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Air Pollution and Cardiovascular Disease

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1. Introduction

Numerous epidemiological studies report consistent associations between exposure to urban air pollution and cardio-respiratory morbidity and mortality. One of the important discoveries of these epidemiological studies during the last decade was that the increased mortality associated with enhanced air pollution exposure was not due only to pulmonary diseases, but mainly to *cardiovascular* diseases. (Zanobetti et al. 2003, Samet et al. 2000, Dockery et al. 1993, Jerrett et al. 2005, Pope et al. 2004a, Pope et al. 2002, Simkhovich, Kleinman and Kloner 2008, Nawrot, Nemmar and Nemery 2006, Hoek et al. 2002, Katsouyanni et al. 2001, Dominici et al. 2003).

The focus in the initial epidemiological research was directed towards the association between both short-term and long-term exposure to air pollution and arterial cardiovascular effects, such as myocardial infarction. These landmark studies, in the beginning of the 90's, were quickly followed by experimental studies in humans and in rodents, to unravel the underlying pathophysiological mechanisms. The number of publications in this field increased exponentially, so that by the beginning of 2011, a search through PubMed using the MeSH terms 'air pollution' and 'cardiovascular disease' retrieved almost 1300 hits.

Ambient environmental air pollutants include gaseous (carbon monoxide, nitrogen oxides, sulfur dioxide, ozone) and particulate components. The particulate component, particulate matter (PM), is subdivided based on size ranges into 'thoracic particles' (PM_{10}, with a mean aerodynamic diameter <10 μm), 'coarse particles' (>2.5 μm and <10 μm), 'fine particles' ($PM_{2.5}$, <2.5 μm), and ultra-fine particles (UFP, <0.1 μm). Although exposure to some gaseous components has been linked to cardiovascular events, the larger body of evidence points towards the deleterious effects of the particulates in air pollution. Therefore, this chapter will focus mainly on the cardiovascular morbidity induced by PM exposure.

Active cigarette smoking has been established as a major independent cause of cardiovascular disease (HHS 2004). The inhaled dose of fine particles from ambient air pollution, as from secondhand cigarette smoke, is extremely small compared with that from active cigarette smoking. Accordingly, the estimated relative risks from active smoking, even at relatively light smoking levels, are substantially larger than the risks from ambient air pollution or secondhand smoke. However, the risks induced by these latter 2 types of exposure are higher than would be expected from a simple linear extrapolation based on the amount of inhaled PM from active smoking (Pope et al. 2009), and have important public health implications (Nawrot et al. 2011).

Arterial and venous thrombosis share common risk factors (Lowe 2008). The role of air pollution exposure as a risk factor for *arterial* events now being beyond discussion, a few years ago, epidemiologists started investigating a possible association with *venous* thrombotic events. Thus, in 2008, Baccarelli et al. demonstrated a link between chronic exposure to elevated levels of air pollution and deep vein thrombosis (DVT) for the first time. To understand the pathophysiological mechanisms underlying the observed link between air pollution and cardiovascular morbidity, one should take into account the complex interplay of prohemostatic and antihemostatic mechanisms, with different protagonists for the arterial and the venous vasculature. The human cardiovascular system consists of a functional vascular network for blood distribution, subdivided in a systemic and pulmonary circulatory system. The systemic circulation transports oxygenated blood through the arteries from the left heart to the organs and returns oxygen-depleted blood through the veins to the lungs. The pulmonary circulation subsequently transports the oxygen-depleted blood from the heart to the lungs, where it is oxygenated and returned to the heart.

Vascular integrity throughout the vascular tree is maintained by the vessel wall itself, as well as by a complex hemostatic mechanism involving blood platelets and coagulation factors.

The critical need to rapidly form a stable, localized clot in response to vascular injury (='hemostasis') must be balanced with the need to maintain blood flow within the vessels. Different antihemostatic mechanisms prevent clot formation under resting physiological conditions, and limit clot growth to the site of vascular injury. When prohemostatic tendencies proceed beyond the physiological need to maintain vascular integrity, a pathological thrombus may form, obstructing the normal blood flow (='thrombosis'). In the arterial system, thrombus formation induces oxygen-deprivation (ischemia) of the downstream tissues, such as myocardial infarction and cerebral ischemia. The formation of an arterial thrombus largely depends on the activation of blood platelets, and is most often triggered by the rupture of an atherosclerotic plaque. Indeed, the chronic localized deposition of lipids into the arterial vessel wall (atherosclerosis) leads to the formation of plaques that can rupture when unstable, hereby exposing their procoagulant contents to the circulation (Ross 1999). Hence, while often being asymptomatic in itself over many years, atherosclerosis formation may cumulate into an acute burst of symptomatic arterial thrombus formation.

In the venous system, thrombus formation results from a decrease in blood flow, in conjunction with a hypercoagulable state and endothelial dysfunction (Virchow's triad), and most often affects the deep veins of the legs (deep vein thrombosis, DVT). The most serious complication of DVT is the embolisation of clot dislodgements to the lungs (pulmonary embolism, PE).

The following paragraphs will describe how air pollutants affect arterial and venous functionality and lead to pathophysiological manifestations.

2. Particle triggered pathophysiological mechanisms

Inhaled particles deposit in various segments of the human respiratory tract. While the larger PM_{10} particles impact to a large extent in the nasopharyngeal and tracheal region, the smaller $PM_{2.5}$ particles penetrate deeper into the bronchi and bronchioli, whereas the UFP reach the alveolar regions. Inhaled particles are believed to affect the cardiovascular system

through 3 different pathways: interference with the autonomic nervous system, direct translocation of UFP into the systemic circulation and pulmonary inflammation.

PM inhalation deranges the autonomic nervous control of the heart (Brook et al. 2004). Numerous studies (e.g. (Park et al. 2010, Pope et al. 1999)) have shown that, by reducing the heart rate variability, PM may increase the risk for cardiac arrhytmias and sudden death . In addition, elevations in air pollution have been associated with ST-segment depression (Pekkanen et al. 2002, Mills et al. 2007), an impaired cardiac deceleration capacity (Schneider et al. 2010), hypertension (Ibald-Mulli et al. 2001) and increased diastolic blood pressure (Urch et al. 2005). The exact underlying mechanisms remain to be elucidated, but stimulation of irritant receptors in the airways and subsequent reflex activation of the nervous system as well as direct effects of pollutants on cardiac ion channels have been suggested (Brook et al. 2004, Pope et al. 2004b).

A second mechanism of action comprises the translocation of inhaled particles into the systemic circulation. Direct effects may occur via UFP that readily cross the pulmonary epithelial barrier, along with soluble constituents released from the larger particles (e.g. transition metals). Systemic translocation of particles was demonstrated in experimental animal models (Nemmar et al. 2001) (Oberdorster et al. 2002). Although evidence of systemic translocation from human studies is less clear, with both positive (Nemmar et al. 2002, Pery et al. 2009) and negative (Mills et al. 2006) findings, it is likely that this pathway also exists in humans, given the deep penetration of UFP into the alveoli and the close apposition of the alveolar wall and the capillary network. Radioactivity in the systemic circulation was already detected 1 minute after the inhalation of radioactively labelled carbon particles in humans, with peak radioactivity levels between 10 and 20 minutes (Nemmar et al. 2002). When measured in rats under resting conditions, only a small fraction (1.6-2.5%) of intratracheally instilled UFP translocated into the circulation. However, this fraction increased to 4.7% following pretreatment of the lungs with lipopolysaccharides, suggesting a role for pulmonary inflammation in enhancing the extrapulmonary translocation of particles (Chen et al. 2006). Different translocation mechanisms, ranging from endocytosis by alveolar type I and endothelial cells, over phagocytosis by macrophages to passage through widened tight junctions are recognized and depend on the particle surface chemistry (Oberdorster, Oberdorster and Oberdorster 2005). However, a detailed description of the different pathways is beyond the scope of this article. Once UFP have translocated to the blood circulation, they can be distributed throughout the body, and interact with the vascular endothelium or circulating cells, such as blood platelets and leukocytes.

Inhaled PM executes its deleterious effects also via a third, more chronic mechanism, namely pulmonary inflammation and oxidative stress. Exposure to PM induces a proinflammatory response in human lungs (Ghio, Kim and Devlin 2000), consistent with observations in *in vivo* animal models (Nemmar et al. 2003c, Emmerechts et al. 2010) and in vitro cellular models (Mitschik et al. 2008, Alfaro-Moreno et al. 2008). The presence of soluble transition metals in PM enhances the inflammatory responses via increased oxidative stress (Jiang et al. 2000). The PM-induced pulmonary inflammation is followed by the release of inflammatory cytokines, such as interleukin (IL)-1β, IL-6 and granulocyte macrophage colony-stimulating factor (van Eeden et al. 2001) in the circulation, resulting in the release of bone-marrow derived neutrophils and monocytes (Tan et al. 2000).

The generation of a systemic inflammatory response, mostly demonstrated by increases in C-reactive protein (CRP) (Peters et al. 2001b, Hertel et al. 2010), is of major importance in the

pathogenesis of cardiovascular events. Upon PM exposure, IL-6 translocates from the lung into the systemic circulation (Kido et al. 2011) and is directly involved in the regulation of the synthesis of CRP in the liver. Elevated concentrations of IL-6 are associated with an increased risk of cardiovascular events (Ridker et al. 2000, Lindmark et al. 2001) and mortality (Volpato et al. 2001). Knock-out mice that lacked IL-6 were protected against the prothrombotic effects of PM exposure (Mutlu et al. 2007). Increasing evidence points to an extensive cross-talk between inflammation and hemostasis, whereby inflammation leads to activation of blood platelets and of coagulation, and activated blood platelets and coagulation factors also considerably contribute to the inflammatory action (Levi and van der Poll 2010).

In the following paragraphs, the deleterious effects of PM exposure on arterial and venous parameters will be discussed. By virtue of their respective protagonist roles, blood platelet activation will mainly be discussed in the paragraph on arterial events, while coagulation activation will mainly be discussed in the paragraph on venous events. Formally, arterial thrombosis, the basis for myocardial infarction, is the result of vessel wall injury and formation of a platelet-rich thrombus. Venous thrombosis, the basis for VTE (venous thromboembolism) results from coagulation activation and formation of a fibrin-rich thrombus. It should be noted, however, that both blood platelet and coagulation activation intervene in arterial and venous thrombosis, and that both systems highly interact with each other (Prandoni 2009).

3. Air pollution and arterial events

Over the last 2 decades, a vast number of epidemiological studies (reviewed in (Maitre et al. 2006)) have provided convincing evidence to conclude that chronic exposure to PM enhances atherosclerosis and that acute exposure increases the risk of atherosclerotic plaque rupture, triggering arterial thrombosis, myocardial infarction and cardiovascular mortality. Relative risk levels for cardiovascular disease may differ between different studies, due to differences in study design. Short-term effects have been most often studied in time-series and case-crossover studies, while long-term effects have been studied in case-control and cohort studies. Relative risk levels are generally lower in time series studies than in other epidemiological designs. Nevertheless, the associations between cardiovascular disease and PM exposure are consistent, whatever the type of method used (Maitre et al. 2006).

An initial landmark report was that of the Harvard Six Cities study (Dockery et al. 1993), in which a cohort of 8111 adults were followed up for 14 to 16 years. The adjusted overall mortality rate for the most polluted city vs. the least polluted was 1.26 (95%CI 1.08-1.47). Cardiovascular deaths accounted for the largest single category of increased mortality. Each 10 $\mu g/m^3$ increase in long-term levels of $PM_{2.5}$ has been associated with a 8 to 18% increase in cardiovascular mortality (Pope et al. 2004a). An association with mortality was also found for traffic-related air pollution and several traffic exposure variables, although relative risks were small (Beelen et al. 2008). The effects of long-term PM exposure on cardiovascular mortality have been shown elegantly by the demonstration of a parallelism between air quality improvement and reduction in cardiovascular events on a population-based level (Laden et al. 2006, Boldo et al. 2011). A potential benefit in general mortality can be expected within 2 years after the reduction of PM exposure (Schwartz et al. 2008).

The magnitude of these associations appeared to be more pronounced for the smaller $PM_{2.5}$ fraction than for the larger PM_{10} fraction (Puett et al. 2009). Considering a large body of evidence, a recent updated version of the American Heart Association scientific statement on 'Air Pollution and Cardiovascular Disease' (Brook et al. 2010) concluded that per 10 $\mu g/m^3$ increase in long-term levels of $PM_{2.5}$, all-cause mortality increased by an approximate 10%. The mortality risk specifically related to cardiovascular disease appears to be elevated to a similar, or perhaps even greater extent, ranging from 3 to 76% over different studies.

3.1 Chronic PM exposure and atherosclerosis

What etiological agent can explain the link between chronic air pollution exposure and cardiovascular mortality? Künzli et al. provided the first epidemiological evidence for an association with atherosclerosis: living in the areas of Los Angeles with highest annual mean concentrations of ambient $PM_{2.5}$ was associated with an increased intima-media thickness of the carotid artery (Kunzli et al. 2005).

Distance from the residence to a major road correlated with the degree of coronary artery calcification, a measure for atherosclerosis (Hoffmann et al. 2007).

Another study in 5172 adults investigated 20-year PM exposure and found an association, although weaker than in the previous studies, with carotid intima media thickness, but not with other measures of atherosclerosis i.e. coronary calcium and ankle brachial index (Diez Roux et al. 2008).

A recent study demonstrates that long-term PM exposure is not only related to the degree, but also to a faster progression rate of atherosclerosis (Kunzli et al. 2010).

Along with this epidemiological evidence, experimental research also established a link between exposure to PM and the development of atherosclerosis. Repeated exposure to PM_{10} in rabbits was associated with both systemic inflammation and the progression of the atherosclerotic process, the extent of which correlated with the extent of PM_{10} phagocytosed by alveolar macrophages (Suwa et al. 2002).

Exposing genetically susceptible apolipoprotein E-null mice for 6 months to an equivalent concentration of 15.2 $\mu g/m^3$ $PM_{2.5}$ over a lifetime, enhanced abdominal aortic plaque formation as compared to mice exposed to filtered air (Sun et al. 2005). Interestingly, ultrafine (<0.18 μm) particle-exposed mice exhibited significantly larger atheroslerotic lesions than mice exposed to fine (<2.5 μm) particles or filtered air (Araujo et al. 2008).

Atherosclerosis is now considered an inflammatory disease with low density lipoprotein (LDL) cholesterol accumulation in the arteries as the primary risk factor (Ross 1999). However, up to 50% of the patients who develop atherosclerosis do not have high cholesterol (Braunwald 1997). Therefore, it is the relationship between the accumulated lipids and other harmful components of inflammation in the arterial vessel wall that is of concern. LDL infiltration of the arterial vessel wall is followed by oxidative modification to oxidized LDL (ox-LDL) in the subendothelial space and chemotaxis of monocytes. These monocytes differentiate into macrophages and the subsequent phagocytosis of ox-LDL leads to the formation of foam cells and the release of inflammatory mediators, inducing a vicious cycle of inflammation. Further stages include smooth muscle cell proliferation, formation of a fibrous cap with necrotic core and calcification (Ross 1999). Thickening of the vessel wall and obliteration of the vascular lumen induces downstream ischemia of the tissues.

PM exposure can induce atherosclerosis via different pathways: systemically translocated UFP or their chemical constituents induce activation of proatherogenic molecular

pathways in endothelial cells, by oxidative stress. Inflammatory mediators released from the lungs may promote chemotaxis of monocytes into the vessel wall. PM induces high-density lipoprotein (HDL) dysfunction with loss of its anti-inflammatory properties (Araujo and Nel 2009).

Oxidative transformation of LDL into ox-LDL is a key step in the initiation and progression of atherosclerosis (Stocker and Keaney 2004), and circulating levels of ox-LDL are therefore an early marker, and a risk factor for the disease (Wallenfeldt et al. 2004). The correlation between PM exposure and circulating levels of ox-LDL on an individual level was shown by Jacobs et al., demonstrating a dose-dependent association between this parameter and the carbon load of airway macrophages, a personal marker for chronic exposure to fossil fuel derived ultrafine particles (Jacobs et al. 2011).

It has been previously shown that particles can induce oxidative stress both in vitro (Jimenez et al. 2000, Carter et al. 1997) and in exposed animals (Costa and Dreher 1997, Kadiiska et al. 1997, Tao, Gonzalez-Flecha and Kobzik 2003, Araujo et al. 2008).

In agreement with epidemiological findings (Puett et al. 2009), experimental studies suggest that the smaller particles are more pathogenic, as a result of their greater propensity to induce systemic prooxidant and proinflammatory effects (Araujo et al. 2008). Indeed, ambient UFP trigger the induction of the antioxidant gene heme oxygenase 1 (HO-1) to a higher degree than ambient $PM_{2.5}$ or coarse particles, both *in vitro* (Li et al. 2004) and *in vivo* (Araujo et al. 2008, Araujo and Nel 2009). Several mechanisms contribute to the greater proatherogenic potential of UFP: because of their small size, particles < 0.1-0.2 μm contribute very little to overall $PM_{2.5}$ mass. However, they represent >85-90% of the total $PM_{2.5}$ particle number (Sioutas, Delfino and Singh 2005). The high number of UFP, in conjunction with a large surface-to-mass ratio increases the bioavailability of the pro-oxidant chemicals (polycyclic aromatic hydrocarbons, transition metals etc.) present on the UFP's surface. The number of chemicals that are displayed on the surface of particles increases exponentially as the size shrinks below 100 nm (Oberdorster et al. 2005). Deep penetration in the lung and subsequent translocation of UFP into the circulation make these pro-oxidant chemicals more bioavailable at the contact sites of the particles with cells and tissues.

3.2 Acute PM exposure and arterial thrombosis

Not only chronic, but also short-term PM exposure has been linked to cardiovascular mortality: Both the American NMMAPS (National Morbidity, Mortality, and Air Pollution Study (Dominici et al. 2003)) and the European APHEA2 (Air Pollution and Health: A European Approach (Katsouyanni et al. 2001, Zanobetti et al. 2003)) studies (approximately 50 million and 43 million persons included respectively) demonstrated small increases in cardiovascular mortality with increasing PM exposure. In an attempt to evaluate the coherence of studies across continents, the APHENA (A Combined European and North American Approach) analyzed data of these 2 aforementioned studies and Canadian studies (Samoli et al. 2008). The combined effect on all-cause mortality ranged from 0.2% to 0.6% for a 10 $\mu g/m^3$ increase in daily levels of ambient PM_{10}, with greater effects for the elderly (>75 years) and the unemployed. An extensive review of studies investigating a link between short-term PM exposure and cardiovascular mortality is provided in (Brook et al. 2010).

Peters et al. (Peters et al. 2001a) demonstrated an increased risk of myocardial infarction in association with elevated concentrations of fine $PM_{2.5}$, both in the previous 2-hours period

and the day before the onset. Likewise, the onset of myocardial infarction was linked to participation in traffic, as soon as 1 h afterward (odds ratio 2.92, 95%CI 2.22-3.83) (Peters et al. 2004).

Exposure to ambient $PM_{2.5}$ is associated with short-term increases in hospital admission rates for cerebrovascular, peripheral and cardiac ischemic disease, heart rhythm and heart failure, with the strongest association for heart failure (1.28 % 95%CI 0.78-1.78% increase in risk per 10 $\mu g/m^3$ increase in same-day $PM_{2.5}$) (Dominici et al. 2006).

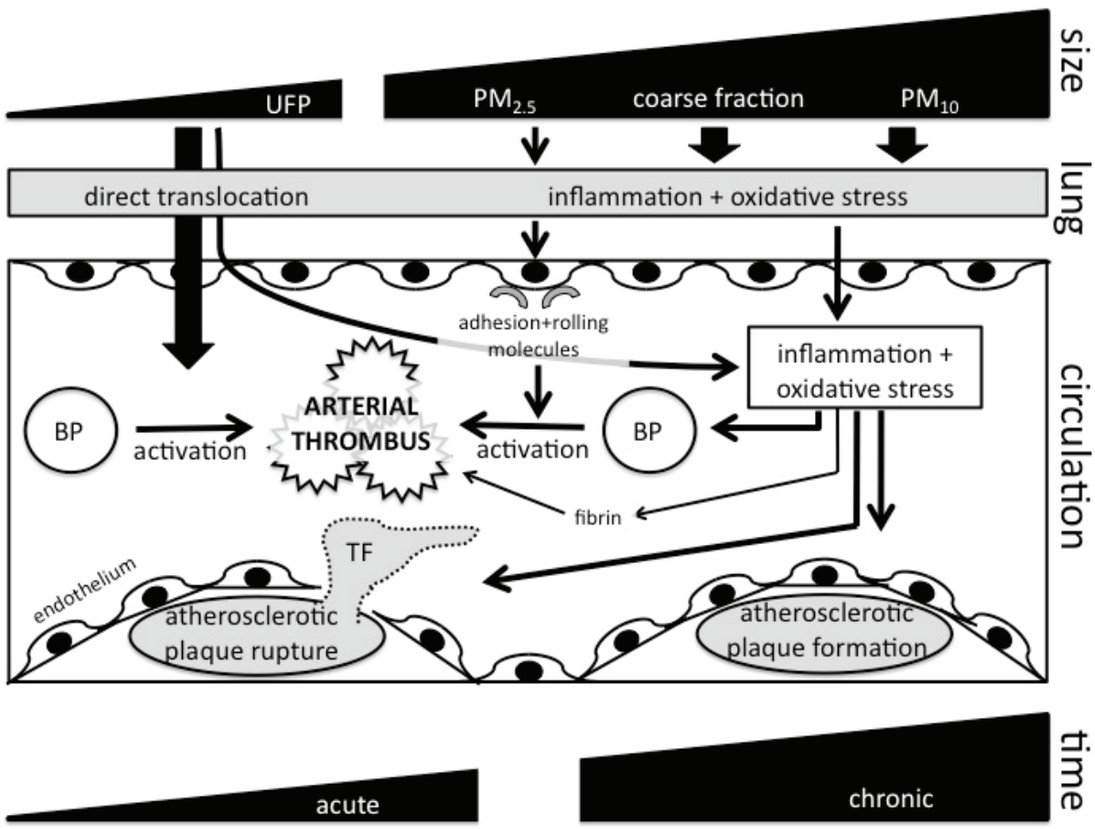
The risk of mortality from coronary heart disease related to PM exposure appears to be higher in women (RR 1.42, 95%CI 1.06-1.90) than in men (RR 0.90, 95%CI 0.76-1.05 per 10 $\mu g/m^3$ increase in $PM_{2.5}$)(Chen et al. 2005). In a study of 65893 postmenopausal women with a median follow-up of 6 years, each increase in long-term levels of $PM_{2.5}$ of 10 $\mu g/m^3$, measured at the women's residence, was associated with a 24% (95%CI 09-41%) increase in the risk of a cardiovascular event, and a 76% (95%CI 25-147%) increase in the risk of death of cardiovascular disease (Miller et al. 2007).

Although the magnitude of the risk on myocardial infarction induced by short-term PM exposure is rather small on a personal level, it is of major importance on a population level, by virtue of the large number of people exposed. Taking into account both risk magnitude and risk prevalence by measurement of the population attributable fraction (PAF), Nawrot et al. showed that a short-term increase in air pollution exposure is an important trigger for myocardial infarction, of similar magnitude (PAF 5-7%) as other well accepted triggers such as physical exertion, alcohol and coffee (Nawrot et al. 2011).

Epidemiological studies suggest an association between short-term increases in PM exposure and atherosclerotic plaque rupture, causing arterial thrombosis and myocardial infarction. In contrast to the growing number of mechanistic studies investigating the role of chronic PM exposure on atherogenesis, the precise mechanisms explaining the role of short-term PM exposure in acute plaque rupture largely remain to be elucidated. However, several epidemiological and mechanistic studies demonstrated that, in parallel to atherosclerotic plaque rupture, direct or indirect activation of circulating blood platelets by PM contributes to the arterial thrombosis risk. Indeed, the extent to which a growing thrombus occludes the vascular lumen may in part depend on platelet hyperactivity.

Under physiological circumstances, the high blood pressure generated on the arterial side of the circulation requires a powerful, almost instantaneous prohemostatic response in order to minimize blood loss from sites of vascular injury. Blood platelets play a critical role in this response. Upon damage of the endothelial cell layer covering the luminal side of blood vessels, circulating blood platelets adhere to the exposed subendothelial matrix through the binding of the glycoprotein (GP) Ib-IX-V receptor to exposed von Willebrand factor (vWF). Blood platelet adhesion is further enhanced by the binding of different GP receptors to other subendothelial matrix proteins, such as collagen and fibrin(ogen). Upon adhesion and activation of the blood platelets by various agonists, vWF and fibrinogen molecules cross-link different platelets, resulting in blood platelet aggregation and the formation of an initial platelet plug which covers the site of endothelial lesion. The simultaneous activation of the coagulation cascade leads to the formation of a network of insoluble fibrin strands that further stabilize the initial platelet plug.

Air pollution exposure can induce an inappropriate activation of blood platelets beyond the physiological need to restore vessel damage, resulting in arterial thrombosis (Fig. 1).



BP: blood platelet, PM: particulate matter, TF: tissue factor, UFP: ultra-fine particles

Fig. 1. Biological pathways linking PM exposure and arterial thrombosis

By exposing healthy volunteers to diluted diesel exhaust, Lucking et al. showed an association with enhanced platelet activity and thrombus formation in an *ex vivo* perfusion chamber, 2 hours and 6 hours after exposure, in conjunction with increased numbers of platelet-neutrophil (+52%) and platelet-monocyte (+30%) conjugates (Lucking et al. 2008).
Short-term, but not long-term PM exposure was found to enhance platelet function, as measured *ex vivo* by a shortening of the closure time of the Platelet Function Analyzer (PFA-100, Siemens Healthcare Diagnostics), in patients with diabetes (Jacobs et al. 2009). In this study, an interquartile range (39.2 μg/m^3) increase in the PM_{10} concentration, measured 2 hours before the clinical investigation at the entrance of the hospital, was associated with a decrease of 21.1 sec (95%CI -35.3 to -6.8) in the PFA-100 closure time. Platelet function was not correlated with leukocyte counts, suggesting that short-term PM exposure may have effects on platelet function independently of systemic inflammation, as was also shown in experimental animal models (Nemmar et al. 2003c).
Ambient PM_{10} levels have also been associated with augmented platelet aggregation 24 to 96 hours after exposure in healthy adults, in the absence of increased CRP or fibrinogen (Rudez et al. 2009). In patients with coronary heart disease, mean concentrations over 24 hours of ambient UFP, but not $PM_{2.5}$ or PM_{10} were positively associated with the levels of soluble CD40 ligand, a marker for platelet activation. No assocations were found with longer time frames, up to 5 days (Ruckerl et al. 2007b).

In experimental conditions using DEP, Nemmar et al. demonstrated a prothrombotic tendency and activation of circulating blood platelets (confirmed by PFA-100), as well as lung inflammation, which persisted up to 24 hr after intratracheal instillation of DEP in hamsters (Nemmar et al. 2003a, Nemmar et al. 2003c).

However, different pathophysiological mechanisms seem to be responsible for the observed prothrombotic risk at different time points. Pretreatment of hamsters with a histamine H1-receptor antagonist, an anti-inflammatory drug, abolished pulmonary inflammation at all time points and reduced DEP-induced thrombosis at 6 and 24 hours post-instillation, indicating a crucial role for inflammation in thrombogenicity at these time points. Likewise, the administration of other anti-inflammatory drugs, such as dexamethasone and selective inhibitors of basophils, macrophages and neutrophils, also significantly reduced the PM-induced prothrombogenicity at 24 hours (Nemmar et al. 2004, Nemmar et al. 2005).

In contrast, pretreatment with the histamine H1-receptor antagonist did not reduce thrombosis as soon as 1 hour after DEP exposure (Nemmar et al. 2003c). Therefore, the early prothrombotic tendency appears not to result from pulmonary inflammation, but possibly from direct effects of systemically translocated particles on the blood platelets and/or the (pulmonary) vessel wall (Nemmar et al. 2003c). The direct activating effect of PM on blood platelets was shown by the addition of as little as 0.5 μg/mL DEPs to untreated hamster blood, significantly shortenening the PAF-100 closure time (Nemmar et al. 2003a), as well as by a dose-dependent (0.1-1 μg/mL) effect of PM on in vitro platelet aggregation in rat blood (Nemmar et al. 2010), although similar experiments in human blood were negative (Rudez et al. 2009).

In agreement with these results, 1 hour after intratracheal instillation, well-defined positively charged ultrafine (60 nm) polystyrene particles significantly enhanced platelet-rich thrombus formation, while 400 nm particles, incapable of systemic translocation, did not affect thrombus formation, despite similar increases in neutrophils, lactate dehydrogenase and histamine levels in the bronchoalveolar lavage fluid (Nemmar et al. 2003b).

Pulmonary instillation of carbon nanotubes elevated platelet-leukocyte conjugates at 6 hours and increased the peripheral thrombotic potential at 24 hours after exposure. Inhibition of P-selectin abrogated these responses (Nemmar et al. 2007). P-selectin is found in storage Weibel-Palade bodies of endothelial cells and in α-granules of platelets, from where it can be expressed on the outer membrane upon activation. Surface expression of P-selectin initiates capture and rolling of circulating leukocytes over stimulated endothelium (Theilmeier et al. 2002) and the formation of platelet-leukocyte conjugates (Yokoyama et al. 2005). Increased levels of platelet-leukocyte conjugates have been demonstrated in Indian women who used biomass as cooking fuel, producing higher levels of PM, as compared to women cooking with a cleaner fuel (liquefied petroleum gas) (Ray et al. 2006). In a panel study of 60 elderly subjects with coronary artery disease, Delfino et al. demonstrated associations between soluble P-selectin levels and the mean 1 to 5-day concentrations of ambient finer particles ($PM_{0.25}$ and $PM_{2.5}$), but not the bigger PM_{10} (Delfino et al. 2009). Taken together, these studies suggest that the release of pulmonary cell-derived mediators (eg. histamine) and the expression of endothelial and platelet surface proteins (eg. P-selectin) after several hours, along with the more rapid activation of circulating platelets by direct contact with UFP may mediate peripheral prothrombotic effects.

4. Air pollution and venous thromboembolism

4.1 Epidemiology

In addition to the well-recognized PM-related adverse effects on the arterial vascular system, recent epidemiological evidence also suggests an association between exposure to PM and venous thromboembolism (VTE). Baccarelli et al. reported a 70% increase in the risk of deep vein thrombosis (DVT) for each 10 μg/m^3 increase of the annual mean level of PM_{10} in the areas of residence of the study subjects (OR 1.70, 95%CI 1.30-2.23) (Baccarelli et al. 2008). The observed exposure-response relationship was approximately linear over the observed PM_{10} range, so that PM_{10} at the higher concentrations within the international limits can still increase the risk of DVT, as compared to the lowest concentration measured. These authors found, in the same study subjects, that living near major traffic roads was also associated with an increased risk of DVT, even after controlling for the community-level PM pollution (Baccarelli et al. 2009). Very recently, exposure to PM has also been associated with hospital admission for VTE in Chile. Both for DVT and for PE, pooled estimates of relative risk of hospitalization were 1.05 (95%CI 1.03-1.06) for a 20.02 μg/m^3 increase in $PM_{2.5}$ (Dales, Cakmak and Vidal 2010).

However, these initial epidemiological reports on the association between air pollution exposure and venous thrombosis were followed by a number of prospective cohort studies that failed to demonstrate an association: 26,450 post-menopausal women, enrolled in the Women's Health Initiative (WHI) Hormone Therapy trials, were randomized to treatment with either hormone therapy or placebo. Regardless of the treatment category, no evidence was found of an association between short- or long-term (up to 1 year) PM exposure and VTE (Shih et al. 2010). Of note, the aforementioned study of Baccarelli et al. also observed lower PM-induced VTE risk among women compared to men (Baccarelli et al. 2008). A prospective study in 13,134 middle-aged persons, including men and women, also provided evidence against an association between VTE and long-term air pollution exposure, as assessed by residential distance to a major road (Kan et al. 2011).

Hence, in contrast to the well-accepted and documented deleterious effects of air pollution exposure on arterial events, data are scarce and the link with venous thrombosis is less straightforward, prompting further epidemiological investigation.

4.2 Pathophysiology

At lower rates of shear found in the venous circulation, the contribution of blood platelets to clot formation is of lesser importance than in the arterial circulation, leaving a protagonist role for the coagulation cascade in venous hemostasis. Activation of the coagulation cascade is initiated by activation of coagulation factor VII (FVII) by binding to tissue factor (TF), expressed on subendothelial cells such as fibroblasts and vascular smooth muscle cells. The complex of TF and activated FVII (FVIIa) initiates a cascade of subsequent coagulation factor activations, resulting in the generation of thrombin. Thrombin (FII) is a key enzyme, converting fibrinogen monomers to fibrin polymers that clot into a fibrin plug, and amplifying the coagulation cascade through activation of FV, FVIII and FXI.

The mechanisms underlying the observed increase in venous thrombosis in association with exposure to air pollution remain largely unknown, and published results with regard to markers of secondary hemostasis activation are conflicting. Although some epidemiological and controlled exposure studies demonstrated an association between PM exposure and

shortening of the prothrombin time (PT) or increased levels of fibrinogen and vWF, others failed to demonstrate positive associations with these or other markers of coagulation, in humans (Table 1). In fact, disappointingly few studies reported on PM-induced coagulatory changes that could form the basis for the observed link between air pollution and DVT. How can this conundrum of PM-induced DVT in the absence of a procoagulant phenotype be explained?

One explanation for the lack of positive associations between PM exposure and measurement of parameters of coagulation might be found in the short observation time frame that was used in most studies. While short-term PM exposure enhances blood platelet activation, a more chronically sustained exposure appears to be necessary to induce significant changes in the coagulatory cascade.

This hypothesis is corroborated by epidemiological findings in which the risk for DVT was only associated with the mean PM concentration over a one year period, and not with any shorter time-point (Baccarelli et al. 2008). This was confirmed by animal studies in which short- term exposure of healthy mice to intratracheally instilled DEP or UPM enhanced arterial, but not venous thrombosis (Emmerechts et al. 2010). In this study, even very high doses of PM (up to 200 μg/mouse), given as a single dose, induced only mild increases in the levels of FVII, FVIII and fibrinogen. Likewise, exposure of rats to concentrated PM from New York City air did not alter levels of fibrinogen, FVII or thrombin-antithrombin complexes (TAT) (Nadziejko et al. 2002).

Significant increases in the level of fibrinogen, or decreases in the levels of the anticoagulant proteins activated protein C or tissue factor pathway inhibitor (TFPI) upon short-term PM exposure have been observed in rodents, but at doses of 100 μg or higher per mouse (Cozzi et al. 2007, Inoue et al. 2006). One study stands out among other studies on procoagulant changes and PM exposure: Mutlu et al. observed a pronounced prothrombotic phenotype in mice upon a single intratracheal instillation of as few as 10 μg of PM_{10}, characterized by shortenings in bleeding time, PT and aPTT, and relatively high increases in the levels of circulating blood platelets, FVII, FVIII, FX and fibrinogen (Mutlu et al. 2007). The reason for the discrepancy between this and other studies being unclear, this study is of value since it demonstrated the absence of a PM-induced prothrombotic phenotype in interleukin-6 (IL-6) knock-out mice, recognizing a major role of inflammatory factors in the induction of procoagulant changes following PM exposure.

Indeed, although some studies suggest a short-term effect of directly translocated UFP through the activation of the coagulation cascade via contact activation, as demonstrated *in* vitro (Kilinc et al. 2010), evidence seems to favor a more prominent role for inflammatory changes related to chronic PM exposure. In this context, it is of interest that the only coagulation factor for which the associations with air pollution were consistent over different studies in humans is fibrinogen (Table 1), an acute phase protein that is upregulated during inflammatory processes.

However, although considered to be a (minor) risk factor, elevated levels of fibrinogen seem unlikely to be solely responsible for the PM-induced increased risk of DVT.

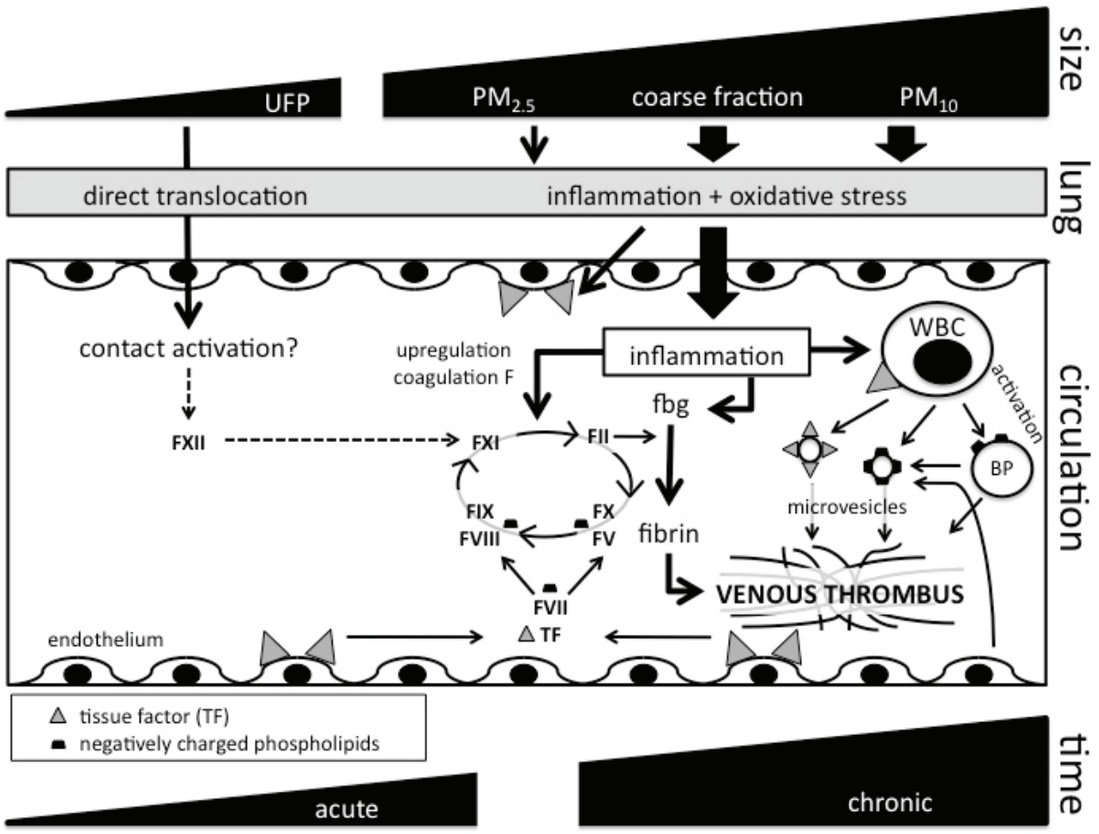
Through the expression of procoagulant proteins and lipids on their surface, microvesicles (also called microparticles, a term we prefer to avoid in the context of pollution by particles) could offer an alternative explanation. Microvesicles are circulating vesicles released from stimulated or apoptotic cells in the vasculature, or during thrombogenesis in the bone marrow, with a mean diameter smaller than 1 μm. Through their surface expression of

reference	subjects				exposure			coagulatory changes	
author + year	n	type	mean age (SD or range)	gender (% male)	controlled exposure	type of air pollution	exposure time	significant changes	no significant changes
(Seaton et al. 1999)	112	NA	70 (7)	?	no	ambient PM_{10}	3 days	FVII (-), fbg (-)	
(Ghio et al. 2000)	38	healthy subjects	26 (0.7)	95	yes	concentrated $PM_{2.5}$	2h	fbg	
(Pekkanen et al. 2000)	7205	healthy subjects	NA	69	no	ambient PM_{10}	1-3 days	fbg	
(Ghio et al. 2003)	20	healthy subjects	25 (0.8)	70	yes	concentrated $PM_{2.5}$	2h	fbg	D-dim, PC, vWF
(Riediker et al. 2004)	9	healthy subjects	27 (23-30)	100	no	in-vehicle $PM_{2.5}$	9h	vWF	
(Beckett et al. 2005)	12	healthy subjects	35 (23-52)	50	yes	zinc oxide particles	2h		fbg, FVII, vWF
(Blomberg et al. 2005)	15	COPD patients	66 (56-72)	NA	yes	diesel exhaust	1h		fbg, D-dim, vWF
(Barregard et al. 2006)	13	healthy subjects	34 (20-56)	46	yes	wood smoke	4h	FVIII	fbg, FVII, D-dim, vWF
(Ruckerl et al. 2006)	57	CHD patients	66 (6)	100	no	ambient $PM_{2.5}$ and PM_{10}	1-5 days	FVII (-), vWF	fbg, D-dim
(Baccarelli et al. 2007)	1218	healthy subjects	44 (11-84)	40	no	ambient PM_{10}	t0 - 30days	PT	aPTT, fbg, AT, PC, PS
(Carlsten et al. 2007)	13	healthy subjects	25 (20-42)	85	yes	diesel exhaust	2h		D-dim, vWF
(Chuang et al. 2007)	76	healthy students	21 (18-25)	65	no	ambient $PM_{2.5}$ and PM_{10}	1-3 days	fbg	
(Ruckerl et al. 2007a)	1003	MI survivors	65 (45-78)	69	no	ambient $PM_{2.5}$ and PM_{10}	1-4 days	fbg	
(Scharrer et al. 2007)	20	healthy subjects	29 (8)	60	yes	welding fume	1h		FVIII, vWF, AT
(Brauner et al. 2008)	41	healthy subjects	67 (60-75)	51	yes	indoor $PM_{2.5}$ and PM_{10}	2 days		fbg, FII+VII+X
(Lucking et al. 2008)	20	healthy subjects	26 (21-44)	NA	yes	diesel exhaust	1-2h		PT, aPTT
(Rudez et al. 2009)	40	healthy subjects	41 (15)	35	no	ambient PM_{10}	6h-4days		fbg,TG
(Samet et al. 2009)	19	healthy subjects	18-35	53	yes	concentrated ambient UFP	2h	D-dim	fbg, FIX, FXII, vWF
(Bonzini et al. 2010)	37	steel plant workers	42 (7)	100	no	occupational PM_{10}	1-3 days	PT,TG	aPTT, D-dim
(Stewart et al. 2010)	19	T2DM patients	48 (9)	47	yes	carbon UFP	2h		FVII, FIX, D-dim, TF
(Thompson et al. 2010)	45	healthy subjects	27 (19-48)	49	no	ambient $PM_{2.5}$	t0 - 7 days		fbg
(Jacobs et al. 2011)	70	DM patients	57 (14)	53	no	carbon load in alveolar Mφ	NA		vWF

COPD: chronic obstructive pulmonary disease, MI: myocardial infarction, CHD: coronary heart disease, DM: diabetes mellitus, T2DM: type 2 diabetes mellitus, PM: particulate matter, UFP: ultra-fine particles, Mφ: macrophages, PT: prothrombin time, aPTT: activated partial prothrombin time, AT: antithrombin, PC: protein C, PS: protein S, F: factor, fbg: fibrinogen, D-dim: D-dimers, vWF: von Willebrand factor, TG: thrombin

Table 1. Associations between PM exposure and coagulatory changes according to different studies.

negatively charged phospholipids and of tissue factor (TF), they create a procoagulant surface on which coagulation factors can bind and be activated (Morel et al. 2006). Indeed, the initial concept that TF presence is limited to a hemostatic envelope surrounding blood vessels has been challenged by the identification of 'blood borne' TF, either on circulating white blood cells or microvesicles, as a soluble protein, or possibly on stimulated endothelial cells (Pawlinski et al. 2010).



BP: blood platelet, F: factor, fbg: fibrinogen, PM: particulate matter, TF: tissue factor, UFP: ultra-fine particles, WBC: white blood cell

Fig. 2. Biological pathways linking PM exposure and venous thrombosis

A role for microvesicles has been suggested by the work of Bonzini et al., investigating blood samples collected in steel-production plant workers. Besides shortening the PT, elevated PM exposure also enhanced thrombin generation, but only when measured in an assay without the exogenous addition of a coagulation trigger or negatively charged phospholipids (Bonzini et al. 2010). These findings suggest that PM exposure may induce the release of small amounts of endogenous TF and/or negatively charged phospholipids that may function as triggers of thrombin generation in the assay system. Circulating microvesicles might well be the source of these triggers. This hypothesis is corroborated by animal studies demonstrating elevated numbers of procoagulant microvesicles, 24 hours after intratracheal instillation of carbon nanotubes in mice (Nemmar et al. 2007). Likewise, when stimulated *ex vivo*, blood platelets from mice exposed to concentrated ambient PM for 2 weeks released more microvesicles relative to platelets from ambient air-exposed control

animals (Wilson et al. 2010). However, observational or controlled exposure studies in humans are needed for further confirmation. Figure 2 summarizes the possible pathophysiological pathways linking PM exposure and venous thrombogenicity.

5. Endothelial function and fibrinolysis

The effects of air pollution on the endothelial function and the fibrinolytic system have mainly been investigated in controlled exposure studies by 2 research groups who joined forces. The groups of Newby and Blomberg used exposure chambers to expose healthy and compromised volunteers to the diluted exhaust of an iddling diesel engine for several hours in randomized cross-over studies. They demonstrated an impaired bradykinin-induced endothelial release of tissue plasminogen activator (t-PA) upon diesel exhaust inhalation (estimated reduction of net t-PA release of 34%) (Mills et al. 2005, Mills et al. 2007), in addition to an attenuated agonist-induced increase in blood flow at 6 hours post-inhalation, in the absence of inflammatory changes (Mills et al. 2005). At 24 hours post-inhalation, endothelium-dependent vasodilatation (induced by acetylcholine and bradykinin) remained impaired, while endothelium-independent vasodilatation (using sodium nitroprusside and verapamil) and t-PA release were unaffected, in the presence of mild sytemic inflammation (Tornqvist et al. 2007).

These and other (Bonzini et al. 2010, Chuang et al. 2007, Ghio et al. 2003, Samet et al. 2009) studies did not demonstrate an assocation between PM exposure and baseline levels (not bradykinin-induced) of t-PA.

While studies, based on controlled exposure to diluted diesel exhaust (Mills et al. 2007, Tornqvist et al. 2007, Carlsten et al. 2007) or concentrated ambient particles (Ghio et al. 2003), did not observe increases in the levels of plasminogen activator inhibitor-1 (PAI-1), some epidemiological or animal studies, focussing on urban PM, did: a study in 76 young healthy students demonstrated elevated PAI-1 concentrations in association with the mean $PM_{2.5}$ or PM_{10} concentration at their university's campus over 1 to 3 days (Chuang et al. 2007). Likewise, urban PM upregulated PAI-1 levels, 24 hours after intratracheal instillation in mice (Cozzi et al. 2007).

PM exposure could also impair the endothelial repair mechanisms by reducing the number of endothelial progenitor cells, as demonstrated by a recent report (O'Toole et al. 2010).

Taken together, these studies indicate a potential deleterious effect of PM inhalation on the endothelial and fibrinolytic function that may aggravate the prothrombotic phenotype induced by blood platelet and coagulation activation.

6. Conclusions

A wide array of epidemiological and experimental studies have provided persuasive evidence that air pollutants, the PM fraction in particular, contribute to cardiovascular morbidity and mortality. By virtue of the heterogeneity in both study design and the composition of the PM considered by these studies, it is not surprising that not all findings have been consistent. However, considering the overall weight of scientific evidence, some general conclusions can be drawn: through the induction of inflammation and oxidative stress, the inhalation of particulates, especially the finest fractions ($PM_{2.5}$ and UFP), over longer time periods contributes to atherosclerotic plaque formation. At shorter time points (<24 h), these particles may induce plaque rupture and activate blood platelets, leading to

acute peripheral arterial events such as myocardial infarction. Blood platelet activation within the first few hours is inflammation-independent, most probably resulting from direct contact with systemically translocated particles and/or activated endothelium. Thereafter, inflammatory changes are responsible for further platelet activation.

Although evidence linking PM exposure with venous thromboembolic events is less established than with arterial events and warrants further investigation, recent findings suggest that chronic air pollution exposure is also a risk factor for venous thrombosis. Inflammatory changes, along with the generation of circulating procoagulant microvesicles might be of larger importance than coagulation factor upregulation, favoring a role for the larger particles (PM_{10}) with higher pro-inflammatory endotoxin content on their surface.

Air pollution exposure may not be the highest risk factor for arterial or venous thrombosis on an individual level. However, because of the huge number of persons exposed, on a global scale it is a major, and more importantly, a modifiable risk factor for cardiovascular disease and mortality.

7. References

Alfaro-Moreno, E., T. S. Nawrot, B. M. Vanaudenaerde, M. F. Hoylaerts, J. A. Vanoirbeek, B. Nemery & P. H. Hoet (2008) Co-cultures of multiple cell types mimic pulmonary cell communication in response to urban PM10. *Eur Respir J,* 32**,** 1184-94.

Araujo, J. A., B. Barajas, M. Kleinman, X. Wang, B. J. Bennett, K. W. Gong, M. Navab, J. Harkema, C. Sioutas, A. J. Lusis & A. E. Nel (2008) Ambient particulate pollutants in the ultrafine range promote early atherosclerosis and systemic oxidative stress. *Circ Res,* 102**,** 589-96.

Araujo, J. A. & A. E. Nel (2009) Particulate matter and atherosclerosis: role of particle size, composition and oxidative stress. *Part Fibre Toxicol,* 6**,** 24.

Baccarelli, A., I. Martinelli, V. Pegoraro, S. Melly, P. Grillo, A. Zanobetti, L. Hou, P. A. Bertazzi, P. M. Mannucci & J. Schwartz (2009) Living near major traffic roads and risk of deep vein thrombosis. *Circulation,* 119**,** 3118-24.

Baccarelli, A., I. Martinelli, A. Zanobetti, P. Grillo, L. F. Hou, P. A. Bertazzi, P. M. Mannucci & J. Schwartz (2008) Exposure to particulate air pollution and risk of deep vein thrombosis. *Arch Intern Med,* 168**,** 920-7.

Baccarelli, A., A. Zanobetti, I. Martinelli, P. Grillo, L. Hou, S. Giacomini, M. Bonzini, G. Lanzani, P. M. Mannucci, P. A. Bertazzi & J. Schwartz (2007) Effects of exposure to air pollution on blood coagulation. *J Thromb Haemost,* 5**,** 252-60.

Barregard, L., G. Sallsten, P. Gustafson, L. Andersson, L. Johansson, S. Basu & L. Stigendal (2006) Experimental exposure to wood-smoke particles in healthy humans: effects on markers of inflammation, coagulation, and lipid peroxidation. *Inhal Toxicol,* 18**,** 845-53.

Beckett, W. S., D. F. Chalupa, A. Pauly-Brown, D. M. Speers, J. C. Stewart, M. W. Frampton, M. J. Utell, L. S. Huang, C. Cox, W. Zareba & G. Oberdorster (2005) Comparing inhaled ultrafine versus fine zinc oxide particles in healthy adults: a human inhalation study. *Am J Respir Crit Care Med,* 171**,** 1129-35.

Beelen, R., G. Hoek, P. A. van den Brandt, R. A. Goldbohm, P. Fischer, L. J. Schouten, M. Jerrett, E. Hughes, B. Armstrong & B. Brunekreef (2008) Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). *Environ Health Perspect,* 116**,** 196-202.

Blomberg, A., H. Tornqvist, L. Desmyter, V. Deneys & C. Hermans (2005) Exposure to diesel exhaust nanoparticles does not induce blood hypercoagulability in an at-risk population. *J Thromb Haemost,* 3**,** 2103-5.

Boldo, E., C. Linares, J. Lumbreras, R. Borge, A. Narros, J. Garcia-Perez, P. Fernandez-Navarro, B. Perez-Gomez, N. Aragones, R. Ramis, M. Pollan, T. Moreno, A. Karanasiou & G. Lopez-Abente (2011) Health impact assessment of a reduction in ambient PM(2.5) levels in Spain. *Environ Int,* 37**,** 342-8.

Bonzini, M., A. Tripodi, A. Artoni, L. Tarantini, B. Marinelli, P. A. Bertazzi, P. Apostoli & A. Baccarelli (2010) Effects of inhalable particulate matter on blood coagulation. *J Thromb Haemost,* 8**,** 662-8.

Brauner, E. V., L. Forchhammer, P. Moller, L. Barregard, L. Gunnarsen, A. Afshari, P. Wahlin, M. Glasius, L. O. Dragsted, S. Basu, O. Raaschou-Nielsen & S. Loft (2008) Indoor particles affect vascular function in the aged: an air filtration-based intervention study. *Am J Respir Crit Care Med,* 177**,** 419-25.

Braunwald, E. (1997) Shattuck lecture--cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med,* 337**,** 1360-9.

Brook, R. D., B. Franklin, W. Cascio, Y. Hong, G. Howard, M. Lipsett, R. Luepker, M. Mittleman, J. Samet, S. C. Smith, Jr. & I. Tager (2004) Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation,* 109**,** 2655-71.

Brook, R. D., S. Rajagopalan, C. A. Pope, 3rd, J. R. Brook, A. Bhatnagar, A. V. Diez-Roux, F. Holguin, Y. Hong, R. V. Luepker, M. A. Mittleman, A. Peters, D. Siscovick, S. C. Smith, Jr., L. Whitsel & J. D. Kaufman (2010) Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation,* 121**,** 2331-78.

Carlsten, C., J. D. Kaufman, A. Peretz, C. A. Trenga, L. Sheppard & J. H. Sullivan (2007) Coagulation markers in healthy human subjects exposed to diesel exhaust. *Thromb Res,* 120**,** 849-55.

Carter, J. D., A. J. Ghio, J. M. Samet & R. B. Devlin (1997) Cytokine production by human airway epithelial cells after exposure to an air pollution particle is metal-dependent. *Toxicol Appl Pharmacol,* 146**,** 180-8.

Chen, J., M. Tan, A. Nemmar, W. Song, M. Dong, G. Zhang & Y. Li (2006) Quantification of extrapulmonary translocation of intratracheal-instilled particles in vivo in rats: effect of lipopolysaccharide. *Toxicology,* 222**,** 195-201.

Chen, L. H., S. F. Knutsen, D. Shavlik, W. L. Beeson, F. Petersen, M. Ghamsary & D. Abbey (2005) The association between fatal coronary heart disease and ambient particulate air pollution: Are females at greater risk? *Environ Health Perspect,* 113**,** 1723-9.

Chuang, K. J., C. C. Chan, T. C. Su, C. T. Lee & C. S. Tang (2007) The effect of urban air pollution on inflammation, oxidative stress, coagulation, and autonomic dysfunction in young adults. *Am J Respir Crit Care Med,* 176**,** 370-6.

Costa, D. L. & K. L. Dreher (1997) Bioavailable transition metals in particulate matter mediate cardiopulmonary injury in healthy and compromised animal models. *Environ Health Perspect,* 105 Suppl 5**,** 1053-60.

Cozzi, E., C. J. Wingard, W. E. Cascio, R. B. Devlin, J. J. Miles, A. R. Bofferding, R. M. Lust, M. R. Van Scott & R. A. Henriksen (2007) Effect of ambient particulate matter exposure on hemostasis. *Transl Res,* 149**,** 324-32.

Dales, R. E., S. Cakmak & C. B. Vidal (2010) Air Pollution and hospitalization for venous thromboembolic disease in Chile. *J Thromb Haemost*.

Delfino, R. J., N. Staimer, T. Tjoa, D. L. Gillen, A. Polidori, M. Arhami, M. T. Kleinman, N. D. Vaziri, J. Longhurst & C. Sioutas (2009) Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to potential causal component mixtures and mechanisms. *Environ Health Perspect,* 117**,** 1232-8.

Diez Roux, A. V., A. H. Auchincloss, T. G. Franklin, T. Raghunathan, R. G. Barr, J. Kaufman, B. Astor & J. Keeler (2008) Long-term exposure to ambient particulate matter and prevalence of subclinical atherosclerosis in the Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol,* 167**,** 667-75.

Dockery, D. W., C. A. Pope, 3rd, X. Xu, J. D. Spengler, J. H. Ware, M. E. Fay, B. G. Ferris, Jr. & F. E. Speizer (1993) An association between air pollution and mortality in six U.S. cities. *N Engl J Med,* 329**,** 1753-9.

Dominici, F., A. McDermott, M. Daniels, S. L. Zeger & J. M. Samet (2003) Mortality among residents of 90 cities. In Revised Analyses of Time-Series Studies of Air Pollution and Health. *Boston, MA: Health Effects Institute***,** 9-24.

Dominici, F., R. D. Peng, M. L. Bell, L. Pham, A. McDermott, S. L. Zeger & J. M. Samet (2006) Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA,* 295**,** 1127-34.

Emmerechts, J., E. Alfaro-Moreno, B. M. Vanaudenaerde, B. Nemery & M. F. Hoylaerts (2010) Short-term exposure to particulate matter induces arterial but not venous thrombosis in healthy mice. *J Thromb Haemost,* 8**,** 2651-61.

Ghio, A. J., A. Hall, M. A. Bassett, W. E. Cascio & R. B. Devlin (2003) Exposure to concentrated ambient air particles alters hematologic indices in humans. *Inhal Toxicol,* 15**,** 1465-78.

Ghio, A. J., C. Kim & R. B. Devlin (2000) Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. *Am J Respir Crit Care Med,* 162**,** 981-8.

Hertel, S., A. Viehmann, S. Moebus, K. Mann, M. Brocker-Preuss, S. Mohlenkamp, M. Nonnemacher, R. Erbel, H. Jakobs, M. Memmesheimer, K. H. Jockel & B. Hoffmann (2010) Influence of short-term exposure to ultrafine and fine particles on systemic inflammation. *Eur J Epidemiol,* 25**,** 581-92.

HHS (2004) The Health Consequences of Smoking: A Report of the Surgeon General. *US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health*.

Hoek, G., B. Brunekreef, S. Goldbohm, P. Fischer & P. A. van den Brandt (2002) Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet,* 360**,** 1203-9.

Hoffmann, B., S. Moebus, S. Mohlenkamp, A. Stang, N. Lehmann, N. Dragano, A. Schmermund, M. Memmesheimer, K. Mann, R. Erbel & K. H. Jockel (2007) Residential exposure to traffic is associated with coronary atherosclerosis. *Circulation,* 116**,** 489-96.

Ibald-Mulli, A., J. Stieber, H. E. Wichmann, W. Koenig & A. Peters (2001) Effects of air pollution on blood pressure: a population-based approach. *Am J Public Health,* 91**,** 571-7.

Inoue, K., H. Takano, M. Sakurai, T. Oda, H. Tamura, R. Yanagisawa, A. Shimada & T. Yoshikawa (2006) Pulmonary exposure to diesel exhaust particles enhances coagulatory disturbance with endothelial damage and systemic inflammation related to lung inflammation. *Exp Biol Med (Maywood),* 231**,** 1626-32.

Jacobs, L., J. Emmerechts, M. F. Hoylaerts, C. Mathieu, P. H. Hoet, B. Nemery & T. S. Nawrot (2011) Traffic Air Pollution and Oxidized LDL. *PLoS One,* 6.

Jacobs, L., J. Emmerechts, C. Mathieu, M. F. Hoylaerts, F. Fierens, P. H. Hoet, B. Nemery & T. S. Nawrot (2009) Air pollution related prothrombotic changes in persons with diabetes. *Environ Health Perspect,* 118**,** 191-6.

Jerrett, M., R. T. Burnett, R. Ma, C. A. Pope, 3rd, D. Krewski, K. B. Newbold, G. Thurston, Y. Shi, N. Finkelstein, E. E. Calle & M. J. Thun (2005) Spatial analysis of air pollution and mortality in Los Angeles. *Epidemiology,* 16**,** 727-36.

Jiang, N., K. L. Dreher, J. A. Dye, Y. Li, J. H. Richards, L. D. Martin & K. B. Adler (2000) Residual oil fly ash induces cytotoxicity and mucin secretion by guinea pig tracheal epithelial cells via an oxidant-mediated mechanism. *Toxicol Appl Pharmacol,* 163**,** 221-30.

Jimenez, L. A., J. Thompson, D. A. Brown, I. Rahman, F. Antonicelli, R. Duffin, E. M. Drost, R. T. Hay, K. Donaldson & W. MacNee (2000) Activation of NF-kappaB by PM(10) occurs via an iron-mediated mechanism in the absence of IkappaB degradation. *Toxicol Appl Pharmacol,* 166**,** 101-10.

Kadiiska, M. B., R. P. Mason, K. L. Dreher, D. L. Costa & A. J. Ghio (1997) In vivo evidence of free radical formation in the rat lung after exposure to an emission source air pollution particle. *Chem Res Toxicol,* 10**,** 1104-8.

Kan, H., A. R. Folsom, M. Cushman, K. M. Rose, W. D. Rosamond, D. Liao, F. Lurmann & S. J. London (2011) Traffic exposure and incident venous thromboembolism in the atherosclerosis risk in communities (ARIC) study. *J Thromb Haemost*.

Katsouyanni, K., G. Touloumi, E. Samoli, A. Gryparis, A. Le Tertre, Y. Monopolis, G. Rossi, D. Zmirou, F. Ballester, A. Boumghar, H. R. Anderson, B. Wojtyniak, A. Paldy, R. Braunstein, J. Pekkanen, C. Schindler & J. Schwartz (2001) Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. *Epidemiology,* 12**,** 521-31.

Kido, T., E. Tamagawa, N. Bai, K. Suda, H. H. Yang, Y. Li, G. Chiang, K. Yatera, H. Mukae, D. D. Sin & S. F. Van Eeden (2011) Particulate matter induces translocation of IL-6 from the lung to the systemic circulation. *Am J Respir Cell Mol Biol,* 44**,** 197-204.

Kilinc E, van Oerle R, Borissoff JI, Oschatz C, Gerlofs-Nijland ME, Janssen NA, Cassee FR, Sandstrom T, Renne T, Ten Cate H, Spronk HM. Factor XII Activation is Essential to Sustain the Procoagulant Effects of Particulate Matter. *J Thromb Haemost*. 2011.

Kunzli, N., M. Jerrett, R. Garcia-Esteban, X. Basagana, B. Beckermann, F. Gilliland, M. Medina, J. Peters, H. N. Hodis & W. J. Mack (2010) Ambient air pollution and the progression of atherosclerosis in adults. *PLoS One,* 5**,** e9096.

Kunzli, N., M. Jerrett, W. J. Mack, B. Beckerman, L. LaBree, F. Gilliland, D. Thomas, J. Peters & H. N. Hodis (2005) Ambient air pollution and atherosclerosis in Los Angeles. *Environ Health Perspect,* 113**,** 201-6.

Laden, F., J. Schwartz, F. E. Speizer & D. W. Dockery (2006) Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study. *Am J Respir Crit Care Med,* 173**,** 667-72.

Levi, M. & T. van der Poll (2010) Inflammation and coagulation. *Crit Care Med,* 38**,** S26-34.

Li, N., J. Alam, M. I. Venkatesan, A. Eiguren-Fernandez, D. Schmitz, E. Di Stefano, N. Slaughter, E. Killeen, X. Wang, A. Huang, M. Wang, A. H. Miguel, A. Cho, C. Sioutas & A. E. Nel (2004) Nrf2 is a key transcription factor that regulates antioxidant defense in macrophages and epithelial cells: protecting against the proinflammatory and oxidizing effects of diesel exhaust chemicals. *J Immunol,* 173**,** 3467-81.

Lindmark, E., E. Diderholm, L. Wallentin & A. Siegbahn (2001) Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy. *JAMA,* 286**,** 2107-13.

Lowe, G. D. (2008) Common risk factors for both arterial and venous thrombosis. *Br J Haematol,* 140**,** 488-95.

Lucking, A. J., M. Lundback, N. L. Mills, D. Faratian, S. L. Barath, J. Pourazar, F. R. Cassee, K. Donaldson, N. A. Boon, J. J. Badimon, T. Sandstrom, A. Blomberg & D. E. Newby (2008) Diesel exhaust inhalation increases thrombus formation in man. *Eur Heart J,* 29**,** 3043-51.

Maitre, A., V. Bonneterre, L. Huillard, P. Sabatier & R. de Gaudemaris (2006) Impact of urban atmospheric pollution on coronary disease. *Eur Heart J,* 27**,** 2275-84.

Miller, K. A., D. S. Siscovick, L. Sheppard, K. Shepherd, J. H. Sullivan, G. L. Anderson & J. D. Kaufman (2007) Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med,* 356**,** 447-58.

Mills, N. L., N. Amin, S. D. Robinson, A. Anand, J. Davies, D. Patel, J. M. de la Fuente, F. R. Cassee, N. A. Boon, W. Macnee, A. M. Millar, K. Donaldson & D. E. Newby (2006) Do inhaled carbon nanoparticles translocate directly into the circulation in humans? *Am J Respir Crit Care Med,* 173**,** 426-31.

Mills, N. L., H. Tornqvist, M. C. Gonzalez, E. Vink, S. D. Robinson, S. Soderberg, N. A. Boon, K. Donaldson, T. Sandstrom, A. Blomberg & D. E. Newby (2007) Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. *N Engl J Med,* 357**,** 1075-82.

Mills, N. L., H. Tornqvist, S. D. Robinson, M. Gonzalez, K. Darnley, W. MacNee, N. A. Boon, K. Donaldson, A. Blomberg, T. Sandstrom & D. E. Newby (2005) Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. *Circulation,* 112**,** 3930-6.

Mitschik, S., R. Schierl, D. Nowak & R. A. Jorres (2008) Effects of particulate matter on cytokine production in vitro: a comparative analysis of published studies. *Inhal Toxicol,* 20**,** 399-414.

Morel, O., F. Toti, B. Hugel, B. Bakouboula, L. Camoin-Jau, F. Dignat-George & J. M. Freyssinet (2006) Procoagulant microparticles: disrupting the vascular homeostasis equation? *Arterioscler Thromb Vasc Biol,* 26**,** 2594-604.

Mutlu, G. M., D. Green, A. Bellmeyer, C. M. Baker, Z. Burgess, N. Rajamannan, J. W. Christman, N. Foiles, D. W. Kamp, A. J. Ghio, N. S. Chandel, D. A. Dean, J. I. Sznajder & G. R. Budinger (2007) Ambient particulate matter accelerates coagulation via an IL-6-dependent pathway. *J Clin Invest,* 117**,** 2952-61.

Nadziejko, C., K. Fang, L. C. Chen, B. Cohen, M. Karpatkin & A. Nadas (2002) Effect of concentrated ambient particulate matter on blood coagulation parameters in rats. *Res Rep Health Eff Inst*, 7-29; discussion 31-8.

Nawrot, T. S., A. Nemmar & B. Nemery (2006) Air pollution: To the heart of the matter. *Eur Heart J,* 27, 2269-71.

Nawrot, T. S., L. Perez, N. Kunzli, E. Munters & B. Nemery (2011) Public health importance of triggers of myocardial infarction: a comparative risk assessment. *Lancet,* 377, 732-40.

Nemmar, A., S. Al-Salam, S. Zia, S. Dhanasekaran, M. Shudadevi & B. H. Ali (2010) Time-course effects of systemically administered diesel exhaust particles in rats. *Toxicol Lett,* 194, 58-65.

Nemmar, A., P. H. Hoet, D. Dinsdale, J. Vermylen, M. F. Hoylaerts & B. Nemery (2003a) Diesel exhaust particles in lung acutely enhance experimental peripheral thrombosis. *Circulation,* 107, 1202-8.

Nemmar, A., P. H. Hoet, P. Vandervoort, D. Dinsdale, B. Nemery & M. F. Hoylaerts (2007) Enhanced peripheral thrombogenicity after lung inflammation is mediated by platelet-leukocyte activation: role of P-selectin. *J Thromb Haemost,* 5, 1217-26.

Nemmar, A., P. H. Hoet, B. Vanquickenborne, D. Dinsdale, M. Thomeer, M. F. Hoylaerts, H. Vanbilloen, L. Mortelmans & B. Nemery (2002) Passage of inhaled particles into the blood circulation in humans. *Circulation,* 105, 411-4.

Nemmar, A., P. H. Hoet, J. Vermylen, B. Nemery & M. F. Hoylaerts (2004) Pharmacological stabilization of mast cells abrogates late thrombotic events induced by diesel exhaust particles in hamsters. *Circulation,* 110, 1670-7.

Nemmar, A., M. F. Hoylaerts, P. H. Hoet, J. Vermylen & B. Nemery (2003b) Size effect of intratracheally instilled particles on pulmonary inflammation and vascular thrombosis. *Toxicol Appl Pharmacol,* 186, 38-45.

Nemmar, A., B. Nemery, P. H. Hoet, N. Van Rooijen & M. F. Hoylaerts (2005) Silica particles enhance peripheral thrombosis: key role of lung macrophage-neutrophil cross-talk. *Am J Respir Crit Care Med,* 171, 872-9.

Nemmar, A., B. Nemery, P. H. Hoet, J. Vermylen & M. F. Hoylaerts (2003c) Pulmonary inflammation and thrombogenicity caused by diesel particles in hamsters: role of histamine. *Am J Respir Crit Care Med,* 168, 1366-72.

Nemmar, A., H. Vanbilloen, M. F. Hoylaerts, P. H. Hoet, A. Verbruggen & B. Nemery (2001) Passage of intratracheally instilled ultrafine particles from the lung into the systemic circulation in hamster. *Am J Respir Crit Care Med,* 164, 1665-8.

O'Toole, T. E., J. Hellmann, L. Wheat, P. Haberzettl, J. Lee, D. J. Conklin, A. Bhatnagar & C. A. Pope, 3rd (2010) Episodic exposure to fine particulate air pollution decreases circulating levels of endothelial progenitor cells. *Circ Res,* 107, 200-3.

Oberdorster, G., E. Oberdorster & J. Oberdorster (2005) Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect,* 113, 823-39.

Oberdorster, G., Z. Sharp, V. Atudorei, A. Elder, R. Gelein, A. Lunts, W. Kreyling & C. Cox (2002) Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats. *J Toxicol Environ Health A,* 65, 1531-43.

Park, S. K., A. H. Auchincloss, M. S. O'Neill, R. Prineas, J. C. Correa, J. Keeler, R. G. Barr, J. D. Kaufman & A. V. Diez Roux (2010) Particulate air pollution, metabolic

syndrome, and heart rate variability: the multi-ethnic study of atherosclerosis (MESA). *Environ Health Perspect,* 118**,** 1406-11.

Pawlinski, R., J. G. Wang, A. P. Owens, 3rd, J. Williams, S. Antoniak, M. Tencati, T. Luther, J. W. Rowley, E. N. Low, A. S. Weyrich & N. Mackman (2010) Hematopoietic and nonhematopoietic cell tissue factor activates the coagulation cascade in endotoxemic mice. *Blood,* 116**,** 806-14.

Pekkanen, J., E. J. Brunner, H. R. Anderson, P. Tiittanen & R. W. Atkinson (2000) Daily concentrations of air pollution and plasma fibrinogen in London. *Occup Environ Med,* 57**,** 818-22.

Pekkanen, J., A. Peters, G. Hoek, P. Tiittanen, B. Brunekreef, J. de Hartog, J. Heinrich, A. Ibald-Mulli, W. G. Kreyling, T. Lanki, K. L. Timonen & E. Vanninen (2002) Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease: the Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study. *Circulation,* 106**,** 933-8.

Pery, A. R., C. Brochot, P. H. Hoet, A. Nemmar & F. Y. Bois (2009) Development of a physiologically based kinetic model for 99m-technetium-labelled carbon nanoparticles inhaled by humans. *Inhal Toxicol,* 21**,** 1099-107.

Peters, A., D. W. Dockery, J. E. Muller & M. A. Mittleman (2001a) Increased particulate air pollution and the triggering of myocardial infarction. *Circulation,* 103**,** 2810-5.

Peters, A., M. Frohlich, A. Doring, T. Immervoll, H. E. Wichmann, W. L. Hutchinson, M. B. Pepys & W. Koenig (2001b) Particulate air pollution is associated with an acute phase response in men; results from the MONICA-Augsburg Study. *Eur Heart J,* 22**,** 1198-204.

Peters, A., S. von Klot, M. Heier, I. Trentinaglia, A. Hormann, H. E. Wichmann & H. Lowel (2004) Exposure to traffic and the onset of myocardial infarction. *N Engl J Med,* 351**,** 1721-30.

Pope, C. A., 3rd, R. T. Burnett, D. Krewski, M. Jerrett, Y. Shi, E. E. Calle & M. J. Thun (2009) Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: shape of the exposure-response relationship. *Circulation,* 120**,** 941-8.

Pope, C. A., 3rd, R. T. Burnett, M. J. Thun, E. E. Calle, D. Krewski, K. Ito & G. D. Thurston (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA,* 287**,** 1132-41.

Pope, C. A., 3rd, R. T. Burnett, G. D. Thurston, M. J. Thun, E. E. Calle, D. Krewski & J. J. Godleski (2004a) Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation,* 109**,** 71-7.

Pope, C. A., 3rd, M. L. Hansen, R. W. Long, K. R. Nielsen, N. L. Eatough, W. E. Wilson & D. J. Eatough (2004b) Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. *Environ Health Perspect,* 112**,** 339-45.

Pope, C. A., 3rd, R. L. Verrier, E. G. Lovett, A. C. Larson, M. E. Raizenne, R. E. Kanner, J. Schwartz, G. M. Villegas, D. R. Gold & D. W. Dockery (1999) Heart rate variability associated with particulate air pollution. *Am Heart J,* 138**,** 890-9.

Prandoni, P. (2009) Venous and arterial thrombosis: Two aspects of the same disease? *Clin Epidemiol,* 1**,** 1-6.

Puett, R. C., J. E. Hart, J. D. Yanosky, C. Paciorek, J. Schwartz, H. Suh, F. E. Speizer & F. Laden (2009) Chronic fine and coarse particulate exposure, mortality, and coronary heart disease in the Nurses' Health Study. *Environ Health Perspect,* 117**,** 1697-701.

Ray, M. R., S. Mukherjee, S. Roychoudhury, P. Bhattacharya, M. Banerjee, S. Siddique, S. Chakraborty & T. Lahiri (2006) Platelet activation, upregulation of CD11b/ CD18 expression on leukocytes and increase in circulating leukocyte-platelet aggregates in Indian women chronically exposed to biomass smoke. *Hum Exp Toxicol,* 25**,** 627-35.

Ridker, P. M., N. Rifai, M. J. Stampfer & C. H. Hennekens (2000) Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation,* 101**,** 1767-72.

Riediker, M., W. E. Cascio, T. R. Griggs, M. C. Herbst, P. A. Bromberg, L. Neas, R. W. Williams & R. B. Devlin (2004) Particulate matter exposure in cars is associated with cardiovascular effects in healthy young men. *Am J Respir Crit Care Med,* 169**,** 934-40.

Ross, R. (1999) Atherosclerosis--an inflammatory disease. *N Engl J Med,* 340**,** 115-26.

Ruckerl, R., S. Greven, P. Ljungman, P. Aalto, C. Antoniades, T. Bellander, N. Berglind, C. Chrysohoou, F. Forastiere, B. Jacquemin, S. von Klot, W. Koenig, H. Kuchenhoff, T. Lanki, J. Pekkanen, C. A. Perucci, A. Schneider, J. Sunyer & A. Peters (2007a) Air pollution and inflammation (interleukin-6, C-reactive protein, fibrinogen) in myocardial infarction survivors. *Environ Health Perspect,* 115**,** 1072-80.

Ruckerl, R., A. Ibald-Mulli, W. Koenig, A. Schneider, G. Woelke, J. Cyrys, J. Heinrich, V. Marder, M. Frampton, H. E. Wichmann & A. Peters (2006) Air pollution and markers of inflammation and coagulation in patients with coronary heart disease. *Am J Respir Crit Care Med,* 173**,** 432-41.

Ruckerl, R., R. P. Phipps, A. Schneider, M. Frampton, J. Cyrys, G. Oberdorster, H. E. Wichmann & A. Peters (2007b) Ultrafine particles and platelet activation in patients with coronary heart disease--results from a prospective panel study. *Part Fibre Toxicol,* 4**,** 1.

Rudez, G., N. A. Janssen, E. Kilinc, F. W. Leebeek, M. E. Gerlofs-Nijland, H. M. Spronk, H. ten Cate, F. R. Cassee & M. P. de Maat (2009) Effects of ambient air pollution on hemostasis and inflammation. *Environ Health Perspect,* 117**,** 995-1001.

Samet, J. M., F. Dominici, F. C. Curriero, I. Coursac & S. L. Zeger (2000) Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. *N Engl J Med,* 343**,** 1742-9.

Samet, J. M., A. Rappold, D. Graff, W. E. Cascio, J. H. Berntsen, Y. C. Huang, M. Herbst, M. Bassett, T. Montilla, M. J. Hazucha, P. A. Bromberg & R. B. Devlin (2009) Concentrated ambient ultrafine particle exposure induces cardiac changes in young healthy volunteers. *Am J Respir Crit Care Med,* 179**,** 1034-42.

Samoli, E., R. Peng, T. Ramsay, M. Pipikou, G. Touloumi, F. Dominici, R. Burnett, A. Cohen, D. Krewski, J. Samet & K. Katsouyanni (2008) Acute effects of ambient particulate matter on mortality in Europe and North America: results from the APHENA study. *Environ Health Perspect,* 116**,** 1480-6.

Scharrer, E., H. Hessel, A. Kronseder, W. Guth, B. Rolinski, R. A. Jorres, K. Radon, R. Schierl, P. Angerer & D. Nowak (2007) Heart rate variability, hemostatic and acute inflammatory blood parameters in healthy adults after short-term exposure to welding fume. *Int Arch Occup Environ Health,* 80**,** 265-72.

Schneider, A., R. Hampel, A. Ibald-Mulli, W. Zareba, G. Schmidt, R. Schneider, R. Ruckerl, J. P. Couderc, B. Mykins, G. Oberdorster, G. Wolke, M. Pitz, H. E. Wichmann & A. Peters (2010) Changes in deceleration capacity of heart rate and heart rate variability induced by ambient air pollution in individuals with coronary artery disease. *Part Fibre Toxicol,* 7**,** 29.

Schwartz, J., B. Coull, F. Laden & L. Ryan (2008) The effect of dose and timing of dose on the association between airborne particles and survival. *Environ Health Perspect,* 116**,** 64-9.

Seaton, A., A. Soutar, V. Crawford, R. Elton, S. McNerlan, J. Cherrie, M. Watt, R. Agius & R. Stout (1999) Particulate air pollution and the blood. *Thorax,* 54**,** 1027-32.

Shih, R. A., B. A. Griffin, N. Salkowski, A. Jewell, C. Eibner, C. E. Bird, D. Liao, M. Cushman, H. G. Margolis, C. B. Eaton & E. A. Whitsel (2010) Ambient Particulate Matter Air Pollution and Venous Thromboembolism in the Women's Health Initiative Hormone Therapy Trials. *Environ Health Perspect*.

Simkhovich, B. Z., M. T. Kleinman & R. A. Kloner (2008) Air pollution and cardiovascular injury epidemiology, toxicology, and mechanisms. *J Am Coll Cardiol,* 52**,** 719-26.

Sioutas, C., R. J. Delfino & M. Singh (2005) Exposure assessment for atmospheric ultrafine particles (UFPs) and implications in epidemiologic research. *Environ Health Perspect,* 113**,** 947-55.

Stewart, J. C., D. C. Chalupa, R. B. Devlin, L. M. Frasier, L. S. Huang, E. L. Little, S. M. Lee, R. P. Phipps, A. P. Pietropaoli, M. B. Taubman, M. J. Utell & M. W. Frampton (2010) Vascular effects of ultrafine particles in persons with type 2 diabetes. *Environ Health Perspect,* 118**,** 1692-8.

Stocker, R. & J. F. Keaney, Jr. (2004) Role of oxidative modifications in atherosclerosis. *Physiol Rev,* 84**,** 1381-478.

Sun, Q., A. Wang, X. Jin, A. Natanzon, D. Duquaine, R. D. Brook, J. G. Aguinaldo, Z. A. Fayad, V. Fuster, M. Lippmann, L. C. Chen & S. Rajagopalan (2005) Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. *JAMA,* 294**,** 3003-10.

Suwa, T., J. C. Hogg, K. B. Quinlan, A. Ohgami, R. Vincent & S. F. van Eeden (2002) Particulate air pollution induces progression of atherosclerosis. *J Am Coll Cardiol,* 39**,** 935-42.

Tan, W. C., D. Qiu, B. L. Liam, T. P. Ng, S. H. Lee, S. F. van Eeden, Y. D'Yachkova & J. C. Hogg (2000) The human bone marrow response to acute air pollution caused by forest fires. *Am J Respir Crit Care Med,* 161**,** 1213-7.

Tao, F., B. Gonzalez-Flecha & L. Kobzik (2003) Reactive oxygen species in pulmonary inflammation by ambient particulates. *Free Radic Biol Med,* 35**,** 327-40.

Theilmeier, G., C. Michiels, E. Spaepen, I. Vreys, D. Collen, J. Vermylen & M. F. Hoylaerts (2002) Endothelial von Willebrand factor recruits platelets to atherosclerosis-prone sites in response to hypercholesterolemia. *Blood,* 99**,** 4486-93.

Thompson, A. M., A. Zanobetti, F. Silverman, J. Schwartz, B. Coull, B. Urch, M. Speck, J. R. Brook, M. Manno & D. R. Gold (2010) Baseline repeated measures from controlled human exposure studies: associations between ambient air pollution exposure and the systemic inflammatory biomarkers IL-6 and fibrinogen. *Environ Health Perspect,* 118**,** 120-4.

Tornqvist, H., N. L. Mills, M. Gonzalez, M. R. Miller, S. D. Robinson, I. L. Megson, W. Macnee, K. Donaldson, S. Soderberg, D. E. Newby, T. Sandstrom & A. Blomberg

(2007) Persistent endothelial dysfunction in humans after diesel exhaust inhalation. *Am J Respir Crit Care Med,* 176**,** 395-400.

Urch, B., F. Silverman, P. Corey, J. R. Brook, K. Z. Lukic, S. Rajagopalan & R. D. Brook (2005) Acute blood pressure responses in healthy adults during controlled air pollution exposures. *Environ Health Perspect,* 113**,** 1052-5.

van Eeden, S. F., W. C. Tan, T. Suwa, H. Mukae, T. Terashima, T. Fujii, D. Qui, R. Vincent & J. C. Hogg (2001) Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM(10)). *Am J Respir Crit Care Med,* 164**,** 826-30.

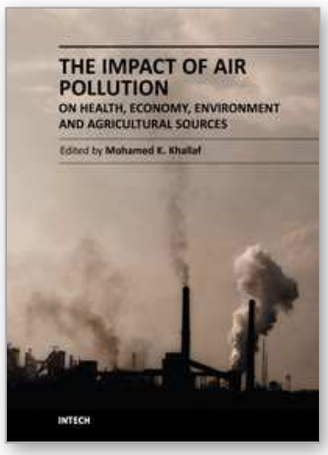
Volpato, S., J. M. Guralnik, L. Ferrucci, J. Balfour, P. Chaves, L. P. Fried & T. B. Harris (2001) Cardiovascular disease, interleukin-6, and risk of mortality in older women: the women's health and aging study. *Circulation,* 103**,** 947-53.

Wallenfeldt, K., B. Fagerberg, J. Wikstrand & J. Hulthe (2004) Oxidized low-density lipoprotein in plasma is a prognostic marker of subclinical atherosclerosis development in clinically healthy men. *J Intern Med,* 256**,** 413-20.

Wilson, D. W., H. H. Aung, M. W. Lame, L. Plummer, K. E. Pinkerton, W. Ham, M. Kleeman, J. W. Norris & F. Tablin (2010) Exposure of mice to concentrated ambient particulate matter results in platelet and systemic cytokine activation. *Inhal Toxicol,* 22**,** 267-76.

Yokoyama, S., H. Ikeda, N. Haramaki, H. Yasukawa, T. Murohara & T. Imaizumi (2005) Platelet P-selectin plays an important role in arterial thrombogenesis by forming large stable platelet-leukocyte aggregates. *J Am Coll Cardiol,* 45**,** 1280-6.

Zanobetti, A., J. Schwartz, E. Samoli, A. Gryparis, G. Touloumi, J. Peacock, R. H. Anderson, A. Le Tertre, J. Bobros, M. Celko, A. Goren, B. Forsberg, P. Michelozzi, D. Rabczenko, S. P. Hoyos, H. E. Wichmann & K. Katsouyanni (2003) The temporal pattern of respiratory and heart disease mortality in response to air pollution. *Environ Health Perspect,* 111**,** 1188-93.



The Impact of Air Pollution on Health, Economy, Environment and Agricultural Sources

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This book aims to strengthen the knowledge base dealing with Air Pollution. The book consists of 21 chapters dealing with Air Pollution and its effects in the fields of Health, Environment, Economy and Agricultural Sources. It is divided into four sections. The first one deals with effect of air pollution on health and human body organs. The second section includes the Impact of air pollution on plants and agricultural sources and methods of resistance. The third section includes environmental changes, geographic and climatic conditions due to air pollution. The fourth section includes case studies concerning of the impact of air pollution in the economy and development goals, such as, indoor air pollution in México, indoor air pollution and millennium development goals in Bangladesh, epidemiologic and economic impact of natural gas on indoor air pollution in Colombia and economic growth and air pollution in Iran during development programs. In this book the authors explain the definition of air pollution, the most important pollutants and their different sources and effects on humans and various fields of life. The authors offer different solutions to the problems resulting from air pollution.

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