REVIEW / SYNTHÈSE

Chronic obstructive pulmonary disease: a novel risk factor for cardiovascular disease[1]

Don D. Sin and S.F. Paul Man

Abstract: Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality in Canada and elsewhere. It affects 5% of all adult Canadians and is the fourth leading cause of death. Interestingly, the leading causes of hospitalizations and mortality among COPD patients are cardiovascular events. In the Lung Health Study, over 5 800 patients with mild to moderate COPD were studied. Forty-two to 48% of all hospitalizations that occurred over the study's 5-year follow-up period were related to cardiovascular complications. Various population-based studies suggest that independent of smoking, age, and gender, COPD increases the risk of cardiovascular morbidity and mortality twofold. Alarmingly, some bronchodilators, which are commonly used to treat symptoms in COPD, may increase the risk of cardiovascular morbidity and even mortality among COPD patients. In this paper, we discuss the epidemiologic evidence linking COPD and cardiovascular events as well as the potential mechanism(s) which may be responsible for this association.

Key words: COPD, FEV1, cardiovascular events, C-reactive protein.

Résumé : La bronchopneumopathie chronique obstructive (BPOC) est l'une des cause majeures de morbidité et de mortalité au Canada et ailleurs dans le monde. Au Canada, elle touche 5 % des adultes et constitue la quatrième cause de décès. Fait intéressant, les principales causes d'hospitalisation et de mortalité chez les patients atteints de BPOC sont des événements cardiovasculaires. Une étude sur la santé pulmonaire « the Lung Health Study » a été menée sur 5800 patients présentant une BPOC légère à modérée. De 42 à 48 % des hospitalisations qui ont eu lieu pendant la période de suivi de 5 ans ont été reliées à des complications cardiovasculaires. Diverses études basées sur une population suggèrent qu'indépendamment du tabagisme, de l'âge et du sexe, la BPOC augmente le risque de morbidité et de mortalité cardiovasculaires d'un facteur deux. Fait inquiétant, certains bronchodilatateurs, qui sont couramment utilisés pour traiter les symptômes associés à la BPOC, pourraient augmenter le risque de morbidité cardiovasculaire et même la mortalité chez les patients présentant une BPOC. Dans cet article, nous discutons des données épidémiologiques liant la BPOC aux événements cardiovasculaires ainsi que du ou des mécanismes qui pourraient être à l'origine de cette association.

Mots clés : BPOC, VEMS, événements cardiovasculaires, protéine-C réactive.

[Traduit par la Rédaction]

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by an airflow obstruction that is not fully reversible (Pauwels et al. 2001). In over 80% of cases, cigarette smoking is felt to be the putative cause for the disease. In Canada, COPD affects over 5% of the adult population (Health Canada 1993). Its prevalence has risen by 41% since 1982, and its age-adjusted death rate has increased by 17% between 1966 and 1982 (Mannino et al. 2002). In Canada each year, 1.5 million hospital days are spent collectively taking care of COPD patients. Approximately 12% of these stays occur in critical care units, translating into huge economic costs for society, estimated to be over $900 million annually in Canada and $23 billion in the US (Health Canada 1993). By 2020, COPD will be the third leading cause of death (currently 4th) (Murray and Lopez 1997) and the 5th leading cause of disability (currently 12th) worldwide (Michaud and Murray 2001).

Despite rapid advances in our understanding of its pathophysiology over the last 2 decades, COPD remains largely an untreatable disease. Aside from smoking cessation, there

Received 4 June 2004. Published on the NRC Research Press Web site at http://cjpp.nrc.ca on 1 February 2005.

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[1]This paper is one of a selection of papers published in this Special Issue, entitled Young Investigator's Forum.

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 doi: 10.1139/Y04-116 © 2005 NRC Canada

are no existing therapies that can modify the natural course of COPD (Sin et al. 2003). Smoking cessation is, therefore, the single most important intervention for these patients. However, even in the best programs, fewer than a third of smokers remain sustained quitters after 1 year, and fewer than 25% remain smoke-free after 5 years (Anthonisen et al. 1994). Pulmonary rehabilitation is generally reserved for patients with moderate-to-severe disease. In the short term, pulmonary rehabilitation decreases exertional dyspnea and improves health status. However, over the long term, unless the skills and knowledge taught in the pulmonary rehabilitation programs are reviewed and reinforced on a regular basis, the salutary benefits of rehabilitation may be lost after 6 to 12 months of follow-up. Moreover, there is an absence of data to indicate that pulmonary rehabilitation prolongs survival in COPD. Only supplemental oxygen (for those with resting hypoxia) has been shown to improve survival in COPD, but resting hypoxia affects a very small minority of patients (Sin et al. 2003). For individuals who are symptomatic (with dyspnea and cough), bronchodilators and theophyllines are used for symptomatic management. Although these therapies greatly improve lung function and relieve symptoms, they do not modify the long-term decline in forced expiratory volume in 1 second (FEV_1), which is the hallmark of COPD (Sin et al. 2003). Importantly, there are some emerging data to suggest that these medications may increase morbidity and mortality in COPD. For instance, ipratropium bromide, which is a short-acting anticholinergic agent, may increase the risk of cardiovascular complications in COPD by 10% to 20% (Anthonisen et al. 2002). In short, the current management of COPD is extremely limited and, by and large, cannot be expected to modify its natural course. Importantly, there is growing concern that some of the medications commonly used in COPD may increase morbidity and mortality.

The reason(s) for the paucity of effective therapies in COPD are likely to be multi-factorial and complex. There is growing recognition that COPD is more than a lung disease. There is compelling evidence that it is a systemic disease (Alessandri et al. 1994; Dahl et al. 2001; Dentener et al. 2001; Eid et al. 2001; Gan et al. 2004; Wouters et al. 2002) with multiple effects on end-organs including organs in the cardiovascular system (Anthonisen et al. 2002; Camilli et al. 1991; Engstrom et al. 2001; Higgins and Keller 1970; Hole et al. 1996; Jousilahti et al. 1996; Sin and Man 2003). The potential effects of COPD on the cardiovascular system may have large clinical relevance because data from large longitudinal studies of COPD patients indicate that the leading cause of hospitalization and mortality in established COPD patients is cardiovascular in nature (Camilli et al. 1991). Moreover, the excess morbidity associated with certain inhaled bronchodilators appears to be driven largely by increased numbers of cardiovascular events (Anthonisen et al. 2002). This paper will review some of the epidemiologic evidence linking COPD with cardiovascular disease (in particular, cerebral infarction, acute coronary syndromes, arrhythmias, and deaths related to these events) and present a potential mechanistic model to explain the association.

Possible pathophysiology

How COPD increases the risk of poor cardiovascular outcomes is largely unknown and unexplained. There is evidence that COPD patients have a perturbed neurohumoral regulatory system, leading to excess sympathetic nervous activity and reduced vagal tone (Heindl et al. 2001). Accordingly, COPD patients have a raised resting heart rate and an increased risk of rhythm disturbances and ectopic beats (Engstrom et al. 2001). Bronchodilators in certain susceptible patients may further worsen the autonomic dysregulation. It is noteworthy that in the Lung Health Study, those assigned to ipratropium had a 3.7-fold higher risk of arrhythmias than those assigned to placebo. In contrast, there were no differences in the risk for ischemic heart disease (relative risk 1.00) between the 2 groups (Anthonisen et al. 2002). Since arrhythmic episodes are more reflective of underlying dysregulation in the autonomic system than are ischemic events, these data suggest that aerosolized ipratropium therapy may further exaggerate sympathetic–parasympathetic imbalances in COPD.

Another potential mechanism may relate to systemic inflammation. There is strong evidence that persistent low-grade systemic inflammation is present in COPD (Gan et al. 2004). We examined data from 6629 participants of the Third National Health and Nutrition Examination Survey in the United States (Sin and Man 2003). When we divided this cohort into those with mild, moderate, or severe airflow obstruction and those without any airflow obstruction, we found that severe airflow obstruction (defined as $FEV_1 < 50\%$ of predicted) increased the probability of having elevated C-reactive protein (CRP) in the systemic circulation by 2.18-fold compared with normal lung function, after adjustments for a variety of factors including age, gender, smoking history, body mass indices, and co-morbidities. Similar relationships were observed when other markers of systemic inflammation such as plasma fibrinogen, blood platelets, or blood leukocytes were considered. These data are consistent with many other studies, which have also shown that systemic inflammation is present in COPD.

The pathogenesis of atherosclerosis is complex and multifactorial. A detailed discussion is beyond the scope of this paper and the readers are referred elsewhere for a more comprehensive discussion on this topic (Lusis 2000; Ross 1999). It is increasingly recognized that low-grade systemic inflammation may play a leading role in plaque formation and rupture (Ross 1999). There are strong epidemiologic data linking systemic inflammation to atherosclerosis, ischemic heart disease, strokes, and coronary deaths (Ridker 2003). Under normal physiologic conditions (and without external insults), the human endothelium does not support leukocyte adhesion, which is the building block of plaque genesis. However, in an inflammatory state (such as diabetes, COPD, or obesity), the endothelium begins to over-express surface adhesion molecules such as vascular cell adhesion molecule-1 that allow circulating white blood cells to adhere to damaged endothelial surfaces. Once the white cells adhere to the endothelium, they trigger a whole series of inflammatory reactions (Lusis 2000). Certain molecules can promote (or amplify) this inflammatory process. The most studied of these molecules is CRP. It is an acute phase protein that responds to infectious or inflammatory stress. Although a variety of different tissues express and produce CRP, circulating CRP is derived mostly from hepatocytes. Hepatocytes up-

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regulate production of CRP in response to various signaling molecules and in particular to interleukin (IL)-6 (Pepys and Hirschfield 2003). When released into the systemic circulation, CRP can up-regulate production of other inflammatory cytokines, activate the complement system, promote uptake of low-density lipoprotein (LDL) cholesterol by macrophages, and foster leukocyte adhesion to vascular endothelium, thereby amplifying the inflammatory cascade. Its production can be tonically increased by chronic low-grade inflammation. In laboratory experiments, it has been shown that CRP actively participates in the development of a pro-inflammatory and pro-atherosclerotic phenotype (Pepys and Hirschfield 2003). It interacts with endothelial cells to stimulate the production of IL-6 and endothelin-1. Since IL-6 is also a potent regulator of CRP synthesis by the hepatocytes, this creates a positive feedback system. CRP was shown to facilitate leukocyte adhesion and transmigration by stimulating the up-regulation of adhesion molecules and monocyte chemotactic protein-1, and to promote macrophage uptake of LDL (Pepys and Hischfield 2003). Not surprisingly given these physiologic functions of CRP, serum CRP level is a strong, independent predictor of cardiovascular morbidity and mortality. In the Framingham Study, for instance, CRP levels of < 1, 1 to 3, and 3 mg/L corresponded to low, moderate and high-risk groups for future adverse cardiovascular events. Other acute phase proteins released by the liver such as plasma fibrinogen can also be used to predict future cardiovascular events (Ridker 2003).

In COPD patients, the nidus for the low-grade systemic inflammation is likely the airways (see Fig. 1). There is evidence to show that small airways of COPD patients are persistently inflamed and that the intensity of the inflammatory process correlates with the severity of COPD (Hogg et al. 2004). Once COPD is established, airway inflammation persists even after many years of smoking cessation. A detailed discussion of the pathophysiology of COPD is beyond the scope of this paper, and the reader is referred elsewhere for a more comprehensive discussion on this topic (Barnes et al. 2003). Briefly, cigarette smoke and other environmental irritants and infectious organisms may activate alveolar macrophages, bronchial epithelial cells, and other cellular elements in the airways of genetically susceptible individuals. Once activated, these cells produce a variety of signaling molecules, called chemokines. These cells also produce cytokines such as IL-8, which recruits neutrophils; macrophage chemotactic protein-1, which recruits monocytes; and interferon-gamma-inducible protein-10, which recruits lymphocytes. Additionally, the cells synthesize and release growth factors, elastolytic enzymes, and metalloproteinases, which by themselves may promote emphysematous changes in lung parenchyma and airway remodeling (Barnes et al. 2003). Alveolar macrophages, bronchial epithelial cells, and certain lymphocytes can also produce IL-6 and IL-1β, which not only induce local pro-inflammatory changes, but may also "escape" into the systemic circulation and stimulate hepatocytes to synthesize acute phase proteins such as CRP and fibrinogen (Pepys and Hischfield 2003). IL-6 and granulocyte macrophage colony stimulating factor may also stimulate the bone marrow to produce leukocytes and platelets (Fujii et al. 2002). These cells and molecules then circulate and may, in conjunction with traditional risk factors such as hypertension, hypercholesterolemia, advanced glycation end products, promote atherogenesis and cardiovascular disease.

COPD and cardiovascular complications

Regardless of the precise mechanism(s) involved, COPD patients are at increased risk of cardiovascular events. Indeed, cardiovascular events (e.g., strokes, acute coronary syndromes, and cardiovascular deaths) are the leading causes of morbidity and mortality in this population. Liao and colleagues, for instance, evaluated close to 2000 participants between the ages of 55 and 72 years, as part of the Atherosclerosis Risk in Communities Study (Liao et al. 1999). All of these participants were free of any neurologic deficits at baseline and did not have a history of a stroke or transient ischemic attacks. Magnetic resonance imaging (MRI) of the brain was performed on these subjects to detect sub-clinical radiographic evidence of cerebral infarction or significant white matter disease in the cerebral cortex. Spirometry was performed to ascertain lung function. Researchers found that compared with the highest FEV_1 quartile, subjects in the lowest quartile had risks for sub-clinical cerebral infarction that were 3-fold higher and white matter disease that were 2-fold higher. These data suggest that impaired lung function is an independent risk factor for ischemic injury to the brain. In another study, Newman and colleagues evaluated 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 performed electron beam tomography to assess coronary artery calcium (which is a surrogate marker for atherosclerosis) on the study participants (Newman et al. 2001). They found that those who reported COPD were 50% more likely to be in the highest quartile of coronary artery calcium scores than those who did not have COPD, adjusted for age, gender, race, pack-years of smoking, triglycerides, and clinical evidence of cardiovascular disease. In a Finnish population-based study, Jousilahti and colleagues found that subjects who had symptoms of chronic bronchitis were ~50% more likely to experience a coronary death than those without these symptoms, adjusted for age, gender, study year, serum total cholesterol, systolic blood pressure, and smoking history (Jousilahti et al. 1996). Engstrom and colleagues in the "Malmo Men Born in 1914" Study showed that airways disease (as defined by a reduced FEV_1 to forced vital capacity ratio) was an independent risk factor for arrhythmias, coronary events, and all-cause mortality (Engstrom et al. 2001). According to the Lung Health Study, the leading cause of hospitalization in individuals with well-characterized COPD is cardiovascular in nature. Indeed, in this study, close to 50% of all hospitalizations were related to the cardiovascular system; only about 14% of hospitalizations were related to COPD exacerbation or pneumonia (Anthonisen et al. 1994). Moreover, 25% of the decedents died from cardiovascular causes (Anthonisen et al. 1994). These data indicate that cardiovascular burden is substantial in COPD.

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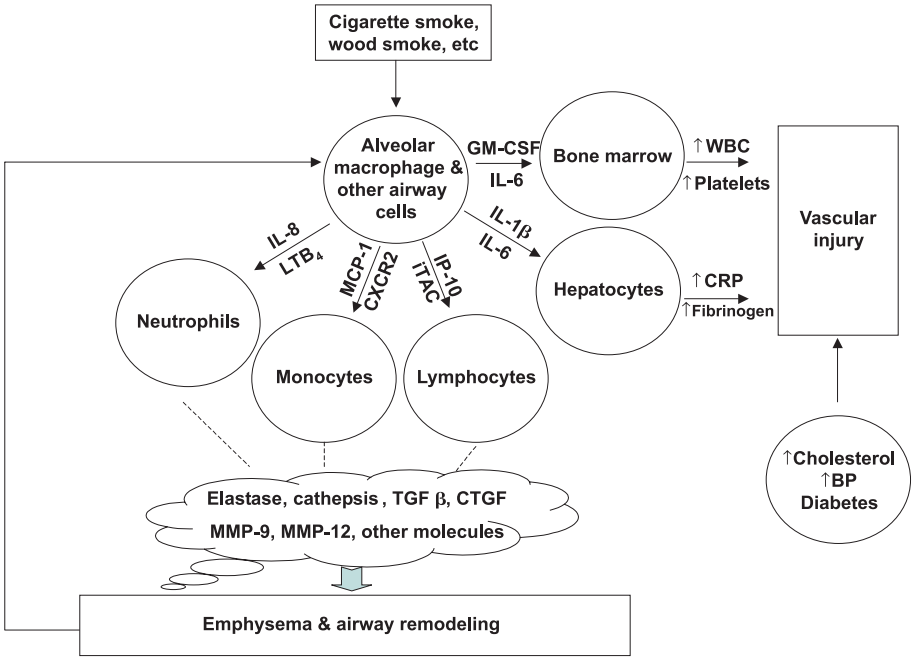
Fig. 1. A model of the pathogenesis of chronic obstructive pulmonary disease. Cigarette smoke and other environmental irritants may activate alveolar macrophages and other cells in the airways (e.g., bronchial epithelial cells) of susceptible individuals. These and other cells in the airways may then produce a variety of signaling molecules, cytokines, and chemokines to activate and recruit pro-inflammatory cells such as neutrophils, lymphocytes, and monocytes into airway lumen and (or) wall. Once activated, these pro-inflammatory cells may release a variety of "toxic" substances, which may promote emphysematous changes in the alveoli and inflammatory changes in the airways. Some of these molecules (e.g., IL-6, IL-1β) may "spill" into the systemic circulation, stimulating hepatocytes to produce acute phase proteins such as C-reactive protein and fibrinogen, and stimulating the bone marrow to synthesize leukocytes and platelets. These pro-inflammatory cells and proteins may then promote vascular injury, in concert with traditional cardiovascular risk factors such as hypercholesterolemia, diabetes, and hypertension. IL, interleukin; TGF, transforming growth factor; MCP, macrophage chemotactic protein; LTB_4, leukotriene B4; MMP, metallomatrixproteinases; I-TAC, interferon-inducible T-cell α-chemoattractant; IP-10, interferon-gamma-inducible protein-10; CTGF, connective tissue growth factor; GM-CSF, granulocyte macrophage colony stimulating factor; CXCR2, chemokine receptor; WBC, white blood cells; CRP, C-reactive protein; BP, blood pressure.



Anti-COPD medications and cardiovascular complications

Disturbingly, use of short- or long-acting bronchodilators has been associated with increased risk of cardiovascular events in COPD. In 1 study, use of ipratropium bromide, a short-acting anti-cholinergic medication, was associated with a 60% increase in adjusted mortality compared with non-use among 827 patients with COPD (Ringbaek and Viskum 2003). The Lung Health Study investigators evaluated 5887 participants with mild to moderate COPD (mean FEV_1: 75% of predicted; mean age 48 years). One third of the participants were assigned in a random fashion to usual care; one third to special intervention (for smoking cessation) plus ipratropium bromide; and one third to special intervention (for smoking cessation) plus placebo puffers (Anthonisen et al. 2002). The subjects were then followed prospectively for 5 years wherein all hospitalizations and deaths were captured by the study investigators. The Study Mortality and Morbidity Review Board assessed all relevant hospitalization and mortality records and codified each of these events (hospitalizations and deaths) in accordance with the review criteria. At the end of the 5 years of the study, all events were collated and analyzed based on an intent-to-treat principle. They found that those assigned to ipratropium bromide had a 26% higher risk of cardiovascular events, compared with the group assigned to placebo. The risk of fatal cardiovascular events was even higher (relative risk, 2.6). The risk of non-fatal cardiovascular events was only modestly elevated (relative risk, 1.19). Although this study was underpowered to detect cardiovascular events, these data nonetheless raised concerns that ipratropium bromide may increase cardiovascular morbidity and mortality in COPD. Similarly, use of short-acting beta-2 agonists has been associated with increased cardiovascular events. Au and colleagues, for example, studied 630 patients with unstable angina or myocardial infarction and 10 486 control subjects enrolled in 7 Veterans Administration Medical Centers, and found that compared with subjects who did not fill a short acting β_2 agonist prescription, patients who had filled a β_2 agonist prescription in the 3 month prior to their index date had ~70% increase in the risk for an acute coronary event (Au et al. 2002). Importantly, the excess risk was limited to those patients who had a prior history of cardiovascular disease; their risk was over 3-fold higher than those who did not use β_2 agonists. Additionally, new users of β_2 agonists had a 7-fold increase in the risk of cardiovascular events. Whether inhaled β_2 agonists or anticholinergics promote systemic inflammation in COPD is not known. Future studies are needed to validate these initial epidemiologic observations and to determine the potential

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mechanisms by which these medications may increase cardiovascular risk in susceptible COPD patients.

Summary

Increasingly, COPD is being recognized as an inflammatory disorder of the airways and lung parenchyma, leading to airway remodeling and lung emphysema. Additionally, COPD is associated with persistent, low-grade inflammation, which may adversely impact on various extrapulmonary organs such as the blood vessels and the heart. Although respiratory failure is a common end-point for patients with advanced COPD, many COPD patients experience cardiovascular complications including stroke, coronary syndromes, arrhythmias, and sudden deaths. Indeed, in mild-to-moderate COPD cardiovascular events are the leading causes of hospitalization and mortality. The mechanisms by which the pulmonary changes of COPD can lead to these cardiovascular events are not clear. One possibility is that the inflammatory process in the airways may spill into the systemic circulation, promoting a state of persistent low-grade systemic inflammation, which then in concert with traditional risk factors such as hypertension and hypercholesterolemia acts to foster plaque formation and rupture in susceptible individuals with COPD. If this model is valid, then anti-inflammatory therapies (either via aerosolized or oral routes) may be able to modify the long-term cardiovascular complications in COPD. Future research is needed in both animal and human models to validate (or refute) this hypothesis and to determine whether anti-inflammatory agents do indeed modify cardiovascular morbidity and mortality in COPD.

Acknowledgements

DDS is supported by a Canada Research Chair (Obstructive Airway Disease) and a Michael Smith/St. Paul's Hospital Foundation Professorship in COPD.

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