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Review Article

Molecular Pathogenesis of Cardiovascular Mortality Associated with Vehicle Emission Pollution

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Abstract

Green house gasses (GHG) emissions is one of the major environmental issues nowadays. Carbon dioxides, as the main part of GHG, are majorly produced from the transportation fields that contribute to 14% of carbon dioxide (CO_2) emissions worldwide. Indonesia, as a developing country, is now facing a rapid development in transportation and industrial sectors. Around 70% of air pollution in Indonesia was due to fossil fuel combustion during the use transportation. Partial combustion of fossil fuel will produce nitrogen oxide (NO_x), volatile organ compound (VOC), CO (carbon monoxide), and particulate matter (PM). Exposure to these compounds has been associated with a higher risk of premature death in several studies, particularly due to acute myocardial infarct (AMI) and atrial fibrillation (AF). This review helps to elaborate and better explain the molecular pathogenesis of this known association. Reactive oxygen species (ROS) is considered to have an important role in cardiovascular diseases, such as causing vasoconstriction, hypertension, atherosclerosis formation and myocardial dysfunction.

Keywords: Vehicle emission, Air pollution, Cardiovascular, Mortality

Introduction

CO_2 is the highest constituent of all GHG emissions worldwide with the total of 76%, followed by methane (16%), nitric oxide (6%) and fluorinated gases (2%). Most of the CO_2 emissions (65%) are from fossil fuel and industrial process. Boden, et al in 2010 reported that global carbon emission from fossil fuel usage have been increased by 90% since 1970 [1].

Asian Development Bank (ADB) stated that around 70% of the total energy consumption worldwide are using fossil fuels as energy sources, including petroleum (30%), coal (22%) and natural gas (19%) [2]. China was the highest CO_2 emission contributors from fossil fuel with 28%, followed by the United State, European Union and India. Indonesia is now considered the 12th highest emitters of carbon dioxide from fossil-fuel burning and cement production, globally [1]. Indonesia is one of the largest producers of fossil fuels and its demand almost doubled between 1990 and 2008 [2].

Transportation sector contributes around 14% of the total CO_2 emissions worldwide, after electricity and heat production (25%), agriculture (24%) and industrial sector (14%). Around 95% of world transportation energy sources are still from petroleum-based fuels, gasoline and diesel [3]. However, in the United State, during 2014, the transportation sector was the second highest of nation GHG emitters (26%), behind electricity production fields (30%). Passenger cars were the largest sources of transportation GHG emissions, followed by trucks, minivan, airplane, ships and boats [4].

Motor vehicle emission was the highest cause of ambient air pollutants in urban Australia and estimated to contribute the total of 82% of nitrogen oxide levels in Southeast Queensland and 60% of CO levels in almost all capital cities. Diesel engines in most trucks, buses and passenger cars were associated with the higher air pollutions [5].

Indonesia is a developing country with such a rapid development in many sectors including transportation and industrial fields, especially in Jakarta as its capital city [6]. Transportation system in Indonesia is still dominated with road transportation, thus more than 90% of the total oil consumption was contributed from them. As a result,

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road transportation in Indonesia produces more than 91% of the total GHG emissions, meanwhile, marine and air transportation produce only 1% and 8% of total GHG emission, respectively [7].

Data from Central Bureau of Statistics (BPS) Jakarta in 2015 reported that the amount of motorcycle in 2014 (74.67%) was the highest among others with 10.54% increase each year. Car passengers were the second highest with 18.64%, and this number is increasing by 8.75% each year [8]. Urbanization causes Jakarta to be one of the most crowded city and the dependency of this urban population on the transportation system, resulting in traffic congestion. Traffic jam worsens the amount of vehicle emission and study in 2002 reported that around 70% of air pollution in Jakarta was contributed by transportation activities [6].

Mechanism of Vehicle Emission Production

The important part of pollutant production is the fuel combustion process. Hydrocarbons in the fuel react with oxygen in the air, forming water and CO_2 during the complete combustion process. However, there will be no perfect combustion mechanisms, and this imperfect combustion will produce air pollutants, such as NO_x, hydrocarbons or VOC and CO [5,9].

Nitrogen oxides are formed under a very high pressure and temperature in engine by converting nitrogen and oxygen in the air. In the excess oxygen condition, such as higher temperature, the NO_X production will increase. CO is produced when fuels are partially oxidized due to not enough oxygen in the combustion engine. Many factors influenced the higher CO production, such as too much fuel mixture, air cleaner failure and faulty fuel pressure. During fuel combustion, small portions of fuels (around 1-5%) are not burned and will form VOC [5].

Another pollutant that is also produced from vehicle exhaust pipes is PM. PM is then classified into coarse PM (PM 2.5-10) and fine PM (PM 2.5). PM that came from the combustion products of diesel and petrol engine are dominated by fine PM [5,10].

Air pollutant from road transportation can also come from non-combustion products, including evaporation and PM. Evaporation occurs when fuel vapor escapes the vehicle engine systems and also during the process of vehicle tanker refueling. Other sources of PM are tire wear, resuspension of road dust and brake linings. PM from these sources is usually coarse PM [5].

As mentioned above, partial combustion produces NO_x, VOC and CO. Ozone molecules (O_3) will then be released when these particles are in contact with the sunlight. Normally, ozone is found in the stratosphere and protects us from sun's ultraviolet radiation. However, the presence of ozone molecules at ground level can cause many serious health problems. The most interesting part is that ozone can be carried far away from where it formed by the wind [9].

The concentration of air pollutant in urban area differs from that in rural area, in which it is twice as much. This difference also observed near the crowded roads compared to background measurement sites with 2-3 times higher. Passengers have higher risks to be exposed by air pollutant. The data shows that there is a 3-fold higher concentration of air pollutant measured in vehicle than background measurement [11].

Health Impacts of Vehicle Emission Pollution

Air pollution is associated with many health issues due to the enhanced ozone layer (O_3) and PM, including chronic obstructive pulmonary disease (COPD), acute lower respiratory illness (ALRI), cerebrovascular disease, ischemic heart disease and lung cancer [12]. Recent report by WHO in 2016 stated that South East Asia's trend of air pollution ($PM_{2.5}$ and PM_{10}) concentration tend to increase over time [13].

Around 3.7 million premature deaths are associated with outdoor air pollution, as reported by WHO in 2012. Low and middle-income countries in South East Asia and Western Pacific had the biggest air pollution problem with a total of 2.6 million deaths (88%). Cardiac ischemia is the most prevalent cause of death (40%), followed by stroke, COPD, lung cancer and ALRI [14].

Inhalation of ozone can cause serious health effects both short term and long term. In short-term effects, it has been studied that ozone is able to precipitate in the acute exacerbation of asthma and COPD patients. Many studies shows that the increasing of premature death's risk was correlated with the higher levels of ozone [9]. A meta-analysis of 39 studies from 1987 - 2000 shows a strong association between short-term effect of ozone exposure and mortality rate. This study also shows the total mortality rate increase 0.87% with most cause of deaths are cardiovascular and respiratory disease [15].

Ruidavets et al reported that ozone exposure in short-term was associated with AMI. Higher risk was found in subjects 55-64 years old with no prior history of ischemic heart disease with RR 1.14. In this study, that also stated that exposure of NO_2 and SO_2 was not significantly associated with AMI [16]. Higher risk of AMI due to air pollution also reported by Wang et al in 2015. The study found NO_2 was associated with higher risk of non-ST elevation myocardial infarcts (NSTEMI). $PM_{2.5}$ is also reported that have association with higher risk of STEMI hospitalization [17].

Paroxysmal atrial fibrillation (PAF) was found significantly associated with increased ozone concentration in an hour before PAF occurred, with odd ratio 2.08. This study also found associations of PAF incidence with NO_2 and $PM_{2.5}$, but were not statistically significant [18]. Similar study by Link et al found that for each 6 $\mu g/m^2$ increase in 2 hours before the arrhythmias occur, the AF risk was increased by 26% [19].

Molecular Pathogensis of Cardiovascular Morality

As mentioned above, ozone and PM have been recognized in several studies as a culprit in cardiovascular morbidity and mortality. The main pathophysiology of cardiovascular injury is vasoconstriction, arterial hypertension, arrhythmia, myocardial ischemia and infarct. ROS, which induced by PM and ozone itself, plays a major role in this pathological changes.

During vasoconstriction, ROS (superoxide anion) converts NO into peroxynitrate, resulting in NO level reduction. NO have already known as a potent vasodilator by dilatation of vascular smooth muscle. The decrease in the level of NO causes endothelial dysfunction and elevates the peripheral vascular resistance [20]. Ozone itself stimulates the release of endothelin-1 (ET-1) and induces vasoconstriction both in peripheral and coronary circulation [21].

Atherosclerosis formation and peripheral arterial vasoconstriction influence the pathogenesis of hypertension. Endothelial dysfunction by NO reduction plays a major role in

atherosclerosis plaque formation. ROS, that not only produced by PM but also ozone, oxidizes low-density lipoprotein (LDL), producing the oxidized LDL (ox-LDL). This ox-LDL attaches to the scavenger receptor, and then sub endothelial macrophage ingests it and initiates the foam cell formation. Atherosclerotic plaque is the accumulation of foam cells formation over the years. Ox-LDL also induces TNF-α and IL-1β release and cause vascular smooth muscle cells proliferation, thereby causing fibrosis and atherosclerosis plaque [20].

Vascular smooth muscle proliferation to intima, due to the presence of vascular growth factor, will cause a thickening of intima layer. Ozone, mediated by IL-2, can also increase the carotid artery intima thickness and become a predictor of vascular disease [21].

As stated before, ET-1 induces coronary vasoconstriction and causes coronary blood flow reduction. It will leads to myocardial ischemia due to the inability of balancing myocardial supply and demand [21]. Myocardial ischemia and infarct can be occur because of atherosclerotic plaque rupture. This mechanism is mediated by ROS by releasing matrix metalloproteinase (MMP) and causing the instability of the plaque. Myocardial ischemia and infarct will then lead to cardiac sudden death [20].

Myocardial dysfunction can also occur from the inhalation responses triggered by ozone inhalation. Ozone induces the release of IL-6, IL-8 and GM-CSF, which alter the cardiac function. TNF-α, also induced by ozone inhalation, reduces the calcium ion flow in intracellular, and alters the cardiac contractiliy [21].

Not only hypertension and ischemic heart disease (IHD), ozone inhalation can cause arrhythmia by autonomic control mediation. Both ozone and particulate matter increase sympathetic activity, therefore causing the reduction in heart rate variability, decreased coronary blood flow, elevation of blood pressure, myocardium inflammation and altered contractility [20,21].

Inhalation of nitrogen dioxide (NO_2) causes oxidation of antioxidant, thus the number of antioxidant is decreasing. NO_2 then causes damages in airways epithelium [22]. Oxidative stress will cause local inflammation in the lung. One proposed mechanism that causes cardiovascular toxicity is the movement of inflammatory cytokines from the lungs into the circulation. This mechanism influences the systemic oxidative stress and inflammation. ROS and cytokines will cause a direct cardiac muscle and vasculature changes [23].

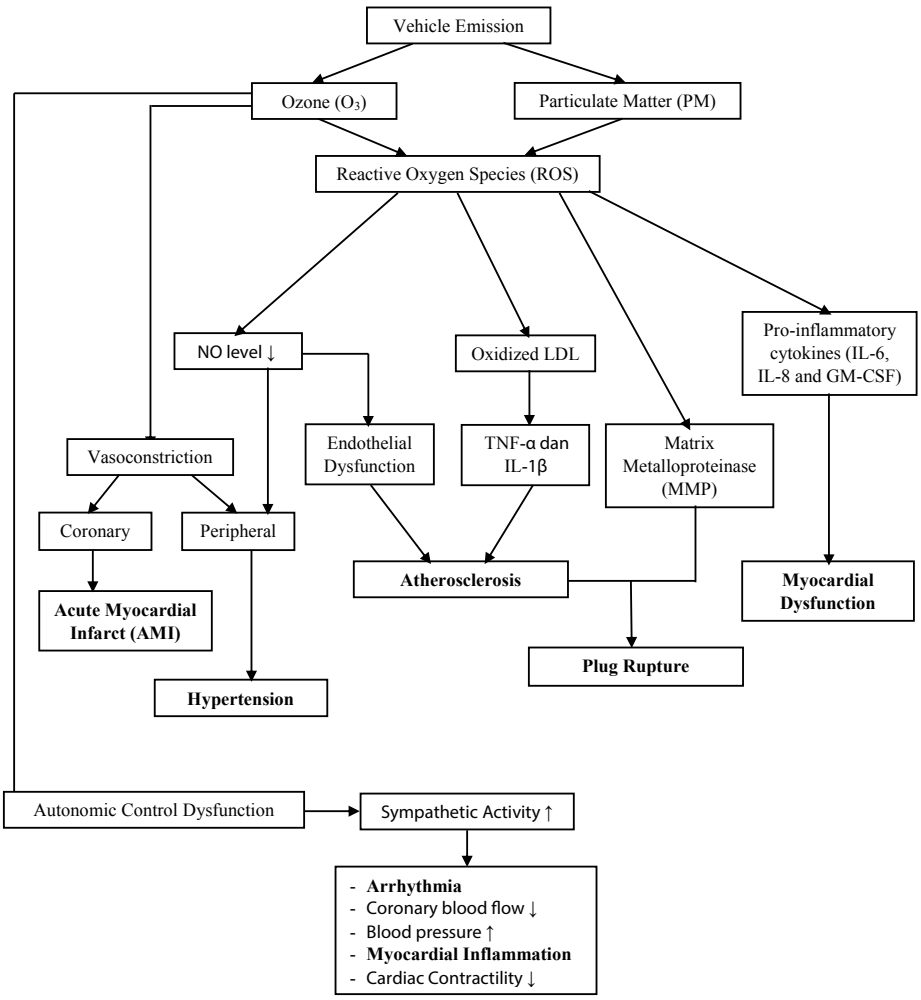

Figure 1: Molecular pathogenesis of cardiovascular mortality due to vehicle emission.

Conclusion

Health impact due to transportation-related air pollution is now considered as the leading environmental issue, particularly the increasing phenomenon of premature deaths due to cardiovascular problems. Many cross-sectional studies have reported that exposure of vehicle emissions are associated with myocardial ischemia and atrial fibrillation. Ozone and particulate matter have a role in pathogenesis of hypertension, atherosclerosis formation, myocardium ischemia and infarct, cardiac dysfunction, also arrhythmias. (Figure 1).

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