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AIRBORNE POLLUTION AND HYPERTENSION

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Introduction

Air pollution is an ubiquitous and highly heterogeneous mixture of particulate matter (PM), with various gaseous compounds and molecules in a vapour phase [1]. The gaseous part of polluted air encompasses nitrogen oxides, sulphur oxides and ozone, while PM includes different elements such as nitrates, sulphates, transition metals, organic and elemental carbon. Fine PM (< 2.5 μm in diameter, known as $PM_{2.5}$) is linked to increased cardiovascular morbidity and mortality [1]. Epidemiological studies have shown that short-term rises in $PM_{2.5}$ are accompanied, within a few days, by additional myocardial infarcts, heart failure exacerbations, cardiac arrhythmias and strokes.

Several mechanisms may explain these observations:

First, an acute autonomic nervous system imbalance, due to $PM_{2.5}$ accumulation within the pulmonary tree and activation of nerve endings and receptors [2]. The effects of airborne pollutants on blood pressure rise may indeed be at least in part mediated by neural autonomic influences. Animal data, obtained by comparing inhalation of Concentrated Ambient Particles (CAPs) and Filtered Air (FA), suggests that acute exposure to CAPs increases arterial blood pressure, and this seems to be mediated by increased peripheral vascular resistance through α-adrenergic sympathetic activation [2]. This hypothesis is supported by the finding that CAPs-related changes in pulse pressure, heart rate, and rate-pressure product were attenuated by the α-adrenergic antagonist prazosin. Moreover, CAPs exposure significantly increased baroreceptor reflex sensitivity. The above findings are consistent with the large body of toxicologic and epidemiologic literature indicating that exposure to ambient PM is associated with increased sympathetic nervous system activity. An increase in baroreceptor reflex sensitivity is consistent with an up-regulation of vagal reflexes [3]. In previous experiments in this animal model and using measures of heart rate variability, CAPs exposure was found to lead to increases in both sympathetic and parasympathetic autonomic tone, although relative parasympatho-excitation predominated [4]. Therefore, air pollution-mediated haemodynamic changes may be attributable to phasic or tonic up-regulation of both sympathetic and parasympathetic tone, which may offset each other and account for the minimal change to heart rate that was observed. Alternatively, the increased baroreceptor reflex sensitivity that was observed may represent activation of a compensatory mechanism to restore arterial blood pressure toward pre-exposure levels. Clearly, additional studies are needed to fully elucidate the mechanisms underlying the observed effects and to determine the sources or constituents of ambient PM responsible for these effects. In particular, the role of β-adrenergic receptors and vasoactive compounds in these haemodynamic responses remains uncertain.

Second, an inflammatory response to air pollution in the lungs, with extended effects outside the pulmonary vasculature [5]. Subsequent cytokine release and immune cell activation will then result in further oxidative stress and endothelial dysfunction. Tumour necrosis factor, interleukin 6, endothelins, and activated leucocytes can also induce systemic up-regulation of reactive oxygen species pathways, through NADPH oxidase and promote eNOS uncoupling. $PM_{2.5}$ exposure reduces the tetrahydropterin level in various organs and these effects may persist for weeks after inhalation [5]. Enhanced vascular responsiveness to a variety of vasoactive substances further reveals that airborne pollution shifts vasomotor tone towards vasoconstriction [5]. Endothelium-dependent vasodilatation impairment is related to PM exposure in high-risk individuals (e.g. those with diabetes) but also in healthy adults [6, 7]. Moreover, a reduction in 48-hour $PM_{2.5}$ levels among elderly subjects, as a result of air filtering in their homes, results in improved microvascular function [8]. Enhanced Nitric Oxide bioavailability, because of reduced systemic inflammation or oxidative stress, can account for this observation. This may explain why PM_{10} air-pollution levels are associated with a heightened amplitude of the reflection wave, leading to significant alterations in central-pulse pressure [9].

Last, inhalation of some metallic component, as well as very small particles, may impair vasomotor regulation after reaching directly into the circulation. As such, passive smoking not only increases plasma nicotine levels and wave reflection when compared to non-tobacco smoke [10], but also results in higher blood pressure levels in the children of smoking parents [11]. In the latter study, parental smoking was found to independently affect systolic blood pressure, even after correction for other risk factors such as body mass index, parental hypertension, or birth weight. Interestingly, the quantitative relationship is established for maternal, but not parental, cigarette consumption. This is probably because mothers are more prone to smoke predominantly at home, whereas fathers consume their cigarettes at work, and thus away from their children.

Table 1. What to expect in case of an air pollution outbreak in hypertensive patients?

Within 3 to 6 days, a 6% increase in admissions for hypertension at the emergency department
An increase in 3–6 mm Hg in systolic blood pressure in untreated hypertensive patients
Rises in blood pressure may be less marked in hypertensive patients who receive antihypertensive therapy
An increase in premature cardiovascular mortality within a few days: each rise in $PM_{2.5}$ mass by 10 $\mu g/m^3$ over 24 hours increases premature cardiovascular mortality by 1%.

Blood pressure and airborne pollution

In this newsletter, we will review whether airborne pollution can exert acute increases in blood pressure, and determine if hypertensive patients are at risk or may be protected against these effects (Table 1).

There is an association between daily levels of NO_2, SO_2 and PM_{10} and emergency department visits for hypertension in Canada, with a three day lag [12]. This association was also observed between PM_{10} and $PM_{2.5}$ with a six day lag. A similar association, but for much larger PM levels, has been reported in China and Brazil [13, 14]. The true effects of air pollution on blood pressure could even be larger than the 6% increased risk for emergency visits for hypertension [12], because elevations in blood pressure will remain unnoticed in most patients. A large study on adults aged over 30 participating in the National Health Interview Survey demonstrated a significant association between self-reported hypertension and annual $PM_{2.5}$ exposure estimation using US EPA monitoring data [15]. An increment of 10 $\mu g/m^3$ $PM_{2.5}$ was associated with an adjusted odds ratio of 1.05 (CI 1.00 to 1.10) for the presence of hypertension.

A higher left ventricular mass index, as measured by cardiac magnetic resonance imaging, was linked to residential proximity to major roads, in a report from the Multi-Ethnic Study of Atherosclerosis [16]. The level of increase was analogous to a 5.6 mm Hg increase in systolic blood pressure among the study participants. This suggested that traffic-related exposures may have increased left ventricular mass by chronically elevating systemic arterial BP, a common cause of left ventricular hypertrophy. Elevated ambient $PM_{2.5}$ levels are associated within 3–5 days with systolic and diastolic blood pressure elevations [17], unless heart rate was lower than 70 bpm in these cardiac rehabilitation patients, suggesting that cardiovascular medication may protect against the hypertensive effects of air pollution. A study in South Korea [18] and a study in six US cities [19] also observed these associations. In the latter study, adjusted blood pressure rose within 1–2 days by 3 mm Hg, and this association was stronger in patients with hypertension, as well as under other conditions such as warm weather and traffic proximity. A study in Detroit [20] reported a 3 mm Hg increase in systolic blood pressure per 10 $\mu g/m^3$ rise in $PM_{2.5}$ with a lag of two days. However, similar rises in $PM_{2.5}$ did not result in comparable blood pressure effects in the different districts of Detroit, and this was attributed to differences in PM composition. The composition, concentration and dimension of the particles gave a specific toxicity profile to the particles and may explain the seasonal variation in the strength of the association between PM exposure

and blood pressure [18]. In warm weather, the effect of PM_{10} on blood pressure increase was more consistent than in cold weather. Last, changes in systolic blood pressure were not significant in patients taking antihypertensive medications (+0.7 mm Hg), compared to those who where untreated (+6 mm Hg).

Controlled animal studies have been performed under different conditions, using different recording systems (mainly tail-cuff and radio telemetry) and have, not surprisingly, reported variable results where blood pressure remained either unchanged, decreased (when very large amounts of PM are administered intrabronchially or intravenously) or increased (*see reference 21 for a more extensive review on this subject*). In controlled human studies (middle aged or elderly healthy adults, and patients with coronary artery disease), blood pressure remained either unchanged or increased in most of the publications [21]. PM exposure rapidly increased diastolic blood pressure in a controlled experimental study in healthy humans focused on blood pressure changes [22].

In a large meta-analysis, air pollution appeared an important trigger for myocardial infarction, even more than a classic cardiovascular risk factor [23]. This study assessed risk exposure in the period ranging from a few minutes to 24 hours before the onset of myocardial infarction. Thus, while air pollution exposure induced a small individual odds ratio for cardiovascular events, it was likely to exert a significant impact on the whole population, with more marked effects in subjects at cardiovascular risk.

Acute vs. chronic effects of airborne pollution on hypertension and cardiovascular disease

Pollution peaks have an acute effect on blood pressure. As such, airborne pollution appears more as a triggering factor of cardiovascular events than a persistent cardiovascular risk factor by itself.

Whether chronic exposure to pollution induces sustained increases in blood pressure is not yet well-established. There is, however, mounting evidence suggesting this may be the case. For example, we have already observed that people living close to major roads present an increased left ventricular mass [16]. Moreover, self-reported hypertension was also positively linked to estimated chronic PM exposure in a survey of more than 130,000 adults [15]. Last, a population-based prospective cohort in Germany of 4,291 participants, where baseline data had been gathered between 2000 and 2003, showed that an interquartile increase in $PM_{2.5}$ of 2.4 $\mu g/m^3$ was associated with an increase in systolic blood pressure of 1.4 mm Hg and diastolic blood pressure of 0.9 mm Hg [24]. This relationship was independent of long-term exposure to road traffic noise and robust to the inclusion of many potential confounders. Thus, in this study, long-term exposure to PM was clearly associated with increased arterial blood pressure.

Studies on telomere length also argue in favour of irreversible deleterious effects of airborne pollution. Telomeres are repetitive sequence nucleotides positioned at the end of chromosomes. They protect extremities from nucleotic degradation, and as such maintain chromosomal structural integrity [25]. In all replicating somatic cells that have been examined, telomere length shortens with age [26–29]. Critically short telomeres are believed to have functional implications, such as the induction of cellular senescence, which is characterised by the expression of specific makers of ageing and the inability of the cell to divide further [26]. Subjects with shorter telomere length in circulating leukocytes have decreased life expectancy [30–32], increased risk for myocardial infarction [33, 34], severe coronary heart disease [35], heart failure [36], hypertension [37], stroke [34] and cancer [38]. Inflammation and oxidative stress accelerate telomere shortening [26, 39, 40]. In humans, telomere length measured in leukocyte DNA decreases with age [30, 31], smoking [41] and oxidative stress [41].

Telomere length in traffic officers exposed to high levels of traffic pollution was also shorter compared to office workers, and this was inversely associated with personal levels of exposure to benzene and toluene [42]. Thus, exposure to traffic pollutants produces an irreversible acceleration of telomere shortening, probably as a result of enhanced oxidative stress and inflammation. Traffic officers in this study showed a reduction in telomere length equivalent to an ageing of 13 years. Similarly, in the normative ageing study, leukocyte telomere length was measured every **32 years [months?]** from 1999 until 2006 among 165 non-smoking men, while black carbon, a marker of traffic-related particles, was measured in 82 locations within the study area [43]. These authors observed that an interquartile range increase in annual black carbon of 0.25 $\mu g/m^3$ was associated with a 7.6% decrease in teleomere length [43], with stronger effects among those aged > 75 years.

Policies which reduce greenhouse gas emissions may result in substantially less exposure to PM_{10}, via reduction of fossil fuel emissions, and it has been estimated that this could prevent 30,000 premature deaths per year by 2020. However, before we achieve this goal, energy-related CO^2 emissions should fall 15% below 1990 levels in developed countries, and 10% below 2010 levels in developing countries [44].

Summary

There is growing evidence that air pollution increases blood pressure. Given its ubiquitous nature, even modest effects on blood pressure can translate into sizeable rises in cardiovascular events at a population level. Recent evidence suggests that even modest rises in nitrogen and sulphur oxides, as well as in PM, enhance consultations for hypertensive emergencies. In addition, delayed rises in blood pressure have also been observed in several other studies, with some evidence that hypertensive patients could be more prone to disclose a rise in blood pressure, unless they take antihypertensive medications. Moreover, there is now evidence that heavy exposure to airborne pollution is accompanied by telomere population shortening, a phenomenon linked with various cardiovascular events and cancer. Greenhouse gas mitigation policies, if successful, may yield substantial health benefits.

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