Pollution and coronary risk: how much does it matter?

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Air pollutants are a complex mixture of gaseous substances and particulate matter (PM). Each component potentially has specific harmful effects on human health, but several experimental and clinical studies have shown a strong impact of fine particles on major adverse cardiovascular events. Most of the available evidence concerns the effects of exposure to PM with a diameter of <2.5 µm (PM2.5) and the risk of developing coronary heart disease through inflammation and oxidative stress. While prolonged exposure to PM2.5 has been shown to be associated with the development of atherosclerosis and cardio-metabolic risk factors, short-term exposure has instead proved to be a trigger for acute coronary events, and especially in subjects with pre-existing coronary artery disease. As such, environmental PM2.5 is a major risk element for global public health. This underlines on the one hand not only the need to adopt and encourage preventive measures especially for individuals with a higher risk profile but also to practice environmental policies that are effective in promoting the reduction of exposure to pollutants.

Introduction

Cardiovascular (CV) diseases are the main cause of morbidity and mortality in industrialized countries. The pathogenesis of atherothrombotic events in general is complex and depends on the well-known modifiable and non-modifiable risk factors such as genetic predisposition, lifestyle and environmental factors; among the latter, atmospheric pollution is attracting increasing attention of researchers. Although there is significant evidence on the harmful multisystem effects of air pollution, a recent joint paper from the European Respiratory Society and the American Thoracic Society has identified the CV system as its main target.

Air pollutants are a complex mixture of gas (nitric oxide, ozone, sulphur dioxide and ammonia), volatile droplets (quinones and polycyclic aromatic hydrocarbons) and particulate matter (PM). Over the past 30 years, several studies have unequivocally correlated air pollutants, and especially PM, to CV disease. PM is a heterogeneous mixture commonly classified on the basis of particle size in coarse PM (PM10: aerodynamic diameter <10 µm), fine (PM2.5: aerodynamic diameter <2.5 µm) and ultra-fine (PM0.1: aerodynamic diameter <0.1 µm). Fine PM is the main component of air pollution that causes CV disease. To date, both short-term exposure-hours or days—and long-term exposure-years or decades—have been shown to be directly or indirectly associated with the risk of coronary heart disease. In fact, while several prospective cohort studies have shown how prolonged exposure to PM2.5 is associated with the development of atherosclerosis and cardio-metabolic risk factors such as arterial hypertension and diabetes mellitus, the short-term exposure to PM2.5 has also been shown to be a trigger for acute coronary events, especially in subjects with pre-existing coronary artery disease.

Air pollution and atherothrombosis

Many epidemiological studies have demonstrated a direct association between prolonged exposure to PM2.5...
and the atherosclerotic burden, estimated through surrogate measures such as carotid intima-media thickness, coronary and aortic calcifications, and ankle-brachial index. In addition, a reduction in the concentration of PM2.5 has been associated with lesser progression of the intima-media carotid thickness, thus reinforcing the biological plausibility and the causal link of the association. Experimental studies on mouse models of atherosclerosis have also shown that chronic exposure to particulate causes progression of vascular lesions; the exposure has also been shown to be associated with characteristics of plaque vulnerability, such as the expression of tissue factor.

In a meta-analysis published in 2014, Cesaroni et al. showed that prolonged exposure to PM was associated with an increased incidence of coronary events in the 11 cohorts included in the European Study of Cohorts for Air Pollution Effects. Specifically, 100,166 subjects with no history of ischaemic heart disease were enrolled from 1997 to 2007 and followed up for an average of 11.5 years. Of these, 5,157 subjects experienced coronary events during the follow-up. The study demonstrated a 13% increase in non-fatal acute coronary events for every 5 µg/m³ increase in PM2.5 exposure, and a 12% increase in coronary events for every 10 µg/m³ increase in PM10. With exposure to other pollutants, on the other hand, there was an association that was also direct, but weak and not statistically significant. Also a more recent meta-analysis published in 2021 showed how prolonged exposure to PM2.5 and PM10 is associated with the risk of myocardial infarction. The researchers included 27 cohort studies conducted from 2004 to 2019 including a total of 6,764,987 patients. The size of the cohorts varied, ranging from 1,120 up to 4,404,046 subjects. The results of the meta-analysis confirmed that increased PM2.5 and PM10 levels were associated with a higher risk of experiencing coronary events. In particular, the relative risk (RR) for each 10 µg/m³ increase in PM2.5 and PM10 was 1.18 (95% confidence interval (CI): 1.11-1.26) and 1.03 (95% CI: 1.00-1.05). Even subgroup analyses, including the analysis of studies conducted before and after 2010, did not show statistically significant differences. Recent data also support the hypothesis that patients with pre-existing coronary heart disease are at greater risk of experiencing acute coronary events than healthy subjects after short-term exposure to higher concentrations of air pollutants. In this regard, a study conducted in urban areas of Utah’s Wasatch Front in the USA evaluated the effects of short-term exposure to fine particles on the risk of developing acute coronary syndrome. The researchers included acute coronary events treated in Intermountain Healthcare Hospitals in Utah between 1993 and 2014. Through a case-control design stratified by time intervals, exposure to fine PM was assessed at the time of each event. The results of the study showed that in subjects with pre-existing coronary artery disease, exposure to high concentrations of fine PM can act as a trigger for acute coronary events, with an increased risk for ST elevation myocardial infarction (STEMI). Indeed, in patients with coronary artery disease already diagnosed by angiography, the odds ratios for every 10 µg/m³ of daily increase in fine PM over 25 µg/m³ were 1.06 (95% CI: 1.02-1.11) for all acute coronary syndromes; 1.15 (95% CI: 1.03-1.29) for STEMI; 1.02 (95% CI: 0.97-1.08) for non-ST elevation acute myocardial infarction, and 1.09 (95% CI: 1.02-1.17) for unstable angina. However, this increased risk was not observed in subjects without pre-existing coronary artery disease.

### Pathophysiological mechanisms

Pathophysiological mechanisms through which atmospheric pollutants, and especially PM2.5, affect the occurrence of CV events are multiple, complex and interdependent. Pollutants are hypothesized to primarily cause increased oxidative stress and lung inflammation. Pro-inflammatory cytokines and reactive oxygen species generated in the lungs can influence the origin, evolution and characteristics of coronary atherosclerotic plaques through a systemic inflammatory response, endothelial dysfunction and prothrombotic activation. Phenomena of autonomic dysregulation were also highlighted in these researches. A systemic inflammatory response and autonomic dysregulation are also the substrate for the development of cardio-metabolic risk factors. The set of these pathophysiological mechanisms conditions the evolution of atherothrombotic phenomena through the progression, stabilization and rupture of plaque, thus representing the substrate for the development of acute coronary syndromes (Figure 1).

### Inflammation and oxidative stress

Exposure to air pollution generates oxidative stress and inflammation in the lungs, and such phenomena are hypothesized to be the initial pathogenetic moment for the activation of signal transduction pathways involved in the pathophysiology of atherothrombotic disease. This mechanism can be amplified when pollutants are themselves oxidants as in the case of ozone or PM2.5. The large surface area of PM2.5 facilitates the adsorption of organic material, heavy metals and other toxic substances and provides space for the formation of oxygen free radicals. The inhalation of PM2.5 activates local cells such as macrophages, dendritic cells and cells of the alveolar endothelium within the pulmonary alveoli. The mediators of oxidative stress and those produced by activated local cells induce an initially localized inflammatory response. This involves the production of biological mediators that activate signalling pathways involved in the systemic inflammatory response. Furthermore, PM2.5 penetrates directly the lower respiratory tract and, by translocation through biological membranes, escapes the host’s defenses and reaches the blood stream and target organs by directly exerting pro-oxidant and pro-inflammatory effects at storage sites. Oxidative stress is therefore pro-inflammatory, and inflammation in turn generates oxidative stress. Confirming the key role of oxidative stress, some recent studies have shown how the enhancement of lung antioxidant defenses through an overexpression of
extracellular superoxide dismutase could reduce the adverse vascular effects resulting from exposure to atmospheric pollution.9

Systemic inflammatory response

Several studies have shown that the inhalation of PM2.5 is associated with the production of pro-inflammatory cytokines such as interleukin-6 and tumour necrosis factor. PM2.5 also induces the synthesis of acute phase proteins, such as C-reactive protein, and vasoactive peptides, such as endothelin 1. Furthermore, data derived from animal models have shown a rapid response of the bone marrow after exposure to air pollution. Recent experimental studies have clarified the nature of this response, demonstrating that prolonged exposure to PM determines the efflux of monocytes from the bone marrow and their subsequent migration to organs and tissues such as the vessels and the adipose tissue. Toll-like receptor-4 (TLR4) and nicotinamide adenine dinucleotide phosphate-oxidase appear to be involved in this process, mediating the effects of PM2.5. Specifically, experimental models have shown how the TLR4 deficiency reduces this increased migration of monocytes from the bone after exposure to PM2.5. The Type 2 chemokine receptor also appears to be involved in the mobilization of these cells.8

Thrombosis

The association between acute exposure to PM and short-term increase in CV mortality suggests the activation of signalling pathways involved in the coagulation cascade and in thrombotic phenomena. Exposure to car traffic has been proven to be, in fact, a trigger of acute myocardial infarction within a few hours. Experimental studies on animal models of arterial thrombosis have shown platelet activation phenomena within 30 min of the intra-tracheal instillation of diesel exhaust gas particles.10 Platelet activation and, in parallel and subsequently, of the blood coagulation cascade, was also highlighted in studies conducted on healthy volunteers following inhalation of diesel exhaust fumes.11 Similarly, in patients with higher CV risk and greater atherosclerotic burden, rapid platelet

Figure 1  Pathophysiology of atherothrombotic phenomena caused by atmospheric pollution. Inhaled pollutants primarily induce oxidative stress and inflammation in the lungs. Pro-inflammatory cytokines and reactive oxygen species generated in the lungs through the systemic inflammatory response, endothelial dysfunction and activation of the blood coagulation cascade influence the origin, evolution and characteristics of coronary atherosclerotic plaques. Through the stimulation of type-C nerve fibres at the nasal, bronchial and pulmonary levels, pollutants also induce phenomena of autonomic dysregulation. The systemic inflammatory response, the autonomic dysregulation and endothelial dysfunction are also the substrate for the development of cardio-metabolic risk factors. These pathophysiological mechanisms condition the evolution of atherothrombotic phenomena favouring progression, instabilization and complications of plaques, thus representing the substrate for developing acute coronary syndromes.
activation was observed after acute inhalation of air pollutants, such as evidenced in diabetic subjects acutely exposed to PM10. Exposure to high concentrations of PM2.5 has been shown to be associated with high plasma concentrations of hypercoagulability markers, such as fibrinogen and D-dimer, and with increased thrombin formation. From a pathophysiological point of view, it was highlighted that the phenomena of platelet activation resulting from the inhalation of the PM are determined both by the direct contact of the platelets with the absorbed particulate and by the pro-inflammatory mediators released into the systemic circulation by the inflamed pulmonary endothelium.4

### Autonomic dysregulation

A dysregulation of the autonomic nervous system with an imbalance of the sympathetic-vagal system in favour of the former has been observed in humans after exposure to coarse and fine environmental particles. To date, it is clear that type-C nasal, bronchial and pulmonary nerve fibres are involved in this type of response, activating, after the inhalation of the PM, different types of receptors such as the transient receptor potential ankyrin 1, the transient receptor potential vanilloid 1 and purinergic channels P2X.8

Numerous observational studies have evaluated the association between PM exposure and heart rate variability (HRV), the latter being a marker of autonomic dysfunction. Overall, the evidence obtained so far shows how this exposure causes an increase in heart rate and a reduction in HRV.12

### Pollution and cardio-metabolic risk

There is a two-way relationship between air pollution and CV risk factors. In fact, if, on the one hand, people with traditional risk factors are at a higher risk of developing CV events after exposure to PM, on the other hand atmospheric pollutants can promote the development of these risk factors. In fact, numerous evidences show how air pollution is implicated in the development of cardio-metabolic risk factors such as arterial hypertension and insulin resistance. The association between air pollution and arterial hypertension has been extensively evaluated and has been the subject of at least four recent meta-analyses. An increase in atmospheric fine PM of 10 µg/m3 is associated with increased systolic-diastolic blood pressure by 1-3 mmHg already after a few days of exposure.6 Regarding insulin resistance, a meta-analysis of cohort studies involving a total of 2 371 907 participants and 21 095 incident cases of Type 2 diabetes mellitus showed that the RR of diabetes increases by 39% for every 10 µg/m3 of PM2.5.13 Another recent meta-analysis of 13 studies published in 2015 highlighted how PM2.5 and NO2 increase the risk of diabetes [hazard ratio (HR): 1.10; 95% CI: 1.02-1.18 and HR: 1.08; 95% CI: 1.00-1.17 per 10 µg/m3 increase of PM2.5 and NO2, respectively].14 The pathophysiological mechanisms underlying this association are an autonomic dysregulation, the increased release of mediators of oxidative stress and inflammation, and altered endothelium-dependent vasodilation.

### Air pollution as a trigger for inflammation and cardiovascular events

In 2021 Abohashem et al. have shown for the first time in humans how air pollution increases leukopoiesis and inflammation at the level of atherosclerotic plaques, and how this is directly and independently associated with major adverse CV events. In this study, the researchers therefore hypothesized the existence of a ‘leukopoietic-arterial axis’ as an underlying pathophysiological mechanism. Specifically, 503 subjects without CV disease underwent a positron emission tomography with fluoro-deoxyglucose coupled with computed tomography to quantify leukopoietic activity and arterial inflammation after exposure to air pollution, defined on the basis of annual exposure to particulates with a diameter of <2.5 µm in the area of residence. The results showed a significant association between higher levels of fine PM and the increase in leukopoiesis and atherosclerosis even after adjustment for traditional CV risk factors and other potential confounding factors. In the study, 40 subjects also experienced major CV events during a mean follow-up of 4.1 years. Again, the highest PM2.5 levels were predictive of major CV events: HR 1.40, 95% CI 1.14-1.74, \( P = 0.002 \) for each standard deviation of PM2.5 increase. Finally, through a mediation analysis, the researchers demonstrated that the increased leukopoietic activity and vascular inflammation would explain the 30% increase in major CV events after exposure to PM2.5.15

### Conclusions

Several observations in recent years have supported the concept of a vulnerable plaque, but also, at the same time, of a vulnerable patient. In this context, stochastic variables often only partially defined, concur in determining individual susceptibility to CV events. Air pollution, and specifically PM, operate in this context, and individual vulnerability is in any case essential in mediating adverse CV events. Cumulative exposure for long periods to PM can promote the development of an underlying state of vulnerability that would predispose to a subsequent CV risk increase, consistent with what happens with any other risk factor. However, the highest percentage of CV events is observed in the cohorts with short-term exposure to higher levels of fine particles. These observations, therefore, highlight a role for PM as direct triggers for acute coronary events.6

In consideration of all these results, air pollution should be now seen as one of the main modifiable risk factors in the prevention of CV diseases. In this sense, if, on the one hand, the use of drugs that contrast the pathophysiological substrate of atherosclerosis, such as statins and perhaps specific anti-inflammatory drugs, is now hypothesized; it should be emphasized even more strongly, on the other hand, that a primary intervention on risk factors is more drastically efficient. Among these,
the healthfulness of living environments should be a primary public health objective, to be strongly and tenaciously pursued.

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