Review Paper

Why Physicians Who Treat Hypertension Should Know More About Air Pollution

Robert D. Brook, MD

Exposure to ambient levels of particulate matter (PM) air pollution increases the risk of a host of cardiovascular diseases and events. One potential mechanism explaining this association is that acute exposure to PM at high concentrations is capable of raising blood pressure within hours to days. Epidemiologic studies confirm that even commonly encountered levels of airborne pollutants can result in a prohypertensive response in humans. Several biologic pathways may be involved, including autonomic nervous system imbalance and arterial vascular dysfunction/vasoconstriction due to systemic oxidative stress/inflammation triggered by PM inhalation. The clinical importance of this vasopressor response and its relative role in promoting cardiovascular events associated with PM remain unclear. Because air pollution exposure is ubiquitous throughout the world, however, all health care providers and especially those who treat hypertension should be aware of this emerging and important biologic relationship. (J Clin Hypertens. 2007;9:629–635) ©2007 Le Jacq

From the Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI
Address for correspondence:
Robert D. Brook, MD, Division of Cardiovascular Medicine, University of Michigan, 24 Frank Lloyd Wright Drive, PO Box 322, Ann Arbor, MI 48106-0739
E-mail: robdbrok@umich.edu
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Almost everyone is probably familiar with the pervasive gray-brown "haze" blanketing many modern cities and industrial regions. Fewer people are aware that this haze is typically transported hundreds of miles, making some level of airborne pollution virtually ubiquitous even in nonurban settings and natural environments.[1] It has become so omnipresent in the past century as to be commonly perceived as a normal natural entity (eg, "the lazy, hazy days of summer"). We have learned to live in a soup of anthropogenic air pollutants without a second thought. Unfortunately, this haze is neither natural nor benign.[1–4] The catastrophic pollution episodes in London and Belgium during the first half of the 20th century first brought to light its potential harmful effects.[5,6] Subsequently, it was commonly believed that the more typically encountered pollution levels would be inconsequential to health.[1,2] But just as it took longer to recognize the risks posed by passive exposure to tobacco smoke over and above those posed by active smoking[7] (and even longer to do something about it), we have also learned that relatively low concentrations of air pollutants are harmful.[3,4] This brief review focuses on reasons for this to be of special interest to health care providers who treat hypertension.

AIR POLLUTION

Air pollution is a heterogeneous mixture of gases, liquids, and suspended particulate matter (PM).[1] PM itself is a complex amalgam of compounds varying in chemistry and ranging in size from several nanometers to 10 μm in diameter. Particulate components and gaseous co-pollutants (eg, ozone, nitrogen dioxide) vary regionally and by their source. In the industrialized world, however, the majority of "fine PM" pollutants smaller than 2.5 μm ($PM_{2.5}$) are derived from the combustion

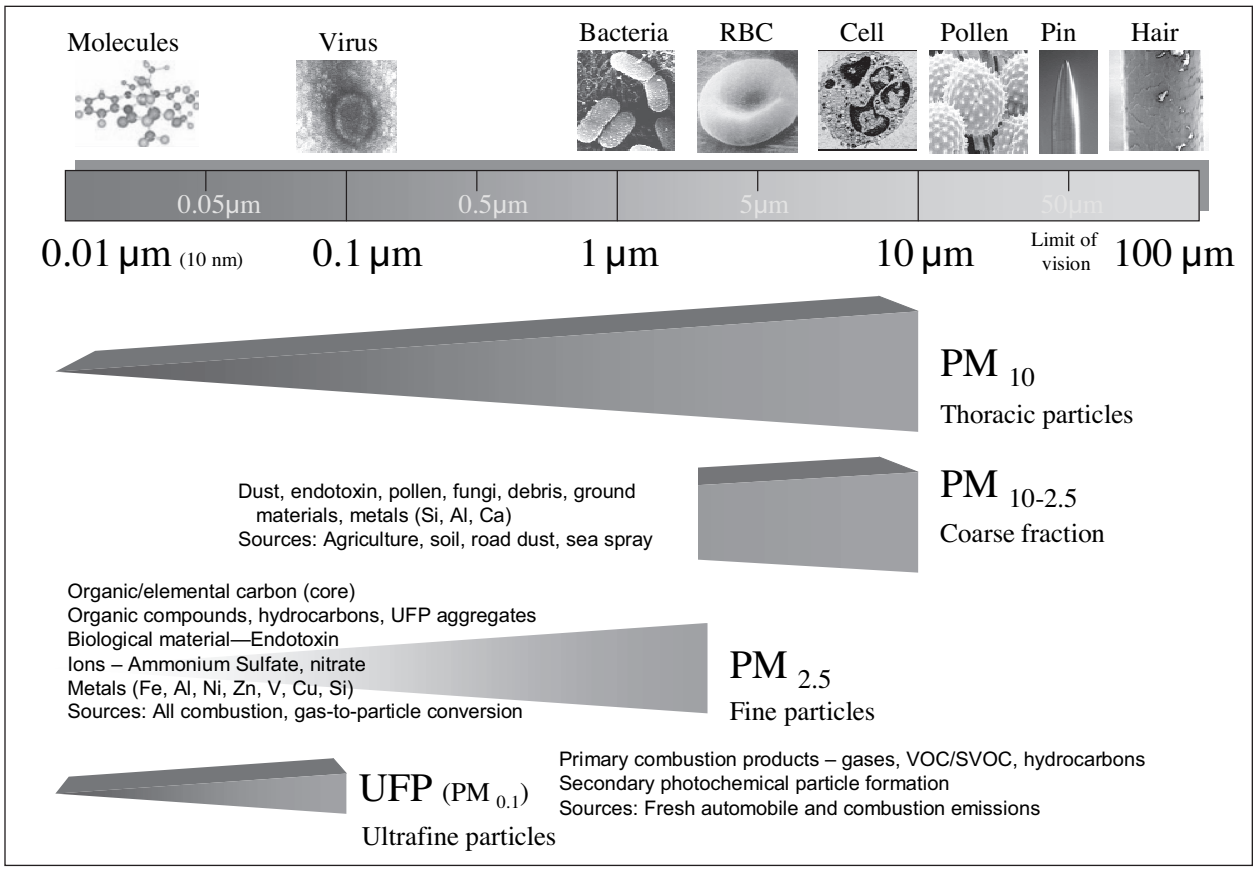

Figure 1. Sources and composition of particulate matter (PM) air pollution. Thoracic particles are all PM air pollutants of a size <10 µg/m³, which are capable of being inhaled deeper into the lungs past the nasopharynx (ie, into the thorax). Coarse fraction particles encompass all thoracic particles that are larger than fine PM (ie, 2.5 – 10 µg/m³ in diameter). Fine particles are all thoracic PM <2.5 µg/m³; while ultrafine PM are those <0.1 µg/m³ in diameter. RBC indicates red blood cell; UFP, ultrafine particles; VOC, volatile organic carbons; SVOC, semi-VOC.

of fossil fuels (Figure 1).[1,2] Most important from a health perspective, hundreds of constituents within $PM_{2.5}$ possess a strong innate pro-oxidative potential and are thus able to impact biological organisms.[1,4,8]

Although various fractions have been associated with human illnesses, it is $PM_{2.5}$ that is most strongly implicated as a possible cause of cardiovascular (CV) diseases.[3,4] Despite that levels have been reduced during the past 3 decades in the United States,[1] present-day concentrations of $PM_{2.5}$ still pose substantial health risks to the public.[3] Hundreds of epidemiologic studies throughout the world have demonstrated that current levels of ambient $PM_{2.5}$ are associated with an increased risk of CV events. Both short- and long-term exposure to fine particles are associated with an increased risk of myocardial infarction, cardiac ischemia, heart failure, stroke, arrhythmias, exacerbations of peripheral arterial disease, hospitalization for CV conditions, and CV death.[3,4] The acute risk to any single individual is relatively small. Because of the ubiquitous nature of constant involuntary exposure, however, outdoor air pollution has been conservatively estimated to cause approximately 800,000 deaths per year worldwide (13th leading cause of mortality).[9,10] Several recent reviews, including a statement from the American Heart Association,[4] have summarized these data and highlighted the plausible biologic mechanisms capable of explaining this association (Figure 2).

Similar to air pollution, hypertension is an extremely prevalent problem. It also happens to be the single leading chronic cause of global mortality.[10] Health care providers thus treat high blood pressure (BP) principally to reduce this risk of future CV events and death.[11] As such, they should also be aware of the health risks posed by PM because it is another commonly encountered CV risk factor.[11] Additional findings have come to light that give further reasons that hypertension experts in particular should care about air pollution.

AIR POLLUTION EXPOSURE AND BP

Animal and human exposure experiments, as well as epidemiologic studies, have demonstrated that

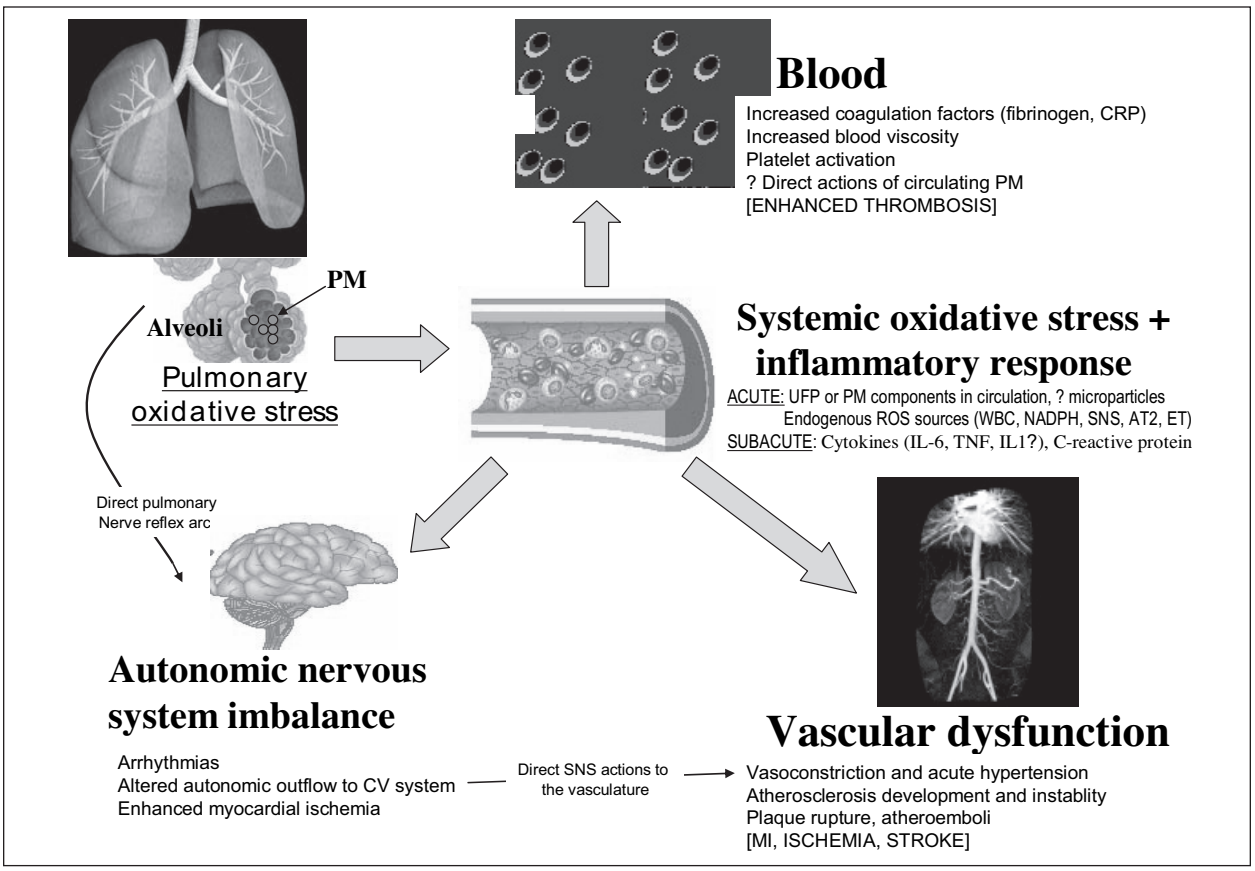

Figure 2. Mechanisms whereby particulate matter (PM) air pollution may cause cardiovascular events and hypertension. CRP indicates C-reactive protein; UFP, ultrafine particles; ROS, reactive oxygen species; WBC, white blood cells; NADPH, nicotinamide adenine dinucleotide phosphate (reduced) oxidase; SNS, sympathetic nervous system; AT2, angiotensin 2; ET, endothelins; IL, interleukin; TNF, tumor necrosis factor; CV cardiovascular; MI, myocardial infarction.

air pollutants are capable of raising BP.[12] The literature linking adverse changes in hemodynamics, endothelial function, arterial compliance, and autonomic activity with both active and passive tobacco smoke lends validity to the biologic plausibility of this association.[7] In a congruent fashion, other related atmospheric parameters such as high altitude, barometric pressure, and temperature are also known to impact BP.[13] Thus, a link between PM exposure and BP changes is viable.[14–25] This review will focus on the most pertinent previously discussed results[12] (Table) along with newly available data.

Our randomized controlled experiments have shown that short-term exposure to high, yet relevant, levels of concentrated ambient urban particles (150 μg/m^3) significantly raise diastolic BP by 6 mm Hg (median increase) within minutes[14] in healthy individuals without a history of hypertension. Follow-up analyses have demonstrated that the vasopressor response was related to the degree of organic carbon exposure (r=0.53; P=.009), which suggests that combustion sources (eg, automobiles) were responsible. Moreover, our ongoing studies continue to indicate a similar magnitude of acute prohypertensive responses within minutes to hours of controlled PM exposure (Bruce Urch, Gage Occupational and Environmental Health Unit, Toronto, Canada, oral communication, March 2007). At present, it is not known whether persons with preexisting hypertension, smokers, or those with underlying CV conditions respond differently (eg, with exaggerated BP increases).

A few epidemiologic studies have demonstrated that the commonly encountered lower levels of ambient $PM_{2.5}$ are also independently capable of elevating BP (Table). In Boston, cardiac rehabilitation patients were found to have an increase in both systolic (2.8 mm Hg) and diastolic (2.7 mm Hg) BP, which correlated with the mean concentration of $PM_{2.5}$ over the previous 5 days.[19] What was most striking is that this increase in BP occurred in response to very small changes in ambient air pollution (Δ10.5 μg/m^3). Similar prohypertensive responses have been noted in Detroit among free-living individuals. Comparably low levels of ambient

Table. Recent Studies Linking Particulate Matter (PM) Air Pollution With Blood Pressure (BP) Changes	
Human Exposure Studies	
Urch et al[14]	Significant (*P*=.017) median diastolic BP increase of 6 mm Hg within 2 hours during exposure to concentrated ambient fine PM from urban Toronto air plus ozone vs the impact of filtered air (crossover study) in 23 healthy adults. No significant change seen for systolic BP.
Mills et al[15]	Borderline nonsignificant increases of 8 mm Hg (*P*=.13) for systolic and 6 mm Hg (*P*=.08) for diastolic BP in 15 subjects after exposure to diesel exhaust fumes for 1 hour compared with filtered air (crossover study).
Gong et al[16]	Systolic BP increased in 12 healthy participants exposed to concentrated ambient fine PM from urban Los Angeles for 2 hours vs filtered air (crossover study). No effect in asthmatic patients.
Epidemiologic Studies	
Linn et al[17]	In 30 participants with lung disease, 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.
Ibald-Mulli et al[18]	In 2607 adults in Germany during an extreme air pollution episode of 1985, systolic BP was elevated by 1.79-mm Hg per 90 $\mu g/m^3$ increase in total air particles. Systolic BP increased by ≈7 mm Hg in subgroups with elevated heart rates and plasma viscosity. Follow-up studies in 131 adults in a multicenter approach in Europe were not able to confirm BP elevations in relation to 24-hour mean PM levels.[21]
Zanobetti et al[19]	In 62 cardiac rehabilitation patients in Boston, BP was increased by 2.8/2.7-mm Hg per 10 $\mu g/m^3$ increase in $PM_{2.5}$ during previous 5 days.
de Paula Santos et al[20]	In 48 healthy adults, interquartile ranges of ambient carbon monoxide and sulfur dioxide were significantly related to ambulatory BP increases of ≈2.5 mm Hg in São Paulo, Brazil. PM_{10} did not relate to BP.
Madsen and Nafstad[34]	In 18,770 Oslo citizens, there was no convincing association between BP and air pollution. In a subgroup of patients with prior heart disease and systolic BP >140 mm Hg, air pollution was associated with a higher BP.
Harrabi et al[35]	In 2612 elderly participants older than 65 years in France, PM_{10} was paradoxically associated with a small reduction in systolic BP.
Animal Exposure Studies	
Wichers et al[22]	Direct bronchial instillation of the largest doses of PM in spontaneously hypertensive rats reduced cardiac output and BP. Limited study relevance to humans because of unrealistic dosing of PM.
Cheng et al[23]	Several days of intermittent exposure to concentrated ambient PM caused small BP reductions (mean arterial pressure decreased 3.3–4.1 mm Hg) in pulmonary hypertensive rats.
Chang et al[24]	Repeated exposure to concentrated ambient $PM_{2.5}$ caused significant BP elevations of 8.7 mm Hg in the spring months. Summer month exposures yielded smaller effects.
Vincent et al[25]	Urban PM exposure caused a significant increase in BP that disappeared with washed PM, indicating that water-soluble (eg, metals) components of PM are responsible.

urban $PM_{2.5}$ raised BP by as much as 5.2 mm Hg systolic (J. Timothy Dvonch, School of Public Health, University of Michigan, oral communication, April 2007). As the BP increase was linearly related to the PM level, it is possible that on days with even higher PM elevations known to occur in Detroit and other urban cities (eg, >65 $\mu g/m^3$), more marked vasopressor responses could occur. Of interest, air pollution raised BP only in certain city regions, which suggests that the chemical composition and constituents played a large role in determining the hemodynamic impact of exposure.

Several controlled experimental animal studies have also implicated PM exposure in BP elevation, although results have not been entirely consistent (Table). Recent studies show that high levels of $PM_{2.5}$ can trigger a significant linear prohypertensive response (+3.9/4.2 mm Hg) over 2 hours in dogs.[26] Interestingly, α-adrenergic blockade mitigated the BP elevation. During hours 2 to 5 of exposure, the BP elevation reached a plateau, while baroreceptor sensitivity was also shown to increase. The results suggest that the mechanism for BP increase may be principally related to peripheral vascular sympathetic stimulation, which is rapidly blunted by compensatory autonomic responses. In addition, it was recently shown that the vasopressor response to angiotensin II was significantly increased (Δ mean arterial pressure elevation of 57 vs 20 mm Hg) in Sprague-Dawley rats exposed to concentrated ambient $PM_{2.5}$ compared with filtered air.[27] Vascular nicotinamide adenine dinucleotide phosphate (reduced) oxidase and Rho-kinase–dependent pathways were found to be involved in the pathogenesis of the BP increase. These results suggest that individuals

with preexisting activation of the renin-angiotensin system (eg, some forms of primary and secondary hypertension) may be predisposed to a greater vasopressor response following PM exposure.

The overall evidence suggests that particulate air pollution is capable of meaningfully raising BP (≈2–10 mm Hg) in a dose-response fashion within hours to days in certain scenarios.[12] Yet not all results have been positive.[12,14] Unfortunately, only a few studies have specifically investigated the hemodynamic impact of PM exposure. Differences and null findings among the available studies are likely explained by differences in the multitude of variables that determine the responses. These include patient characteristics, animal models, differential susceptibilities, BP measurement methods and accuracy, small BP changes and underpowered studies, missed transient effects, time courses of PM exposures and BP evaluations, variability in compensatory hemodynamic reactions, PM concentrations and composition, gaseous co-pollutants, PM sources, exposure mischaracterizations, and exposure models. Further studies are warranted to help better our understanding of this complex relationship. In particular, knowledge of the "responsible" pollution constituents/sources and identification of "at-risk" individuals are important. Perhaps even more important, the potential for long-term pollution exposure to promote the occurrence of chronic hypertension has yet to be reported. If such a positive biologic relationship occurs, it would have enormous public health implications.

POTENTIAL BIOLOGIC MECHANISMS

Several biologic mechanisms have been described whereby air pollution inhalation could trigger an elevation in BP (Figure 2).[12] In brief, deposition of $PM_{2.5}$ constituents deep within the pulmonary tree causes local tissue oxidative stress. The generation of oxidative species may be derived from chemicals within the particles (metals, semiquinones, organic carbon species) or from a subsequent cellular inflammatory response (activated macrophages, pulmonary cells). Variability in the PM composition, gaseous co-pollutants, and susceptibility (antioxidant defenses/enzymes) undoubtedly affect the degree of this response.[1–4]

The local pulmonary reaction is capable of affecting remote vascular sites, leading to a vasopressor response by 3 general pathways.[3,4,12] First, the particles may directly, or via the pulmonary oxidative stress/inflammation, stimulate a host of lung autonomic receptors. These airway receptors are capable of prompting rapid CV responses via neurally mediated reflexes. Activation of these pathways principally leads to systemic vagal withdrawal, along with relative sympathetic hyperactivity. Indeed, experiments have consistently shown reduced overall heart rate variability and, occasionally, altered power spectral analyses, suggesting the triggering of cardiac autonomic imbalance favoring sympathetic tone following PM exposure.[3,4] These autonomic responses could promote hypertension by a variety of means, including acute peripheral arterial vasoconstriction via α-adrenergic receptors,[26] increased cardiac heart rate/output, and in theory by chronically activating the renin-angiotensin system and blunting renal pressure natriuresis. In addition, it has been experimentally shown that this autonomic imbalance can also cause oxidative stress within the CV system by neurogenic sympathetic and parasympathetic receptor activation.[28,29] This could subsequently lead to vascular dysfunction and arterial vasoconstriction.[30]

Second, numerous studies show that the oxidative and inflammatory responses to PM are not isolated to the lungs.[3,4,28,29] Systemic and cardiac oxidative stress, along with higher levels of circulating and vascular pro-inflammatory cells and cytokines, has been shown after PM inhalation.[3,4] These factors are capable of instigating vascular endothelial dysfunction (eg, impaired nitric oxide bioavailability) that could favor vasoconstriction.[30] Indeed, endothelial dysfunction has been demonstrated in animals and humans exposed to air pollution both acutely and chronically.[3,4,12,15,31,32] Moreover, the free radicals (eg, superoxide) could directly or indirectly trigger arterial vasoconstriction via the release of multiple vasoactive molecules (endothelins, angiotensin II, asymmetric dimethylarginine) shown to increase following PM inhalation.[12] Several human and animal studies have demonstrated systemic arterial vasoconstriction, impaired smooth muscle vasodilatory responses, and enhanced vasoconstrictor responsiveness after PM inhalation.[3,4,12,15,31,32]

Finally, many nanometer-sized particles or soluble PM constituents could potentially be translocated into the systemic circulation and reach vascular beds following inhalation.[3,4] This, however, is a controversial subject. The types of PM constituents capable of reaching the circulation (eg, size, chemistry, solubility), their levels in the blood and deposition in organs (eg, meaningful concentrations?), modes of transportation (eg, in plasma vs associated with lipoproteins or cells), and the remaining magnitude of oxidative activity reaching distal vascular sites all remain unknown.

Nevertheless, it is possible that CV tissue oxidative stress could be generated by PM constituents reaching vascular sites.

In theory, the relative importance of the biologic pathways in the etiology of the BP increase may vary with the time duration following exposure. Autonomic imbalance and direct actions of blood-borne particle constituents may be principally responsible for BP changes within minutes, followed by the effects of systemic inflammation hours to days later. Further research will be required to better understand these issues and the overall mechanistic pathways involved.

CLINICAL IMPLICATIONS AND CONCLUSIONS

Although PM exposure can raise BP, the clinical impact of the relatively minor elevations remains unclear. The resultant overall health effect will likely vary depending on the susceptibility of the individual. In addition, the relative contribution that this vasopressor response plays in explaining the multitude of observed adverse CV outcomes caused by PM exposure is not known.[3,4] Nevertheless, similar prohypertensive responses are often hypothetically invoked as potential mediators of the increased risk following several triggering events (eg, sexual activity, mental stress, exercise, use of decongestant medications).[33] It is possible that the BP increase per se and the accompanied increase in myocardial demand, in conjunction with the underlying mechanisms responsible for prompting them (autonomic imbalance, endothelial dysfunction, arterial vasoconstriction) might trigger plaque rupture and/or promote tissue ischemia. This might be observed as clinically overt events such as myocardial ischemia or stroke hours to days later. The hemodynamic changes and ischemia may also play some partial role in promoting the observed increase in heart failure and arrhythmias. Finally, it is plausible that intermittent long-term air pollution exposure could continue to promote BP increases or cause underlying autonomic and vascular changes known to be causal in the etiology of primary hypertension. Thus, sustained exposure to higher levels of PM may contribute to the genesis of chronic hypertension.

In summary, the available evidence suggests that PM air pollution exposure is capable of raising BP over hours to days by a clinically meaningful magnitude in some situations. Nevertheless, many issues remain to be fully elucidated. Foremost is to determine whether long-term exposure actually promotes chronic hypertension and whether reductions in air pollution lead to decreases in BP. In other words, is air pollution a "modifiable" environmental risk factor for hypertension? Future research can help further our understanding of this important public health issue.

Addendum: A recent study demonstrated in Guatemalan women that chronic exposure to fine particulate wood smoke pollution was independently linked to higher blood pressures and that lowering exposure levels was associated with a significant reduction in blood pressure of 3.7/3.0 mm Hg.[36]

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