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Editorial

Is smog innocuous? Air pollution and cardiovascular disease

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ABSTRACT

Air pollution is a significant environmental and health hazard. Earlier studies had examined the adverse health effects associated with short- and long-term exposure to particulate matter on respiratory disease. However, later studies demonstrated that it was actually cardiovascular disease that accounted for majority of mortality. Furthermore, it was not gaseous pollutants like oxides of nitrate, sulfur, carbon mono-oxide or ozone but the particulate matter or PM, of fine or coarse size ($PM_{2.5}$ and PM_{10}) which was linearly associated with mortality; $PM_{2.5}$ with long term and PM_{10} with short term. Several cardiovascular diseases are associated with pollution; acute myocardial infarction, heart failure, cardiac arrhythmias, atherosclerosis and cardiac arrest. The ideal way to address this problem is by adhering to stringent environmental standards of pollutants but some individual steps like choosing to stay indoors (on high pollution days), reducing outdoor air permeation to inside, purifying indoor air using air filters, and also limiting outdoor physical activity near source of air pollution can help. Nutritional anti-oxidants like statins or Mediterranean diet, and aspirin have not been associated with reduced risk but specific nutritional agents like broccoli, cabbage, cauliflower or brussels sprouts, fish oil supplement may help. Use of face-mask has been controversial but may be useful if particulate matter load is higher.

1. Great smog of London

Great smog of 1952 also known as Big Smoke was an episode of severe air-pollution that affected London in December 1952. It was really a collection of airborne particles, arising mostly from the use of coal, culminating in a thick layer of smog over the city, lasting 5 days (from 5–9 December 1952) and then dispersing as quickly as it came. As London was accustomed to heavy fogs, at the time it happened, there was no panic; it just seemed a denser and a longer standing fog, The only problem seemed to be such a low visibility that driving became impossible, all public transport ceased, ambulance service stopped functioning and all outdoor sporting events were called off. The fog even seeped indoors, resulting in the cancellation/abandonment of concerts and movies, since stage could not be viewed from the seats. Since that time there are several myths associated with air pollution (Table 1). However, the health aspects became apparent only after few weeks when medical statistics revealed that the smog had killed 4000 people.[1] As a matter of fact mortality remained elevated for months. The cause was attributed mostly to pulmonary system; asthma, respiratory tract infections: influenza, bronchopneumonia and purulent bronchitis but all this remained speculative because of faulty records. However, it was only more than 4 decades later that Harvard Six Cities study, with a large prospective cohort, for the first time convincingly demonstrated a definite relation between long term environmental pollution exposure and adverse health outcome. In over 8000 adults with 14–16 years of exposure, mortality rate was 26% higher in city with most pollution versus that with least pollution. Interestingly, this study made another surprising observation, it was not respiratory but rather cardiovascular (CVS) deaths which accounted for single largest cause of mortality, nearly half of all mortality (646 out of 1401). Furthermore, the risk for lung cancer and overall cardio-pulmonary mortality was increased by a similar ratio (but numerically numbers were higher for CVS).[2] The largest study to date, ACS Cancer Prevention II study enrolling nearly 500,000 individuals over a 16 year period also revealed that each 10 $\mu g/m^3$ increase in fine particulate matter (PM)contributed to increase in all cause, cardiopulmonary and lung cancer mortality of 4%, 6% and 8%, respectively.[3] Other hospital based studies also suggested specific association between air pollution and acute cardiac events.[4,5] Peter and co-workers provided the first evidence of association between air pollution and acute myocardial infarction (AMI).[6] It was Hoch and co-workers who found that it was exposure to traffic-related pollutants which were more co-relative with mortality than background level of pollutants within the city. Living near a major road was most strongly co-related to mortality in this study.[7] Among the specific CVS causes, 10 $\mu g/m^3$ increase in fine particulate matter contributed to 12% increased risk of CVS mortality, 18% increased risk of coronary artery disease (CAD) and 13% risk of cardiac arrhythmia, heart failure and cardiac arrest.[8] The short-term risks with acute exposure may even be higher. The NMMAPS study

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Table 1
Myths associated with air pollution.

Myth	Reality
Fog/smog is innocuous	Smog has a definite adverse health effects
Health effects of air pollution are related to respiratory system	Majority of deaths related to pollutants are due to cardiovascular causes
Gaseous pollutants are major causes of health effects	Particulate matter in the air are most strongly related to health effects
The health effects are instantaneous	Health effects are both instantaneous and some occur after a lag period

conducted in 50 million individuals spread over 20 largest cities of US revealed that 10 $\mu g/m^3$ increase in coarser PM contributed to 21% increase in all-cause mortality and 31% increase in cardiopulmonary mortality.[9] Air Pollution and Health: a European Approach (APHEA-2) study conducted in another 43 million individuals in 29 European cities revealed an even more robust association between short term exposure and health effects. For each 10 $\mu g/m^3$ increase in coarse PM, daily mortality increased by 0.6% and CVS mortality by 0.7%.[10] Furthermore, this study went on to show that this increased mortality was not due to mere harvesting (temporal displacement of mortality or advancement of mortality by a few days) because after a lag period of 40 days this increase in CVS mortality was even more pronounced - actually more than doubled (1.97%).[11] Again even with short term exposure, direct association has been found with CAD, arrhythmia and heart failure, an increased rates of hospitalization: 0.8% increase for heart failure and 0.7% increase for CAD. In addition increased risk for AMI, implantable cardioverter defibrillator (ICD) discharges myocardial ischemia on stress testing, elevated systolic blood pressure and ischemic stroke have also been demonstrated.[12] In the developing world Beijing, China issued a first "red alert" when air pollution surpassed a level of 200 parts per million of fine particulates (referred to as $PM_{2.5}$) for at least three days on a four-tier index that catalogs air pollutants. The Great Smog of Delhi marked the worst period of bad air quality in New Delhi and adjoining areas in the National Capital Territory of India (between 1 and 9 November 2016). The pollution was reputed to be even worse than the London smog.

2. Mechanism of cardio-toxicity of air pollutants

Currently, combustion of fossil fuel, whether in industrial applications and power plants or exhaust from motor vehicles (airplanes, cars, trucks, or ships) account for the majority of pollution at least in developed countries. The emissions include gases; nitric oxide (NO), nitrogen dioxide (NO_2), carbon monoxide (CO) or sulfur dioxide (SO_2), PM (both solid and liquid) like carbon black, organic carbon, even transition metals and volatile and semi-volatile organic compounds such as benzene, toluene, xylene, and aromatic hydrocarbons. However, as far as health hazards are concerned, while several gaseous pollutants, SO_2, nitrogen oxides, CO, Ozone (O_3) have been implicated to some extent, it is the PM which is the major culprit and has been co-related to total and CVS mortality. Particulate matter is of two types; fine PM – with particle median aerodynamic diameter $<2.5\ \mu m$ called $PM_{2.5}$ and coarse PM – with particle median aerodynamic diameter $<10\ \mu m$ called PM_{10}. Short-term mortality is co-relative of PM_{10} while long term mortality is related to exposure to $PM_{2.5}$. Particulate matter can be directly toxic to circulatory system (soluble components of $PM_{2.5}$ can cross respiratory epithelium into systemic blood stream) but more commonly affects the CVS indirectly. It may incite pulmonary and systemic oxidative stress, resulting into inflammation. The circulatory inflammation (even without significant lung toxicity) may serve as the initiator of a whole cascade of events culminating in alterations in blood rheology and pro-thrombotic effects (increased fibrinogen, enhanced platelet aggregation), alteration in cardiac autonomic system (blunting of cardiac parasympathetic system) leading to rhythm disturbances, endothelial dysfunction leading to vascular spasms and plaque disturbance in short-term and atherosclerosis in long term. The PM_{10} could readily penetrate and deposit in the extra-thoracic and trachea-bronchial tree, while $PM_{2.5}$ can reach the small airways and alveoli. Generally, $PM_{2.5}$ are derived from combustion sources including vehicular exhaust and constitute fine particles like nitrates and sulfates while PM_{10} are derived from natural sources (forest fires, bio-aerosol – endotoxins, fungal spores, pollen, windblown soil), and occupational exposure (grinding, smelting, etc.). Recently a third type of particles have also been described, the ultra-fine particles (UFP) ($<0.1\ \mu m$). They can penetrate deeper into the lungs and even directly enter the bloodstream. They arise from emissions of factory chimneys (smoke stacks) or exhaust from trucks (tail pipes), quickly coalesce together, absorb water, organic material and other gases to grow large to reach a particle size in the range of $PM_{2.5}$. Sulfur dioxides is derived from sulfur containing fuels like diesel, power plants, mining processes and kerosene space heaters but also from forest fires. It can cause toxicity by forming particulate sulfates. Diesel exhaust particles are known to increase interleukin-8 and thus provoke inflammatory cascade. Increased SO_2 levels increase fibrinogen levels. Nitrogen oxides are derived primarily from combustion of fossil fuel including vehicular exhaust and industrial processes. The major problem associated with nitrates is that they can readily form particulate nitrates. Ozone is the predominant component of photo-chemical smog. It can be sourced to vehicular exhaust and industrial processes, acted upon by UV radiation (nitrogen oxides and reactive hydrocarbons). It can induce direct oxidation of both pulmonary and systemic vasculature, resulting in inflammation. It is also known to provoke arterial vasoconstriction. Carbon monoxide derived by incomplete combustion of carbon based fuel; vehicular exhaust, coal combustion, residential wood burning and tobacco smoking acts as a direct toxicant. Both nitrogen oxides and CO are known to impair ICD discharges.[12]

3. Types of studies

There are three types of studies on air pollution

1. Time series or case-crossover studies which are hospital based and evaluate end-points such as daily total mortality, CVS mortality or hospital admissions.
2. Panel studies with repeated measures of clinical endpoints such myocardial revascularization or arrhythmias documented by ECGs, Holter monitors and ICD or even potential markers of arrhythmic risk including changes in myocardial repolarization and altered heart rate variability (HRV).
3. Prospective follow-up studies of cohort of subjects.

The largest body of evidence comes from hospital based studies which provide a statistical link between air pollution and end-points on a short term basis. On the other hand prospective follow-up studies are useful to determine temporal link of associations and determine long term risks. Panel studies are useful to identify link with individual components like arrhythmias.

4. Definition of pollution

In general, contamination of air by smoke and harmful gases such as oxides of carbon, sulfur and nitrogen may be considered as air pollution. Objectively, the standards for ambient air quality for PM have been given buy US EPA. In general daily levels of up to 150 $\mu g/m^3$ of PM_{10} and 65 $\mu g/m^3$ of $PM_{2.5}$ is acceptable. On annual basis, 30 $\mu g/m^3$ of PM_{10} and 15 $\mu g/m^3$ of $PM_{2.5}$ is considered acceptable (Table 2). Anything above this value may be considered as air pollution and it is recommended that the daily levels should not exceed these values >35 times/year.

5. Effect on cardiovascular system

5.1. Acute myocardial infarction

The mechanism of AMI occurrence with air pollution has been well elucidated. Both short term exposure to PM_{10} and $PM_{2.5}$ can induce systemic oxidation, inflammation, elevation of serum fibrinogen contributing to increased platelet reactivity as well endothelial dysfunction and plaque instability. In a large study based on Medicare records PM_{10} was associated with triggering of AMI.[13] Likewise, Peter and co-workers revealed the association of $PM_{2.5}$ with transient risk of AMI at two temporal periods (2 h and 1 day) after exposure.[6] Recently Argacha and co-workers analyzing Belgian STEMI registry demonstrated that $PM_{2.5}$ and NO_2 exposure incrementally increased the risk of ST elevated AMI (STEMI). Interestingly, the risk related to PM appeared greater in the elderly, while younger patients appeared to be more susceptible to NO_2 exposure.[14] In a even more recent study, Zuin and co-workers found a direct correlation between the number patients treated with primary percutaneous coronary interventions for STEMI and the NO_2, PM_{10} and O_3 air concentration levels of the same day.[15] In another recent inter-city study from China, air pollutants like PM_{10}, SO_2, NO_2, CO were associated with a 0.8%, 2.0%, 2.2%, and 1.1% increase in AMI admissions, respectively on 2nd day after exposure while O_3 showed a positive association on day 4, 1.3%.[16]

6. Heart failure

The link of air pollution and heart failure is less certain. The mechanistic basis of acute de-compensation in patients with heart failure involve demand supply mismatch; increasing demand by increased heart rate, blood pressure, and filling pressures and reduced supply due to reduced contractility as also increased myocardial injury. Exposure to $PM_{2.5}$ has been associated with increased systemic blood pressure (BP) and vasoconstriction and pulmonary vasoconstriction leading to increased pulmonary and right ventricular diastolic filling pressures. Onset of arrhythmias or STEMI can also precipitate acute de-compensation. On long term basis exposure to PM may contribute to adverse ventricular re-modeling and a worsening of myocardial fibrosis. Cumulatively, these factors could have synergistic detrimental effects on cardiac function.[17] In a meta-analysis of pollution and heart failure studies, Shah and co-workers revealed that heart failure hospitalization or death were associated with elevations in CO (3.52%/1 ppm), SO_2 (2.36%/10 parts per billion), and NO_2 (1.70% per 10 parts per billion; 1.25–2.16), but not O_3 (0.46%/10 parts per billion) concentrations. Increases in these pollutants were also associated with heart failure hospitalization or death ($PM_{2.5}$ – 2.12%/10 $\mu g/m^3$; PM_{10} – 1.63%/10 $\mu g/m^3$), stronger association seen on the day of exposure, with more persistent effects for $PM_{2.5}$.[17]

Table 2
Current US EPA National Ambient Air Quality Standards for PM.

Time period	PM_{10}, $\mu g/m^3$	$PM_{2.5}$, $\mu g/m^3$
Daily	150	65
Annual	50	15

7. Arrhythmias

Environmental pollution can affect cardiac electrophysiology in many ways. Many of these mechanisms have been elucidated based on ICD studies. In a first of such studies, 100 patients from a US city had 223 ICD discharges for ventricular arrhythmias during the exposure. In this study associations were found with NO_2 (increased defibrillator therapy) and for CO, black carbon, fine particles, NO (increased frequency of discharge).[18] In another cohort of patients followed for >3 years, linear association was found between $PM_{2.5}$, O_3 and cardiac arrhythmias.[19] However, the data regarding the co-relation of environmental pollution and risk of arrhythmias has been inconsistent. A US study and a study conducted in a German and Swedish town showed some correlation between pollutants and arrhythmia; In Swedish and German study 2-h morning PM_{10} values were found associated with ventricular arrhythmias.[20,21] In some other studies such as one conducted in Vancouver, a relatively clean metro area and a large study conducted in city of Atlanta, US there was little evidence for any air pollutant triggering arrhythmias (except coarse particles – $PM_{10-2.5}$ in Atlanta study).[22,23] Another study conducted in Sao Paulo evaluated the occurrence of arrhythmias requiring presentation to emergency department co-relating with environmental pollution. They found that several arrhythmias; sinus tachycardia, atrial fibrillation (AF) and flutter, supraventricular tachycardias, ventricular tachycardia and fibrillation were positively associated with increases in CO, NO_2 and PM_{10}.[24] Evaluating the lag intervals between the air pollution and the onset of arrhythmias they found that the effects were acute and limited to the day of exposure. Furthermore, while other pollutants have a threshold effect, PM_{10} had a linear association. Several mechanisms have been proposed for these effects; alteration in cardiac autonomic system activity (cardiac sympathetic: parasympathetic mismatch), repolarization abnormalities and worsening myocardial ischemic sensitivity. In the Boston ICD study there was a significant association between atrial fibrillation but also probable association with fine particles, NO_2, and carbon black.[19] Another study revealed an increased risk of supraventricular arrhythmias for 5-day mean of $PM_{2.5}$, sulfate and O_3.[25] In a German Holter study, elevated PM and NO_2 concentration increased the risk for supraventricular runs and ventricular runs which correlated with last 1–3 days of air pollution.[26]

Several studies have evaluated correlation between daily variations in environmental pollution and HRV – a marker of parasympathetic input to the heart. Most studies (except in young) reveal association of PM levels with reduction in HRV and thus may explain predisposition to tachy-arrhythmias, sometimes even fatal.[12,27,28] Besides PM, sulfates, nitrates and even O_3 may also reduce HRV.[29]

8. Predisposition of risk to air pollution

There is evidence that not all are affected equally by environmental pollution. The most important predisposition is with pre-existing cardiovascular disease, but also Stransferase M1 deletion (which reduces defense to oxidative stress due to glutathione), diabetes and impaired glucose tolerance, smokers, age and those with COPD.[30]

9. Cardiac arrest

In a study conducted on >5000 individuals in Rome, both PM and CO on the day of exposure predicted sudden cardiac arrest

(SCD).[31] Elderly (>65 years of age), hypertensives and those with chronic pulmonary disease were predisposed to SCD. In a study performed in Indianapolis, increased $PM_{2.5}$ was predictive of witnessed cardiac arrests although no similar association was found in another study performed in US.[32,33]

10. Congenital heart disease

Congenital heart disease has long back been found associated with medications, radiation, infections. An American study found a dose response relationship of CO with ventricular septal defects. Also O_3 levels were found co-relative of valvular, aortic, and truncal defects although no co-relation could be found with PM or other pollutants.[34]

11. Atherosclerosis

While several mechanisms have been proposed linking environmental pollution with atherosclerosis and indeed some early studies suggesting a link of pollution with atherosclerosis a recent meta-analysis evaluating four cross-sectional European studies found no significant co-relation between carotid intima medial thickness (a marker of atherosclerosis), at least with eight commonly known markers of residential pollution like $PM_{2.5}$, traffic load within 100 m of home, and traffic intensity at the nearest road.[35–38]

12. Can the effects of pollution be reversed?

12.1. Community efforts

The individual health risk of environmental pollution may be small, at best it may qualify as a minor risk factor for CAD but the risk to the whole community may be enormous as also likely benefit if the pollution is reduced. World Health Organization has postulated that nearly 8 million disabilities and 800,000 deaths occur per year only related to PM exposure.[39] In the city of London 1 in 50 AMI may be sparked off as a consequence of environmental pollution.

The only way to control this situation is to formulate stringent air control policy (particularly for PM) and ensure strict compliance.[40] Indeed US EPA, UK air quality strategy and the EU Ambient Air Quality Directive has been formulated. Unfortunately even in the most developed countries these criteria may not be met for, e.g. in sate of California air-quality monitoring systems are presently not meeting this standard in 60% of cases.[41] On the other hand there is evidence that if these norms are adhered to there would be a reduction in >40 thousand hospital admissions and >20,000 deaths in US alone.[42]

12.2. Individual efforts

While regulatory measures to reduce emissions at their sources are effective and desirable there is some evidence that an individual action can also help to reduce exposure and personal risk. Awareness of air pollution levels is the key to initiating individual action. It can be achieved by putting in place public air quality alert systems which give appropriate alarms. Individual risk arising from air pollution can be curtailed by choosing to stay indoors, reducing outdoor air permeation to inside, purifying indoor air using air filters, and also limiting physical activity, especially outdoor activity near source of air pollution at least on the days of higher pollution.[43] The risk of air pollution is highest in patients with pre-existing chronic cardiovascular or pulmonary disease, elderly and the children. On the other hand efforts to avoid exposure should be carefully balanced against negative consequences of reduced physical activity. There is limited evidence that the ill-effects of environmental pollution can be mitigated by some therapeutic agents like antioxidant or antithrombotic agents. Statins and aspirin while useful in primary prevention of CAD require validation of their role in air pollution. Diet based interventions have been slightly more favorable. Mediterranean diet was postulated to have beneficial effects in ameliorating adverse effects of pollution, however, multiple randomized controlled trials (RCTs) of vitamin supplements and antioxidants (in Mediterranean and other beneficial diets) have not demonstrated any benefit; rather in some RCTs they have proven harmful.[44] Specific food based antioxidants such as sulforaphanes which are organic compounds found in cruciferous vegetables such as broccoli, cabbage, cauliflower, brussel sprouts, kale etc., may have some potential.[45] Foods rich in nitrates such as beet-root may exhibit a beneficial effect on blood pressure but there is no data to suggest that this may impact upon ill-effects of environmental pollution.[46] Fish oil supplementation by its multitude of effects; on blood lipids as also HRV might be useful.[47]

Table 3
Tips to reduce health risk in individuals exposed to air pollution.

- During high pollution days stay indoors, avoid physical exertion in an outdoor activity located near the source of pollution
- Reduce outdoor air permeation to inside
- Purifying indoor air using air filters
- Some foods rich in sulphorane based antioxidants like broccoli, cabbage, cauliflower, brussels sprouts
- Fish oil supplementation
- Use of respirators – face mask

12.3. Use of respirators

Limited evidence suggests that the use of respirators may be effective in some circumstances.[43] Wearing inexpensive respirators (facemasks) to reduce exposure to air pollutants can be one of the options in highly polluted areas. Its efficacy depends on the type of pollutant, type of filter/adsorbent material, respirator type and conditions of use. While useful to curtail PM, its efficacy with gaseous pollutants remains controversial (dependant on absorbent used and pollutant gas). An effective respirator is expected to reduce the concentration of the pollutant within the face-piece to ≤10% outside. Some evidence suggests that the use of negative pressure generating air-purifiers may reduce cardiovascular risks from exposure to urban PM.[48,49] On the other hand, physiological effects may confound CVS effects (elevated heart rate and variations in BP) that might be attributed to reductions in exposure to PM. Thus benefit with this type of respirator depends on the degree and type of pollution, efficacy of device and its possible physiological effects.[50] Finally, some other adverse effects are also reported with the use of these devices; higher face temperature at rest and exercise, feeling of anxiety and claustrophobia, incomplete fit with dense facial hair as well as social issues with communication (with a mask wearing individual)[43] (Table 3).

13. Conclusions

Air pollution has adverse effects on health, particularly CVS. It can precipitate AMI, heart failure, arrhythmia and even cardiac arrest. Air pollution with particulate matter (both fine and coarse) has been correlated to both CVS and total mortality. While intervention at societal level is most effective some personal steps can be taken to reduce its risk.

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