Cardiovascular effects of air pollution

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ABSTRACT
Air pollution is a heterogeneous mixture of gases, liquids and PM (particulate matter). In the modern urban world, PM is principally derived from fossil fuel combustion with individual constituents varying in size from a few nanometres to 10 μm in diameter. In addition to the ambient concentration, the pollution source and chemical composition may play roles in determining the biological toxicity and subsequent health effects. Nevertheless, studies from across the world have consistently shown that both short- and long-term exposures to PM are associated with a host of cardiovascular diseases, including myocardial ischaemia and infarctions, heart failure, arrhythmias, strokes and increased cardiovascular mortality. Evidence from cellular/toxicological experiments, controlled animal and human exposures and human panel studies have demonstrated several mechanisms by which particle exposure may both trigger acute events as well as prompt the chronic development of cardiovascular diseases. PM inhaled into the pulmonary tree may instigate remote cardiovascular health effects via three general pathways: instigation of systemic inflammation and/or oxidative stress, alterations in autonomic balance, and potentially by direct actions upon the vasculature of particle constituents capable of reaching the systemic circulation. In turn, these responses have been shown to trigger acute arterial vasoconstriction, endothelial dysfunction, arrhythmias and pro-coagulant/thrombotic actions. Finally, long-term exposure has been shown to enhance the chronic genesis of atherosclerosis. Although the risk to one individual at any single time point is small, given the prodigious number of people continuously exposed, PM air pollution imparts a tremendous burden to the global public health, ranking it as the 13th leading cause of morality (approx. 800 000 annual deaths).

INTRODUCTION
Air pollution is a complex mixture of compounds in gaseous [ozone, CO and NOx (nitrogen oxides)] and particle phases [1–4]. In the modern urban and industrial world, the majority of air pollution is derived from fossil fuel combustion (e.g. automobiles, power generation and industry). Cooking and wood burning are additional significant sources in developing nations. Since the advent of the industrial revolution, air pollution has become so omnipresent as to be commonly perceived as a normal or natural entity, hence the phrase: ‘the hazy, lazy days of summer’. Nevertheless, it is neither natural nor benign. Several severe pollution events, such as the infamous London fog episode of 1952 responsible for thousands of deaths, helped bring this to public attention [5]. Although particulate and gaseous pollutants co-exist and may both instigate adverse health effects (e.g. ozone) [6], the most compelling evidence implicates PM (particulate matter) as a major perpetrator of human diseases [1–3]. PM itself is a heterogeneous amalgam of compounds varying in concentration, size, chemical composition, surface area and sources of origin [1–3]. Although it may intuitively seem that PM would pose a health risk mostly to the lungs, the overall evidence indicates that the majority of the adverse effects of PM are upon the...
CV (cardiovascular) system [1–3]. In the present review, I focus on the role that both acute and chronic exposures to PM play in causing CV disease. Passive tobacco smoke is indeed a highly significant source of exposure to air pollution [2] which, although a critically important determinant of health, is outside the scope of this review.

CHARACTERISTICS OF PM AIR POLLUTION

Owing to the complexity of its chemistry, historical precedents and the temporally changing nature of the compounds within ambient air, PM is broadly categorized and regulated by aerodynamic diameter (μm) [2–4]. Figure 1 provides a very general overview of PM characteristics. It is possible, however, that a classification based upon chemistry, particle number or relative toxicity may be more indicative of the health risks. There are thousands of chemicals and constituents within PM that may solely, or in combination, impart biological harm. The actual ‘responsible’ components remain largely unknown; nonetheless, it is generally believed that the myriad of compounds that pose intrinsic redox potential (e.g. metals and organic compounds) and/or those capable of activating endogenous sources of oxidative stress within pulmonary tissue (e.g. immune cells) are likely to be the instigators, rather than inert particles (e.g. elemental carbon). Particle sizes range from clusters of molecules only nanometres in diameter (ultrafine PM < 0.1 μm) through the fine PM fraction (< 2.5 μm) and up to coarse matter close to the visible size range (2.5–10 μm).

‘Fine PM’ < 2.5 μm (PM2.5) has received the majority of attention from a scientific and regulatory standpoint [1–3]. Most epidemiological studies report stronger associations with fine compared with other PM size fractions (e.g. PM10). Moreover, many of the combustion-derived compounds thought to possess toxic potential are contained within PM2.5. The other size fractions, including ultrafine particles (PM < 0.1 μm), vary temporally and spatially within the ambient environment often unrelated to fine PM concentrations. As ultrafine PM levels do not consistently track with PM2.5 [7,8], it is unlikely that the consistent epidemiological findings associated with fine PM [1–3] are simply a surrogate for ultrafine particles being the underlying culprit. The nanoparticles within PM0.1 are very short-lived and are largely found within only a few hundred metres of their sources (e.g. near roadways). Nonetheless, certain aspects of ultrafine PM may implicate them as a cause of human diseases in addition to PM2.5. Owing to the prodigious number of particles per volume of air (several orders of magnitude more than PM2.5), ultrafine PM conveys a large surface area for transporting toxic materials deep within
the pulmonary tree [6,7]. Owing to their minute size, ultrafine particles may even be capable of translocating into the systemic circulation and thus directly interact with multiple organ systems within minutes of exposure [9–11]. However, this capability, along with the biological relevance of unknown numbers/character of ultrafine PM components within the vasculature, remains highly controversial [11]. The fact that very acute exposure to traffic for only minutes (a prime source of ultrafine particles) conveys a particularly large CV health risk suggests that ultrafine particles may indeed prove to be important [12,13]. At present, even less is known about the independent health impact of the coarse PM fraction [14]. Finally, PM rarely exists by itself within ambient air pollution. Particles are constantly changing and interacting with gaseous (NO\textsubscript{x}, SO\textsubscript{2} and ozone) and semi-volatile/volatile compounds (e.g. aldehydes and polycyclic aromatic hydrocarbons). Many of these vapour-phase compounds attach to the surface of PM and/or themselves form secondary aerosol particles. The individual health risk of these constituents alone, or interacting together with PM, remains to be better understood.

Exposure to PM\textsubscript{2.5} is measured by the mass of particles within a volume of air. Average daily and annual levels of exposure range widely worldwide from $\leq 10$ to $> 65 \text{ g/m}^3$. Most urban cities within North America and Europe, however, have average annual levels between 5 and 30 $\text{ g/m}^3$. Peak hourly concentrations and personal levels of exposure within certain micro-environments can actually reach levels exceeding 200–500 $\text{ g/m}^3$. Unfortunately, although air pollution has substantially decreased throughout much of the United States and Western Europe, PM concentrations within megalopolis regions in the developing world (i.e. Asia) are increasing. Daily particle levels may even exceed 200–500 $\text{ g/m}^3$. Put into context, these enormous concentrations are approximately those encountered by passive tobacco smoking (e.g. smoky bars approx. 500–1500 $\mu\text{g/m}^3$). Owing to the consistency of epidemiological studies implicating even present-day lower PM concentrations as a cause of human diseases [3], in 2006 the United States EPA (Environmental Protection Agency) updated the North American Air Quality Standards to be lowered from 65 g/m$^3$ to 35 g/m$^3$ [1–3]. Most urban cities within North America and Europe, however, have average annual levels between 5 and 30 g/m$^3$. Peak hourly concentrations and personal levels of exposure within certain micro-environments can actually reach levels exceeding 200–500 g/m$^3$. Changes in daily (or a few days) averages of PM\textsubscript{2.5} within different regions (e.g. cities). Case cross-over studies can investigate the effect of ‘ultra-acute’ exposures (e.g. 1–2 h) on the risk of CV events. The longer-term studies typically compare survival, or time to event, of individuals living within areas of chronically differing levels of PM\textsubscript{2.5} concentrations.

**EPIDEMIOLOGY OF CV DISEASES ASSOCIATED WITH PM\textsubscript{2.5}**

Since the 1970s, there have been hundreds of epidemiological studies conducted throughout the world demonstrating an association between PM\textsubscript{2.5} and adverse health effects [1–3]. During the 1980s, and more clearly in the 1990s, a growing number of studies reported that even the decreased levels of present-day of air pollution concentrations still appear to be linked with excess mortality. From the mid-1990s onwards, it has become apparent that CV disease is the single leading cause of air-pollution-mediated morbidity and mortality (in terms of absolute risk). Although dozens of studies of varying types conducted throughout widely different parts of the world report associations between PM\textsubscript{2.5} and excess CV event [1–3], not all studies have been positive [15]. However, it is extremely unlikely that publication bias explains the overall consistency, coherence and strength of the associations demonstrated worldwide, as suggested by large reviews of the entire literature [1–2]. A specific investigation of the possible impact of publication bias found that it had no significant effect upon the accuracy of the positive risk estimates reported for mortality in short-term time series studies [15a]. Several comprehensive reviews have recently been published on this topic [1–2], including the most recent Criteria Document by the U.S. EPA [3]. Therefore only a concise summary of the critical epidemiological findings will be provided.

The published observations can be broadly categorized into short-term (time series analyses over a few days of exposure), ultra-acute (case cross-over studies related to a few hours of exposure) and longer-term (cohort survival analyses over years of exposure) studies. There have been many more short-term studies, which in general associate numbers of events (e.g. deaths and hospitalizations) with changes in daily (or a few days) averages of PM\textsubscript{2.5} within different regions (e.g. cities). Case cross-over studies can investigate the effect of ‘ultra-acute’ exposures (e.g. 1–2 h) on the risk of CV events. The longer-term studies typically compare survival, or time to event, of individuals living within areas of chronically differing levels of PM\textsubscript{2.5} concentrations.

**Short-term exposure studies**

Table 1 shows the results of some of the largest short-term studies. From the many studies available [12,13,16–25], Pope and Dockery [1] have summarized that CV death increases by approx. 1% for every 10 $\mu\text{g/m}^3$ short-term daily increase in PM\textsubscript{2.5} concentration. Although present-day levels of air pollution probably have a minimal impact upon the mortality rate of completely healthy individuals (i.e. some degree of sensitivity or underlying disease must be present to be clinically affected) [24], the acute increase in death rate is not due solely to a mortality elevation only among critically ill people, who would have imminently died regardless of exposure (harvesting) [25]. This risk of CV disease appears to be linear without evidence of a safe PM threshold, even down to levels $< 3–5 \mu\text{g/m}^3$ [26,27]. Studies have also shown excess CV morbidity related to higher levels of PM: myocardial infarctions [24,28],
Table 1  Selected epidemiological studies linking short-term air pollution exposure with CV events

<table>
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<tr>
<th>Study</th>
<th>Reference</th>
<th>Major findings</th>
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<tr>
<td>NMMAPS</td>
<td>[16]</td>
<td>Time series study. In approx. 50 million adults from 20 to 100 U.S. cities, it was found in an updated re-analysis that daily cardiopulmonary mortality increases significantly by 0.6 % per 20 ( \mu g/m^3 ) increase in PM10.</td>
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<tr>
<td>APHEA2</td>
<td>[18]</td>
<td>Time series study. In approx. 43 million adults in 29 European cities there was a 1.5 % significant increase in daily CV mortality per 20 ( \mu g/m^3 ) increase in PM10.</td>
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<tr>
<td>COMEAP</td>
<td>[23]</td>
<td>Meta-estimates from the U.K. A 10 ( \mu g/m^3 ) increase in PM2.5 significantly increases the risk of daily CV mortality by 1.4 %.</td>
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<tr>
<td>Medicare population</td>
<td>[30]</td>
<td>Time series study. For 204 U.S. urban counties with approx. 11.5 million Medicare enrollees older than 65 years of age, there were short-term increases in hospitalizations for all types of CV health outcomes (ischaemic heart disease, cerebrovascular disease, heart rhythm, heart failure and peripheral vascular disease).</td>
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<tr>
<td>IHCS</td>
<td>[24]</td>
<td>Case cross-over study. Among 12 065 patients in Utah who had a heart catheterization, an ambient PM2.5 increase of 10 ( \mu g/m^3 ) was associated with a daily increase of 4.5 % in acute ischaemic coronary events; air pollution effects were largest on the concurrent day of event and only significant among patients with ( \geq ) one coronary vessel(s) with pre-existing atherosclerosis (( \geq )70 % stenosis).</td>
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<tr>
<td>AMIR</td>
<td>[12]</td>
<td>Case cross-over study. Among 691 patients with a myocardial infarction, transient exposure to traffic 1 h before the event was associated with an increase in risk for a heart attack (odds ratio of 2.92).</td>
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Table 2  Selected cohort studies linking longer-term air pollution exposure with CV events

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<th>Study</th>
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<th>Major findings</th>
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<td>Harvard Six Cities (extended analysis)</td>
<td>[45]</td>
<td>Cohort survival analysis. The extended 28-year follow-up in approx. 8096 people living in six U.S. cities showed that the relative risk for a CV death was increased significantly by 1.28 per 10 ( \mu g/m^3 ) increase in long-term PM2.5. The decrease in PM2.5 over the study period resulted in a significant reduction in CV mortality (relative risk of 0.69). The air pollution levels during 1 year prior to death predicted mortality equally well compared with the entire duration of the study, suggesting relatively rapid health effects of pollution and that only the annual level prior to mortality is required to predict death rate.</td>
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<tr>
<td>American Cancer Society II (extended analysis)</td>
<td>[39]</td>
<td>Cohort survival analysis. The extended 16-year follow-up performed in approx. 500 000 adults demonstrated a 12 % increase in risk for death from CV causes per 10 ( \mu g/m^3 ) increase in long-term PM2.5 exposure. Death from ischaemic heart disease (18 % increase) was the single largest cause of mortality, with smaller absolute numbers of people (although with similar relative risk elevations) dying from arrhythmias and heart failure.</td>
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<tr>
<td>Woman’s Health Initiative</td>
<td>[41]</td>
<td>In 65 893 healthy post-menopausal women in 36 U.S. cities, an increase of 10 ( \mu g/m^3 ) in long-term PM2.5 exposure was associated with a 24 and 76 % increase in risk of a CV event and CV mortality respectively.</td>
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Cardiac ischaemia [29], heart failure [30–33], arrhythmias and sudden cardiac death [30], strokes [34,35], peripheral arterial disease [30] and excess hospitalizations for various CV conditions [30]. Even as little as a few hours of exposure to PM2.5 can trigger CV events. The risk of myocardial infarctions has been shown to increase by 48 % following exposure to only a 2-h-long elevation of PM2.5 by 25 \( \mu g/m^3 \) [28]. Heart attack risk may be increased by 2.73-fold only 1 h after exposure to traffic [12].

Longer-term exposure studies

Chronic exposure to airborne PM increases the risk CV diseases as well (Table 2). It remains unclear whether there is an incremental health risk conveyed by long-term exposure that is totally independent from the
summation of acute effects that occur over days-to-weeks. For example, are there synergistic health effects (e.g. development of clinically overt coronary artery atherosclerosis due to PM exposure that leads to a CV event years later) that are beyond the additive accumulation of all the PM-attributable acute events (e.g. triggering of plaque rupture and acute myocardial infarction) during the chronic time period [36,37]? Some evidence suggests that weeks-to-months of exposure captures the majority of the risk estimate size [38]. It is possible that repeated exposures over days-to-weeks, not just 1 day, in a susceptible person may be required to trigger an acute event. It may also be that subchronic exposures over weeks may alter plaque stability and/or enhance blood thrombogenecity leading to a CV event in those with underlying coronary artery disease, whereas a single day’s exposure is insufficient. It is also possible that a vulnerable plaque could be ruptured by even 1 h of PM exposure, but the clinically overt event might not actually become apparent until days, or even weeks, later. Differences in risk estimations between short- and longer-term studies may also be related to variations in statistical and study designs, as well as cohort studies being capable of capturing the entirety of the temporal–risk relationship during the years of follow-up. On the other hand, it may also be that chronic air pollution exposure in fact does cause additively greater amounts of adverse health effects than acute or subacute (weeks) of exposure. Regardless, the relative risk of CV mortality estimated by the longer-term exposure cohort studies over years tends to be higher than seen in the acute few days setting [39–41]. A summary of the effect of chronic exposure to PM$_{2.5}$ suggests CV risk elevations ranging from 9.3 to 95% per 10 $\mu$g/m$^3$ increase in particle concentration [1].

From these studies, the WHO (World Health Organization) has estimated outdoor PM as the 13th leading cause of mortality worldwide, responsible for approx. 800 000 deaths/year [42]. CV deaths explain the largest portion of this excess mortality [1,39,43–45]. Although it is difficult to accurately compare the adverse health burden posed by PM upon the CV system compared with the pulmonary system, several studies provide insight that, contrary to what was once thought, heart diseases account for the largest single portion of absolute mortality risk. In the American Cancer Society study, when cardiopulmonary risk was separated into individual components it was found that CV mortality increased by 12%, whereas death from respiratory diseases was actually reduced by a 10 $\mu$g/m$^3$ increase in long-term PM$_{2.5}$ exposure [39]. In a similar fashion, the Harvard Six City follow-up analysis found that chronic PM exposure significantly increased CV but not pulmonary mortality risk [45]. This is not to state that air pollution does not prompt respiratory diseases. Rather, over a long-term time course, many more people in a population die due to CV diseases (i.e. much larger at-risk population and higher basal event rate) than lung diseases and, thus, the modestly larger relative risk of death posed by PM for heart diseases translates into a substantially larger absolute mortality risk. Moreover, air pollution exposure may shift the type of mortality from pulmonary to an earlier CV death even among the smaller number of individuals that are at risk of dying from lung diseases (e.g. those with chronic obstructive pulmonary disease). Short-term exposure findings also show that admission rates increase acutely to a greater extent for CV than pulmonary diseases in terms of absolute numbers of hospitalizations [30].

Very importantly, a reciprocal association between air pollution levels and CV diseases appears to hold true as well. Even relatively short-term reductions in air pollution levels over several months to a few years greatly decreases the rate of CV mortality [43–45]. Thus, at the very least, even if air pollution acts mostly as a triggering event (over hours-to-months) in susceptible patients, such as those with pre-existing (even silent) coronary atherosclerosis, avoiding exposure at a vulnerable time point might prevent a myocardial infarction that may not have occurred until years later or never. On the other hand, it remains entirely possible that a portion of the CV risk conveyed by long-term PM exposure is also explained by chronic adverse health effects superimposed upon the acute.

**Geography and sources of pollution**

CV admissions are most strongly related to PM in the Northeast, Midwest and Southern U.S. regions, whereas exposure in Northwestern U.S. regions may not be associated with any excess risk [15,30]. Small differences in geographic locations, and pollution characteristics, within a single city have been shown to be stronger determinants of CV risk than inter-city risks [46]. Long-term exposure to traffic-related air pollution (living close to a major roadway) is also a particularly strong predictor of myocardial infarction risk [13]. This may be due to the fact that the composition (e.g. sulfate content) and sources of (e.g. automobiles) PM, along with the co-pollutants (e.g. gases and vapour-phase compounds), vary across differing regions. Ambient meteorology may also play a major role in determining exposure characteristics. Thus the role of PM constituents (e.g. specifically transition metals and organic carbon compounds), sources (e.g. specifically traffic pollution) and the impact in regional meteorology requires further investigation.

**BIOLOGICAL MECHANISMS**

Dozens of human panel and controlled exposures, animal exposures, toxicological and basic science/molecular studies have now illustrated a variety of mechanisms whereby PM exposure may be capable of mediating CV...
Figure 2 Broad biological pathways whereby PM may cause CV events

AT2, angiotensin II; CVA, cerebrovascular accident; CHF, congestive heart failure; ET, endothelins; MI, myocardial infarction; ROS, reactive oxygen species; UFP, ultra-fine particles; WBC, white blood cells.

Most end points pertaining to pathway 2 share a single common aetiology: pulmonary tissue oxidative stress induced by PM inhalation [47–59]. Numerous studies confirm that an initial lung oxidative stress may stem from chemicals within the PM mixture (e.g. metals and redox-active compounds) and/or from activation of endogenous lung-based cellular defences (leucocytes or pulmonary cells) in response to deposition of PM. However, some important mediators of CV disease (e.g. endothelins) might be able to be released from the pulmonary tissue without overt lung inflammation or oxidative stress [60].

Regarding pathway 2, pulmonary oxidative stress may be responsible for instigating the systemic CV pro-oxidative [61–68] and pro-inflammatory [69–83] chain reaction observed after PM exposure. Cardiac tissue oxidative stress increases within hours of PM inhalation [61], whereas footprints (e.g. myeloperoxidase, nitrotyrosine and inducible nitric oxide synthase) of elevated free radical generation are found in remote non-pulmonary animal vessels hours to days later [68,84,85]. Pro-inflammatory mediators {cytokines [e.g. IL-6 (interleukin-6)], acute-phase reactants [e.g. fibrinogen and CRP (C-reactive protein)], vasoactive hormones (e.g. endothelins) and activated leucocytes} released from
the pulmonary into the system vasculature may then secondarily trigger a variety of adverse CV reactions. It is important to note, however, that some studies have also reported negative findings (i.e. no signal of a systemic inflammatory response) [1,83]. It is likely that the specific pollution constituents, co-pollutant levels (e.g. gases), the duration of exposure and patient susceptibility play important roles in determining the subsequent responses (or lack thereof). It is also important to note that even the repeated observation of higher levels of pro-inflammatory mediators found within the systemic circulation following PM inhalation does not necessarily prove that their original source is a spill over from pulmonary cells. Hypothetically, immune cells (e.g. monocytes) that remain entirely within the pulmonary vessels as they circulate through the lungs to the rest of the body could become ‘activated’ (if appropriately primed) by the local inflammatory/oxidative signal derived from resident lung cells given their extreme proximity to each other. The initial source of the systemic pro-inflammatory reaction and the detailed mechanisms by which it is conveyed throughout the body following PM exposure require much more investigation.

The three general pathways are not mutually exclusive. They may overlap temporally and/or be principally activated at differing time points. Hyperacutely (within minutes to hours), autonomic imbalance and direct pro-oxidative/inflammatory vascular actions of circulating PM constituents are the most plausible dominant pathways leading to CV events. Acute to subacute responses (hours to days) may be prompted by the former means (pathways 1 and 3) and also by secondarily induced systemic oxidative stress and inflammation (pathway 2). Finally, the chronic actions of PM upon the CV system, such as the enhancement of atherosclerosis, are most likely to be induced by the generation of a chronic pro-inflammatory state (pathway 2). The types and sizes of pollutants inhaled may also determine their toxicity and the relative importance of the pathways. Larger fine or coarse PM cannot be transported into the circulation and will require secondary neural or pro-inflammatory responses to mediate extrapulmonary actions, whereas ultrafine PM (or soluble constituents of larger particles) might directly enter the blood stream. A PM mixture rich in pro-oxidative combustion products (e.g. organic carbon compounds and metals) might trigger more robust responses in a more rapid fashion which differs from less toxic inert PM. These underlying general ‘mediating’ pathways can, in turn, act alone or together to instigate several different types of manifest CV diseases. Air pollution has been shown to cause CV morbidity and mortality due to arrhythmias and sudden death, ischaemic events (e.g. myocardial infarctions and strokes), heart failure, the progression of underlying atherosclerosis and possibly the development of conventional CV risk factors (e.g. hypertension and diabetes).

**Arrhythmias**

Air pollution has been associated with ventricular arrhythmias, implantable defibrillator discharges, atrial fibrillation and ECG repolarization abnormalities [1,2,29,86–89]. In agreement with these observations, a sizeable portion of the CV morbidity and mortality stemming from PM exposure has been shown to be due to cardiac arrhythmias and sudden death [30,39–41,45]. The mechanism responsible is likely to be that the inhalation of particles into the pulmonary tree can alter neural reflexes (general pathway 1), which then disrupt cardiac autonomic balance and lead to myocardial electrical instability [90–93]. Inhaled particles irritate a wide range of pulmonary nerve endings, which generally leads to subsequent PSNS withdrawal [90]. Indeed, PM inhalation has repeatedly been shown to alter HRV (heart rate variability), a marker of cardiac autonomic tone, within minutes to hours [1,2,82,90–93]. Most, but not all, studies show a reduction in overall time domain HRV, indicating a blunted PSNS activity [1]. This has been linked to an adverse CV prognosis and an increased risk of sudden death and ischaemic events [94,95]. Nevertheless, several questions remain including the importance of gaseous co-pollutants (e.g. NOx and SO2) [93,97], the role of pollution source (e.g. traffic) [98], patient susceptibility [99,100], whether the altered HRV is a causal mediator of events compared with an epiphenomenon and whether altered HRV actually reflects changes in central nervous system autonomic outflow (and in what pattern to different organs).

Previous observations demonstrate that patients with reduced capacities to defend against oxidative stress (e.g. a glutathione S-transferase M1 polymorphism) have a more robust alteration in HRV [101,102]. This is important as it demonstrates further the central role of ‘oxidative stress’ as a fundamental core pathway whereby PM imparts biological harm. However, the question now arises whether the generation of oxidative stress (perhaps in pulmonary tissue) is somehow required to trigger the neural reflex/reduced HRV and that the presence of particles within the pulmonary tree is not adequate. Alternatively, these findings could be explained if the reduced HRV is an illustration of impaired cardiac ion channel function induced by systemic oxidative stress after PM inhalation and not necessarily that it reflects changes in autonomic balance. Despite uncertainties, environmentally relevant levels of PM do appear capable of rapidly altering HRV, potentially reflecting alterations in autonomic balance and/or cardiac electrical stability, which may cause arrhythmias and sudden death.

**Atherosclerotic and ischaemic events**

Exposure to air pollution and automobile traffic has been shown to trigger myocardial ischaemia [29,103,104] and infarctions [12,28] within hours following exposure. The risks of strokes [34,35] and hospitalizations for
ischaemic events increase as well [30]. A central cause of these ischaemic events could be PM-induced vascular dysfunction and vasoconstriction. Endothelial dysfunction, impaired smooth muscle dilation and/or both findings have been reported at the resistance and conduit artery level in humans [104–109] and in animal/basic science ex vivo studies [84,85,111–120]. Gaseous pollutants such as SO2 may also be linked to endothelial dysfunction [110]. PM2.5 can also cause a pro-hypertensive response in humans and animals [121–123]. Subsequently, endothelial dysfunction, vasoconstriction and increased blood pressure could each (or in conjunction) trigger atherosclerotic plaque instability, leading to myocardial infarctions and strokes and/or promote myocardial ischaemia in susceptible people.

All three general pathways may play roles in causing this vascular dysfunction. The systemic oxidative stress and inflammation following air pollution exposure can decrease the bioavailability of NO in the vasculature [85,112–114], tipping the balance toward vasoconstriction. Several of the circulating pro-inflammatory factors (e.g. IL-6, TNF-α) and mediators of oxidative stress (e.g. H2O2) [59] shown to increase after PM inhalation blunt vascular NO activity [1]. Relative SNS hyperactivity could also impair endothelial function by reducing NO bioavailability [124] and/or by promoting vasoconstriction via α-adrenergic receptor activation. Even without pulmonary inflammation, PM inhalation may also enhance the release into the systemic circulation of direct vasoconstrictors such as endothelins [120], augment the bioactivity of the vasoconstrictor AngII (angiotensin II) [116] and/or directly augmenting smooth muscle contractile responses (e.g. alter Rho kinase activity or myosin light-chain kinases) via oxidative stress mechanisms [85,115]. Certain PM constituents (e.g. metals and organic compounds) might also reach the systemic circulation and, thus, directly instigate pro-oxidative stress reactions within the vasculature, leading to catabolism of NO and the release of vasoconstrictors [125]. However, this final pathway remains highly controversial. Finally, several studies in both humans and animals suggest that chronic PM exposure may enhance the progression and instability of underlying atherosclerosis by pro-inflammatory mechanisms, thus promoting further future ischaemic events [126–129].

Enhanced thrombosis

PM inhalation can also enhance arterial thrombosis and coagulation [130–138]. As with other biological mechanisms, not all studies have been positive [139]. Nonetheless, with underlying vulnerable atherosclerotic plaques, the generation of a pro-thrombotic milieu could trigger arterial thrombosis and subsequent acute ischaemic events. After air pollution exposure, studies have suggested that these effects could be caused by increases in fibrinogen and blood viscosity, elevated CRP, increased platelet reactivity, altered coagulation factors (e.g. tissue factor), histamine, enhanced IL-6-dependent pathways, expression of microvascular surface adhesion molecules and reduced release of fibrinolytic factors (e.g. tissue plasminogen activator) [104,105,130–138]. The relative roles of systemic inflammation, altered autonomic balance and direct effects of PM constituents acting upon blood-borne mediators of thrombosis remain largely unknown.

Heart failure

PM air pollution is linked to an increased risk of heart failure exacerbations and hospital admissions [30–33]. It is possible that both the pro-ischaemic and arrhythmic effects of PM exposure could be responsible; however, a recent study in mice has also shown that pulmonary PM deposition can impair the ability of lung alveoli to clear fluid due to reduced membrane Na,K-ATPase activity [140]. This effect was prevented by antioxidant defences, suggesting once again that oxidative stress plays an important role.

Instigation of traditional risk factors

Short-term air pollution exposure can trigger an increase in arterial blood pressure within hours to days [120–123]. Many of the pro-inflammatory/oxidative reactions, the vascular dysfunction and the autonomic imbalance instigated by PM may prompt the chronic development of overt hypertension [123]. However, whether long-term exposure can promote a sustained elevation in blood pressure remains unknown at present. Moreover, it is also possible that PM exposure could also promote insulin resistance, thereby increasing the risk of future diabetes mellitus and the metabolic syndrome [141]. In support of this hypothesis, a recent study has demonstrated that NO2, a marker of traffic exposure, was independently correlated with the prevalence diabetes in women [142]. Owing to the enormous number of individuals exposed continuously worldwide, even small effects of air pollution on chronic levels of blood pressure and glucose would have tremendous public health importance.

In summary, the experimental findings provides ample evidence to demonstrate the plausibility that air pollution can actually cause CV disease. It is clear that exposure to PM can trigger acute CV events via many mechanisms in susceptible individuals. Although long-term air pollution exposure may enhance underlying atherosclerosis and could conceivably increase the risk for hypertension and diabetes, the clinical significance of these putative chronic effects remains unclear.

FUTURE RESEARCH

Our knowledge from both an epidemiological and mechanistic standpoint regarding the association between
PM and CV health has expanded greatly in the past decade. Although a host of finer biological details remain to be fully understood, there is no question that the original penultimate goal for studying the mechanisms involved (i.e. to provide an overall plausibility for the epidemiology) has been reached. Thus future research providing a more detailed mechanistic understanding would mostly serve the quest to enhance human scientific knowledge in general and perhaps better our overall understanding of biology. Not that these noble aims are not important; however, the main point is that no more mechanistic details are required in order to provide a fundamental ‘plausibility’ for the epidemiological findings (and thus to act by reducing air pollution). It is my humble suggestion that the priority of air pollution findings (and thus to act by reducing air pollution). It is my humble suggestion that the priority of air pollution research should now be re-focusing on means to achieve the ‘ultimate’ goal: how to best save lives and improve the overall human condition.

In this context, there are several areas where future research could be particularly helpful. Foremost is a greater understanding of the most ‘responsible’ pollutants for causing the greatest disease burden. For example, identifying the most toxic/harmful to health sources (e.g. traffic), specific chemical compounds (e.g. metals, organic species and gaseous co-pollutants) and vulnerable places/times of exposure. In this fashion, the most critical pollutants can be most effectively targeted for reduction. Alternatively, it may be found that the health effects from the pollution mixture is too non-specific to target individual chemicals or that they occur in response to a host of different PM subtypes and sources and that only an overall reduction in most/all components can adequately assure a decrease in the associated CV mortality. Identifying individuals at greatest risk or those most susceptible, along with practical mechanisms to feasibly reduce the risks of exposure and/or subsequent health problems once exposed, are warranted. Finally, a comprehensive assessment of the health benefits from these measures is important.

From a biological standpoint, a key remaining uncertainty is the mechanism(s) and/or pathway(s) whereby the original insult to the lungs induced by PM inhalation is conveyed to the systemic vasculature and the heart (where a host of adverse responses have already been shown to occur that could feasibly trigger CV events). What are the specific signalling mediators (e.g. cytokines, inflammatory cells, mediators of oxidative stress and soluble PM components) and how can they be therapeutically mitigated? Finally, understanding the pertinence (e.g. relative importance) among the large host of different responses shown to be triggered by air pollution (e.g. vascular dysfunction, enhanced thrombosis and autonomic imbalance), or alternatively the lack of any one single predominant factor, in actually causing the observed human CV mortality is critically important to investigate.

CONCLUSIONS

PM air pollution exposure over both the short- and long-term is associated with an increased risk of CV morbidity and mortality. Even PM$_{2.5}$ inhalation over a few minutes to hours can trigger myocardial infarctions, cardiac ischaemia, arrhythmias, heart failure, strokes and sudden death. More long-term exposures may also enhance the risk of developing chronic CV diseases. A multitude of plausible mechanistic explanations have now been demonstrated that could alone or together explain the observational findings. Although the finer details of all of the responsible mechanisms and pollutants are not fully described, this should not stop the medical and scientific communities from supporting efforts to maintain optimal air quality in order to protect their patients and the public health at large (information for healthcare providers at: http://www.airnow.gov/). To paraphrase an aphorism: you do not need to know every last detail about the archer who shot you with a poison arrow, before you know that you need to pull the arrow out.

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