NEW HORIZONS

Malignant Coronary Artery Disease in Young Indians–A Challenge of the New Millenium

H. S. Rissam, S. Kishore, N. Trehan

Introduction

At the threshold of the new millenium, coronary artery disease (CAD) is looming large as the new epidemic afflicting Indians at a relatively younger age with severe and diffuse form of lesions. Recently, the subject of CAD in Indians (referred as immigrants or Asian Indians or South Asians when outside India) has become a challenge for many research centres worldwide (1,2). The prevalence of CAD has progressively increased in India during the last half of the century, particularly among the urban population (3). The conventional risk factors namely hypertension, diabetes mellitus (DM), hypercholesterolemia and tobacco smoking do not fully explain the vulnerability of Indian community to coronary atherosclerosis. Insulin resistance, hyperinsulinemia, hypertriglyceridemia, low levels of HDL-C, central obesity, high Lipoprotein-a (Lp-a), high LDL-C, low levels of Antioxidants (Vitamin A, E, Beta-Carotene), rising affluence, rapid modernization associated with sedentary but stressful life-style in summation are suggested as additional risk factors for CAD. They too do not fill all the blanks in information. Infections like Chlamydia in association with ***yet unknown agents,*** may be the other aetiological factors.

CAD in Indians–The emerging scenario

The risk of CAD in Indians is 3-4 times higher than White-Americans, 6-times higher than Chinese and 20-times higher than Japanese (4,1). Indians are prone as a community to CAD at a much younger age (5,6). The disease pattern is severe and diffuse. Premature CAD is defined a cardiac events occuring before the age of 55 in men and 65 in women. In its severe form, it is defined as CAD occuring below age of 40 years. CAD is affecting Indians 5-10 years earlier than other communities. Indian also show higher incidence of hospitalization, morbidity and mortality than other ethnic groups (7). This global phenomenon of prematurity and severity suggests that the disease starts at an early age and has a malignant and progressive course (8). (There is a parallel corollary between CAD in Indians and the malignant course of Rheumatic fever, Rheumatic heart disease with associated severe pulmonary hypetension observed by Indian cardiologists in sixties). In the Western population incidence of CAD in the young is up to 5% as compared to 12-16% in Indians (9,10). In some studies from India the percentage of patients below the age of 45 years

From the Department of Telecardiology, Escorts Heart Institute & Research Centre, New Delhi-110 025 India.
Correspondence to : Dr. H. S. Rissam, Senior Consultant & Head Department of Telecardiology, Escorts Heart Institute & Research Centre, New Delhi-110 025 India.

suffering from Acute Myocardial Infarction (AMI) is reported as high as 25-40% (11,12). In Great Britain the first AMI among Indians at age less than 40 years is reported 10 times higher than local Whites (13). In Singapore, mortality from CAD below 30 years of age is 10 times higher in Indian than Chinese population of the same age group (14). 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.

Young patients from other communities do not show extensive disease (15), whereas in young Indians there is often three vessel disease with poor prognosis (16). The post-infarction course is also worse in Indians as compared to Whites. This is reflected by three-times higher rate of reinfarction and two-times higher rate of mortality (17,19).

In an observation in Middle East out of patients admitted in CCU with acute MI below the age of 40 years, 80% were Indian-expatriates as compared to 20% of native Arabs, whereas demographically Indian expatriates are about 10% of the local population (20).

The prevalence of CAD is two-times higher (10%) in urban than in rural India (21,22). South Indians have higher prevalence, 7% in rural and 14% in urban areas. The vulnerability of urban Indians to CAD is possibly related to different nutritional, environmental and life-style factors. The Body Mass Index in Urban Indians as compared to rural Indians is 24 vs 20 in males and 25 vs 20 in females. Unfortunately, the on-going urbanization of rural India is likely to narrow down these differences.

Migration from rural to urban environment and migration from India to industrialized countries is another 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 is in the organization for a longer period. New affluence is associated with sedentary life-style and higher consumption of calories, saturated fats, salt, tobacco and alcohol. These factors contribute to obesity, dyslipidemia, hypertension, hyperuricemia and diabetes mellitus.

Therefore, there has to be *high index of suspicion* for CAD in Indians above the age of thirty years. The risk factor evaluation must start earlier. Investigations like treadmill, stress Echo, Stress thallium and coronary angiography should be more liberally recommended.

Risk Factors (Conventional and New)

There is a need for identifying and correcting the conventional risk factors like hypertension, diabetes mellitus, smoking, hyperlipidemia, tobacco consumption and central obesity at much younger age. 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.

Hypertension remains a standard risk factor associated with CAD. Prevalence of hypertension is increasing in urban population, as compared to rural population. In metropolitan cities the prevalence is as high as 11%-27% (3,23). The prevalence of diatetes mellitus (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 (24). In contrast to decreasing mean cholesterol levels in the USA, the mean serum cholesterol level in urban Indians in rising. 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 higher risk of CAD.

Smoking increases the risk of CAD by 3-5 times. In the first world countries smoking has significantly decreased and is socially looked down upon. In contrast, in India smoking is increasing particularly in the younger generation. As the demand is falling in the West, tobacco traders are dumping this atherogenic material in the Indian market. In seventies tobacco consumption in Indian per adult was 0.7 kg / year, it is likely to increase to 0.9 kg / adult / year by the year 2000. In India the consumption of tobacco is 6.1% of the world total un-manufactured tobacco, 20% is in the form of cigarettes, 40% is in the form of bidies and rest as smokeless tobacco product. 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.

Central obesity, depicted by waist to hip ratio is an independent risk factor for CAD, even modest increase in body fat with central distribution increases the risk further (24).

NEW RISK FACTORS : Lipoprotein-a (Lp-a) is now recognized as an independent risk factor for CAD. It is a genetic risk factor. It is not affected by any level of life-style modifications like changes in diet and exercise. Lp-a is ten-times more atherogenic than LDL-C (25). It promotes early atherosclerosis and thrombosis. Lp-a is stronger risk factor than DM for CAD in younger women. 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 (26). Lp-a levels in cord blood are higher among Indian newborns than Chinese newborns and this difference is also associated with a four-fold higher CAD - related mortality in Indians than Chinese in Singapore (27). Lp-a levels above 30 mg/dl are associated with three-fold higher risk of CAD. Lp-a levels over 40 mg/dl increases the risk associated with cigarette smoking by 1.9 times, with DM by 3.4 times, with high total cholesterol by 4.2 times, with hypertension by 4.6 times, with high TC/HDL ratio by 6.9 times and with high homocysteinaemia by 9.3 times (28).

In Indian patients with CAD, high triglycerides levels are found more often than high cholesterol levels. Triglycerides bring change in LDL particle size, density, distribution and composition producing smaller denser and more atherogenic particles (29). Estimation of triglycerides level gives an indirect measurement of LDL particles size. An increase of triglycerides from 90 mg/dl to 180 mg/dl is associated with doubling the incidence of CAD (30). Increase in triglycerides by 90 mg/dl has the same effect on coronary atherosclerosis, as increase in age by 10 years (31). Earlier, there has been an under-emphasis on the significance of triglycerides as a risk factor for CAD. Indians world-wide demonstrate a triad of high triglycerides with high LDL-C levels and low HDL levels. This triad combined with high levels of lipoprotein-a constitutes the deadly lipid quartet.

Higher levels of **Apolipoprotein-B (Apo-B)** are reported in one-third of Indian males. This factor in combination with low levels of HDL and hypertriglyceridemia results in formation of small dense LDL which increases the risk of CAD more than three times.

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 as mentioned above, constitute an important risk factor for CAD. A 75 % prevalence of phenotype-B is seen in Asian Indians in contrast to 25% in White population (2).

High levels of **Plasminogen Activator Inhibitor-1 (PAI-I)** in Indians are reported in association with hypertriglyceridemia and hyperinsulinemia. This combination promotes thrombosis by impairing fibrinolysis (32).

Insulin Resistance Syndrome (IRS) is an important risk factor for early development of CAD in Indians (33). Indians, as compared to Europeans, have higher resistance to insulin mediated glucose uptake in association with hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and low levers of HDL-C.

Serum Fibrinogen is an independent and newer risk factor for CAD. Fibrinogen increases the blood viscosity and plays a key-role in thrombosis. Both factors promote coronary atherosclerosis.

Hyperhomocysteinaemia : Homocysteine is a sulfur containing aminoacid which is a new and independent risk factor for CAD and stroke. Homocysteine causes vascular damage by its deleterious effects on endothelial functions and its pro-thrombotic, pro-oxidant and mitogenic effects (34). The risks are comparable with the cigarette smoking and dyslipidemias.

Infections and CAD : Various infections, viral and bacterial, have been implicated. Amongst them, Chlamydia pneumoniae is considered as an important risk factor for CAD (35). This is so surmised because high antibody titres to chlamydia-lipopolysaccharide are found in patients of AMI. It is thought that AMI may be precipitated by exacerbation of Chlamydia pneumoniae infection. Atherosclerosis represents an exaggerated inflammatory reaction to injury of the endothelial layer of the arterial wall. A systemic infective episode produces generalised arteritis including coronary arteritis with diffuse lesions. These lesions may be further worsened by pro-atherosclerotic factors like smoking, hypertension, diabetes and dyslipidemia. The mechanism could be occuring other way round i. e. coronary endothelium which has already developed atherosclerotic plaques due to conventional risk factors, on getting further inflammed by a systemic infection, undergoes aggravation of plaque activity 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.

Conclusions

In order to combat the on-slaught of CAD among young Indians and to reduce the acute events like Acute Myocardial Infarction with associated complications like left ventricular failure, pulmonary edema, cardiogenic shock, life-threatening arrhythmias and left ventricular dysfunction, it is mandatory to have **high index of suspicion** of CAD in our population particularly in those who present with atypical symptoms. Evaluation of conventional risk factors like hypertension, diabetes mellitus, obesity, dyslipidemia and smoking must be done in men from the age of 30 years onwards and in women of post-menopausal age. Triglycerides, LDL-C and HDL-C estimations must be a part of routine evaluation. In major hospitals the laboratory facilities for evaluation of newer risk factors namely lipoprotein-a, apolipoproteins, fibrinogen, hyperhomocysteinemia, PAI-I, and hyperinsulinemia must be introduced. **In asymptomatic individuals** with background of coronary risk factors after the age of 30 years, investigations including stress ECG/stress Echo/stress Thallium must be periodically performed. In subjects with **evidence of exercise induced reversible ischemia,** coronary angiography must be carried out. In **symptomatic**

individuals mandatory coronary angiography must be done to delineate the culprit lesions for timely and appropriate intervention.

New modalities like coronary angioplasty, stents, laser revascularisation and surgical bypass techniques with videoscopic and Robotic assistance have universally brought down morbidity and mortality. From Indian point of view, there is need to plan strategies for preventing and halting coronary atherosclerosis which is fast spreading as a malignant epidemic among the young. In the industrialized countries there is a continuing decline of CAD during the last three decades. Between 1965-1990, CAD mortality has decreased by 60% in Japan and Finland and by 50% in USA, Canada, France and Australia (36, 37). This has been possible by, focussing on public education programmes for modifying the known risk factors and by targeting high risk individuals. **This achievement of the industrialized nations must become a lesson and an inspiration for the cardiac faculty and the policy makers in India.**

References

1. Enas EA, Garg A, Davidson MA *et. al.* Coronary heart disease and its risk factors in the first generation immigrant Asian Indians to the United States of America. *Indian Heart J* 1996 ; 48 : 343-54.
2. Enas A Enas, Salim Yusuf. Third meeting of the International Working Group on Coronary Artery Disease in South Asians. *Indian Heart J* 1999 ; 51 : 99-103.
3. Rajeev Gupta. Epidemiological Evolution andRise of Coronary Heart Desease in India. *South Asian J Preventive Cardiology* 1977 ; 1 : 14-20.
4. Enas EA. High rates of CAD in Asian Indians in the United States despite intensive modification of life style. What next? Current Science 1998 Vol. 74.
5. Janus ED, Postiglione A, Singh RB *et. al.* The modernization of Asia. Implications for coronary heart disease. *Circulaltion* 1996 ; 94 : 2671-73.
6. McKiegue PM, Ferrie JE, Pierpoint T *et. al.* Association of early-onset coronary heart disease in South Asian men with glucose intolerance and hyperinsulinemia. *Circulation* 1993 ; 87 : 152-61.
7. Enas EA, Dhawan J, Petkar S. Coronary artery disease in Asian Indians. Lessons learnt and the role of lipoprotein-a. *Indian Heart J* 1996 ; 49 : 25-34.
8. Enas EA, Mehta JL. Malignant coronary artery disease in young Asian Indians. Thoughts on pathogenesis, prevention and treatment. *Clin Cardiol* 1995 ; 18 : 131-35.
9. Negus BH, Williard JE, Glamann DB *et. al.* Coronary anatomy and prognosis of young asymptomatic survivors of myocardial infarction. *Am J Med* 1994 ; 96 : 354-58.
10. Mammi MVI, Pavithran P, Rahman P *et. al.* Acute MI in North Kerala. A 20 year hospital based study. *Indian Heart J* 1991 ; 43 : 93-96.
11. Bahuleyan CG. Hospital data on coronary artery disease from North Kerala. In : Cardiovascular Disease Prevention by Vijayaraghavan G (editor). Trivandrum. 1997 ; 54-59.
12. Girija G. Risk factors profile of patients with acute MI. In : Cardiovascular Disease Prevention by Vijayaraghavan G (editor). Trivandrum. 1997 ; 26-27.
13. Hughes K, Lun KC, Yeo PPB. Cardiovascular disease in Chinese Malays and Indians in Singapore. Difference in mortality. *J Epidemiol Community Health* 1990 ; 44 : 24-28.
14. Rajadurai J, Arokiasami J, Pasamanichan K *et. al.* Amei-Lin O. Coronary disease in Asians. *Aus NZ J Med* 1992 ; 22 : 345-48.
15. Sharma SN, Koul U, Sharma S, Wasir HS *et. al.* Coronary arteriographic profile in young and old Indian patients with ischemic heart disease. A comparative study. *Indian Heart J* 1990 ; 42 : 365-69.
16. Danarag TJ, Acker MS, Danaraj *et. al.* Ethnic group differences in coronary heart disease in Singapore. An analysis of necropsy records. *Am Heart J* 1959 ; 58 : 516-26.
17. Wilkinson P, Sayer J, Laji K *et. al.* Comparison of case fatality in South Asians and White patients after acute myocardial infarction. *BMJ* 1996 ; 312 : 1330-33.
18. Wild S, McKeigue P. Cross sectional analysis of mortality by country of birth in England and Wales 1970-92. *BMJ* 1997 ; 314 : 705-10.
19. Reddy KS. Cardiovascular disease in India. World Health Stat. *Q*1993 ; 46 : 101-107.
20. Rissam HS, Banzal S, Jamal A. Profile of acute myocardial infarction in Indians in Kingdom of Saudi Arabia (unpublished data).

21. Destefano F, Merrit RK, Anda RF. Trends in coronary heart disease in the US, 1980 through 1989. *Arch Intern Med* 1993 ; 153 : 2489-94.

22. Bhatia ML. Prevalence of CAD in India : a contemporary view *Indian Heart J* 1995 ; 47 : 339-42.

23. Chadha SL, Radhakrishnan S, Ramachandran K, Kaul U, Gopinath N. Prevalence, awareness and treatment status of hypertension in urban population of Delhi. *Indian J Med Res* 1990 ; 92 : 233-40.

24. Enas A Enas, Salim Yusuf, Jawahar Mehta. Meeting of the International Working Group on Coronary Artery disease in South Asians. *Indian Heart J* 1998 ; 48 : 727-32.

25. Lawn RM. Lipoprotein (a) in heart disease *Sci Am* 1992 ; 266 : 54-60.

26. Bhatnagar D, Anand I, Durington PN *et. al.* Coronary risk factors in people from Indian subcontinent in West London and their siblings in India *Lancet* 1995 ; 345 : 405-409.

27. Low PS, Heng C, Saha N, Tay J. Racial variation of cord plasma lipoprotein concentrations in relation to coronary risk levels. A study of three ethnic groups in Singapore. *Pediatr Res* 1996 ; 40 : 718-22.

28. Hopkins PN, Wu L, Hunt S, James B, Vincent G, Williams R. Lipoprotein (a) interactions with lipid and nonlipid risk factors in early familial coronary artery disease. *Arterioscler Thromb Vasc Biol* 1997 ; 17 : 2783-92.

29. Lamarche B, Tchernof A, Moorjani S *et. al* Small dense low-density lipoprotein particles as a predictor of the risk of ischaemic heart disease in men. Prospective results from Quebac Cardiovascular Study. *Circulation* 1997 ; 95 : 69-75.

30. Jeppesen J, Hein H, Suadicani P, Gyntelberg F. Relation of high TG-low HDL cholesterol and LDL cholesterol to the incidence of ischemic heart disease. An 8 year follow-up in the Copenhagen male study. *Arterioscler Thromb Vasc Biol* 1997 ; 17 : 1114-20.

31. Drexel H, Amann F, Beran J *et. al.* Plasma triglycerides and three lipoprotein cholesterol fractions are independent predictors of extent of coronary atherosclerosis. *Circulation* 1994 ; 90 : 2230-35.

32. Hamstein A, Walldius G, Szamosi A *et. al.* Plasminogen activator inhibitor in plasma risk factor for recurrent myocarial infarction. *Lancet* 1987 ; 3-9.

33. Hughes LO. Insulin, Indian origin and ischemic heart disease. *Int J Cardiol* 1990 ; 26 : 1-4.

34. Welch GN, Loscalzo J. Homocysteine and athero-thrombosis. *New Engl J Med* 1998 ; 338 : 1042-50.

35. Gupta S, Camm AJ. Chronic infections in the aetiology of atherosclerosis–the case of Chlamydia pneumoniae. *Clin Cardiol* 1997 ; 20 : 829-36.

36. Fox R. Trends in cardiovascular mortality in Europe. *Circulation* 1997 ; 96 : 3817.

37. Destefano F, Merrit RK, RFA. Trends in coronary heart disease in the United States, 1980 through 1989. *Arch Inter Med* 1993 ; 153 : 2489-94.