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Cardiovascular Effects of Ambient Particulate Air Pollution Exposure

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An association between high levels of air pollutants and human disease has been known for more than half a century. Air pollution is composed of a heterogeneous mixture of compounds including ozone (O_3), carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen oxides (NO_x), liquids, and particulate matter (PM). Substantial epidemiological evidence implicates air pollution, particularly PM, as a major risk factor with serious consequences on human health.[1–3] Of particular interest in PM are the particles that are ≤ 10 μm in diameter (PM_{10}) because they are the PM that ultimately enters the lungs.[4] PM is further divided into coarse (10 to 2.5 μm; $PM_{10-2.5}$), fine (<2.5 μm; $PM_{2.5}$), and ultrafine (<0.1 μm; $PM_{0.1}$) particles.[1] These particles are composed of solid and liquid components that originate from vehicle exhaust, road dust, smokestacks, forest fires, windblown soil, volcanic emissions, and sea spray. Particle size, surface area, and chemical composition determine the health risk posed by PM. Particulate and gaseous pollutants coexist in the air and may induce adverse health effects, whereas compelling data implicate PM as a major perpetrator of various types of human disease. PM rarely exists by itself within the ambient environment because gaseous and semivolatile/volatile compounds (ie, aldehydes and polycyclic aromatic hydrocarbons) are constantly changing and interacting. Many of these vapor-phase compounds attach to the surface of PM and/or by themselves form secondary aerosol particles.

Because of their small size, $PM_{2.5}$ and $PM_{0.1}$ are inhaled deeply into the lungs, with a portion depositing in the alveoli and entering the pulmonary circulation and presumably the systemic circulation. The adverse effects of PM on the cardiovascular system have been established in a series of major epidemiological and observational studies.[5–9] Although life expectancy has been improved significantly since air pollution levels have been reduced,[10–13] the mechanisms of the effects of air pollution on cardiovascular disease remain unclear. In this review, the primary effects of PM on the cardiovascular system are summarized, along with potential mechanisms involved in disease progression. In addition, PM-exaggerated cardiovascular-associated disorders such as obesity and metabolic syndrome are also described in relation to progression after PM exposure.

Cardiac Events and Hospital Admission

Cardiac function requires an appropriate interplay among 3 key components: balanced tone of the autonomic nervous system, adequate myocardial function as the motor unit, and rhythmic initiation and conduction of electric impulses to maintain the sequence and latency of atrial and ventricular activation and repolarization.[14] PM exposure can result in significant changes in many cardiovascular indexes such as heart rate, heart rate variability, blood pressure, and blood coagulability.

Epidemiological studies have shown an association between air pollution and adverse health effects since the 1930s.[15] In the 1970s, broad investigations were conducted on human health, in particular pulmonary and cardiovascular diseases.[16–18] Since the 1990s, studies of air pollution and cardiovascular diseases have intensified, especially relative to cardiovascular mortality and hospital admission for sudden cardiac events.[19–23] Specifically, Burnett et al[19] examined the effect of ambient air pollution on cardiac disease exaggeration by relating daily fluctuations in admissions to 134 hospitals for congestive heart failure in the elderly to daily variations in ambient concentrations of CO, NO_2, SO_2, O_3, and the coefficient of haze in the 10 largest cities in Canada for the 11-year period of 1981 to 1991. They found that the daily high-hour ambient CO concentration recorded on the day of admission displayed the strongest and most consistent association with hospitalization rates among the pollutants. The same group studied the ambient air pollution mix on cardiorespiratory disease exacerbation in the summers of 1992 through 1994 and found that the increase in O_3, NO_2, and SO_2 corresponded to an 11% and 13% increase in daily hospitalizations for respiratory and cardiac diseases, respectively. The inclusion of any one of the particulate air pollutants in multiple regression models did not increase these percentages.[20]

In an examination of effect size estimates across large differences in both the levels of potential confounding factors and their correlation with airborne particle concentration, particle concentration was found to be a significant risk factor for elevated mortality, and the relative risk was for a 100-mg/m^3 increase in total suspended particulate (TSP)

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concentration.[21] To separate the effects of different air pollutants, daily counts of admissions to all hospitals in Tucson, Ariz, for cardiovascular disease in persons age ≥65 years were analyzed and indicated that both PM_{10} and CO were associated with increased risk of cardiovascular hospital admissions, with admissions increased by 2.75% for an interquartile range increase (23 mg/m^3) in PM_{10} and by 2.79% for an interquartile range increase (1.66 ppm) in CO.[23] It is increasingly recognized that exposure to ambient PM contributes to significant adverse health effects and is a risk factor for the development of ischemic cardiovascular events via exacerbation of atherosclerosis, coronary artery disease, and the triggering of myocardial infarction, even within hours after exposure.[24] Studies have demonstrated a significant elevation in the incidence of life-threatening myocardial infarctions[25] and cardiac arrhythmias[26] in the immediate periods (hours to days) after exposure to high levels of atmospheric $PM_{2.5}$.

PM pollution is also linked to an increased risk for hospital admission for cardiovascular and respiratory diseases,[27] increased risk of myocardial infarction among the elderly,[28] triggering of acute cardiac decompensation in heart failure patients,[29] and an increase in the rate of hospital admissions for exacerbation of congestive heart failure.[30] Recently, variations in the relative risk of hospitalization associated with ambient exposure to $PM_{2.5}$ total mass and chemical composition were investigated in the United States from 1999 through 2005. This study found a positive, statistically significant association between county-specific estimates of the short-term effects of $PM_{2.5}$ on cardiovascular and respiratory hospitalizations and county-specific levels of vanadium, elemental carbon, or nickel $PM_{2.5}$ content, especially in the northeast region.[31,32] There is a body of literature, from as early as the 1970s,[33] indicating a correlation between air pollution and hospital admission for an acute event. Table 1 depicts selected investigations of air pollution and hospital admissions, particularly resulting from sudden cardiac events.

Changes in Heart Rate and Cardiac Function

In an attempt to investigate associations between ambient PM and cardiovascular function in a repeated-measures study in Boston residents, exposure to $PM_{2.5}$ with an average concentration of 15.5 μg/m^3 was associated with decreased vagal tone, resulting in reduced heart rate variability.[56] In another study that evaluated changes in mean heart rate and heart rate variability in humans, there was an association between exposure to PM_{10} on a previous day of 100 μg/m^3 and significantly increased heart rate by 5 to 10 bpm, suggesting that changes in cardiac autonomic function, reflected by changes in mean heart rate and heart rate variability, may be part of the pathophysiological mechanism linking cardiovascular mortality and PM.[57] In the Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study,[58] elevations in PM predicted risk for exercise-induced ST-segment depression in subjects with coronary artery disease. Another study in 3827 participants who underwent cardiac magnetic resonance imaging between 2000 and 2002 found that participants living within 50 miles of a major roadway had a higher cardiac function–left ventricular mass index associated with $PM_{2.5}$ elevation, indicating chronic vascular end-organ damage from traffic-related environmental exposure.[59] Several other studies have demonstrated a link between changes in heart rate and PM levels in mice[60] and elderly humans.[61] The possible mechanisms involved in these events include disturbances in cardiac autonomic control,[62] reduction in cardiac vagal control,[63] decreases in parasympathetic tone,[64] and an imbalance in cardiac autonomic control.[65]

Thrombosis and Other Changes in Hemostasis

PM has been associated with transient increases in plasma viscosity, acute-phase reactants, and endothelial dysfunction, as well as altered autonomic control of the heart. The effect of intravenous or intratracheal administration of ultrafine polystyrene particles, diesel exhaust particles, or $PM_{2.5}$ on thrombus formation was investigated, indicating the effects of circulating particles on changes in hemostasis.[66–71] In 3256 randomly selected men and women 25 to 64 years of age, high concentrations of SO_2, CO, and TSP were associated with increased plasma viscosity.[72] The Holland group studied ≈330 deaths during 1986 to 1994 and found that embolisms and thrombotic changes were increased after exposure to CO, O_3, and SO_2.[73] In a double-blind randomized crossover study, 20 healthy volunteers were exposed to dilute diesel exhaust and filtered air in the United Kingdom and Sweden; postexposure thrombus formation, coagulation, platelet activation, and inflammatory markers were measured. These investigators found that diesel exhaust inhalation increased thrombus formation and platelet-neutrophil and platelet-monocyte aggregates.[74]

Other epidemiological data link PM exposure to an augmentation of systemic inflammation as measured by C-reactive protein,[26] an acute-phase protein associated with adverse outcomes in patients with unstable ischemic syndromes. In this prospective cohort survey in 1984 to 1985 with a 3-year follow-up of 631 randomly selected men 45 to 64 years of age who were free of cardiovascular disease at entry, the odds of observing C-reactive protein concentrations >5.7 mg/L (>90th percentile) tripled at normal ambient PM concentrations, and increases of 26 μg/m^3 total suspended particles (mean of 5 days) raised the odds of having a C-reactive protein level 50% greater than the 90th percentile.[26] Increased levels of fibrinogen, platelets, and white blood cell counts were also associated with exposure to TSP.[75,76]

The regulation of fibrinolysis is another important aspect of endothelial function. Small areas of endothelial denudation and thrombus deposition are a common finding on the surface of atheromas and are usually subclinical. Therefore, endogenous fibrinolysis of the lesion might prevent thrombus propagation and vessel occlusion.[77] Nevertheless, under adverse proinflammatory states or imbalances in the fibrinolytic system, microthrombi may propagate and ultimately lead to arterial occlusion and tissue infarction.[78] In a series of double-blind, randomized crossover studies, both healthy men and patients with stable coronary artery disease were exposed to dilute diesel exhaust (PM, 300 μg/m^3) for 1 hour while performing intermittent exercise[79–81] and were then

Table 1. The Effect of Air Pollution on Acute Hospital Admission

Authors	Key Findings	Diseases	Pollutants	Subjects	Year	Location	Reference
Burnett et al	Exposure associated with 11% and 13% increased daily hospitalizations for respiratory and cardiac diseases, respectively	Respiratory and cardiac diseases	PM_{10}, O_3, NO_2, SO_2, CO	Not specific	1992–1994	Ontario, Canada	20
Dominici et al	Short-term exposure to $PM_{2.5}$ associated with increased hospital admission for cardiovascular and respiratory diseases	Cardiovascular and respiratory disease	$PM_{2.5}$	>65 y of age	1999–2002	204 US counties	27
Wellenius et al	Exposure associated with increased hospital admission for CHF	CHF	PM_{10}	≥65 y of age	1986–1999	7 US cities	30
Bell et al	Strong relationship between $PM_{2.5}$ and hospitalization for respiratory and cardiovascular diseases, especially in the Northeast region, with a 1.49% increase in hospitalizations of cardiovascular diseases per 10-$\mu g/m^3$ increase in same-day $PM_{2.5}$	Respiratory and cardiovascular diseases	$PM_{2.5}$	≥65 y of age	1999–2005	202 US counties	31
Bell et al	Higher $PM_{2.5}$ content of nickel, vanadium, and elemental carbon associated with higher risk of cardiovascular and respiratory hospitalizations	Cardiovascular and respiratory diseases	$PM_{2.5}$ and chemical composition	≥65 y of age	1999–2005	106 US counties	32
Morgan et al	Exposure associated with increased hospitalization for respiratory and heart disease, with increase in daily maximum 1-h particulate concentration associated with an increase of 3.01% in COPD and 2.82% in heart disease admissions	Respiratory and heart disease	$PM_{2.5}$, O_3, NO_2, PM_{10}	All ages	1990–1994	Sydney, Australia	34
Schwartz et al	Exposure associated with hospital admissions for heart disease, with daily variation in PM_{10} associated with 2.48% increase and daily variation in CO associated with 2.79% increase	Heart disease	PM_{10}, CO	≥65 y of age	1988–1990	8 US counties	35
Prescott et al	Exposure associated with emergency hospital admission for cardiac and respiratory disease, positive association with PM_{10}, and negative association with O_3	Cardiac and respiratory disease	PM_{10}, CO, NO_2, O_3	All ages	1981–1995	UK	36
Linn et al	Exposure associated with increased hospitalization for cardiopulmonary illness, with a 25th to 75th percentile increase in CO predicting an increase of 4% in cardiovascular admission; NO_2 and PM_{10} but not O_3 showed similar increases in cardiovascular disease	Cardiopulmonary disease	PM_{10}, CO, NO_2, O_3	Adults	1992–1995	Los Angeles, US	37
Janssen et al	PM_{10} associated with hospital admissions, especially for cardiovascular disease, in 14 cities in summer and winter	Cardiovascular disease	PM_{10}	Not specific	1993	14 US cities	38
Wong et al	Air pollution similarly associated with daily cardiorespiratory admissions in both cities, with significant positive association observed with PM_{10}, NO_2, SO_2, and O_3 in both cities	Cardiorespiratory disease	PM_{10}, O_3, SO_2, NO_2	All ages	1992–1997	Hong Kong, London	39
McGowan et al	PM_{10} exposure associated with cardiorespiratory admission, with 3.37% increase in respiratory admissions and 1.26% rise in cardiac admissions for each interquartile rise in PM_{10}	Cardiorespiratory disease	PM_{10}, CO, SO_2, NO_x	All ages	1988–1998	New Zealand	40
Mann et al	Exposure associated with hospital admission for myocardial infarction, with a 1-ppm increase in CO associated with a 3.60% increase in same-day IHD admissions with a secondary diagnosis of CHF, a 2.99% increase in persons with a secondary diagnosis of ARR, and a 1.62% increase in IHD admissions in persons without either secondary diagnosis	Myocardial infarction	PM_{10}, NO_2, CO	≥40 y of age	1988–1995	California	41
Koken et al	Exposure associated with increased hospitalization for cardiovascular disease, with O_3 associated with an increase in the risk of hospitalization for acute myocardial infarction, coronary atherosclerosis, and pulmonary heart disease; SO_2 for cardiac dysrhythmias; and CO for congestive heart failure	Cardiovascular disease	PM_{10}, CO, SO_2, O_3, NO_2	>65 y of age	1993–1997	Colorado	42
Fung et al	Exposure to SO_2 associated with daily cardiac hospital admission, with a percentage increase in daily admission of 2.6% for current-day SO_2, 4.0% for 2-d mean level, and 5.6% for 3-d mean level for an increase in interquartile range of 19.3 ppb; the contributing effect of SO_2 remained significant for all 3 levels when PM_{10} was included	Cardiac disease	SO_2, PM_{10}	≥65 y of age	1995–2000	Ontario, Canada	43

(*Continued*)

Table 1. Continued

Authors	Key Findings	Diseases	Pollutants	Subjects	Year	Location	Reference
Chang et al	Exposure, especially to PM_{10}, associated with increased hospital admissions for cardiovascular disease	Cardiovascular disease	PM_{10}, O_3, NO_2, CO	Not specific	1997–2001	Taiwan	44
Hosseinpoor et al	CO exposure associated with increased hospitalization for angina pectoris, with each unit increase in CO causing a 1.00 increase in the number of admissions	Angina pectoris	NO_2, CO, O_3, SO_2, PM_{10}	Not specific	1996–2001	Iran	45
Maheswaran et al	Exposure associated with coronary heart disease mortality and hospital admission, with admission rate ratios of 1.00, 1.01, and 0.88 for the lowest NO_x, PM_{10}, and CO quintiles, respectively	Coronary heart disease	NO_x, PM_{10}, CO	≥45 y of age	1994–1998	UK	46
Wellenius et al	Exposure associated with transiently increased ischemia but not hemorrhagic stroke, with an interquartile range increase in PM_{10} associated with a 1.03% increase in admissions for ischemic stroke on the same day	Cardiac ischemia	PM_{10}	≥65 y of age	1990	9 US cities	47
Low et al	Exposure associated with stroke hospital admission, with statistically significant, independent exacerbating effects of SO_2 and PM_{10}	Stroke	O_3, NO_2, SO_2, CO, PM_{10}	Adults	1995–2005	New York, NY	48
Barnett et al	Exposure associated with adult cardiovascular hospital admissions, with all pollutants except O_3 significantly associated with 5 categories of cardiovascular disease admissions in the elderly	Cardiovascular disease	NO_2, CO, $PM_{2.5}$, PM_{10}, O_3	All ages	1998–2001	Australia, New Zealand	49
Johnston et al	PM_{10} exposure positively associated with respiratory disease and ischemic heart disease admissions, especially in indigenous people	Respiratory disease	PM_{10}	All ages	2000–2005	Australia	50
Migliaretti et al	Significant association between the increase in emergency hospital admission for respiratory causes and exposure, with a mean increase in emergency hospital attendance of 2.20% and 2.55% per 10-$\mu g/m^3$ increase in exposure to SO_2 and TSP, respectively, and a mean increase of 5.30% per 1-mg/m^3 increase in exposure to CO	Respiratory disease	SO_2, CO, TSP	Adults	1997–1999	Italy	51
Peng et al	Significant associations between $PM_{10-2.5}$ and hospital admissions for cardiovascular and respiratory diseases, with a 10-$\mu g/m^3$ increase in $PM_{10-2.5}$ associated with a 0.36% increase in cardiovascular disease admissions on the same day	Cardiovascular and respiratory diseases	$PM_{2.5}$, PM_{10}, $PM_{10-2.5}$	>65 y of age	1999–2005	US	52
Yang et al	CHF admission associated with air pollutants on warm days in the single-pollutant model of PM_{10}, NO_2, CO, or O_3	CHF	PM_{10}, NO_2, CO, O_3	Adults	1996–2004	Taiwan	53
Middleton et al	Increased risk of hospitalization with PM_{10} and O_3, with every 10 $\mu g/m^3$ increase in daily average PM_{10} associated with a 0.9% increase in all-cause and 1.2% increase in cardiovascular admissions	All-cause, especially cardiovascular disease	PM_{10}, O_3	All ages	1999–2004	Cyprus	54
Lin et al	Positive association between respiratory hospital admissions and ambient O_3 level 2 d before admission in 5 of the 11 regions	Respiratory disease	O_3	0–17 y of age	1999–2001	New York	55

CHF indicates chronic heart failure; BC, black carbon; OC, organic carbon; IHD, ischemic heart disease; and ARR, arrhythmia.

challenged by intrabrachial bradykinin, acetylcholine, sodium nitroprusside, and verapamil. Although there was a dose-dependent increase in blood flow with each vasodilator, this response was attenuated with bradykinin, acetylcholine, and sodium nitroprusside infusions 2 hours after exposure to diesel exhaust, which persisted at 6 hours. Bradykinin caused a dose-dependent increase in plasma tissue plasminogen activator that was suppressed 6 hours after exposure to diesel.[79] In a double-blind, randomized crossover study, 20 men with a prior myocardial infarction were exposed in 2 separate sessions to dilute diesel exhaust (300 $\mu g/m^3$) or filtered air for 1 hour during periods of rest and moderate exercise in a controlled-exposure facility. Exercise-induced ST-segment depression was found in all patients, but there was a greater increase in the ischemic burden during exposure to diesel exhaust. Exposure to diesel exhaust reduced the acute release of endothelial tissue plasminogen activator other than aggravating preexisting vasomotor dysfunction.[81] In these studies, the acute release of tissue plasminogen activator, which is a key regulator of endogenous fibrinolytic capacity, was reduced after diesel exhaust inhalation. This effect persisted for 6 hours after the initial exposure,[79] with the magnitude of this reduction comparable to that seen in cigarette smokers.[82] This antifibrinolytic effect further underscores the prothrombotic potential of air pollution, especially under circumstances of vascular injury.

Baccarelli et al[83] performed several studies of air pollution exposure and changes in blood homeostasis. To investigate the association between pollution levels (PM_{10}, CO, NO_2, SO_2, and O_3) and changes in global coagulation tests such as prothrombin time and activated partial thromboplastin time, 1218 normal subjects from the Lombardia region in Italy

Table 2. Effect of Air Pollution on Changes in Blood Homeostasis

Authors	Key Findings	Pollutants	Subjects	Year	Location	Reference
Peters et al	Exposure associated with increased plasma viscosity, with an odds ratio of 3.6 for plasma viscosity above the 95th percentile of the distribution comparing measurements during the air pollution episode with nonepisode measurements in men and an odds ratio of 2.3 for women	TSP, SO_2, CO	25–64 y	1984–1985	Augsburg, Germany	72
Hoek et al	Exposure associated with increased embolism, thrombosis, and mortality, with heart failure deaths responsible for ≈30% of the cardiovascular deaths related to PM_{10}, SO_2, CO, and NO_2	PM_{10}, CO, SO_2, NO_2	All ages	1986–1994	The Netherlands	73
Lucking et al	Exposure associated with increased ex vivo thrombus formation and in vivo platelet activation, with thrombus formation under low- and high-shear conditions increased by 24% and 19%, respectively	Diesel exhaust	21–44 y	2008	UK, Sweden	74
Mills et al	Exposure associated with inhibition of endogenous fibrinolytic capacity, with a greater increase in the ischemic burden during exposure to diesel exhaust	Diesel exhaust	59–61 y	2007	UK	81
Baccarelli et al	Exposure associated with changes in global coagulation function, with PT shorter with higher PM_{10} and NO_2	PM_{10}, NO_2, SO_2, CO, O_3	11–84 y	1995–2005	Italy	83
Baccarelli et al	Exposure associated with altered coagulation function and DVT risk, with each increase of 10 $\mu g/m^3$ in PM_{10} associated with a 70% increase in DVT risk	PM_{10}	18–84 y	1995–2005	Italy	84
Baccarelli et al	Living near major traffic roads associated with increased risk of DVT, with the increase in DVT risk approximately linear over the observed distance range from 718 to 0 m	Not specific (distance from major roads)	18–84 y	1995–2005	Italy	85
Ray et al	Exposure associated with activated circulating platelets and increased leukocyte-platelet aggregates, with the MFI of CD11b on the surface of circulating monocytes and PMN of biomass users increased by 50% and 68%, respectively, and a 62% and 48% increase in MFI observed in CD18 expression on the surface of these cells in biomass users	PM2.5, PM10	21–60 y	2003–2004	India	86

DVT indicates deep venous thrombosis; MFI, mean fluorescence intensity; PMN, polymorphonuclear leukocytes; and PT, prothrombin time.

were tested. Results showed that air pollution is associated with changes in global coagulation function, suggesting a tendency toward hypercoagulability after short-term exposure to air pollution. The effects of exposure to PM_{10} on the risk of developing deep vein thrombosis in 870 patients and 1210 control subjects from the Lombardy region in Italy between 1995 and 2005 were then tested, with findings suggesting that long-term exposure to PM_{10} is associated with altered coagulation function and deep vein thrombosis risk.[84] Using distance from roads as a proxy for traffic exposure to further investigate whether living near major traffic roads increased the risk of deep vein thrombosis, they examined 663 patients with deep vein thrombosis of the lower limbs and 859 age-matched control subjects from cities with populations of >15 000 inhabitants in the Lombardia region in Italy from 1995 through 2005. They found that the risk of developing deep vein thrombosis was increased for subjects living near a major traffic road compared with those living farther away, which was approximately linear over the observed distance range and was not modified after adjustment for background levels of PM, indicating that living near major traffic roads is associated with an increased risk of developing deep vein thrombosis.[85] A summary of these effects is presented in Table 2.

Atherosclerosis

The main pathway by which PM contributes to increased cardiac risk is by initiating and promoting atherosclerotic progression, the underlying cause of most cardiovascular diseases.[87–89] Atherosclerotic lesions can lead to ischemia of

the heart, brain, or extremities. The disruption of a vulnerable but not necessarily stenotic atherosclerotic plaque in response to hemodynamic stress has been suggested as a mechanism that can trigger a myocardial infarction. Air pollution may induce atherosclerosis in the peripheral arteries, coronary arteries, and aorta. Short-term exposure to elevated PM has been associated with increased acute cardiovascular mortality, especially with an at-risk subset of the population, whereas prolonged exposure has been considered a causative factor for atherosclerosis.[1] In an epidemiological study, Pope et al[7] reported that $PM_{2.5}$ exposure is a risk factor for cause-specific cardiovascular disease mortality via mechanisms that likely include pulmonary and systemic inflammation, accelerated atherosclerosis, and altered cardiac autonomic function.

The precise pathway through which PM induces the initiation and progression of atherosclerosis has not been determined, but 2 hypotheses have been proposed and assessed experimentally. The original hypothesis proposed that inhaled particles provoke an inflammatory response in the lungs, with consequent release of prothrombotic and inflammatory cytokines into the circulation.[90] The alternative pathway proposed that inhaled, insoluble $PM_{2.5}$ or $PM_{0.1}$ could rapidly translocate into the circulation, with the potential for direct effects on homeostasis and cardiovascular integrity.[91] The ability of $PM_{0.1}$ to cross the lung-blood barrier is likely to be influenced by a number of factors, including particle size and charge, chemical composition, and propensity to form aggregates.[3] Once in the circulation, $PM_{0.1}$ can interact with the vascular endothelium or have direct effects on atherosclerotic plaques, causing local oxidative stress and proinflammatory effects similar to those seen in the lungs. Through either direct translocation into the circulation or secondary pulmonary-derived mediators, PM augments atherogenesis and causes acute adverse thrombotic and vascular effects.

In a series of animal models, mice fed high-fat chow and exposed to ambient $PM_{2.5}$ demonstrated marked increases in plaque area, 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, indicating that exposure to low concentrations of $PM_{2.5}$ altered vasomotor tone, induced vascular inflammation, and potentiated atherosclerosis.[92,93] Consistently, Chen and Nadziejko[94] exposed apolipoprotein E–knockout mice and apolipoprotein E–, low-density lipoprotein receptor–deficient mice to ambient $PM_{2.5}$ and demonstrated that subchronic exposure to ambient PM in these mice had a significant impact on the size, severity, and composition of aortic plaque. The $PM_{0.1}$ component could have a greater atherogenic effect than the $PM_{2.5}$ fraction. Araujo et al[95] compared the proatherogenic effects of ambient particles <0.18 μm (ultrafine particles) with the effects of particles <2.5 μm in apolipoprotein E–knockout mice. Ultrafine PM–exposed mice exhibited significantly larger early atherosclerotic lesions than mice exposed to $PM_{2.5}$ or filtered air. In addition, exposure to ultrafine particles resulted in an inhibition of the antiinflammatory capacity of plasma high-density lipoprotein and greater systemic oxidative stress. Their data showed that exposure to concentrated ultrafine PM rich in polycyclic aromatic hydrocarbons produced more inflammation, systemic oxidative stress, and atheroma formation than the fine fraction in apolipoprotein E–knockout mice. In the Watanabe heritable hyperlipidemic rabbit model, 4-week exposure to ambient PM_{10} resulted in dose-dependent alveolar and systemic inflammatory responses and progression of atherosclerosis in the coronary arteries and aorta.[89] The volume fraction of coronary atherosclerotic lesions was increased in response to PM_{10} exposure. The atherogenic effects were correlated with the extent of PM phagocytosed by alveolar macrophages in the lung and coupled with an enhanced release of bone marrow monocytes. These precursors of macrophages play a key role in atherogenic inflammatory responses. In addition, exposure to PM_{10} caused an increase in plaque cell turnover and extracellular lipid pools in coronary and aortic lesions, as well as in the total amount of lipids in aortic lesions. Therefore, progression of atherosclerosis and increased vulnerability to plaque rupture may underlie the relationship between PM and increased cardiovascular death.

A panel study in Los Angeles provided the first evidence of a link between long-term PM exposure and atherosclerosis in humans.[96] This study, using data from 798 participants in 2 clinical trials, found that a 10-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with an increase in carotid intima-media thickness, an ultrasonic measure of atheroma. For a cross-sectional exposure contrast of 10 $\mu g/m^3$ $PM_{2.5}$, carotid intima-media thickness increased by 5.9% (95% confidence interval, 1 to 11). Adjustment for age reduced the coefficients, but further adjustment for covariates indicated robust estimates in the range of 3.9% to 4.3%. Among older subjects ($\geq$60 years of age), women, never smokers, and those reporting lipid-lowering treatment at baseline, the associations of $PM_{2.5}$ and carotid intima-media thickness were larger, with the strongest associations in women 60 years of age (15.7%; 95% confidence interval, 5.7 to 26.6), suggesting that long-term ambient PM exposure may affect the development of atherosclerosis in humans. In a study examining the role of traffic-related, long-term exposure to $PM_{2.5}$ (mean concentration, 22.8 $\mu g/m^3$) in 4494 adult participants from the Heinz Nixdorf Recall Study, a 50% reduction in the distance between the residence and a main road resulted in a 10.2% increase in coronary artery calcification.[97] These studies support the concept that air pollution causes a progression of atherosclerosis. In a cross-sectional analysis, Allen et al[98] investigated exposure to $PM_{2.5}$ and residential proximity to major roads in relation to abdominal aortic calcification, a sensitive indicator of systemic atherosclerosis. Aortic calcification was measured by computed tomography among 1147 persons in 5 US metropolitan areas enrolled in the Multi-Ethnic Study of Atherosclerosis. They found a slightly elevated risk of aortic calcification with a 10-$\mu g/m$ contrast in $PM_{2.5}$, and the $PM_{2.5}$-associated risk of aortic calcification was stronger among participants with long-term residence near a $PM_{2.5}$ monitor and among participants not recently employed outside the home. Their findings revealed a strong relationship between ambient PM and systemic

Table 3. Effect of Air Pollution on the Development of Atherosclerosis

Authors	Key Findings	Pollutants	Subjects	Year	Location	Reference
Pope et al	Exposure associated with acute ischemic coronary events (unstable angina and myocardial infarction), with $PM_{2.5}$ elevated by 10 $\mu g/m^3$ associated with increased risk of acute ischemic coronary events of 4.5%	$PM_{2.5}$	Adults	1994–2004	US	8
Kunzli et al	Exposure associated with an increase in CIMT; with a cross-sectional exposure contrast of 10 $\mu g/m^3$ $PM_{2.5}$, CIMT increased by 5.9%	$PM_{2.5}$	≥40 y	1998–2003	California	96
Hoffmann et al	Long-term residential exposure associated with coronary atherosclerosis, with a reduction in the distance between the residence and a major road by half associated with a 7.0% higher CAC	$PM_{2.5}$	45–74 y	2000–2003	Germany	97
Allen et al	Associations with systemic atherosclerosis stronger among participants with less exposure, with elevated risk of aortic calcification with a 10-$\mu g/m$ contrast in $PM_{2.5}$	$PM_{2.5}$	45–84 y	2000–2002	US	98

CIMT indicates carotid intima-media thickness; CAC, coronary artery calcification.

atherosclerosis. A summary of these effects on the development of atherosclerosis is presented in Table 3.

Vasomotor Tone Alterations and Hypertension

The effect of air pollution on vascular dysfunction and blood pressure change has been investigated in both humans and animals for years. In 2607 men and women 25 to 64 years of age who participated in the Augsburg Monitoring of Trends and Determinants in Cardiovascular Disease survey in association with air pollution episodes in Europe in January 1985, continuous concentrations of TSP and SO_2 were associated with an increase in systolic blood pressure.[99] In an investigation of the associations between $PM_{2.5}$ and blood pressure during 631 repeated visits for cardiac rehabilitation in 62 Boston residents with cardiovascular disease, data analyses indicated that for an increase from the 10th to the 90th percentile in mean $PM_{2.5}$ levels during the 5 days before the visit (10.5 $\mu g/m^3$), there was a 2.8-mm Hg increase in resting systolic, a 2.7-mm Hg increase in resting diastolic, and a 2.7-mm Hg increase in resting mean arterial blood pressure. The mean $PM_{2.5}$ level during the 2 preceding days (13.9 $\mu g/m^3$) was associated with a 7.0-mm Hg increase in diastolic and a 4.7-mm Hg increase in mean arterial blood pressure during exercise in persons with resting heart rate ≥70 bpm, but it was not associated with an increase in blood pressure during exercise in persons with heart rate <70 bpm.[100] In a study conducted in Italy comparing 68 traffic policemen and 62 control subjects (all male) at rest and during a symptom-limited incremental exercise test, 26 traffic policemen and none of the control subjects experienced exercise-induced ECG abnormalities or hypertension, and the traffic-exposed group demonstrated a number of significant changes in cardiorespiratory measures on exercise testing, suggesting that long-term occupational exposure to urban pollutants reduces resistance to physical effort and increases the risk of cardiovascular and respiratory effects.[101]

In an investigation of 40 healthy white male nonsmokers spontaneously breathing ambient air in Paris, France, gaseous pollutants were found to affect large-artery endothelial function, whereas PM exaggerated the dilatory response of small arteries to ischemia.[102] In detail, reactive hyperemia was significantly and positively correlated with $PM_{10-2.5}$. An increase in PM, over the span of 2 weeks, was significantly correlated with an increase in reactive hyperemia. Endothelial function was impaired by ordinary levels of pollution in healthy young male subjects in an urban area and may be reduced by 50% between the least and the most polluted day.[102] Potential mechanisms for PM-associated changes in blood pressure have been suggested to include an increase in sympathetic tone and/or the modulation of basal systemic vascular tone.[103] Two studies showing associations between air pollution and blood pressure followed up subjects with chronic obstructive pulmonary disease. Linn et al[104] found that an increase of 33 $\mu g/m^3$ ambient PM_{10} was associated with a 5.7-mm Hg increase in systolic blood pressure. In contrast, Brauer et al[105] studied 16 nonsmoking chronic obstructive pulmonary disease patients residing in Vancouver equipped with a $PM_{2.5}$ monitor for seven 24-hour periods. They found that although no associations between air pollution and lung function were statistically significant, weak associations were observed between particle concentrations and increased supraventricular ectopic heartbeats and decreased systolic blood pressure. No consistent associations were observed between any particle metric and diastolic blood pressure, heart rate, heart rate variability (root mean square of successive differences or SD of normal to normal), symptom severity, or bronchodilator use. Of the pollutants measured, ambient PM_{10} was most consistently associated with health parameters. In nonsmoking healthy and asthmatic volunteers exposed to concentrated fine ambient particulates (CAP) compared with filtered air, systolic blood pressure was decreased in asthmatics and increased in healthy subjects during CAP exposure relative to filtered air. Cardiovascular (but not respiratory) symptoms increased slightly with CAP in both groups.[106] However, in 25 healthy adults exposed to 2-hour inhalation of ≈150 $\mu g/m^3$ of CAP plus O_3, exposure to CAP plus O_3 caused a significant brachial artery vasocon-

striction compared with filtered-air inhalation,[107] suggesting that $PM_{2.5}$ CAP exposure (with or without O_3) was inversely associated with systolic blood pressure in asthmatics but positively associated in healthy subjects.[106,107]

In addition to the epidemiological and clinical studies, animal studies have provided evidence related to the mechanism of action of air pollution exposure–induced changes in blood pressure. In an angiotensin II-induced hypertensive Sprague-Dawley rat model, exposure to concentrated ambient $PM_{2.5}$ for 10 weeks induced prolonged blood pressure recovery compared with the filtered air–exposed group.[108] In this study, aortic vasoconstriction to phenylephrine was potentiated with exaggerated relaxation to the rho-kinase (ROCK) inhibitor Y-27632 and an increase in ROCK-1 messenger RNA levels and superoxide production in the $PM_{2.5}$-exposed group, suggesting that short-term $PM_{2.5}$ exposure exaggerates hypertension through superoxide-mediated upregulation of the Rho/ROCK pathway.[108] Subsequently, in a murine model exposed to concentrated ambient $PM_{2.5}$ for 12 weeks followed by a 14-day infusion of angiotensin II in conjunction with fasudil, a Rho kinase antagonist, $PM_{2.5}$ exposure was found to potentiate angiotensin II–induced hypertension, which was abolished with fasudil treatment.[109] In addition, $PM_{2.5}$ exposure increased angiotensin II–induced cardiac hypertrophy, collagen deposition, and cardiac and vascular RhoA activation, suggesting that cardiovascular health effects are indeed the results of air pollution exposure.[109]

Other Cardiovascular-Associated Events

Air pollution exposure has been linked to cerebrovascular diseases such as stroke. In a study conducted in England and Wales in the early 1980s, stroke mortality showed strong correlations with atmospheric pollution levels in both the winter and summer. These correlations were strengthened by standardization for season and temperature.[110] By examining death certificates in Philadelphia on 5% of the days with the highest particulate air pollution and 5% of the days with the lowest particulate air pollution during the years 1973 to 1980, the researchers showed that the relative risk of dying of a stroke was elevated on days of high pollution.[22] The effect of air pollution exposure on stroke was also confirmed in Japan in 1980 to 1995 during the summer season.[111] In a recent investigation examining the association of long-term exposure to $PM_{2.5}$ with cardiovascular events, 65 893 postmenopausal women without previous cardiovascular disease in 36 US metropolitan areas from 1994 to 1998 were studied. The results showed that each increase of 10 $\mu g/m^3$ was associated with a 24% increase in the risk of a cardiovascular event and a 76% increase in the risk of death resulting from cardiovascular disease. The risk of cerebrovascular events was also associated with increased levels of $PM_{2.5}$.[9]

Air pollution has recently been linked to diabetes mellitus and obesity. A study conducted in 270 Boston residents that measured 24-hour average ambient levels of air pollution ($PM_{2.5}$, particle number, black carbon, and sulfates) ≈500 m from the patient examination site found that diabetes mellitus confers vulnerability to the effects of particles associated with coal-burning power plants and traffic.[112] Recently, in a high-fat diet–induced obesity mouse model, $PM_{2.5}$-exposed mice exhibited marked whole-body insulin resistance, systemic inflammation, and an increase in visceral adiposity. These were all associated with abnormalities in vascular relaxation to insulin and acetylcholine, increased adipose tissue macrophages, and increased inflammatory cell adhesion in the microcirculation, providing a new link between air pollution and type 2 diabetes mellitus.[113]

Conclusions

Cardiovascular diseases have caused significant human and public health burden, with sustained reductions in air pollution exposure associated with increased life expectancy.[10] Although significant improvements have been achieved in terms of air quality in the past decades, "clear sky visibility" over land has decreased globally over the past 30 years (except in Europe),[114] indicating that we still have a long way to go in reducing air pollution levels and associated diseases. Future investigations into air pollution–induced cardiovascular diseases must not only include more studies to determine the mechanisms of action but also examine the role of each specific component of air pollution to determine what combination of particles is to blame for this sudden increase in environment-induced health concerns. This information is paramount for policy makers to determine acceptable levels of air pollution and to design ways to minimize the harmful effects of particles on the body.

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