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Gender differences in the prevalence of coronary artery tortuosity and its association with coronary artery disease

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ABSTRACT

Background: Little is known about the significance of severe coronary tortuosity (SCT) despite it being a relatively common finding on coronary angiography. We examined whether the presence of tortuosity was influenced by gender or cardiac risk factors.

Methods and results: We examined 870 patients (Men = 589, Women = 281) who presented to Westmead Hospital, Sydney, Australia for invasive coronary angiography for the assessment of chest pain due to suspected CAD. Female gender and age were significantly associated with SCT ($p < 0.001$ for age) with 45.2% of women having SCT as opposed to 19.7% of men ($p < 0.001$). Men with SCT had lower Extent scores only compared than those without tortuosity (22.4 vs. 32.4, $p = 0.003$). However, women with SCT had less severe coronary artery disease than those with no SCT as measured by both the Extent score (12.4 vs. 19.1, $p = 0.03$) and Gensini score (10.4 vs. 15.5, $p = 0.02$).

Conclusion: There is a significant relationship between coronary artery tortuosity and gender. Women with severe tortuosity are more likely to have normal coronary arteries or less severe disease than men despite presenting with chest pain.

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1. Introduction

Tortuosity of the coronary arteries is not an uncommon finding on coronary angiography however it is seldom reported by cardiologists. Whether tortuosity plays a role in angina is not known despite some evidence that people with severe coronary tortuosity (SCT) and normal coronary arteries display myocardial perfusion defects [1]. Aging and hypertension are thought to be known risk factors for the development of tortuosity in coronary, femoral, cerebral and carotid arteries [2,3]. Tortuosity may not be a benign entity. Traditional reporting of angiograms using stenosis severity is the predominant method of evaluating suspected ischemic chest pain with functional imaging used in intermediate or uncertain cases. This may lead to a lack of representation of mechanisms other than obstructive epicardial disease in the development of ischemic chest pain syndromes.

There is a paucity of literature on the clinical significance of coronary tortuosity and the association of gender and cardiac risk factors on its development. We conducted this study to further evaluate the relationship between coronary artery tortuosity in patients presenting for coronary angiography for the investigation of chest pain.

2. Methods

2.1. Study population

1680 participants were recruited for the AHES from January 2010 and January 2012. These were people who presented to Westmead Hospital, Sydney, Australia for invasive coronary angiography for the assessment of chest pain due to suspected CAD. Patients were referred for investigation by a cardiologist for outpatient or inpatient investigation. The decision to pursue angiography was made by the referrer who was not involved in the subsequent recruitment of the patients to the study. Participants were consented to the study prior to or following invasive coronary angiography. Exclusion criteria were presentation with acute myocardial infarction, unstable angina, cardiogenic shock. Of the 1680 examined in the AHES study, 870 patients (Men = 589, Women = 281) were included in this analysis. 489 participants were excluded because they had a previous history of coronary artery bypass

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grafting (n = 191) and/or previous coronary artery stent (n = 298). A further 321 were excluded if the tortuosity could not be assessed in all three vessels.

Patients were interviewed to obtain demographic characteristics, medical history and behavioral habits. Both interview and review of medical record were used to determine the presence of risk factors and to obtain medication use and confirm medical history. The study was approved by the Westmead Hospital (Sydney West Local Health Network) ethics committee, and was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent.

2.2. Evaluation of coronary artery disease

Diagnostic coronary angiography was performed via a femoral or radial approach. The technique employed was determined by vascular accessibility of the patient and operator preference. Selective coronary injections were performed after intracoronary nitroglycerin and filmed in standard projections with a Siemens Bi-Plane radiographic unit (Siemens Healthcare, Germany). All angiograms were filmed at 15 frames/s. Cine runs were stored at the time of acquisition in DICOM format.

Angiograms were analyzed offline by a cardiologist (author J.C.) blinded to the medical history and adjunctive investigations. Two orthogonal views were examined in end-diastole to maximize contrast enhancement and vessel diameter. The image with the most severe stenosis was used for each evaluated segment of the coronary arteries. To allow more accurate assessment and classification of lesion severity [4] each lesion that was visually scored as greater than 50% luminal obstruction in a vessel that was ≥1.5 mm diameter was further analyzed by quantitative coronary analysis (QCA) using validated computerized edge-detection software (QCAPLUS, Sanders data Systems, Palo Alto, California, USA). Coronary angiograms were analyzed systematically for:

1) *Vessel score*: A Vessel score was calculated based on the number of vessels with significant obstructive coronary disease. The American College of Cardiology (ACC) taskforce definition from 2011 uses 50% stenosis to define significant vessel disease [5]. This definition was used for the left main coronary artery, right coronary, left anterior descending and left circumflex arteries. Scores ranged from 0 to 4, depending on the number of vessels with greater than 50% stenosis [6]. Left main artery stenosis was scored as double vessel disease.
2) *Gensini score:* This was calculated using the results of the QCA analysis and visual estimation of stenosis severity [7]. This score divides the three coronary arteries into several sub-segments. The percent diameter stenosis is scored from zero to 32 depending on the severity of the stenosis: Zero if normal, 1 for 1–25%, 2 for 25–50%, 4 for 50–75%, 8 for 75–90%, 16 for 99% and 32 for total occlusion. Each segment is given a multiplying factor (from 0.5 for the distal segment to 5 for the left main coronary artery) depending on the significance of the myocardial area supplied by that segment. The sum of the scores gives the Gensini score, which provides an indication of the severity of coronary artery disease stenoses and has been used as a tool to assess the relationship between coronary and other vascular disease [7–10].
3) *Extent score:* this score indicates the percentage of the coronary arterial tree involved by angiographically detectable coronary atheroma independent of the stenosis severity [11]. Luminal irregularity as identified on angiography represents coronary atherosclerosis. The proportion of the vessel with irregularity is multiplied by a factor for each vessel representing the length of the artery. The scores are: left main artery, 5; left anterior descending artery, 20; main diagonal branch (or branches), 10; first septal perforator, 5; left circumflex artery, 20; obtuse marginal artery and posterolateral branch each, 10; right coronary artery, 20; and main posterior descending branch, 10. When the major lateral wall branch was a large obtuse marginal or intermediate vessel with no posterolateral branches, these were given a factor of 20, and the left circumflex artery a factor of 10. The scores for each vessel were added to give a total score out of 100, that is the percentage of the coronary intimal surface area containing coronary atheroma. When a vessel was occluded and the distal vessel was incompletely visualized by coronary collateral flow, the proportion of the vessel not visualized was given the mean score of the remaining arteries.
4) Tortuosity: was identified by the presence of ≥3 bends (defined as ≥45° change in vessel direction) along the main trunk of at least one coronary artery (LAD, LCX, RCA) present in both systole and diastole as previously described [12,13]. We defined severe coronary tortuosity (SCT) as the presence of at least one vessel with tortuosity consistent with our definition.

3. Statistical analysis

Data were analyzed using SAS 9.2 (Statistical Analysis Package, SAS Institute, 2011, North Carolina, USA). All categorical data were reported as percentages and continuous variable expressed as mean ± standard deviation (SD). Student's *t*-test was used for the comparison of demographic data that were continuous variables and chi-squared analysis for categorical variables. Relationships between SCT, gender, age, cardiovascular risk factors (hypertension, diabetes, smoking and hyperlipidemia) and the three coronary artery scores were assessed using Pearson correlations using binary variables for the analysis of risk factors. The odds ratio for tortuosity by gender was examined using logistic regression with men being the reference. A general linear model adjusting for age was used to test the difference in Extent and Gensini scores for men and women with SCT and no SCT. Statistical significance was considered present when $p < 0.05$.

4. Results

4.1. Patient characteristics

The study cohort was predominantly male (67%) with an average age of 59.3 years. Men were of significantly younger age than women (Table 1). There were no significant differences in the presence of traditional cardiac risk factors except for a higher proportion of women having hypertension (75.5 vs. 66.4%, $p = 0.02$) and more men having a history of smoking (73.1% vs. 41.9%, $p < 0.001$). As expected, women were shorter and had a lower body weight ($p < 0.001$). A larger proportion of women had SCT compared to men (45.2% vs. 19.7%, $p < 0.001$). The Gensini, Extent and Vessel scores were substantially higher for the cohort of men compared to women ($p < 0.001$ for all scores).

4.2. Gender comparison of arteries affected by severe coronary tortuosity

The arterial distribution of SCT by gender is shown in Table 2. The LAD was the single artery most affected by SCT. A large number of people had severe tortuosity in both the LAD and LCx. More women had all three vessels affected (19.7% vs. 6.0%), whereas men predominantly had a single vessel affected (63.2% vs. 48%).

Table 3 shows that women were significantly more likely to have tortuosity in any major epicardial coronary artery compared to men. The odds ratio for a woman to have any vessel affected by SCT, compared to a man, was 2.71 ($p < 0.001$).

4.3. Prevalence of risk factors in the cohort with severe coronary tortuosity

Table 4 shows the prevalence of risk factors in the study population comparing those with severe coronary tortuosity to those without it. The overall prevalence of SCT was 28% (244/870). Women contributed

Table 1
Demographic and clinical characteristics of participants stratified by gender.

Characteristics	Women (n = 281)	Men (n = 589)	p-Value
Sex (%)	32.3	67.7	<0.001
Age, yrs	63.4 (10.7)	59.3 (11.7)	<0.001
Body height, m	1.59 (0.07)	1.72 (0.08)	<0.001
Body weight, kg	76.1 (16.4)	87.7 (19.8)	<0.001
BMI, kg/m^2	30.2 (6.4)	29.6 (6.0)	0.16
Waist:height ratio	61.7 (9.1)	58.9 (8.1)	<0.001
Blood pressure (mm Hg)			
Systolic	127 (21)	129 (19)	0.08
Diastolic	73 (13)	75 (13)	0.03
Mean arterial	91 (13)	93 (13)	0.02
Ever smoked (%)	41.9	73.1	<0.001
History of hyperlipidemia (%)	87.3	82.2	0.11
History of hypertension (%)	75.5	66.4	0.002
History of diabetes (%)	34.9	28.6	0.06
Current medications (%)			
Aspirin	36.3	39.3	0.41
Clopidogrel/Prasugrel/Ticagrelor	15	13.4	0.30
Nitrate	13.2	7.1	0.004
Beta-blocker	24.2	20.5	0.22
Calcium Channel Blocker	21.7	14.6	0.009
ACE-inhibitor	21	19.4	0.57
Angiotensin II Receptor antagonist	30.6	20	0.001
Alpha-blocker	2.5	2.8	0.85
Statin	56.6	41.4	<0.001
Presence of SCT	45.2	19.7	<0.001
Extent score	16.1 (13.1, 19.2)	30.5 (27.7, 33.2)	<0.001
Gensini score	13.4 (11.2, 15.6)	24.7 (22.5, 26.9)	<0.001
Vessel score	0.82 (0.65, 1.00)	1.72 (1.5, 1.9)	<0.001

Data are presented as mean (±SD) or as % of total cohort. Extent, Gensini and Vessel scores are presented as mean (LCL, UCL).
SD, standard deviation; LCL, lower confidence limits; UCL, upper confidence limit; SCT, severe coronary tortuosity.
p-Values <0.05 are significant.

the highest proportion of persons in the group with SCT (52% vs. 24.6%, $p < 0.001$). Age greater than 65 years old was positively related to the presence of SCT ($p < 0.001$). Of particular note is the prevalence of hypertension was not statistically significant between the two groups. The average Extent score was 18.8 for the SCT group and 28.5 for the no SCT group ($p < 0.001$). For the Gensini score the SCT cohort average was 16.8 compared to 22.6 for the no SCT cohort ($p = 0.001$). More people had a Vessel score of 0 in the SCT group (52.4% vs. 44.7%, $p = 0.04$). Table 5 compares the Extent and Gensini scores for women and men for the SCT and no SCT subgroups. Both scores are lower for women than men and those with SCT have significantly lower Extent and Gensini scores.

Table 2
Gender comparison of arteries affected by severe coronary tortuosity.

Artery	All patients with SCT (n = 244)	Men (n = 117)	Women (n = 127)
LAD	85 (34.8)	36 (30.7)	49 (38.6)
LCx	20 (8.2)	14 (12.0)	6 (4.7)
RCA	30 (12.3)	24 (20.5)	6 (4.7)
LAD and LCx	55 (22.5)	22 (18.8)	33(26.0)
LCx and RCA	18 (7.4)	12 (10.3)	6 (4.7)
LAD and RCA	4 (1.6)	2 (1.7)	2 (1.6)
Three vessels	32 (13.1)	7 (6.0)	25 (19.7)

Values presented as n (%).
SCT, severe coronary tortuosity; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery.

4.4. Correlation of risk factors and scoring systems with severe coronary tortuosity

There was a positive association between age and the risk of SCT as shown in Table 6 ($r = 0.19$, $p < 0.001$ for any vessel having SCT). There was a negative correlation between SCT and being male, a relationship seen in all arteries ($r = -0.30$, $p < 0.001$). Hypertension and diabetes were not correlated and there was a weak association with smoking (previous or current) only for the LAD and LCx. There was a small, but significant negative relationship between SCT and the Extent score ($r = -0.14$, $p < 0.001$), Gensini score ($r = -0.10$, $p = 0.01$) and

Table 3
Odds ratio of having a vessel with severe coronary tortuosity.

Gender	Any vessel		LAD		LCx		RCA	
	n (%)	OR (CI)	n (%)	OR (CI)	n (%)	OR (CI)	n (%)	OR (CI)
Women (n = 281)	127 (45.2)	2.71 (1.87–3.91)	66 (23.5)	2.59 (1.59–4.20)	113 (40.2)	3.99 (2.67–5.98)	39 (13.9)	1.40 (0.80–2.44)
Men (n = 589)	117 (19.8)	Ref.	45 (7.6)	Ref.	77 (13.1)	Ref.	45 (7.6)	Ref.
p-Value		<0.001		<0.001		<0.001		0.004

Odds ratio for women having coronary tortuosity with men as a reference.
Tortuosity outcome for all 3 arteries was adjusted for age and body mass index.
p-Values were calculated by chi-square; significance at $p < 0.05$.
OR, odds ratio; CI, confidence interval, LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; Ref, reference.

Table 4
Prevalence of risk factors in people with tortuous vs. non-tortuous arteries.

Factor	SCT group (n = 244)	No SCT group (n = 626)	p-Value
Hypertension	174 (71.3)	419 (66.9)	0.22
Lipids	131 (53.7)	373 (59.6)	0.69
Age > 65	108 (44.3)	197 (31.5)	<0.001
Smoking	49 (20.1)	162 (25.9)	0.07
Diabetes	65 (26.6)	201 (32.1)	0.11
Female Gender	127 (52.0)	154 (24.6)	<0.001
Vessel score 1–3	109 (44.7)	328 (52.4)	0.04
Gensini score	16.8 (14.0, 19.6)	22.6 (20.6, 24.7)	0.001
Extent score	18.8 (15.4, 22.2)	28.5 (25.8, 31.2)	<0.001

Frequencies presented as n (% of each group).
Extent and Gensini score expressed as mean (LCL,UCL).
SCT, severe coronary tortuosity; LCL, lower confidence limit; UCL, upper confidence limit.
p-Value significant at $p < 0.05$.

Table 5
Gensini and Extent score for tortuous vs. non-tortuous groups by sex.

Score	SCT group		No SCT group	
	Women	Men	Women	Men
Gensini score	10.4 (1.6)[a]	21.1 (2.5)[b]	15.5 (1.5)[a]	25.4 (1.2)[b]
Extent score	12.4 (2.3)[c]	22.4 (3.0)[d]	19.1 (2.1)[c]	32.4 (1.5)[d]

General linear model corrected for age to compare significance in the Extent and Gensini scores between the SCT and no SCT groups by sex. Extent and Gensini score expressed as mean (SD).
p-Values for SCT vs. no SCT: a = 0.02, b = 0.12, c = 0.03, d = 0.003.
p-Value significant at $p < 0.05$.
SCT, severe coronary tortuosity; SD, standard deviation.

Vessel score ($r = -0.10$, $p = 0.003$). The RCA was less associated than the LAD and LCx for all the factors examined.

5. Discussion

In a large cohort of people with suspected ischemic chest pain referred for coronary angiography, we report a statistically higher proportion of women displaying severe coronary tortuosity with less coronary artery disease. This is the first study to our knowledge to have examined differences in coronary tortuosity in men and women and explored the concomitant severity of coronary artery disease using three different scoring systems.

Coronary tortuosity is a relatively frequent entity encountered in coronary angiography. Its significance has not been investigated in many large trials and as a result there is little known about the overall effect of severe coronary tortuosity on the risk of developing ischemic chest pain and coronary artery disease. Our study adds to the prior literature by showing that women have more SCT in the absence of significant coronary artery disease and that risk factors other than age are not associated with the presence of tortuosity.

Women with suspected ischemic chest pain undergoing invasive coronary angiography have less extensive epicardial atheroma. Women display a greater symptom burden and higher rate of functional disability compared to men, but present with a lower prevalence of obstructive epicardial stenoses and more diffuse atherosclerosis and microvascular dysfunction [14]. Further, despite the lower prevalence of obstructive disease, women can display evidence of ischemia on functional assessments such as pressure wire studies, myocardial perfusion imaging and magnetic resonance imaging [15,16]. These findings suggest that chest pain is likely to have a different pathophysiological mechanism in women compared to men and that traditional risk factors and standard diagnostic techniques may play an alternative role.

Similar to a previous study [17], we found that in conjunction with female gender, aging was a major predictor of coronary tortuosity. Other traditional risk factors are thought not to influence the development of SCT [17]. This finding was also supported by our study. It was reported some decades ago that the incidence of tortuosity increased as the heart size and mass decreased [2]. This is of interest as it is also thought women in general, have smaller hearts than men [18].

Our study shows that women are more likely to have SCT in the presence of less severe epicardial coronary disease, a finding reported in a small study by Davutoglu et al. [19] Extent, Gensini and Vessel scores were lower than those with SCT a finding supported by Li et al. [20] which showed that SCT had a negative correlation with coronary atherosclerosis. This contrasts to studies by Smedby and Bergstrand [21] and Wood et al. [22] who found that in femoral arteries, tortuosity is more often coinciding with atherosclerotic disease. This is could be due to the coronary vessels being smaller and influenced by the myocardial structure and dynamics. It was shown by Turgut et al. [13] that impaired left ventricular relaxation might increase coronary tortuosity. Further, SCT is more prominent in people with chronic pressure overload and is less when there is volume overload [23]. This supports the hypothesis that tortuosity is the consequence of underlying myocardial alterations, however the exact nature of these remains indiscernible.

Gaibazzi et al. [1] studied patients with non-obstructive epicardial disease and found those with reversible myocardial perfusion defects on contrast stress echocardiography had more SCT. This finding gives some evidence for tortuosity precipitating myocardial ischemia.

The pathophysiology of ischemic chest pain due to coronary artery tortuosity has been rarely studied. However, it is hypothesized that SCT leads to a reduction in filling pressures in the distal vessel and hence microcirculation. This is thought to be due to the significant hemodynamic shearing forces that form in tortuous arteries [24,25]. A quantitative study by Li et al. [26] found that the reduction in coronary perfusion pressure was dependent upon the severity of coronary tortuosity. This relationship was studied previously in the carotid artery as well as in fluid model studies [27,28].

Table 6
Pearson correlations for severe coronary tortuosity.

Variable	LAD		LCX		RCA		Any vessel	
	r	p	r	p	r	p	r	p
Sex (male)	−0.22	<0.001	−0.31	<0.001	−0.10	0.00	−0.30	<0.001
Age	0.12	<0.001	0.20	<0.001	0.11	0.00	0.19	<0.001
History of hypertension	0.03	0.42	0.02	0.49	0.07	0.0361	0.04	0.22
Diabetes	−0.05	0.12	−0.04	0.20	0.01	0.7487	−0.60	0.07
Smoker (previous or current)	−0.08	0.01	−0.13	<0.001	0.04	0.1986	−0.12	<0.001
Extent score	−0.14	<0.001	−0.12	0.001	−0.08	0.0242	−0.14	<0.001
Gensini score	−0.11	<0.001	−0.08	0.01	−0.08	0.0253	−0.10	0.005
Vessel score	−0.10	0.002	−0.10	0.003	−0.06	0.0959	−0.10	0.003

p-Values significant at $p < 0.05$.
LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery.

Coronary tortuosity is seen frequently on coronary angiography in patients with chest pain however is not traditionally reported as it unclear whether there is a functional significance of this finding. The importance of SCT remains elusive and warrants further investigation. It is conceivable that impaired coronary filling results in reduced pressures in the distal coronary vasculature leading to ischemia. The finding of SCT on angiography may predict an increased risk of cardiovascular disease as tortuosity may be the result of structural and functional alterations of the heart that have occurred as an adaptive mechanism to a yet unknown stimulus.

In our study of patients with chest pain undergoing coronary angiography, we demonstrate a potential association of severe coronary tortuosity and chest pain syndromes. This is of particular interest for women who despite having less obstructive coronary artery disease have a higher burden of recurrent chest pain. The etiology of these chest pain syndromes remains of great interest. It is possible that severe coronary tortuosity causes myocardial perfusion abnormalities and is not a benign finding on coronary angiography. The association of tortuosity with ischemia warrants further investigation with prospective studies utilizing functional assessments such as pressure wire studies, coronary flow reserve, myocardial perfusion imaging and myocardial resonance studies. It would also be of value to examine the long-term effect of tortuosity on the incidence of myocardial infarction, progression of chest pain and whether it may be used as marker for future cardiac events.

6. Limitations

Our study represents a group of patients from a single center with a broad demographic, all of who were symptomatic and being investigated and medically treated for suspected ischemia. This limits the generalizability of our results to similar care settings and the general population. There is no standardized definition for coronary artery tortuosity in the literature and as such, the diagnosis of SCT remains variable and comparison of various studies is challenging. We were unable to correlate the findings in our study with functional assessments that would have provided substantial information on the theories presented. Tortuous coronary arteries were not further evaluated with IVUS or multidetector computed tomography, which may provide insight as to whether arterial remodeling was present in the arterial segment showing tortuosity by angiography. Hence, the outcomes and conclusions are subject to the constraints inherent in these types of analyses. Further, the study did not examine long-term outcomes.

Disclosures, conflicting or competing interests

The Authors declare that there is no conflict of interest.

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