that are free of atherosclerosis), suggesting that the stimulus for the inflammation is upstream of the coronary circulation.

There are circumstantial data to indicate that this "upstream" trigger can be lung inflammation. First, although all causes of systemic inflammatory response are associated with acute coronary syndromes, the most convincing and strongest appears to be acute respiratory infections (21). Using the U.K. General Practice Research Database (which contains health information on 5 million patients), Smeeth and colleagues demonstrated a strong association between the onset of respiratory infection and the risk of acute myocardial infarction (MI) (nearly fivefold increased risk of MI within 1–3 d of the onset of respiratory infection). In contrast, the onset of another infectious or inflammatory stimulus such as acute urinary tract infection (UTI) had only a modest impact on the risk of acute MI (1.6-fold increase in risk within 3 d of onset of UTI symptoms) (21). Importantly, the excess risk of MI related to respiratory tract infections can be greatly attenuated in these patients by influenza vaccination (33). The efficacy of influenza vaccination in preventing MIs and other cardiovascular end points has been corroborated by Phrommintikul and colleagues, who showed in a randomized controlled trial a 30% reduction in major cardiovascular events including death, and hospitalization related to acute coronary syndrome, stroke, or heart failure over 1 year in patients with significant vascular disease who were treated with inactivated influenza vaccine compared with those who were not (34). Second, in human models of lung injury and inflammation related to air pollution, a causal relationship between air pollution and cardiac ischemia has been established. For instance, Mills and colleagues exposed men with stable ischemic heart disease to dilute diesel exhaust (which induces lung inflammation [35]) for 1 hour during exercise. Exposure to diesel exhaust significantly impaired the fibrinolytic response and greatly increased myocardial ischemia compared with exposure to filtered air (20). Third, although there is no good animal model to evaluate the effects of lung injury/inflammation on atherosclerotic plaque rupture, Kido and colleagues (36) have shown that in mice treated with urban air pollution particles (less than $10 \mu m$ in diameter), these particles induce an acute inflammatory response in the lung, which "spills" into the systemic circulation causing systemic inflammation. This systemic inflammatory response, in turn, is related to acute endothelial dysfunction of systemic blood vessels (36). Removing inflammatory mediators such as IL-6, on the other hand, restores the integrity of the vascular endothelium (36). The importance of lung inflammation in inducing clot formation in arterial vessels was also shown

A

Lung inflammation

Systemic inflammation

Vascular Inflammation

B

Acute Lung Injury

Systemic Oxidative Stress & Inflammation

- •↑CRP and fibrinogen
- •↑Cytokines (TNFα, IL-1β, IL-6)
- •Monocyte & platelets recruitment from the bone marrow
- •↑ROS & oxLDL

Destabilize Plaques

Endothelial activation & dysfunction

- •↑Endothelial permeability
- •↑ET-1, ↓NO
- •↓Vasodilatation

↑ adhesion molecule expression
↑ Monocyte recruitment
↑ROS & uptake of oxLDL
↑ foam cells and plaque lipid content
↑ Smooth muscle cell proliferation
↑ Proteinase activity (MMP's)
↓ Fibrose cap of plaques

↑Vascular Events

Heart Attacks & Strokes

Figure 1. (*A*) A theoretical model of how lung inflammation contributes to atherothrombosis. Cigarette smoke, air pollutants, and infectious organisms induce an inflammatory response mediated by macrophages and airway epithelial cells. This interaction produces an array of inflammatory mediators in airspaces and lung tissues that have the ability to translocate or "spill over" into the blood stream, inducing a systemic inflammatory response. These circulating proinflammatory mediators such as tumor necrosis factor (TNF)-α, IL-1β, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) have the ability to stimulate the bone marrow and accelerate the release of granulocytes, monocytes, and platelets into the vascular space. Mediators such as IL-1β and IL-6 also stimulate the liver to produce acute-phase proteins such as C-reactive protein and coagulation factors such as fibrinogen and factor VIII, generating a procoagulation state. Last, mediators such as TNF-α, IL-6, and IL-1β are known to directly activate vascular endothelium. Together this proinflammatory milieu produces a "perfect storm" for activation of plaque tissues, plaque progression, and destabilization. Leukocytes released from the bone marrow are preferentially recruited in the inflamed lung tissues, fueling the inflammatory response in the lung, generating a vicious cycle. AM = alveolar macrophages; MCP-1 = monocyte chemoattractant protein-1; PMN = polymorphonuclear cells. (*B*) A theoretical model of how acute lung inflammation leads to acute ischemic events. Acute lung inflammation induces systemic oxidative stress, increasing reactive oxidative species (ROS) and oxidizing low-density lipoproteins (oxLDL). It also unleashes a cascade of downstream inflammatory responses (i.e., increased cytokines, acute-phase proteins, and leukocytes) that impacts systemic blood vessels in two ways: (*1*) activation of the endothelium, causing increased permeability and endothelial dysfunction; and (*2*) activation of atherosclerotic plaques, making them more vulnerable to rupture (increasing the plaque content of oxLDL, recruitment of smooth muscle cells and leukocytes into the plaque tissues, and causing thinning of the plaque cap), and promoting thrombus formation leading to vascular events such as acute myocardial infarction. CRP = C-reactive protein; ET-1 = endothelin-1; ICAM-1 = intercellular adhesion molecule-1; MMPs = matrix metalloproteinases; VCAM-1 = vascular cell adhesion molecule-1.

previously by Mutlu and colleagues (37). They acutely exposed wild-type C57/BL6 mice to small air pollution particles twice, 3 minutes apart, and demonstrated that acute exposure to these particles promoted a prothrombotic state, characterized by increased plasma expression of fibrinogen and platelets and enhanced factor VIII activity (37) and accelerated blood coagulation in the common carotid artery after application of ferric chloride. Interestingly, removal of alveolar macrophages by intratracheal application of clodronate, or the acute-response cytokine, IL-6, restored this procoagulation state, suggesting the importance of lung inflammation in mediating thrombus formation in carotid vessels (37). Together these and other data (38, 39) provide a strong rationale for implicating lung inflammation in acute coronary events. Figure 1A shows some potential pathways by which chronic lung inflammation induced by cigarette smoke, air pollution, or infection could contribute to cardiovascular disease, and Figure 1B shows how acute lung injury could trigger acute vascular events such as heart attacks.

Clinical Implications

There are strong mechanistic links between acute and chronic lung injury and inflammation, atherosclerosis, and acute vascular events. As such, clinicians managing patients with a significant smoking history or occupational or home exposure to dust and particles should evaluate both the cardiovascular and respiratory systems for abnormalities. This integrated approach is enabled in part due to the advent of ECG- gated multidetector computed tomography (MDCT), which allows clinicians to image and visualize lung disease (e.g., emphysema) and coronary vessel disease (e.g., atherosclerosis) in the same patient at one setting. The cross-sectional nature of the data acquisition allows not only for lumenographic assessment but also for the detection and, to an extent, characterization of coronary atherosclerosis (40). Significant abnormalities can then be pursued using more specific tools such as angiography (in the case of atherosclerotic plaques) or detailed lung function measurements (in the case of emphysema). Moreover, there are some "emerging" therapies that may be beneficial for both the cardiovascular and respiratory systems. For instance, statins, which have a clear salutary role in preventing acute coronary events in those with hyperlipidemia (41), may reduce morbidity and mortality in respiratory patients who demonstrate low-grade systemic inflammation (as evidenced by elevated C-reactive protein) even in the absence of significant hypercholesterolemia (42). There is a large

randomized controlled trial currently underway evaluating the role of statins in reducing exacerbations related to COPD, which will address the question of whether or not statins can improve health outcomes in COPD. Because the risk of myocardial infarction is highest in patients with COPD during exacerbations, statins (if proven to reduce exacerbation rates) may also decrease cardiovascular events in patients with COPD by a route independent of their effects on serum lipids (14). Similarly, an integrated approach may also benefit patients with established cardiovascular disease. For instance, β-blockers are life-preserving in patients with ischemic heart disease (43) or congestive heart failure (44). However, there is concern that patients with COPD may experience deterioration in lung function when β-blockers are used. Indeed, the use of noncardioselective β-blockers such as carvedilol leads to reductions in lung function and 6-minute walk distance compared with cardioselective β-blockers such as bisoprolol (45). Thus, prior knowledge of the pulmonary status of patients with ischemic heart disease or heart failure may modify the choice of β-blockers used for these patients. Intriguingly, independent of their beneficial effects on the cardiovascular system, numerous observational data suggest that β-blockers may reduce the risk of exacerbations and even mortality in patients with COPD (46, 47). Thus, in the future, drugs originally developed to reduce cardiovascular morbidity and mortality may be used to treat patients for lung disease. Another example is lorsartan. Lorsartan is an angiotensin II receptor antagonist, which reduces adverse cardiovascular events in those with hypertension (48) or congestive heart failure (49). However, studies suggest that losartan may have salutary effects in patients with emphysema (50, 51). Similar to drug discovery, biomarker discovery may be aided by better understanding the interactions between the cardiovascular and pulmonary systems. For instance, it may be possible that "markers" of lung injury or inflammation in the plasma or serum of patients with ischemic heart disease may provide incremental prognostic information beyond traditional risk factors such as hypertension, hypercholesterolemia, hemoglobin A1C, and C-reactive protein. Consistent with this notion, Hill and colleagues showed that plasma surfactant protein-D may be a promising biomarker to predict cardiovascular mortality in patients with angiography-proven atherosclerosis (52). The reverse may also be true with biomarkers of cardiovascular stress predicting the prognosis of patients with chronic lung disease. Consistent with this notion, van Gestel and colleagues have shown that plasma N-terminal pro-B–type natriuretic peptide

levels were significantly associated with 1-year mortality in patients with COPD undergoing vascular surgery (53).

CONCLUSIONS

The worldwide burden of lung and cardiovascular diseases is enormous and growing. In the past, respiratory and cardiovascular researchers have largely stayed in "silos." However, emerging data strongly indicate a direct link between lung injury and inflammation and cardiovascular disease. By exploiting this new knowledge, it may be possible to discover new therapeutic targets, and biomarkers to produce better outcomes of patients with lung and cardiovascular diseases. However, several important questions remain unanswered. First, although it is well established that acute respiratory triggers of inflammation such as air pollution particles and respiratory infectious organisms induce acute coronary syndromes, the precise molecular pathways by which this occurs are largely unknown. Previous research has implicated alveolar macrophages and IL-6; however, there may be other, more salient molecules and cells involved in this process, which need to be discovered. Moreover, with the advent of highly sensitive (and specific) molecular and genetic techniques (such as sequencing) to detect bacterial and fungal organisms, there is growing recognition of a rich and complex microbial flora in lungs, which may become disturbed by cigarette smoking and in COPD (16, 54). In the future, it will be important to evaluate the possible role of the lung microbiome in the pathogenesis of COPD and its link with CVD. Second, it remains unknown whether the treatment of lung injury and inflammation with inhaled medications, in particular, corticosteroids, can lead to improved cardiovascular health outcomes. To date, data on the use of inhaled corticosteroids in patients with COPD have been mixed (55, 56). However, neither of these studies was designed to study the effects of these drugs on cardiovascular end points. A well-designed, properly powered, clinical trial will be needed in the future to determine whether by mitigating lung inflammation, cardiovascular outcomes can be modified. More importantly, by better understanding the molecular links between chronic and acute lung inflammation and cardiovascular disease, new compounds may be developed that can selectively target pathways relevant to this process and thereby produce excellent outcomes, while minimizing side effects.

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