the recent FLAME (Effect of Indacaterol Glycopyrronium vs Fluticasone Salmeterol on COPD Exacerbations) dual bronchodilator study careful documentation of exacerbation histories in the previous year was employed with electronic monitoring during the trial and expected exacerbation rates were achieved (12).

The COPD management landscape is currently changing, and we now know that in higher risk patients ($FEV_1 < 50\%$ predicted and with a history of prior exacerbations), a dual bronchodilator (indacaterol/glycopyrronium) is more effective than a LABA/ICS in reducing exacerbations, with the study performed in patients with COPD where only 20% had two or more exacerbations in the previous year (12). Thus, studies are now required in a similar COPD patient group when roflumilast is added to dual bronchodilators and compared with standard therapy. However, these studies will need enhanced exacerbation detection and monitoring to achieve true exacerbation rates.

Meanwhile, the results from the RE²SPOND trial suggest that the addition of oral roflumilast is especially effective in a group of “super exacerbators” who are at risk of very frequent exacerbations and hospital admission and these patients should be specifically targeted for additional antiinflammatory therapy on top of standard COPD therapy. We now need to further understand mechanisms of this important “super exacerbator” COPD patient group. ■

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Hidden in Plain Sight: Lung Impairment in Ischemic Heart Disease

Chronic obstructive pulmonary disease (COPD) and ischemic heart disease (IHD) share multiple risk factors, including age and cigarette smoking, but it is now well established that independent of these risks, the frequency of IHD is greater in patients with COPD than in the general population (1). The additional risk conferred by the presence of COPD is on the order of twofold to fivefold, making the disease a powerful proatherosclerotic condition comparable in magnitude to other

chronic inflammatory conditions, such as rheumatoid arthritis and systemic lupus erythematosus (2). In fact, except for cigarette smoking, the population-attributable risk for mortality due to cardiovascular disease is greater for airflow obstruction than for other risk factors, such as hypertension, hyperlipidemia, and obesity (3). There has been a recent push for greater cardiovascular disease assessment in patients with COPD, across all ranges of disease severity (4), and although this may have resulted in a greater awareness of IHD among caregivers for patients with COPD, very little is known about the converse situation: what is the awareness of COPD among caregivers for patients with IHD?

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Numerous studies have examined the prevalence of airflow obstruction in patients with IHD, but these are limited by small sample size (5–9), admixture with large proportions of participants without IHD limiting generalization (6), participants limited to a diagnosis of post myocardial infarction (5, 9) and post percutaneous coronary intervention (7), and heterogeneous disease definitions for IHD (6, 8, 10). These studies also did not differentiate diagnosed from undiagnosed airflow obstruction and did not examine the additional respiratory morbidity resulting from the concurrence of COPD and IHD. In this issue of the *Journal*, Franssen and colleagues (pp. 568–576) analyzed data from the well-characterized ALICE (Airflow Limitation in Cardiac Diseases in Europe) study, a large population study of participants with diagnosed IHD drawn from cardiovascular outpatient clinics (11). They report two important findings: first, a substantial proportion (one-third) of participants with IHD had undiagnosed airflow obstruction; and second, this presence of airflow obstruction was associated with significant additional morbidity in the form of respiratory symptoms, impaired health status, and emergency room visits. Although the latter is not surprising, attention must be focused on the high frequency of undiagnosed airflow obstruction in a population that shares risk factors for COPD and probably had significant symptom burden, and yet never had spirometric testing. It is even more striking that one in five had moderate to severe airflow obstruction that remained undiagnosed. Of those with airflow obstruction, only one-third were previously diagnosed to have COPD. Focused screening and early diagnosis of airflow obstruction in IHD can alleviate the symptom burden of these patients. It is not known if adequate treatment of airflow obstruction in this population can modulate the cardiovascular risk (12), but a case can certainly be made for reducing respiratory morbidity. Of note, of patients with and without airflow obstruction, two-thirds of patients in both groups were on short-acting bronchodilators, but very few were on longer-acting bronchodilators.

There are a number of possible mechanisms that make the high frequency of airflow limitation in IHD biologically plausible. Airflow limitation and COPD are associated with some of the same risk factors as IHD, namely aging and senescence, cigarette smoking, environmental pollution, and perhaps sex predispositions (3). In addition, a number of interactive pathways are common to both disease processes, including increased systemic inflammation and oxidative stress, a genetic predisposition, activation of the renin-angiotensin system, and perhaps physical inactivity (3). It is pertinent to note in this study that the Framingham risk scores were clinically similar in participants with IHD and airflow obstruction compared with those without airflow obstruction, underlining that the traditional risk scores do not always capture the entirety of cardiovascular risk in patients with COPD. Those with airflow obstruction did have higher levels of biomarkers of cardiovascular risk, such as C-reactive protein; additional risk models that include lung function are needed to better predict cardiovascular risk in those with airflow obstruction.

The findings of this study are important and should provoke significant consternation and soul searching within the cardiopulmonary community. By studying a homogenous group of patients with established IHD, and by applying epidemiologically robust definitions that encompass multiple components of IHD, the authors ensure that their findings are applicable to patients with

IHD in the general community. However, some limitations of the study merit discussion. About one-third of participants with airflow obstruction had congestive heart failure, which can result in obstructive spirometry due to peribronchovascular congestion and airway reactivity, restrictive spirometry due to pulmonary edema, or a mixed obstructive–restrictive spirometry. It is generally recommended that patients be euvoletic before spirometry for these reasons, and although one presumes the participants of this outpatient clinic study were reasonably euvoletic, this might result in airflow obstruction independent of structural lung disease characteristic of COPD. Second, although the authors found that a small percentage of participants had lung restriction on spirometry, the diagnosis of restriction was made on prebronchodilator spirometry; a small but significant number of participants can have reduced vital capacity due to air trapping and pseudo-restriction. Although the presence of airflow limitation is associated with increased respiratory morbidity, this is not surprising, and the presence of COPD in IHD has been previously shown to increase long-term mortality after myocardial infarction and coronary interventions (13); of greater interest is the frequency of combined cardiac and respiratory events in these patients. The respiratory outcome data were collected cross-sectionally, and future studies examining this issue should assess clinical outcomes longitudinally. None of these limitations should detract from the most important finding of this study, the severe underdiagnosis of airflow obstruction and COPD in patients with IHD.

So what gives? What are the factors underlying such poor appreciation for the coexistence of these two common diseases with shared risk factors? Perhaps it is due to the convergence of the significant overlap in the cardinal symptoms of dyspnea and exercise intolerance, poor awareness of COPD as a risk factor for accelerated atherosclerosis, and increasingly specialized practice patterns among physicians and other health care providers. In the era of super-specialization and fragmented care, one only hopes enough cardiologists read this important article and change practice patterns. ■

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Ambient PM_{2.5} and Health: Does PM_{2.5} Oxidative Potential Play a Role?

A major mechanism by which fine particulate matter (particulate matter with aerodynamic diameter $\leq 2.5 \mu\text{m}$ [PM_{2.5}]) may induce adverse health effects is oxidative stress, the imbalance between oxidants and antioxidants in the body. This may occur through inhalation of oxidants on particles or the generation of reactive oxygen species in the lungs by particle components (1). There is increasing interest in development of assays to measure PM_{2.5} oxidative potential (OP), the potential for particles to generate reactive oxygen species. A common assay measures the depletion of an antioxidant added to PM_{2.5} sample extract. Antioxidants include glutathione (GSH) and ascorbic acid (AA), both found in lung lining fluid, and dithiothreitol (DTT), a chemical surrogate for cellular reductants. Implementation of these assays is relatively new and takes considerable time and expertise. Thus, PM_{2.5} OP measurements are generally unavailable for population-based epidemiologic studies, which require, often retrospectively, temporal and spatial information on exposures over extended periods.

In this issue of the *Journal*, Weichenthal and colleagues (pp. 577–586) examine modification of short-term associations of PM_{2.5} and respiratory emergency room visits by long-term PM_{2.5} OP in 15 cities in Ontario, Canada (2). The application of two antioxidant depletion assays, GSH and AA, to characterize PM_{2.5} OP (percentage antioxidant depletion/ μg PM_{2.5}) is a strength of this work. Different assays are sensitive to different aerosol components and, hence, sources. For example, OP^{AA} is sensitive to the transition metal copper and mobile sources via brake wear and road dust (3), whereas OP^{DTT} is sensitive to some transition metals but also organic aerosols, particularly those from fresh biomass burning, those oxidized with chemical aging, and tailpipe- and road dust-related components of mobile sources (4, 5). As such, one assay cannot fully characterize PM_{2.5} OP, and the different assays can lead to differences in observed health effects (3, 6). Use of a limited number of widely accepted assays and more comparisons

between assays are needed to better synthesize the findings from different studies of PM_{2.5} OP.

PM_{2.5} OP data in this study were from analysis of tapered element oscillating microbalance filters, which is innovative; these filters are commonly archived as part of PM_{2.5} compliance monitoring. The authors discuss several limitations regarding OP exposure assessment, including the use of filters from 2012 to 2013 to represent the 2004 to 2011 study period. Two limitations deserve special attention. First, long-term PM_{2.5} OP levels for each city were determined using pooled data from 6-week integrated filter samples (ranging from one to seven filters per site, from one to three sites per city). Given that OP/ μg PM_{2.5} changes substantially by season (the extent of which depends on the specific assay) (7), the observed OP levels may have been highly influenced by the number of days and seasons included in the pooled measure for each site. Second, the loss of volatile PM components, such as organic aerosols that may have high OP activity (5), from tapered element oscillating microbalance filters (which were heated to 30°C during sampling, changed only every 6 weeks, and possibly stored for an extended period before OP analysis) may have led to an underestimate of PM_{2.5} OP in cities with higher proportions of volatile PM_{2.5}, depending on which aerosol components the assay was sensitive to. These issues may have affected the characterization of long-term city-to-city differences in PM_{2.5} OP.

A main epidemiologic analysis considered by the authors was modification of short-term PM_{2.5} health associations by long-term city-level estimates of PM_{2.5} OP. In exploratory analyses restricted to days with 3-day moving average PM_{2.5} levels below 10 $\mu\text{g}/\text{m}^3$, associations of PM_{2.5} and respiratory visits were significantly stronger for cities in the highest compared with lowest OP^{GSH} quartile. There was no evidence of modification by OP^{AA}. The authors suggest that “regional differences in glutathione-related oxidative potential may play an important role in explaining between-city differences in the respiratory health effects of PM_{2.5}.” Heterogeneity in PM health effects has been documented by a