Review

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Cardiovascular implications of exposure to traffic air pollution during exercise

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Summary

Regular aerobic exercise is recommended by physicians to improve health and longevity. However, individuals exercising in urban regions are often in contact with air pollution, which includes particles and gases associated with respiratory disease and cancer. We describe the recent evidence on the cardiovascular effects of air pollution, and the implications of exercising in polluted environments, with a view to informing clinicians and other health professionals. There is now strong evidence that fine and ultra fine particulate matter present in air pollution increases cardiovascular morbidity and mortality. The main mechanisms of disease appear to be related to an increase in the pathogenic processes associated with atherosclerosis. People exercising in environments pervaded by air contaminants are probably at increased risk, due to an exercise-induced amplification in respiratory uptake, lung deposition and toxicity of inhaled pollutants. We make evidence-based recommendations for minimizing exposure to air-borne toxins while exercising, and suggest that this advice be passed on to patients where appropriate.

Introduction

Regular aerobic exercise promotes a range of physiological changes that correlate with decreased morbidity and increased longevity.[1] Accordingly, health professionals recommend regular endurance training in order to maintain health, and also as a therapeutic intervention in certain diseases (e.g. hypertension, diabetes mellitus, coronary heart disease). Many exercise programs involve training in outdoor areas, which in urban environments may be near roadways, in close proximity to motor vehicles. Automobile emissions are estimated to be the greatest single contributor to urban air pollution, and their toxic constituents contribute to respiratory disease and cancer.[2] We discuss recent findings on the lesser-known cardiovascular effects of acute and chronic exposure to air pollution, with particular emphasis on the potential health implications of exercising in environments permeated by automotive pollution.

Components of automotive pollution

A diverse mixture of suspended particles and gases containing reactive free radical species is released into the atmosphere as a consequence of fuel

combustion. The ambient air pollution is mostly ($\sim$99.4%) invisible to the naked eye, unless present in very high concentrations, in which case it may be seen as the haze commonly associated with large cities. Particulate matter air pollution is a heterogeneous mixture of solids and liquids that are generally classified according to aerodynamic diameter, as coarse (<10 μm; PM_{10}), fine (<2.5 μm; $PM_{2.5}$) or ultrafine (<0.1 μm; $PM_{0.1}$) particles. Individual particles may be complex chemical mixtures comprising different biochemically active components on the outside compared to the inside. Presently, the air quality standards for PM_{10} and $PM_{2.5}$ in the US are 50 μg/m^3 and 15 μg/m^3 respectively, which represent the annual maximal allowable arithmetic means for particulate matter. In the UK, the recommended limit of PM_{10} over a 24-h period is 50 μg$\cdot$m^3, which is regularly exceeded. Some contend that these standards may be too low, considering that deleterious health effects may be elicited after regular exposure to concentrations lower than these in outdoor air.[3]

The major gaseous components of automotive pollution include sulphur dioxide (SO_2), carbon monoxide (CO), nitrogen oxides (NO_x) and ozone (O_3). A variety of readily evaporable toxic volatile organic compounds (e.g. benzene, ethylene) are also emitted from unburnt fuel, as well as during the fuel combustion process. Indeed, the interaction of these compounds with NO_x forms additional O_3 in the presence of heat and sunlight. Another class of over 100 chemicals formed during incomplete burning of fuel and other organic substances (e.g. wood and tobacco) is that of the polycyclic aromatic hydrocarbons (e.g. benzo(a)pyrene, fluorine), many of which are known carcinogens.[4] Ultimately, air pollution comprises a complex mixture of thousands of chemicals and chemical interactions.

Cardiovascular epidemiological evidence

Early epidemiological studies examining the relationship between chronic exposure to automotive pollution and disease found an unexpectedly increased incidence of cardiovascular mortality in workers exposed to high levels of pollution.[5,6] Initially, these findings were inconclusive, because investigators were unable to account for the potential confounding variable of cigarette smoking. However, more recent and well-controlled epidemiological studies have supported these original findings by consistently observing an association between ambient concentrations of particulate

matter and cardiovascular morbidity[7–9] and mortality.[2,3,10–12] Indeed, these relationships remain, despite air pollution levels being lower than the recommended national standards of each country. $PM_{<2.5}$ appears to be the most studied and may be of more risk to health, possibly due to these very small particles penetrating the lower regions of the lung and entering the circulation.[13]

Studies have demonstrated a significant elevation in the incidence of life-threatening myocardial infarctions[8] and cardiac arrhythmias[7] in the immediate period (hours to days) following exposure to high levels of atmospheric fine particulate matter. Similarly, the presence of fine and ultrafine particulate pollution has predicted the risk for exercise-induced ST-segment depression (indicative of myocardial ischaemia) in subjects with coronary heart disease.[9] Other epidemiological data link air pollution to an augmentation of systemic inflammation, as measured by C-reactive protein,[14] an acute-phase protein associated with adverse outcome in patients with unstable ischaemic syndromes. Interestingly, compared to controls, patients with diabetes mellitus were more than twice as likely to be admitted to hospital with heart-disease-related pathology when atmospheric PM_{10} increased by 10 μg/m^{3,15} suggesting that certain populations may be more susceptible to particulate pollution. Indeed, frail individuals with existing heart and lung disease have also been shown to be more susceptible to the effects of air pollution, as this population had an increased risk of death after exposure to PM_{10} levels that were within the national standard for the US.[3] All these large-scale studies show a persistent concentration-dependent association between air pollution and cardiovascular risk.

Cardiovascular mechanisms of action

The main pathway by which particulate air pollution contributes to increased risk is probably by direct augmentation of atherosclerosis,[16–18] the underlying cause of most cardiovascular disease. The aetiology of atherosclerosis is multifactorial, but the process may be initiated and promoted by toxic insult to the endothelium, and is associated with chronic inflammation as well as high circulating concentrations of metabolites indicative of oxidative stress.[19] Table 1 summarizes some of the experimental work on exposure to automotive pollution relevant to atherosclerosis.

It has only recently been established that ultrafine particles translocate to the circulation directly after inhalation,[13] which provides an explanation

Table 1 Studies relevant to atherogenesis examining the effect of exposure to automotive pollutants

Pollutant	Experimental model	Outcome
Carbon monoxide (10–100 ppm)[22,49]	Bovine pulmonary artery endothelial cells	↑Endothelial derived peroxynitrite (↑oxidative stress) ↑apoptotic cell death
Carbon monoxide (50 ppm)[21]	Rat aorta	↑Aortic nitrotyrosine ↑low-density lipoprotein oxidation
1,3-Butadiene (20 ppm)[17]	Cockerels	↑Atherosclerotic plaque size
Nitrogen dioxide (14 ppm)[20]	Human plasma	↓Ascorbic acid ↓uric acid ↓protein thiol groups ↓vitamin E ↓bilirubin ↓ubiquinol-10 ↑lipid peroxidation
Carbon monoxide (5–25% carboxyhaemoglobin, HbCO)[26]	Human coronary arteries perfused with blood at different HbCO levels	↑Cholesterol uptake into arterial wall
Phenanthraquinone[37]	Bovine aortic endothelial cells (1 µmol/l)	↓Endothelial nitric oxide synthase activity ↓Endothelium-dependent vasorelaxation
	Rat aortic rings (5 µmol/l)	
	Rat intraperitoneal injection (0.36 mmol/kg)	↑Systolic and diastolic blood pressure ↓nitric oxide metabolites
Diesel exhaust particles[27, 38]	Rat thoracic aorta (1–100 µg/ml)	↓Endothelium-dependent vasorelaxation
	Hamster (5–500 µg)	↑Blood platelet activation
Particulate matter (<10 µm)[18]	Watanabe heritable hyperlipidaemic rabbits	↑Polymorphonuclear leukocytes ↑coronary and aortic atherosclerotic lesions
Particulate matter (<2.5 µm) and ozone[29]	Healthy humans	↑Brachial artery vasoconstriction
Whole diesel exhaust (PM$_{10}$ at 300 µg/m^3)[3,28]	Healthy humans	↑Systemic and pulmonary inflammatory response

for the route by which toxic pollutants may systemically affect the blood, vasculature and organs such as the heart. Several studies have reported diminished antioxidant defences and increased markers of oxidative damage (e.g. malondialdehyde) in plasma and endothelial cells after exposure to components of automotive pollution such as CO and nitrogen dioxide (NO_2).[20–23] Workers chronically exposed to high pollutant levels have plasma that is more susceptible to oxidation, possibly due to depletion of water-soluble antioxidants.[24] These detrimental blood and cellular changes may increase the oxidation of circulating low-density lipoproteins, thus making these particles more susceptible to increased uptake into the arterial wall and accelerating atherogenesis.[25] This hypothesis is supported by the demonstration that lipid uptake into the arterial wall is increased in human coronary arteries perfused with blood containing low levels of carboxyhaemoglobin.[26] Additional cardiovascular risk may also arise from thrombotic complications as a consequence of increased platelet activation[27] and an elevated inflammatory response[28] caused by systemic infiltration of air pollution.

In humans, environmentally relevant concentrations of $PM_{2.5}$ and O_3 acutely augment brachial artery vasoconstriction.[29] Rats exposed to the same pollutants also show elevated concentrations of plasma endothelin-1, a powerful vasoconstrictor.[30] These data are of particular interest to cardiovascular risk in humans, because augmented vasomotor tone (vasoconstriction) has the potential to increase myocardial afterload and ischaemia. Each time the heart contracts, a pressure wave travels through conduit arteries of low resistance to peripheral arteries of higher resistance. A portion of the pressure wave is reflected back to the heart (wave reflection) and the intensity of this reflection is dependent on the tone of the large conduit arteries. Increased large artery vasoconstriction causes increased wave reflection, such that there is an early return to the heart of the arterial pressure waveform. This early returning waveform boosts central (aortic) systolic blood pressure (afterload), in addition to diminishing the time and pressure of coronary artery perfusion, thus promoting ischaemia.[31] If regular exercise in a polluted environment exacerbates this effect, risk would be enhanced, because *central*, and not peripheral, blood pressure correlates with left ventricular hypertrophy,[32] carotid intima media thickness[33] and all-cause mortality.[34]

Abnormal function of the endothelial cells lining the arteries has been implicated in early atherogenesis, possibly due to decreased bioavailability of nitric oxide, leading to vasoconstriction, smooth muscle cell proliferation and thrombotic processes.[35] Benzo(a)pyrene, a cytotoxic component of air pollution, can alter gene expression and enhance the proliferation of vascular smooth muscle cells,[36] a structural change that accompanies atherosclerosis. Further, phenanthraquinone, a constituent of diesel exhaust, inhibits nitric oxide production in bovine endothelial cells, increases blood pressure and suppresses nitric-oxide-mediated vasodilatation in rats.[37] Inhibition of endothelial-dependent vasorelaxation has also been demonstrated in isolated ring preparations of rat thoracic aortas exposed to diesel[38] and motorcycle exhaust particles.[39] Taken together, these data imply that normal vascular homeostasis is interrupted by exposure to auto pollution, and this would help to explain excessive cardiovascular morbidity and mortality from air pollution.

Exercise and automotive pollution

A primary reason why exercising individuals may be at heightened risk for disease is because, even at low intensities, a significant rise in pulmonary ventilation and diffusion capacity occurs,[40] meaning that the concentration of inspired particles will increase. Indeed, the total amount of particulate matter deposited in the lungs of exercising humans has been shown to be directly related to minute ventilation, and greater deposition has been demonstrated during slower, deeper breathing rather than rapid and shallow breathing.[41] Daigle et al.[42] recently determined that the total amount of $PM_{0.1}$ deposited in the respiratory tract of humans during moderate exercise was approximately five times that at rest. Additionally, the fractional penetration of pollutants to the lung is greater when breathing by mouth compared to the nose. This effect is attributed to increased absorption of gases and deposition of particles in the nasopharyngeal region ('scrubbing' action), which is bypassed with oral breathing.[43] During exercise, particularly at higher intensities, a greater portion of air is taken in via the mouth,[44] thus again increasing the load of inhaled toxicants.

As expected, the total lung burden of inhaled particles increases as the concentration of ambient pollutants increases.[43] Blood levels of toxins may rapidly reach harmful levels, as was shown in New York City runners after 30 min of exercise near busy roadways. This activity evoked an acute rise in blood carboxyhaemoglobin levels from 1.7% to 5.1%,[45] which is similar to those found in regular cigarette smokers. Of particular interest was the

finding that during exercise, only low concentrations of pollutants (O_3 and NO_2) were required to cause similar lung damage to that achieved by high concentrations of the same compounds at rest.[46] Also, animals exercising during exposure to O_3 had more severe lung parenchymal lesions than at rest with the same O_3 concentration.[47] Finally, uptake of pollutants into the lower respiratory tract[43] and lung tissue damage[46] appears to be higher when inspired compounds are in a mixture (i.e. formaldehyde and ammonium nitrate) rather than in isolation. These findings imply firstly, that some chemicals may act in a synergistic manner to adversely effect health and secondly, exercise may exacerbate toxic effects. A summary of the interaction between air pollution, exercise and cardiovascular risk is shown in Figure 1.

Recommendations

Clinicians should not be dissuaded from encouraging people to exercise, since epidemiological studies indicate that the benefits of regular exercise outweigh potential harm.[1,48] However, given the evidence linking air pollution to disease, together with the possibility that exercising near road traffic may intensify harmful effects, it is advisable to avoid or minimize exposure to air-borne contaminants. Accordingly, we recommend that physicians
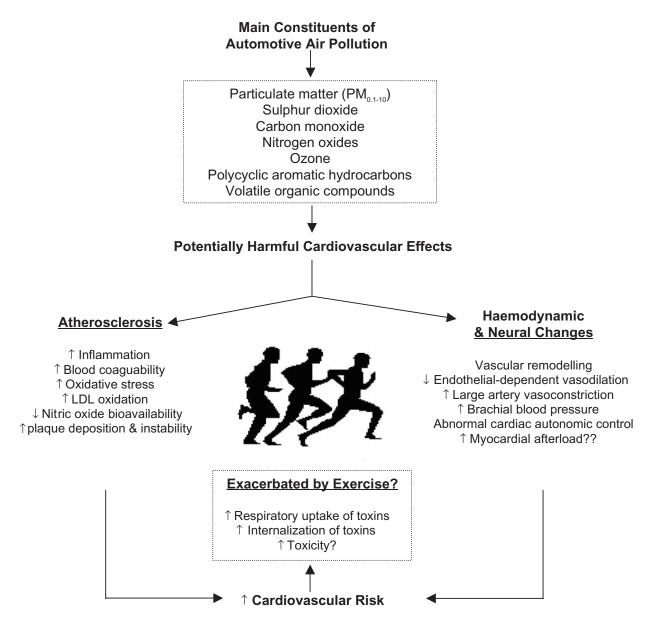

Main Constituents of Automotive Air Pollution

Particulate matter ($PM_{0.1-10}$)
Sulphur dioxide
Carbon monoxide
Nitrogen oxides
Ozone
Polycyclic aromatic hydrocarbons
Volatile organic compounds

Potentially Harmful Cardiovascular Effects

Atherosclerosis

↑ Inflammation
↑ Blood coaguability
↑ Oxidative stress
↑ LDL oxidation
↓ Nitric oxide bioavailability
↑ plaque deposition & instability

Haemodynamic & Neural Changes

Vascular remodelling
↓ Endothelial-dependent vasodilation
↑ Large artery vasoconstriction
↑ Brachial blood pressure
Abnormal cardiac autonomic control
↑ Myocardial afterload??

Exacerbated by Exercise?

↑ Respiratory uptake of toxins
↑ Internalization of toxins
↑ Toxicity?

↑ **Cardiovascular Risk**

Figure 1. Summary of the potentially adverse effects of automotive pollution on the cardiovascular system.

and other health professionals advise patients undertaking an exercise program to *exercise outdoors in parks and recreation areas away from busy roadways or industrial sites*. This advice does not take into consideration regional differences in ambient pollutant levels that vary with the time of day. Therefore, in large cities where the ambient atmospheric levels of particulate matter regularly exceed national air safety standards (i.e. London), it may be useful to limit exercise sessions to the hours of the day when air pollution is likely to be less concentrated (i.e. early hours of the morning). Importantly, some populations may be especially sensitive to air pollution (i.e. children, elderly, diabetics or those with existing heart or lung disease) and care should be given to offer prescriptive advice to these people in particular.

Conclusions

There is now strong evidence that traffic air pollution aggravates the risk for cardiovascular disease in a concentration-dependent manner. While there is no doubt that regular physical activity is of great benefit to health and longevity, both in healthy individuals and those with pre-existing cardiovascular conditions, exercising in urban environments in close contact with motor vehicles and high ambient levels of particulate matter will increase the total amount of inspired toxins, and most likely increase the risk of disease. Despite the evidence, it is not uncommon to see individuals exercising in highly polluted areas such as alongside busy suburban roadways, and through inner cities congested with motor vehicles, which may be more harmful than beneficial. The purpose of this review was to inform clinicians and other health professionals of the hazards of exercising in environments pervaded by automotive pollution, so that they may appropriately advise patients on avoidance.

Acknowledgements

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