Air pollution: to the heart of the matter

Tim S. Nawrot1*, Abderrahim Nemmar1,2, and Benoît Nemery1

1 School of Public Health, Occupational and Environmental Medicine, Unit of Lung Toxicology, KULeuven, Herestraat 49, O&N 706, B-3000 Leuven, Belgium and 2 Department of Physiology, College of Medicine, Sultan Qaboos University, Al-khod, Sultanate of Oman

Online publish-ahead-of-print 4 September 2006

This editorial refers to 'Impact of urban atmospheric pollution on coronary disease'† by A. Maitre et al., on page 2275

Air pollution consists of both gaseous and particulate-matter pollutants. The former include nitrogen dioxide (NO2), ozone (O3), and sulphur dioxide (SO2). The latter consist of particulate matter of varying aerodynamic diameter, as defined by cutoff points—for example, particles with diameters of <10 μm (PM10) or <2.5 μm (PM2.5). Because of their small size, these particles can be inhaled deeply into the lungs and deposited in the alveoli. Why should cardiologists care about ambient air? It has long been known that air pollution can adversely affect human health. Extreme levels of pollution may cause markedly increased mortality rates; in this regard one often refers to the Meuse valley fog of 19301 or the London smog of 1952. These episodes initiated successful efforts and legislation to reduce air pollution. Nevertheless, even at current ambient pollution levels, the relation between pollution and excess morbidity and mortality still exists. However, the nature of the pollutants and the type of health effects have shifted, with a special emphasis now being placed on the heart rather than the lungs. Maitre et al.2 gathered the available epidemiological evidence on the association between coronary disease and air pollution at current ambient concentrations. From both biological and public health perspectives, one should distinguish between acute and long-term effects of air pollution.

Acute exposure

Dozens of studies have investigated the acute effects of air pollution. Classically, time series studies form the epidemiological design to study the immediate effects of air pollution on acute mortality and morbidity by relating day-to-day variations in atmospheric pollutants with daily variations in deaths or disease. A relatively novel approach to study acute health effects was provided by the case-crossover design. It was developed in the early 1990s by Maclure3 to study effects of short-term exposures on the risk of acute events, such as myocardial infarction. In the case-crossover design, the hazard period is defined as the average time period that is relevant for the acute effect of the event, and this period is compared with appropriate control times.

From the overview of Maitre et al., it appears that the association between myocardial infarction and air pollution is stronger in the case-crossover studies than in time-series analyses, which might be due to a better control of confounding and, hence, fewer random errors in the case-crossover design. For instance, weather-related differences over the seasons may modify or even confound the association between air pollution and mortality. Indeed, both high and low temperatures increase mortality, and temperature is closely associated with pollution. Because of these complex relations, simple statistical adjustments may be inadequate and some effects of pollutants may in fact be associated primarily with outdoor temperature.

In this context, we recently analysed Belgian mortality data, stratified across seasons and across quintiles of outdoor temperature.4 The effect sizes, expressed as the percentage increase in mortality on days in the highest season-specific PM10 quartile vs. the lowest season-specific PM10 quartile, were 7.8% in summer, 6.3% in spring, 2.2% in autumn, and 1.4% in winter (interaction significant), thus showing that the short-term effect of PM10 on mortality strongly depends on season or outdoor temperature, even in a temperate climate. A similar pattern was observed for cardiovascular mortality. Last year, Schwartz5 addressed the problem of collinearity between outdoor temperature and ozone concentrations by using a case-crossover approach, taking a control day with the same temperature as the event day. During the warm season, mortality was 37% higher for a 10 p.p.b. increase in maximum hourly ozone concentration, with matching on outdoor temperature.

These findings remove the uncertainty that stemmed from possible inadequate control for outdoor temperature on the mortality air pollution association.

Chronic exposure

A landmark report was that of the Harvard Six Cities study.6 In a cohort of 8111 adults with 14–16 years of follow-up, the adjusted overall mortality rate for the most polluted city vs. the least polluted city was 1.26. Cardiovascular deaths accounted for the largest single category of the increased mortality. Among air pollutants, elevation of PM2.5 was...
most strongly associated with mortality. Recently, Pope et al. linked mortality statistics over a 16-year period to chronic exposure to multiple air pollutants in ~500,000 adults who resided in all 50 states of USA. Mean annual PM$_{2.5}$ concentration linearly enhanced cardiovascular mortality, with a significant increase in the risk of death from ischaemic heart disease of 1.18 for a 10 $\mu$g increase in PM$_{2.5}$. The risks for arrhythmia, heart failure, or cardiac arrest mortality were also increased (RR 1.13). Künzli et al. studied the association between long-term exposure to fine particulates and carotid intima-media thickness in subjects living in different areas of Los Angeles. For a contrast of 10 $\mu$g/m$^3$ in PM$_{2.5}$, carotid intima-media thickness was ~4–5% thicker.

**What are the mechanisms linking coronary events with air pollution?**

Before concluding that the reported epidemiological associations are causal, plausible pathophysiological mechanisms are required. The mechanisms for these acute and chronic cardiovascular effects of inhaled pollutants have not yet been entirely elucidated, but the lungs are likely to play an important role. The inflammation that occurs in the lungs in response to damage caused by reactive gases or by the deposition of particles may have systemic consequences. In other words, the lungs are not merely a portal of entry for pollutants; they probably also mediate cardiovascular responses to a substantial extent.

In their review, Maître et al. explained the epidemiological findings by two main mechanistic pathways: (1) inhalation of pollutants might provoke a local inflammatory response with the consequent release into the circulation of pro-thrombotic and inflammatory cytokines; a systemic response of this nature would put individuals with coronary atheroma at increased risk of cardiac events; (2) exposure to pollutants may also have an adverse effect on cardiac autonomic control, leading to an increased risk of arrhythmia in susceptible patients. With regard to the first line of evidence, Nemmar et al. investigated how particles may affect thrombus formation. Diesel exhaust particles significantly and dose dependently enhanced arterial or venous thrombus formation during the first hour after intratracheal instillation in hamsters. The data suggested that diesel exhaust particles are prothrombotic through particle-induced platelet activation. Pre-treatment with a histamine H1-receptor antagonist (diphenhydramine) abolished the diesel exhaust particle-induced neutrophil thrombotic effects. In apoE- mouse model, long-term exposure to low concentrations of PM$_{2.5}$ altered vasomotor tone, induced vascular inflammation, and potentiated atherosclerosis, thus supporting also the epidemiological observations of adverse cardiovascular effects of long-term exposure to urban air pollution. In other words, long-term effects of air pollution might slightly change the survival curve (ageing) of a population.

In this regard, several studies support the idea that telomere length indicates biological age (ageing) and that individuals with shorter telomeres might be more susceptible to age-related disease than can be expected by their chronological age. Considering telomeres in white blood cells as a marker of accumulated oxidative stress and of the ageing process, the long-term consequences of air pollution could be studied at a more fundamental biological level in an epidemiological context. So far, neither experimental nor epidemiological studies have linked telomere length with air pollution. However, considering smoking as an extreme form of exposure to air pollution, shorter telomere length was observed in smokers compared with non-smokers.

**Who is susceptible?**

At the level of the population, acute effects of air pollution on cardiovascular endpoints have been noted to be significant from middle-age onwards. The highest risk appears to be in people with pre-existing cardiac disease. Drugs that modify oxidant defences may influence the susceptibility to particle-induced inflammatory or prooxidative responses. In addition to their cholesterol lowering effect, statins also have potent anti-inflammatory properties. Schwartz et al. found that the effect of PM$_{10}$ on heart rate variability was confined to persons missing the allele for GSTM1 (lower oxidative stress defence), but the association was only apparent in those who were not under statin treatment.

By putting the evidence of the last decade on air pollution and cardiovascular risk together, the publication of Maître et al. will contribute to the recognition of air pollution as a cardiovascular risk factor by cardiologists. Thus susceptible segments of the population, such as those with heart disease, should take precautions and limit exposure on days with high levels of pollution to prevent the triggering effects of air pollution. In most countries, information on air quality is available on the web. Physicians and cardiologists may play an important role in increasing awareness of the potential risks of exposure to air pollution, but this should be communicated in such a way that patients do not experience disproportionate stress and should be integrated with information on the detrimental health effects of extreme outdoor temperatures as well. Adopting simple behavioural changes in high-risk groups such as preventing high physical activity on days with high levels of air pollution and/or with extreme high or low outdoor temperatures might preclude triggering a coronary event in susceptible segments of the population. Of course this does not contradict efforts directed to the established risk factors, such as smoking, diet, and lack of exercise. Furthermore, to reduce the adverse health effects of air pollution significantly, the heart of the matter remains that further efforts must be made to reduce air pollution by appropriate legislation and its enforcement.

**Acknowledgement**

T.S.N. is a fellow of the Flemish Scientific Fund (FWO).

**Conflict of interest:** none declared.

**References**


Clinical vignette

doi:10.1093/eurheartj/ehi848

Online publish-ahead-of-print 28 March 2006

Carcinoid heart disease as shown by 64-slice CT coronary angiography

Alice M. Veitch*, Gareth J. Morgan-Hughes, and Carl A. Roobottom

Departments of Radiology and Cardiology, Derriford Hospital, Plymouth, UK

* Corresponding author. E-mail address: amveitch@doctors.org.uk

An 82-year-old woman presented with disseminated ovarian carcinoid tumour. She subsequently developed signs of heart failure thought to be secondary to carcinoid heart disease. CT images were taken in our 64-slice scanner with ECG-gating. The CT images revealed markedly thickened pulmonary valve leaflets, without calcification, seen in short and long axis in Panels A (arrows) and B. The pulmonary valve failed to fully close in diastole (Panel A). The tricuspid valve was also significantly thickened, again without calcification, in contrast to the normal appearance of the mitral valve (Panel C). The right atrium (RA) was markedly dilated, with the presence of a flap valve communication (Panel C, arrow) between the right and left atria. Severe tricuspid regurgitation was demonstrated, with failure of apposition of the valve leaflets, a dilated IVC, and reflux of contrast down the hepatic veins. The right ventricle (RV) was also dilated (Panel D). Mitral and aortic valves appeared normal. We found MSCT to be a useful tool in evaluating carcinoid heart disease.

Panel A. Short-axis view of the pulmonary valve in diastole showing the three thickened valve leaflets (arrows) with failure of apposition. Ao, aorta.

Panel B. Long-axis view of the pulmonary valve showing a thickened valve without calcification. PA, pulmonary artery.

Panel C. Four-chamber view showing thickened tricuspid valve leaflets with failure of apposition, a dilated RA, and a flap valve (arrow) communicating between RA and left atrium (LA).

Panel D. Long-axis view showing a dilated RV and thickened pulmonary valve leaflets.