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Original Article

Quantitative angiography in South Asians reveals differences in vessel size and coronary artery disease severity compared to Caucasians

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Abstract: South Asians are one of the highest risk ethnic groups for development of coronary artery disease (CAD) mortality and morbidity. Previous studies have investigated whether South Asians exhibit differences in angiographic coronary artery disease compared to Caucasians, with inconsistent results. We conducted a retrospective observational study comparing South Asians undergoing cardiac catheterization at a tertiary care institution with Caucasians who underwent catheterization at the same time and location to assess whether South Asians demonstrated smaller coronary artery size and/or increased angiographic coronary artery disease. Demographic and laboratory data were retrospectively abstracted. Quantitative coronary angiographic analysis of all three coronary arteries was performed using the edge-detection method. South Asian patients were younger (57 versus 64 years, p=0.004) and showed higher prevalences of diabetes, dyslipidemia, and acute coronary syndrome compared with Caucasians (40% versus 16%, p=0.004; 65% versus 46%, p=0.04; and 37% versus 10%, p<0.001; respectively). South Asians exhibited smaller normalized proximal LAD luminal diameters (1.56 versus 1.72 mm/m^2, p=0.04) when compared to Caucasians. South Asians also displayed more severe CAD as determined by both increased mean percent stenosis in the proximal LAD and RCA segments (22.7% versus 11.1%, p=0.004; and 24.5% versus 13.9%, p=0.0001, respectively) as well as a higher number of patients with multiple diseased vessel segments. South Asians demonstrated more severe CAD compared to Caucasians undergoing cardiac catheterization as evidenced by smaller proximal LAD luminal diameters, higher mean percent stenosis per vessel, and more patients with multivessel disease. Further study is warranted to better define factors important in the development of CAD and inform risk stratification in this high-risk population.

Keywords: Coronary artery disease, South Asian, quantitative coronary angiography

Introduction

South Asians (also referred to as Asian Indians) originate from a large geographic area including India, Pakistan, Bangladesh, Nepal, and Sri Lanka. They comprise approximately one-fifth of the global population, and nearly 1% of the US population [1]. Epidemiologic studies of South Asian immigrants in developed countries have documented markedly increased rates of coronary artery disease (CAD) and CAD mortality compared to other ethnic groups [2,3]. South Asians residing in urban environments in the Indian subcontinent also display increased CAD prevalence [4,5]. In addition, South Asians also present earlier clinically with more diffuse and aggressive CAD compared to Caucasians [6].

Other ethnic groups have also shown increased rates of CAD and CAD mortality upon migration to developed regions. However, the increase in CAD risk observed in South Asians exceeds that of other migrant groups [1-4,7]. Although traditional CAD risk factors including increased age, diabetes, hypertension, smoking, dyslipidemia, and family history have been shown to be important in South Asians, current evidence suggests that these risk factors alone cannot ac-

count for the extent of CAD and CAD-related mortality observed in this population [2-4,8]. Furthermore, South Asians display a lower prevalence of traditional risk factors when compared to other ethnic groups, although the prevalences of dyslipidemia and diabetes among South Asians have been increasing over the past decade [8,9]. Moreover, South Asians display higher rates of post-infarct and post-CABG morbidity and mortality when compared to other ethnic groups [7,10,11].

Smaller coronary artery luminal diameter potentially reflects neointimal thickening, which has been recognized as an important early step in the development of complex atheromatous plaque [12]. Hence, the likely presence of neointimal thickening as reflected by small coronary artery luminal diameter may represent a manifestation of more severe atherosclerotic vascular disease, corresponding to the increased CAD morbidity and mortality observed in South Asians relative to other ethnic groups [13-16]. Among prior studies investigating this issue, there are considerable differences in approach and methodology, and phenotypic data remain sparse and inconsistent. We sought to compare a cohort of South Asians with Caucasians referred for cardiac catheterization at a major US medical center. We hypothesized that South Asian individuals would exhibit more severe coronary artery disease as measured by smaller coronary artery luminal diameters corrected for body surface area, mean percent stenosis, and number of segments involved compared to controls.

Materials and methods

We designed a retrospective observational study comparing South Asian patients who underwent cardiac catheterization at the Hospital of the University of Pennsylvania with Caucasians who underwent cardiac catheterization on the same dates as the South Asian patients. The primary outcome was coronary artery luminal diameter as determined by proximal reference vessel diameter measured using quantitative coronary angiography with normalization for body surface area. This took luminal diameters proximal to the minimal luminal diameter within each vessel segment in an attempt to exclude areas of focal stenosis. As a secondary outcome, we compared coronary artery disease severity between South Asian and Caucasian patients by measuring minimal luminal diameter within each vessel segment and then determining the mean percent stenosis in each vessel segment as well as the number vessel segments with obstructive disease among patients in both groups.

South Asian patients were identified via name recognition from a database of patients who had cardiac catheterization between January 1st, 2002 and May 31st, 2007 at two hospitals within our institution. Confirmation of patient race was obtained from cardiac catheterization reports and the medical record when possible (approximately 75% of cases). Patients identified as an ethnicity other than South Asian were excluded. Caucasian patients were chosen at random from a compilation of lists of patients who underwent cardiac catheterization on the same dates as the South Asian cases after exclusion of non-Caucasians using a random number generator (total n = 386 for Caucasians). We randomly selected one Caucasian per South Asian patients, as additional matching yields minimal increases in statistical power. Charts were retrospectively abstracted for demographic and laboratory data including total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels (mg/dl). Statin use was also extracted.

Quantitative coronary angiography (QCA) was performed on the original diagnostic angiograms via the edge-detection method using Medcon Quantitative Measurement QCA [15]. The coronary tree was divided into nine segments, and proximal reference diameters as well as minimal luminal diameters were recorded. In the case of the left circumflex coronary artery (LCx), the proximal and distal segments of the vessel with the largest luminal diameter in the LCx system was analyzed, whether this was the true LCx or a large proximal obtuse marginal branch. Entire angiograms from patients with prior coronary artery bypass grafting were excluded from QCA analysis, as were vessel segments in which stents were present. All images were calibrated to the lumen of a standard 6-French coronary angiography catheter after contrast filling. A single observer (R.K.H.) performed all analyses under the supervision of an experienced angiographer (R.L.W.). Intra-observer variability was assessed using the Spearman coefficient, with a value of 0.84 for left main segments, 0.77 for proximal left

Table 1. Study Group Characteristics

	South Asians (n=63)	Caucasians (n=61)	*P-value*
Demographics (mean +/- SD or %)			
Age	57 +/- 11	64 +/- 13	0.004
Male gender	76	73	0.91
Body mass index (kg/m^2)	26.1 +/- 5.8	29.2 +/- 5.7	0.004
Body surface area (m^2)	1.86 +/- 0.20	2.01 +/- 0.25	< 0.001
Hypertension	67	74	0.39
Diabetes mellitus	40	16	0.004
Dyslipidemia	65	46	0.04
Statin therapy	60	59	0.94
Smoking	27	38	0.20
Family history of CAD	46	20	0.002
Triple vessel disease	24	8	0.01
Lipid values, mg/dL (n)			
Total cholesterol	161 +/- 47 (33)	177 +/- 46 (41)	0.15
LDL-cholesterol	80 +/- 34 (29)	105 +/- 44 (35)	0.01
LDL-cholesterol on statin	75 +/- 28 (20)	101 +/- 32 (20)	0.008
HDL-cholesterol	48 +/- 12 (32)	53 +/- 20 (37)	0.21
Triglycerides	168 +/- 114 (33)	150 +/- 74 (43)	0.43
Indication for Catheterization (%)			
Positive stress test or preoperative	42	56	0.108
Angina	23	34	0.133
Acute coronary syndrome	35	10	< 0.001

anterior descending coronary artery (LAD) segments, 0.86 for mid LAD segments, 0.60 for distal LAD segments, 0.54 for proximal left circumflex coronary artery (LCx) segments, 0.92 for proximal right coronary artery (RCA) segments, 0.75 for mid RCA segments. While diameters were measured for other vessel segments, these measurements showed Spearman coefficient values < 0.50, and hence were excluded from all analyses. The presence of obstructive coronary artery disease in each segment was defined as a difference between the reference and minimal luminal diameters divided by the reference diameter equal to or > 0.50. Statistical analysis was performed using Stata 10.0 (College Station, Texas).

The sample size was determined by the number of identified South Asian cases for whom demographic, laboratory, and angiographic data were available. Data were summarized descriptively. Dichotomous variables were tested with Fisher's exact test and continuous variables were tested with a t test. Statistically significant variables in bivariate analysis were tested in multivariable models, and statistical significance was defined by p<0.05. This study was conducted in accordance with Declaration of Helsinki and was approved by Institutional Review Board of the University of Pennsylvania.

Results

Baseline patient characteristics are shown in **Table 1**. Patients in both groups were middle-aged, mostly male, and most were hypertensive. South Asian patients were younger (57 versus 64 years, p=0.004), and as expected, exhibited smaller body surface areas (1.86 versus 2.01 m^2, p<0.001) and lower body mass indices (26.1 versus 29.2 kg/m^2, p<0.001). Diabetes, dyslipidemia, and family history of CAD were more common in the South Asian group (40% versus 16%, p=0.004; 65% versus 46%, p=0.04; and 46% versus 20%, p=0.002; respectively). The prevalence of statin therapy was approximately equivalent between the two groups. LDL-cholesterol was significantly lower in the South Asian group, and this difference persisted with adjustment for statin therapy (80 versus 105 mg/dL, p=0.01, and 75 versus 101 mg/dL, p=0.008, respectively). The values for HDL-cholesterol, total cholesterol and triglycerides were not different between the two groups. Approximately three-fold more South Asians underwent cardiac catheterization for an

Table 2. Normalized coronary artery luminal diameters.

	South Asians	Caucasians	*P-value*
mm/m², mean +/- SD (n)			
Left Main	2.39 +/- 0.49 (60)	2.41 +/- 0.68 (59)	0.70
LAD			
proximal	1.56 +/- 0.45 (60)	1.72 +/- 0.44 (61)	0.04
mid	1.21 +/- 0.41 (61)	1.33 +/- 0.41 (61)	0.08
distal	0.71 +/- 0.26 (61)	0.83 +/- 0.26 (61)	0.01
LCx			
proximal	1.59+/- 0.40 (61)	1.53 +/- 0.50 (61)	0.46
RCA			
proximal	1.42 +/- 0.42 (61)	1.57 +/- 0.42 (59)	0.29
mid	1.32 +/- 0.40 (60)	1.34 +/- 0.40 (59)	0.75

Table 3. Coronary Artery Disease Severity

	South Asians	Caucasians	*P-value*
Mean % stenosis by segment, (95% CI)			
Left Main	4.93 (3.99 to 5.87)	4.10 (3.14 to 5.06)	0.22
LAD			
proximal	22.7 (15.8 to 29.6)	11.1 (7.50 to 14.6)	0.004
mid	24.6 (18.3 to 30.9)	19.9 (15.4 to 24.4)	0.23
distal	18.0 (14.3 to 21.6)	12.3 (9.74 to 14.8)	0.01
LCx			
proximal	16.6 (12.3 to 20.9)	15.1 (10.5 to 19.7)	0.63
RCA			
proximal	24.5 (20.2 to 28.8)	13.9 (11.2 to 16.6)	0.0001
Mid	16.4 (13.0 to 19.9)	16.8 (12.0 to 21.6)	0.

acute coronary syndrome compared to Caucasians in this study (37% versus 10%, p<0.001) and were found to have higher rate of triple-vessel disease (24% versus 8%, p<0.001). There was a significantly higher number of South Asian patients with a positive family history of CAD (46% versus 20%, p=0.002).

Complete angiographic data were not available for three South Asian subjects (5%) and two Caucasians (3%). As shown in **Table 2**, QCA analysis of reference vessel diameters demonstrated that South Asians had smaller proximal and distal left anterior descending (LAD) luminal diameters when compared with Caucasians even after normalization for body surface area (1.56 versus 1.72 mm/m², p=0.04, and 0.72 versus 0.82 mm/m², p=0.01). There were no significant differences in left main, mid LAD, left circumflex, or right coronary artery luminal diameters between the two groups. As displayed in **Table 3**, South Asians also exhibited greater CAD disease severity compared with Caucasians as measured higher mean percent stenosis in the proximal LAD (22.7% versus 11.1%, p=0.004), distal LAD (18.0% versus 1.3%, p=0.01), and proximal RCA (24.5% versus 13.9%, p=0.0001). South Asians also demonstrated greater disease severity as measured by the number of patients with multiple disease segments, as show in **Figure 1.**

Discussion

The findings of this study support the hypothesis that South Asians exhibit more severe CAD compared with Caucasian patients referred for cardiac catheterization at a tertiary care center. South Asians displayed smaller proximal LAD luminal diameters when normalized for body surface area, likely as a reflection of more significant atherosclerosis. South Asians also ex-

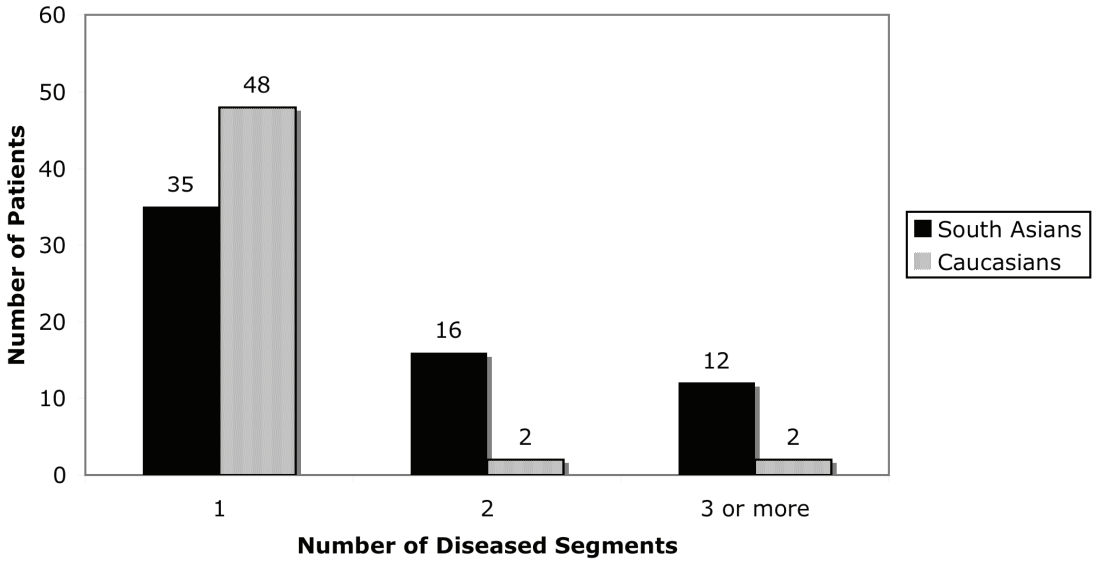

Figure 1. Coronary artery disease severity as determined by number of patients with multiple diseased vessel segments. Patients were divided into groups based on the number of vessels segments with obstructive disease, as shown on the x-axis, with the number of patients in each group displayed on the y-axis. While more Caucasian patients had single-segment disease, more South Asian patients had multiple diseased segments compared with Caucasians, as indicated by the higher number of South Asians in the groups with multiple diseased segments.

hibited more extensive CAD as measured by both increased mean percent stenosis and the number of patients with multiple diseased vessel segments when compared to Caucasians. This study corroborates the findings of a recently published study examining a smaller cohort of South Asians and Caucasians in prospective controlled fashion [15].

While the difference in proximal LAD luminal diameter between South Asians and Caucasians is most likely a manifestation of more diffuse and significant atherosclerosis, our method of QCA cannot distinguish whether this difference is actually indicative of intimal thickening versus genetically-determined anatomic size difference. However, given the observations that neointimal thickening represents an early stage in the development of complex atheromatous plaque, and epidemiological evidence suggesting that South Asians exhibit higher rates of CAD mortality and morbidity, it is more likely that the difference in normalized proximal luminal LAD diameters observed in this study is related to more advanced atherosclerosis that cannot detected solely by conventional angiography. Some prior studies of similar size and scope have suggested that there are no differences in coronary artery size between South Asians and Caucasians. These studies examined vessel segments free of significant disease and/or patients who were free of CAD or CAD risk factors such as diabetes and dyslipidemia, sometimes focusing on a single vessel segment or a few proximal vessel segments for each patient, and did not normalize coronary artery diameters to body surface area [13,17]. Our study sought to examine a real-world population presenting to the cardiac catheterization laboratory, where coronary luminal diameter would most likely reflect the presence and severity of CAD. Moreover, our study normalized coronary luminal diameters to body surface area and examined all major segments of the coronary tree that are relevant in a standard clinical angiogram. While there were statistically significant differences in distal LAD luminal diameters and mean percent stenosis in the distal LAD between South Asians and Caucasians, the intra-observer variability observed among distal vessel segment measurements in our QCA analyses hampers interpretation of these findings.

Prior studies have described an increased prevalence of diabetes, glucose intolerance, and the metabolic syndrome among South Asians as a possible explanation for their increased rates of CAD mortality and morbidity

[18-21]. Diabetes may well serve as a link between potential genetic predisposition and premature CAD in South Asians. Indeed, a positive family history of CAD was three times more common among the South Asian patients in this study. Moreover, South Asians in this study underwent catheterization for acute coronary syndromes more commonly than Caucasians. These findings were observed despite the fact that South Asians in this study had lower LDL-cholesterol levels compared to their Caucasian counterparts. Together, these findings lend support to the hypothesis that the observations of smaller proximal LAD luminal diameters and higher mean percent stenosis among South Asians compared with Caucasians in the present study could reflect more diffuse atherosclerosis in the South Asian group, but further studies are necessary to rigorously address this hypothesis. Given that South Asians often manifest with CAD at younger ages and exhibit event rates that are often underestimated by current risk prediction algorithms, aggressive risk stratification among South Asians with a family history of CAD may be warranted [1,8,21].

Several important limitations are evident in our study. While the retrospective observational study design is efficient and well suited for the study of rare events such as obstructive CAD among South Asian patients at our institution, we are unable to infer causality or relate the findings of coronary luminal diameter or CAD severity to clinical outcomes. The control group is not inherently homogenous with the exception of Caucasian race, and may therefore introduce unmeasured bias or confounding. The small sample size, retrospective design, and referral-based study population limit statistical power and introduce potential referral bias, a form of selection bias. The tertiary care setting limits generalizability of our findings to the general adult population. Name-based classification of South Asian origin is crude and prone to error, but has been demonstrated to be of use in accurately classifying South Asians living in developed Western nations [22]. Importantly, the difference in indications for catheterization between the two groups in this study may have confounded our results given that patients with acute coronary syndromes may have smaller coronary artery luminal diameters due to advanced atherosclerosis, and acute coronary syndromes were more common among South Asian individuals in our study. Statistical adjustment for indication would have reduced sample size in each group, thereby further limiting power. Future studies should specifically target larger samples to better define this relationship. The observation that South Asians more commonly underwent cardiac catheterization for acute coronary syndromes may also reflect limited access to preventative health care, which may have introduced further unmeasured confounding. The retrospective design precluded implementation of standardized laboratory studies and angiography protocols for all patients studied. Since patient conditions and angiography protocols were not predetermined, the QCA analysis may be prone to random error due to the use of vasodilators and the occurrence visual defects related to images in which the target vessel segments were situated at the angiogram periphery, although this would bias our results towards the null.

Despite these limitations, this study reaffirms prior investigations suggesting that South Asians have smaller coronary artery luminal diameters compared to Caucasians and reiterates a possible role of coronary artery size in affecting increased CAD risk and mortality among South Asians. This study supports the observation that South Asians exhibit more severe coronary artery disease at an earlier age when compared to Caucasians [9]. Overall, these findings underscore the need for further study of this high-risk population to better and inform ethnocentric risk stratification and disease prevention among South Asians.

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Conflicts of Interests

The authors have no relevant conflicts of interest to report.

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