

Relapse of chronic obstructive pulmonary disease and myocardial infarction: what is the connection?

Pierfranco Terrosu*

SICGe - Società Italiana di Cardiologia Geriatrica

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Albeit largely underappreciated, chronic obstructive pulmonary disease (COPD) constitutes a major risk factor for cardiovascular diseases in general and for coronary disease in particular. The incidence of myocardial infarction, in fact increases rapidly, after relapse of COPD, with a peak event rate during the first week in the worst forms (those requiring hospitalization). Even though the precise mechanism is not completely defined, it is likely derived from two pathogenetic causes: (i) mismatch between myocardial demand and offer of O₂ (not fully demonstrated and limited to few cases); (ii) acute coronary thrombosis, probably due to a systemic inflammatory reaction, brought upon by multiple interaction between the infective agent and the host immune system.

Introduction

It is now unquestionable that the mortality of chronic obstructive pulmonary disease (COPD) is mainly cardiovascular rather than respiratory. Surprisingly, the link between COPD and coronary heart disease goes far beyond what is expected on the basis of shared risk factors: the prevalence of ischaemic heart disease is, in fact, exceptionally high (estimated between 20% and 60% of patients with COPD depending on the populations studied) and significantly more frequent than the general population (respectively 12.5% vs. 4.7% with $P < 0.0001$ in the Lucas-Ramos study).¹ Data cannot be explained by cigarette smoking alone and/or the coexistence of other cardiovascular risk factors. Multiple scientific evidence also indicates that in the 'stable' phase of COPD, the risk of acute myocardial infarction is increased by about 2-3 times compared to the control population without lung disease, a figure that suggests that COPD should be considered a greater risk factor, in the same way as diabetes or dyslipidaemia. Moreover, the aspect of greatest clinical (and conceptual) interest concerns the impressive frequency with which an instability of heart conditions and myocardial infarction is diagnosed in patients hospitalized for acute exacerbation of COPD

(AE-COPD). Given that exacerbation represents a catastrophic event in the natural history of the disease, capable of imparting an abrupt deterioration of lung function, what is most striking is the close relationship that exists between AE-COPD and acute coronary events. Beyond the complex mechanisms that link the two cardiac and pulmonary pathologies, scientific evidence indicates that the incidence of acute myocardial infarction increases significantly (RR 1.34 $P < 0.001$ in Goto's meta-analysis)² to the 30 days post-AE-COPD compared to the pre-AE-COPD phase. Although relevant, the observation of a peak of risk in the month following an AE-COPD, risks giving generic and somewhat limited information, in the sense that it tends to underestimate the real extent of the problem. This is because the relationship between AE-COPD and myocardial infarction is influenced by two essential variables, which modulate the interrelation between the two phenomena: (i) the time-dependence of the risk; (ii) the degree of severity of the AE-COPD.

Time-dependence of risk

The evaluation usually used, which involves a 30-day pre- and post-AE-COPD observation period is not the most suitable to quantify the risk since the frequency of acute heart attack is highly variable in these first weeks. In fact, the probability of ischaemic myocardial damage increases by about 2-5 times in the first 3 days after AE-COPD³⁻⁵ and

*Corresponding author. Email: pterrosu@hotmail.com

gradually decreases in 1 month, maintaining a modest increase in risk for up to 1 year.⁶ Therefore, the maximum time-risk window can be placed in the first week after AE-COPD, when the probability of acute coronary events reaches its peak compared to the pre-AE-COPD phase (which in itself represents a risk situation).

Degree of severity of acute exacerbation of chronic obstructive pulmonary disease

Even more surprising (at least in quantitative terms) is the relationship between the clinical entity of AE-COPD and the incidence of myocardial infarct. The more severe forms of AE-COPD (in fact those requiring hospitalization) are associated with a much higher frequency of myocardial infarction than the minor forms treated at home: respectively RR 8.00 [confidence interval (CI) 5.81-11.01] in severe forms vs. RR 1.96 (CI 1.5-2.52) ($P < 0.0001$) on days 1-3 after AE-COPD and RR 7.78 (CI 5.82-10.59) vs. RR 1.53 (CI 1.19-1.97) ($P < 0.001$) on days 4-7.⁵ In summary, we can say that AE-COPD is accompanied by an early peak of coronary events, particularly high in the first week and in the most severe (i.e. hospitalized) forms.

Mechanisms of the relationship between chronic obstructive pulmonary disease and atherosclerosis

The mechanisms underlying the COPD-myocardial infarction relationship are a source of discussion and still not clarified. In theory, we can artificially recognize two different problems, albeit with close interconnections, certainly useful for teaching purposes: on the one hand, COPD in the stable phase, which preferentially favours the development and progression of atherosclerosis; on the other, the AE-COPD which has greater potential for acute illness, with instability of the plaque and provocation of an acute heart attack. One of the most accepted hypotheses is that persistent airway inflammation is at the basis of cardiovascular and coronary risk in particular. In fact, COPD is characterized by an intense inflammatory process, rich in neutrophils, macrophages, and pro-inflammatory cytokines, which can extend to the systemic circulation. Beyond theoretical speculations, there is evidence of how COPD is associated with systemic oxidative stress,⁷ activation of circulating inflammatory cells,⁸ and an increase in plasma cytokines, such as PCR, IL-6, and TNF- α .⁹ These are all elements that indicate generalized inflammation that is no longer confined to the lungs, a crucial element in the facilitation-acceleration of the atherosclerotic process. Second, although the relationship between airway obstruction and cardiovascular risk is not well known, the involvement of an alteration of the systemic arterial structure is likely, characterized on the one hand by a loss of elastic fibres, and on the other by a pro-atherosclerotic effect. Given that generalized inflammation is probably the fundamental pathogenetic element of these alterations, COPD vasculopathy is demonstrated by two main observations: (i) endothelial dysfunction; (ii) increase in the stiffness of the great arteries.¹⁰ The alteration of the endothelium occurs from the early stages of COPD and translates from a

clinical-experimental point of view into a reduced flow-mediated endothelial vasodilation directly proportional to the degree of respiratory insufficiency.¹¹ The increase in arterial stiffness¹⁰ is a direct cause of an increase in cardiac work and is a predictive variable of cardiovascular risk. Third, COPD is associated with unexpected frequency with the metabolic syndrome,¹² another condition closely related to atherosclerosis and cardiovascular risk. Since both conditions (both COPD and metabolic syndrome) are characterized by a chronic inflammatory state, a two-way vicious circle is likely to arise in which the two pathologies tend to aggravate each other. However, there are further little-known links that go beyond the inflammatory state, links that involve hormonal and/or functional influences. Experimentally, pulmonary infection causes a strong local oedematous inflammatory reaction in the obese rat, which is surprisingly abolished by adiponectin produced by adipose tissue.¹³ In the clinical settings, hyperglycaemia induces an enhanced bronchial reactivity, with an easier bronchospasm compared to controls.¹⁴ Furthermore, taking into account the negative effect of diabetes on the course of COPD, with a direct proportional relationship between blood sugar levels and the frequency of lung infections and COPD mortality.¹⁵

Mechanisms of the relationship between acute exacerbation of chronic obstructive pulmonary disease and myocardial infarction

In this pro-atherogenic context, is inserted the sudden clinical instability caused by AE-COPD. The event is basically linked to an infectious process of the airways, favoured or not favoured by cigarette smoke. The high risk of acute myocardial infarction that AE-COPD involves, especially in the days immediately following, is favoured by the various pro-atherosclerotic changes that COPD causes. In general, two distinct infarct mechanisms are possible: (i) ischaemic discrepancy myocardial damage; (ii) 'classic' myocardial infarction from acute coronary thrombosis.

Discrepancy myocardial infarction is probably the least frequent event, confined to the earliest phase of COPD AE (while on the contrary the risk of infarction continues, although decreasing, for the first month and up to 1 year).⁶ The prerequisite for a discrepancy damage is a haemodynamic alteration, in relation to the loss of elasticity and hyper-distension of the lungs typical of COPD and emphysema ('static hyperinflation'). During AE-COPD, the over-distension of the lung increases sharply, because bronchial-alveolar inflammation and tachypnoea hinder exhalation. It follows that the amount of air inhaled in a single inspiratory act is not completely eliminated during the next exhalation (*Figure 1*).

This 'dynamic hyperinflation' sharply increases lung volumes to a new equilibrium, characterized from the circulatory point of view by a compression of the capillaries of the small circle.¹⁶ As a result, there is an obstructed flow in the pulmonary veins and a reduced filling of the left ventricle, aggravated by the concomitant overload of the right ventricle, which in turn causes straightening of the interventricular septum and 'bulging' in the left ventricle.

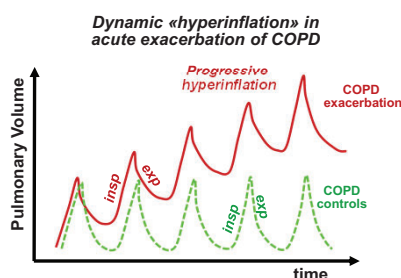


Figure 1 Dynamic ‘hyperinflation’ during an acute exacerbation of chronic obstructive pulmonary disease. Lung volume increases progressively for each respiratory act until a new balance is reached. The end result is an acute distension of the lungs.

Ultimately, we will have a low systemic flow downstream and lung congestion upstream. In practice, the conditions for an acute discrepancy between consumption and supply of myocardial O_2 occur in AE-COPD. On the one hand, cardiac work increases, not only for tachycardia linked to fever and reflex sympathetic stimulation but also for a sharp increase in arterial stiffness¹⁰ and therefore in the after-load of the left ventricle. On the other hand, the fall of the systemic range secondary to the low filling of the left ventricle compromises coronary perfusion and reduces the availability of O_2 (with the aggravation of hypoxaemia caused by ventilatory changes). This explains the frequent elevations of troponin during AE-COPD, the greater the more important the severity of AE-COPD, and haemodynamic changes.

‘Classic’ myocardial infarction from acute coronary thrombosis

It is theoretically possible that a plaque instability is caused by a direct invasion of the infectious agent (there are reports of a virus or bacterium within the atheromatous lesion), however this possibility does not have a convincing demonstration and could be important only in a minority of cases. In reality, the relationship between AE-COPD and coronary thrombosis is very complex and is identified in an indirect relationship between airway infections and coronary atherosclerosis, mostly based on a series of inflammatory-immune reactions. The first element is represented by the interrelation between infectious agent and innate immunity. The lipo-polysaccharides of the bacterial wall stimulate the activation of macrophages through a link between surface chemical groups and Toll receptors. The same chemical groups are exposed by the cells in case of apoptosis and by the LDL when they are oxidized.¹⁷ It follows that the reaction of the macrophages is stereotyped and responds indifferently to endogenous (cellular damage) or exogenous (infectious agent) stimuli. The practical consequence is that there is a synergy between bacteria, oxidized LDL, and apoptotic debris through the same Toll receptors as the macrophages,¹⁷ the consequence of which is the inflammatory reaction and phagocytosis. Since the inflammatory cells of the lung spread in the systemic circulation, this mechanism can enhance coronary inflammation and promote plaque rupture and myocardial infarction. Second element appears to be the involvement of

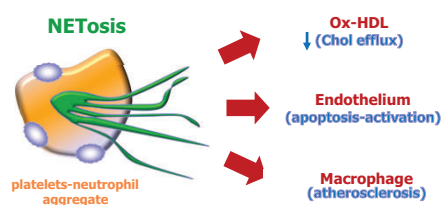


Figure 2 The circulating neutrophil-platelet complexes cause an immune reaction with extracellular exposure of chromatin and histone of the leucocyte called NETosis (neutrophil extracellular traps). NETosis induces a diverse series of phlogistic responses that include HDL oxidation, endothelium activation, and macrophage stimulation.

platelets. In recent years, it has been observed, especially in the case of viral infection (and especially in the case of flu), which the body’s first defence is ensured by a process of endocytosis of the virus by platelets.¹⁸ This phenomenon guarantees a net reduction of the viral load, since the platelets do not have a nucleus and the virus ‘trapped’ in the cytoplasm is not able to replicate. It is good to remember that this reaction does not involve a platelet aggregation (which is instead induced by the stimulus of the P2Y12 receptor), while the link between virus and Toll platelet receptor induces an innate immune response. The platelets are unable to completely defeat and digest the virus and, through an increase in the complement C3, stimulate the arrival of neutrophils and the formation of platelet-neutrophil complexes.¹⁸ Following these stimuli, the neutrophil undergoes a particular immune reaction called NETosis (‘neutrophil extracellular traps’), characterized by the extracellular exposure of the chromatin and histone filaments with a bactericidal and pro-inflammatory effect (i.e. with a reference to monocytes-macrophages)¹⁹ (Figure 2). The final way of this complex sequence of events is the activation of circulating monocytes, which can enhance the inflammatory process of coronary plaque and clinical instability. In this sense, it is at least suggestive that in the ‘culprit’ coronary lesions a drastic increase in the number of NETosis of the polymorphonucleate is observed, while this does not occur in the controls or in the non-culprit lesions of the same patient.²⁰ Consider that NETosis is a powerful pro-thrombotic stimulus, which can be crucial in acute coronary occlusion. The third element of connection between lung infection and myocardial infarction is still an immune response, but of a particular type. It is commonly believed that innate immunity, by its generic and non-specific nature, has no ‘memory’ (unlike acquired immunity which recognizes the antigen after some time and contrasts it with specific antibodies). In fact, in recent years, evidence has accumulated showing that macrophages maintain an exalted reactivity for many months after the attack of an infectious agent. It is a defence mechanism that represented an important advantage in our ancestors, as the response of macrophages to repeated infections became more and more prompt and effective. This type of process called ‘trained immunity’²¹ is due to an epigenetic modification of the monocyte cells, which enhances their reactivity and the production of cytokines for a long time. The biological price to be paid, in our

current reality, is that the exalted macrophage reaction in the context of coronary atherosclerosis can increase the risk of plaque rupture and acute myocardial infarction. It is one of the reasons accounting for the risk of myocardial infarction after an AE-COPD that is maximum in the first few days but remains high for up to one year (with progressively lower intensity). If these observations are correct, it is explained why, for example, flu vaccines can prevent myocardial infarction, by blocking the virus before the activation of innate immunity. On the contrary, an antibiotic treatment is not effective because it acts too late, after the bacterium has already stimulated the inflammatory-immune reaction.

Conclusions

In conclusion, AE-COPD enhances the risk of acute myocardial infarction, especially in the first week and in the most severe forms, i.e. those requiring hospitalization. The mechanism can be, albeit more rarely, ischaemic damage due to the discrepancy between supply and demand for myocardial O₂. More frequently, lung infection causes an intense systemic inflammatory reaction, both with a direct action of the pathogen on the monocytes and with an indirect mechanism that starts from the virus-platelet interaction and leads to an inflammatory-immune leucocyte activation. The common final event of these processes would be the exaltation of plaque inflammation and acute rupture/thrombosis of coronary atheromatous lesions.

Conflict of interest: none declared.

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