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Toxicology and Applied Pharmacology 207 (2005) S477 – S482
Toxicology and Applied Pharmacology
www.elsevier.com/locate/ytaap

Review

Particulate matter and heart disease: Evidence from epidemiological studies

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Received 15 July 2004; revised 6 October 2005; accepted 1 April 2005
Available online 28 June 2005

Abstract

The association between particulate matter and heart disease was noted in the mid-nineties of last century when the epidemiological evidence for an association between air pollution and hospital admissions due to cardiovascular disease accumulated and first hypotheses regarding the pathomechanism were formulated. Nowadays, epidemiological studies have demonstrated coherent associations between daily changes in concentrations of ambient particles and cardiovascular disease mortality, hospital admission, disease exacerbation in patients with cardiovascular disease and early physiological responses in healthy individuals consistent with a risk factor profile deterioration. In addition, evidence was found that annual average $PM_{2.5}$ exposures are associated with increased risks for mortality caused by ischemic heart disease and dysrhythmia. Thereby, evidence is suggesting not only a short-term exacerbation of cardiovascular disease by ambient particle concentrations but also a potential role of particles in defining patients' vulnerability to acute coronary events. While this concept is consistent with the current understanding of the factors defining patients' vulnerability, the mechanisms and the time-scales on which the particle-induced vulnerability might operate are unknown.

Keywords: Acute coronary events; Air pollution; Atherosclerosis; Epidemiology; Mortality; Particulate matter

Contents

Introduction

Associations between ambient particulate matter and heart disease were recognized in the mid-nineties when evidence was accumulating that an increased number of hospital admissions were observed on days with high concentrations of particulate matter (Schwartz, 1995; Schwartz and Morris, 1995). In the same year, Seaton et al. (1995) put forward a hypothesis for a pathomechanism linking ambient concentrations of particles with cardiovascular disease exacerbation. Subsequently, research was initiated to substantiate the findings from epidemiological studies and to elucidate the pathomechanisms responsible for these observed associations. Research during the past years has indeed substantiated earlier findings and the pathomechanisms discussed today have broadened but still comprise the starting hypothesis. Recently, several reviews

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0041-008X/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.taap.2005.04.030

have assessed the evidence for the association between ambient air pollution and cardiovascular disease exacerbation (Brook et al., 2003, 2004; Schulz et al., 2005). Therefore, this review will, in its first part, focus on examining the evidence on coherent findings from epidemiological studies. In the second part, the review will assess the evidence provided by the combination of long-term and short-term health effect studies and identify current questions.

Short-term health effects of ambient air pollution on the cardiovascular system

Short-term health effects of ambient particles on the cardiovascular system span a wide range of coherent findings (Fig. 1). They include evidence of cardiovascular disease exacerbation as noted by multi-center studies assessing the association between ambient air pollution and cardiovascular disease mortality (Schwartz et al., 2003; Zanobetti et al., 2003). Consistent with these findings, an elevated number of hospital admissions due to cardiovascular diseases are recorded in association with ambient levels of air pollution (Schwartz et al., 2003; Zanobetti et al., 2003; Janssen et al., 2002; Le Tertre et al., 2002). Among the specific cardiovascular diseases studied, ischemic heart disease and more specific myocardial infarctions may be more frequent in association with short-term fluctuations of ambient air pollution (D'Ippoliti et al., 2003; Peters et al., 2001a, 2001b).

In order to evaluate the impact of air pollution on patients with pre-existing diseases, previous hospitalization might be used to define a potentially susceptible subgroup. Cohorts of patients with hospitalization for cardiovascular diseases and/or prescriptions indicative of certain chronic disorders have been studied for mortality in association with air pollution. These studies indicated that patients with chronic obstructive pulmonary disease (Sunyer et al., 2000), patients with congestive heart disease (Goldberg et al., 2001; Kwon et al., 2001), and patients with previous myocardial infarction (Bateson and Schwartz, 2004) or diabetes (Bateson and Schwartz, 2004; Zanobetti and Schwartz, 2002) are at risk to experience acute exacerbation of their disease on days with high concentrations of air pollution.

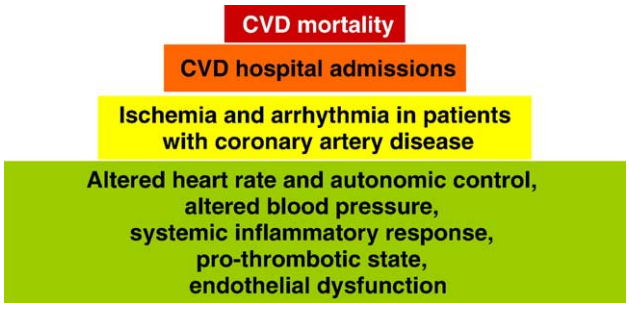

Fig. 1. Coherent effects on the cardiovascular system observed for short-term fluctuations of ambient air pollution.

Because severe acute events are rare, studies are underway to study the association between disease exacerbations in patient populations to provide coherent observations of the health effects of ambient air pollution on the cardiovascular system. It has been reported that patients with coronary artery disease experience signs of ischemia during moderate exertion in association with ambient concentrations of fine and ultrafine particles 2 days before (Pekkanen et al., 2002). In addition, patients with implanted cardioverter defibrillators were more likely to receive interventions due to ventricular tachycardia or ventricular fibrillation in association with ambient air pollution 2 days before (Peters et al., 2000a, 2000b).

The majority of studies assessing the associations between ambient air pollution and cardiovascular outcomes are assessing early physiological responses which may transiently alter the risk factor profile of the subjects. Acceleration of heart rates and diminished heart rate variability in association with air pollution have been documented in elderly persons (Pope et al., 1999a, 1999b, 2004a, 2004b; Liao et al., 1999, 2004; Gold et al., 2000; Holguin et al., 2003), in random samples of the population (Peters et al., 1999), and in occupational cohorts (Magari et al., 2001). Some of the studies on heart rate variability reported an immediate response within hours (Gold et al., 2000; Magari et al., 2001), or on the same day (Pope et al., 1999a, 1999b; Liao et al., 1999), whereas effects on heart rate seemed to accumulate in association with prolonged elevated air pollution concentration (Pope et al., 1999a, 1999b; Peters et al., 1999). Other recent studies are providing incomplete but intriguing results suggesting that particle-induced pulmonary and systemic inflammation, accelerated atherosclerosis, and altered cardiac autonomic function may be part of the pathophysiological pathways linking particulate air pollution with cardiovascular mortality (Peters and Pope, 2002). It has been shown that particles deposited in the alveoli lead to activation of cytokine production by alveolar macrophages (Crystal, 1991) and epithelial cells (Dye et al., 1999), to recruitment of inflammatory cells (Driscoll et al., 1997), and to bone marrow stimulation (Tan et al., 2000; Terashima et al., 1997). Increases in plasma viscosity (Peters et al., 1997), fibrinogen (Pekkanen et al., 2000; Schwartz, 2001), and C-reactive protein (Peters et al., 2001a, 2001b) have been observed in samples of randomly selected healthy adults in association with particulate air pollution. Endothelial dysfunction has been induced by controlled particle exposures (Brook et al., 2002), and small increases in blood pressure may occur in association with elevated concentrations of ambient particles (Ibald-Mulli et al., 2001, 2004; Linn et al., 1999). These are observed in healthy subjects, healthy elderly subjects, as well as subjects with underlying cardiovascular disease. Small samples of subjects may encounter inherent limitations to assess the role of host-factors in defining susceptibility. While within samples of elderly subjects those with diagnosed cardiovascular disease might be more susceptible (Holguin et al., 2003; Liao et al.,

2004), efficient treatment might reduce the impact of air pollution in groups of patients with coronary artery disease, and therefore, finding might be less consistent (Ibald-Mulli et al., 2004).

The link between short-term and long-term cardiovascular health effects of ambient air pollution

Short-term fluctuation in ambient air pollution may therefore be considered as being linked to changes in the cardiovascular risk factor profiles and to exacerbation of cardiovascular disease. What remains unresolved today is the contribution of these effects to the observed health effects of long-term exposures. Generally, ambient particle concentrations were observed to be associated with cardiopulmonary mortality in cohort studies (Dockery et al., 1993; Pope et al., 2002; Hoek et al., 2002). Pope and colleagues found that based on data from the American Cancer Society Study II, there is a 12% increased risk for cardiovascular disease mortality in association with a 10 μg/m^3 $PM_{2.5}$ increase in the annual averages (Pope et al., 2004a, 2004b). This increase was due to ischemic heart disease with an increased risk of 18% per 10 μg/m^3 $PM_{2.5}$ and dysrhythmia with an increased risk of 15% per 10 μg/m^3 $PM_{2.5}$.

A recently published consensus report (Naghavi et al., 2003a, 2003b) introduced the concept of a vulnerable patient who is prone to encounter acute coronary events. Key elements predicting disease are atherosclerosis with vulnerable plaques, vulnerable blood prone to form thrombi and a vulnerable myocardium prone to develop arrhythmia. Atherosclerosis is a complex chronic inflammatory process resulting from the interaction between modified lipids, inflammatory cells such as monocytes and T-lymphocytes, and cellular elements of the endothelial walls such as smooth muscle cells and endothelial cells (Ross, 1999; Glass and Witztum, 2001). It is characterized by endothelial dysfunction and by subendothelial accumulation of lipids, inflammatory cells, and fibrous tissue. Furthermore, these plaques are a dynamic system, and the vulnerable ones prone to rupture are characterized by active inflammation, a thin cap with a lipid core, fissures, endothelial denudation with superficial platelet aggregation, or an associated vascular stenosis larger than 90% (Naghavi et al., 2003a, 2003b). Systemic indexes of inflammation, such as high concentrations of C-reactive protein, or endothelial dysfunction as measured by impaired flow-mediated vasodilatation in the brachial artery can be used to detect pan-arterial vulnerability. Vulnerable blood is associated with a thrombogenic and hypercoagulatory state. It can be characterized by abnormal lipoprotein profiles, non-specific markers of inflammation or serum markers of the metabolic syndrome, as well as by markers of blood hypercoagulability, increased platelet activation and aggregation, and increased coagulation factors (Naghavi et al., 2003a, 2003b).

The exact mechanism linking elevated concentrations of inflammatory markers and blood coagulation to the final acute coronary event is not completely known. Our current understanding of the pathophysiology of acute coronary syndromes suggests, however, that such an event does not necessarily require a hemodynamically relevant stenosis. It is triggered by the erosion, fissure or, eventually, rupture of a vulnerable plaque. This may occur in response to external hemodynamic stress on the plaque cap (Muller et al., 1994), but also to increased internal stress due to rapid growth of the plaque lipid core. Reduced collagen production by vascular smooth muscle cells and increased production of matrix degrading enzymes, both induced by inflammatory mediators and leading to weakening of the plaque cap, represent important mechanisms here.

As pro-inflammatory cytokines effectively induce tissue factor, its up-regulation may trigger endothelial cells to change their antithrombotic properties into a pro-coagulant, clot-promoting state. This mechanism might not only lead to plaque rupture but also to a more extensive clot formation and complete obstruction of the coronary arteries, promoting myocardial infarction and sudden cardiac death (Newby et al., 1999). Thus, the risk of adverse events increases with an enhanced inflammatory state.

Künzli and colleagues have proposed a conceptual framework for the relation between the short-term and long-term health effects of air pollution (Kunzli et al., 2001). It is conceivable that ambient air pollution triggers cardiovascular disease exacerbation due to day to day variations in ambient air pollution concentrations (Fig. 2). In addition, it has been proposed that ambient air pollution

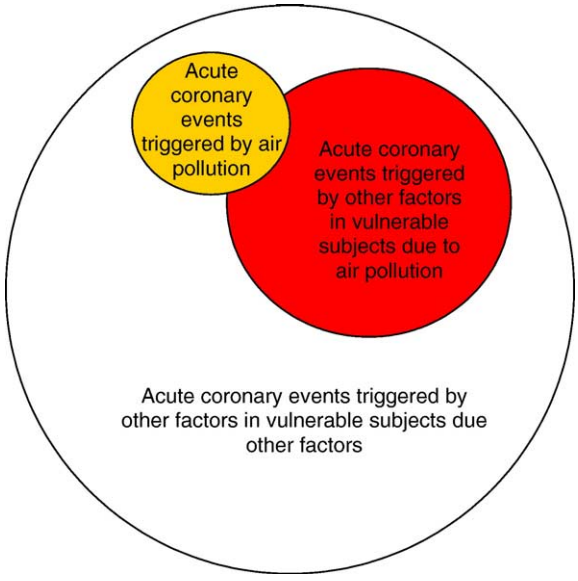

Fig. 2. Schematic drawing of the impact of air pollution on patients' vulnerability to acute coronary events (modified after (Kunzli et al., 2001)). The size of the circles does not reflect the relative impact of these different contributions. Vulnerability as defined by Naghavi and colleagues (Naghavi et al., 2003a, 2003b) comprises vulnerable plaques, a pro-thrombotic state of the blood and a vulnerable myocardium leading to acute coronary events.

might promote atherosclerosis (Peters et al., 2000b). Instillation of PM_{10} sampled from an urban area led to bone marrow activation and progression of atherosclerotic leasons in hyperlipidemic rabbits (Suwa et al., 2002). Repeated exposures to elevated ambient air pollution concentrations might not only transiently deteriorate risk factor profiles, but might also lead to increase the vulnerability of the patients by, for example, promoting the progression of atherosclerosis (Fig. 2). In addition, non-fatal acute coronary events also increase the frailty in the population as, for example, myocardial infarction survivors have an increased risk for a subsequent event. The exact mechanism by which air pollution may contribute to the vulnerability of a patient over extended times periods is unknown. In addition, the risk attributable to ambient air pollution for inducing vulnerability to coronary events on a population basis has not been assessed.

For risk assessment applications, this knowledge is crucial for the following reasons: (a) In scenarios of continuing exposures, we need estimates for the time until a long-term health effect of air pollution can be anticipated to be present on population level to adequately model the impact of increased exposure or abatement strategies. (b) In scenarios where exposure from a source is discontinued, the air pollution-induced vulnerability of the population and its persistence on a population level determines the continuation of an air pollution-attributable impact on the population.

Until to date, only indirect evidence for the reversibility of air pollution-induced vulnerability with respect to cardiovascular disease exists. The first evidence comes from the extended American Cancer Society Study, which had a follow up between 1982 and 1998 (Pope et al., 2002). The effect estimates for the risk of $PM_{2.5}$ are equivalent when the 1979–1983 $PM_{2.5}$ exposure or the 1999–2000 $PM_{2.5}$ exposure is considered. The second clue might be the results of the coal ban in Dublin, which resulted in a 10% decrease in cardiopulmonary mortality which was observed after a 35.6 $\mu g/m^3$ reduction in black smoke from the ban on (Clancy et al., 2002). The difference in mortality observed after the coal ban was larger than one would have predicted based on the APHEA II results (Katsouyanni et al., 2001) for daily fluctuations in black smoke concentrations. Thirdly, time-series studies assessing the lag–structure of air pollution effects have noted a cumulative effect associated with elevated concentrations over weeks in addition to an immediate effect (Zanobetti et al., 2003). Furthermore, data on smoking cessation suggested that the risk for fatal and non-fatal myocardial infarction is substantially reduced and that the benefit of smoking cessation manifests itself within 2 years (Godtfredsen et al., 2003). Based on these observations, one might hypothesize that the impact of air pollution on vulnerability for acute coronary events might be operating on the time scale of 1 or 2 years. However, generally, it is to be said that while it is today acknowledged that patients' vulnerability to coronary events is changing over the life-time, the mechanisms as well as the times scales are mostly unknown. It is possible that genetic polymorphisms may contribute to the susceptibility of individuals with respect to air pollution as triggers of acute coronary events as well as to the promotion of coronary vulnerability (Peters, 2004). Candidate pathways might be the genes regulating inflammatory responses to unspecific stimuli as well as detoxifying enzymes which may determine the severity of oxidative stress. At this point in times, it seems that the most important challenge in order to fully understand the mechanisms by which particulate air pollution might lead to cardiovascular disease exacerbation will be to understand the link between short-term and long-term cardiovascular health effects induced by ambient air pollution.

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