Perspective: ambient air pollution: inflammatory response and effects on the lung's vasculature

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Abstract: Particulates from air pollution are implicated in causing or exacerbating respiratory and systemic cardiovascular diseases and are thought to be among the leading causes of morbidity and mortality. However, the contribution of ambient particulate matter to diseases affecting the pulmonary circulation, the right heart, and especially pulmonary hypertension is much less documented. Our own work and that of other groups has demonstrated that prolonged exposure to antigens via the airways can cause severe pulmonary arterial remodeling. In addition, vascular changes have been well documented in a typical disease of the airways, asthma. These experimental and clinical findings link responses in the airways with responses in the lung's vasculature. It follows that particulate air pollution could cause, or exacerbate, diseases in the pulmonary circulation and associated pulmonary hypertension. This perspective details the literature for support of this concept. Data regarding the health effects of particulate matter from air pollution on the lung's vasculature, with emphasis on the lung's inflammatory responses to particulate matter deposition and pulmonary hypertension, are discussed. A deeper understanding of the health implications of exposure to ambient particulate matter will improve our knowledge of how to improve the management of lung diseases, including diseases of the pulmonary circulation. As man-made ambient particulate air pollution is typically linked to economic growth, a better understanding of the health effects of exposure to particulate air pollution is expected to integrate the global goal of achieving healthy living for all.

Keywords: particulate matter, pulmonary immune responses, pulmonary hypertension, cardiovascular, airways, pulmonary circulation.

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This perspective proposes that ambient air pollution could have a significant clinical impact on pulmonary hypertension. This topic is understudied: a current PubMed search for “pulmonary hypertension, air pollution, excluding cigarette or tobacco” returned 36 entries, and only one was specific to the topic of this review. In contrast, a PubMed search for “asthma, air pollution, excluding cigarette or tobacco” returned 2,968 entries, and a search for “cardiovascular, air pollution, excluding cigarette or tobacco” returned 1,679 entries. This perspective provides a summary of the global impact of air pollution on health in general and discusses deposition of particulate air pollutants in the airways and resulting effects in the airways, the systemic circulation, and in the pulmo-

nary circulation. The latter aspect is strengthened by our own new experimental data showing that air pollution can exacerbate pulmonary arterial remodeling and lead to a significant increase in the pressure in the pulmonary circulation in mice.

URBAN FOG OF PARTICULATE AIR POLLUTION

Particulate air pollution has been of great health concern since the increased mortality reported as a result of the “London Fog” in 1952.¹ Similarly, incidents in Belgium in 1930 (the Meuse fog)² and in Pennsylvania in 1948 (the Donora fog)³ showed that air pollution can be deadly. In these episodes, the particulate matter (soot/polluted dust) was thought to confer a large proportion of

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the observed morbidity and mortality.⁴ These disastrous incidents prompted government and policy interventions that resulted first in the Air Pollution Control Act and then in the Clean Air Act.³

Since the 1950s, great strides have been made to reduce particulate air pollution. The first step has been the measurement of air pollution levels. Today, this information is freely available on the internet for many regions: the American Lung Association for the United States (State of the Air app), CiteAir II for many European cities (<http://www.airqualitynow.eu/>), and the Embassy of the United States or the Chinese government for Beijing. For measurements of particulate matter (PM), levels are fractionated according to size, which determines their ability to be retained in the lungs.⁵⁻⁸ PM₁₀ (particles up to 10 µm in aerodynamic diameter) deposit in the nasal passages or larger airways; PM_{2.5} (particles smaller than 2.5 µm in aerodynamic diameter) can reach the alveoli. Pressure by concerned residents has succeeded in convincing public officials to measure and publish air pollution levels⁹ or to achieve reduction in air pollution.¹⁰ Lowering emissions has improved health outcomes.¹¹ In contrast to the successful efforts by established industrialized countries to reduce the effects of air pollution,¹¹ record-breaking pollution levels have been measured in the winter of 2013 in Beijing, China.⁹ High levels of particulate air pollution are also a major problem in many other countries throughout the world,^{11,12} e.g., Mongolia,¹³ Iran,¹⁴ and India.¹⁵ Depending on the geographical location and weather conditions, small cities can also suffer from air pollution that significantly surpasses guideline values year-round or during specific seasons.^{6,16}

HEALTH EFFECTS OF PARTICULATE AIR POLLUTION

The World Health Organization has published a review of the most recent scientific data concerning the adverse health effects of PM_{2.5} exposure.¹⁷ PM_{2.5} levels have been linked to many diseases, including cardiovascular and respiratory diseases, diabetes, and neurodevelopment and cognitive impairment.^{17,18} Surprisingly, the most prominent detrimental health effects of ambient PM_{2.5} air pollution for hospital admissions and mortality have been observed in the cardiovascular system.^{11,19,20}

URBAN PARTICULATE AIR POLLUTION AND THE AIRWAYS

The idea that air pollution with high PM_{2.5} levels could precipitate inflammatory and remodeling changes in the lungs,⁶ thus exacerbating chronic conditions such as asthma and increasing asthma incidence, has long been proposed. Experimental studies suggest that the deposi-

tion of PM on epithelial cells that line the airways activates inflammatory signaling cascades.²¹⁻²³ In addition, ambient PM pollution may alter systemic immunologic and systemic inflammatory responses.²⁴⁻²⁶

The inflammatory response is thought to predispose and exacerbate the asthmatic response to inhaled allergens, thereby precipitating the signs of asthma.²¹⁻²³ In mice, instillation of PM_{2.5} in a dose-dependent manner, increases the production of T helper 2 (Th2)- and T helper 1 (Th1)-related cytokines and respective transcription factors, upregulates toll-like receptors on alveolar macrophages,²⁷ and activates complement²⁸ and T cell responses.²⁹ In keeping with the different response patterns triggered by ambient PM, atopic and nonatopic children have shown exacerbations of asthma that were correlated with exposure to indoor PM.³⁰ A clinical association between outdoor air pollution and asthma has documented the contribution of road traffic pollution to chronic asthma, particularly in children.³¹⁻³⁴ For example, a recent study showed that levels of nitrogen dioxide (NO₂), a traffic-related air pollutant, and PM₁₀ were linked with increased risk of developing asthma later in life.³⁴ However, on a wider geographical level—for example, between countries—the levels of particulate air pollution are not correlated with asthma or respiratory allergies.^{35,36}

First-responder immune cell types, such as alveolar macrophages and dendritic cells, are stressed and activated by air pollutants, such as diesel exhaust particles.^{25,27,37,38} Furthermore, particle-induced inflammation responses of the first-responder cells in the lungs result in stimulation of the bone marrow, maturation and release of progenitor cells, and recruitment of monocytes via the vasculature to the alveoli.^{25,38-41} This inflammatory response to ambient PM also affects the developing adaptive immune response by changing the molecular profiles in both alveolar macrophages and dendritic cells. The most pronounced changes in the behavior of antigen-presenting cells occur as result of the communication between airway epithelial cells and dendritic cells.⁴²⁻⁴⁷ For example, CCL20 (chemokine CC ligand 20), a chemoattractant for immature dendritic cells and T cells (in particular Th17 cells), TSLP (thymic stromal lymphopoietin), and GM-CSF (granulocyte-macrophage colony-stimulating factor) activate airway dendritic cells and enhance the ability of these cells to present antigen. This molecular interaction also includes the regulation of specific microRNA expression, in particular that of miR375.⁴⁸

Interestingly, new reports show widespread vascular responses in asthma, indicating a coordinated response of the airways and the lung's vasculature to allergen exposure.⁴⁹⁻⁵¹ These types of observations and data from their own experimental studies⁵² prompted Dr. Said and his col-

leagues⁵³ to propose the hypothesis that asthma and pulmonary hypertension share a key pathogenic mechanism.

URBAN PARTICULATE AIR POLLUTION AND THE CARDIOVASCULAR SYSTEM

The adverse effects of ambient PM pollution on the cardiovascular system are a major contributor to mortality.^{11,18,19,54} Because of exposure to ambient PM pollution, cardiovascular and circulatory diseases surpassed exacerbation of infections and other respiratory disorders as the major burden of disease in 2010.¹¹ This outcome strongly suggests that PM deposition in the airway or alveolar epithelium has effects beyond the airspaces. Numerous mechanisms have been proposed to explain the mechanisms by which PM exerts cardiovascular effects. The ability of PM to activate autonomic neuronal reflexes in the lungs, resulting in functional cardiac changes and vasoconstriction, has been hypothesized.^{18,55} But this process alone is not sufficient to account for the structural changes in the cardiovascular system, including atherosclerosis, ischemic heart disease, and stroke, that are attributed to ambient PM exposure.¹⁸ Several additional mechanisms have been proposed to explain the cardiovascular structural changes induced by exposure to ambient PM_{2.5} (Fig. 1),^{5,18,56,57} including the following. (1) Ambient PM deposited in the airspaces translocates into the blood stream, directly via adhesion and diffusion into the adjacent blood vessels or indirectly via lymph fluid movement through the lymph node.⁵⁷⁻⁶⁰ This process has been experimentally documented for ultrafine (nano-)particles that have an aerodynamic diameter in the nanometer range. (2) Deposited ambient particles disintegrate and dissolve partially (or fully) and release harmful chemicals (metals, organic compounds) that translocate directly into adjacent blood vessels or indirectly, via the lymph through the lymph node, into the blood stream.^{5,56} (3) Particles are phagocytosed in the airspaces, resulting in inflammation and migration of inflammatory cells (macrophages, dendritic cells) to the lymph nodes, followed by transport of the particles in the blood stream.⁶¹ (4) Deposits of ambient PM initiate inflammation in the airspaces with the release of cytokines and other inflammatory mediators into the vasculature and transfer via the cardiovascular system.¹⁸

THE LUNG'S VASCULATURE, PULMONARY HYPERTENSION, AND CIGARETTE SMOKE EXPOSURE

To optimize gas exchange, the architecture of the vasculature in the lungs is intricately linked to the air-carrying airways and alveoli. The pulmonary artery carries the blood from the right heart to the capillary bed of the alveoli

and respiratory bronchi. Constriction, inflammation, thickening (i.e., remodeling) and loss of branches of the pulmonary arteries lead to pulmonary hypertension.^{62,63}

Cigarette smoking is one of the toxic environmental exposures that cause respiratory diseases, including chronic obstructive pulmonary disease (COPD) and lung cancer.⁶⁴⁻⁶⁷ In addition, cigarette smoke exposure may be a risk factor for individuals who have pulmonary hypertension, as suggested by clinical data⁶⁸ and animal studies.^{69,70} Dissecting the molecular mechanism of COPD-associated pulmonary hypertension induced by cigarette smoke exposure in mice, Dr. Weissmann and colleagues⁷⁰ showed that the pathway to cigarette smoke-induced pulmonary hypertension involved oxidative and nitrosative stress followed by accumulation of proteins that are rendered less functional by nitrosylation. Genetic susceptibility factors are additional determinants of the extent and severity of pulmonary arterial remodeling and right heart hypertrophy in response to tobacco smoke exposure, as shown in studies of different mouse strains from Dr. Gordon's laboratory.⁶⁹ Tobacco smoke can also trigger pulmonary vascular remodeling in smokers who have not yet developed COPD.⁷¹⁻⁷³ The fine PM in secondhand smoke is similar to the PM of air pollution, and secondhand smoke can induce inflammation and cause cardiovascular disease.⁷⁴

PULMONARY ARTERIAL REMODELING TRIGGERED BY IMMUNE RESPONSES ELICITED IN THE AIRWAYS

In experimental animals—mice and rats—there is clear evidence from several different groups that prolonged antigen exposure via the airways can induce severe pulmonary arterial remodeling, with thickening of the wall, disorganization of the smooth muscle cell layer, and smooth muscle cell proliferation.⁷⁵⁻⁷⁹ Particulate⁷⁵ and soluble⁷⁶⁻⁷⁹ antigens can elicit this remodeling response. Our own work⁷⁶ has shown that this remodeling response is dependent on the presence of CD4⁺ T cells and Th2 cytokines (interleukin: IL-4, IL-13), mediators known for their critical role in asthma.⁸⁰ The role of IL-13 in pulmonary arterial remodeling has been supported by studies of transgenic mice overexpressing IL-13 in the airways.⁸¹ In addition, mice that have IL-25, a major inducer of IL-13, elicited in the airways by antigen exposure or transgenic expression also demonstrate pulmonary arterial remodeling.⁸² BMPR2, a receptor known for its central role in the development of pulmonary hypertension when present at a hypomorphic state, with decreased activity, has been shown to be a regulator of the asthmatic airway hyperreactivity response.⁸³ Our own data have shown that antigen expo-

Figure 1. Routes of transfer of particulate matter (PM) from the airways to peripheral organs and inflammatory response. PM effects in the heart and other organs involve dissemination of PM via blood vessels (gray arrows) or drainage via the lymphatics (gray line) to the lymph node, followed by dissemination via blood vessels (gray arrow). Translocated materials include: (a) the PM itself (nanoparticles), (b) components of disintegrated PM, (c) phagocytic immune cells that have phagocytosed PM and that migrate via the lymphatics to the lymph nodes, and (d) inflammatory mediators (e.g., cytokines) produced in the lungs in response to PM deposits. A color version of this figure is available online.

sure via the airways efficiently triggers the pulmonary hypertension phenotype in mice that carry a hypomorphic *BMPR2*.⁸⁴ Taken together, these findings strengthen the notion⁵³ that responses in the airways and in the pulmonary vasculature can be linked and that this may occur via coordinated molecular signals.

AMBIENT PARTICULATE AIR POLLUTION AND PULMONARY VASCULAR CHANGES

Figure 2 shows the results from our study designed to test the hypothesis that PM_{2.5} would exacerbate antigen-induced pulmonary arterial remodeling in mice. We found that when given PM_{2.5} alone at a dose of 25 µg per instillation, the equivalent of 1.25 mg/kg body weight, mice did not show arterial remodeling, even when we used a sensitive immunohistochemistry method coupled with computer analysis (Fig. 2). In keeping with the published literature using PM_{2.5} sampled in Beijing,²⁷ New York City,⁸⁵ or Baltimore,^{28,29,86} the dose of PM_{2.5} that we used did

not elicit significant airway inflammation, as determined by bronchoalveolar lavage cellularity (Fig. 2). In order to focus on the exacerbating role of PM_{2.5}, we used a low dose, approximately half the concentration of PM_{2.5} that has been reported to elicit a significant inflammatory response,^{27,85,86} and an antigen, ovalbumin (OVA), that in nonimmunized mice has very mild proinflammatory activity.⁸⁷ Our data clearly show that immunized mice that were challenged with PM_{2.5} given together with the mild antigen had significantly exacerbated pulmonary arterial remodeling when compared with immunized mice challenged with the antigen alone (Fig. 2).

AMBIENT PARTICULATE AIR POLLUTION AND PULMONARY HYPERTENSION

Figure 3 shows the results from our study designed to test the hypothesis that PM_{2.5} would trigger pulmonary hypertension induced by an antigen in mice. Right ventricular systolic pressures were measured by heart catheter-

ization via the jugular vein.⁸⁸ Immunized mice that were challenged with the combination of PM2.5 and an antigen demonstrated significantly increased right ventricular pressures, but mice challenged with the antigen or with PM2.5 alone did not (Fig. 3). The significant increase in the right ventricular pressures in the group of mice challenged with PM2.5 and antigen was detected with two analysis methods, comparisons of group medians (Fig. 3A) and contingency table analysis (Fig. 3B).

The data shown in Figures 2 and 3 represent a hypothesis-generating finding, suggesting that even low-dose PM2.5 can have clinical significance for pulmonary hypertension if PM2.5 exposure is added to another inflammatory condition, such as inflammation induced by exogenous (infectious or inhaled) or endogenous (autoimmunity) antigens. Furthermore, high-dose PM2.5 exposure may even further increase the risk for developing pulmonary arterial remodeling and pulmonary hypertension. Barriers to obtaining clinical data to test this hypothesis are expected to be overcome in the near future by noninvasive diagnostic techniques, such as echocardiography, computed tomography, and magnetic resonance imaging (MRI), that will complement the current gold standard in diagnosing pulmonary hypertension, invasive right heart catheterization.

A recent study, presented at the American Thoracic Society meeting in 2013, showed that living in proximity to roadways, and therefore being exposed to high levels of PM2.5 and nitrogen oxides, was associated with greater right ventricular mass and changes in right ventricular function, as detected by cardiac MRI.⁸⁹ Right ventricular mass is a measure of strain, which could be caused by molecular changes in the right ventricle or changes in the pulmonary circulation, in turn causing limitations in the blood flow.⁸⁹ While this study needs further mechanistic exploration and confirmation, it is in keeping with our observations, as shown in Figures 2 and 3, and indicates that air pollution can exacerbate parameters of the pulmonary hypertension phenotype. Further support for this notion comes from clinical studies in humans exposed to indoor⁹⁰ or outdoor⁹¹ air pollution and from experimental studies in animals.⁹²⁻⁹⁴ Residents of low- and middle-income countries often are exposed to high indoor PM levels because of biomass fuel use. In this setting, indoor PM is thought to be a significant risk factor for developing pulmonary hypertension and right heart failure.⁹⁰ In children living in Mexico, outdoor exposure levels of PM2.5 were associated with increased pulmonary arterial pressures (measured by echocardiography) and with elevated plasma endothelin-1 levels.⁹¹ Exposure of mice to urban PM resulted in increased production of endothelin-1

in the lungs.⁹² Endothelin-1 is a potent biological mediator of arterial constriction and has an important role in pulmonary hypertension.^{95,96} Exposure of rats to concentrated ambient PM impaired the relaxation response of pulmonary arteries to nitric oxide⁹³ and induced pulmonary hypertension.⁹⁴ Batalha and colleagues⁹⁴ also observed a decrease in the ratio of lumen or wall thickness of the pulmonary arteries, an indicator of vascular remodeling, which was associated with the content of silica in the ambient PM.

This latter finding may hint toward a generalizable biological effect of silica on the pulmonary vasculature. Individuals exposed to silica-containing dust, e.g., miners of coal, stone, or gold, can develop a condition called silicosis/pneumoconiosis. Silicosis has been recognized as an occupational disease caused by air pollution exposure in the coal mines since the mid-1840s;⁹⁷ the original articles from that time period are freely available on the Scottish Mining Website. Silicosis is characterized by chronic lung inflammation and fibrosis and includes other comorbidities, such as pulmonary hypertension and chronic cor pulmonale (right heart failure).⁹⁸⁻¹⁰¹ Silicosis, despite some decline,¹¹ is still the most prevalent occupational lung disease, occurring globally, for example, in the United States, China, South America, and Africa.¹⁰² Because of the severity of the condition and the lack of an effective treatment or a cure, silicosis has been placed on a list of diseases targeted for elimination by the World Health Organization.¹⁰³ Interestingly, construction and glass dust containing silica/silicates/silicon were also constituents of the World Trade Center dust,^{104,105} and pulmonary arterial thickening has been reported as part of the pathological findings in a small group of exposed individuals who developed chronic, progressive lung disease.¹⁰⁶ Exposure to silica crystals, and thus the potential for pulmonary vascular effects, can occur in many environments; a constituent of cement and glass, silica can be released into urban ambient air during construction activities.¹⁰⁷ Moreover, silica, a main constituent of soil, is a component of desert dust storms and volcanic eruptions and can reach urban and rural areas.¹⁰⁸ A large amount of silica-containing dust is also expected to be produced by the sand mining needed for hydraulic fracturing of oil and gas.¹⁰⁹

SUMMARY

More research is needed to understand the effects of ambient PM on the pulmonary circulation. PM constituents that translocate from the airspaces to the lung's vasculature, by one of the molecular processes (Fig. 1)^{18,56} thought to cause systemic left heart cardiovascular mor-

Figure 2. Significant exacerbation of pulmonary arterial remodeling due to combined exposure to antigen and urban PM2.5 (particulate matter <2.5 μm in aerodynamic diameter). **A**, **B**, Arterial remodeling as average remodeling score per lung (**A**) and as percentage of severely remodeled arteries in the lungs (**B**); box plots with individual data points, $n = 4-10$. **C**, Numbers of eosinophils (**i**), neutrophils (**ii**), and CD11c+ cells (**iii**; note linear scale) in the bronchoalveolar lavage samples; bar graphs show means, standard error of the means (SEM), and individual data points ($n = 6-10$). **D**, **E**, Blood vessel muscularization. **D**, Representative histological sections from a phosphate-buffered-saline (PBS)-exposed mouse (**i**) and a PM-exposed mouse (**ii**) stained with anti-smooth muscle actin (dark; scale bars = 50 μm). **E**, Quantitative analysis of muscularization as percentage of blood vessels that were in each of the following categories: none (<30% of the circumference positive for smooth muscle actin staining), partial (30%–80% of the circumference positive), or full (>80% of the circumference positive); bar graphs show means, SEM, and individual data points ($n = 4-5$). In **A**–**C**, significant differences ($P < 0.05$, 2-tailed, unpaired Mann-Whitney test) relative to groups of mice exposed to saline (**a**) or ovalbumin (OVA; **b**) are indicated; ns: not significant. The study was performed in two independent experiments using C57BL/6 wild-type mice that were purchased from Jackson Labs and housed in specific pathogen-free conditions under the supervision of the Institutional Animal Care and Use Committee at New York University Medical Center as described.^{41,84} The mice were immunized by intraperitoneal injection with OVA complexed to alum and given intranasal challenges in a 50- μL volume per dose using the described schedule.^{41,76,84} PM2.5 was collected in New York City by Dr. Gordon's group, as described,⁸⁵ and diluted in saline to a concentration of 0.5 mg/mL. The intranasal dose of OVA was 100 μg , and for the OVA-PM instillations, OVA and PM2.5 were mixed to achieve final concentrations of 100 and 25 μg per instillation, respectively.

Figure 3. Exposure to the combination of antigen (ovalbumin [OVA]) and urban ambient particulate matter (PM) causes increased pressures in the pulmonary circulation. Right ventricular systolic pressure (RVSP) is shown by notched box plots and circles showing individual data points (A) and by a bar graph showing the number of observations of RVSP less or greater than 26 mmHg (B). Data were pooled from two independent experiments; $n = 4$ –10. The letter a indicates $P < 0.05$ compared to group of mice exposed to saline by 2-tailed, unpaired Mann-Whitney test (A) or by χ^2 test and 2-tailed Fisher's exact test (B); ns: not significant. A color version of this figure is available online.

bidity and mortality, may also cause right heart morbidity and mortality because of changes in the pulmonary vasculature. Studies in experimental animals show that exposure to ambient PM can cause significant changes in the pulmonary vasculature, on the morphological, functional, and molecular levels,^{92,94} and that PM significantly exacerbates the pulmonary vascular response to antigen (Figs. 2, 3). These data suggest that exposure to ambient PM could exacerbate comorbidities, causing pulmonary hypertension and contributing to right heart failure. This could mirror the documented effects of ambient PM with respect to the left heart.^{11,18,19} Exposure to silica-containing PM mixed with chemicals from coal or fossil fuels (miner's cor pulmonale) is perhaps the best-documented cause of air pollution exposure-induced pulmonary hypertension.^{98–101} However, silica-containing ambient PM is also generated by natural and man-made phenomena. In addition to silica, other components of ambient outdoor PM (specifically, urban PM) and indoor PM may also increase the risk for developing pulmonary arterial remodeling and pulmonary hypertension (Fig. 2).⁸⁹ A deeper knowledge of the networked responses to ambient PM by the lung's immune and vascular cells and how these relate to cardiovascular function will improve our

ability to manage vascular diseases of the lungs and pulmonary hypertension.

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Conflicts of Interest: None declared.

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Figure 2. (continued)

Bronchoalveolar lavage,^{76,84} arterial remodeling,^{76,84} and blood vessel muscularization⁸⁴ were analyzed as published. The percentage of severely remodeled arteries was calculated as a fraction of arteries given the score 1.5 or 2 (severely thickened arterial wall with irregularity of wall thickening and cellular disorganization).⁷⁶ In comparison, a score of 0 represented a normal artery, and a score of 1 was given for mild, circular thickening of the artery wall. A color version of this figure is available online.

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