Chapter - I

Introduction
The heart is basically a muscular mechanical pump. Its main function is to provide a continuous flow of substrates and oxygen to various parts of the body through blood in amounts appropriate to their metabolic needs. It also renders a steady circulation and maintains uniform pressure for removal of the metabolic by-products from tissues. Normally the heart works continuously throughout lifetime of the individual without interruption. In order to maintain a regularity of pumping action of the heart, an adequate supply of substrates and oxygen to the myocardium as well as removal of the metabolic by-products by the coronary circulatory system is essential. Consequently, the integrity of the functions of cardiovascular system is highly susceptible to attenuation or interruption of coronary blood flow.

Most of the mortality in cardiovascular disease is contributed by ischemic heart disease, which is usually caused by impaired of coronary arterial blood flow to the myocardium. A prolonged period of severe ischemia eventually leads to irreversible cell death causing myocardial infarction. Despite increased awareness of the general public concerning the importance of minimizing the risk factors associated with arterial obstruction disease, such as hyperlipidemia, hypertension, diabetes and cigarette smoking, ischemic heart disease remains the leading cause of morbidity and mortality in India.

At the threshold of the new millennium, coronary artery disease (CAD) is looming large as the new epidemic afflicting Indians earlier in life than in other ethnic groups, relatively higher in younger ages with more severity and extensiveness, to follow a malignant course. These domestic issues which still continue to challenge our healthcare system, as daunting as they appear to be, are dwarfed by the impending crisis of cardiovascular health on an international level. We are in the midst of a true cardiovascular pandemic. It has been apparent for the past decade that heart disease is the leading cause of death, disability, and healthcare expenses worldwide. According to World Health Organization (WHO) estimates, cardiovascular disease (CVD) killed 14.7 million individuals in 1990, and 17 million in 1999. Cardiovascular disease is responsible for 30% of all deaths worldwide each year. It is often assumed that atherosclerosis is a disease of affluent, industrialized countries. However, 80% of these
deaths occur in low-to-middle income population of varying size like China, Russia, Poland, Mauritius, Argentina, and India.

Recently, studies on Indian immigrants in various parts of the world have documented their increased predisposition to cardiovascular disease in comparison with the native populations in these regions, the problem assuming considerable proportions of a challenge for many research centers worldwide. The prevalence of CAD, several-fold higher than in developed countries, has progressively increased in India during the latter half of the last century, particularly among the urban population. Projections based on the Global Burden of Disease study estimate that by the year 2020, the burden of atherothrombotic cardiovascular disease (CAD) in India would surpass that in any other region in the world. In India, CAD has been predicted to assume epidemic proportions by the year 2015. The mortality attributable to CAD in India is expected to rise by 103% in men and by 90% in women from 1985 to 2015. This predilection to CAD is attributed to a clustering of various traditional and nontraditional risk factors, which are believed to constitute the atherogenic phenotype characteristic of Indians. In addition to the conventional risk factors, namely, hypertension, diabetes mellitus (DM), hypertriglyceridaemia, low levels of HDL-C, central obesity, lipoprotein-(a) (Lp-a), high LDL-C, and low levels of antioxidants (vitamin A, E, beta-carotene), rising affluence, rapid modernization associated with sedentary but stressful life-style, consumption of junk foods in summation are also suggested as additional risk factors for CAD. These too, however do not fill in all the blanks in information.

The risk of CAD among Indians is 20% to 50% higher than Whites in Canada, South Africa, and UK, 300% to 400% higher than the Chinese in Canada and Singapore, and 20 times higher than Blacks in South Africa, 3-4 times higher than White Americans, 6 times higher than the Chinese, and 20 times higher than the Japanese. Young Indians are more prone to be afflicted by severe and diffuse form of CAD at a much higher rate than the other ethnic group.

Premature CAD is defined as cardiac events occurring before the age of 55 in men and 65 in women. Indians are afflicted by CAD 5-10 years earlier than other communities and severe forms of CAD occur below the age of 40 years. The rate of first MI has been
reported to be five times higher among Indian men compared to Europeans and the mean age at first MI is about 5 years lower for Indian men (50.2 vs. 55.5 years)\textsuperscript{16}. Indians also show higher incidence of hospitalisation, morbidity, and mortality than other ethnic groups. This global phenomenon of prematurity and severity suggests that the disease starts at an early age and has a malignant and progressive course\textsuperscript{17}. In the Western population, incidence of CAD in the young is up by 5% as compared to 12-16% in Indians\textsuperscript{18}. In some studies from India, the percentage of patients below the age of 45 years suffering from myocardial infarction (MI) is reported as high as 25-40%\textsuperscript{19}. In a prospective comparison of 131 men, the rate of first MI was five times higher among Indian men compared to Europeans in the study\textsuperscript{16}. In Great Britain the incidence of first MI among Indians at age less than 40 years is reported 10 times higher than local Whites\textsuperscript{20}. In Singapore, where all MI in the country are systematically entered in the registry, the incidence of MI is 3-fold higher among Asian Indians than Chinese men and women\textsuperscript{21}. Asian Indians undergoing coronary artery bypass grafting (CABG) have mortality almost twice the mortality of Whites\textsuperscript{22}. Angiographically, Indians have 15 times higher rate of CAD than Chinese, and 10 times higher rate than local Malays below the age of 40 years. In the 10-year prospective follow-up of the St. James Survey in Trinidad, the age-standardized ratio of CAD incidence in Asian Indians is 2-fold higher than Whites and 7-fold higher than Blacks\textsuperscript{23}. The post-infarction course is also worse in Indians as compared to Whites. This is reflected by three-times higher rate of re-infarction and two-times higher rate of mortality\textsuperscript{24}. In an observation in the West Asia, out of all patients admitted in coronary care unit (CCU) with acute MI below the age of 40-years, 80% were Indian expatriates as compared to 20% among native Arabs, whereas demographically Indian expatriates are about 10% of the local population\textsuperscript{25}. A study conducted on first-generation immigrant Indian physicians in the United States of America recorded that myocardial infarction (MI) or angina was three times more in Indian men (mean age 46.4 years) compared to the men in the Framingham Offspring Study, where the prevalence of age was adjusted (7.2% vs. 2.5%)\textsuperscript{8}. The prevalence of CAD is two times higher (10%) in urban than in rural India\textsuperscript{26}. Many scientists, investigated from the beginning in the 1960s through the 1990s to estimate the prevalence of CAD in several urban\textsuperscript{9,11,27} and rural \textsuperscript{28,29} populations. Overall,
prevalence estimates obtained from studies performed in the last decade range between 7.6% and 12.6% for urban population and 3.1% to 7.4% for rural population. The difference in prevalence between the urban and rural populations has been accounted for by the dissimilar prevalence of risk factors in generally in these two groups. The vulnerability of CAD in Indians is possibly related to different dietary habits, environmental, and life-style factors. Many regional, economic, political, and cultural imbalance are also seen to influence the impact of each of these issues at the local level which makes uniform global recommendations difficult or impractical. Migration from rural to urban environment and migration from India to industrialized countries are additional special risk factor for our people. Migration is usually associated with stress of seeking and maintaining the new job, stress of coping with the new job-expectations, and stress of competing with the peer-group who are in the organization longer. Abrupt affluence is associated with sedentary life-style and higher consumption of calories, saturated fats, salt, tobacco, and alcohol. These factors contribute to obesity, dyslipidaemia, hypertension, hyperuricaemia, and diabetes mellitus.

Therefore, there exists high indices of suspicion for CAD in Indians. So it is high time to adapt a more aggressive approach for preventing and treating of both conventional and emerging risk factors, which is warranted especially in the case of Asian Indians. Though the CAD is a fatal disease with no known radical cure, yet it is also highly predictable, preventable, and treatable with the existing knowledge, provided the risk-factor evaluation is promptly started.

**Conventional Risk factors**

Hypertension, diabetes mellitus, smoking, hyperlipidaemia, tobacco consumption, obesity, and reduced physical activity are considered known conventional risk factors for CAD. Male sex is more prone to CAD but post-menopausal females need special attention, as they constitute a distinct sub-group at a high risk for CAD.

High blood pressure (BP) is a stronger risk factor for stroke than for CAD. In a recent study it has been observed that even high normal levels (systolic BP 130-139 mm Hg and/or diastolic BP 85 to 89 mm Hg) are associated with doubling of CAD risk.
Prevalence of hypertension is increasing in urban population as compared to in rural population. In metropolitan cities the prevalence is as high as 11%-27% \(^3\). Hypertension is closely correlated with salt and alcohol intake and obesity. A 5% increase in weight is associated with a 20% to 30% increase in the odds of developing hypertension.

The prevalence of DM is about 20% in middle age and additional 20% may be having impaired glucose tolerance, even moderate elevation of glucose in Indians is associated with increased risk of CAD. Approximately 80% of deaths in diabetic patients are attributable to cardiovascular disease (CVD), which in turn is highly correlated with dyslipidemia\(^3\). An elevated level of TC is the strongest risk factor for CAD\(^3\). TC levels correlate well with the presence and severity of CAD in Asian Indians similar to Whites\(^4\). In contrast to decreasing mean cholesterol levels in the USA, the mean serum cholesterol level in urban Indians is rising. For instance in Delhi, the mean serum cholesterol level has risen from 160 mg/dl in 1982 to 199 mg/dl in 1994\(^3\). Indians even with lower levels of serum cholesterol have a higher risks of CAD.

Tobacco use (both cigarettes and beedi) is strongly related to CAD and increases the risk of CAD by 3-5 times. Current smoking of >10 cigarettes or beedi a day is associated with a 6.7-fold increase in the risk of MI\(^3\). In a prospective case–control study conducted in Bangalore\(^3\). 200 patients with a first acute myocardial infarction (AMI) were compared with 200 age- and sex-matched controls. The adjusted odd ratios for smoking (either cigarettes or beedis), hypertension and fasting blood glucose (FBG) level >140 mg/dl as risk factors for MI are 3.7, 3.0 and 2.8, respectively. Studies have shown that 40-50% of the males in India are smokers. For Indians, tobacco remains a major risk factor as it is used in different forms.

Obesity is associated with increased risk of hypertension, diabetes, dyslipidemia and CAD, which is becoming a global epidemic\(^3\). The majority of patients with high blood pressure are overweight, and hypertension is more frequent in obese subjects\(^3\). A 10 kg higher body weight is associated with a 3.0 mm Hg higher systolic and 2.3 mm Hg higher diastolic blood pressure. These increases translate into an estimated 12% increased risk for CAD and 24% increased risk for stroke\(^3\). In contrast, in patients with
known CVD or after acute myocardial infarction, overall obesity as assessed by BMI is inversely related to mortality\textsuperscript{39}. Abdominal obesity is a risk factor for CVD worldwide. Central obesity is an independent risk factor for CAD, even modest increase in body fat with central distribution increases the risk further\textsuperscript{32}. In Indian population with CAD, high triglyceride levels are reported more often than high cholesterol levels. The role of elevated triglyceride (Tg) levels in the pathogenesis of atherosclerotic cardiovascular disease remains a controversial issue\textsuperscript{40}. In spite of it most of the studies showed an association between elevated Tg levels and CAD\textsuperscript{41}. Some studies have indicated that there is an increased risk of CAD in the presence of Tg levels $\geq 204$ mg/dl when the ratio of LDL-cholesterol to HDL-cholesterol exceeds 5\textsuperscript{42}. Triglycerides bring change in LDL particle size, density, distribution, and composition producing smaller, denser, and more atherogenic particles\textsuperscript{43}. Estimation of triglyceride level gives an indirect measurement of LDL particle size. An increase of triglycerides from 90 mg/dl to 180 mg/dl is associated with doubling the incidence of CAD\textsuperscript{44}. The role of leisure-time and work-related physical activity in determining risk of CAD in native Indian patients has not been as well studied. In a study of an urban community in Rajasthan\textsuperscript{45}, it was found that more than 70% of the subjects were categorized as having a sedentary lifestyle. The adjusted odds ratios for a sedentary lifestyle as a risk factor for CAD was 1.7 in males and 4.5 in females. Although these conventional risk factors do not fully explain the excess burden of CAD, these risk factors appear to be doubly important in Indians, and remain the principal targets for prevention and treatment.

**EMERGING RISK FACTORS**

Despite the long list of traditional and conventional risk factors involved, 50% of the CAD still remains unexplained. This led researcher to think of novel risk factors, which might contribute to CAD. Studies on migrant Indians have suggested that the excess risk for CAD seen among Indians could partly be explained by these risk factors\textsuperscript{46,47}. Some of the newer risk factors like Lipoprotein (a), Homocysteine, Plasma fibrinogen, C-Reactive protein, etc., are very significant to diagnosis of coronary artery disease.
Over the last several decades, it has become amply evident that oxidative stress plays a significant role in the pathogenesis of coronary atherosclerosis and its complications. Many relatively recent studies demonstrated an association of increased oxidative stress on the one hand and diabetes, hypertension, cigarette smoking and dyslipidemia on the other hand, which are well known risk factors for atherosclerosis. Indeed, it appears that oxidative stress accounts for both vascular disease and serves as risk factors in CAD.

The LDL-cholesterol types are described as phenotypes A, B, or C, which are genetically determined. Patients with LDL phenotype-B have predominantly small and dense LDL-particles, which constitute as an important risk factor for CAD. A 75% prevalence of phenotype-B is reported in Asian Indians in contrast to 25% in white population. A number of studies suggest that reactive oxygen species (ROS) oxidize lipids and that the oxidatively modified LDL is a more potent proatherosclerotic mediator than the native unmodified LDL. The suggestion is based on the observations that high plasma levels of oxidised-LDL (ox-LDL) are present in patients with atherosclerosis and that antibody to ox-LDL is detected in plasma of most patients with atherosclerosis. Strong evidence in favor of a pro-atherosclerotic role for ox-LDL comes from a number of studies demonstrating the noxious effects of ox-LDL on various components of the arterial wall.

Lipoprotein (a) (Lp-a) is a complex of Apoprotein (a) and LDL, is a strong independent risk factor for premature CAD in many populations including Whites, Chinese, and Japanese. The mechanisms underlying this relationship is uncertain, but in vitro studies suggest that lipoprotein (a) may influence cholesterol uptake, and inhibit fibrinolysis. Lipoprotein (a) has also been implicated in enhanced oxidation and foam cell formation. It is a genetic risk factor, not affected by any level of lifestyle modifications and is 10-times more atherogenic than LDL-C. It promotes early atherosclerosis and thrombosis. In Indians, both in India and abroad, the levels of Lp-a are higher as compared to the whites in Great Britain, suggesting a genetic propensity. Relationship of Lp (a) to CAD is continuous and graded; a level of 15-20 mg/dl is now considered the threshold.
One third of the Indian males have higher levels of apolipoprotein-B (Apo-B). This factor in combination with low levels of HDL and hypertriglyceridaemia results in formation of small dense LDL, which increases the risk of CAD more than three times. **Insulin resistance**, and the compensatory increase in insulin secretion bring about a state of chronically increased insulin and glucose levels in the blood (hyperinsulinemia and hyperglycemia) and thus is a predecessor for diabetes. Reaven explored the association of insulin resistance with CAD and suggested that diabetes is a part of the insulin resistance syndrome also called the metabolic syndrome, which includes central body obesity, dyslipidemia, and hypertension. Insulin Resistance Syndrome is a precursor of diabetes and a common pathogenic mechanism for the development of CAD. McKeigue et al. have suggested that a pattern of insulin resistance and associated metabolic abnormalities might underlie the high rates of CAD and type 2 diabetes among South Asian people. It is an important risk factor for early development of CAD in Indians. This syndrome consists of hyperinsulinemia, atherogenic dyslipidemia, glucose intolerance, prothrombotic state, central obesity, and hypertension.

**Homocysteine:** Several recent studies have investigated the contribution of homocysteine to CVD risk both among immigrant Indians and those living in India. Homocysteine is a sulfur containing amino acid, which is a new and independent risk factor for CAD and stroke. It causes vascular damage by its deleterious effects on endothelial functions and by its pro-thrombotic, pro-oxidant, and mutagenic effects. The risks are comparable with the risk of cigarette smoking and dyslipidemias. Studies on migrant Indians have shown higher levels of homocysteine compared to the native population. However, studies on its association with CAD among native Indians have been consistently negative.

**Infections and CAD:** Various infections, viral and bacterial, have been implicated. Among them, *Chlamydia pneumoniae* is considered an important risk factor for CAD. This is surmised so because high antibody titers to *chlamydia-lipopolysaccharide* are found in patients of AMI. It is thought that AMI may be precipitated by exacerbation of *Chlamydia pneumoniae* infection.
Oxidative stress and antioxidant in CAD: Cardiovascular diseases, cancer, diabetes mellitus, etc., stressful conditions that lead to formation of excessive free radicals, are a major internal threat to cellular homeostasis of aerobic organisms. Free radicals are formed in human body both in physiological and pathological conditions in cytosol, mitochondria, lysosomes, peroxisomes and plasma membranes. These free radicals are extremely reactive and unstable chemical species, which react with proteins, lipids, carbohydrates and nucleic acids in the body. Antioxidants may delay or prevent various steps in free radical formation. ROS are cleared from the cell by enzymatic antioxidant systems including superoxide dismutases (SODs), catalase, and glutathione peroxidase, or the nonenzymatic system including alpha-tocopherol, ascorbic acid, glutathione, uric acid, etc., prevent free radical chain reaction. When these antioxidant defence systems get exhausted, that is when generation of free radicals exceeds beyond their scavenging capacity, free radical mediated damage results.

In this instant situation unrestrictedly produced free radicals injure the endothelial layer of the arterial wall. A systemic infective episode produces generalized arteries including coronary arteries with diffuse lesions. These lesions may be further worsened by pro-atherosclerotic factors like smoking, hypertension, diabetes, and dyslipidemia. The mechanism could be occurring other way round, that is, coronary artery endothelium which has already developed atherosclerotic plaques due to conventional risk factors, on getting further inflamed subsequently by a systemic infection, leads to aggravation of plaque formation and thrombosis, precipitating an acute coronary event. Whether fuel is poured over the fire or fire is added to the fuel is a subject for further research for fact finding.

Coronary artery disease (CAD) remains the major cause of morbidity and mortality in all developed countries as well as in developing countries in the world. In India, it has already climbed the ‘Charts’ from 14th to 4th place, only behind tuberculosis, communicable diseases and malnutrition. Though lipids and lipoproteins are important risk factors for CAD, they do not account for the disease in 30 to 40% of the population with CAD. Other risk factors including smoking, hypertension, diabetes mellitus, etc.,
do not predict subsequent CAD risk accurately in Indians. But in fact Indians have a high incidence of CAD, which is not entirely explained by conventional risk along with emerging risk factors also.

In this apparently perplexing situation caused by the interwoven mesh of free radical formation, antioxidant scavenging, atherogenesis and an effective functional state of free radical oxidant-antioxidant relation, it is virtually impossible to individually trace out the implicit path of each component in the mesh. But at the same time it is also equally true that each component retains its own functional identity within the whole system. In this situation investigations of the role of free radical and antioxidant system either in maintenance of a balanced oxidant-antioxidant state or readjustment of a pre-existing state during tracking of this 'atherosclerotic state' throughout a course of atherogenesis may provide some clue to unravel some distinct areas of this mysterious linkage of free radicals-CAD-antioxidants. In the light of this foregoing information and ideas it is intended to undertake a research on “STUDIES ON RISK FACTORS ASSESSMENT OF CORONARY ARTERY DISEASE WITH SPECIAL EMPHASIS TO LIPID PROFILE PEROXIDATION AND ANTIOXIDANT STATUS” in the following plan:

- The primary purpose of this study is to relate coronary artery disease and the ROS/RNS at the cellular level.
- Role of free radicals in the pathogenesis and diagnosis of coronary artery disease.
- Role of antioxidants, both dietary and endogenous, which may be important protective factors.
- Role of Nitric Oxide (NO), which is an important RNS that embraces normal health and CAD.
- Evaluation of a practicable index for prognosis and diagnosis of coronary artery disease (CAD).
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