Air Pollution and Atherosclerosis

17

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17.1 Introduction

There is increasing concern around the impact that air pollution has on human health. The Global Health Observatory of the WHO has determined that worldwide air pollution contributes to 5.4% of all deaths from any causes [1, 2]. The higher impact has been recorded in highly industrialized countries as well as in developing countries with large population residing in urban areas. Along with cigarette smoking and secondhand smoke, the exposure to polluted air is now recognized as an important environmental contributor to cardiovascular morbidity and mortality. Indeed, ambient air pollution ranks among the top ten modifiable disease risk factors along with low physical activity, high-sodium diet, high cholesterol, and drug use. Studies reporting an association between high levels of air pollution and health deterioration had been published with increasing frequency since the end of the last century [3–8]. However, convincing epidemiological evidence has become available only recently [9–18] and has called the attention of the medical community, regulatory agencies, and public administrators on air pollution as a main risk factor for cardiovascular disease morbidity and mortality in the population at large.

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17.2 Air Pollution and Atherosclerosis: The Epidemiological Evidence

In the past two decades, a number of human cross-sectional, time-series, and cohort studies have suggested a strong link between the level of particulate matter (PM) from industrial, farming, household, or mobile exhaustions and the progression of atherosclerosis [19, 20]. The first focused epidemiological study published in 2005 investigated 798 residents of Los Angeles [21]. Air pollution exposures were estimated individually based on PM values recorded by local pollution-monitoring stations. The study concluded that for every 10 μg/m^3 rise in PM, aortic intima-media thickness (ITM) increases by 4% after adjustment for potential confounding variables. Similar conclusions were reached by assessing the effect of living close to a main urban road [22]. The coronary artery calcium, used as a biomarker of coronary atherosclerosis, was found to increase by 60% in the sample exposed to the higher PM burden. Halving the distance between the residence and a main road resulted in a 10.2% increase in coronary artery calcification. In a large prospective multicenter study (Multi-Ethnic Study of Atherosclerosis and Air Pollution, aka MESA Air), the relationship between long-term air pollution exposure and the progression of subclinical atherosclerosis has been investigated over several years [23–25]. In the study, long-term exposure to PM 2.5 was found to be significantly associated with decreased endothelial function and increased IMT progression even during a relatively short follow-up period. Importantly, the trial demonstrated that reducing exposure to PM 2.5 can slow IMT progression. Recently, the German Heinz Nixdorf Recall Study group has reported that long-term exposure to fine PM is an independent risk factor associated with subclinical atherosclerosis [26, 27]. The study included a population-based cohort of 4814 randomly selected participants, and thoracic aortic calcification was used to monitor the progression of atherosclerosis. The studies cited and others have been the subject of recent excellent review articles [24, 28–33]. The reader is directed to this literature for an in-depth examination of the study design and the conclusions reached in different population cohorts. A consensus panel has recently concluded that increased levels and exposure to PM are strongly and positively associated to accelerated progression of atherosclerosis [34]. The findings have been a significant driving factor for researchers to identify mechanism(s) by which PM affects the cardiovascular system and particularly the progression of atherosclerosis. In this review article, the experimental evidences linking exposure to polluted air to the development of atherosclerosis are presented.

17.3 Effect of Air Pollutants on Atherogenesis in Experimental Animals

Air pollutants are heterogeneous both physically and chemically. The complex mixture includes particles of different size (mainly PM 10, PM 2.5, and PM of size lower than 1 μm), fumes, and gases such as carbon monoxide (CO), nitrogen

dioxide (NO_2), sulfur dioxide (SO), and ozone (O_3). The particles are a mix of dust and liquid droplets composed of chemicals, acids, metals, and soil. Air pollutants from different sources are endowed with distinct health risk profiles and each may be preferentially linked to pulmonary diseases, systemic inflammation and oxidative stress, endothelial dysfunction, pro-thrombotic and coagulant changes, or to the progression of atherosclerosis.

Investigations on the pathogenesis mechanism underlying the pro-atherogenic effect of various air pollutants have made use of atherosclerosis-prone animals. To this end, Suwa et al. have utilized Watanabe heritable hyperlipidemic (WHHL) rabbits that naturally develop systemic atherosclerosis [35]. The animals were exposed to PM 10 concentrate suspended in saline by intrapharyngeal instillation twice a week for 4 weeks. The results indicated that repeated exposure to urban air PM 10 elicits a systemic inflammatory response and accelerate atherosclerosis in the coronary arteries and aorta of the animals. The severity of the atherosclerotic lesions correlated with the extent of PM 10 phagocytosed by alveolar macrophages in the lung. The qualitative histological observations demonstrated extensive atherosclerosis in the aorta, increase of the lipid-laden areas, and increased cellular lipid turnover. In another study [36], female WHHL were exposed to PM 10 by intratracheal instillation twice a week for 4 weeks, and the recruitment of BrdU-labeled monocytes into the vessel walls and the atherosclerotic plaques were measured through quantitative histology. The exposure to PM 10 increased the number of BrdU-labeled monocytes adherent to the endothelium covering the plaques and promoted the subendothelial migration of the monocytes at the site of plaque formation. In order to investigate the effect of air pollution on the ultrastructural properties of atherosclerotic plaques induced by PM 10 in WHHL rabbits, concentrated ambient particulate matter was instilled into the lungs of the rabbits twice per week for 4 weeks [37]. When examined by transmission electron microscopy, atherosclerotic plaques of PM-treated rabbits displayed increased accumulation of macrophage-derived foam cells compared to saline-treated animals. In addition, type IV collagen was present in the thickened extracellular matrix material beneath the endothelium at the site of plaque formation. These ultrastructural changes are likely to increase the probability of plaque rupture that may trigger a thrombotic event.

Atherosclerosis-prone mice (apoE−/−) fed with a high-fat diet [38], exposed to PM 2.5 at tenfold ambient concentrations for 6 h/day, 5 days per week for a total of 6 months, had a significant increase of lipid content in the aortic arch compared to animal fed with the same diet and breathing filtered air. The exposed animals displayed marked increases in macrophage infiltration, expression of the inducible isoform of nitric oxide synthase, increased generation of reactive oxygen species, and greater immunostaining for the protein nitration product 3-nitrotyrosine. In a similar study, apoE−/− mice were exposed to concentrated PM 2.5 ultrafine particles, and the progression of their atherosclerosis is compared to that in animals breathing filtered air [39]. The exposure to PM 2.5 resulted in a much earlier appearance of large atherosclerotic lesions. A deterioration of the HDL anti-inflammatory capacity and a significant increase of the level of genetic markers for systemic oxidative stress were also recorded. To investigate the effect of diesel exhaustion particles on

the progression of atherosclerosis induced by a pro-atherogenic diet [40], apoE−/− mice fed with a Western diet received a twice-a-week oropharyngeal instillation of diesel exhaust particulate or alternatively saline for 4 weeks. A larger number of atherosclerotic lesions per vessel and more buried fibrous caps were observed in animals instilled with the solution containing diesel particulate matter. The pro-atherosclerotic effect was concomitant with pulmonary inflammation and systemic oxidative stress. In a recent study [41], atherosclerosis development accelerated in apoE−/− mice exposed to ambient ultrafine particles (UFP) with diameter smaller than 180 nm. UFP contain pro-oxidant or otherwise toxic organic chemicals. When these agents were removed by heating the UFP, the level of biomarkers of oxidative stress and the sizes of arterial plaques were significantly reduced. This has led the authors to conclude that removal of organic constituents from ambient particles affords a significant reduction of toxic cardiovascular effects of air pollution exposure. In order to investigate the gene expression alterations leading to accelerated atherosclerosis, global gene expression analysis was performed on atherosclerotic plaques from apoE−/− mice exposed for 6 h/day, 5 days/week for 5 months, to filtered air or concentrated (tenfold) ambient air from an area located 40 km north of New York City [42]. The gene expression profiling showed upregulation of genes linked to inflammation, proliferation, matrix remodeling, and oxidative stress, involved in classical mechanisms of atherosclerosis and plaque progression.

The impact of chronic exposure to urban air on the susceptibility of LDL to oxidative modifications and the development of anti-oxLDL antibodies in blood has been investigated in hyperlipemic mice (LDLR−/−) exposed to ambient or filtered air for 4 months [43]. Exposure to polluted air led to a significant increase of circulating oxidized LDL shown as well by the immune response to the modified lipoproteins. When ApoE(−/−) or LDLR(−/−) mice were exposed to filtered air or concentrated ambient PM 2.5 for 6 months [44], PM 2.5 increased the quantity of oxidized cholesterol (7-ketocholesterol) carried by low-density lipoproteins leading to its accumulation in atherosclerotic plaques. At the cellular level, macrophages from mice exposed to the particulate matter displayed increased uptake of oxidized lipoproteins. In apoE−/− mice, both acute and subchronic inhalation of traffic-generated air pollution lead to increased plasma oxLDL as well as the expression of the oxLDL receptor LOX-1 in vascular endothelial cells [45]. Expression of LOX-1 is increased in systemic arteries following exposure to diesel and gasoline emissions and ozone. Blocking LOX-1 through injection in animals of specific anti-LOX1 antibodies prevents exhaust-induced aortic lipid peroxidation and inflammation. Diesel exhaust emissions contain a large number of ultrafine particles, enriched in organic content such as polycyclic aromatic hydrocarbons. The exposure of apoE−/− mice to diesel exhaust for 2 weeks reduced HLD anti-inflammatory and antioxidant activity. These changes were negatively correlated with paraoxonase enzymatic activity in plasma and to activation of the 5-lipoxygenase pathway in the liver, leading to the formation of peroxidated lipids [46].

Animal studies have allowed researchers to address the key question of the relationship between the dose of exposure to pollutants and the progression and magnitude of atherosclerosis effect based on specific end points. To this regard, particularly

instructive experiments have been carried out to compare the effect produced by PM to that produced by passive tobacco smoke on the atherosclerosis progression in apoE−/− mice [47]. By performing noninvasive (high-resolution ultrasounds) sequential measurements of the plaques in the aortic arch, PM at doses one-third those of tobacco smoke induced comparable degrees of plaque at similar time points. The results demonstrate that PM induces atherosclerosis at a pace comparable to that of passive smoke inhalation, but at much lower μg/mm^3 concentration. The results also demonstrated a nonlinear dose-response effect of PM and the progression of atherosclerosis. Whereas exposure to low levels of PM is associated to a rapid increase in cardiovascular risk, the strength of the correlation lessen as the concentration of inhaled PM increases. To investigate this effect further, the dose-response effect of the inhalation of increasing concentration of diesel engine emissions on atherosclerosis has been evaluated in apoE−/− mice [48]. In this experiment, the animals were exposed for 6 h/day for 50 days to increasing concentrations of diesel-exhausted material or to particulate-filtered diesel exhaust. The exposure to the emissions induced dose-related alterations in gene markers of vascular remodeling and aortic lipid peroxidation. An increase number of macrophages and accumulation of collagen was observed, consistent with the presence of advanced and more fragile atherosclerotic plaques prone to rupture.

17.4 Atherogenic Activity of the Particulate Matter and Potential Mechanisms of Action

An important question relates to the mechanisms underlying the transference of toxicity from pulmonary exposures to PM to the development of atherosclerosis. The inflammation hypothesis [49–51] proposes that inhaled particles bind to or are taken up by the lung alveolar macrophages and epithelial cells and activate the cells to an extent that induces a marked pulmonary inflammation. Inflammatory and pro-oxidative mediators (e.g., cytokines and activated immune cells) then enter the circulation and alter cardiovascular function. There is ample experimental evidence that exposure to air PM initiates an inflammatory response and oxidative stress in the lung [52–54]. The inhaled air pollutants can trigger local oxidative stress by reacting with protective secretions of the airways, thus generating reactive oxygen species (ROS) through the Fenton reaction [55, 56]. Ultrafine particles may also penetrate the cells of the alveolar surface and upon reaching the mitochondria affect the cell respiratory cycle [57]. When the PM-generated ROS overwhelm the pulmonary stress response system, an inflammatory reaction is triggered which releases mediators and further activates pro-inflammatory transcription factors. The released mediators (e.g., cytokines and ROS) readily enter the circulation, cause systemic injury to endothelial cells, and enhance the endothelial barrier permeability [58]. This facilitates the entry of fine and ultrafine PM into the blood stream where they can reach peripheral tissues and elicit further inflammatory and toxic effects [59–61]. A plethora of pro-inflammatory cytokines are released from alveolar macrophages following exposure to PM [62, 63]. PM 2.5 particles are recognized by

intimal macrophages via Toll-like receptors (TLRs), TLR2 and TLR4. The binding of the particulate to macrophages activates the NF-κB pathway which in turn leads to the releases of cytokines and chemotactic agents [64, 65]. The involvement of TLR4 in the PM 2.5-mediated reaction of macrophages has been demonstrated in TLR4-deficient mice. In spite of being chronically challenged with PM 2.5, the animals displayed a normal cytokine profile [66]. There is compelling evidence that PM 2.5-derived ROS at level found in the body following exposure to polluted air have the potential to trigger an atherogenic cascade by generating oxidized LDL and altering the function of vascular cells [59, 67, 68]. The oxidized lipoproteins are taken up by vessel-resident macrophages, which in the process are converted into lipid-laden foam cells. Macrophages can also phagocytize PM 2.5 and, as a consequence, undergo apoptosis [69]. Necrotic remnants of macrophages contribute to the formation of the atheroma necrotic core which is surrounded by foam cells, smooth muscle cells, and extracellular matrix. In endothelial cells, PM 2.5 increases ROS level through p38 mitogen-activated protein kinase and heat shock protein 27-dependent pathways [58]. ROS may be also generated through a cell intrinsic pathway via the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase pathway. PM exposure induces the production of NADPH oxidase-derived superoxide in monocytes and aortic tissue thus contributing through an alternative pathway to atherosclerosis progression [66]. Finally, ROS by scavenging the vasodilator NO produced by the endothelial cells can trigger vascular constriction leading to hypertension [70]. The pro-atherogenic effect of air PM mediated by the induction of a pro-inflammatory and pro-oxidant state is enhanced when the pollutant itself has high oxidizing potential as in the case of ozone or PM 2.5, which contains organic chemicals, transition metals, and high surface areas, all of which can contribute to local generation of ROS.

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