The Egyptian Heart Journal 70 (2018) 381–387

Contents lists available at ScienceDirect

The Egyptian Heart Journal

journal homepage: www.elsevier.com/locate/ehj

Original Article

Validity of tortuosity severity index in chest pain patients with abnormal exercise test and normal coronary angiography ☆

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ARTICLE INFO

Article history:
Received 24 February 2018
Accepted 14 July 2018
Available online 26 July 2018

Keywords:
Chest pain
Coronary tortuosity
Normal coronary angiography

ABSTRACT

Background: Coronary tortuosity (CT) had different definitions and scores in literature with unclear pathophysiological impact.
Objectives: To study degree of CT and it's relation to ischemic changes in patients with angina but normal coronary angiography (CA).
Methods: We conducted a prospective study at University hospitals between May 2016 and January 2017. We included 200 consecutive patients who underwent CA due to chest pain assumed to be of cardiac origin, and their CA was normal (no diameter stenosis >30%, nor myocardial bridging). Patients were prospectively divided into 2 groups based on the presence (n = 113) or absence (n = 87) of ischemic changes during stress study and compared for clinical, echocardiographic and CA characteristics. A newly proposed Tortuosity Severity Index (TSI) was developed into significant (mild/moderate CT with more than 4 curvatures in total, or severe/extreme CT with any number of curvatures) or not significant TSI (mild CT with curvatures less than or equal to 4 curvatures in total).
Results: Patients with ischemic changes had the highest rate of CT (76.5 vs 18%, p = 0.004) compared to those without. CT mostly affects the left anterior descending (LAD) coronary artery in mid and distal segments. Females, elderly, and hypertensives with left ventricular hypertrophy were strongly related to CT. Multivariate logistic regression analysis identified CT with significant TSI as the only predictor of ischemic changes in these patients (OR = 6.2, CI = 2.5–15.3, P = <0.001).
Conclusions: Coronary tortuosity is a strong predictor of anginal pain among patients with normal CA, despite positive stress study. This finding is more pronounced among elderly, hypertensive female patients.

1. Introduction

Coronary arteries are relatively straight blood vessels running on the surface of the pericardium that supply the heart muscle with blood[1]. Various forms of Coronary tortuosity (CT) have been described in clinical investigations, most commonly twisting, looping, curving/curling, angulation and kinking vessels[1–3]. These abnormal geometries may lead to flow alterations that can cause reduced blood supply to the heart tissues and lead to ischemia[4]. Although cardiologists often encounter CT, it's mechanism and impact is not well studied. CT had been correlated with clinical conditions as coronary artery disease[1], diabetes[4], hypertension[3], and age[5]. However, even when no other diseases or abnormalities are present, tortuosity can cause various dysfunctions. For patients with normal or near-normal coronary angiograms, the prevalence of severely tortuous coronary arteries was reported to be seven times higher in patients who demonstrated reversible perfusion defects compared to those without it[4]. Different definitions and scores were used to describe CT [3,4,6], in this study we developed a simple tortuosity severity index (TSI) in an attempt to standardize CT analysis. This study hypothesizes that patients with anginal chest pain syndrome who demonstrate reversible ischemic changes on stress study but had angiographically normal coronary arteries would demonstrate a higher prevalence of significant CT compared to patients without ischemic changes.

☆ All authors listed takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
Peer review under responsibility of Egyptian Society of Cardiology.
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https://doi.org/10.1016/j.ehj.2018.07.002
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2. Patients and Methods

2.1. Study design and patient's selection

This is a single center prospective cross-sectional study. We evaluated adult patients who were electively referred to the cardiac catheterization laboratory for coronary angiography because of a clinical suspicion of coronary ischemia based on the presence of typical angina and who demonstrated ischemic changes on stress testing. To be included in the study, Coronary arteries should be normal or near normal. Typical angina was defined as having 3 characteristics: substernal chest discomfort, was provoked by exertion or emotional stress, and was relieved by rest or nitroglycerin. Atypical angina was defined as meeting 2 of the above characteristics. Exclusion criteria included the presence of obstructive coronary disease (≥50% diameter stenosis) and to avoid any conflict we even excluded any patient with any diameter stenosis >30%, history of acute coronary syndrome, prior percutaneous coronary intervention or coronary artery bypass grafting, coronary ectasia, spasm, fistula or myocardial bridging, peripheral arterial disease, renal insufficiency (creatinine > 1.5 mg/dL), abnormal ejection fraction (<55%), or presence of another likely explanation of angina such as pulmonary hypertension, hypertrophic cardiomyopathy, myocarditis, or valvular heart disease. Patients fasted overnight, and peripheral blood samples were obtained for fasting lipids. The study was approved by the Assiut University institutional review board and complies with the Declaration of Helsinki. A written informed consent was obtained from all patients. Among 684 patients with chest pain syndrome presenting between May 2016 and January 2017, and scheduled for coronary angiography; 153 refused their inclusion and 331 revealed to have significant coronary artery disease (this is an exclusion criterion for this part of our study and will be discussed in details in another report); the remaining 200 patients were eligible for inclusion and comprised the final study group (Fig. 1).

2.2. Study groups

Patients were prospectively categorized into 2 groups based on the presence or absence of ischemic changes during stress study and compared for baseline clinical, electrocardiographic and echocardiographic characteristics.

2.2.1. Stress electrocardiography (ECG)

Was offered to all patients enrolled in the study 1 week before angiography. Stress study was done by Mortara XScribe device using Mortara VERITAS™ algorithm for 12-lead stress ECG interpretation (Milwaukee, Wisconsin, USA) using well-established institutional protocols[7,8]. 155 patients completed the study successfully to identify significant ECG changes in the form of depressed ST segment or T wave changes in relation to chest pain.

2.2.2. Two-dimensional echocardiography (ECHO)

Detailed ECHO assessment including segmental wall motion assessment, left ventricular (LV) mass, LV mass index and ejection fraction was calculated[9]. **Stress ECHO** was used in 45 cases when stress ECG cannot be performed effectively. It was performed using high dose dobutamine in accordance with well-established institutional protocols[10]. Reversible wall motion abnormalities, on stress ECHO were documented by an independent operator.

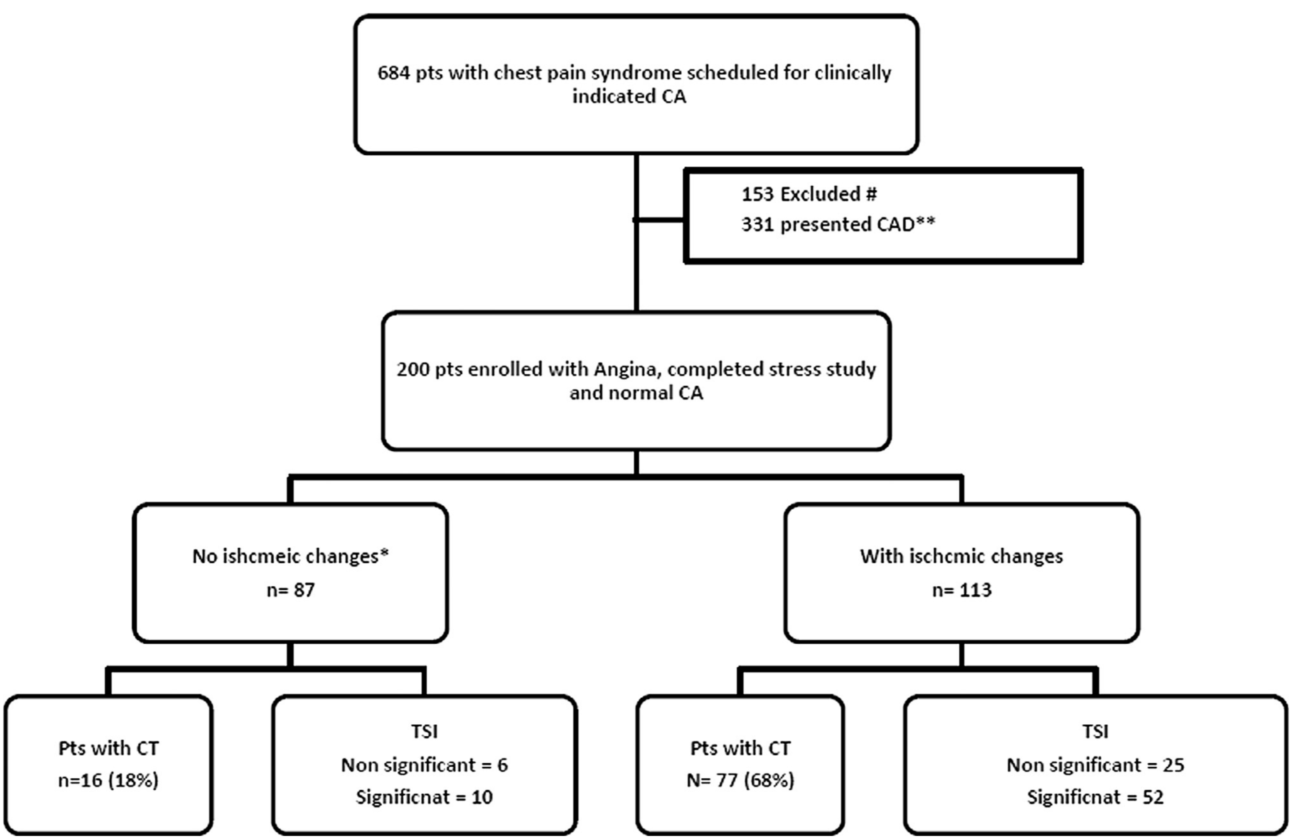

Fig. 1. Flow chart of the study. *Ischemic changes = dynamic ECG changes in ST/T waves related to chest pain on stress ECG or reversible wall motion abnormalities on stress ECHO; **exclusion criteria for this part of our study and will be discussed in details in another report; # excluded patients was based on the exclusion criteria presented previously. CA = coronary angiography; CAD = coronary artery disease; CT = coronary tortuosity; TSI = tortuosity severity index; pts = patients.

2.2.3. Coronary angiography (CA)

All patients underwent CA within 1 week after stress study. Standard femoral approach was used. Angiograms were evaluated for the presence of significant stenosis in major epicardial coronary arteries and their branches (vessel diameter more than 2.5 mm) by an experienced cardiologist blinded to the stress study results. Off-line maximum percent lumen decrease was determined for any visually evident stenosis using standard quantitative coronary angiographic software (Medis Medical Imaging systems, Leiden, the Netherlands)[11]. All patients to be included in the study their CA should be normal or near normal (less than 30% coronary artery stenosis at quantitative CA). Myocardial bridge of any grade and coronary ectasia were an exclusion criterion. The coronary arteries segmentation by SYNTAX score was used to analyze the distribution of CT[12,13].

2.2.4. Coronary tortuosity (CT) diagnosis and analysis

CT was identified by the presence of $\geq$3 curvatures >45° change in vessel direction along main trunk of $\geq$1 artery, present both in systole and diastole, in vessels only >2.5 mm in diameter. Each coronary artery was examined for the presence or absence of tortuosity, its location according to SYNTAX segmentation, number of curvatures and degree of the angle of deviation from an arbitrary straight vessel line according to the following grading: **Mild tortuosity** (means the degree of the angle of deviation is range from 45 up to less than 90°); **Moderate tortuosity** (range from 90 up to less than 180°); **Severe tortuosity** (more than 180°) and **Extreme tortuosity (or coronary loop**; defined as the presence of a full 360° loop in the contour of the vessel around an arbitrary line passing between the beginnings of the tortuosity till its end) (Fig. 2). All patients' angiograms were assessed off-line by two experienced interventionists (A.H. and A.Y.) blinded to the enrollment group. CT was detected using a standardized predefined protocol with fixed view angles for each artery. The inter-observer agreement was calculated with weighted Kappa statistics and showed good agreement (k = 0.96, P = 0.001).

2.2.4.1. Coronary angulations. Main concern during CT detection was, if it is truly a tortuosity or only a 2D angulation? So at least 2 views for each artery were used to confirm the number and degree of curvatures. Left anterior descending coronary artery (LAD) was assessed in antero-posterior and left anterior oblique views with cranial angulations, the left circumflex coronary artery (LCX) in right and left anterior oblique with caudal angulations, while the right coronary artery (RCA) in left and right anterior oblique views (Fig. 2).

2.2.4.2. Tortuosity Severity Index (TSI). This index was developed at Assuit university hospital by consensus among experts in interventional cardiology. TSI was calculated, for each coronary artery, as a sum of scores including 2 components (a) the number of curvatures in each vessel, and (b) the degree of angle of deviation; from a virtual straight line along the main vessel course; either mild, moderate, severe or extreme tortuosity. The TSI was assigned either: **significant TSI** (defined as mild/moderate CT with more than 4 curvatures in total, or sever/extreme CT with any number of curvatures even one) or **non-significant TSI** (mild/moderate CT with curvatures less than or equal to 4 curvatures in total) (Fig. 3).

3. Statistical analysis

Categorical variables were presented as counts and proportions (percentages) and compared by Pearson chisquare analysis or Fisher exact test. Normal distribution of continuous data was tested using a Kolmogorov-Smirnov test. Continuous and normally distributed data are presented as mean ± SD and were compared by unpaired *t*-test. Not-normally distributed data are expressed as median with interquartile range (IQR), and the Mann-Whitney *U* test was used to compare differences between two groups. The inter-observer agreement was calculated with weighted Kappa statistics. Correlations were done by Spearman correlation coefficient test. Univariate and Multivariate logistic regression analyses

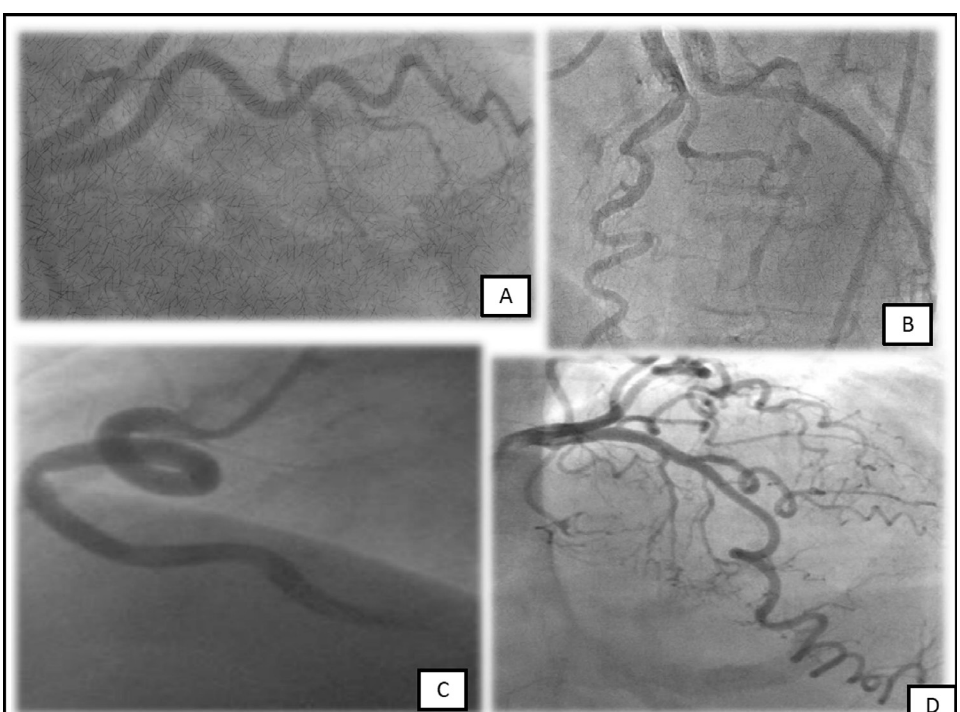

Fig. 2. Consist of 4 parts describing the degree of angulation of coronary tortuosity (CT). A = Mild CT in Ramus intermedius, B = Moderate CT in LAD, C = Extreme CT with loop in RCA, D = Sever CT in LAD. LAD; left anterior descending artery, LCX; left circumflex artery, RCA; right coronary artery.

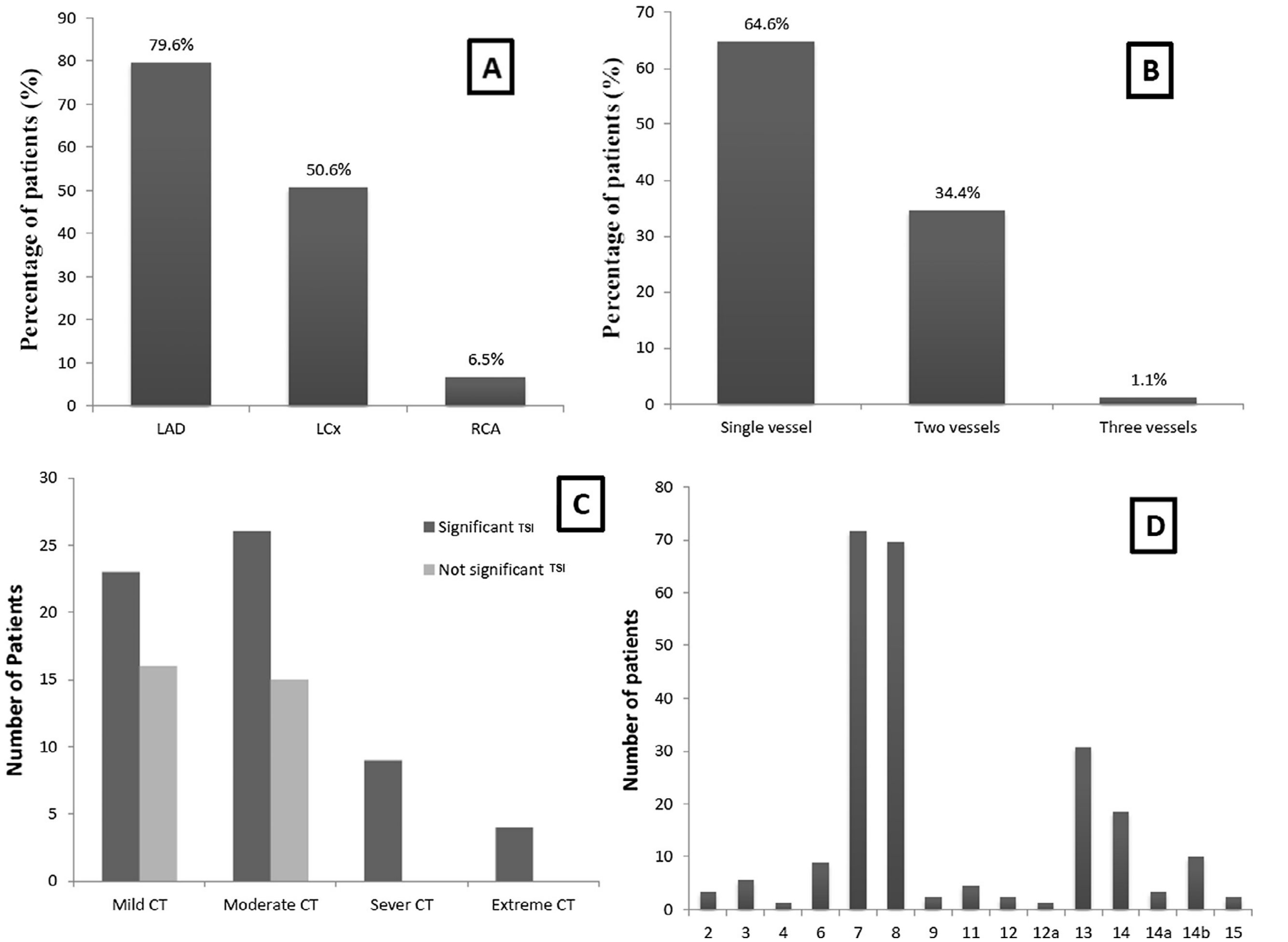

Fig. 3. Consist of 4 parts analyzing the anatomical variation of coronary tortuosity (CT). A. shows that the percentage of patients with CT more common in LAD than LCX or RCA. B. shows that the percentage of single vessel with CT is more common than multi-vessel CT. C panel represent the grading of tortuosity severity index (TSI) either significant or not in each category of CT based on degree of the angle of deviation either mild, moderate, severe or extreme tortuosity. D panel present which segment of the coronary artery, according to SYNTAX score segmentation, is more affected by CT. segments 7 and 8 in LAD are more affected than other segments then segments 13 and 14 in LCX. LAD; left anterior descending artery, LCX; left circumflex artery, RCA; right coronary artery.

were performed using all potentially relevant variables to identify baseline independent predictors of ischemic changes in patients with normal CA. All P-values are two tailed, and statistical significance was defined if $P < 0.05$. All analyses were performed with SPSS version 22.0 statistical software (SPSS Inc., Chicago, IL, USA).

4. Results

The main demographic, clinical, echocardiographic and angiographic characteristics of the 200 patients with normal/ near normal coronary arteries are listed in Table 1. There were 93 patients (46.5%) with CT in $\geq$1 coronary artery, almost 80% in LAD especially in segments 7 and 8 according to SYNTAX score segmentation, 65% of CT was in single vessel as shown in Fig. 3.

Patients were divided into 2 groups based on the absence (groupI) or presence (group II) of ischemia at stress testing, there were significantly higher prevalence of female gender, hypertension, diabetes mellitus and severe LV hypertrophy (LVH) in group II compared to group I (Table 1). Patients in group II had the highest rate of CT (68% vs. 18%, p = 0.004) and significant TSI (46% vs. 11%, p < 0.001) compared to group I (Table 1). Table 2 presents demographic, clinical, echocardiographic and angiographic characteristics of the same 200 patients reclassified into groups based on the presence or absence of CT. Patients with CT were more commonly females, older in age and hypertensive. Furthermore, LVH was observed more frequently in those patients. By further analysis of the degree of LVH, patients with CT had the severest degree of LVH compared with those without CT (Table 2). Univariate logistic regression analysis identified several factors for prediction of ischemic changes in those patients including female gender, hypertension, diabetes, LV mass, sever LV hypertrophy and CT. But when putting all risk factors together in the multivariate logistic regression model, CT was the only significant predictor of ischemic changes in patients with normal coronary angiography (OR = 6.2, 95%CI = 2.5–15.3, P < 0.001) (Table 3). Presence of significant TSI was associated with 10 folds increase in the odds of having ischemic changes by further analysis (OR = 10.2, CI = 4.6–22.5, P < 0.001). There is a clear interaction between the effect of CT and LV mass/index, as the CT effect reduced to 6 folds, instead of 9 folds, with addition of LV mass to the regression model. This interaction confirms the correlation between CT and hypertension in our study.

5. Discussion

Our study endorse that patients with chest pain syndrome, positive stress study, and angiographically normal coronary arteries demonstrate a six-fold higher prevalence of CT compared to

Table 1
Clinical, echocardiographic and angiographic criteria of the study population allocated into 2 groups; according to the presence or absence of ischemic changes.

Characteristics	Total patients No = 200	Group I No ischemic changes No = 87	Group II With ischemic changes No = 113	P value
Female gender	125 (62.5%)	46 (52%)	79 (70%)	0.02
Age, y	54.29 ± 9.74	53.7 ± 10.4	54.7 ± 9.2	0.50
Hypertension	111(55.5%)	36(41.4%)	75 (66.6%)	0.001
Diabetes mellitus	61(30.5%)	19(21.8%)	42 (37.2%)	0.02
Dyslipidemic	67(33.5%)	23(26.4%)	44 (38.9%)	0.06
Smoker	71(35.5%)	34(39%)	36 (31%)	0.29
Family history of CAD	58 (29%)	23(26.4%)	35 (31%)	0.23
Weight, kg	75.4 ± 12.2	76.7 ± 12	74.3 ± 12	0.17
Height, cm	165.1 ± 7	166.1 ± 7	164.1 ± 7	0.16
BSA, m^2	1.86 ± 0.6	1.88 ± 0.5	1.84 ± 0.5	0.51
Medications				
Aspirin	135 (67.5%)	58 (67%)	77 (68%)	0.45
β- blockers	93 (46.5%)	35 (40%)	46 (41%)	0.9
ACEI/ARB	57 (28.5%)	25 (28%)	32 (28%)	0.8
Diuretics	30 (15%)	12 (13%)	18 (15%)	0.45
Statins	56 (28%)	24 (27%)	32 (28%)	0.22
Nitrates	82 (41%)	34 (39%)	48 (42%)	0.9
Total cholesterol, mg/dL	198 ± 36	196 ± 36	189 ± 39	0.78
Stress ECG preformed	155	55	100	0.04
Stress ECHO performed	45	32	13	
Ejection Fraction (%)	60 ± 8	60 ± 7	61 ± 6	0.58
LV mass, g	180.8 ± 57.2	161.7 ± 49	195.5 ± 58	<0.001
LV Mass index, g/m^2				
Mild LVH	108 (54%)	10(11.49%)	18 (15.9%)	<0.001
Moderate LVH	28 (14%)	5(5.75%)	16 (14.2%)	
Severe LVH	21 (10.5%)	6(6.9%)	37 (32.7%)	
Coronary tortuosity present	93 (46.5%)	16(18.3%)	77 (68.1%)	0.004
Number of bends (IQR)	9.9 ± 1.8 (3–12)	4.3 ± 1.5 (3–8)	5.6 ± 1.8 (3–12)	0.09
Degree of angulation				
Mild CT	39 (19.5%)	6 (7%)	33 (29%)	0.09
Moderate CT	41 (20.5%)	10 (11%)	31 (27%)	
Sever CT	9 (4.5%)	0	9 (10%)	
Extreme CT	4 (2%)	0	4 (3.5%)	
Tortuosity Severity Index				
Non significant TSI	31 (15.5%)	6 (7%)	25 (22%)	<0.001
Significant TSI	62 (31%)	10 (11.5%)	52 (46%)	

Data are presented as mean ± standard deviation, number (%) of patients, or median (IQR = interquartile range). CAD = coronary artery disease; ECG = electrocardiogram; ECHO = echocardiography; BSA = Body surface area; CT = Coronary tortuosity; LV = left ventricle; LVH = left ventricular hypertrophy; TSI = tortuosity severity index.

patients without ischemic changes. Almost two-thirds of patients with ischemic changes on stress testing, revealed CT with significant TSI on subsequent coronary angiogram. Among patients with chest pain syndrome and normal coronary arteries, those with CT more frequently reported typical angina, with ST-segment deviation at stress ECG or reversible wall motion abnormalities at stress ECHO. This cluster of findings is strongly suggestive for a significant role of CT in patients with chest pain syndrome and no obstructive epicardial coronary artery disease. Our study demonstrates that CT was the only significant predictor of ischemic changes in such patients, but whether CT is a cause or just a marker of another mechanism such as LV hypertrophy, cannot be ascertained.

Subgroup of patients in the present study (113 of 200) would be correctly defined as having true ischemic heart disease by virtue of a history of effort angina and a positive provocative stress test results[14]. CT was significantly more prevalent in of such patients (68%). Syndrome X may represent a plausible explanation to the remaining one third of patients with true ischemia. Microvascular dysfunction (or syndrome X) is usually held responsible for angina with normal coronary arteries, but the evidence in favor of a unique pathogenesis in all such diverse patients is contradictory; chest pain with normal coronaries is reasonably explained by different mechanisms[4,14–16]. The pathophysiology of ischemic chest pain due to CT has been recently studied. However, it is hypothesized that CT 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 and altered flow dynamics that form in tortuous arteries[16,17]. During exercise, CT may represent greater resistance to blood flow, in such a way that compensatory mechanisms of flow adjustment may not be enough to keep an adequate flow and lead to myocardial ischemia[18]. Furthermore, CT was associated with increased Plateletcrit, mean platelet volume, platelet:large-cell ratio, neutrophil:lymphocyte ratio and platelet:lymphocyte ratio, even in the absence of coronary artery disease[19]. So patients with CT may have exercise related chest pain and positive stress ECG in accordance with our study.

Arterial tortuosity has been described in several vascular systems and organs[1,20]. The etiology of CT is still unclear. Traction and pressure in the lumen are two forces that tend to lengthen a vessel. These two forces together are opposed by a retractive force[16,17]. Normally, the retractive force is equal and opposite to the sum of the traction and pressure forces resulting in a stable length of the vessel[21,22]. The retractive force is generated almost entirely by elastin. Degeneration of elastin in the arterial wall leads to aneurysmal dilatation and development of arterial tortuosity[22]. In general, tortuosity of arteries is caused by age-dependent or pathological changes of the elastic material in the vessels[23].

Table 2
Clinical, echocardiographic and angiographic criteria in of the study population, subclassified based on presence or absence of coronary tortuosity.

Characteristics	Patients without CT (N = 107)	Patients with CT (N = 93)	P. value
Female gender	53(49.5%)	72(77.4%)	<0.001
Age	52.9 ± 10.2	55.9 ± 9	0.029
Hypertension	40(37.4%)	71(76.3%)	<0.001
Diabetes mellitus	30(28%)	31(33%)	0.08
Dyslipidemic	32(30%)	35(37%)	0.09
Smoker	36(33.6%)	35(37.6%)	0.58
Family history of CAD	32 (30%)	26(27.9%)	0.51
Weight, kg	76.7 ± 11.9	74 ± 12.5	0.123
Height, cm	165.8 ± 8.3	164.6 ± 6.8	0.255
BSA, m^2	1.88 ± 0.5	1.84 ± 0.5	0.51
Medications			
Aspirin	73 (68%)	62 (66%)	0.45
β- blockers	51 (47%)	42 (45%)	0.93
ACEI/ARB	33 (30%)	24 (26%)	0.8
Diuretics	18 (17%)	12 (13%)	0.45
Statins	30 (28%)	26 (28%)	0.82
Nitrates	43 (40%)	39 (41%)	0.93
Total cholesterol, mg/dL	198 ± 37	196 ± 39	0.55
Ejection Fraction (%)	60 ± 8	61 ± 6	0.45
LV mass, g	149.3 ± 43.2	217.2 ± 49.4	<0.001
LV Mass index, g/m^2			
Mild LVH	9(8.4%)	19(20.4%)	<0.001
Moderate LVH	3(2.8%)	18(19.4%)	
Severe LVH	3(2.8%)	40(43%)	

Data are presented as mean ± standard deviation, number (%) of patients. CAD = coronary artery disease; ECG = electrocardiogram; ECHO = echocardiography; BSA = Body surface area; CT = Coronary tortuosity; LV = left ventricle; LVH = left ventricular hypertrophy.

In accordance with our study, Lebedeva and his colleges[24] included 48 patients with anginal chest pains who underwent myocardial scintigraphy and coronary angiography. The prevalence of CT was 37.5%, multi-arterial in 8.3% and more frequent in female (66.7%). In our study of CT, the LAD was the most commonly affected artery, this comes in agreement with Gaibazzi et al.[4], but different from other study which found the circumflex artery to be more commonly affected[22]. This difference may be explained on the basis that we included only the vessel ≥2.5 mm in our analysis.

As regard age, patients with CT in our study were more commonly older in age. On the contrary Groves et al.[6] did not find any correlation between aging (over 65 years) and CT. However, several other researchers have reported this relationship[16,22].

Regarding gender, in this study patients with CT were more commonly females, in agreement with several studies[6,22]. It was reported some decades ago that the incidence of tortuosity increased as the heart size and mass decreased[25]. This is of interest as it is also thought women in general, have smaller hearts than men[22,23].

CT has been regarded for decades as a mere curiosity and usually associated with the presence of arterial hypertension. In our study we found that CT was more common in hypertensive patients, which was 1st reported in 1982, in a group of 70 patients who all underwent coronary angiography, and left ventriculography (10 patients who also underwent a study with myocardial scintigraphy), describe "corkscrew tortousity" in coronary angiography (without associated obstructions) in 83.7% of patients and suggest that subendocardial ischemia may be related to the increase of ventricular mass with a lower coronary reserve[26]. This correlation was also documented by Jakob et al.[22] However, other studies[4,6] did not find this relation between CT and hypertension. Both studies did not measure the LV mass index and used a different definition of CT compared to our study which may explain this difference. Furthermore; it was shown by Turgut et al.[3] that impaired left ventricular relaxation might increase CT and CT is more prominent in people with chronic pressure overload and is less when there is volume overload. This finding also comes in agreement with our results, where patients who had LVH by echocardiography associated with CT more than those with normal LV mass and LV mass index. This supports the hypothesis that CT is the consequence of underlying myocardial alterations; however the exact nature of these remains indiscernible.

The study by Gaibazzi et al.[4] detected CT in 35% of study population, this is lower than that in our study (46.5%). This can be explained by the difference in the definition used for CT. There is no accepted clear definition of CT in the literature, only few previous reports addressed this issue[4,6,16,18]. We defined CT as >3 curvatures >45° in diastole in vessels >2.5 mm in diameter, then we further analyzed CT in each artery based on the number of curvatures and degree of its angulation form an arbitrary straight line, developing a new simple TSI. For our definition, it is somehow between the definition chosen by Gaibazzi et al.[4] (≥3 curvatures but ≤90° during diastole), Dagianti et al.[18] (≥4 bendings with an angle less than 60°, present both in systole and in diastole) and Zegers et al.[16] (≥3 curvatures ≥120° during diastole) and the more restrictive one chosen by Groves et al.[6] (2 consecutive 180° turns). From our point of view, our TSI [significant TSI (defined as mild/moderate CT with more than 4 bends in total, or sever/extreme CT with any number of bends) or otherwise non-significant TSI] is more clinically applicable and proved to be highly significantly related to ischemic changes in patients with angina and normal coronary arteries compared to older tortuosity severity index by Jakob et al.[22] (percent ratio of calculated shortest distance divided by total length of the coronary artery). This definition with a

Table 3
Logistic regression analysis for prediction of ischemic changes in patients with angina and normal coronary angiography.

Predictors	Univariate logistic regression[a]			Multivariate logistic regression		
	Exp (B)	95% CI	P	Exp (B)	95% CI	P
Female	2.1	1.1–3.7	0.014	1.2	0.6–2.3	0.58
Hypertension	2.7	1.5–4.9	<0.001	1.35	0.59–3.04	0.47
Diabetes	2.1	1.1–3.9	0.02	3.04	0.67–13.7	0.14
Dyslipidemia	0.7	0.9–3.2	0.06	0.4	0.09–1.9	0.28
Smoking	2.1	0.4–11.3	0.34			
Age	0.9	0.9–1.02	0.47			
LV mass	1.01	1.006–1.017	<0.001	1.0	0.99–1.01	0.99
LV mass index						
Mild	2.8	1.2–6.7	0.01	1.1	0.37–3.3	0.85
Moderate	5.02	1.7–14.7	0.003	1.4	0.36–5.5	0.60
Severe	9.7	3.7–24.9	<0.001	2.1	0.6–7.5	0.23
Coronary tortuosity	9.4	4.8–18.5	<0.001	6.2	2.5–15.3	<0.001

[a] Univariate logistic results were measured using Mantel Hanzel common Odds Ratio estimate test. LV = left ventricle.

precise angle cutoff is needed for scientific purposes and requires more studies in different patient's populations to be validated.

Limitations of our study include: 1- using visual assessment of angiography for of 3D coronary curvatures detection, has its inherent limitations and it's a subject for bias. However, the striking visual appearance of CT at an angiogram cannot be missed on critical revision. Furthermore to avoid subjective bias, 2 experienced interventionists blinded to the enrollment group detected CT using a standardized predefined protocol with fixed view angles for each artery with good inter-observer agreement. 2- Lack of myocardial perfusion evidence of ischemia in our patients' is a clear limitation mainly due to budget restraints. However, stress ECG and ECHO is a clear everyday practice for our patients with generalized acceptance of their results. 3- The proposed TSI needs large sample size to confirm its practical validity.

6. Conclusions

Coronary tortuosity is a strong predictor of anginal pain among patients with normal CA, despite positive stress study. This finding is more pronounced among elderly, hypertensive female patients. Our study proposes a new TSI for quantification of CT, which requires further validation in upcoming clinical studies.

Funding

The authors received no specific funding for this work.

Conflicts of interest

The authors have declared that no competing interests exist.

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