Introduction

Chronic obstructive pulmonary disease (COPD) is a clinical process characterized by airflow limitation that is not fully reversible. This limitation is, in general, chronic and progressive, and is associated with an abnormal pulmonary inflammatory response to harmful particles or gases, in particular the components of tobacco smoke. Impaired lung function in patients with COPD is associated with a greater number of cardiovascular events and cardiac deaths, although the mechanisms underlying this association are poorly understood. A relationship between COPD and cardiovascular disease, linked to a systemic inflammatory component, has even been detected in patients with mild or moderate obstruction. In fact, there is evidence that small reductions in respiratory flow can increase cardiovascular morbidity and mortality by 2 or 3 times. Inflammation is not only a primary etiologic factor in the development of COPD; it is also recognized as an important pathophysiological element in the origin of atherosclerosis. In addition to the role that tobacco smoke plays in triggering inflammation in patients with COPD, other factors, such as dyslipidemia and obesity can cause vascular endothelial damage through oxidative stress. Different therapeutic strategies, including smoking cessation and statin therapy, can act on the inflammatory component and oxidative stress. This approach to treatment could influence the origin and progression of cardiovascular complications associated with COPD and reduce mortality among patients with this disease.

Epidemiology

COPD is the fourth leading cause of morbidity and mortality both in Spain and in other developed countries and represents a public health problem of utmost importance. According to the World Health Organization, the worldwide prevalence of this disease—which currently affects 52 million people—will double by 2020. This increase would make COPD the third leading cause of death worldwide. In Spain, its estimated prevalence is, according to the findings of the IBERPROC study, 9% in men more than 40 years old and 20% in those more than 65 years old. Moreover, it is thought that the incidence of the disease will continue to increase in the coming decades. Such figures suggest that COPD will become one of the most costly diseases for the health care system.

Risk Factors

The main risk factors for triggering inflammation in patients with COPD are smoking and exposure to harmful airborne particles. Other factors, such as obesity or dyslipidemia, are implicated in the development of systemic inflammation and, therefore, in the vascular endothelial damage that may lead to the appearance of cardiovascular events.

Smoking

The main etiologic factor in the development of COPD is smoking. This harmful habit is also a basic risk factor for the onset of other diseases including cardiovascular ones. It has been repeatedly shown that tobacco smoke is responsible for a number of effects that increase cardiovascular risk: platelet activation, decrease in plasminogen tissue activator concentrations, increase in plasminogen-1 activator inhibitor concentrations, and the tendency to induce a prothrombotic state in the body. In addition, high-density lipoprotein cholesterol concentrations decrease whereas the concentrations of low-density lipoprotein cholesterol, triglycerides, and very low-density lipoproteins increase, and there may also be effects on endothelial function in the arterial walls.

Both systemic and vascular fibrinogen and other hemostatic factors that participate in thrombosis are elevated.
in all inflammatory states. This inflammation—induced by lung injury and respiratory infections—predisposes smokers to coronary artery lesions.\textsuperscript{13,14} In addition, elevations of C-reactive protein (CRP), which behaves as a marker of systemic inflammation, is associated with the presence of other cardiovascular risk factors such as age, smoking, hypertension, obesity, and dyslipidemia. An increase in serum concentrations of CRP might therefore predict whether significant COPD is present or even its severity. In fact, in patients who smoke, the increase in serum concentrations of this protein is much more marked.\textsuperscript{12,15,16}

Smoking cessation, in addition to being the most effective and efficient way of reducing the risk of COPD and slowing its progression,\textsuperscript{23} is associated with a decrease in the number of acute cardiac events and with an improvement in arteriosclerotic vascular lesions that might be present.\textsuperscript{18} Nevertheless, we should note that, in line with the study by Sin and Man,\textsuperscript{2} the relationship between changes in forced expiratory volume in 1 second (FEV\textsubscript{1}) and the onset of atherothrombotic complications occurs independently of the effects of tobacco smoke.

### Harmful Air Particles

A variety of mechanisms might explain how airborne particulate pollution might induce the development of cardiac disease.\textsuperscript{4} First, inflammation in the lung might destabilize the autonomic nervous system thereby favoring the appearance of cardiac arrhythmias.\textsuperscript{19} Second, the production of certain cytokines in the lung, such as interleukin (IL) 6, might favor hypercoagulation, which would predispose the individuals to thrombotic processes.\textsuperscript{20} In addition, other cytokines, such as granulocyte-macrophage colony-stimulating factor, might lead to an increased activation or greater circulation of leukocytes, which, in turn, would induce inflammatory rupture of the atherosclerotic plaques.\textsuperscript{21} We should remember that cytokines produced by the lung trigger hepatic synthesis of acute phase reactant proteins, such as CRP and fibrinogen, which are also prothrombotic. In fact, overall, thrombotic diathesis is the mechanism most strongly associated with and the best predictor of cardiovascular morbidity and mortality.\textsuperscript{22}

### Dyslipidemia

A range of studies have found that the increase in serum concentrations of low-density lipoprotein cholesterol is associated with increases in circulating concentrations of CRP as well as with an increase in the risk of cardiovascular death, myocardial damage, transient ischemic attack, and admission to hospital for unstable angina.\textsuperscript{23} Similarly, subsequent studies have shown the efficacy and safety of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) when used to reduce serum concentrations of CRP and, therefore, the risk of suffering cardiovascular disease.\textsuperscript{24} As mentioned earlier, smoking decreases the serum concentrations of high-density lipoprotein cholesterol and increases concentrations of low-density lipoprotein cholesterol, triglycerides, and very low-density lipoproteins, thereby favoring the appearance of cardiovascular events.\textsuperscript{12}

Drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase such as statins are used to prevent and treat cardiovascular diseases.\textsuperscript{25,26} They also have other important effects, including their capacity to increase synthesis of nitric oxide and prostacyclins, inhibit thrombosis, and reduce inflammatory response.

### Obesity

Obesity may reasonably be supposed to compromise the effectiveness of respiratory mechanics and so increase the work needed to carry out activities of daily living. Some studies have, however, found that mortality is actually lower in patients with COPD if they are also obese.\textsuperscript{27,28} Weight loss in patients with COPD has been attributed to the systemic effects of certain cytokines synthesized in the lung, in particular, those of tumor necrosis factor (TNF) \(\alpha\).\textsuperscript{29} Several studies have indeed shown that serum concentrations of this substance are increased in patients with COPD who lose weight.\textsuperscript{4,30,31} Nevertheless, it has yet to be clarified whether these factors play a role in patients with cardiac disease or whether they might be relevant in patients with COPD who are also somewhat overweight.

What is evident, in contrast, is that adipose tissue actively participates in regulating the pathophysiological mechanisms responsible for the inflammatory reaction and the immune response of the organism. The function

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**Figure.** Lung inflammation in chronic obstructive pulmonary disease (COPD) may lead to acute and chronic conditions that, mediated by circulating cytokines, contribute to the appearance of cardiovascular events. CRP indicates C-reactive protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-6, interleukin 6; TNF-\(\alpha\), tumor necrosis factor \(\alpha\).
of adipokines (leptin and adiponectin in particular) is important not only in atheromatosis but also in the inflammatory response in COPD and, perhaps, in the possible link between this disease and cardiovascular disorders.32

**Exacerbations**

Exacerbations of COPD may accentuate inflammatory processes. Chronic infections by certain Gram-negative bacteria or *Chlamydia pneumoniae* seem to favor the inflammatory reaction seen in atherosclerosis,3,33 Furthermore, systemic inflammation, oxidative stress, hyperfibrinogenemia, and increases in the vasoconstrictor peptide endothelin-1—all of which are often found in COPD exacerbations—might contribute to the deterioration in endothelial and vascular function and, therefore, to the onset of cardiovascular and cerebrovascular disease.9,34,35

**Lung Function**

Sin and Man,1 in an attempt to demonstrate that impaired lung function is a risk factor for cardiovascular events, carried out a study in which they found that for every 10% decrease in FEV1, overall mortality increased by 14%, cardiovascular mortality by 28%, and coronary complications by at least 20%. They also observed that the decrease in the ratio of FEV1 to forced vital capacity was an independent risk factor for coronary events, with an increase in likelihood of 30%. In patients with COPD who also had ventricular arrhythmias, the risk of coronary disease doubled. In short, these findings seem to suggest that COPD is, in itself, an independent risk factor for cardiovascular morbidity and mortality. Furthermore, in the aforementioned study, it was also observed that the increase in serum concentrations of CRP doubled the probability of cardiac lesions.

On the other hand, the increase in work of breathing that occurs in COPD, particularly during exercise, when the respiratory muscles account for half the total oxygen uptake, may be a major problem in patients with compromised cardiac function.36

**Pulmonary Hypertension**

Several possible mechanisms may explain the development of pulmonary hypertension in patients with COPD. Some of the most important are loss of pulmonary vascular bed, vasoconstriction triggered by hypoxia, capillary microthrombosis, and circulatory stasis caused by polycythemic hyperviscosity.4 Pulmonary hypertension usually causes chronic cor pulmonale, which is characterized by right ventricular hypertrophy, dilatation, and finally failure.37 Fluid and electrolyte homeostasis is also affected through secretion of the natriuretic hormone in response to hypoxia and dilatation of pulmonary veins and right heart chambers.38 Clinically, it is therefore often difficult to distinguish between an exacerbation of COPD and an exacerbation of chronic heart failure. In this sense, it may useful to measure the serum concentrations of brain natriuretic peptide (BNP).39

**Biological Markers**

The numerous epidemiological studies carried out to date have identified, among other things, several markers that open up a range of possibilities in the study of cardiovascular disease. It might be supposed that the assessment of these new markers, whether or not in conjunction with traditional risk factors, might help to more accurately predict the probability of the onset of the aforementioned COPD-related events. It also seems clear that COPD itself may be useful as a sort of “biological marker” of ischemic heart disease and vice versa. Thus, an increasing number of studies have found frequent elevations in serum concentrations of a range of mediators of inflammatory response in patients with COPD. The following sections will therefore analyze some of the markers that currently appear most important.

**Brain Natriuretic Peptide**

BNP is a peptide hormone that is synthesized mainly in the left ventricle and that has been attributed vasodilatory and diuretic properties.40 The idea that the heart has “an endocrine function”41 has led to this substance being studied as a marker with diagnostic and prognostic value in patients with heart failure. BNP is synthesized in the myocardium as a pre-prohormone (known as pre-proBNP) and then cleaved into 2 molecules, proBNP and a peptide signal. The proBNP is in turn cleaved into BNP itself and an N-terminal peptide with no biological activity (NT-proBNP).42

When assessing these substances in clinical practice, it should be remembered that increased serum concentrations of BNP and NT-proBNP in heart failure associated with other disorders do not confirm that the patient’s dyspnea is of cardiac origin as other diseases such as COPD may also lead to elevations. We should also be aware that several studies have shown that the increase in BNP and NT-proBNP might be useful as a marker of severity and, therefore, as a prognostic indicator of COPD and chronic cor pulmonale because this increase reflects water-electrolyte imbalances produced by hypoxia and pulmonary vein and right chamber distension.37,43,44

**D-dimer**

D-dimer is one of the degradation products of fibrin and is released through the action of plasmin. In clinical practice, it is a marker of the presence of fibrin and can be used to detect this molecule. D-dimer levels are always high provided coagulation is activated and fibrin is generated. Measurement of D-dimer levels is therefore useful in the diagnosis of venous thrombosis and pulmonary embolism. It is one of the most extensively studied hemostatic variables because of its relationship with cardiovascular diseases,45 although serum concentrations are also elevated in smokers compared to nonsmokers.46

**Adipokines (Adipocytokines)**

Adipokines are substances secreted by adipose tissue. However, only leptin and adiponectin (and perhaps resistin,
adipsin, and visfatin) originate principally in adipocytes. Inflammatory and infectious stimuli increase the concentrations of leptin, thereby activating monocytes and inducing a type 1 helper T cell response, which favors atheromatosis and triggers a proinflammatory cascade. In contrast, an inflammatory stimulus decreases the concentrations of adiponectin. This reduces concentrations of anti-inflammatory cytokines and vascular cell adhesion molecules, and also favors atheromatosis and facilitates inflammatory response.47

Bruno et al42 have found evidence in different studies that leptin is overexpressed in the submucosa of patients with COPD and that there is an inverse relationship between the presence of leptin-positive cells and FEV1, and the ratio of FEV1 to forced vital capacity. In addition, expression of leptin is related to COPD severity according to the Global Initiative for Chronic Obstructive Lung Disease classification. Therefore, elevated leptin and adiponectin concentrations seem to be associated with inflammatory response and with cardiovascular events in patients with COPD.

Fibrinogen

Hyperfibrinogenemia increases cardiovascular risk by favoring fibrin formation and platelet aggregation and by increasing plasma viscosity.48 The synthesis and concentration of fibrinogen depend on inherited genetic polymorphisms, but also on environmental conditions such as smoking. Although the studies that have been carried out so far are inconclusive, it seems that polymorphism of the fibrinogen-β gene might modify the effect of smoking on circulating fibrinogen.49 Furthermore, when the onset of hyperfibrinogenemia coincides with COPD exacerbations, this might contribute to endothelial dysfunction and, therefore, to the onset of cardiovascular and cerebrovascular diseases.9,50

C-Reactive Protein

CRP is an acute phase reactant protein synthesized by the liver in response to the trigger from IL-6 (Table). It has a proinflammatory and proatherogenic effect on endothelial cells through increases in the expression of adhesion and chemotactic molecules. It also favors the release of proinflammatory cytokines such as IL-1β and TNF-α by monocytes. The proinflammatory actions seem to be mediated, at least in part, by activation of the nuclear transcription factor κB (NF-κB), although endothelial damage, production of oxygen free radicals, and migration and activation of smooth muscle cells in the vascular walls may also play a role.51,52

It has also been widely suggested that inflammation contributes to the progression of atherosclerosis. For example, elevated CRP not only seems to be the main risk factor for developing cardiovascular diseases,53,54 but it also adds prognostic value to the Framingham score.55 Given that COPD is also an inflammatory disease, serum concentrations of this protein are usually increased, but an increase is also seen in active smokers who do not have the disease.12 Statins56 and oral or inhaled corticoids56,57 lower serum concentrations of CRP in patients with COPD. These drugs therefore decrease systemic inflammation and so also decrease the risk of suffering a cardiovascular event.

Tumor Necrosis Factor α

TNF-α, also known as cachectin, is a protein that plays a mediating role in inflammatory response by intervening at the start of the cytokine cascade. It is found in high concentrations in the respiratory secretions of patients with COPD, particularly during exacerbations.58,59 Serum concentration and production by peripheral blood monocytes are also high in patients with COPD who lose weight60 (Table). Furthermore, TNF-α inhibits the expression of skeletal muscle proteins through activation of NF-κB.60 Now that these findings have been confirmed by several studies,31,61-63 and given that obesity is a known risk factor for cardiovascular morbidity and mortality, it is possible that the relationship between cardiovascular disease and COPD could be mediated by TNF-α, which could therefore be considered a biological marker of clinical interest. Clearly, further studies are needed to support this hypothesis.

Metalloproteinases

Metalloproteinases (MMPs)—in particular MMP-1, MMP-2, and MMP-9—are collagenases that regulate the homeostasis of the lung matrix, which is made up principally of collagen and other proteins.64 Some of them, particularly MMP-9, have been considered as possible markers of remodeling given that local overproduction

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<th>Function of Cytokine Mediators in COPD</th>
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<tr>
<td>Cytokines Derived From Monocytes and Macrophages</td>
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<td>Mediator</td>
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Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; IL, interleukin; MMP, metalloproteinase; TIMP, tissue inhibitor of metalloproteinases-1; TNF-α, tumor necrosis factor α.
of MMP-9 has been observed along with imbalances between MMP-9 and its inhibitor, the tissue inhibitor of metalloproteases-1 (TIMP-1), in patients with COPD. Therefore, the balance between proteases and their inhibitors could be what best reflects the severity of the disease. This balance would show a progressive change from healthy individuals to patients with COPD. However, further studies are needed to clarify whether these enzymes really do play a role in the prognosis of the disease.

In blood vessels, MMPs, by decreasing the amount of collagen, make the atherosclerotic plaques more fragile. This process, in combination with the underlying arterial inflammation, would facilitate plaque rupture and, as a result, the onset of clinical manifestations of ischemia.

Markers of Oxidative Stress

The imbalance between exogenous oxidants and endogenous antioxidants, in addition to acting as an inflammatory factor mediated by cytokines, also causes lesions in the extracellular matrix and the epithelium of the airway. Several studies have shown that exposure to tobacco smoke can induce oxidative stress and release of inflammatory mediators in the airway, a process which in turn causes structural changes in susceptible individuals and could give rise to a progressive decline in lung function. In addition, an increasing number of studies have found a relationship between oxidative stress induced by smoking and cardiovascular diseases.

Therefore, abnormalities in the genes coding for antioxidant enzymes present in the lung and airway, such as superoxide dismutase, glutathione-S-transferase, microsomal epoxide hydrolase, and hemooxygenase-1, might increase oxidative stress and favor lung injury caused by smoking.

Neopterin

Neopterin is a marker of the activation of the monocyte-macrophage system and release of this molecule is related to the capacity of these cells to produce oxygen free radicals. Neopterin modulates the intracellular oxidative state and gives rise to translocations of NF-κB units to the nucleus, thereby increasing expression of proinflammatory genes that code cytokines such as IL-6 and TNF-α. Interferon γ, released by type 1 helper T cells and other cytolytic cells, is the most potent cytokine at inducing the synthesis of this substance and the one that leads to the greatest increase in neopterin concentration in body fluids. The concentration of neopterin correlates with the concentrations of interferon γ, in turn released by activated T cells. Therefore, neopterin is a sensitive marker of cellular immunity, as concentrations reflect the state of oxidative stress arising from immune system activation.

It has been found that concentrations of neopterin and other markers of cellular immunity are higher in patients with COPD than in healthy controls, an observation that could be associated with greater susceptibility to respiratory tract infections in these patients. In addition, an increasing number of studies have found that the concentration of neopterin is a good prognostic indicator of the progression of atherosclerosis and of the onset of adverse cardiovascular events in hypertense patients and those with coronary artery disease.

Other Markers of Inflammatory and Oxidative Response

A range of inflammatory mediators participate in the pathogenesis of COPD. For example, IL-1β, in addition to acting as a chemoattractant of neutrophils and a trigger of T-cell response, participates in the process of tissue repair through increased deposition of collagen fibers. Transforming growth factor β (TGF-β) participates in the pathway that leads from inflammatory response to airway remodeling and repair by activating enzymes such as MMP-9. In patients with COPD, overexpression of TGF-β has been found in the bronchial epithelium and in macrophages in the small airway.

Detection of nonvolatile inflammatory mediators and markers, such as leukotriene B₄, IL-8, 8-isoprostane, and measurement of the pH of exhaled breath condensate, provides a noninvasive means of assessing inflammatory and oxidative lung response (Table). In a group of patients with COPD, Izquierdo et al found that those who were suffering primarily from pulmonary emphysema had lower concentrations of these markers in exhaled breath condensate. This finding, together with the lack of correlation between serum and condensate concentrations, indicates that the relative concentrations of markers of inflammation and oxidative stress may vary depending on whether they are measured systemically or locally.

Muscle Enzymes

For several years, studies have found that ventilatory and gas-exchange abnormalities alone cannot account for the exercise intolerance of patients with COPD and that other factors, such as skeletal muscle dysfunction, might also contribute. The biochemical and histochemical findings of a study of citrate synthetase, β-hydroxyacyl-coenzyme A dehydrogenase, and lactate dehydrogenase, suggest a change in aerobic metabolism and a shift towards anaerobic glycolytic metabolism. Some studies have shown that physical exercise not only improves respiratory and cardiac function, but also increases the activity of citrate synthetase and β-hydroxyacyl-coenzyme A dehydrogenase, thereby reducing glycolytic enzymes concentrations.

Conclusions

A considerable body of evidence points to an association between COPD and the onset of cardiovascular diseases, such that COPD might, in itself, be a risk factor for cardiovascular events. Systemic inflammation might play
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a concurrent role in the pathogenesis and natural history in both types of disease. In addition to smoking and exposure to inhaled particles, other agents that trigger inflammation in COPD might be important, such as dyslipidemia, obesity, and exacerbations. All these are able to damage the vascular endothelium by means of oxidative stress, thereby contributing to the onset of cardiovascular and cerebrovascular diseases. The development of therapeutic strategies able to act directly on inflammatory response and oxidative stress might be beneficial and reduce both morbidity and mortality due to cardiovascular and respiratory processes.

A host of studies have shown that many of the biological markers such as CRP and plasma fibrinogen that reflect the presence of vascular damage are also present in patients with COPD. The measurement of serum concentrations of these markers may be useful, whether or not in conjunction with assessment of traditional risk factors, to predict the likelihood of cardiovascular complications in these patients and, in turn, to provide a prognosis.

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