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# Air Pollution And Arterial Hypertension.

# A New Risk Factor Is In The Air

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# Disclosures

None related to this article

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#### Abstract

Air pollution is one of the greatest environmental threats and has been implicated for several adverse cardiovascular effects including arterial hypertension. However, the exact relationship between air pollution exposure and hypertension is still unclear. Air contamination provokes oxidative stress, systemic inflammation and autonomic nervous system imbalance that subsequently induce endothelial dysfunction and vasoconstriction leading to increased blood pressure. The aim of this review was to describe the potential mechanisms by which air pollution contributes to hypertension and to summarize the consequences of short and long term exposure.

#### Introduction

According to the World Health Organization (WHO), urban air pollution is an important cause of global mortality being responsible for approximately 800000 premature deaths each year. Outdoor contamination has been recognized as the 13<sup>th</sup> leading cause of mortality globally, especially in low and middle-income countries where air pollution concentrations continuously rise (1,2).

The adverse effects of air pollution on cardiovascular health have become the focus on a series of major epidemiologic and observational studies (3-8). Economic expansion, industrial growth and climate change contribute to increased levels of outdoor contamination in developing nations while the composition and the sources of air pollutants vary across different regions (9,10).

Short and long-term exposure to air pollution is associated with high blood pressure (BP) through inflammation, oxidative stress and arterial remodeling. Recent studies suggest that even modest rises in airborne pollutants can trigger an increase in arterial BP within hours (11). Inhalation of air pollutants affects heart rate (HR), heart rate variability (HRV), vascular tone, blood coagulability and promotes atherosclerosis. Even short term exposures to air pollution have been associated with increased cardiovascular morbidity and deaths from myocardial ischemia, arrhythmia and heart failure (1,9).

In this context, both the American Heart Association (2010) and the European Society of Cardiology (2015) have issued official statements

discussing the impact of air pollution exposure to cardiovascular health (12,13).

The aim of this review was to analyze the biological mechanisms responsible for the air pollution induced cardiovascular toxicity and to describe the consequences of short and long term exposures to the cardiovascular system, focusing on hypertension (HTN).

#### Air pollution

Historically, in 1872, Robert Angus Smith published the first air pollution-related study and described air pollutants as components of urban air and "acid rains". The 20<sup>th</sup> century was also marked by major incidents caused by air contamination. In December 1930, air pollutants from chimney exhausts were entrapped by a thick fog and a toxic cloud was created that resulted in 60 deaths in the Meuse Valley in Belgium. Additionally, the accumulation of industrial air pollutants from a local smelting plant caused 20 deaths and 400 hospital admissions in Pennsylvania 20 years later. In 1952, a heavy fog from local stoves and industrial plants increased all hospital admissions and respiratory disease-related admissions by 48% and 163% respectively in London. Since then the adverse health effects of air pollution have been remarkably multiplied. Recent epidemiological and clinical evidence suggest that respiratory diseases along with cardiovascular toxicity are considered as the major consequences of air pollution contamination with increased rates of hospitalization and mortality (6,14-16).

Air pollution is defined as the contamination of outdoor and indoor environments by any agent that could modify the natural characteristics of the

atmosphere. Outdoor air pollution is produced by fossil fuel combustion (i.e. automobiles, power generation and industry), construction and demolition activities, forest fires and volcanic emissions and encompasses a mixture of particulate matters (PM), with various gaseous compounds and molecules in a vapor phase and an aerodynamic diameter (AD) ranging from 2.5 to 10  $\mu$ m (PM10), below to 2.5  $\mu$ m (PM2.5; Fine PM) and below to 0.1  $\mu$ m (PM0.1; Ultrafine PM). The gaseous part of polluted air includes nitrogen oxides, carbon monoxide (CO), sulfur dioxide (SO<sub>2</sub>) and ozone (O<sub>3</sub>) (9,10,15).

Solid fuels in cooking or heating, poor ventilation and tobacco products release gases or particles that contribute to indoor contamination. In more developing nations, air- conditioning systems, passive cigarette, smoke exposure and newer sealed office buildings conduce to increased levels of indoor air pollution (10).

Both gaseous air pollutants and PM are implicated as potentially harmful to health. However, the most deleterious effects are attributed to PM because of the broad range of toxic substances that they contain (2).

#### **Biological mechanisms**

Three putative pathways implicate air pollution exposure to cardiovascular system. First, the provocation of systemic inflammation and/or oxidative stress. Second, the activation of autonomic nervous system and third the translocation into the circulation with the potential for direct effects on hemostasis and cardiovascular integrity (Figure) (1,17).

The type and size of inhaled pollutants determine the relative importance of the mechanisms. Larger PM cannot be transported directly into

the circulation and require secondary neural or pro-inflammatory responses to mediate extrapulmonary actions whereas ultrafine PM or soluble constituents of larger particles might directly enter into the blood stream (1).

Pope et al demonstrated that fine PM exposure is a risk factor for cause-specific cardiovascular disease mortality via these mechanisms that might be overlapped and/or be generated at different time points. Within minutes to hours, the alteration of systemic autonomic balance and the direct oxidative/inflammatory vascular actions of circulating air pollutants are the main mechanisms promoting adverse cardiovascular events (second and third pathway). These pathways in combination with secondary induced systemic oxidative stress and inflammation (first pathway) are prompted between hours to days after the exposure (1,6).

**First pathway.** The inhaled air pollutants promote the release of a variety of pro-oxidative/inflammatory (cytokines, activated immune cells or platelets) and/or vasoactive mediators (endothilin) into the systemic circulation. Indeed, particle breathing might trigger systemic inflammation, atherosclerosis and endothelial dysfunction resulting in increased systemic vascular residence and HTN. Of note, the duration of exposure, the co-pollutant levels and the patient sensibility are able to determine the subsequent responses (1,9,18).

**Second pathway.** The accumulation of air pollutants to the pulmonary tree can directly stimulate lung nerve reflexes leading to systemic autonomic imbalance that subsequently favors vasoconstriction and raises of HRV (1,17,18).

Third pathway. The inhalation of some metallic component, as well as very small PM, might be able to pass through the alveolar capillary membrane reaching directly into the systemic circulation and impair vasomotor regulation. The size and charge, the chemical composition and the propensity to form aggregates determine the ability to cross the lung–blood barrier (9,15,18).

#### Cardiovascular effects of air pollution

Airborne pollution appears as a triggering factor of cardiovascular events provoking significant changes in HR, HRV, vascular tone, blood coagulability and BP. While some of the effects are developed acutely, the progression of atherosclerosis accelerates as a response to the chronic exposure to elevated concentrations of air pollutants (15).

Likewise, air pollution was related with lower high-density lipoprotein (HDL). Oxidative stress and inflammation might promote changes in HDL structure and function that result in proatherogenic or dysfunctional HDL (19).

Arrhythmias and HRV. Air contamination has been correlated with elevated risk of rapid ventricular response due to paroxysmal atrial fibrillation. In addition, ventricular arrhythmias were remarked to vulnerable patients with acutely predisposing conditions that increase ventricular electrical instability. These observations emphasize the potential link between air pollution and sudden cardiac deaths. A potential eventual responsible mechanism is the inhalation-mediated irritation of a wide range of pulmonary nerve endings that subsequently leads to parasympathetic nervous system withdrawal (20,21).

A study of 21 residents from Boston, investigated the relationship between ambient particles and cardiovascular function and demonstrated that exposure to PM2.5 and  $O_3$  decreases HR and HRV due to autonomic nervous system imbalance (22).

**Ischemic events.** Air pollution related studies have demonstrated the correlation between the elevated concentrations of air pollutants and the risk of unstable angina and myocardial infarction (23-27). Short-term exposure to PM2.5 elevated by  $10 \ \mu g/m^3$  contributes to acute coronary syndromes (ACS), especially among patients with underlying coronary artery disease. Likewise, the risk of acute myocardial infarction is higher after long-term exposure to traffic (23,26).

In a large meta-analysis published in 2011, contamination was indicated as an important trigger for myocardial infarction with similar magnitude as other well accepted triggers such as physical exertion, alcohol, and coffee (28).

The central cause in triggering acute ischemic events might be endothelial dysfunction, vasoconstriction and HTN (15). It is possible that a vulnerable plaque could be ruptured by even one hour of PM exposure, but the clinically overt event might not actually become apparent until days or even weeks later. Indeed, repeated exposures over days-to-weeks might be required to alter plaque stability and/or enhance blood thrombogenecity triggering an acute event in those with underlying coronary artery disease, whereas a single day's exposure is insufficient (1).

**Thrombosis and coagulation.** Air pollution exposure might enhance arterial thrombosis and coagulation. Several studies have demonstrated that

these effects could be caused by increased fibrinogen, blood viscosity and platelet reactivity, elevated CRP, altered coagulation factors (i.e. tissue factor), histamine, enhanced Interleukin-6- dependent pathways, expression of microvascular surface adhesion molecules and reduced release of fibrinolytic factors (i.e. tissue plasminogen activator) (1,29).

Likewise, Baccarelli et al revealed the relationship between air pollution exposures and hypercoagulability in two studies. High levels of air pollutants were correlated with shorter prothrombin time (PT). Conversely, no association was found between air pollutant levels and activated partial thromboplastin time (APTT), fibrinogen, antithrombin and proteins C and S. In addition, the risk of deep vein thrombosis was also elevated (30,31).

**Heart failure.** Ambient pollutants are linked to an increased risk of heart failure exacerbations and hospitalizations as a result of both ischemic and arrhythmic effects due to exposure (1).

**Cardiovascular outcomes**. Various studies worldwide have shown that air pollution exposure is associated with adverse cardiovascular outcomes and might increase hospital admissions and mortality in the sort or in the long run (Table). The former estimate the acute effects of contamination exposure and include time-series analyses over a few days. The latter evaluate the chronic effects of contamination in cohort survival analyses over years of exposure (7,11,16,32).

During the past decade the risk of emergency admissions for myocardial infarction was elevated by 0.7% per 10 µg/m<sup>3</sup> increase in ambient PM10 levels among elderly residents of 21 US cities. Subsequently, similar raise in PM2.5 concentrations was associated with increase in hospitalization

risk for heart failure by 1.3%, cerebrovascular disease by 0.8% and peripheral vascular disease by 0.9% in 204 US cities (16,32).

A strong relationship between mortality and environmental contamination was demonstrated by the Air Pollution and Health European Approach Study (APHEA2). Indeed, rises of PM and black smoke by  $10 \ \mu g/m^3$ were correlated with increases of 0.8% and 0.6% in cardiovascular and respiratory deaths respectively indicating their role as predictors of daily deaths (33,34).

#### Hypertension

In most individuals, the combination of genetic and behavioral factors predisposes to HTN. However, less attention is paid to other potentially modifiable factors that can also affect BP, such as air pollution (35). It is impressive that even short term exposure might trigger a rapid and significant increase (36,37).

Pathophysiologically, air pollution exposure can trigger oxidative stress and systemic inflammation that subsequently induce endothelial dysfunction, autonomic nervous system imbalance and vasoconstriction. In addition, PM can also reduce daytime sodium excretion and decrease the normal nocturnal reduction in BP. If this happens repeatedly, the impaired renal handling of excess sodium may partly contribute to elevated BP (17,38,39).

A diverse group of conditions associate with increased noise level, including roadway traffic, airplanes and occupational noises, has been implicated in increasing BP. The linear relationship between decibel intensity

and BP response is often mentioned. Individuals with cardiovascular disease, men and those who exposed to high traffic noise levels > 55 dB are also at greater risk for noise related development of HTN. In addition, the quantitative correlation between road traffic noise and HTN was also revealed in several European studies for every 5 dB increase of the road traffic noise level (35,40-42).

Perhaps, nocturnal loud noise might be even more detrimental than daytime one. During the night reduced sympathetic and increased parasympathetic tone leads to a decrease of BP called dipping. Nighttime noise causes sleep disturbances and activation of sympathetic nervous system that might prevent BP dipping (43-45).

For aircraft noise, the Hypertension and Exposure to Noise near Airports (HYENA) study found a significant increase in BP with increases in nocturnal noise, but no significant correlation with day-time noise. Likewise, a Swiss study demonstrated an adverse effect of railway noise on BP, particularly during the night. Another study that also investigated the effect of noise pollution (aircraft, road traffic, indoor) on BP during night-time sleep revealed increases in both systolic and diastolic BP by 5-7 mmHg and 3-7 mmHg respectively. BP was assessed every 15 min although the noise event (over 35 dB) could have happened anytime within this interval (43,46,47).

Household air pollution from solid fuels and indoor PM2.5 exposure might contribute to elevated BP. According to a study the use of improved cooking stoves among Guatemalan women resulted in lower PM2.5 exposure and subsequently, lower BP levels. These findings were consistent with another study that occurred in rural China and included women that used

biomass for heating or cooking. A 1-log-µg/m3 rise in PM2.5 exposure increased systolic BP by 4 mmHg and diastolic BP by 2 mmHg in women older than 50 years of age. PM2.5 exposure was positively correlated with systolic BP among younger women but the association was not statistically significant (48,49).

A higher left ventricular mass index (LVMI) was observed to people living close to major roads according to a report from the Multi-Ethnic Study of Atherosclerosis. The participants showed an adjusted 1.4 g/m higher LVMI, a difference in mass corresponding to a 5.6 mmHg greater systolic BP. This suggested that traffic-related exposures might be associated with increased LVMI by chronically elevating systemic arterial BP, a common cause of left ventricular hypertrophy (50).

In January 1985, an air pollution episode occurred throughout central Europe resulting in hospital admissions for cardiovascular diseases including arrhythmias, ACS and strokes that were elevated by 49%, 30% and 57% respectively (51). During this episode the systolic BP was elevated by 1.8 mmHg per 90  $\mu$ g/m<sup>3</sup> suspended particulates and 0.8 mmHg per 80  $\mu$ g/m<sup>3</sup> SO<sub>2</sub>. Further increases in BP by 6.9mmHg and 7.8mmHg was observed in subgroups with high plasma viscosity and high HR respectively (52).

There is also evidence that in Detroit, a highly-polluted US city, increased PM2.5 levels by 10  $\mu$ g/m<sup>3</sup> resulted in a 3 mmHg increase in systolic BP during 2002-2003. The relationship between air pollution exposures and the risk of HTN was also demonstrated in a meta-analysis of 17 epidemiological studies whereas one third of 300000 participants developed HTN (11,53).

Recently, the European Study of Cohorts for Air Pollution Effects (ESCAPE) showed that prolonged exposure to air pollution and traffic noise might be associated with greater incidence of self-reported high BP. Among 41072 people living in Norway, Sweden, Denmark, Germany and Spain none of them had HTN at the beginning of the study. However, 15% of them reported development of HTN or were initiated on BP-lowering medications within 5-9 years of follow-up period. For every 5  $\mu$ g/m<sup>3</sup> of PM2.5, the risk of HTN increased by 22% in people living in the central and southern Europe compared to those living in Scandinavia (54).

## High risk population

There are several categories of individuals or subsets of patients that might be at higher risk for air pollution mediated cardiovascular events. Some observations suggest that the elderly and those with low socioeconomic status are particularly susceptible populations. The cardiovascular risk might be increased by the existence of comorbidities such as chronic lung disease, coronary heart disease, heart failure and diabetes mellitus. There is no convincing evidence that gender, race and other preexisting coronary risk factors (i.e. obesity, dyslipidemia) affects the risk of cardiovascular episodes due to air pollution (8,15).

#### Conclusions

Air pollution is linked to cardiovascular toxicity and as a triggering factor potentially induces HTN mainly due to autonomic nervous system imbalance and subsequent vasoconstriction. Furthermore, patient

susceptibility might play an important role in determining the exact hemodynamic responses. The major strategy in decreasing the harmful effects of air pollution is the reduction of air pollutants themselves.

Figure. Major biological pathways linking air pollution to cardiovascular diseases



ANS: Autonomic Nervous System

Table. Studies investigating the cardiovascular effects of air pollution

Study	Year	Patients	Men	Age	Air pollutant	Findings
Gold et al	2000	21	48%	53-87	PM, O <sub>3</sub>	Decreased HRV
Peters et al	2001	772	63%	45-75	PM2.5	Increased risk of ACS
Ibald-Mulli et al	2001	2607	51%	25-64	PM, SO <sub>2</sub>	Increased risk of HTN
Pekkanen et al	2002	45	53%	60-70	PM, NO <sub>2</sub> , CO	Increased risk of ACS
Hoek et al	2002	5000	NA	55-69	NO <sub>2</sub> , black smoke	Short life expectancy
Brook et al	2002	25	60%	25-45	PM, O <sub>3</sub>	Vasoconstriction
D'Ippoliti et al	2003	6531	NA	NA	PM, NO <sub>2</sub> , CO	Increased risk of ACS
Urch et al	2005	23	57%	25-45	PM2.5, O <sub>3</sub>	Increased risk of HTN
Dockery et al	2005	203	75%	19-90	PM, NO <sub>2</sub> , CO, SO <sub>2</sub> , O <sub>3</sub>	Increased risk of arrhythmias
Rich et al	2006	203	79%	45-78	PM2.5, NO <sub>2</sub> , CO, SO <sub>2</sub> , O <sub>3</sub>	Increased risk of PAF
Pope et al	2006	12865	66%	50-75	PM2.5	Increased risk of ACS
Tonne et al	2007	5049	56.4%	≥25	PM2.5	Increased risk of ACS
Baccarelli et al	2007	1218	40%	11-84	PM10, CO, NO, SO <sub>2</sub>	Reduced PT
Miller et al	2007	65893	0%	50-79	PM2.5	Increased risk of CAD
Baccarelli et al	2009	1522	42%	18-84	PM10	Increased risk of DVT
Van Hee et al	2009	3827	47%	45-84	PM2.5	Increased LVMI
Dvonch et al	2009	347	60%	NA	PM2.5	Increased risk of HTN
Fuks et al	2011	4291	50%	45-75	PM2.5, PM10	Increased risk of HTN
Regicor study	2014	3700	47%	35-83	NO <sub>2</sub>	Increased risk of HTN
Sister study	2015	43629	0%	35-76	PM2.5, NO <sub>2</sub>	increased risk of HTN
Cai et al	2016	>300000	NA	NA	PM2.5, PM10, SO <sub>2</sub> , NO <sub>2</sub>	Increased risk of HTN
ESCAPE study	2017	74354	44%	47-71	PM2.5	Increased risk of HTN
Bell et al	2017	6654	47%	45-84	PM2.5, black carbon	Decreased HDL

ACS: acute coronary syndrome, CAD: coronary artery disease, CHF: congestive heart failure, CO: carbon monoxide, DVT: deep vein thrombosis, HDL: high-density lipoprotein, HRV: heart rate variability, HTN: hypertension, LVMI: left ventricular mass index, NA: non-available, NO: nitric oxide, NO<sub>2</sub>: nitrogen dioxide, O<sub>3</sub>: ozone, PAF: paroxysmal atrial fibrillation, PM: particulate matters, PT: prothrombin time, SO<sub>2</sub>: sulfur dioxide

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# Highlights

- Air pollution is nowadays considered to be a new risk factor for hypertension
- Even brief exposure to air pollution might trigger a rapid and significant increase of blood pressure
- Elderly and those with comorbidities are at higher risk for air pollution mediated cardiovascular events