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Particulate Matter and Cardiovascular Health Effects

Akeem O. Lawal and Jesus A. Araujo
Division of Cardiology, Department of Medicine,
David Geffen School of Medicine,
University of California, Los Angeles, CA
USA

1. Introduction

Several studies have shown that exposure to air pollution leads to important adverse health effects resulting in increased morbidity and mortality (Brook, Franklin et al. 2004; Bhatnagar 2006; Brook, Rajagopalan et al. 2010). According to the World Health Organisation, air pollution constitutes the 13th leading cause of mortality in the world (WHO 2009). Increased mortality is mostly due to increased cardiovascular diseases in the exposed population, particularly those of ischemic nature (Pope, Burnett et al. 2004). While air pollutants are composed of a mixture of particulate matter (PM) and gases such as carbon monoxide, ozone, sulphur oxide and nitrogen oxide, recent studies have shown that the particulate matter component of air pollution is mainly responsible for the cardiovascular health effects (Araujo and Nel 2009). This chapter will mostly focus on the links between PM, atherosclerosis and ischemic heart disease.

2. Particulate matter and sources of exposure

2.1 Classification of particulate matter

Particulate matter is constituted by compounds of varying sizes, numbers, chemical composition, and derived from various sources. They are mainly classified according to their size and divided into the following categories: i) Thoracic particles, with an aerodynamic diameter less than 10 micrometers (< 10 μm), ii) Coarse particles, with an aerodynamic diameter greater than 2.5 micrometers and less than 10 micrometers ($PM_{2.5-10}$), iii) Fine particles, less than 2.5 micrometers and iv) Ultrafine particles (UFP), less than 0.1 micrometers (<0.1 μm) (Table1) (U.S.EPA 2004).

2.2 Sources of PM emissions

The characterization of PM emissions is rather complicated by limitations in the measuring instrumentation. In addition, emissions from the same sources change with time and operating conditions. What is actually released by the source of the emissions may not be what is found in the atmosphere at varying distances from the sources, since particulates

undergo a variety of chemical and physical transformations after they have been released into the atmosphere (Robinson, Donahue et al. 2007). Particulates are emitted directly from various sources such as fossil fuel combustion (primary particles) like diesel and gasoline exhaust particles or are formed from gases through chemical reactions involving atmospheric oxygen (O_2), water vapor (H_2O), free radicals such as nitrate (NO_3^-) and hydroxyl ($\cdot OH$) radicals, reactive species such as ozone (O_3), organic gases from anthropogenic and natural sources and pollutants such as nitrogen oxides (NOx) and sulfur dioxide (SO_2) (U.S.EPA 2004).

As shown in Table 1, various sources are involved in the generation of particles via different mechanisms that result in particles with distinct lognormal modes in the particle-size distributions by number and volume (nucleation, Aitken, accumulation and coarse modes). Nucleation and Aitken modes contain particles derived from the combustion of fossil fuels and are due to the nucleation of gas-phase compounds to form condensed-phase species in particles that are newly formed with little chance to grow (nucleation mode) or in newly formed particles in the process of coagulation (Aitken mode). These modes of generation are responsible for the ultrafine particles, emitted indeed from the combustion of fuels such as diesel and gasoline used in the operation of motor vehicles, aircrafts and ships. In the accumulation mode, particles grow in size and accumulate either by coagulation or by condensation, responsible for the generation of the bigger fine particles that are also emitted

Particles	Sources	Mode of generation	Aerodynamic diameter (μm)	Atmospheric half-life
Ultrafine particles (UFP)	Combustion of fossil fuels (gasoline & diesel) and emissions from mobile sources (aircrafts, ships, motor vehicles)	Fresh emissions, secondary photochemical reactions (nucleation mode)	< 0.1	Minutes to hours
Fine particles (FP)	Residential fuel combustion, power plants, tailpipe and brake emissions and Oil refineries	Condensation, coagulation conversion of gas-to-particle (accumulation mode)	<2.5	Days to weeks
Coarse particles (CP)	Suspension from construction, plant and animal fragments, disturbed soil (mining, farming)	Evaporation of sprays, suspension of dusts, mechanical disruption (crushing, grinding, abrasion of surfaces)	2.5-10	Minutes to hours
Thoracic particles (TP)	-	-	<10	-

Source: Modified from Araujo (Araujo and Nel 2009).

Table 1. Size fractions of PM emissions into the atmosphere.

from fuel combustion as well as power plants, oil refineries, tail pipe and brake emissions. The coarse mode contains coarse particles ($PM_{2.5-10}$) derived from the suspension of material from construction, disturbed soil as well as plant and animal fragments. Most of the coarse particles in the PM_{10} are emitted into the atmosphere from the process and open dust sources of fugitive emissions. The process sources are associated with industrial operations such as rock crushing while the open dust sources are those that produce non-ducted emissions of solid particles formed from forces of wind or machinery acting on exposed material. The latter include particulate emissions from industrial sources associated with the open transport, storage, transfer of raw, intermediate and waste aggregate materials and nonindustrial sources such as unpaved roads and parking lots, paved streets and highways, agricultural tilling and heavy construction activities (WRAP 2004). Different sources involved in the generation of ambient particulate can be classified depending on their mobility, into mobile vs. non-mobile sources, as shown in table 2.

Sources	Percentage contribution (% total/ % within category)
Mobile Sources *	28%
1. On-road Mobile Sources	10%
i. Heavy Gasoline Vehicles	3%
ii. Light Gasoline Trucks	10%
iii. Cars& Motorcycles	15%
iv. Diesel Vehicles	72 %
2. Non-road Mobile Sources	18%
i. Railroads	7%
ii. Aircraft	7%
iii. Marine	10%
iv. Gasoline Equipment	20%
v. Diesel Equipment	56%
Not Mobile Sources *	72%
$PM_{2.5}$ Emissions by Source Sector **	
Road Dust	21.5%
Industrial Processes	12.1%
Electricity Generation	11.5%
Fires	9.2%
Residential Wood combustion	8.5%
Waste Disposal	6.2%
Non-road Equipment	6.0%
Fossil fuel combustion	4.8%
On road vehicles	3.0%
Solvent Use	0.2%
Fertilizer and Livestock	0.03%
Miscellaneous	17.0%

* Based on data from the 1999 National Air Quality and Emissions Trends Report (U.S.EPA 1999).
** Based on data from the 2005 National Summary of Particulate matter emissions by source sector (U.S.EPA 2005).

Table 2. Different sources of $PM_{2.5}$ emissions into the atmosphere.

2.2.1 Mobile sources

Emissions from mobile sources contribute significantly to measured levels of particulate matter. These emissions mainly consist of fine and ultrafine particles. According to the report of the 1999 National Emissions by Source in several US states (USEPA 1999), the mobile sources include: 1) On-road sources, which account for ~ 10% of the total emissions in US and include emissions from Cars and Motorcycles (15%), Diesel vehicles (72%), Light Gasoline Trucks (10%) and Heavy Gasoline Vehicles (3%), 2) Non-road sources, which accounts for 18% of total emissions in US including emissions from Marine (10%), Diesel (56%) and Gasoline Equipment (20%) (Table 2). Indeed, emissions from diesel vehicles accounted for about three-quarter of the on-road emissions (USEPA 1999). Importantly, particles derived from motor vehicles seem to be especially potent in increasing cardiovascular mortality (Laden, Neas et al. 2000; Pekkanen, Peters et al. 2002) and cardiac hospital admissions (Janssen NA 2002).

2.2.2 Non-mobile sources

Emissions from Non-mobile sources, also known as the Point Sources, contribute in a larger degree to the total PM emitted into the atmosphere throughout the US (Table 2) (USEPA 1999). Point sources are stationary, large and identifiable sources of emissions that release pollutants into the atmosphere. According to the National Emissions statistics of $PM_{2.5}$ throughout the US in 1999, non-mobile sources include large industries such as manufacturing plants, power plants, fires, residential wood combustion, waste disposal, non road equipment, paper mills and refineries (table 2) (USEPA 1999). Additional sources include biogenic non-anthropogenic sources such as trees and vegetation, oil and gas seeps and microbial activity (USEPA 1999).

3. Particulate matter, duration of exposure and cardiovascular health effects

Exposure to air pollutants has been associated with increased risk for adverse cardiovascular health effects, mostly attributed to those in the particulate phase. Indeed, ambient particulate matter (PM) has been linked to a whole variety of atherothrombotic endpoints (Ghio, Hall et al. 2003; Pope, Muhlestein et al. 2006; Baccarelli, Martinelli et al. 2009). Although epidemiological studies with PM_{10} and $PM_{2.5}$ show that exposure to these particles are associated with adverse cardiovascular effects such as myocardial infarction and stroke death, greater effects are associated with the smaller particle sizes ($PM_{2.5}$) (Analitis, Katsouyanni et al. 2006; Pope 2006; Zanobetti and Schwartz 2009). Thus, the risk of cardiovascular mortality posed by PM_{10} exposure could be in a good degree due to its fraction of particles < 2.5 μm in diameter ($PM_{2.5}$). According to the World Health Organization, exposure to PM may be responsible for an estimate of about 800,000 excess deaths worldwide in each year as a result of myocardial infarction, arrhythmias or heart failure (WHO 2002). Several epidemiological studies have shown that the increased risk in cardiovascular morbidity and mortality occurs as a result of both short- and long-term exposures to PM as summarized in Table 3.

Duration of exposure	*Type of Study*	*Study*	*No. of subjects*	*Exposure variable*	*Outcome variable*	*Major Findings*	*Ref.*
Short-term exposure studies	Time Series	NMMAPS	~50 million	PM_{10}	Daily CP mortality	20 μg/m³ increases in PM_{10} caused 0.6% increased in daily CP mortality in adults from 20 to 100 US cities and hundreds of countries.	(Dominici, Zeger et al. 2000; Dominici, McDermott et al. 2003; Peng, Dominici et al. 2005; Dominici, Peng et al. 2007)
		NCHS	NCHS data on 112 US cities	$PM_{2.5}$	Daily CV mortality	10 μg/m³ increase in 2-day averaged $PM_{2.5}$ caused 0.98% and 0.85% increase in daily all cause and CV mortality respectively	(Baccarelli, Martinelli et al. 2009)
		APHEA2	~43 million	PM_{10}	Daily CV mortality	20 μg/m³ increases in PM_{10} caused a 1.5% increased in daily CV mortality in adults from 29 European cities.	(Katsouyanni 2003; Analitis, Katsouyanni et al. 2006)
		APHENA	NMMAPS, APHEA2 & Canadian studies	PM_{10}	Daily CV mortality	10 μg/m³ increase in PM_{10} caused 0.2 to 0.6% increased in daily all-cause mortality in individuals from the US (90 cities), Europe (22 cities) and Canada (12 cities), mostly in individuals>75-year old.	(Samoli, Peng et al. 2008)
	Case cross-over	IHCS	~12865	$PM_{2.5}$	Ischemic coronary events	10 μg/m³ increases in $PM_{2.5}$ caused a 4.5% increase in daily acute ischemic coronary events in patients in UTAH. Patients with pre- existing CAD have significant increased frequency.	(Pope, Muhlestein et al. 2006)
		MI Registry in Augsburg (data from KORA)	691	Traffic	MI	Exposure to traffic for 1 h increases the relative risk for an MI by 2.92 before the event.	(Peters, von Klot et al. 2004)

Duration of exposure	*Type of Study*	*Study*	*No. of subjects*	*Exposure variable*	*Outcome variable*	*Major Findings*	*Ref.*
Long-term exposure studies	Prospective Cohort	American Cancer Society II (extended analysis)	~500000	$PM_{2.5}$	CV mortality	10 μg/m^3 increase long-term exposure to $PM_{2.5}$ in a 16-year study caused 12% increased in risk for CV death. The largest cause of mortality was due to Ischemic heart disease and smaller numbers of people died from arrhythmias and heart failure	(Pope, Burnett et al. 2004)
		Harvard Six Cities (extended analysis)	8096	$PM_{2.5}$	CV mortality	10 μg/m^3 increase long-term exposure to $PM_{2.5}$ in a 28-year study of six US cities residents show a 1.28% increased in relative risk for CV. Significant reduction in CV mortality was observed in some cities and this correlate with decrease in $PM_{2.5}$	(Laden, Schwartz et al. 2006)
		NHS	66250	PM_{10}	Acute events of CV and CV mortality	10 μg/m^3 increase in long-term exposure to PM_{10} caused a 43% increased in fatal CAD disease among nurses from northeastern US	(Puett, Schwartz et al. 2008)
		Woman's Health Initiative	65893	$PM_{2.5}$	CV acute events and CV mortality	10 μg/m^3 increases in long-term exposure to $PM_{2.5}$ caused a 24% and 76% increase in CV acute events and CV mortality respectively in healthy post-menopausal women in 36 US cities.	(Miller, Siscovick et al. 2007)

NMMAPS, National Morbidity, Mortality and Air Pollution Study; APHEA2, Air Pollution and Health: A European Approach; IHCS, Intermountain Heart Collaborative Study; APHENA, Air Pollution and Health: A Combined European and North American Approach study; CV, Cardiovascular; CP, Cardiopulmonary; MI, Myocardial Infarction; KORA, Cooperative Health Research in the Region of Augsburg; NCHS, National Center for Health Statistics. Modified from (Araujo and Brook 2011)

Table 3. Selected studies showing a relationship between exposure to PM of different lengths of duration and increased cardiovascular morbidity and/or mortality.

3.1 Short-term exposures

Although the mechanisms involved in the generation of PM-mediated adverse cardiovascular health effects are still not clear, several studies have shown that short-term exposures to PM results in cardiovascular systemic effects (Table 3). Thus, in a study carried out in eight European cities, zero to one-day exposure to PM_{10} and black smoke associated with a significant increase in cardiac hospital admission in subjects of all ages and ischemic heart disease in people over 65 years (Le Tertre, Medina et al. 2002). Results from the National Morbidity, Mortality, and Air Pollution study (NMMAPS) and the Air Pollution and Health: A European Approach (APHEA2) involving ~50 and ~43 million subjects respectively found that there was 0.6 and 1.5 % increase in daily cardiopulmonary mortality rate for every 20 $\mu g/m^3$ increase in PM_{10}, respectively (Dominici, McDermott et al. 2003; Analitis, Katsouyanni et al. 2006). Several studies have also shown that exposure to $PM_{2.5}$ result in similar or even larger magnitudes of association. For instance, in the Intermountain Heart Collaborative Study (IHCS) involving 12,865 subjects, 10 $\mu g/m^3$ increases in ambient $PM_{2.5}$ associated with a daily increase of 4.5% in acute ischemic coronary events. Studies have also shown that short-term exposures to PM associated with increased risk for hospitalization for cardiovascular diseases. Dominici et al showed among 11.5 million U.S medicare enrollees > 65 year old that admission rates for all cardiovascular causes increased in association with 10 $\mu g/m^3$ increases in $PM_{2.5}$, leading to an increase of 0.44% in ischemic heart, 1.28% in heart failure and 0.81% in cerebrovascular diseases (Dominici, McDermott et al. 2003). There is also evidence that exposure to UFP associates with increased risk for cardiac hospital admissions, as discussed in section 6.

3.2 Long-term exposures

A number of studies have also shown an association between long-term exposures to PM and cardiovascular morbidity and mortality (Table 3). Thus, in an extended analysis (16-year follow-up) of a cohort survival study from the American Cancer Society, 10 $\mu g/m^3$ increases in long-term exposure to $PM_{2.5}$ associated with a 12% increase in CV deaths, most of which was due to ischemic heart disease, with a smaller percentage due to arrhythmias and heart failure (Table 3) (Pope, Hansen et al. 2004). This study suggests that long-term PM exposures carry greater cardiovascular risk as compared with the magnitude of risk observed in studies evaluating short-term exposures. An even stronger correlation was observed in the Women Health Initiative Study involving 65,893 post menopausal women, which showed 24% and 76% increase in cardiovacular acute events and mortality, respectively (Miller, Siscovick et al. 2007).

4. Particulate matter and cardiovascular ischemic effects

It is noteworthy that PM-mediated enhancement of cardiovascular morbidity and mortality is mostly due to the promotion of ischemic events, such as myocardial infarction. The fact that PM exposures associate with cardiovascular ischemic endpoints both in the short-term as well as long-term exposure studies suggests that PM activates various pathways resulting in both short- as well as long-term effects.

Indeed, several studies have shown that short-term (hours to days) exposures to PM significantly enhance cardiovascular risk (Peters, Frohlich et al. 2001; Miller, Siscovick et al. 2007). Although the mechanisms by which exposure to PM induces cardiac ischemic events such as myocardial infarctions are not yet well defined, several studies have suggested that PM can be associated with hemodynamic, hemostatic as well as cardiac rhythm alterations that may account for some of the PM-induced acute cardiac events. In support of this observation, there are significant associations between exposure to ambient PM and acceleration of heart rate, diminished heart rate variability (Pope and Kalkstein 1996; Peters, Doring et al. 1997), ventricular fibrillation, increased number of therapeutic intervention in patients with implanted cardiovascular-defibrillators (Peters, Liu et al. 2000) and increased plasma viscosity (Peters, Doring et al. 1997).

Many studies have also reported a strong correlation between long-term exposure to $PM_{2.5}$ and cardiac ischemic endpoints as shown above, which strongly suggests that PM-enhancement of atherosclerosis could be one of the pathogenic mechanism(s). Indeed, several studies involving human subjects have shown significant associations between $PM_{2.5}$ exposure and atherosclerosis. Thus, in a cross-sectional study carried out in 798 individuals in Los Angeles by Kunzli et al, carotid intima-medial thickness (CIMT) was found to increase by 5.9% for every 10 $\mu g/m^3$ rise in $PM_{2.5}$ levels (Kunzli, Jerrett et al. 2005). Same group found an acceleration in the annual rate progression of CIMT among individual living within 100 m of a highway which was more than twice the population mean progression (Kunzli, Jerrett et al. 2010). In another study, Hoffman et al found an association between coronary artery calcification (CAC) scores, an index of coronary atherosclerosis, and long-term residential exposure to high traffic (Hoffmann, Moebus et al. 2007). They found that in 4,494 participants, subjects living within 101-200 m, 51-100 or less than 50 m from a major road showed 8%, 34% and 63% increase respectively in the probability of having CAC compared with subjects living >200 m. Furthermore, Diez Roux et al reported a 1-3% increase in CIMT per 21 $\mu g/m^3$ increase in PM_{10} or 12.5 $\mu g/m^3$ increase in $PM_{2.5}$ in subjects exposed to PM_{10} over long-term (20-year means and 2001 mean) and 20-year $PM_{2.5}$ respectively (Diez Roux, Auchincloss et al. 2008). Likewise, in a related study, Allen et al reported an increase risk for aortic calcification with $PM_{2.5}$ exposure (Allen, Criqui et al. 2009). All these studies confirm that exposure to PM triggers-off the development of atherosclerosis in humans, which may be a major mechanism how long-term exposure to PM leads to enhanced cardiovascular ischemic endpoints.

Three putative "general mediating" pathways (Fig.1) have been proposed for the cardiovascular effects of air pollutants such as: 1) Autonomic nervous system imbalance, 2) Induction of pumonary and thereby systemic inflammation/oxidative stress via "spill-over" of mediators (e.g. cytokines, activated white cells/platelets) into the systemic circulation, 3) Access of particles or specific chemical constituents into the systemic circulation which thereby cause direct affects upon the heart and vasculature (Araujo and Brook 2011) (Fig.1). Some of the PM-mediated short-term effects may be related to pathway #1. On the other hand, the occurrance of long-term effects strongly suggests that PM would promote atherosclerosis, likely via a combination of pathway #2 and #3. However, while it has been proposed that UFP could access the systemic circulation (pathway #3), clear confirmation of this possibility is still lacking.

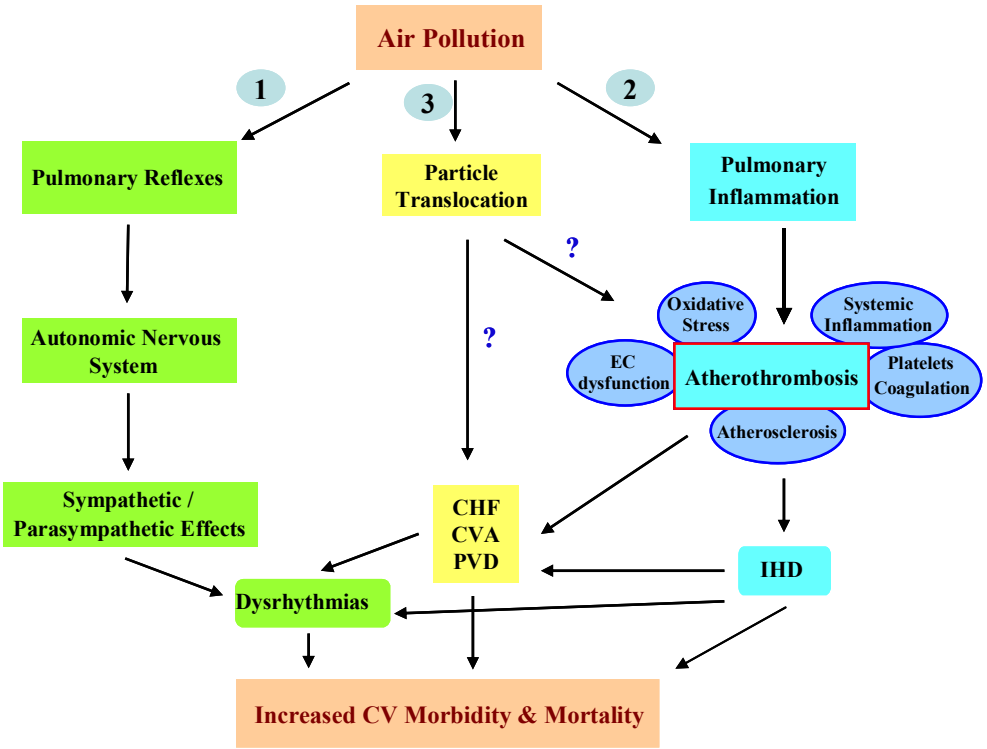

Fig. 1. **Possible mechanisms that link exposure to PM with cardiovascular diseases**. Three mediating pathways are proposed. Air pollution can; 1) Activate the autonomic nervous system resulting in the alteration of heart rate viability and induction of dysrhythmias, 2) Enhance atherothrombotic processes that can lead to development of pulmonary oxidative stress and inflammation with systemic "spill-over" of inflammatory mediators, 3) Particles and/or their chemical constituents can translocate directly to the systemic circulation. CHF= Congestive heart failure, CVA= Cerebrovascular accident, PVD= Peripheral vascular disease, EC= Endothelial cells, IHD= Ischemic heart disease. Taken from (Araujo and Brook 2011).

It is possible then that the predominant mechanism(s) mediating PM-enhancement of cardiovascular ischemic events could be different among studies that evaluate short- vs. long-term effects. In addition, particulate of different size fractions as well as originating from different sources could exhibit significant differences in their ability to induce systemic vascular effects as will be discussed in the next two sections below.

5. What determines PM-related cardiovascular toxicity?

5.1 Particle size

The ability of PM to induce adverse health effects in humans may be a function of a number of factors, some of which are likely to determine its deposition in the respiratory tract and ability to induce both local pulmonary as well as systemic vascular effects. These factors include, among others, size, shape, composition and density of ambient particles

Particle size appears to be an important determinant of PM toxicity. For instance, while PM_{10} has been associated with ischemic cardiovascular events, there is increasing evidence that smaller particles may be responsible for most of cardiovascular adverse health effects. Thus, $PM_{2.5}$ and UFP are thought to be more toxic than larger particles, which may be partly based on their ability to access deeper portions into the lungs. These particles can pass the proximal airway of the respiratory system (throat and larynx) and get deposited into the tracheobronchial airway of the lungs or in the gas exchange region (alveolar ducts or alveoli of the lungs)(Oberdorster, Oberdorster et al. 2005). However, as population studies have shown that the strengths of association of PM with cardiovascular effects are larger with $PM_{2.5}$ than with PM_{10}, which is in support of the notion that a small particle size would facilitate cardiovascular toxicity, there is still a paucity of epidemiological studies in relation to the cardiovascular effects of UFP.

5.2 Importance of chemical composition and redox potential

Particles of different sizes have different chemical composition and redox potential that may affect their ability to act through the various pathways. It appears that PM ability to trigger and/or enhance reactive oxygen species (ROS) production, resulting in tissue oxidative stress, may be of key importance in cardiovascular tissues. For instance, PM-mediated ROS formation may be central in the enhancement of atherosclerosis by PM, likely due to the promotion of systemic prooxidant and proinflammatory effects. Since atherosclerosis is characterized by lipid deposition and oxidation in the arterial wall, factors that promote lipid oxidation and retention in the artery wall may exacerbate the pathogenic process. These lipids are derived from plasma low-density lipoprotein (LDL) particles that travel into the arterial wall and get trapped in the subendothelial space where they can be oxidatively modified (Steinberg 1997; Araujo, Barajas et al. 2008). Several studies using different PM size fractions (PM_{10}, $PM_{2.5}$, UFP) to expose different animal models (apoE$^{-/-}$ mice, LDL-R$^{-/-}$ mice and hyperlipidemic rabbits) via different modes of exposure (inhalation of CAPs, oropharyngeal/intratracheal instillation) converge to demonstrate that PM exposure leads to enhanced atherosclerotic lesions or plaques with altered composition, suggesting that the associations encountered in epidemiological studies are very likely to be causal (Araujo 2011a).

Experimental animal data also supports the notion that particulate of the smallest size may be able to induce larger proatherogenic effects. Araujo et al reported that exposure of apoE$^{-/-}$ mice to concentrated ambient particles (CAPs) in the fine and ultrafine-size ranges resulted in a significant increase of lipid peroxidation in the liver and triggering of a Nrf2-regulated antioxidant response in mice exposed to ultrafine particulate, likely to be indicative of the greater levels of oxidation induced by ultrafines. Stronger prooxidant effects led to bigger atherosclerotic plaques in mice exposed to ultrafines (Araujo, Barajas et al. 2008). The greater

toxicity of UFP could be due to their greater content in prooxidant organic chemicals, greater bioavailability for those reactive compounds due to their larger surface-to-mass ratio and/or greater lung retention (Araujo and Nel 2009). Indeed, UFPs contained twice as much organic carbon (OC) as FP did, accompanied by an increase in the relative content of polyaromatic hydrocarbon (PAH), which may have been one of the factors why UFP induced greater enhancement of aortic atherosclerosis than $PM_{2.5}$ did (Araujo, Barajas et al. 2008). In addition, transition metals have also been largely implicated in the PM hazardous health effects (Ntziachristos, Froines et al. 2007; Ayres, Borm et al. 2008). While there is a large experimental evidence that points out towards these various candidates, there is no substantial evidence that links PAH contents with adverse cardiovascular effects as of yet.

5.3 Factors determining susceptibility

PM cardiovascular toxicity could also be influenced by different susceptibility to PM-mediated systemic effects. Indeed, epidemiological, toxicological and controlled human exposure studies have examined whether the health effects of PM are modulated by preexisting conditions such as coronary artery disease, congestive heart failure, obesity, age and diabetes among others. Several reports identify obesity as a likely susceptibility factor. For instance, short-term exposure to PM has been shown to associate with a reduction in heart rate variability (Schwartz, Litonjua et al. 2005) and higher levels of plasma inflammatory markers such as IL-6 and C-reactive protein in a greater degree among obese individuals (Dubowsky, Suh et al. 2006). Studies of the Veteran's Normative Aging and Women's Health Initiative Cohorts also show that long-term exposure to PM associated with an increase in inflammatory markers and cardiovascular events in individuals with body mass index (BMI) ≥ 25 kg/m^2 compared with < 25 kg/m^2 (Zeka, Sullivan et al. 2006; Miller, Siscovick et al. 2007). In addition, it appears that preexistent congestive heart failure increases the susceptibility to PM-induced cardiovacular events and mortality (Bateson and Schwartz 2004; Pope 2006). Additional studies are required to confirm these findings and better dissect potential susceptibility factors.

6. Relationship between sources of emission and cardiovascular health effects

While different sources of emission may generate pollutants with different physicochemical characteristics, the mechanisms involved in PM-mediated enhancement of cardiovascular morbidity and mortality have been assumed to be common to all particulate derived from various sources (Figure 1). However, this may be an oversimplification of a rather complex relationship that has not been well studied yet, partly due to the lack of understanding about the critical toxic components of air pollution that are responsible for the cardiovascular effects.

PM from different sources may trigger and/or enhance ROS formation which may lead to tissue oxidative stress, inflammation, endothelial dysfunction, resulting in the formation of atherosclerotic plaques (Figure 2). The particular source of emission is to play an important role in determining particle size and chemical composition. It should also be noted that some elements in PM are more source-specific than others and therefore, the extent of PM induction of cardiovascular effects may largely depend on the specific source of PM. For

instance, elements such as iron and zinc are mostly derived from steel production while nickel is linked to oil combustion (Li Z 2004; Zheng L 2004; Qin Y 2006). Some elements might be site-specific. For instance, coal and oil combustion at power plants are the main source of sulphur in Canada. Therefore, better understanding of the sources and type of emissions may help to elucidate the particle components responsible for cardiovascular toxic effects.

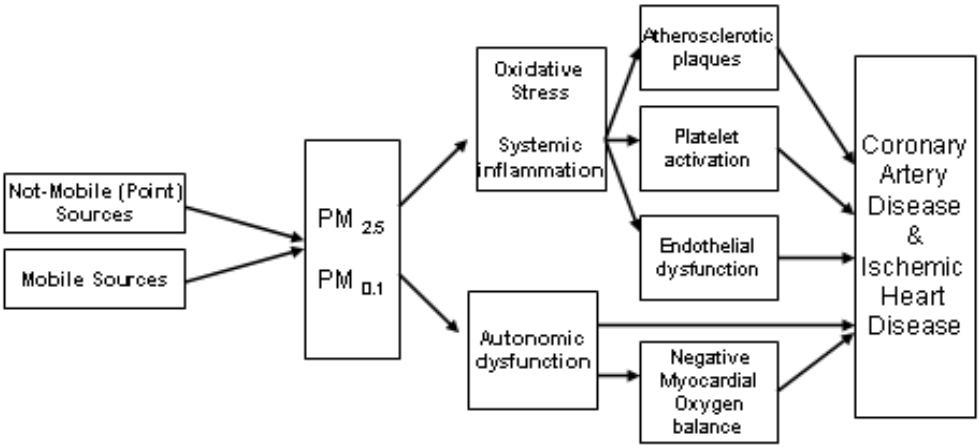

Fig. 2. **Mechanisms involved in the development of ischemic heart disease generated from PM emitted from different sources.** PM, emitted from different sources, may induce various systemic effects and modulate various pathways resulting in enhanced ischemic heart disease events.

One clear example about the difficulties to study the influence of the source of exposures on health effects is in relation to the particle size. Numerous studies have shown that combustion-derived particles from mobile sources are associated with increased cardiovascular morbidity and mortality. Studies have shown that $PM_{2.5}$ exhibits a larger association with cardiovascular endpoints than PM_{10}. These associations have been established mostly using metrics based on PM mass. However, there has been a notion that even smaller particles such as ultrafines would be more active to induce cardiovascular effects based on experimental in-vitro and animal evidence (Schulz, Harder et al. 2005; Araujo, Barajas et al. 2008) but supportive epidemiological evidence is somewhat weaker. Exposure to UFP comes from both mobile as well as non-mobile sources but capturing their toxicity is rather difficult since they are very dependant on the proximity to the source and the conventional particle mass or particle number-based metrics are inadequate to fully capture their toxic potential. Therefore, dissecting the actual contribution of the source of PM to cardiovascular events is difficult as no adequate parameters have so far been used to assess the contribution of UFP at the point of exposure in relation to the point of emission. Despite the short-comings related to the use of total particle number concentration to estimate UFP concentration, studies have shown that exposure to UFP significantly associates with increased hospital admissions due to acute myocardial infarction (Lanki, Pekkanen et al. 2006; von Klot, Peters et al. 2005) as well as heart failure (Belleudi, Faustini et

al.; Dominguez-Rodriguez, Abreu-Afonso et al. 2011 et al.), summarized in table 4. Unfortunately, UFP assessment was only made based on particle number concentration whereas a more comprehensive characterization of the UFP and the particular source of emissions would have been very informative.

Study	Number of cardiac hospital admissions	Environmental exposure parameters	Types of cardiac admissions	Mayor findings
(von Klot, Peters et al. 2005)	6655 first hospital readmissions	PNC PM_{10} Gases (CO, NO_2, O_3)	Acute MI Angina pectoris, HF Dysrhythmia	Cardiac readmissions increased by 2.1% and 2.6% per each increase of 10 μg/m^3 of PM_{10} and 10 000 particles/cm^3, respectively
(Lanki, Pekkanen et al. 2006)	26 854 first MI admissions	PNC PM_{10} Gases (CO, NO_2, O_3)	Acute MI	Hospitalization for first MI increased by 0.5% per each increase of 10 000 particles/cm^3 (lag 0). Associations were greater among fatal events and subjects < 75 years
(Belleudi, Faustini et al. 2010)	90 056 cardiac hospital admissions	PNC PM_{10} $PM_{2.5}$	HF ACS Other cardiac causes	HF and ACS increased by 2.4% and 2.3% respectively per each increase of 10 μg/m^3 of PM2.5 (lag 0). HF increased by 1.7% per each increase of 9392 particles/cm^3 (lag 0)
(Dominguez-Rodriguez, Abreu-Afonso et al. 2011)	3229 hospital admissions	PNC PM_{10} $PM_{2.5}$ PM_1 Gases (CO, SO_2, NO_2, O_2)	HF ACS	UFP found to be a risk factor for HF admissions compared to admissions for ACS (odds ratio = 1.4)

ACS, acute coronary syndromes; HF, heart failure; MI, myocardial infarction; PM, particulate matter; PNC, particle number concentration; UFP, ultrafine particles. Modified from (Araujo 2011b).

Table 4. Studies linking exposure to ultrafine particles and cardiac hospital admissions.

The assessment of Nickel content exemplifies another situation where a thorough characterization of the source of emissions might prove to be helpful. Nickel (Ni) is an important metal produced from the combustion of fossil fuels. Ni content in $PM_{2.5}$ has been identified as an indicator of oil combustion not only from mobile sources such as vehicles (Brook2004) and ships (Ying, Yue et al. 2009) but also from industries such as cement production, asbestos mining and milling, iron and steel foundries, municipal waste sludge incineration and cooling tower. Exposure to Nickel, Lead and Sulfur have been reported to significantly correlate with all-cause mortality in a study involving 6 US cities (Laden, Neas et al. 2000). Ni has also been reported to induce coronary vasoconstriction, decreased heart rate variability, increased incidence of arrhythmias, increased expression of cardiac cytokines IL-6 and TGF-β, and monocytic cell infiltration in animal models (Rubanyi and Kovach 1980). Lippman et al found that exposure of $apoE^{-/-}$ mice to $PM_{2.5}$, containing Ni at an average concentration of 43 ng/m^3 for 6h/day, 5d/wk for 6 months in Tuxedo, NY resulted in acute changes in heart rate, heart rate variability and enhanced atherosclerosis (Lippmann, Ito et al. 2006). It turns out that elevated concentrations of Ni in that area were in relation to Ni emitted from the International Nickel Company at Sudbury Ontario at a distance of more than 800 km away from NYC (Lippmann, Ito et al. 2006). Exposures to a similar $PM_{2.5}$ mass but with different Ni contents that would determine different degrees of atherosclerosis would certainly substantiate the role of Ni metal in PM-mediated atherogenesis.

7. Conclusions

Several conclusions can be drawn about the cardiovascular effects of PM as follows: a) Short and long-term exposure to PM associates with various cardiovascular endpoints, especially of ischemic nature, likely in a causal manner, b) PM-induction of systemic prooxidative and proinflammatory effects appears to be key in the development of atherosclerosis, c) Particle size and chemical composition are important determinants of PM cardiovascular toxicity, d) Thorough characterization of the sources of exposure may help to identify toxic components of air pollution.

Dissecting the actual contribution of each source of emissions to the CV effects would involve a more comprehensive characterization of the type of emissions that would need to go beyond PM mass-based metrics and include qualitative analysis. No single source is likely to account for all PM-mediated cardiovascular events in a dense urban setting and instead, various sources may contribute in different degrees in different locations. Therefore, to better assess the contribution of each source of emission to cardiovascular events, consideration should be given to the type of emission source, composition of the PM derived from the source of emissions and the proximity of the emission source to contact, among other factors.

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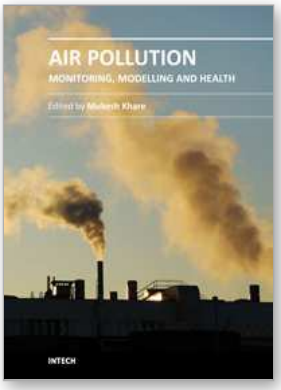

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Air pollution has always been a trans-boundary environmental problem and a matter of global concern for past many years. High concentrations of air pollutants due to numerous anthropogenic activities influence the air quality. There are many books on this subject, but the one in front of you will probably help in filling the gaps existing in the area of air quality monitoring, modelling, exposure, health and control, and can be of great help to graduate students professionals and researchers. The book is divided in two volumes dealing with various monitoring techniques of air pollutants, their predictions and control. It also contains case studies describing the exposure and health implications of air pollutants on living biota in different countries across the globe.

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