Chronic Obstructive Pulmonary Disease as a Risk Factor for Cardiovascular Morbidity and Mortality

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Chronic obstructive pulmonary disease and other disorders, associated with reduced lung function, are strong risk factors for cardiovascular events, independent of smoking. Overall, when the lowest quintile of lung function, as measured by FEV_1, is compared with the highest quintile, the risk of cardiovascular mortality increases by approximately 75% in both men and women. Having symptoms of chronic bronchitis alone increases the risk of coronary deaths by 50%. Reduced ratio of FEV_1 to FVC by itself is a modest independent risk factor for coronary events, increasing the risk by 30%. However, if patients have ventricular arrhythmias, the risk of coronary events is increased twofold, suggesting that the cardiotoxic effects of obstructive airways disease are amplified in those who have underlying cardiac rhythm disturbances. In general, for every 10% decrease in FEV_1, all-cause mortality increases by 14%, cardiovascular mortality increases by 28%, and nonfatal coronary event increases by almost 20%. These data indicate that chronic obstructive pulmonary disease is a powerful, independent risk factor for cardiovascular morbidity and mortality.

Keywords: cardiovascular disease; chronic obstructive pulmonary disease; epidemiology; FEV_1; lung function

Chronic obstructive pulmonary disease (COPD) affects over 5% of the adult population and is the only major cause of death in the United States and elsewhere whose morbidity and mortality are increasing (1, 2). COPD affects over 16 million people in the United States and its prevalence has risen by 41% since 1982, while the age-adjusted death rate has increased by 17% between 1966 and 1982 (1). COPD accounts for approximately 750,000 hospitalizations every year in the United States, and 10 to 12% of these stays occur in critical care units (1). The economic costs for COPD are $24 billion per annum in the United States; direct medical expenditures (related mostly to hospital-based care) account for 61% of the total costs (3). Unfortunately, the best forecasts suggest that the burden of COPD in the United States and elsewhere will continue to escalate over the next 20 to 30 years. In fact, by 2020, the World Health Organization predicts that COPD will become the third leading cause of death (currently fourth) and the fifth leading cause of disability (currently twelfth) worldwide (4, 5). Ironically, National Institutes of Health funding of research in COPD is currently the lowest among all major causes of mortality in North America (6).

Although these figures on COPD morbidity and mortality are alarming, they are only a "tip of the iceberg," because airflow obstruction is an important contributor to other common causes of morbidity and mortality. Data from multiple studies across different jurisdictions indicate that one of the leading but underrecognized causes of death in COPD is ischemic heart disease (7–9). Large population-based studies suggest that patients with COPD are two to three times more at risk for cardiovascular mortality, which accounts for about 50% of the total number of deaths (8, 10, 11). Indeed, although not generally recognized, poor lung function has been shown to be as powerful a predictor of cardiac mortality as established risk factors such as total serum cholesterol (12). In view of the relevance of cardiovascular outcomes in patients with COPD, in the present section, we will systematically and critically review the epidemiologic link between COPD and cardiovascular morbidity and mortality.

THE RELATIONSHIP BETWEEN FEV_1 AND CARDIOVASCULAR DISEASE

Individuals with reduced FEV_1 are at increased risk for atherosclerosis. Zureik and colleagues (13) performed a cross-sectional study on 194 healthy, middle-aged men free of coronary heart disease to determine the relationship between FEV_1 and pulse wave velocity, a surrogate measurement for central arterial stiffness, endothelial dysfunction, and atherosclerosis. They showed that independent of other well established risk factors for atherosclerosis, reduced FEV_1 was associated with increased pulse wave velocity. For every decrement of 193 ml in FEV_1, the participants' pulse wave velocity increased by 2.5 meters per second. FEV_1 accounted for 6.8% of the total variation in the pulse wave velocity. Reduced FEV_1/FVC ratio was also negatively related to pulse wave velocity, suggesting that airways disease was an independent risk factor for central arterial stiffness.

Several groups have reported on the relationship between FEV_1 and cardiovascular mortality using population-based studies. The Honolulu Heart Program (14) prospectively followed 5,924 generally healthy, middle-aged men (about half were current smokers) for 15 to 18 years. They found that compared to those in the highest quintile of FEV_1, individuals in the lowest FEV_1 quintile had an elevated risk of cardiovascular mortality (relative risk [RR], 1.93; 95% confidence interval [CI], 1.46–2.54). Higgins and Keller (15), using the Tecumseh Cohort, reported a stronger association. Compared to those with FEV_1 greater than or equal to 2.0 L, those with FEV_1 less than 2.0 L had a fivefold increase in the RR of cardiovascular mortality (RR, 5.03; 95% CI, 3.07–8.22). In the Harvard Six Cities Study, Speizer and colleagues (16) reported an RR of 2.74 (95% CI, 1.93–3.90) in women and 1.42 (95% CI, 1.07–1.90) in men, comparing the lowest FEV_1 quartile to the highest quartile. However, these studies were relatively old, raising some concerns that time-publication bias may have accounted for these findings. To address this concern, in Table 1, we have summarized results from studies published since 1990 that have evaluated the relationship between FEV_1 and cardiovascular mortality (12, 17–19). In the Buffalo cohort, for instance, Schunemann and colleagues (17) reported an RR of 1.96 (95% CI, 0.99–3.88) in women and 2.11 (95% CI, 1.20–3.71) in men, once again comparing the lowest FEV_1 quintile to the highest quintile. Hole and colleagues

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TABLE 1. BASELINE CHARACTERISTICS OF INCLUDED STUDIES REPORTED SINCE 1990 AND THE ASSOCIATION BETWEEN FEV_1 AND CARDIOVASCULAR MORTALITY

Author	Study Population	Sample Size	Age (*yr*)	Male (%)	Mean FEV_1 (*L or % of predicted*)	Current Smokers (%)	FEV_1 Categorization (*% predicted or L*)	Follow-up (*yr*)	RR of Cardiovascular Mortality (*95% CI*)	Adjusted Factors
Hole (12)	Renfrew & Paisley, UK	15,411	45–64 (range)	46	2.83*	36	Quintiles	15	1.56 (1.26, 1.92)*	Age, smoking status & history, blood pressure, serum cholesterol, BMI, social class
					1.99†		(⩽ 73-75% vs. ⩾ 108–113%)		1.88 (1.44, 2.47)†	
Schunemann (16)	Buffalo/Erie County, U.S.	1,195	47	46	2.8	58	Quintiles	29	2.11 (1.20,3.71)*	Age, education, smoking status, blood pressure, BMI
							(< 80% vs ⩾ 109–114%)		1.96 (0.99,3.88)†	
Hospers (17)	Vlagtwedde-Vlaardingen, Netherlands	5,382	36	54	98%	55	<80% vs. ⩾ 100%	~25	1.82 (1.42,2.34)	Sex, age, smoking status, BMI
Knuiman (18)	Busselton, Australia	4,277	49	49	95%*/100%†	45*/24†	10% decrease in FEV_1 percent predicted	20 to 26	1.10 (1.03, 1.18)*	Age, smoking status & history, symptoms, coronary heart disease, cardiovascular risk factors
									1.07 (1.00, 1.24)†	

* Male values.
† Female values.

(12) from the United Kingdom reported an RR of 1.88 (95% CI, 1.44–2.47) in women and 1.56 (95% CI, 1.26–1.92) in men, comparing the lowest quintile of FEV_1 to the highest quintile. In this study, when the lowest quintile of FEV_1 was compared with the highest quintile, the population attributable risk for deaths related to ischemic heart disease was 26% (95% CI, 19–34%) in men and 24% (14–34%) in women, independent of the burden associated with cigarette smoking. In other words, reduced FEV_1 accounted for 26% of all deaths related to ischemic heart disease in men and 24% in women. The magnitude of the mortality burden attributed to reduced FEV_1 was similar to the burden imposed by hypercholesterolemia. In the same study, comparison of total serum cholesterol (between the lowest quintile to the highest quintile levels) produced a population attributable risk of 21% in men and 25% in women for deaths related to ischemic heart disease.

Although there is some heterogeneity in the results across the studies, these studies indicate that reduced FEV_1, independent of established risk factors such as cigarette smoking, total cholesterol, and hypertension, is an important risk factor for cardiovascular mortality. In general, when the lowest quintile of FEV_1 is compared with the highest quintile, the risk of cardiovascular mortality increases by approximately 75% in both men and women. In certain populations, reduced FEV_1 may be responsible for 20 to 30% of deaths related to ischemic heart disease. Although there are many causes of reduced FEV_1 in the community, approximately 80% of adults (45 years and older) with impaired FEV_1 (i.e. < 80% predicted) have airways obstruction (20). Thus, reduced FEV_1 among adults is a reasonable surrogate for COPD in population-based studies.

THE RELATIONSHIP BETWEEN RATE OF FEV_1 DECLINE AND CARDIOVASCULAR DISEASE

Individuals susceptible to COPD experience an accelerated decline in FEV_1. Indeed, rapid decline in FEV_1 is a hallmark of COPD (21). In the Malmö "Men Born in 1914" Study, the cardiovascular event rate among smokers in the high, middle, and low thirds with regard to the decline in FEV_1 was 56.0, 41.0, and 22.7 events, respectively, per 1,000 person-years (p for trend = 0.01) (22). In the Baltimore Longitudinal Study of Aging (23), individuals who experienced the most rapid decline in FEV_1 over a 16-year follow-up were three to five times more likely to die from a cardiac cause of death than those who had the slowest decline in FEV_1, after adjustments for age, baseline FEV_1, smoking status, hypertension status, body mass index, and mean serum cholesterol level. Even among lifetime nonsmokers, accelerated decline in FEV_1 was associated with a 5- to 10-fold increase in the risk for cardiac deaths, which suggests that the relationship between changes in FEV_1 and cardiovascular events occurs independently of the effects of smoking. Whether cigarette smoking interacts and modifies the relationship between accelerated decline in FEV_1 and cardiovascular outcomes, however, is unclear.

THE RELATIONSHIP BETWEEN FEV_1 TO FVC RATIO AND CARDIOVASCULAR DISEASE

Although in the general adult population the most common cause of reduced FEV_1 is obstructive airways disease, false positives can occur, because restrictive disorders could also decrease FEV_1. Reduced FEV_1/FVC ratio, on the other hand, is a more specific indicator of airways disease in the general population. In the "Men Born in 1914" Study, Engström and colleagues (11) followed prospectively 621 men, 68 years of age, for approximately 13 years. During this time, all coronary events, defined as fatal or nonfatal myocardial infarction or deaths from ischemic heart disease, were ascertained. Data linkages were performed using National Cause of Death Registry, the Swedish Hospital Discharge registry, and the Malmö Myocardial Infarction Registry. In close to 60% of the cases, the causes of death were verified through an autopsy. Compared to those in the highest FEV_1/FVC quintile (ratio ⩾ 77.3%), those in the lowest FEV_1/FVC (⩽ 66.3%) quintile had risks of coronary events that were on average 73% higher (p = 0.01 adjusted for tobacco consumption, former smoking, alcohol consumption, angina pectoris, physical activities, and diabetes). The risk for frequent or complex ventricular arrhythmia was 83% higher in the lowest FEV_1/FVC quintile compared with the highest quintile.

Sin and Man (24) examined data from 6,629 participants of the Third National Health and Nutrition Examination Survey

in the United States. The cohort was divided into four mutually exclusive groups based on their lung function (no, mild, moderate, or severe airflow obstruction). Participants with severe airflow obstruction (defined as $FEV_1 < 50\%$ of predicted and FEV_1/FVC ratio $\leqslant 70\%$) were 2.1 times more likely to have electrocardiographic evidence of probable or possible (prior) myocardial infarction. The odds (risk) were also elevated in those with moderate airflow obstruction (defined as FEV_1 50–80% of predicted) (odds ratio, 1.4) but not to the same extent as that observed with severe airflow obstruction. Interestingly, participants with severe airflow obstruction were, respectively, 2.18 and 2.74 times more likely to have elevated C-reactive protein (CRP, $\geqslant 2.2$ mg/L) and highly elevated circulating CRP levels (> 10.0 mg/L) than those without airflow obstruction, after adjustments for a variety of factors including age, sex, smoking history, body mass indices, and comorbidities. Participants with moderate airflow obstruction were 1.41 and 1.56 times more likely to have elevated and highly elevated circulating CRP levels. These data provide additional support to the concept that obstructive airways disease is an independent risk factor for ischemic heart disease, which may in part be explained by the systemic inflammatory effects of COPD on the coronary vasculature (*see* accompanying articles by Wouters [pp. 26–33] and MacCallum [pp. 34–43] in this issue).

With respect to the endpoint of coronary events, airflow obstruction, as measured by a reduced FEV_1/FVC ratio, may be an effect modifier. In the study by Engström and coworkers (11), reduced FEV_1/FVC ratio by itself was a modest independent risk factor for coronary events (RR, 1.30). Presence of arrhythmias in those with normal FEV_1/FVC was not associated with coronary events (RR, 1.01). However, the combination of reduced FEV_1/FVC ratio and presence of arrhythmias increased the risk of coronary events by over twofold (RR, 2.43; 95% CI, 1.36–4.32). These data suggest that airflow obstruction impacts synergistically on the diseased heart to make it more vulnerable to acute coronary events.

THE RELATIONSHIP BETWEEN COPD AND CARDIOVASCULAR DISEASE

Jousilahti and colleagues (10) studied 9,342 men and 10,102 women, born between 1913 and 1947 in Finland. In this carefully conducted population-based study, a positive response to the question, "Do you cough on most days and nights as much as 3 months each year?" was associated with an approximately 50% increase in the risk for coronary deaths than those without this symptom, adjusted for age, study year, serum total cholesterol, and amount of smoking (RR, 1.55; 95% CI, 1.26–1.90 in men and 1.41; 95% CI, 0.92–2.16 in women). In the Multifactor Primary Prevention Trial (25), individuals who had daily cough and sputum production were 42% more likely to die from cardiovascular events than those without any respiratory symptoms (95% CI, 16–75%) adjusted for age.

Newman and colleagues (26) studied 614 men and women, 65 years of age and older, as part of the Cardiovascular Health Study. Along with a careful ascertainment of cardiovascular risk factors, these investigators also performed electron beam tomography to assess coronary artery calcium on the study participants. They found that the prevalence of self-report of COPD was 77 to 91% higher in the group with the highest quartile of coronary artery calcium compared to the group with the lowest quartile (adjusted odds ratio, 1.47; 95% CI, 1.002–2.15; $p = 0.048$).

The leading causes of mortality in those with obstructive airways disease are cardiovascular in nature. In the Tucson Epidemiologic Study of Airways Obstructive Disease (8), only 8% of the decedents who had antemortem spirometric evidence of obstructive airways disease as defined by FEV_1/FVC ratio of less than 65% died directly from their airway disease (as the underlying cause of death). Even among those with severe obstructive airways disease (defined as FEV_1/FVC $< 65\%$ and $FEV_1 < 50\%$ of predicted), less than a quarter died from respiratory failure. Even among those in whom obstructive airways disease is mentioned as a contributing cause of death, cardiovascular causes are listed as the primary cause of death in nearly 50% of the cases, whereas malignancy was the primary cause in 11% of the cases. Pulmonary causes constituted only 29% of the cases. However, some caution should be exercised in interpreting disease-specific mortality data in COPD. Because the information provided on death certificates was not validated through autopsies, the extent to which diagnostic misclassification confounded the findings is not known. Nevertheless, these data, in the context of previously mentioned studies, suggest that a large proportion of patients with COPD die from cardiovascular complications.

The Lung Health Study investigators (27) studied 5,887 smokers, aged 35 to 60 years, with mild to moderate airways obstruction. Study participants were randomized to three arms: usual care plus placebo; special intervention for smoking cessation plus ipratropium; and special intervention for smoking cessation plus placebo. During the initial 5-year follow-up, 2.5% of the original cohort died, and 25% of those died of a cardiovascular event. Approximately 13% of the cohort experienced at least one hospitalization during the 5-year follow-up. Cardiovascular events accounted for 42% of the first hospitalizations and 48% of the second hospitalizations. The rate of hospitalization for lower respiratory tract infection was only a third of that for cardiovascular illnesses. For every 10% decrease in FEV_1, all-cause mortality increased by 14%, cardiovascular mortality increased by 28%, and nonfatal coronary event increased by almost 20%, after adjustments for relevant confounders such age, sex, smoking status, and treatment assignment.

UNANSWERED QUESTIONS

Although there is a growing body of literature linking COPD with cardiovascular events, there remain many unanswered questions. First, there is a scarcity of studies that evaluated COPD as a potential effect modifier of cardiovascular events in individuals with pre-existing heart disease. Second, it is not clear whether COPD amplifies the adverse effects of cigarette smoking on the cardiovascular system or whether it acts predominantly via the smoke–heart disease causal pathway. Third, the mechanisms through which COPD contributes to atherosclerosis and, ultimately, cardiovascular events are not fully known. The potential pathways are discussed in accompanying sections by MacCallum and Wouters. Finally, it is not clear whether anti-COPD interventions, aside from smoking cessation, can modify cardiovascular risks in COPD. Clearly, future work is needed in this area to evaluate current and future anti-COPD therapies to determine their effects on cardiovascular outcomes among patients with COPD.

SUMMARY

The epidemiologic evidence linking COPD and cardiovascular morbidity and mortality is strong. Even after adjustments for traditional cardiovascular risk factors such as serum total cholesterol, hypertension, obesity and smoking, patients with COPD have a two- to threefold increase in the risk of cardiovascular events including death. For every 10% decrease in FEV_1, cardiovascular mortality increases by about 28%, and nonfatal coronary event increases by about 20% in mild to moderate COPD. Even among

individuals with severe airways obstruction ($FEV_1 < 50\%$ of predicted), the leading causes of death are cardiovascular in nature. The potential mechanisms, which may be responsible for this relationship, are discussed elsewhere.

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