Coronary artery tortuosity: comparison with retinal arteries and carotid intima-media thickness

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Abstract

Background and aim: We conducted a prospective study to investigate the possible relationship between the tortuosity of coronary arteries (TCA) and carotid intima-media thickness (CIMT), and also compare TCA to retinal artery tortuosity.

Methods: One hundred and five participants with nonsignificant coronary plaque or normal coronary angiogram were included. To determine subclinical atherosclerosis, maximum CIMT was measured. Retinal tortuosity was evaluated ophthalmically.

Results: Among all demographic variables and risk factors, only female gender and height were significantly associated with TCA (p = 0.001, p = 0.01, respectively). Retinal artery tortuosity and retinal artery atherosclerosis were more common in patients with TCA compared to patients without TCA (p < 0.001, R = 0.6; p = 0.002, R = 0.4, respectively). CIMT was greater in participants with TCA than patients without TCA (p = 0.001), and also the presence of carotid artery plaque was more common in patients with TCA (p < 0.001). There was a significant correlation between the presence of subclinical atherosclerosis and TCA (p = 0.005, R = 0.3). Likewise, a significant correlation was found between subclinical atherosclerosis and retinal artery tortuosity (p = 0.02, R = 0.3). Multivariate analysis identified female gender (p < 0.008), retinal artery tortuosity (p < 0.001), and CIMT (p = 0.02) as independent predictors of TCA.

Conclusions: These results indicate that, whatever the mechanism is: 1) TCA is associated with female gender and short stature; 2) TCA is associated with subclinical atherosclerosis even in patients with entirely normal appearing coronary arteries on coronary angiography; 3) Retinal artery tortuosity is correlated with TCA and can be a surrogate for systemic arterial tortuosity.

Key words: atherosclerosis, tortuosity, coronary, retinal artery

INTRODUCTION

Arterial tortuosity has been described in several vascular systems and coronary tortuosity has also been described explicitly [1, 2]. Coronary tortuosity with or without visible lesions is a common entity encountered by cardiologists during coronary angiography. Haemodynamic shearing forces due to flow are involved in tortuous vessels and may affect the formation and development of coronary atherosclerosis. And additionally, non-physiologic and oscillatory wall shear stress may give rise to acute coronary syndromes by means of rupture of atherosclerotic plaques [3–5]. Tortuosity of coronary arteries (TCA) is also a common finding seen with ageing and hypertension due to elongation and dilatation of the arteries associated with left ventricular hypertrophy [6, 7].

Neither the clinical significance of coronary tortuosity with normal coronary arteries, nor the relationship between coronary tortuosity and subclinical atherosclerosis, have been described in the literature. By accepting carotid intima-media thickness (CIMT) as a surrogate for subclinical atherosclerosis, we conducted a prospective study to investigate the possible relationship between TCA and CIMT. We therefore aimed to test our hypotheses: 1) Is coronary tortuosity a manifestation of subclinical atherosclerosis? We sought to determine this hypothesis by comparing coronary tortuosity to CIMT.
2) Is coronary tortuosity a component of systemic arterial tortuosity? We sought to determine this hypothesis by comparing coronary artery tortuosity to retinal artery tortuosity.

**METHODS**

**Study patients**

Patients with chest pain or positive exercise test referred to a single centre for coronary angiography between February 2010 and May 2010, and who met the entry criteria for the study, were invited to participate. 105 consecutive participants (aged 30–81 years) with nonsignificant coronary plaques or apparently normal coronary angiograms were included in the study. Group 1 consisted of 58 individuals with coronary tortuosity, and group 2 consisted of 47 individuals without coronary tortuosity.

Subjects were excluded if they had significant coronary artery disease (CAD) (presence of at least one lesion causing ≥ 50% diameter stenosis), previous surgical/pcructaneous coronary revascularisation, atrial fibrillation, left ventricular systolic dysfunction, hypertrophic cardiomyopathy, or significant valvular disease. The study was approved by the Local Research Ethics Committee, and all subjects provided their informed consent before enrollment.

**Assessment of cardiovascular risk factors**

Cardiovascular risk factors were determined by interviewing patients at the time of examination. In all subjects, a fasting blood sample was collected at the beginning of cardiac catheterisation for detailed lipid analysis. Total plasma cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were measured. Systolic blood pressure of ≥ 140 mm Hg, or diastolic blood pressure of ≥ 90 mm Hg in at least two separate readings or taking antihypertensive medications was accepted as hypertension. Diabetes mellitus was diagnosed if the fasting plasma glucose level was ≥ 126 mg/dL, or requiring previous or ongoing pharmacologic therapy. Weight and height were measured without shoes and with light clothing, and body mass index was calculated as body weight [kg] divided by the square of height [m²]. Current cigarette smoking was defined as active smoking within the past 12 months.

**Transthoracic echocardiography**

Complete transthoracic echocardiography was performed in all subjects (Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway). All patients underwent a comprehensive examination, including M-mode, two-dimensional and Doppler echocardiography in order to rule out left ventricular dysfunction or cardiomyopathy. Left ventricular hypertrophy was defined according to the recommendations of the American Society of Echocardiography guidelines, 2005 version.

**Coronary angiography**

Coronary angiography in multiple views was performed according to the standard Judkins or Sones technique using a Philips Integris H 5000 system. At least five views, including two orthogonal views, were acquired for the left coronary artery and at least two orthogonal views for the right coronary artery. Angiographic results were interpreted by angiographers who had no knowledge of the status of retinal artery findings. 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, present both in systole and in diastole (Fig. 1) [8]. Coronary flow was objectively quantified by two independent observers using the corrected thrombolysis in myocardial infarction (TIMI) frame count method. Patients with a corrected TIMI frame count greater than two standard deviations from the normal published range for the particular vessel were considered as having slow coronary flow, while those who had a corrected TIMI frame count within two standard deviations of the published normal range were classified as having normal coronary flow [9]. Identification of visible non-critical coronary angiographic plaque (in diameter stenosis) was based on visual evaluation by the cardiologist. The observer who made the diagnosis of

Figure 1. Example of tortuous (A) and non-tortuous (B) coronary arteries
Coronary tortuosity and subclinical atherosclerosis

Carotid artery ultrasonography
Carotid artery ultrasonography was performed using a 13-MHz linear transducer (Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway). The protocol involved scanning both common carotid arteries. To determine subclinical atherosclerosis, maximum right and left intima-media thicknesses were measured in the distal segment of both common carotid arteries. Subclinical atherosclerosis was defined as maximum right and left intima-media thickness ≥ 1.0 mm (Fig. 2) [10]. Atherosclerotic plaque was determined as obtaining the measurable presence of arterial bed roughness, homogeneous or heterogeneous echogenicity with presence or absence of calcium. Carotid artery ultrasonographies were interpreted by two cardiologists who had no knowledge of the status of retinal arteries and coronary angiogram.

Retinal artery tortuosity and atherosclerosis
Ophthalmic evaluation was performed to reveal retinal tortuosity using digital imaging with a Topcon TRC-50IA retinal fundus camera without knowledge of the coronary tortuosity status of the patients (Fig. 3). When there was a discrepancy in the presence and severity of a tortuosity and atherosclerotic changes between the two eyes of a participant, or in different areas of the same eye, the more affected eye or region was used to describe the stage for that participant.

Statistical analysis
Data was analysed using SPSS (Statistical Package for Social Sciences) version 10.0. Continuous variables were reported as mean ± standard deviations. For the bivariable analysis, when the variables were parametric, the difference of averages test (Student’s t-test) was used; in the case of variables with more than two categories, the one-way ANOVA test was carried out. Categorical variables were expressed as counts or percentages, and compared using a $\chi^2$ test. The correlation between two variables was studied with the Pearson test. In all two sided analyses, a p-value < 0.05 was considered to be statistically significant. Multivariate analysis was performed using stepwise logistic regression analysis. Coronary tortuosity was used as the dependent variable. The following variables were used: gender, height, insignificant coronary artery plaques, CIMT, carotid artery plaques, retinal artery tortuosity and retinal artery atherosclerosis.

RESULTS
Patient characteristics
Demographic data and risk factor variables for the participants undergoing coronary angiography are presented in Table 1. The results are presented and stratified by the presence of other variables. Observer variability was determined by reassessment of 30 randomly selected subjects. There was no intra-observer variability for the assessment of the presence or absence of coronary tortuosity.

Figure 2. Example of increased (A) and normal (B) intima-media thickness

Figure 3. Example of tortuous (A) and non-tortuous (B) retinal arteries
(Group 1) or absence (Group 2) of coronary artery tortuosity. Group 1 included 58 patients (13 men and 45 women; mean age 55.5 ± 10 years) and Group 2 included 47 patients (25 men and 22 women; mean age 53.8 ± 12 years). From all demographic variables and risk factors, only female gender and smaller stature (height) were significantly associated with coronary angiographic tortuosity (p = 0.001, p = 0.01, respectively). There was a significant correlation between coronary bend number and CIMT (R = 0.3, p = 0.02; Fig. 4).

**Status of retinal artery and carotid artery in patients with and without coronary artery tortuosity**

The identification of visible non-critical coronary angiographic plaques (in diameter stenosis) was not associated with coronary artery tortuosity (Table 2). The presence of coronary slow flow, the appearance of irregularity or entirely normal coronary angiography were not associated with coronary artery tortuosity. However, retinal artery tortuosity and retinal artery atherosclerosis were more common in patients with coronary artery tortuosity (p < 0.001, p = 0.002, respectively). Likewise, CIMT was greater in participants with coronary tortuosity compared to patients without coronary tortuosity (p = 0.001), and also the presence of carotid artery plaque was more common in patients with coronary artery tortuosity (p < 0.001).

**Subclinical atherosclerosis and coronary/retinal artery tortuosity**

There was a statistically significant correlation between the presence of subclinical atherosclerosis and coronary artery tortuosity (p = 0.005, R = 0.3). Likewise, a significant correlation was found between subclinical atherosclerosis and retinal artery tortuosity (p = 0.02, R = 0.3).

**Multivariate analysis**

Multivariate analysis was performed using stepwise logistic regression to obtain variables involved in tortuosity status. Multivariate analysis identified female gender (p < 0.008), retinal artery tortuosity (p < 0.001), and carotid artery intima-media thickness (p = 0.02) as independent predictors of coronary artery tortuosity.
Coronary tortuosity and subclinical atherosclerosis

DISCUSSION

In the evaluation of clinical significance of coronary artery tortuosity, we established for the first time that short stature, female gender, CIMT and retinal artery tortuosity were strongly associated with coronary artery tortuosity. In this study, the presence of coronary angiographic non-critical plaque or coronary wall irregularities were not associated with coronary tortuosity. We confirm our hypotheses that: 1) Coronary artery tortuosity is associated with subclinical atherosclerosis even in the case of a normal coronary angiogram; and 2) Coronary artery tortuosity might be a component of systemic arterial tortuosity demonstrated by means of retinal artery tortuosity.

Coronary tortuosity is usually not noticed or recorded by cardiologists at the time of coronary angiography. Groves et al. [11] revealed that the presence of severe tortuosity was associated with a statistically significant lower incidence of significant CAD. Also, they found that CAD risk factors were not predictors of coronary tortuosity.

However, the aetiology and clinical importance of coronary tortuosity in patients with a normal coronary angiogram are still unclear. There is currently no conclusive data in the literature dealing with the association between coronary artery tortuosity and subclinical atherosclerosis. According to the findings of our study, we suggest that coronary tortuosity, even in subjects without atherosclerotic stenosis on coronary angiogram, can be used as a marker of both systemic arterial tortuosity and subclinical atherosclerosis. A recent study conducted by Owen et al. [12], in which they did not compare the retinal arteries with coronary arteries tortuosity, revealed that retinal arteries tortuosity is strongly linked with established cardiovascular risk factors.

Notably, most of our participants were referred to coronary angiogram for chest pain or abnormal exercise stress test. The combination of coronary tortuosity without documented significant atherosclerotic stenosis in patients with anginal complaints and an abnormal exercise stress test has been described in very few cases [13]. In this case series, the authors propose a mechanism that coronary tortuosity may lead to flow alteration resulting in a reduction in coronary perfusion pressure distal to the coiling of the coronary artery ultimately leading to ischaemia. Interestingly, recent studies have suggested that severely tortuous coronary arteries without severe stenosis might cause myocardial ischaemia [14, 15]. However, any causative interrelationship between coronary tortuosity and ischaemia needs to be clarified. In order to determine the impact of coronary tortuosity on coronary perfusion, coronary flow reserve or fractional flow reserve calculations can be used in further studies.

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Table 2. The status of coronary arteries plaque, coronary slow flow, retinal artery tortuosity, carotid artery intima-media thickness, and retinal artery atherosclerosis in patients with and without coronary artery tortuosity

<table>
<thead>
<tr>
<th></th>
<th>Coronary tortuosity present (n = 58)</th>
<th>Coronary tortuosity absent (n = 47)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with LAD plaque</td>
<td>18</td>
<td>21</td>
<td>0.10</td>
</tr>
<tr>
<td>Subjects with CX plaque</td>
<td>14</td>
<td>18</td>
<td>0.08</td>
</tr>
<tr>
<td>Subjects with RCA plaque</td>
<td>16</td>
<td>17</td>
<td>0.27</td>
</tr>
<tr>
<td>Coronary slow flow</td>
<td>14</td>
<td>10</td>
<td>0.82</td>
</tr>
<tr>
<td>Retinal artery, mild tortuosity</td>
<td>43</td>
<td>9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Retinal artery, severe tortuosity</td>
<td>8</td>
<td>2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Carotid intima-media thickness [mm]</td>
<td>0.88 ± 0.22</td>
<td>0.69 ± 0.17</td>
<td>0.001</td>
</tr>
<tr>
<td>Subjects with carotid plaque</td>
<td>28</td>
<td>5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Retinal artery atherosclerosis grade 2</td>
<td>36</td>
<td>14</td>
<td>0.002*</td>
</tr>
<tr>
<td>Retinal artery atherosclerosis grade 3</td>
<td>7</td>
<td>4</td>
<td>0.002*</td>
</tr>
<tr>
<td>Retinal artery atherosclerosis grade 4</td>
<td>3</td>
<td>1</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

*χ² 16.9; df: 4; LAD — left anterior descending, CX — circumflex, RCA — right coronary artery

Table 3. Subclinical atherosclerosis and coronary/retinal arteries tortuosity

<table>
<thead>
<tr>
<th></th>
<th>Intima-media thickness &gt; 1 mm (n = 33)</th>
<th>Intima-media thickness £ 1 mm (n = 72)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary tortuosity bend numbers</td>
<td>16.9 ± 9.5</td>
<td>11.6 ± 8.2</td>
<td>0.005</td>
</tr>
<tr>
<td>Retinal artery, mild tortuosity</td>
<td>28</td>
<td>22</td>
<td>0.02*</td>
</tr>
<tr>
<td>Retinal artery, severe tortuosity</td>
<td>7</td>
<td>3</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

*χ² 13.4; df: 2
Traction and pressure in the lumen are suggested as two forces that tend to lengthen a vessel. These two forces are opposed by retractive force. Under normal conditions, the retractive force is equal and opposite to the sum of the traction and pressure forces resulting in a stable length of the vessel [16]. It has been suggested that the retractive force is generated by elastin. Thus, degeneration of elastin in the arterial wall may lead to aneurysmal dilatation and the development of arterial tortuosity [16].

Tortuosity of arteries is generally attributed to age-dependent or pathological changes of the elastic material in the vessels. We did not find any relationship between age and tortuosity in our study. Elastin as an actor for development of tortuosity has been pointed out for arterial tortuosity syndrome in children, a rare autosomal recessive connective tissue disorder associated with generalised tortuosity and elongation of all major arteries. The role of elastin on the pathophysiology of coronary tortuosity in adults is still unclear.

According to our study, female gender and short stature were correlated with coronary tortuosity. However, classical risk factors and other baseline clinical characteristics of subjects with and without tortuosity were similar. A higher proportion of females affected with coronary tortuosity has also been documented [17].

Some determinants have been suggested for tortuosity of coronary arteries. Differences in tortuosity have been observed between left circumflex and left anterior descending coronary arteries. It has also been demonstrated that tortuosity increases during systole and is more pronounced in left circumflex than in left anterior descending coronary arteries in hypertensive patients [17]. In our study, there was no relationship between hypertension/left ventricular hypertrophy and tortuosity. Also, we did not find selective involvement of any specific coronary arteries. Interrelation between impaired left ventricular relaxation and coronary tortuosity has been suggested, which implies haemodynamic interaction of tortuosity and ventricular relaxation [18].

Interestingly, we found that retinal artery tortuosity was an independent predictor for coronary artery tortuosity, implying the systemic nature of tortuosity. Thus, we could tell that coronary artery tortuosity can be inferred from fundoscopic examination of the retina.

In the present study, an important finding was that coronary artery tortuosity even in the case of normal coronary angiography was strongly associated with increased intima-media thickness. From that standpoint, one of the implications of the present study is that coronary artery tortuosity might be used as a surrogate for subclinical atherosclerosis.

**Limitations of the study**

One limitation was the small sample size. Second, further evaluation of tortuous coronary arteries with intravascular ultrasound, which provides accurate characterisation of vessel lumen and wall geometry, may provide insights as to whether arterial remodelling is present in the arterial segment which displays tortuosity.

Another drawback of the study is the strict inclusion criteria for minimising the possible effects of confounding factors on outcomes; therefore the conclusions may not apply to patients with severe CAD. Thus, our study findings do not represent the general population. We cannot make assertive statements about the generalisability of these correlations. Further studies should be performed to clarify our findings. The presence of tortuosity in both coronary arteries and retinal arteries can be an indicator of systemic tortuosity. Coronary angiography is a poor imaging modality in identifying mild CAD. We used angiography to rule out significant CAD. In an ideal study, intravascular ultrasound should be used to define the association between coronary tortuosity and coronary atherosclerosis, instead of using carotid atherosclerosis as a surrogate. The lack of a standard protocol for CIMT assessment and the inherent limitations of CIMT such as its being operator dependent is another limitation of the present study. Other methods of non-invasive assessment for subclinical atherosclerosis such as coronary artery calcium detection by multi detector computed tomography or ankle-brachial index can be incorporated in future studies.

Additionally, it should be noted that one component of this stress state is blood flow induced shear stress; others are wall stresses. Shear stress is mainly sensed by the endothelium. Wall stresses are much larger and directly related to deformation of the vessel wall, induced by blood pressure. The coronary arterial tree has many curved vessel segments and contains numerous bifurcations. Bifurcations, side branches and inner wall of vessel curvature are the risk points of atherosclerotic plaque formation where the flow profile may be disturbed and/or turbulent. The reason why atherosclerosis development occurs at preferential sites is still not fully understood. It should be kept in mind that it depends on mechanical, chemical and genetic factors, not only ‘arterial geometry’. Large prospective trials comparing groups of women with straight and tortuous coronary arteries matched with regard to age and risk factors need to be conducted.

**CONCLUSIONS**

These results indicate that, whatever the mechanism is:
1) Coronary artery tortuosity is associated with female gender and short stature; 2) Coronary tortuosity is associated with subclinical atherosclerosis even in the entirely normal appearance of coronary arteries on angiography; therefore coronary tortuosity might be considered as a marker of subclinical atherosclerosis; 3) Coronary tortuosity correlated with retinal artery tortuosity implies that coronary tortuosity might be a component of systemic arterial tortuosity. Coronary tortuosity taken as a marker of systemic atherosclerosis in routine practice and the role of intensive risk factor modification and use of anti-atherosclerotic agents like statins should be tested in further studies.

**Conflict of interest:** none declared
References

Krętość tętnic wieńcowych: porównanie z tętnicami siatkówki i ocena grubości kompleksu błony wewnętrznej oraz środkowej tętnicy szyjnej

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Streszczenie

Wstęp i cel: Autorzy przeprowadzili prospektywne badanie w celu oceny możliwych zależności między krętym przebiegiem tętnic wieńcowych (TCA) a grubością kompleksu błony wewnętrznej i środkowej (IMT) tętnicy szyjnej oraz porównania TCA z krętością tętnic siatkówki.


Wyniki: Spośród wszystkich zmiennych demograficznych i czynników ryzyka tylko płeć żeńska i wzrost były istotnie związane z TCA (odpowiednio p = 0,001 i p = 0,01). Krętość tętnic siatkówki i zmiany miażdżycowe w tętnicach siatkówki występowaly częściej u pacjentów z TCA niż u osób bez TCA (odpowiednio p < 0,001; R = 0,6 i p = 0,002; R = 0,4). Grubość IMT tętnicy szyjnej była większa u osób z TCA niż u pacjentów bez TCA (p = 0,001); ponadto w grupie osób z TCA częściej stwierdzano obecność blaszek miażdżycowych w tętnicach szyjnych (p < 0,001). Wykazano istotną korelację między obecnością bezobjawowej miażdżycy a TCA (p = 0,005; R = 0,3). Istotna korelacja istniała również między bezobjawową miażdżycą a krętością tętnic siatkówki (p = 0,02; R = 0,3). W analizie wieloczynnikowej wykazano, że płeć żeńska (p < 0,08), krętość tętnic siatkówki (p < 0,001) i grubość IMT (p = 0,02) były niezależnymi czynnikami predykcyjnymi TCA.

Wnioski: Powyższe rezultaty wskazują, że niezależnie od mechanizmów 1) TCA wiąże się z płcią żeńską i niskim wzrostem; 2) TCA wiąże się z bezobjawową miażdżycą, nawet u pacjentów z całkowicie prawidłowym obrazem tętnicy wieńcowych w badaniu angiograficznym; 3) krętość tętnic siatkówki koreluje z TCA i może być zastępczym wskaźnikiem krętości tętnic w krażeniu systemowym.

Słowa kluczowe: miażdżyca, kręty przebieg naczyń wieńcowych, tętnica siatkówkowa

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