Toxicol. Res.
Vol. 30, No. 2, pp. 71-75 (2014)
Open Access http://dx.doi.org/10.5487/TR.2014.30.2.071
pISSN: 1976-8257 eISSN: 2234-2753 **Thematic Perspectives**

Toxicological Research
Official Journal of
Korean Society of Toxicology
Available Online at http://www.ToxicolRes.org

Air Pollution Exposure and Cardiovascular Disease

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(Received June 19, 2014; Revised June 26, 2014; Accepted June 27, 2014)

Ambient air pollution (AAP) and particulate matters (PM) have been closely associated with adverse health effects such as respiratory disease and cardiovascular diseases. Previous studies have examined the adverse health effects associated with short- and long-term exposure to AAP and outdoor PM on respiratory disease. However, the effect of PM size ($PM_{2.5}$ and PM_{10}) on cardiovascular disease has not been well studied. Thus, it remains unclear how the size of the inhalable particles (coarse, fine, or ultrafine) affects mortality and morbidity. Airborne PM concentrations are commonly used for ambient air quality management worldwide, owing to the known effects on cardiorespiratory health. In this article, we assess the relationship between cardiovascular diseases and PM, with a particular focus on PM size. We discuss the association of $PM_{2.5}$ and PM_{10}, nitrogen dioxide (NO_2), and elemental carbon with mortality and morbidity due to cardiovascular diseases, stroke, and altered blood pressure, based on epidemiological studies. In addition, we provide evidence that the adverse health effects of AAP and PM are more pronounced among the elderly, children, and people with preexisting cardiovascular and respiratory conditions. Finally, we critically summarize the literature pertaining to cardiovascular diseases, including atherosclerosis and stroke, and introduce potential studies to better understand the health significance of AAP and PM on cardiovascular disease.

Key words: Particulate matter, Air pollution, Cardiovascular disease

INTRODUCTION

The adverse health effects of exposure to particulate matter (PM), including particles with a median aerodynamic diameter < 2.5 μm ($PM_{2.5}$) and < 10 μm (PM_{10}), are of great concern to governments and health organizations worldwide (1,2). The pulmonary effects of air pollution containing $PM_{2.5}$ and PM_{10} include increased respiratory symptoms, decreased lung function, and increased incidence of chronic cough, bronchitis, and conjunctivitis (3-5). Furthermore, epidemiological and clinical studies have increasingly shown that air pollution is associated with not only respiratory and pulmonary diseases but also cardiovascular diseases. As a result, the adverse health effects of air pollution have been increasingly recognized in recent years.

Clinical, mechanistic, and epidemiological studies of the effects of long- and short-term exposure to air pollution and the sizes of PM have provided evidence supporting adverse health effects after air pollution exposure. Epidemiological studies and pathophysiological data have also shown that air pollution exposure is related with general morbidity and mortality due to respiratory and cardiovascular diseases (3,6,7,8,9,10,11,12). Furthermore, the aerodynamics of PM can affect the severity of adverse health effects. In general, PM with lower aerodynamic diameters, including fine and ultrafine (< 100 nm) PM, are associated with more serious adverse effects after both short-term exposure to an ele-

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Abbreviations: AAP: Ambient air pollution, PM: Particulate Matter, NO_2: Nitrogen dioxide, CO: Carbon monoxide, SO_2: Sulfur dioxide, O_3: Ozone, CO: Carbon monoxide, CO_2: Carbon dioxide, NO_2: Nitrogen dioxide, NO_3: Nitric oxide, AD: Aerodynamic diameter, WHO: World Health Organization, RR: Relative Risk, CI: Confidence Interval, AMI: Acute Myocardial Infarction, NMMAPS: The National Morbidity, Mortality and Air Pollution Study, APHEA: Air Pollution and Health European Approach, DBP: Diastolic Blood Pressure, SBP: Systolic Blood Pressure

vated concentration of pollutants or after long-term exposure (13,14). In addition, adverse health effects can be exacerbated in vulnerable populations, including those with preexisting cardio-respiratory diseases and the elderly. As a result, these populations tend to have more complicated health problem after air pollution exposure than healthy groups (15).

The relationship between air pollution and respiratory diseases, such as chronic obstructive pulmonary disease and asthma, is well established. However, the relationship between air pollution and cardiovascular disease remains unclear. Nevertheless, recent clinical and epidemiological data suggest the two may be related. In this review, we discuss how air pollution and PM may affect the pathogenesis of cardiovascular disease, with a particular focus on the effect of PM size on cardiovascular disease.

PARTICULATE MATTER ($PM_{2.5}$ AND PM_{10})

The many sources of air pollution are broadly divided into two categories, natural phenomena and human activities. For example, volcanoes, wildfires, or land dust are classified as natural phenomena, whereas human activities, also termed anthropogenic sources, include carbon monoxide (CO) from vehicle exhausts or sulfur dioxide (SO_2) from industrial process. Human-generated sources of air pollution are a major problem and cause most harmful adverse health effects. In addition, chemical reactions of primary emissions in the atmosphere cause the formation of secondary pollutants. For example, ozone (O_3) is generated by the reaction of volatile hydrocarbons with sunlight. Secondary air pollution particles result in a complex mixture of gaseous substances, including carbon monoxide (CO), carbon dioxide (CO_2), nitrogen dioxide (NO_2), and nitric oxide (NO_3), as well as PM.

PM is associated with the most severe air pollution-induced health effects. Like other components of air pollution, PM may contain toxic substances and transport them into the respiratory tract. The effect of PM on the body can depend on PM size, which is related to its aerodynamic diameter (AD). Most PM_{10} particles have an AD range from 2.5 to 10 μm, and are deposited in the nasal cavities and upper airways. However, $PM_{2.5}$ and $PM_{0.1}$ particles with ADs < 2.5 and < 0.1 μm, respectively, may penetrate the lung alveoli and enter into the bloodstream, thereby exerting their adverse health effects (16-18). Furthermore, studies in animal models have shown that $PM_{2.5}$ can be taken up by alveolar macrophages and endothelial cells, indicating that air pollution can have direct health effects (16,17,19,20). Consequently, the ambient PM composition and size are considered the most important indicator of the adverse health effect effects of air pollution. However, recent analysis suggests that the greatest health threat due to air pollution is cardiovascular disease.

EPIDEMIOLOGICAL STUDIES OF $PM_{2.5}$ AND PM_{10}

Epidemiological studies assessing the relationship between air pollution and cardiovascular disease have emerged in the past twenty years. Using clinical data, these studies have distinguished the short- and long-term effects of air pollution on cardiovascular disease (3,9,21,10,22,23). Epidemiological studies have shown that $PM_{2.5}$ has a stronger correlation with adverse health effects than PM_{10}. However, assessing only $PM_{2.5}$ levels is not adequate for understanding the risk for adverse events, as larger particles can be detrimental to health, such as through the exacerbation of asthma.

There is a substantial health affected associated with a short-term exposure to PM_{10}, which is related to black smoke and the total suspended particles in the air. However, fine particles ($PM_{2.5}$) also caused adverse health effects. Importantly, ultrafine particles (UPs or PM0.1) can cause health effects through translocation directly into the systemic circulation.

The World Health Organization (WHO) reported that ambient air pollution was responsible for 3.7 million deaths in 2012, representing 6.7% of total deaths worldwide, and was the cause of 16% of lung cancer deaths, 11% of chronic obstructive pulmonary disease-related death, 29% of heart disease and stroke, and approximately 13% of deaths due to respiratory infection. Exposure to air pollution containing $PM_{2.5}$ is closely associated with cardiovascular disease, as assessed in a large study from metropolitan areas in the United States. The increased risk of lung cancer and cardiovascular death after exposure to $PM_{2.5}$ was also seen in a cross-sectional study. In a study that followed 8111 adults in six cities in the United States (U.S.) over 14-to-16-years, mortality rates were 1.26 fold and 1.37% higher among people who lived in the most polluted cities versus in the least polluted sites (24,25). Similar results were obtained when examining the association between air pollution and lung cancer (Relative Risk (RR) 1.27; 95% Confidence Interval (CI) 0.96-1.69) and cardiovascular deaths in adult cohort from 1974 to 1990 in six U.S. cities. In this work, the authors found that the risk of death due to cardiovascular disease increased with every 10 $\mu g/m^3$ of $PM_{2.5}$ in the air (3,24).

CARDIOVASCULAR DISEASES ASSOCIATED WITH $PM_{2.5}$

Several reports document the relationship between $PM_{2.5}$ and cardiovascular disease. Gold *et al.* (26) demonstrated a significant increase in cardiovascular disease, from 0.5% to 1.5%, for every 5~6 $\mu g/m^3$ increase in $PM_{2.5}$. Further, they showed a 69% increase in cardiovascular deaths after acute exposure to particulate air pollution. Interestingly, acute exposure to $PM_{2.5}$ resulted in a higher rate of death due to cardiovascular than respiratory disease (69% cardiovascu-

lar versus 28% respiratory) (26). Further, a study of 500,000 teens and adults with a 16-year follow-up revealed that risk of ischemic heart disease, heart failure, arrhythmias, and cardiac arrest increased 8~18% for every 10.5 μg/m^3 in $PM_{2.5}$ (5). The American Heart Association issued an updated announcement on the effects of particulate air pollution on cardiovascular disease including evidence from studies published through March 2009. Further, the Environmental Protection Agency (EPA) has also recognized the association between $PM_{2.5}$, cardiovascular disease, and morbidity outcomes. Importantly, developing nations have $PM_{2.5}$ levels that are 10 times higher than the U.S. National Ambient Air Quality Standards.

A study on emergency admissions in Boston reported a significant association of NO_2 and $PM_{2.5}$ with the risk of acute myocardial infarction (27). A previous large-scale study from 21 U.S. cities also reported an association between NO_2 and PM_{10} exposure and risk for hospitalization (28). This Intermountain Heart Collaborative Study revealed a 4.5% increase in coronary artery disease with every 10 μg/m^3 increase in $PM_{2.5}$ (29).

These results reinforce the impact $PM_{2.5}$ on public health. Cardiovascular disease caused by air pollution is one of the most critical health problems worldwide.

CARDIOVASCULAR DISEASES ASSOCIATED WITH PM_{10}

A study of association between air pollution and cardiovascular diseases was carried out in the U.S. and in Europe. The concentration of fine PM and the rate of cardiovascular disease were analyzed from 50 million people living in the 20 largest cities and metropolitan area in the U.S. (The National Morbidity, Mortality and Air Pollution Study, NMMAPS). This study revealed that a 0.68% increase in cardiopulmonary mortality was associated with a 10 μg/m^3 increase in PM_{10} on the day before death (10,30,31). Similar results were also found in the Air Pollution and Health European Approach (APHEA-2) study, which analyzed 43 million people in 29 major European cities. They also show that air pollution and cardiovascular diseases were closely related with PM_{10}. For every 10 μg/m^3 rise in PM_{10}, the risk for cardiovascular death increased 0.76%, which was a higher rate than respiratory disease. Thus, representative data from the U.S. and Europe, PM_{10} indicated a close association between air pollution and cardiovascular diseases (32,30,31).

The studies of PM_{10} also indicated a relationship between air pollution and cardiovascular diseases, such as heart disease, and stroke. Studies showed that as PM_{10} levels increased 10 μg/m^3, there was a corresponding increase in hospitalization for ischemic heart disease (0.7%) and congestive heart failure (0.8%) (33). In addition, a relationship between air pollution with a PM_{10} and stroke has also been reported. Further, inhalable particles and changes to ambient air conditions, such as warmer versus drier air, grass pollen, upper respiratory infections, SO_2 have been correlated with asthma exacerbation and stroke admission in the U.S. (34). A similar study from Denmark also reported a relationship between increased stroke risk and particle air pollution (27,29,33,35).

AIR POLLUTION AND BLOOD PRESSURE

Numerous studies assessing the relationship between air pollution and cardiovascular disease have also investigated changes in blood pressure. It is well known that both air pollution and increased blood pressure contribute to an elevated risk cardiovascular disease. The study revealed that particle pollution was associated with a significant rise in blood pressure. These studies showed that for every 10.5 μg/m^3 increase in $PM_{2.5}$ levels, there was a 2.8 mmHg increase in systolic blood pressure (SBP) and 2.7 mmHg increase in diastolic blood pressure (DBP) in patients over five days in Boston. Similar studies have also shown that increases in SBP (5.2 mmHg) were observed with increased $PM_{2.5}$ levels in Detroit. According to these studies, there is a close correlation between increased blood pressure and PM (36). A study of 23 normotensive patients showed significant rises DBP (6 mmHg) after a two hour exposure to $PM_{2.5}$ and O_3 (37). According to this study, carbon content in air pollution PM was strongly associated with the increase in blood pressure. Further, increases in SBP (2.6 mmHg) and DBP (2.4 mmHg) are significantly influenced by CO levels (38). Importantly, air pollution doubled the risk for obesity, hypertension, chronic pulmonary disease, and cardiovascular disease in older people (39,40).

CONCLUSION

In this review, we discuss the relationship between exposure to PM, with specific focus on $PM_{2.5}$ and PM_{10}, and adverse health effects and mortality. Both $PM_{2.5}$ and PM_{10} air pollution concentrations have a marked and close association with adverse health effect, such as heart disease, stroke, blood pressure, and cardiovascular diseases. Nevertheless, epidemiological studies exhibit a stronger correlation of adverse health effects with $PM_{2.5}$ than with PM_{10}. However, data is limited to studies that examine both PM_{10} and $PM_{2.5}$ pollution. In addition, future evaluation will require examination of the adverse health effects associated with individual types of pollution. Study of mixed air pollution will also be important because motorized traffic emissions in urban cities emit noxious fumes that result in a mixture of air pollution. Furthermore, more studies examining the effects of coarse and ultrafine particles are needed. Therefore, we suggest that more efficient studies are urgently needed to establish the effect of air pollution on cardiovascular diseases. Air pollution is an important pub-

lic health issue, causing cardiovascular and pulmonary diseases worldwide.

ACKNOWLEDGEMENTS

We thank all fellow member of the Inhalation Toxicology Center for helpful discussion and critical comments. In addition, this study was also supported by the $PM_{2.5}$ research center supported by Ministry of Science, ICT, and Future Planning (MSIP) and National Research Foundation (NSF) of Korea (2014M3C8A5030620).

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