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EDITORIAL

Airborne pollution and cardiovascular disease: burden and causes of an epidemic

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This editorial refers to 'Long-term exposure to air pollution is associated with survival following acute coronary syndrome', by C. Tonne and P. Wilkinson, doi:10.1093/eurheartj/ehs480

The first well-known episode of air pollution causing a marked mortality peak developed in London during the great smog between 5 and 9 December 1952. In those days, air pollution—owing to a combination of high atmospheric pressure, absence of wind and rain, and intensive domestic heating with low-quality coal as fuel—caused as many as 12 000 deaths. To give an idea of the dramatic dimension of that episode, the number of London victims of German bombs was 30 000 during the Second World War.[1] More recently, in 2008, the World Health Organization (WHO) estimated that urban outdoor air pollution caused 1.34 million premature deaths worldwide, an annual number that can be contrasted with the 4.8 million premature deaths attributable to smoking.[2] According to WHO, the impressive number of deaths attributed to bad air had increased by 16% from 2004 to 2008, with little reason to imagine that the situation has improved in subsequent recent years.[2]

Air pollution affects the whole planet, particularly densely populated metropolitan areas of Eastern and Southern China, Northern India, and the emerging countries of South-East Asia. Europe is not spared, particularly Benelux and the South and East of the continent. The main pollutants are distinguished as primary—such as NO_x and SO_2 produced directly from car traffic, industrial emissions, and domestic heating—and secondary (typically ozone), that stem from primary pollutants as a consequence of chemical reactions taking place in the atmosphere. Particulate matter (PM) in the inhaled air, primary or secondary in origin, is considered more and more as the main culprit for the pollution-related increase in global mortality, particularly for the smaller particles of < 2.5 μm in aerodynamic diameter ($PM_{2.5}$) and the ultrafine particles ($PM_{0.1}$) that penetrate not only the alveolar gas-exchange space but also the systemic blood circulation.[3] Respiratory diseases, triggered by the acute and chronic inhalation of gaseous and corpuscular airborne substances, were originally considered to be the main cause for the pollution-associated increase in mortality and morbidity. More recently, cardiovascular diseases have emerged as a greater threat to human health caused by air pollution.[4] A broad summary of the evidence stemming from an array of time-series, case-crossover, and cohort studies tells us that an ~ 10% increase in cardiovascular mortality is determined by a relatively modest (and thus frequently occurring) increase of 10 μg/mm^3 in terms of short- and long-term exposure to PM.[4] Tonne and Wilkinson[5] now add to this compelling evidence further epidemiological data stemming from a huge UK database, that included > 150 00 patients who had previously developed acute coronary syndromes (ACS), with a 4-year follow-up and almost 40 000 incident deaths. Their main findings were higher mortality rates for post-ACS patients exposed to higher levels of pollution, with a 20% increased risk of deaths for any 10 μg/mm^3 $PM_{2.5}$ increase.[5]

With this background, what are the mechanistic links between inhaled PM and the development of cardiovascular disease? A multitude of experimental and clinical studies indicate that thrombosis, inflammation, atherosclerosis, and automatic dysregulation interplay in this multifactorial process (*Figure 1*). Rodents exposed to PM doses comparable with those to which people are exposed in metropolitan areas develop platelet function abnormalities and haemostatic changes, ultimately resulting in intravascular thrombus formation.[6] Activation in the lung of inflammatory cells (endothelial cells, macrophages, and circulating neutrophils) leads to a marked local increase of cytokines such as interleukin-6 that may act as a stimulus for subsequent systemic inflammation, leading in turn to hypercoagulability and enhanced thrombogenesis.[7] In humans, the most significant and comprehensive mechanistic insights stem from several studies carried out by Mills *et al.*,[8–10] who demonstrated in healthy people and patients with coronary artery disease that the finest PM contained in diesel exhaust, inhaled under controlled experimental conditions by these volunteers, inhibited vasodilatation in response to agonists, and also induced prothrombotic changes in blood such as hypofibrinolysis. Evidence for a hypercoagulable state also comes from epidemiological studies carried out in Lombardy, the densely populated Italian region in the Po river plain characterized by a particularly high degree of airborne pollution. The degree of exposure to

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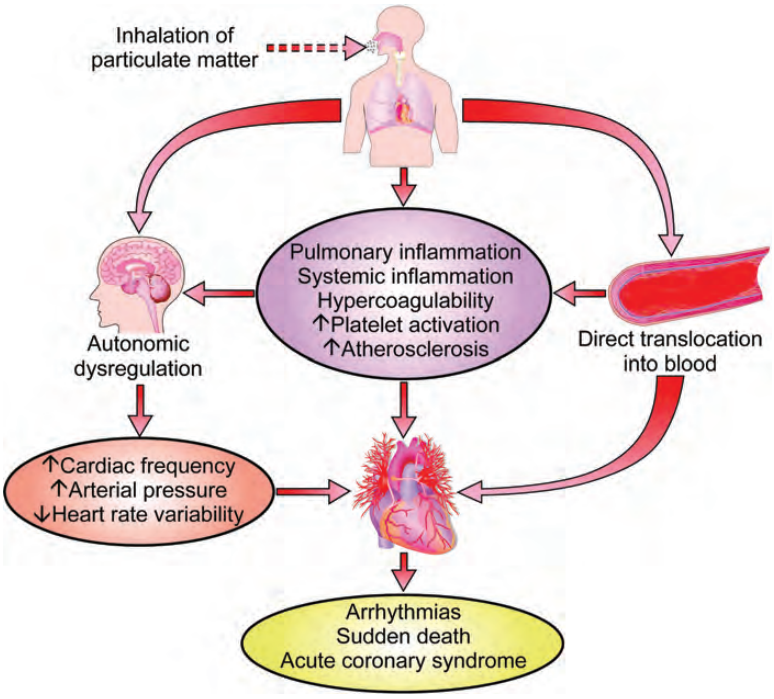

Figure 1 Mechanisms of action of the inhalation of particulate matter on cardiac functions and cardiovascular disease.

Table 1 Practical recommendations in order to reduce exposure to airborne pollutants

Use cars and motorbikes as little as possible: always consider public transport alternatives
Avoid walking and cycling in streets with high traffic intensity, particularly during the rush hour. On many websites there are applications that help in the choice of the most favourable routes
Run and exercise in parks and gardens, but avoid major traffic roads. Choose rainy rather than sunny days, because air pollution is less
Limit taking infants outdoors during highly polluted times (i.e. rush hour or in proximity to industrial sources or narrow streets with a high level of automobile traffic). Because pollutants are higher closer to the ground, try to keep infants in baby carriers (slings or pouches) rather than in prams/pushchairs
A diet rich in fruits and vegetables containing antioxidants may help to counteract the effects of air pollution

PM was positively associated with a shortening of a global coagulation test, the prothrombin time, and higher plasma concentrations of the prothrombotic amino acid homocysteine, particularly in smokers.[11,12] Pertaining to atherogenesis, exposure of apo-E-deficient animals to PM enhanced the progression of atherosclerosis, that also depended upon a proinflammatory effect of PM.[13] In particular, exposed animals display an overproduction of reactive oxygen species, which are implicated in the initiation and progression of atherosclerosis via several mechanisms including oxidation of LDLs and monocyte infiltration within the vessel wall.[14]

These experimental data were subsequently substantiated in humans. For instance, a biomarker of atherosclerosis such as carotid intima medial thickness becomes progressively more abnormal in proportion to the annual degree of exposure to ambient $PM_{2.5}$ concentrations.[15] Another biomarker of atherosclerosis, coronary artery calcium content, increased in proportion to the degree of proximity of residential exposure to car traffic.[16] A further mechanism of the adverse effects of PM exposure on the cardiovascular system is related to autonomic dysregulation. A number of experimental and clinical studies indicate that PM exposure decreases heart rate variability, a well-established risk factor for arrhythmias and sudden cardiac death.[17] The increased sympathetic drive may be due to the activation of pulmonary neurological reflex arcs and to direct effects of pollutants on cardiac ion channels, that are also thought to be the mechanisms and mediators of the hypertensive effects of air pollution.[18]

All in all, there is unequivocal evidence that mechanisms such as hypercoagulability, inflammation, atherosclerosis, and autonomic dysregulation interplay to increase cardiovascular mortality and morbidity in people exposed acutely and chronically to air pollution. The increased mortality related to long- and short-term exposure to pollutants occurs principally, but not exclusively, in susceptible individuals such as the elderly, the obese, and those with diabetes and pre-existing cardiovascular disease, as shown by Tonne and Wilkinson.[5]

What can be done in practice to control this important cause of cardiovascular morbidity and mortality, that in several countries is becoming more and more prominent? The most important message is that reduction in the amount of pollutants in

metropolitan areas does indeed decrease cardiovascular mortality within a time interval as short as a few years,[19] providing at the same time strong evidence for causality and stimulus towards adequate action by public health authorities. The impressively huge number of deaths worldwide due to air pollution would be substantially reduced—by ~ 1 million annually from the current estimate of 1.34 million—if the WHO recommendations pertaining to the limits of $PM_{2.5}$ concentrations were implemented.[2] The responsibility for controlling air pollution rests on national governments of the planet, that are responsible for the implementation of an array of public health measures that would help to reduce pollution. Because this formidable goal is beyond the reach of individual interventions, what can be done by clinicians who take care of patients at increased risk of cardiovascular disease owing to their exposure to air pollution? First, and most importantly, we must make patients aware of the existence of this risk, and encourage them to be cognizant of the media alerts on air quality in their living areas. Moreover, *Table 1* lists a number of simple and practically feasible recommendations that may be shared with patients at risk. Finally, the European Society of Cardiology should consider developing and producing scientific statements on air pollution and cardiovascular disease, similar to those prepared and published in 2004 and 2010 by the American Heart Association.[4]

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