Letters to the Editor

Atheromatous Plaque Reflects Serum Total Cholesterol Levels: A Comparative Morphologic Study of Endarterectomy Coronary Atherosclerotic Plaques Removed from Patients from the Southern Part of India and Caucasians from Ottawa, Canada

P. J. VARGHESE, S. B. ARUMUGAM, K. M. CHERIAN, V. WALLEY, A. FARB, R. VIRMANI: *Clin Cardiol* 1998;21:335–340

To the Editor:

Asian Indians around the globe have one of the highest rates of coronary artery disease (CAD), despite the fact that nearly half of them are lifelong, passionate vegetarians.¹ When compared with Americans, Europeans, and other Asians, the incidence, prevalence, hospitalization, and mortality from CAD among Asian Indians are three- to fourfold higher at all ages and five- to tenfold higher under the age of forty.² The four cardinal coronary risk factors (high blood pressure, high serum cholesterol, cigarette smoking, and diabetes) have consistently failed to fully explain the excess burden of CAD in this population.³ Therefore, I was intrigued by the report of the “first study” by P. J. Varghese *et al.*, demonstrating smaller coronary vessels in Asian Indians than their counterparts in the West.⁴ They suggest that “this difference in vessel size may explain why Asian Indians manifest disease at a younger age than their counterparts in the West.” However, the difference in vessel size did not reach a statistical significance (4.6 ± 2.9 mm vs. 5.6 ± 3.0 mm, $p = 0.07$). No adjustment was made for the body mass. The failure to obtain and adjust for the body mass of the study populations may have led to erroneous conclusions that help perpetuate the misconceptions about the role of coronary artery size in the excess burden of CAD in Asian Indians, as discussed below.

Dhawan *et al.*⁵ investigated the coronary artery diameters of 72 male Caucasians and 70 male Asian Indians undergoing consecutive coronary angiograms in the United Kingdom. Measurements of proximal disease-free segments of the three major coronary arteries were made using the catheter tip as the calibrating object. Adding the diameters of the left anterior descending, circumflex, and right coronary arteries derived the total coronary artery diameter. Although Asian Indians had significantly smaller total vessel diameters compared with Caucasians (12.8 mm vs. 13.8 mm, $p = 0.01$), they also had smaller body surface area (1.84 m², vs. 1.90 m², $p < 0.05$). After adjusting for body surface area, the total vessel diameter was not different (6.95 mm vs. 7.25, $p = \text{NS}$). Thus, the smaller coronary artery diameter in Asian Indians appears to be a function of a smaller body mass.

Although the smaller size of the coronary arteries may be of some significance in the success of revascularization procedures, the vessel size is unlikely to be an important factor in the pathogenesis of premature CAD among Asian Indians or any other population. It has now been well established that the risk of coronary occlusion is not proportional to the prior severity of coronary stenosis and that the majority of myocardial in-

farctions occur at sites of less than severe stenosis.⁶ Asian Indians develop first myocardial infarction about five to ten years earlier than Caucasians.² If a greater relative luminal narrowing by a given plaque in smaller coronary arteries results in an earlier manifestation of CAD, women who have smaller coronary arteries (due to smaller body mass) should also have earlier manifestations of CAD than men. In reality, women the world over lag 10 to 15 years behind men for development of clinical manifestations of CAD.⁷ Likewise, other Asians such as Chinese and Japanese also have smaller body mass and smaller coronary arteries than Caucasians, but CAD among them is neither premature nor severe. As a matter of fact, CAD rates among Chinese Americans are sixfold lower than among Asian Indians in California.⁸

I agree with Varghese *et al.* in seeking other etiologies for the severe premature CAD among Asian Indians. Although far from conclusive, a “deadly quartet” of emerging risk factors appears to provide a plausible explanation for the excess burden of CAD among this population.⁹ This quartet consists of the well known lipid triad [high triglycerides, low high-density lipoprotein (HDL), and borderline high low-density lipoprotein (LDL) in combination with elevated levels of lipoprotein(a) [Lp(a)]]. The resulting “deadly lipid tetrad,” while common among Asian Indians, is uncommon among other populations on epidemiologic studies. Although Hispanics have a high prevalence of lipid triad, they have low Lp(a) levels. Conversely, blacks have higher levels of Lp(a), but low prevalence of lipid triad. Furthermore, the pathologic effects of elevated Lp(a) levels among blacks may be significantly mitigated by an otherwise antiatherogenic lipid profile consisting of high levels HDL, and low levels of triglycerides and LDL common among them.¹⁰

Several studies have reported high Lp(a) levels in Asian Indians in India, the United Kingdom, the United States, Canada, and Singapore.¹¹ Lp(a) levels > 30 mg/dl are found in 23 to 50% of Asian Indians.¹² In addition to being highly thrombogenic Lp(a) is ten times as atherogenic as LDL. Lp(a) levels are largely genetically determined.¹³ Since stable lifelong levels are reached in infancy, the pathologic processes associated with elevated Lp(a) start 10 to 20 years earlier than other risk factors. This results in marked prematurity and severity of CAD, two characteristic features of CAD in Asian Indians.¹⁴ More important, the CAD risk increases exponentially, by a factor of 100, when elevated levels of Lp(a) occur in combination with a high total/HDL ratio (> 5.8).¹⁵ The concomitant elevation of triglyceride levels may further increase the CAD risk exponentially.¹⁶ High triglycerides and high total/HDL chole-

terol ratio (due to low HDL) have been universal findings among Asian Indians.¹⁴ Thus, the high prevalence of the lipid tetrad rather than the smaller size of the coronary arteries appears to explain the malignant atherosclerosis in young Asian Indians. This distinction is of more than academic interest, since dyslipidemia is highly amenable to preventive and therapeutic interventions.¹¹ Such measures, rather than changes in the size of the coronary arteries, best explain the substantial decline in CAD among Asian Indians in many countries.

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References

1. Enas EA, Yusuf S, Mehta J: Prevalence of coronary artery disease in Asian Indians. *Am J Cardiol* 1992;70:945-949
2. Enas EA, Mehta J: Malignant coronary artery disease in young Asian Indians: Thoughts on pathogenesis, prevention and treatment. *Clin Cardiol* 1995;18:131-135
3. Enas EA, Garg A, Davidson M, Nair V, Huet B, Yusuf S: Coronary heart disease and its risk factors in first-generation immigrant Asian Indians to the United States of America. *Indian Heart J* 1996;48:343-353
4. Varghese PJ, Arumugan SB, Cherian KM, Walley V, Farb A, Virmani R: Atheromatous plaque reflects serum total cholesterol levels: A comparative morphologic study of endarterectomy coronary atherosclerotic plaques removed from patients from the southern part of India and Caucasians from Ottawa, Canada. *Clin Cardiol* 1998;21:335-340
5. Dhawan J, Bray C: Are Asian coronary arteries smaller than caucasian? A study of angiographic coronary artery size in estimation during life. *Int J Cardiol* 1995;49:267-269
6. Ambrose J, Fuster V: The risk of coronary occlusion is not proportional to the prior severity of coronary stenoses. *Heart* 1998;79:3-4
7. Barratt-Connor E, Cohn B, Wingard D, Edelstein S: Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *J Am Med Assoc* 1991;265:627-631
8. Klatsky AL, Tekawa I, Armstrong M, Sidney S: Asian Americans born in India and Pakistan are at high risk of coronary disease hospitalization. *Am J Pub Health* 1994;84:1672-1675
9. Enas EA, Dhawan J, Petkar S: Coronary artery disease in Asian Indians: Lessons learned so far and the role of Lp(a). *Indian Heart J* 1997;49:25-34
10. Enas EA: Cardiovascular disease in Asian Americans and Pacific Islanders. *Asian Am & Pac Islander J Health* 1996;1:163-175
11. Enas EA, Yusuf S, Sharma S: Coronary artery disease in South Asians: Second Meeting of the International Working Group, 16 March 1997, Anaheim, California. *Indian Heart J* 1998;50:105-113
12. Anand S, Enas EA, Pogue J, Haffner S, Pearson T, Yusuf S: High levels of lipoprotein(a) in South Asians in North America. *Metabolism* 1998;47:182-184
13. Enas EA: Risk of primary and recurrent acute myocardial infarction from lipoprotein(a). *J Am Coll Cardiol* 1997;29:887-889
14. Enas EA, Yusuf S, Mehta J: Meeting of the International Working Group on Coronary Artery Disease in South Asians. *Indian Heart J* 1996;48:727-732
15. Solymoss BC, Marcil M, Wesolowska E, Gilfix BM, Lesperance J, Lampeau L: Relation of coronary artery disease in women, 60 years of age, to the combined elevation of serum lipoprotein(a) and total cholesterol to HDL cholesterol ratio. *Am J Cardiol* 1993;72:1215-1219
16. Enas EA: Hypertriglyceridemia and elevated lipoprotein(a) are major risk factors for coronary events in middle-aged men. *Am J Cardiol* 1996;78:859-860

Authors' reply:

We are delighted to see that Dr. Enas has taken a great interest in our paper¹ and has written a long letter. In this letter, Dr. Enas brings up three areas of disagreement with our paper:

- (1) size of the coronary arteries in South Indians
- (2) the mechanism of prematurity of coronary artery disease (CAD) in South Indians
- (3) the role of lipids in the formation of atheromatous plaque.

In our anatomic study, we clearly show that coronary arteries of South Indians are smaller than those of Canadians. This was done by taking a series of sections from the site of endarterectomy. Sr. Enas challenges this observation by quoting an angiographic study that shows significantly smaller total vessel diameter in male Asian Indians compared with Caucasians (12.8 mm vs. 13.8 mm, $p = 0.01$) but becomes insignificant when corrected for body surface area. First of all, angiographic studies are notorious for their variability;² therefore, the standards of reference for vessel size are anatomic studies. Coronary artery size is dependent on heart size and not body surface alone³ and therefore should not be corrected for body surface area. For example, a hypertensive patient with a hypertrophied heart often has large vessels⁴ irrespective of the body surface area. Ischemic heart is often hypertrophied,⁵ and for that reason we did not use body surface area.

Since the vessel is small in size, a small plaque burden can cause a critical lesion in South Indians compared with the large vessels of Caucasians. This small plaque burden may occur early in the evolution of the disease. This explains the premature nature of the disease in South Indians. Dr. Enas refutes this hypothesis by pointing out that women have small vessels, yet they do not develop coronary artery disease prematurely. This argument is totally flawed because Dr. Enas ignores the protective effect of estrogen in the early years of a woman's life. Once women reach menopause, they catch up with men and even supercede them.⁶ We still feel that vessel size plays a major role in the premature CAD of South Indians.

Dr. Enas agrees with us that traditional risk factors, including high serum cholesterol, do not explain premature CAD in South Indians. Yet he continues to emphasize the role of lipid triad in the pathogenesis of CAD. The very reason we undertook this morphologic study of atherosclerotic plaque was to define the role of serum cholesterol in plaque formation. In our study, we clearly show that total serum cholesterol truly reflects the lipid content of the plaque; and the plaque of South Indians who have low serum total cholesterol has a significant amount of proteoglycan instead of necrotic core. Previous studies from our laboratory also show a good correlation of serum cholesterol and plaque morphology of men with CAD who died suddenly.⁷ If Dr. Enas is suggesting that Lp(a) is the etiology of the morphologic characteristics that we described in the plaques of South Indians, we do not have any evidence for that.

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