

The effect of air pollution on haemostasis

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Keywords

Particulate matter, thrombosis, transepithelial passage, platelet activation, microvesicles, cardiovascular risk

Summary

Ambient environmental air pollutants include gaseous and particulate components. In polluted air, especially particulate matter seems responsible for cardiovascular complications: It consists of a heterogeneous mixture of solid and liquid particles with different diameters ranging from large thoracic to ultrafine particles, with a diameter < 100 nm. Ultrafines can penetrate deeply into the lung to deposit in the alveoli. Cardiovascular manifestations result both from short-term and long-term exposure and have been linked to interference with the autonomic nervous system, direct translocation into the systemic circulation, pulmonary inflammation and oxidative stress. Thrombotic complications associated with air pollution comprise arterial and probably venous thrombogenicity.

This review describes the existing epidemiological and experimental evidence to explain the rapid induction of myocardial infarction within 1–2 hours after exposure to polluted air and advances several explanations as to why more chronic exposure will lead to enhanced venous thrombogenicity. Mechanisms such as platelet activation, endothelial dysfunction, coagulation factor changes and microvesicle production are discussed.

Schlüsselwörter

Feinstaub, Thrombose, transepitheliale Passage, Thrombozytenaktivierung, Mikrovesikel, kardiovaskuläres Risiko

Zusammenfassung

Luftschadstoffe in der Umwelt enthalten gasförmige und korpuskuläre Bestandteile. Für kardiovaskuläre Komplikationen scheint besonders der Feinstaub in der schadstoffbelasteten Luft verantwortlich zu sein: Er enthält eine heterogene Mischung aus festen und flüssigen Bestandteilen, deren Durchmesser im Bereich zwischen großen thorakalen bis hin zu ultrafeinen Partikeln (Durchmesser < 100 nm) liegt. Ultrafeine Partikel können tief in die Lunge eindringen und sich in den Alveolen ablagern. Sowohl die kurzfristige als auch die Langzeitexposition führen zu kardiovaskulären Krankheitsbildern, die auf Störungen des autonomen Nervensystems, die direkte Translokation in den systemischen Kreislauf, entzündliche Lungenveränderungen sowie auf oxidativen Stress zurückgeführt wurden. Zu den feinstaubabhängigen thrombotischen Komplikationen gehören arterielle und wahrscheinlich auch venöse prothrombotische Effekte.

In dieser Übersicht werden die epidemiologische und experimentelle Daten dargestellt, welche die rasche Auslösung eines Myokardinfarkts innerhalb von 1–2 Stunden nach Exposition gegenüber verschmutzter Luft erklären. Verschiedene Erklärungsmodelle werden vorgestellt, weshalb die eher chronische Exposition die venöse Thrombogenität erhöht. Mechanismen wie Thrombozytenaktivierung, endotheliale Dysfunktion, Veränderungen der Gerinnungsfaktoren und Produktion von Mikrovesikeln werden diskutiert.

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Numerous epidemiological studies reported consistent associations between exposure to urban air pollution and cardiorespiratory morbidity and mortality (1–4). Over the last two decades, a vast number of both epidemiological and mechanistic studies have provided convincing evidence to conclude that chronic exposure to particulate matter (PM) enhances atherosclerosis and that acute exposure increases the risk of blood platelet sensitization, in association with unstable atherosclerotic plaques triggering arterial thrombosis and myocardial infarction (5–9). 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) (10, 11). In view of the generalized character of exposure in modern society, air pollution likely poses a major public health burden (12).

Air pollution

Ambient environmental air pollutants include gaseous (carbon monoxide, nitrogen oxides, sulphur dioxide, ozone) and particulate components. The particulate component, particulate matter (PM), consists of a heterogeneous mixture of solid and liquid particles suspended in air, and is subdivided based on size range (► Fig. 1) into

- thoracic particles (PM₁₀) with a mean aerodynamic diameter < 10 µm,
- coarse particles: > 2.5 µm and < 10 µm,
- fine particles (PM_{2.5}) < 2.5 µm, and
- ultrafine 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 polluted air.

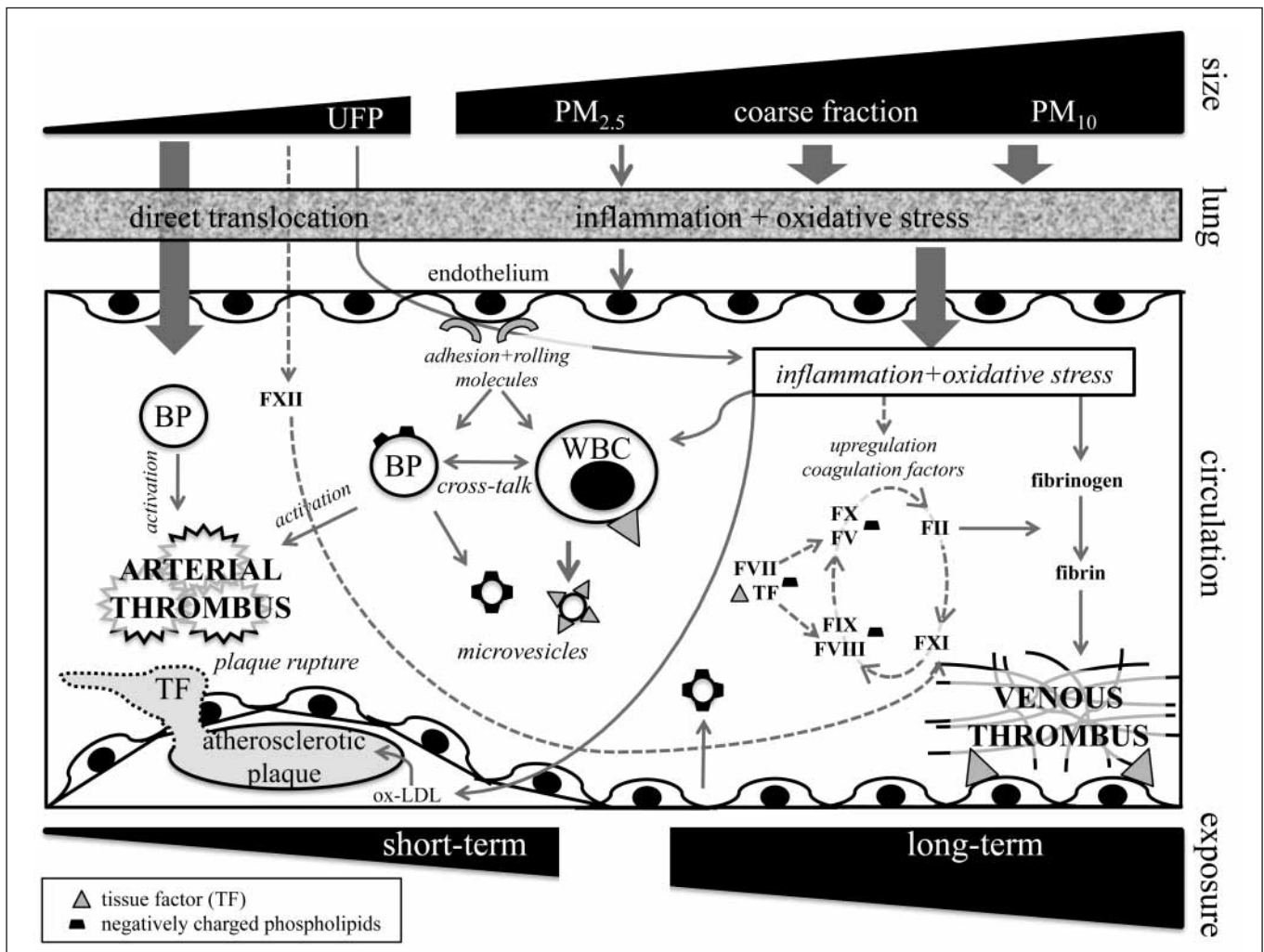


Fig. 1 Pathophysiological mechanisms responsible for haemostasis activation during short and long term exposure to air pollution

In general, $PM_{2.5}$ originates mostly from combustion sources, whereas the coarse fraction derives predominantly from natural sources, especially crustal material (including windblown soil) and grinding processes. Important bioaerosols (e. g. endotoxin, pollen grains and fungal spores) are found mostly in the coarse fraction (and larger particles). Upon inhalation, larger particles demonstrate a greater fractional deposition in the extrathoracic and upper tracheobronchial regions, whereas smaller particles (e. g. $PM_{2.5}$) show greater deposition in the deep lung. By virtue of their small size ($<0.1 \mu m$), UFP penetrate deeply into the lungs and deposit in the alveoli. UFPs account for a major portion of the actual numbers of particles within PM, and have a high surface area-to-mass ratio, po-

tentially leading to enhanced biological toxicity, in spite of their limited mass (5).

Inhaled particles are believed to affect the cardiovascular system through three pathways:

- interference with the autonomic nervous system (12),
- direct translocation of UFP into the systemic circulation (13, 14),
- pulmonary inflammation and oxidative stress (15, 16).

In the following paragraphs, first epidemiological studies on PM-related cardiovascular mortality and arterial and venous disease will be discussed, followed by an overview of the different underlying pathophysiological mechanisms. By virtue of the high shear rates found in the arterial cir-

ulation, blood platelet activation plays a protagonist role in arterial thrombosis, leading to myocardial infarction and stroke. At lower rates of shear, such as 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 haemostasis. 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 (17).

Epidemiological studies

Cardiovascular mortality

Both the American NMMAPS (National Morbidity, Mortality, and Air Pollution Study) (18) and the European APHEA2 (Air Pollution and Health: A European Approach) (19, 20) 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 (21). The combined effect on all-cause mortality ranged from 0.2% to 0.6% for a 10 $\mu\text{g}/\text{m}^3$ increase in daily levels of ambient PM_{10} , with greater effects in 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 (12).

Not only short-term, but also long-term PM exposure is associated with increased cardiovascular mortality. An initial landmark report was that of the Harvard Six Cities study (22), 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 versus 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 $\mu\text{g}/\text{m}^3$ increase in long-term levels of $\text{PM}_{2.5}$ has been associated with a 8 to 18% increase in cardiovascular mortality (9). An association with mortality was also found for traffic-related air pollution and several traffic exposure variables, although relative risks were small (23).

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 (24, 25).

A potential benefit in general mortality can be expected within two years after the reduction of PM exposure (26).

The magnitude of these associations appeared to be more pronounced for the smaller $\text{PM}_{2.5}$ fraction than for the larger PM_{10} fraction (27). Considering a large body of evidence, a recent updated version of the American Heart Association scientific statement on Air Pollution and Cardiovascular Disease (12) concluded that per 10 $\mu\text{g}/\text{m}^3$ increase in long-term levels of $\text{PM}_{2.5}$, 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.

Arterial cardiovascular events

In general, two large underlying mechanisms can be distinguished:

- Short-term PM exposure increases the risk of arterial thrombosis, including myocardial infarction and stroke, while
- long-term PM exposure enhances atherosclerotic plaque formation.

An increased risk of myocardial infarction has been observed with elevated $\text{PM}_{2.5}$ concentrations in the preceding 2 hours and 24 hours (28). Likewise, participation in traffic has been linked to the onset of myocardial infarction, as soon as 1 h afterward (odds ratio 2.92, 95%CI 2.22–3.83) (29).

Exposure to ambient $\text{PM}_{2.5}$ 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 $\mu\text{g}/\text{m}^3$ increase in same-day $\text{PM}_{2.5}$) (1).

Although the magnitude of the risk for myocardial infarction induction 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 (30).

Several epidemiological studies demonstrated an association between prolonged exposure to air pollution and the intima-media thickness of the carotid artery (CIMT), a measure for subclinical atherosclerosis. Both the mean 1-year (31) and the mean 20-year (32) concentrations of outdoor $\text{PM}_{2.5}$, measured at the study persons' residential address, have been associated with increased CIMT. Similarly, the distance from the residence to a major road is correlated with the degree of coronary artery calcification, another measure for atherosclerosis (33).

In addition to these cross-sectional studies that demonstrate an association between PM exposure and the degree of atherosclerosis, a recent study reports that long-term $\text{PM}_{2.5}$ exposure is also related to a faster progression rate of atherosclerosis (34). Annual CIMT progression rate among those living within 100 m of a highway was more than twice the population mean progression (34).

Venous thromboembolism

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) (10, 11, 35). Short-term exposure to PM has 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 $\mu\text{g}/\text{m}^3$ increase in same-day levels of $\text{PM}_{2.5}$ (11).

Baccarelli et al. reported a 70% increase in the risk of deep vein thrombosis (DVT) for each 10 $\mu\text{g}/\text{m}^3$ 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) (10). 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 (35).

These initial epidemiological reports on the existence of an association between air pollution exposure and venous thrombosis were soon 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 for an association between short-term or long-term (up to 1 year) PM exposure and VTE (36). Another 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 (37). It needs to be emphasized, however, that both studies were not originally designed to examine air pollution.

Pathophysiological mechanisms

Atherosclerosis

Atherosclerosis is now considered an inflammatory disease with low density lipoprotein (LDL) cholesterol accumulation in the arteries as the primary risk factor (38). However, up to 50% of the patients who develop atherosclerosis do not have high cholesterol (39). 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 (38).

Oxidative transformation of LDL into ox-LDL is a key step in the initiation and progression of atherosclerosis (40). It has been previously shown that air pollution particles can induce oxidative stress both *in vitro* (41, 42) and in exposed animals (8, 16, 43, 44). A correlation between PM exposure and circulating levels of ox-LDL 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 (45).

PM exposure can further enhance atherosclerosis via the release of inflammatory mediators from the lungs that promote chemotaxis of monocytes into the vessel wall, and via the induction of high-density lipoprotein (HDL) dysfunction with loss of its anti-inflammatory properties (15).

These epidemiological findings are sustained by several experimental studies in animals. Prolonged exposure to PM has been associated with the progression of atherosclerosis in rabbits, the extent of which correlated with the extent of PM₁₀ phagocytosed by alveolar macrophages (46), and with enhanced abdominal aortic plaque formation in genetically susceptible apolipoprotein E-null mice (47).

In agreement with epidemiological findings (27), these experimental studies suggest that the smaller particles are more pathogenic, as a result of their greater propensity to induce systemic prooxidant and proinflammatory effects (8). Indeed, ambient UFP trigger the induction of the anti-oxidant gene heme oxygenase 1 (HO-1) to a higher degree than ambient PM_{2.5} or coarse particles, both *in vitro* (48) and *in vivo* (8, 15). 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 (49). 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.

Blood platelet activation

Arterial thrombosis is to a large extent determined by atherosclerotic plaque rupture, but is also favored by the presence of unstable plaques with activated endothelium and micro-fissures, facilitating the recruitment of sensitized circulating platelets (50) and blood platelet activation. Blood platelet activation was found to be associated with short-term, but not long-term PM exposure, as evidenced *ex vivo* by a shortening of the closure time of the Platelet Function Analyzer (PFA-100, Siemens Healthcare Diagnostics), in patients with diabetes (51). In this study of Jacobs et al., an interquartile range (39.2 µg/m³) increase in the PM₁₀ concentration, measured 2 hours before the clinical investigation at the entrance of the hospital, was associated with a decrease of 21.1 s (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 (6). Enhanced platelet activity and thrombus formation in an *ex vivo* perfusion chamber was demonstrated 2 to 6 hours after exposure of healthy volunteers to diluted diesel exhaust (52). Platelet activation was also obvious from associations between ambient PM₁₀ levels in the 24 to 96 hours period prior to blood sampling and augmented platelet aggregation, in healthy volunteers (53), and from associations between mean ambient UFP concentrations over 24 hours and levels of the platelet activation marker soluble CD40 ligand, in patients with coronary heart disease (54). No associations were found with longer time frames, up to five days (54).

By exposing hamsters to diesel exhaust particles (DEP) via intratracheal instillation, Nemmer et al. demonstrated an activation of blood platelets (confirmed by PFA-100), in conjunction with lung inflammation, resulting in a prothrombotic

tendency which persisted up to 24 hours after exposure (6, 55). Pretreatment of hamsters with anti-inflammatory agents abolished pulmonary inflammation at all time points and reduced DEP-induced thrombosis at 6 and 24 hours post-instillation (56, 57) but not as soon as one hour after DEP exposure (6).

Therefore, the early prothrombotic tendency was ascribed to direct effects of systemically translocated particles on the blood platelets and/or the (pulmonary) vessel wall, independent of inflammation (6). This hypothesis was confirmed by demonstrating enhanced platelet-rich thrombus formation, one hour after intratracheal instillation of well-defined ultrafine (60 nm) polystyrene particles, while 400 nm particles, not capable of systemic translocation, did not affect thrombosis, despite similar increases in neutrophils, lactate dehydrogenase and histamine levels in the bronchoalveolar lavage fluid (58). The direct activating effect of PM on blood platelets has been demonstrated *ex vivo* (55) and *in vitro* (59).

At later time points, the arterial prothrombotic tendency appears to be inflammation-driven, with P-selectin playing a central role. 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 (50) and the formation of platelet-leukocyte conjugates (60). Pulmonary instillation of carbon nanotubes elevated platelet-leukocyte conjugates at 6 hours and increased the peripheral thrombotic potential at 24 hours, in mice. Inhibition of P-selectin abrogated these responses (7). 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) (61). An association between soluble P-selectin levels and the mean 1- to 5-day concentrations of ambient fine particles ($PM_{0.25}$ and $PM_{2.5}$), was observed in a panel study of 60 elderly subjects with coronary artery disease (62).

Coagulation activation

The mechanisms of PM-induced blood platelet activation that underlie the association between PM exposure and arterial thrombosis are now well established. In contrast, the pathophysiological mechanisms explaining the observed link between PM exposure and VTE remain largely unknown. Although increases in the levels of coagulation factors seem the most likely explanation, published data for this interpretation are conflicting and unconvincing. A few epidemiological and controlled exposure studies in humans demonstrated an association between PM exposure and shortening of the prothrombin time (PT) (63, 64) or increased levels of FVIII (65), D-dimers (66) or von Willebrand factor (VWF) (67, 68). However, a much larger number of studies failed to demonstrate associations with these and other coagulation parameters such as PT (52), activated partial thromboplastin time (aPTT) (52, 63, 64), FVII (65, 69–71), FVIII (72), FIX (66, 71), FXII (66) D-dimers (64, 65, 68, 71, 73–75) or VWF (45, 65, 66, 69, 72–75), in humans.

In fact, the only coagulation parameter for which an association with air pollution exposure is more or less frequently described in the literature is fibrinogen (54, 73, 76–78), although, yet again, contested by many other studies (53, 63, 65, 66, 68–70, 74, 79). Fibrinogen is also an acute phase protein that is up-regulated during inflammatory processes. The crucial role of inflammation in the generation of a procoagulant phenotype has been demonstrated by Mutlu *et al.* (80). Wild-type mice exposed to 10 μ g PM via a single intratracheal instillation showed shortenings in bleeding time, PT and aPTT, and relatively high increases in the levels of circulating blood platelets, FVII, FVIII, FX and fibrinogen. This prothrombotic phenotype was absent in IL-6 knockout mice (80). Likewise, the PM-induced upregulation of plasminogen activator-1 (PAI-1), an inhibitor of fibrinolysis, disappeared upon treatment of mice with a TNF- α inhibitor (81), demonstrating the determining role of cytokines.

The studies of Mutlu stand out among other studies on the procoagulant effects of

PM in mice. Indeed, a few other experimental studies in rodents observed procoagulant changes in levels of fibrinogen, activated protein C, tissue factor pathway inhibitor (TFPI) or PAI-1, but only at doses of 100 μ g or higher of PM per mouse (82, 83). In addition, exposure of rats to concentrated PM from New York City air did not alter levels of fibrinogen, FVII, PAI-1 or thrombin-antithrombin complexes (TAT) (84). One study measured increased levels of FVII and FVIII upon intratracheal instillation of unphysiologically high concentrations (100 and 200 μ g/mouse) PM, but not at 25 μ g/mouse, a dose more representative for the daily human exposure under very polluted conditions (85). This study demonstrated that a short-term exposure to PM enhanced experimental arterial thrombosis, but not venous thrombosis *in vivo*.

Indeed, an explanation for the lack of positive associations between PM exposure and classical parameters of coagulation might be found in the short duration of exposure investigated, varying from a few hours to a few days, in most experimental studies. While short-term PM exposure unequivocally enhances blood platelet activation, a more chronically sustained exposure could be necessary to induce significant changes in the coagulation 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 (10).

Taken together, these findings indicate that exposure-induced changes in the levels of coagulation factors, if any, are unlikely to be solely or primarily responsible for the PM-induced increased risk of DVT. Kiliç *et al.* offer an alternative explanation by demonstrating a procoagulant response in mice that was tissue factor (TF)-dependent at 4 h post-exposure. At 20 h, the procoagulant response no longer depended on TF, but on contact activation, as it was absent in FXII^{-/-} mice (86). These studies indicate a role for circulating triggers of coagulation, a role that could, at least in part, be fulfilled by microvesicles.

Microvesicles

Microvesicles (also called microparticles, a term we prefer to avoid in the context of pollution by particles) are circulating vesicles with a mean diameter smaller than 1 μm that are released from stimulated or apoptotic cells in the vascular bed. Procoagulant proteins, such as tissue factor (TF), and lipids on their membranes generate a procoagulant surface on which coagulation factors can bind and be activated to promote coagulation (87). Through the interaction between P-selectin and PSGL-1, circulating monocyte-derived microvesicles (88) can constitute a continuous delivery of TF to a growing thrombus (89). In addition, these microvesicles, as well as microvesicles derived from blood platelets, red blood cells and endothelial cells, expose a procoagulant phospholipid surface to which coagulation factors can bind (87). Elevated numbers of circulating microvesicles have been demonstrated in patients with VTE (90, 91). In a recently published case-control study comprising 186 VTE patients and 418 healthy controls, individuals with microvesicle concentrations above the 90th percentile of the controls' distribution had a 5-fold increased risk of having had a previous VTE, as compared to those with microvesicle concentrations below the 10th percentile (91).

A role for microvesicles in the induction of an exposure-associated procoagulant phenotype has been suggested by Bonzini et al., who investigated 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 (64). These findings suggest that PM exposure may induce, as part of a systemic inflammatory response, the release of small amounts of endogenous TF (by circulating monocytes) 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 (7). 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 (92).

Endothelial function

In a series of complementary studies, healthy and compromised volunteers were exposed for several hours to the diluted exhaust of an idling diesel engine, and vasodilation was assessed upon exposure to different agonists as a measure of endothelial function. At 6 hours post-inhalation, an attenuated agonist-induced vasodilation was observed (93, 94), in the absence of inflammatory changes (93). At 24 hours post-inhalation, endothelium-dependent vasodilation (induced by acetylcholine and bradykinin) remained impaired, while endothelium-independent vasodilation (using sodium nitroprusside and verapamil) was unaffected, in the presence of mild systemic inflammation (95). PM exposure could also impair the endothelial repair mechanisms by reducing the number of endothelial progenitor cells (96). Endothelial cells release both profibrinolytic and antifibrinolytic proteins. Whether PM exposure interferes with this release remains controversial. While some studies demonstrate an association between PM exposure and levels of PAI-1 in humans (78) and in mice (82), others failed to demonstrate associations with PAI-1 (73, 75, 94, 95) or with the profibrinolytic protein tissue plasminogen activator (t-PA) (64, 66, 73, 78). Overall, PM inhalation could exert a potential deleterious effect on the endothelial function that may aggravate the prothrombotic phenotype induced by blood platelet and coagulation activation.

Based on the aforementioned literature, several pathophysiological pathways that could explain the link between PM exposure and arterial and venous thrombosis, can be combined as summarized in ► Figure 1. Oxidative stress induced by long-term exposure to the finest particulates enhances atherosclerotic plaque formation.

Within a few hours upon acute inhalation, UFP penetrate deeply into the lung and pass the epithelial-endothelial barrier of the alveoli to translocate into the circulation where they activate blood platelets. Pulmonary inflammation and oxidative stress induced by longer-term exposure to PM, and possibly other constituents of air pollution, activate the pulmonary endothelium via cytokine-mediated cellular cross-talk (97). Through the surface expression of P-selectin and other adhesion molecules, such as ICAM-1 and VCAM-1 (85), on the large pulmonary endothelial bed, WBC are recruited to the pulmonary vessel wall, are activated and migrate into the lung. P-selectin and VWF expression also support platelet rolling and adhesion to the lung, followed by platelet sensitization (98, 99). Cross-talk between WBC and blood platelets favors further mutual activation (7). Platelet activation, in conjunction with micro-fissures present in the vasculature of cardiovascularly compromised persons or even the rupture of an atherosclerotic plaque, provoke arterial thrombosis. Externalization of phosphatidylserine upon cell activation modifies the neutral membrane charge with loss of phospholipid asymmetry, leading to a cascade of events which disrupt the interactions between membrane and cytoskeleton proteins in various cells, eventually resulting in the release of procoagulant microvesicles in the circulation. TF expression on WBC and on circulating microvesicles, in conjunction with contact activation, triggers coagulation in the presence of high concentrations of fibrinogen, enhancing venous thrombus formation.

Conclusion

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.

This review summarizes the underlying pathophysiological pathways. By virtue of the heterogeneity in both study design and the composition of the PM considered by the different studies, it is not surprising that all findings are not consistent. Nonetheless,

considering the overall weight of scientific evidence, and because of the huge number of persons exposed, it has become clear that exposure to air pollution poses a major risk factor for both arterial and venous cardiovascular disease on a global scale.

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Conflict of interest

The authors declare, that they have no conflict of interest.

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