You Are What You Breathe: Evidence Linking Air Pollution and Blood Pressure

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Exposure to particulate matter (PM) air pollution increases the risk for myocardial infarctions, strokes, and cardiovascular mortality. A variety of responsible mechanisms have been described, including PM-induced elevations in blood pressure. Observational studies and controlled experiments have provided evidence that PM is capable of acutely increasing blood pressure in certain scenarios. Enhanced sympathetic tone and vascular dysfunction due to PM-induced systemic oxidative stress/inflammation are leading explanations. The hemodynamic responses to air pollution may be altered by underlying cardiovascular risk factors and the chemical composition of the PM. However, even the small elevations in blood pressure observed following certain exposures to PM have tremendous public health implications, due to the ubiquitous nature of air pollution.

Introduction

Air pollution is a complex, heterogeneous mixture of gases and particulate matter (PM) [1••]. In our modern industrial and urban society, exposure to air pollution is ubiquitous and actually increasing throughout certain parts of the world. At the same time, epidemiologic studies have demonstrated that several gaseous (eg, ozone) and PM pollutants are associated with adverse health effects [1••,2•,3,4]. Individual constituents possess toxic potential, alone and in combination with others. However, in terms of cardiovascular disease, adverse outcomes have been most strongly linked to fine PM that is less than 2.5 μm in diameter (PM2.5) [1••,2•,3]. PM2.5 itself is a complicated amalgam consisting of organic/elemental carbon, sulfates, nitrates, and various metals. Its composition, concentration, and chemistry vary both temporally and by location [1••]. In the United States, the major source of PM exposure is from fossil fuel combustion (eg, automobiles, power plants, industry).

Both acute and long-term exposures to PM2.5 have been consistently associated with increased cardiovascular events [1••,2•,3]. Elevated levels have been shown to rapidly (within hours) increase the risk for myocardial infarctions [5•], stroke [6], arrhythmias [7], myocardial ischemia [8], and cardiovascular mortality [3]. For example, the risk for a myocardial infarction is raised by almost threefold within 1 hour after exposure to automobile traffic [9]. Cardiopulmonary mortality increases by 0.31% within a day after a minor 10 $\mu g/m^3$ increase in PM level [3]. To put this into perspective, the current Environmental Protection Agency (EPA) regulations allow daily average concentrations to be as high as 65 $\mu g/m^3$ [1••]. Short-term inhalation of PM2.5, even within current standards, is thus capable of triggering biological responses that promote acute cardiovascular events. These include changes in autonomic balance (vagal withdraw) favoring heart conduction abnormalities and the instigation of systemic inflammation/oxidative stress [1••,10–12]. The latter responses are plausible causes for the endothelial dysfunction, arterial vasoconstriction, and prothrombotic/coagulant changes previously demonstrated following PM exposures [1••,10–12]. Thus, PM is capable of playing at the very least a facilitative role in instigating acute cardiovascular events in susceptible individuals.

It has been appreciated that the cardiovascular mortality related to long-term (12.0% per 10 $\mu g/m^3$) is much greater than that due to acute PM exposure (0.31%–1.0% per 10 $\mu g/m^3$) [1••,13•]. This order of magnitude difference suggests that in addition to a summation of acute events, long-term PM2.5 exposure may also have proatherosclerotic effects. In this manner, air pollution may in itself be a risk factor for cardiovascular disease and not simply a trigger of acute events. Evidence supporting this hypothesis has recently been reported in animal models and in a human cross-sectional study in which PM exposures were related to systemic atherosclerosis [14,15,16•]. PM-induced pro-oxidant and inflammatory immune responses can cause endothelial dysfunction and low-denisty lipoprotein–oxidation, processes fundamental to the atherosclerosis process [1••,10–12,17]. Air pollution may thus play a direct role in worsening atherosclerosis.

An additional (but not mutually exclusive) explanation for the relatively higher long-term adverse health effects

may be that they result from indirect mechanisms. Air pollution could also worsen and/or promote the genesis of the "established" causal cardiovascular risk factors. Most individuals (>90%) with cardiovascular disease have at least one traditional risk factor [18]. More than 90% of myocardial infarctions worldwide are attributable to these known factors [19]. It follows that the direct contribution of other novel factors, such as PM, must be relatively small in comparison. This suggests that a substantial portion of the adverse long-term effects of air pollution are likely to be mediated indirectly via worsening of the established causal factors.

An important risk factor that has the potential to be negatively impacted by air pollution is blood pressure (BP). Hypertension is the single largest cause of worldwide mortality due to a chronic illness [20]. Every 20/10 mm Hg increase in arterial pressure, even within the normotensive range, doubles the risk for cardiovascular disease [21]. Therefore, there are profound public health ramifications if the ubiquitous exposure to PM increases BP, even to a minor extent. The remainder of this review is focused on the evidence and potential mechanisms linking air pollution and BP.

Epidemiologic Evidence Linking PM2.5 with Increased Blood Pressure

The results of observational studies regarding the effect of PM on BP have been mixed [22–24]. The discrepancies are a result of variations in: patient populations, potential exposure mischaracterizations, chemical compositions of the pollutants, medication effects, lack of adjustments for other confounders (eg, activity, stress), and suboptimal determinations of BP [23]. Although some studies do not report an association [24], several recent epidemiologic findings have demonstrated a positive relationship between PM exposure and increased BP in humans. The first such association was reported by Linn *et al.* [25] in the Los Angeles area in 1999. In 30 subjects with lung disease, it was found that during a 4-day period, a 10 $\mu g/m^3$ increase in PM was related to a 0.95 and 1.7 mm Hg increase in diastolic and systolic BP, respectively. The study was limited by its small size and ability to adjust for weather and other environmental confounders.

In a much larger study of 2607 individuals in Germany, an association between ambient PM levels and BP was also found [26]. In January 1985, a severe air pollution episode occurred in Europe. During this period, an increase in BP was observed. However, the association disappeared after adjustments for meteorologic parameters. In more detailed analysis, in a subgroup of participants, BP was significantly related to continuous measurements of total air particulate levels, even after adjustments for other risk factors and meteorology. Systolic BP was elevated 1.79 mm Hg per 90 $\mu g/m^3$ increase in total particulates during the same day. Importantly, in a group of individuals with elevated heart rates (90th percentile) and elevated plasma viscosity (90th percentile), the pressor responses were much greater. Systolic BP increased by 7.76 and 6.93 mm Hg in each group, respectively, for the same elevation in particulates. This suggests that certain individuals may be more prone to a hypertensive response to PM, depending on their underlying physiology and/or concomitant cardiovascular risk factors.

Recently, an important study of 62 Boston-area residents with cardiovascular disease corroborated a positive relationship between PM exposure and BP [27••]. During repeated measures of BP for cardiac rehabilitation, mean PM2.5 concentrations were associated with a 2.8 and 2.7 mm Hg elevation in systolic and diastolic BP (per 10.5 $\mu g/m^3$ PM2.5 increase during the previous 5 days). This study has particular strengths in that it included numerous repeated measures of BP, actual determination of respirable PM2.5 levels rather than total particulates, and a susceptible population known to be at risk for the effects of air pollution. The hypertensive response was more pronounced in relation to the average 5-day PM2.5 level compared with the less significant impact of the more acute effects (previous 48-hour concentrations). The authors speculated that the mechanisms responsible require a more prolonged time course to reach maximal effect.

Experimental Evidence that PM2.5 Increases Blood Pressure

Many controlled human exposure studies to concentrated ambient PM2.5 (CAP), or other air pollutants (eg, diesel exhaust), have investigated various cardiovascular responses during the past few years [1••]. Most experiments did not include BP response as a specific or pre-specified outcome. In addition, only crude measures of BP as a safety parameter and/or very few readings have usually been reported [22,23,28]. It is well established that BP is highly variable [29]. Its accurate measurement is also prone to numerous errors and sources of variation [30]. Relatively small, yet clinically meaningful, changes in BP (eg, 2–4 mm Hg) can easily be masked by these shortcomings.

Recognizing these issues, utilizing more meticulous experimental techniques we recently investigated the acute effect of CAP exposure on BP [31••]. Twenty-three healthy normotensive adults were exposed to 147 $\mu g/m^3$ of CAP from downtown Toronto + ozone (121 PPB [parts per billion]) for 2 hours and to filtered air (placebo) on a separate occasion. BP was measured every 30 minutes during the actual exposure period with an automated oscillometric arm cuff. Filtered air had no significant effect on BP (0/+1 mm Hg median change), whereas CAP + ozone significantly increased diastolic BP compared with baseline levels and to the response during placebo exposure (-1/+6 mm Hg median change). There was a linear and progressive increase in median diastolic BP (from 69 to 78 mm Hg). Among the pollutants, the organic carbon fraction of PM2.5 was the

sole factor related to the BP change (r = 0.53, $P = 0.009$). This suggests that certain organic components within particulate matter are capable of triggering a rapid hypertensive response when inhaled by healthy adults.

In animal studies, inconsistent BP findings have been reported depending on the type of pollutants, means and timing of exposures, and animal models used [32–35]. However, two recent publications using more sophisticated radiotelemetry methods to continuously assess hemodynamics have demonstrated significant increases in BP during air pollution exposures [34,35]. Repeated CAP exposures on 4 days in the spring to spontaneously hypertensive rats caused a significant peak mean BP increase of 8.7 mm Hg [34]. There was a less prominent hypertensive trend during summer exposures. This suggests that differing chemical compositions of PM can produce varied hemodynamic responses. A similar study performed earlier by the same researchers using pulmonary hypertensive rats did not demonstrate any BP increase, confirming that various animal models may react differently [33]. In a separate experiment, rats exposed to ambient Ottawa PM were found to have significant increases in BP and endothelins [35]. This effect was not found when the particles were washed and soluble components, such as transition metals, were removed. This corroborates that the character of the PM exposure can play an important role in determining the cardiovascular responses.

Potential Mechanisms

Several biological pathways could be responsible for affecting cardiovascular hemodynamics in response to PM (Fig. 1). In overview, PM-induced changes in 1) autonomic balance and/or 2) systemic oxidative/inflammatory reactions promoting vascular dysfunction are the prime candidate explanations [1••,10–12]. Overlapping and different mechanisms may also be responsible for alterations in BP at varying time points. Increased BP due to PM exposure has been shown to occur both rapidly (2 hours) [31••] and in a more delayed fashion (1–5 days) [27••]. Rapid responses within minutes to hours may be triggered by pathways that are different from those responsible for subacute (hours to days) and more chronic effects. However, the mechanisms may not be mutually exclusive and may overlap.

An acute change in autonomic tone is a leading explanation for the rapid increase in BP. PM inhalation alters autonomic balance favoring vagal withdraw and sympathetic nervous system (SNS) stimulation [1••,10–12]. This effect has been illustrated most consistently by alterations in heart rate variability in humans and animals within minutes of exposure. Human airways, from nasopharynx to alveoli, are innervated by several types of stimuli receptors capable of instigating rapid reflex cardiovascular responses following stimulation by PM inhalation [36]. Most of these neurally mediated reflexes promote a hypertensive response. If cardiac SNS activity is enhanced (or there is vagal withdraw), both positive chronotropic and inotropic changes could occur [36]. In one small study of rats, an index of cardiac output was found to increase after PM exposure [34]. Moreover, if SNS activity is similarly enhanced at other organs, BP may increase by additional mechanisms (Fig. 1). Most notably, several studies in humans and animals have shown significant arterial vasoconstriction following PM inhalation [28,37]. The altered autonomic balance may be playing a direct role in mediating this vasoconstriction and thereby the BP elevation. If these responses are not limited to the short-term, increased renal SNS tone could in theory enhance sodium retention (ie, shift pressure natriuresis) and thus promote chronic hypertension [38]. However, currently there are no published studies that have investigated any putative chronic autonomic changes related to PM exposure.

Beyond the effects of SNS activation, BP may be elevated as a direct consequence of resistant arteriole vascular dysfunction. Analogous to passive tobacco smoke [39], PM inhalation has been shown to trigger endothelial dysfunction in humans and animals [1••,10–12,40•]. Several studies have demonstrated a reduction in nitric oxide–mediated vasodilatation in response to endothelial-dependent vasodilators. The underlying mechanisms responsible are most likely PM-mediated systemic oxidative stress and inflammation [1••,10–12]. Following inhalation, free radicals are generated within the pulmonary tissues as a direct effect of various chemical components on the particles. In addition, pulmonary and inflammatory cells respond (following their activation due to interactions with PM) by their own generation of free radicals/reactive oxygen species and with cytokine release. Evidence supports that this response is not limited to the pulmonary vasculature, but is seen systemically. Elevated blood levels of white blood cells, fibrinogen, pro-inflammatory cytokines, and C-reactive protein have been shown [1••,41]. Several markers of enhanced systemic oxidative stress have also been demonstrated in humans in relation to PM exposure [1••,41,42]. Consequently, peripheral arterial endothelial dysfunction may occur. Inflammation and oxidative stress are key mediators of vascular dysfunction via altering endothelial nitric-oxide synthase function and by reducing nitric-oxide bioavailability through a variety of mechanisms [43]. In further support of this hypothesis, CAP exposure to rats has been shown to increase blood asymmetric dimethyl arginine levels, the endogenous inhibitor of nitric-oxide synthase [44]. However, the time course of these events has not been firmly established. It is likely that this mechanism of systemic inflammation and oxidative stress due to spillover from the pulmonary circulation would require many hours to impair vascular function. Thus, this may be a more delayed pathway causing changes in vascular tone and elevated BP over several hours to days.

However, passive tobacco smoke exposure is capable of impairing endothelial function and triggering vaso-

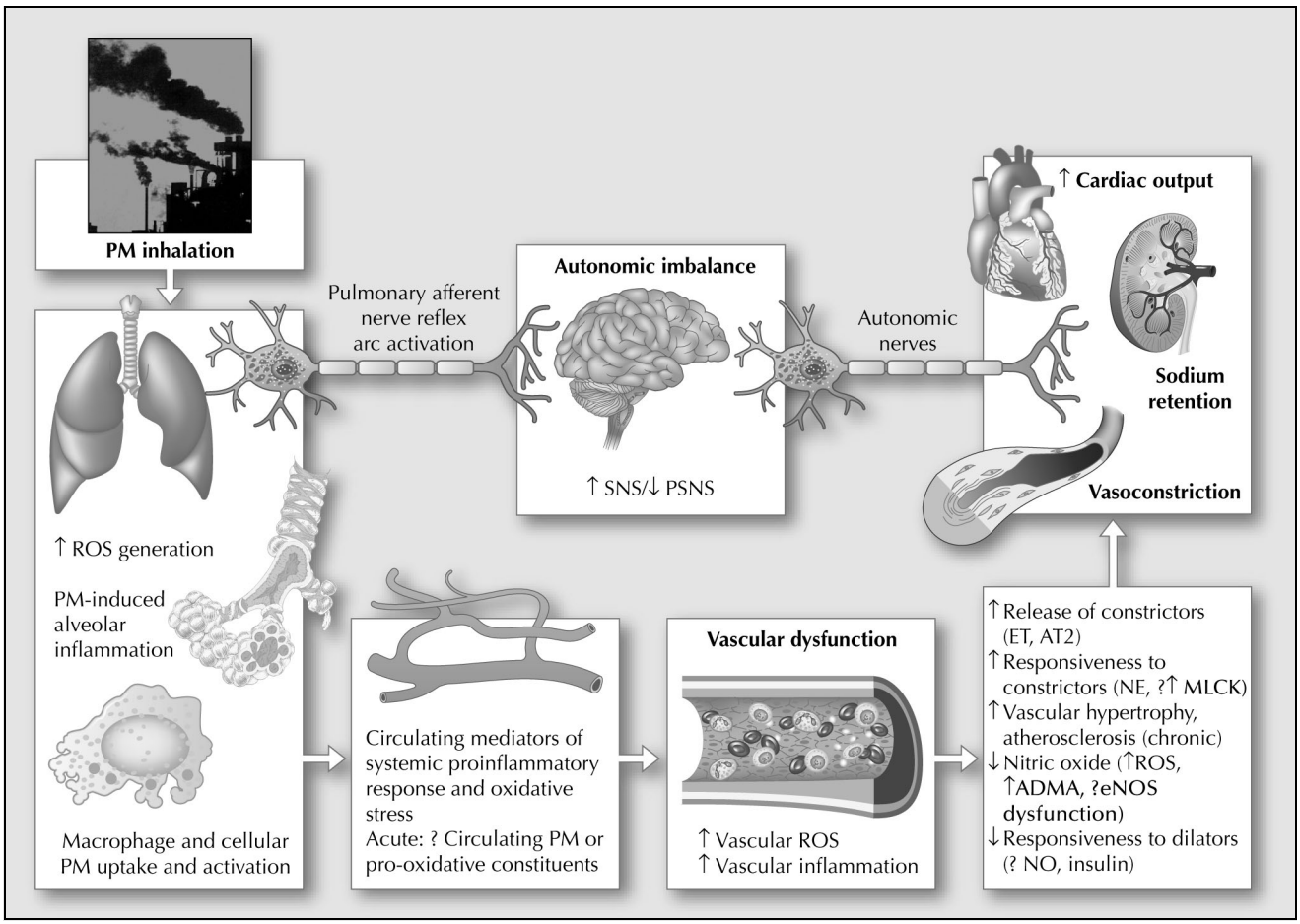

Figure 1. Mechanisms whereby air pollution exposure could trigger elevations in blood pressure. ADMA—asymmetric dimethyl arginine; AT2—angiotensin; eNOS—endothelial nitric oxide synthase; ET—endothelin; MLCK—myosin light-chain kinase; NE—norepinephrine; NO—nitric oxide; PM—particulate matter; PSNS—parasympathetic nervous system; ROS—reactive oxygen species; SNS—sympathetic nervous system.

constriction within minutes [39]. Therefore, it is plausible that PM inhalation could produce the same acute hemodynamic effects. Indeed, enhanced cardiac oxidative stress has been shown to occur within 2 hours after CAP exposure in animal models [45•]. The source of this rapid increase in free radical/reactive oxygen species generation within cardiovascular tissues distal to the pulmonary circulation remains uncertain. Vascular responses to increased circulating cellular activation and cytokine production would likely require a longer time course. An alternative and more rapid pathway may be via the direct effects of circulating ultrafine PM. Some evidence suggests that very small particles (< 0.1 μm) and certain soluble constituents, such as metals, are capable of rapidly entering the systemic circulation following their inhalation [1••,10,41]. Direct effects of PM constituents, such as organic carbon components (semiquinones and aldehydes) and transition metals, upon interactions with the vasculature, may acutely trigger the generation of oxidative stress and/or upregulate local oxidant-producing enzymes, such as NAD(P)H oxidases [46]. A full review on the mechanisms of PM-induced cardiovascular oxidative stress outlines these pathways in greater detail [47]. There is also evidence, for example, that acute autonomic changes may also play a role in the oxidative stress via receptor-mediated pathways [47]. Regardless of the mechanisms, the result of increased vascular tissue reactive oxygen species formation (oxidative stress) would be a very rapid impairment in nitric-oxide bioavailability, triggering vascular dysfunction and possibly vasoconstriction.

A reduction in stimulated nitric-oxide bioavailability promotes acute vasoconstriction by favoring the actions of vasoconstricting factors (enhanced vasoconstrictor responsiveness) and by effects of the resulting oxidative stress upon smooth muscles. In addition, however, increases in direct arterial vasoconstrictors have also been shown following PM exposure. CAP inhalation can rapidly increase circulating levels of endothelins [1••,10]. Urban PM, in particular the water-soluble metal components, has been shown to induce pulmonary artery vasoconstriction. Interestingly, losartan prevented this vasoconstriction in one study [48]. This suggests that activation of local vascular angiotensin receptors play a role in the acute vasoconstriction mediated by PM exposure. Finally, there is some evidence that PM-induced reactive oxygen species may enhance vascular tone by

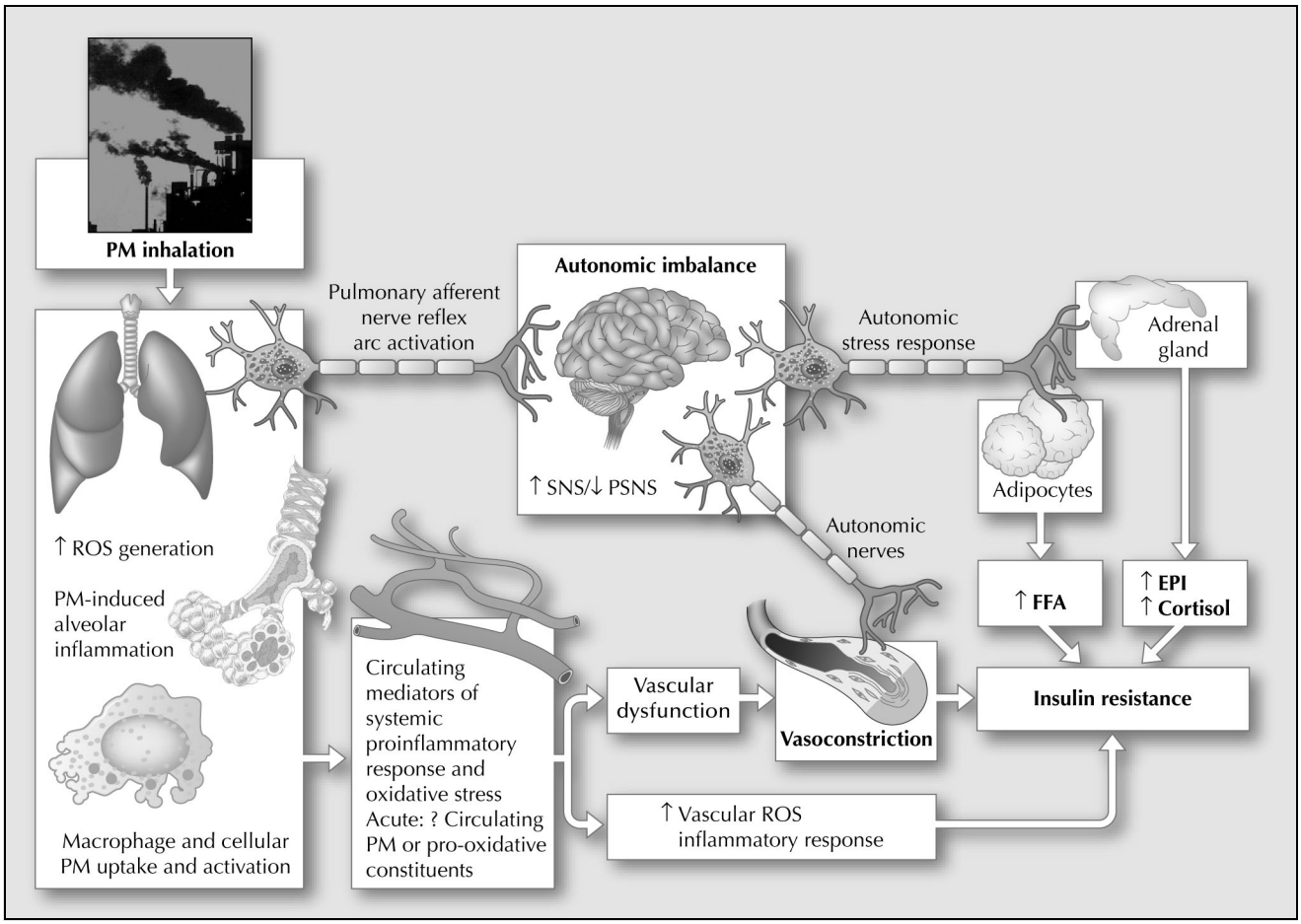

Figure 2. Mechanisms whereby air pollution exposure could contribute to the development of insulin resistance. EPI—epinephrine; FFA—free fatty acid; PM—particulate matter; PSNS—parasympathetic nervous system; ROS—reactive oxygen species; SNS—sympathetic nervous system.

sensitizing calcium-dependent myosin light-chain kinase activity in smooth muscles [49].

In summary, elevations in BP have been shown to occur both acutely (within 2 hours) and subacutely (1–5 days) after PM exposure. Blood vessels may constrict as rapidly as within 2 hours. Evidence supports that an acute enhancement of SNS tone following PM exposure could be capable of causing the rapid elevations in BP via vasoconstriction and increased cardiac output. In theory, this pathway could also promote chronic changes in arterial pressure. Only a more delayed reduction in nitric oxide–dependent vasomotion due to systemic oxidative stress/inflammation has thus far been shown to occur in human studies. However, increased activity of several direct vasoconstrictors (endothelins, free radicals, angiotensin) may additively promote vasoconstriction and hypertension in a more rapid fashion. The mechanisms responsible for the rapid increase in cardiovascular oxidative stress and the enhanced activities of several vasoconstrictors have yet to be fully elucidated. However, the direct effect on the vasculature of circulating PM components capable of triggering redox reactions is a leading explanation. In theory, this oxidative stress could also promote hypertension by altering the activity of soluble guanylate cyclase (reducing smooth muscle responsiveness to nitric oxide) and by activating rho kinase pathways (sensitizing calcium-mediated vasoconstriction).

Air Pollution: A Cause of the Metabolic Syndrome?

Air pollution may promote the development of insulin resistance. Systemic inflammation and oxidative stress, known responses to PM exposure [1••,10,41], play important pathophysiologic roles underlying impaired insulin signaling at the cellular level [50]. Pancreatic insulin secretion may also be dysfunctional. PM exposure could additively instigate insulin resistance by several other mechanisms. These include the consequences of enhanced SNS outflow: increased lipolysis/free fatty acids, elevated counter-regulatory hormones, and the direct tissue effects of β-receptor activation. Endothelial dysfunction and arteriolar vasoconstriction can also impair nutritive skeletal muscle tissue perfusion (Fig. 2). In support of the plausibility behind this hypothesis is the established relationship between passive tobacco smoke and insulin resistance [39]. In addition, a linkage between total state air release for all industries and the prevalence of diabetes

($r = 0.54$, $P = 0.000057$) in the United States has been reported [51•]. Due to the tremendous public health implications, the potential relationship between air pollution and the metabolic syndrome deserves investigation.

Implications of a Relationship Between PM and BP

In a thorough review of the literature, Lipfert *et al.* [22] concluded in 2003 "that associations between mortality and air quality are not mediated through blood pressure, nor vice versa." Indeed, a few well-done studies have not found a significant effect of air pollutants on BP [24]. However, many of the more compelling studies discussed in the previous sections were not yet available at the time of this review [27••,31••,32]. Based on these results, the sum of the evidence to date supports the notion that PM exposure can acutely raise BP in certain settings. The degree of response is likely determined by the underlying cardiovascular status of the individual plus the characteristics of the pollutants. In some scenarios, BP may increase by large amounts, whereas in others, there may be little effect.

Due to this variability and because physiologic responses may be transient and relatively small, it is vital that BP is measured extremely accurately and preferably in a continuous manner when investigating the hemodynamic effects of PM. For example, in our original report, no differences in pre- versus post-exposure BP values were found [28]. The measurements were performed only for safety during endothelial function testing. However, when less crude methods of BP responsiveness were used, a large previously unobserved hypertensive response was discovered [31••]. Poor measurement and/or undermeasurement of BP can thus lead to erroneous study findings. In particular, transient and rapid effects may go unnoticed. In previous studies and in the literature review, lack of meticulous BP measurements, inappropriate study designs (ie, underpowering, no a priori–described BP end points), and lack of continuous hemodynamic determination may have masked significant effects and therefore biased results to the null. The "real" strength of the association between PM and BP may therefore have been underestimated. Future studies may help clarify this issue.

To better characterize the hemodynamic effects of PM in humans, use of continuous noninvasive BP measurement and/or 24-hour ambulatory monitoring should be considered. The BP responses should also be qualified by the underlying health status of the study individuals and/or the animal models used. Some animals may respond with hypertensive reactions, whereas others may not. The particular PM components responsible for any BP change should also be better characterized. It is possible that exposure to the same concentration of total PM mass may result in large increases in BP in one situation, while having no effect in another due to variations in chemical constituents. Additionally, the putative mechanisms should be more thoroughly evaluated in both animal and human studies. With this in mind, the response of cardiovascular tissues to PM contact ex vivo may greatly differ from the integrated physiologic response following inhalation. For this reason, controlled exposure to CAP offers the best vehicle to investigate the relevant biology.

Conclusions

Small, but clinically relevant, elevations in BP have been demonstrated in response to particulate air pollution in certain settings. The extent to which this hypertensive response plays a role in mediating the acute increase in cardiovascular events and strokes due to PM exposure is not adequately characterized. Whether air pollution contributes to the development of chronic hypertension and interindividual differences in BP across cities (environmental locations) remains to be clarified. However, even a small impact of air pollution on BP has tremendous public health implications. Future investigations may help to better our understanding of this complex issue.

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