Ambient Particle Inhalation and the Cardiovascular System: Potential Mechanisms

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Well-documented air pollution episodes throughout recent history have led to deaths among individuals with cardiovascular and respiratory disease. Although the components of air pollution that cause the adverse health effects in these individuals are unknown, a small proportion by mass but a large proportion by number of the ambient air particles are ultrafine, i.e., less than 100 nm in diameter. This ultrafine component of particulate matter with a mass median aerodynamic diameter less than 10 µm (PM_{10}) may mediate some of the adverse health effects reported in epidemiologic studies and for which there is toxicologic evidence to support this contention. The exact mechanism by which ultrafine particles have adverse effects is unknown, but these particles have recently been shown to enhance calcium influx on contact with macrophages. Oxidative stress is also to be anticipated at the huge particle surface; this can be augmented by oxidants generated by recruited inflammatory leukocytes. Atheromatous plaques form in the coronary arteries and are major causes of morbidity and death associated epidemiologically with particulate air pollution. In populations exposed to air pollution episodes, blood viscosity, fibrinogen, and C-reactive protein (CRP) were higher. More recently, increases in heart rate in response to rising air pollution have been described and are most marked in individuals who have high blood viscosity. In our study of elderly individuals, there were significant rises in CRP, an index of inflammation. In this present review, we consider the likely interactions between the ultrafine particles the acute phase response and cardiovascular disease. *Key words*: acute phase response, atherosclerosis, cardiovascular, coagulation, inflammation, PM_{10}. — *Environ Health Perspect* 109(suppl 4):523–527 (2001). *http://ehpnet1.niehs.nih.gov/docs/2001/suppl-4/523-527donaldson/abstract.html*

Background

Historical data (*1*) reveal well-documented air pollution episodes that led to deaths, the majority of which occurred among individuals with known cardiovascular and respiratory disease. During a 5-day fog in December 1930, 63 people died in the Meuse Valley in Belgium, with most deaths occurring on days 4 and 5 of the episode. Older persons with previously known diseases of the heart or lungs accounted for the majority of fatalities. In Donora, Pennsylvania, 20 people died and approximately 7,000 experienced acute illness in October 1948; people 55 years of age and older were most severely affected. The episode in London in December 1952 resulted in at least 4,000 extra deaths, the greatest increase being in those 45 years of age and older. Therefore, it has long been suspected that particulate pollution may precipitate premature death not only from lung but also from heart disease. In the last decade it has become apparent this is still true, even at the much lower particle concentrations prevalent today. Moreover, there is also evidence that life in a polluted climate may contribute to long-term risks of death from heart disease. It is not intuitively obvious how low concentrations of particles in the lung could cause such effects on another organ. This has led some to question the causative conclusions drawn from the epidemiologic observations. In 1995 we proposed a hypothetical mechanism whereby particles reaching the lung lining cells could influence blood coagulability and thus lead to heart disease (*2*). Our hypothesis required addressing two mysteries. First, why should the pulmonary and systemic effects be evident at such low airborne mass concentrations compared to, for example, the U.K. occupational nuisance dust standard. Second, how could such concentrations influence the cardiovascular system as well as the lung? In answering the first, we suggested that the number and possibly the surface area rather then the mass concentration of particles were driving the effect. In answering the second, we proposed that lung inflammation might have effects on blood coagulability, which in turn could provoke myocardial infarction. In the present article we review subsequent investigations of these and related hypothetical mechanisms for the effects of particulate matter with a mass median aerodynamic diameter less than 10 µm (PM_{10}) on the cardiovascular system. We focus especially on ultrafine particles because they have been a major part of our research.

Acute versus Chronic Effects

The effects of ambient particles in epidemiologic studies are conventionally considered to be either acute, seen in time-series studies or chronic, seen in cohort studies. In this article we describe both chronic and acute effects together, as the underlying mechanisms are the unifying factor in this review. Furthermore, the effects under discussion are largely speculative, at least regarding mechanism, and it is difficult to define the nature of acute versus chronic. There is reason, for example, to believe that multiple low-level acute effects would culminate in a chronic effect. However, Table 1 classifies the potential cardiovascular effects of particles fairly arbitrarily as chronic or acute.

Ultrafine Particles in Ambient Air

There is ample evidence that a small proportion by mass but a large proportion by number of the particles in ambient air are ultrafine in size, i.e., less than 100 nm in diameter (*3–5*). It has been suggested (*6–8*) that the ultrafine component of PM_{10} may mediate some of the adverse health effects reported in epidemiologic studies of the relationship between exposure to environmental particles and adverse health effects. Considerable toxicologic evidence supports the idea that ultrafine particles have special toxicity compared to the same material as larger particles (*9*). Other components of PM, such as transition metals and endotoxin, could mediate adverse effects, but these are not discussed extensively here.

The very small (< 50 nm) nucleation particles generated directly by combustion and photochemical activity are unstable and persist only briefly as singlet particles, aggregating to form larger accumulation particles. These particles range in size from a few tens of nanometers up to a micrometer or so (*10*). Ultrafine particles from all sources

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Table 1. Postulated effects of particles on the cardiovascular system classified as to the time scale of the effect.

Effect	Time scale
APR	Acute
Atherogenesis	Chronic
Atheromatous plaque destabilization/rupture	Acute/chronic
Thrombogenesis	Acute
Cardiac arrhythmia	Acute
Heart rate variability	Acute or chronic

aggregate readily if produced at a sufficient concentration. They may also adhere to the surface of larger nonultrafine particles to form heterogeneous aggregates. Some of these accumulation particles would not be ultrafine by the < 100 nm convention, but each would comprise ultrafine particles. This leads to the questions, does this aggregation lead to loss of toxicity, or do the larger particles retain the toxicity of their component ultrafines? And, if the latter, what is the mechanism? One obvious possibility is that they disaggregate on deposition in the lung to release individual particles that then act as if they had been inhaled as singlets. Aggregates of ultrafine particles of carbon black instilled into the lungs of rats have been shown to generate more inflammation than aggregates of nonultrafine carbon black (*11*,*12*). This increase in toxicity may be a consequence either of disaggregation into singlet particles or of the ability of particles in aggregates to continue to exert effects via a large surface area.

Because most exposures occur indoors, the contribution of indoor-derived particles such as environmental tobacco smoke could potentially produce the effects described in this review.

Oxidative Stress Caused by Particles

Pathogenic Particles in General

There is extensive evidence that particles of various sorts associated with lung disease, e.g., asbestos, coal mine dust, quartz, cause oxidative stress in cell-free systems in exposed cells and in lungs of rats after experimental exposure (*13*). There is a link between oxidative stress and inflammation via activation of oxidative stress-responsive transcription factors such as nuclear factor kappa B (NF-κB) and activator protein 1, which control proinflammatory genes via redox changes within the cell (*14*).

PM_{10} and $PM_{2.5}$

There is accumulating evidence that PM_{10} and PM with a mass median areodynamic diameter less than 2.5 µm ($PM_{2.5}$) also have intrinsic ability to cause oxidative stress in cell-free systems (*15*) in cells exposed *in vitro* (*16*,*17*) and in exposed animals (*18*,*19*). The mechanism of this oxidative stress is considered to be mediated by transition metals, as shown by a number of studies (*15*,*17*,*19*).

Transition metals, derived from fuel combustion, are present in PM along with ultrafines. The relative importance of these two potential pathogenic factors is unclear, i.e., it is not clear whether there can be generation of oxidative stress and inflammation from ultrafines by mechanisms other than their ability to release transition metals and subsequently generate a Fenton reaction in the lung milieu. Understanding such mechanisms is of more than theoretical importance; future control of the adverse effects of particulate pollution will depend on an understanding of the toxic components in order to set appropriate standards. Such standards, at least in theory, might be based on particle numbers, numbers below a certain diameter, surface area, or any component of the particle such as metal content.

Ultrafine Particles

We have investigated ultrafine particles of carbon black [(ufCB); 14 nm primary particle diameter] that we had previously shown to have greater inflammogenicity than nonultrafine respirable CB (260 nm primary diameter) at low lung dose following instillation (*11*,*12*,*20*). ufCB also causes more oxidative stress than the same mass of fine CB to cells in culture, as measured by reduced glutathione (GSH) levels.

We have investigated whether transition metals are responsible for the additional ability of ufCB to cause inflammation compared to CB at the same mass dose. Treatment of the ufCB with a transition metal chelator, a maneuver that decreases the oxidative activity of PM_{10} (*21*), had no effect on the ability of ufCB to cause inflammation in rat lungs (*12*). Moreover, the soluble fraction collected from the ufCB particles, which contains all the oxidative (*21*) and inflammogenic (*19*) potential of some PM samples, did not itself cause inflammation (*12*). We deduce from these experiments that ultrafine particles of some types, including CB, can cause inflammation via nontransition metal-mediated pathways.

The mechanism of the generation of oxidative stress is unknown, but studies with the dye dichlorofluorescein, which fluoresces in the presence of oxidants, have shown that ufCB has much more surface free radical activity than nonultrafine CB, suggesting a direct generation of oxidative stress at the particle surface (*22*).

There are chemical reasons for supposing that very small particles may have much more reactive surfaces than the same material in larger form, because of rearrangement of their surface atoms in order to maintain their structure. Whatever the precise mechanisms, evidence to date suggests that both a factor associated with the size of particles and also the transition metals contained in them may act separately as mediators of lung injury.

Modulation of Intracellular Calcium as a Mode of Action of Ultrafine Particles

The various adverse health effects induced by exposure to PM are likely to involve the upregulation of proinflammatory mediators such as cytokines and chemokines. The intracellular pathways by which PM, transition metals, and ultrafine particles modulate the gene expression of proinflammatory mediators are uncertain.

Recent studies reveal that noncytotoxic doses of ufCB and ultrafine latex particles induce alterations in calcium signaling in both human monocytic cell lines and in rat bronchoalveolar lavage cells (> 85% macrophages) (*23*,*24*). Intracellular calcium is involved in the control of inflammatory responses to conditions such as sepsis (*25*), as well as in the control of transcription factors such as NF-κB and nuclear factor of activated T cells (*26*).

Interestingly, ultrafine particles have only a small, but significant, effect on the resting cytosolic calcium concentration of macrophages (*24*). The full effect of the ultrafine particles on macrophages was not observed until a second stimulus, thapsigargin, which releases endoplasmic reticulum calcium stores, was added. In releasing these intracellular stores, thapsigargin, like inositol 1,4,5-trisphosphate, initiates an influx of extracellular calcium via plasma membrane calcium channels. The ultrafine particles enhanced this "calcium release–activated calcium current" across the plasma membrane by as much as 2.5-fold (*23*,*24*). These data suggest that in the presence of a second stimulus, for example, a proinflammatory mediator, ultrafine particles can have a substantial effect on intracellular calcium-signaling pathways and, potentially, on expression of proinflammatory genes. Hence, susceptible individuals, including those with preexisting inflammation, may be more responsive to PM exposure because they are already primed for calcium stimulation by cytokines in the inflammatory milieu. Priming of type II epithelial cell lines by tumor necrosis factor-α (TNF-α) enhances the interleukin (IL)-8 production of these cells in response to residual oil fly ash or quartz exposure (*27*).

The exact mechanism by which ultrafine particles are able to enhance calcium influx on stimulation of the macrophages is unknown; however, addition of antioxidants such as nacystelin or mannitol partially inhibited the response (*23*), indicating a role for reactive oxygen species in this pathway. In view of the central role that calcium plays in the functions of cells, such findings lead to a better understanding of the mode of action of ultrafines.

Oxidative Stress and the Cardiovascular System

Oxidative stress in the lungs following particle exposure is to be anticipated for the reasons mentioned above. It is likely to arise first at the particle surface and then be augmented by oxidants generated by any recruited inflammatory leukocytes. It is central to this review to consider what impact the generation of oxidative stress in the lungs might have for the cardiovascular system.

Increased Airspace Epithelial Permeability

An important consideration is that oxidative stress, and especially depletion of reduced GSH, can increase the permeability of the lung epithelium (*28*), allowing passage of particles and particle-loaded macrophages into the interstitium. This could allow particles access to the endothelial cells, the blood, and potentially even to be transported to other organs, although presently there is little evidence to support this. Increased epithelial permeability may also allow diffusible molecules produced in the lungs in response to particles to enter the interstitium and possibly gain access to the circulation. These mediators could include those shown in Table 2 and could have the effects shown.

Atheromatous Plaques

Atheromatous plaques form in arteries, and in the coronary arteries are the underlying lesions leading to angina and myocardial infarction, causes of morbidity and death associated epidemiologically with particulate air pollution. We can differentiate between chronic effects on atheroma formation and development, and acute events that lead to plaque rupture. Plaque formation is accelerated by increased low-density lipoprotein (LDL) cholesterol [and decreased high-density lipoprotein (HDL) cholesterol], smoking, increased vasoactive amines, diets low in fruit and vegetables and high in fat (particularly saturated fat), lack of physical activity, and genetic predisposition. Many of these risk factors, such as the intensity of exposure to air pollution, are associated with socioeconomic deprivation. Increased oxidation of LDL is a key feature of foam cell and atheroma development, and transition metals can enhance both direct LDL oxidation (*29*) and oxidation of LDL by monocytes (*30*). It is possible, therefore, that transition metal-derived oxidants or other oxidative activity generated by particles could oxidize LDL and this could be proatherogenic.

Plaques typically contain inflammatory cells, smooth muscle cells, foam cells, and a lipid-rich core capped by a fibrous layer of connective tissue and fibroblasts (*31*). The lipid core of the plaque is highly thrombogenic, and when the plaque ruptures, thrombosis in the vessel commonly results, leading to infarction (*31,32*). The production and release of acute phase reactants, such as C-reactive protein (CRP), as a result of increased inflammation have been proposed as a marker of unstable atheromatous plaques and underlying atherosclerosis (*33*). Thrombosis may also arise from plaque endothelial erosion when there is denudation of the overlying endothelium exposing the basement membrane (*31*). Thrombus forms against this and adheres to the surface of the plaque. Any effect of particle deposition in the lung that favors either endothelial erosion, plaque rupture, or production of clotting factors would increase the likelihood of a thrombus forming.

Table 2. Mediators from lung cells that could have systemic effects.

Mediator	Lung cell of origin	Likely systemic effect
IL-1, IL-6, TNF-α	Macrophages, epithelial cells	APR
Fibrinogen	Epithelial cells	Procoagulant
Factor VII	Lung macrophages	Procoagulant
Oxidized LDL	Lung lining fluid	Atherogenic

The Acute-Phase Response (APR)

APR and the Clotting System

In response to our original suggestion that air pollution effects on the heart were mediated by increases in blood coagulability, Peters et al. (*34*) investigated plasma viscosity, which is determined largely by plasma fibrinogen concentration, in a population in relation to a severe air pollution episode. They found that viscosity was higher during the incident, suggesting that the pollution might have been responsible. More recently, they have shown that increases in heart rate in response to air pollution are most marked in individuals who have high blood viscosity, perhaps defining a susceptible group (*34*). Prescott et al. (*35*) also reported that people with high concentrations of plasma fibrinogen might be more susceptible to the adverse cardiovascular effects of particulate air pollution. Estimates of interaction of fibrinogen with a binary indicator of black smoke pollution were 1.15 (confidence interval 0.93–1.44; $p = 0.2$), so limitations of power meant that evidence relating this interaction was not conclusive. In contrast, our own study of elderly individuals found no significant changes in fibrinogen or factor VII in relation to exposure to particles over a year, although we did find rises in CRP, an index of inflammation, and falls in platelets and red blood cells in relation to rises in PM_{10} (*36*). These results suggested an effect of particles on endothelial function, leading to sequestration of red cells and platelets, a response that could theoretically impair circulation and promote thrombosis.

Ghio and co-workers report increased bronchoalveolar lavage neutrophils and blood fibrinogen after inhalation of concentrated ambient particles (CAPs) at exposures that ranged from 23.1 to 311.1 µg/m^3 (*37*).

Fibrinogen, CRP, and factor VII are part of the acute-phase response, which is mediated by cytokines released during inflammatory reactions. Increases in any proteins of the clotting cascade present an increased possibility of coagulation. In addition, raised concentrations of fibrinogen and factor VII are recognized long-term risk factors for myocardial infarction.

We have found increases in factor VII in rats following a short exposure to ufCB but no such effect with nonultrafine CB (*38*). However, we found no increase in fibrinogen up to 7 days postexposure to ufCB in these experiments. Factor VII could be produced in the liver by mediator signals from the lungs or could be made in the lungs *in situ* by macrophages (*39*).

APR and cardiovascular disease. CRP is an acute-phase protein produced in the liver in response to injury, infection, or other inflammatory stimuli (*40*). Studies have shown a positive association between CRP and coronary artery disease (*41,42*). In a survey of 388 British men 50–69 years of age, the prevalence of coronary artery disease increased 1.5-fold for each doubling of CRP level (*42*). We have shown an association between increases in PM_{10} and elevation of plasma CRP (*36*). The explanation of the association of coronary artery disease with CRP is thought to be in the atherogenic effects of chronic inflammation (*42,43*), although it is conceivable that the increase is due to cytokines released by cells in the plaques of people with extensive atheroma.

CRP in plaques. If raised, CRP is per se a risk factor for cardiovascular disease. Moreover, it appears to increase in association with PM_{10} exposure, and there could be a link between these two observations. Increased CRP could increase as a consequence of plaque instability but might also contribute to it. Certainly, CRP has been found in plaques, and from its disposition it has been hypothesized that it facilitates the uptake of lipids by macrophages accumulating in atherosclerotic lesions (*44*). It has also been suggested that it might participate both in cytolysis, enlarging the necrotic area in plaques, and/or in the phagocytic scavenging of the necrotic tissue. (*44*). Facilitating uptake of lipid and enlarging necrotic areas in plaques could be seen as contributing to their instability. Enzymatic modification of tissue-deposited LDL confers CRP-binding capacity on the molecule, which enhances complement activation; this could lead directly to recruitment of cells and enhanced inflammation in plaques, which leads to destabilization (*45*). Such enzymatic modification could arise from leukocyte proteases released from cells in the plaque.

Although CRP may contribute to plaque instability, it also has well-documented anti-inflammatory effects. There may be a temporal relationship in the pro- and anti-inflammatory properties of CRP that depends on the various microenvironments (such as acidity and proteolytic activity) it experiences during the evolution of an inflammatory focus (*46*).

As noted above, we have reported increased CRP in association with rises in city center PM_{10} (*36*). This suggests that particles are able to stimulate APR. In individuals with pre-existing high CRP and already at risk, increases in PM_{10} may increase the likelihood of plaque destabilization and rupture by further elevating CRP. The mechanism for CRP increase is likely to be the production of the APR, with cytokines produced in the lung passing to the liver and stimulating CRP production. Individuals with unstable plaques and with increased CRP as a marker of these events may thus have a further increase by deposition of particles.

Although direct transport of particles or components of PM such as ultrafine particles or metals to the liver cannot as yet be ruled out, it seems unlikely that a biologically sufficient concentration would reach the cells of the target organ after dilution in the circulation.

It is notable that CAPs alone have little effect on blood indices, as shown by Clarke et al. (*47*) in dogs, although the concentrator used in the study does not concentrate ultrafine particles.

Interactions between particles and CRP. In addition to being a marker of risk, a mechanism for CRP as a pathogenic factor in particle-exposed individuals comes from the known effects of CRP. If deposition of particles in the lungs during high PM episodes causes even mild inflammation, there could be increased permeability that would allow CRP to enter the lungs more readily from plasma, although increases in lung lining fluid CRP could also arise from alveolar macrophage production of CRP (*48*). The presence of CRP could modify the response to particles such that it enhances their ability to cause inflammation. An obvious way this could arise is via the complement-activating effects of CRP (*49*). Any enhanced production of C5a could lead to increased chemoattraction of cells to the particle-exposed lungs. CRP bound to particles could also be an important modifier of the interaction of CRP with the complement system inflammatory response, as CRP has been reported to change its activity on becoming surface bound (*46*).

There could also be direct effects from oxidative activities of particles or their associated metals. Human CRP has been shown to acquire the ability to augment platelet reactivity when treated with a transition metal-ascorbate system that generates reactive oxygen intermediates (*50*). CRP modified by such treatment showed no appreciable activation of platelets in the absence of platelet activators such as platelet-activating factor, thrombin, or adenosine diphosphate; but in the presence of the modified CRP, irreversible activation of platelets occurred with low doses of platelet-activating factor and other stimulatory agents. Moreover, proteolytic fragments of CRP are associated with activation of alveolar macrophage TNF-α and macrophage chemotactic protein-1 production and upregulation of adhesion molecules (*51*). Such proteolysis could be mediated by lung macrophages attempting to phagocytose particles and therefore could be of potential importance in forming an exaggerated response. More research on the role of CRP in modifying the lung's response to particles is warranted.

Evidence of Systemic Oxidative Stress in Susceptible Populations and After Particles

Evidence indicates that systemic oxidative stress does occur in groups at risk from the adverse effects of PM. Rahman and MacNee (*52*) have shown decreases in Trolox equivalent antioxidant capacity (TEAC), a global measure of plasma antioxidant capacity that assesses all antioxidants including GSH, vitamin C, and vitamin E but does not discriminate between them, in the plasma of patients with chronic obstructive pulmonary disease, asthma, and those who smoke. We have also reported that instillation of PM_{10} (*11*) and inhalation of ufCB at 1 mg/m^3 for 7 hr, decreased plasma TEAC in rats (*53*), demonstrating systemic oxidative stress. The elderly have been identified as being at risk from PM_{10}, and one study in asymptomatic elderly nuns has shown that those with increased CRP, suggesting the presence of an inflammatory reaction, showed a decreased antioxidant profile in plasma (*54*). Such individuals could be susceptible to PM, as they already have oxidative stress that could be augmented by further stress from particles. The critically ill are also a potential target for the effects of PM_{10}. Increased oxidative stress has been observed in individuals with, for example, sepsis, shock, the need for mechanical ventilation, organ dysfunction, acute respiratory distress syndrome, and disseminated intravascular coagulation. Similar changes have also been noted in patients following surgery and in the presence of an acute-phase response (*55*).

An animal model of cardiovascular disease (*56*), the spontaneously hypertensive rat, had higher basal levels of oxidative stress, measurable as bronchoalveolar lavage thiobarbituric acid derivatives, than normal rats. On challenge with residual oil fly ash there was greater injury in the hypertensive rats; they had an attenuated antioxidant response which may have contributed to injury. This supports the contention that cardiovascular disease patients may have oxidative stress that is a susceptibility factor for particle effects.

Conclusion

Good toxicologic evidence supports the contention that PM acts in the lung to cause oxidative stress, and the epidemiologic evidence provides the toxicologist with clues as to mechanisms for the adverse actions of PM on the cardiovascular system. In this review we have sought to bring these findings together, suggesting pathobiologic processes whereby PM, and especially the ultrafine component, might have effects on the cardiovascular system (Figure 1). Pathologic end points relevant to plaque rupture, endothelial erosion, hemostasis, and coagulation should be used in toxicologic studies. Transition metals could have essentially the same effects as ultrafine particles in generating oxidative stress and adversely affecting the cardiovascular system. The relative importance of the components of PM such as ultrafine particles and transition metals in causing the various known effects of PM requires considerable further research effort.

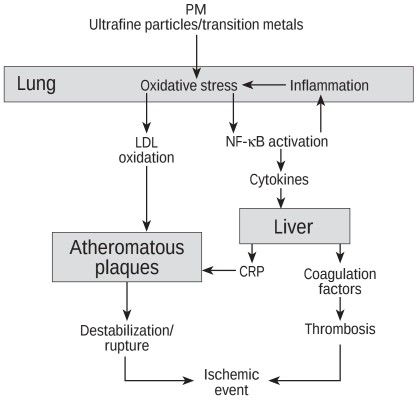

Figure 1. Diagram of the hypothetical events leading from deposition of particles in the lungs to ischemic events.

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