Arterial Tortuosity
Novel Implications for an Old Phenotype

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● **Online Data Supplement**

Arterial tortuosity, that is, the presence of abnormal twists and turns of one or several arteries has been recognized for decades and associated with older age, female sex, high blood pressure, and other cardiovascular risk factors.[1,2] The recent identification of arterial tortuosity as a hallmark of genetic arteriopathies, such as Loeys-Dietz syndrome (LDS)[3] together with the demonstration of an association of arterial tortuosity with spontaneous coronary artery dissection (SCAD) and fibromuscular dysplasia (FMD),[4] have shed new light on this old phenotype. Arterial tortuosity may be a marker of vascular fragility or a useful indicator of underlying arteriopathies. As such, it could find its place in the diagnostic evaluation, cardiovascular risk stratification, and prognostic assessment of various vascular conditions.[3–7] However, incorporation of this arterial phenotype into clinical practice requires standardization in terms of definition, measurement, and normalcy criteria, as well as further evaluation in retrospective and prospective studies involving specialists with different backgrounds. The scope of this review is to summarize current knowledge on arterial tortuosity with emphasis on middle-size and large arteries and to pave the way for a multidisciplinary clinical research initiative devoted to this intriguing vascular biomarker.

Definition and Classification of Arterial Tortuosity

Perhaps the first description of vascular tortuosity can be found in Leonardo da Vinci's anatomic drawings,[8] where he associates it with the process of aging, describing the superficial vessels of the arm as tortuous in the old as opposed to the vessels of the young, presented as straight (Figure S1 in the online-only Data Supplement).

Tortuosity may affect virtually any arterial bed, from small size vessels, such as subungual capillaries and retinal arteries to middle and large size arteries, such as the coronary, cerebrovascular or iliac vessels, as well as the aorta itself. It can be either localized to a single vessel or widespread, in the latter case, usually reflecting the presence of an underlying arteriopathy. It may be diagnosed at various ages and progress over time.

A variety of terms have been used to describe different types of arterial tortuosity. In 1965, Weibel and Fields[9] proposed a classification for the morphological variation of the internal carotid artery. They defined tortuosity as an S- or C-shaped elongation or undulation. Kinking was described as an acute angulation, its severity ranging from mild (angle ≥60°) to moderate (angle between 30° and 60°) and severe (angle <30°). Looping has been defined as an exaggerated S-shaped curve and Coiling as a circular course.[9–11] Another term more recently used is the S-curve, described as a redundancy of the middistal internal carotid artery causing an S-shaped curve.[12] Several other related terms and markers of tortuosity can be found in Table 1.

Bullitt et al[13] described 3 patterns of vascular tortuosity:

- Type I includes high-amplitude–low-frequency tortuosity, sinuous curves in long vessels, corresponding to the aforementioned C- or S- shape curves.
- Type II is defined as medium-amplitude–medium-frequency curves.
- Type III is characterized by low-amplitude–high-frequency tortuosity, usually appearing as tight coils.

Mechanisms of Arterial Tortuosity

Clinical and experimental studies have demonstrated a strong association between vessel tortuosity and mechanical factors, such as blood pressure, blood flow, axial tension, and wall structural changes.[14]

Anatomic Aspects

Arterial tortuosity is likely to develop from abnormalities of relative vascular elongation.[15] Vascular elongation may arise from: a redundant vascular route during primary arteriogenesis; a mismatch between arterial lengthening and the parallel growth of surrounding anatomic structures during childhood and adolescence; a further stimulus to arterial elongation

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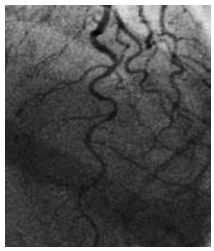
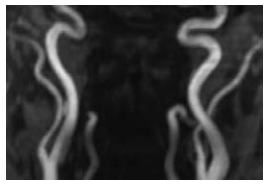
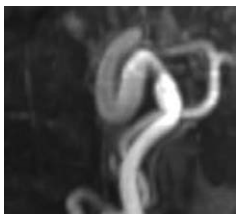
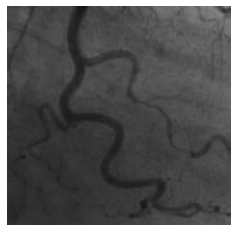
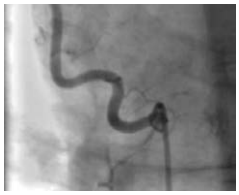
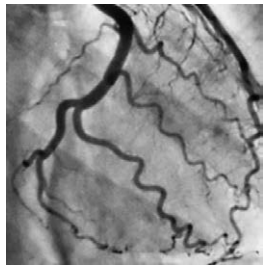
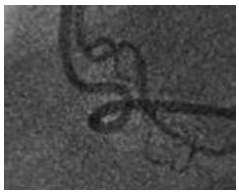
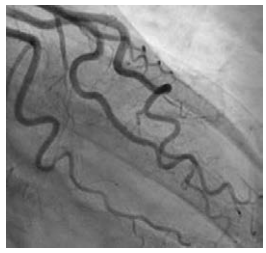
Table 1. Arterial Tortuosity: Definitions and Patterns

Patterns of Tortuosity	Description		Markers of Tortuosity	Description	
Tortuosity[9]	S- or C-shaped elongation		S-curve sign[4]	Internal carotid artery redundancy creating an S-shaped curve	
Kinking[9,10]	Acute arterial angulation		Intravessel symmetry sign[4]	Symmetrical curvatures on a coronary artery	
Looping[11]	C- or S-shaped deformity with 2 turns in the vessel with angles <90°		Multivessel symmetry sign (Portuguese Man of War sign)[4]	Symmetrical curvatures of similar angle on multiple coronary arteries	
Coiling[11]	360° turn in the vessel		Corkscrew sign[4]	Helical course of a coronary artery ≥360° perpendicular to the epicardial plane	

occurring in adulthood; or the skeletal changes of senescence (such as height loss because of spinal disk and joint degeneration).

The sites and patterns of tortuosity are dependent on key anatomic factors. These include:

- Anatomic fixation—vascular elongation between 2 fixed points will give rise to tortuosity.[16] For example, the cervical and vertebral vessels are effectively fixed at their cranial extent by the skull and at their caudal extent by the aorta. Any redundancy in length (or reduction in height), therefore, has a limited space over which to dissipate.
- Vessel branch points—can act as points of relative fixation, determining both sites and pattern of tortuosity. Redundancy in a vessel with multiple branch points providing points of constraint is more likely to lead to a series of small loops (eg, a distal coronary artery) than a large conduit with no branches where the extra length will take the shape of a single loop or a simple S (eg, the proximal right coronary). It is likely that the relative size of the branches compared with the mother vessel impacts the degree of constraint and the nature of the tortuosity. In the case of a large mother vessel with tiny branches (eg, the aorta), the branches will have less of a constraining effect and redundancy will likely develop over a longer length and with fewer turns. For small mother vessels where the "daughter" branches are of similar diameter, these will have a more constraining effect.
- Vessel diameter—this provides a fundamental limit to the rate of change of angle per unit length such that large arteries require a longer path length to generate tighter angles than small vessels. Hence, tortuous retinal arterioles can turn multiple times in a few millimeters, whereas a single carotid S-loop will involve an excess of a centimeter of vessel. For a large diameter coronary artery (such as the proximal right), the rate of change of angle will always be less than in the small terminal branches. This means that low amplitude high-frequency tortuosity is a feature of smaller vessels, whereas high

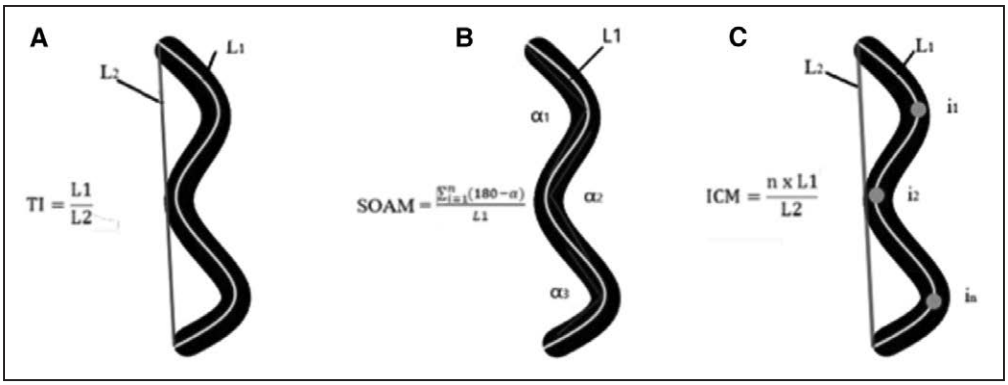


Figure 1. Most used quantitative methods for measuring arterial tortuosity. **A**, Tortuosity index (TI) equals the ratio between the length along the centerline (L1) and the linear distance between the 2 end points (L2). **B**, Sum of angles method (SOAM) is defined as the ratio between the sum of all angles (α) and the length along the centerline (L1). **C**, inflection count metric (ICM) equals the number (n) of inflection points (i) along a curve multiplied by the total path length (L1) and divided by the distance between the end points (L2).

amplitude low-frequency tortuosity is a feature of larger vessels.

Tortuosity may be dynamic (eg, in coronary vessels during systole versus diastole, but also in other arteries depending on body position). When measuring tortuosity, it is, therefore, important to clearly state the conditions of measurement.[4]

An optimal assessment of arterial tortuosity should take into account all the fundamental anatomic considerations as mentioned above.

Pathophysiology

See in the online-only Data Supplement.

How to Measure Arterial Tortuosity

Measuring and reporting the tortuosity of an artery remains a challenging task in the absence of a standardized, universally accepted method.

Currently, several types of methods are used:

Qualitative methods:

- Visual estimation of a vessel's tortuosity, most often used in clinical setting.[10,12]
- Counting the number of loops.[4]

More refined, quantitative methods (recently proposed):

- Methods based on the Tortuosity Index (TI) or Distance Metric (DM) or Distance Factor Metric, defined as the percent ratio of calculated shortest distance between the end points divided by actual length of the arterial segment considered[17,18] (Figure 1). One of the limitations of this method is that it can miss local tortuosity depending on the selection of the 2 end points.
- Methods based on the number and the angulation of loops:
  - The Sum of Angles Metric is a simple 2-dimensional assessment defined as the sum of all angles (deviation from the straight path in degrees) at points of angulation, normalized by path length (Figure 1). It is most effective for the measurement of high-frequency–low-amplitude coils.[13]
  - Eleid et al[4] defined coronary tortuosity as the presence of ≥3 consecutive curvatures of 90° to 180°, measured at end-diastole in a major epicardial artery and classified it as severe if it involves ≥2 consecutive curvatures of ≥180° and as mild if it involves ≥3 consecutive curvatures of 45° to 90° in a major epicardial artery, or ≥3 consecutive curvatures of 90° to 180° in an artery <2 mm in diameter. Furthermore, they calculated the tortuosity score as a sum of scores for each coronary artery, considering 0 for no tortuosity, 1 for mild tortuosity, 2 for tortuosity, and 3 for severe tortuosity.
  - Hart et al[19] described a method of measuring the tortuosity of blood vessel segments and blood vessel networks as the integral of the square of the curvature.
- Mixed methods, for example, Inflection Count Metric: this more comprehensive method implies counting the number of inflection points along a curve, multiplying this number (plus 1) by the total path length and dividing it by the distance between end points[18] (Figure 1). As such, it incorporates the information of both TI and sum of angles metric in a single assessment and may be preferred to them.
- Complex methods: Bullitt et al[13] compared 3 types of tortuosity metrics validated for 2-dimensional (DM, inflection count metric, and sum of angles metric) using 3-dimensional in intracerebral vessels. Inflection count metric seemed effective in recognizing the first 2 of 3 types of abnormal tortuosity (type I: sinuous curves in long, normally straight vessels and type II: tightly packed cluster with erratic directional changes). In contrast, sum of angles metric seemed to be the most effective in recognizing the third type of abnormality, characterized by high-frequency, low-amplitude coils. Diedrich et al[20] implemented a DM-based method creating a tortuosity curve and then, using numeric phantoms, applied this DM tortuosity curve to brain magnetic resonance angiography images to detect increased tortuosity in a hypertensive population compared to controls. Other complex 3-dimensional computer-based methods integrating the TI have been developed.[21,22]

Of note, the qualitative or semiquantitative methods (eg, visual scores) may be preferred to highly sophisticated mathematical approaches, at least for clinical purposes. Still, the complexity of tortuosity can be fully apprehended only in 3-dimension, and the development of high spatial resolution imaging and new generation post processing softwares may

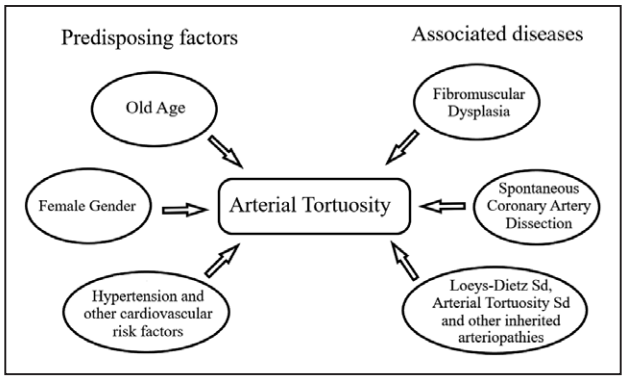


Figure 2. Conditions associated with arterial tortuosity.

facilitate the implementation of such complex approaches in clinical practice.

Factors and Conditions Associated With Arterial Tortuosity

This section deals with factors and conditions associated with arterial tortuosity (Figure 2), with the exception of the inherited arteriopathies, SCAD, and FMD, which will be discussed in specific sections. Notably, current studies are heterogeneous, often small, and comprehensive multivariate analyses are usually lacking.

Age

The influence of age on aortic tortuosity remains controversial. Although previous works showed no correlation[23] or an inverse correlation[24] between aging and tortuosity of the thoracic aorta, in a recent study including 210 patients, the length of the thoracic aorta was significantly related to age (r=0.54), and it increased by 59 mm (males) or 66 mm (females) on computed tomography angiography between the ages of 20 and 80 years. Elongation was most pronounced in the proximal descending aorta, which showed an almost 2.5-fold length increase during life. The tortuosity of the proximal descending aorta was moderately associated with age (r =0.38; P=0.004) and increased from a mean DM of 1.07 (at age 20 years) to 1.21 (at age 80 years).[25]

The association of arterial tortuosity with age has also been studied for the aortic branches.

In a series of 490 patients who underwent arteriography of the lower extremities for claudication, the arterial segments located proximally to the inguinal ligament were tortuous in 63% of patients and extremely tortuous in 11%, and vascular tortuosity was found to increase with age.[26] In another Color Doppler ultrasound study including 469 patients, carotid abnormalities (defined as tortuosity, kinking and coiling) were more frequent in patients older than 65 years than in younger subjects (70% versus 29%; P<0.001).[1] Similarly, in a large retrospective study based on cervical Doppler ultrasounds, Martins et al[27] found internal carotid artery abnormalities, including tortuosity (carotid kinking 80%, coiling in 16% and looping in 1%) in 2678 patients (13.5%) out of a total of 19 804 patients examined.

Sex

Several studies suggest an association between arterial tortuosity and female sex. Underlying pathophysiologic mechanisms may include mechanical factors, such as the smaller diameter of arteries in women versus men, leading to decreased wall strain in the premenopausal years, whereas at older age

Table 2. Genetic Syndromes Associated With Arterial Tortuosity

Syndrome Prevalence	Main Clinical Features	Transmission Genes	Arterial Tortuosity
Marfan syndrome 10/100 000	Ghent-2 criteria for diagnosis	Autosomal dominant *FBN1* encoding fibrillin	Aortic tortuosity means more severe aortic phenotype, higher probability of aortic dissection.[6]
	Aortic root dilatation or dissection		
	Ectopia lentis, arachnodactyly, pectus carinatum		
Loeys-Dietz syndrome 1/100 000	Hypertelorism, bifid uvula/cleft palate	Autosomal dominant *TGFBR1, TGFBR2, SMAD2, SMAD3, TGFB2, TGFB3*	Head, neck arterial tortuosity[44–46] most prominent but can be generalized.
	Arterial/aortic aneurysms and tortuosity, early aortic rupture		
Aneurysms osteoarthritis syndrome <1/1 million	Early-onset osteoarthritis	Autosomal dominant *SMAD3*	Tortuosity of cerebral, thoracic and abdominal arteries[47,48]
	Arterial/aortic tortuosity and aneurysms		
	Hypertelorism, abnormal palate or uvula		Early-onset dissections at smaller diameters[49]
Autosomal recessive cutis laxa 1B 1/1 million	Redundant, inelastic skin, joint laxity, hernias	Autosomal recessive *FBLN4/EFEMP2*	Aortic aneurysms, arterial tortuosity, stenosis[50]
	Developmental delay, craniofacial anomalies		Neck and brain vessel tortuosity, lethal in infants[51]
	Elongation, arterial tortuosity		
Arterial tortuosity syndrome <1/1 million	Tortuosity, elongation, stenosis or aneurysms in major and medium-size arteries	Autosomal recessive *SLC2A10*	Case reports in adults; marked tortuosity of the aorta and middle-size arteries[52]
Menkes disease incidence 2.8/1 million	Hypotonia, developmental delay, seizures, skin and joint laxity, twisted hair, hypopigmentation, bladder diverticulae	X-linked *ATP7A*. Deficient Cu-dependent enzymes	Case reports of marked cerebrovascular tortuosity[53]

the opposite is true. Hormonal factors and their changes over lifetime also have an impact on inflammation, atherosclerosis, and arterial remodeling. Estrogen decreases deposition of collagen and increases deposition of elastin.[28] In contrast, progesterone attenuates the increase in elastin deposition observed with 17-β-estradiol alone. Accordingly, high cyclic progesterone levels in premenopausal women may attenuate the beneficial effects of 17-β-estradiol on the elastin/collagen ratio of the vascular wall. After menopause, low 17-β-estradiol levels enhance vascular stiffness and lower arterial compliance, resulting in more stiffened arteries and higher pulse pressure in elderly women than in age-matched males.[28,29]

In the large study of Martins et al,[27] already mentioned above, the prevalence of internal carotid artery anomalies was higher in females than in males (17% versus 10% $P<0.01$). Along the same lines, a study including 870 patients (32% women) who underwent coronary angiography for chest pain found a significant relation between female sex and coronary artery tortuosity (45% versus 19.7%, $P<0.001$).[30] Finally, Groves et al[31] studied coronary tortuosity in 1221 patients who underwent coronary angiography. Severe coronary tortuosity, defined as 2 consecutive 180° turns in a major epicardial artery was found in 12.5% of all cases. The proportion of female patients was significantly higher in the tortuosity group (71% versus 50%; $P=0.039$).

Hypertension

Thirty-four years ago, studying Streptozotocin-induced diabetic rats and hypertensive rats obtained by renal artery clipping, Factor et al[32] found a higher prevalence of vascular abnormalities (myocardial microvascular tortuosity, focal constrictions, and microaneurysm formation) in hypertensive-diabetic rats versus controls or diabetic animals (number of vessels with abnormalities: 8.4 versus 2.1 versus 2.0; $P<0.0001$). These alterations were also present in normoglycemic hypertensive rats but to a lesser extent (4.4 versus 2.1, $P<0.01$).

The association between arterial tortuosity and hypertension was subsequently documented in human studies. Pancera et al[33,34] showed an association between arterial hypertension and kinking of the carotid artery assessed by Echo-Doppler in 2 cross-sectional studies, including 3300 ($P<0.001$) and 590 patients ($P<0.02$), respectively. In the study of Li et al,[35] 723 out of 1010 patients undergoing coronary angiography for chest pain were hypertensive, and the prevalence of coronary tortuosity was 39%. In multivariate logistic regression analysis, hypertension was an independent predictor of coronary tortuosity ($P=0.006$). In 2018, in hypertensive patients, the same authors found an association between coronary artery tortuosity, systemic inflammation, and the risk of lacunar infarction.[36]

Diabetes Mellitus

Diabetes mellitus seems to be mostly associated with tortuosity of small vessels (arterioles); see online-only Data Supplement.

Obesity

A limited number of studies also suggest an association between tortuosity and body mass index. In a Chinese case-control study including 116 patients with bilateral internal carotid artery tortuosity and 116 matched controls, TI was linearly associated with body mass index ($P<0.001$). For each increase of 1 kg/m^2, there was a corresponding 1.59-fold increase in the risk of carotid artery tortuosity ($P<0.001$), which persisted after adjustment for classical cardiovascular risk factors.[37] Similarly, a Japanese study including 45 post-stroke patients found a correlation between tortuosity of the aorta, body mass index ($P<0.01$), and waist circumference ($P<0.05$).[38]

Atherosclerosis

Atherosclerosis has a controversial role in the pathophysiology of arterial tortuosity (see online-only Data Supplement).

Other

Arterial tortuosity is also a feature of sickle cell disease.[39] More limited evidence suggests an association between arterial tortuosity and abnormal left ventricular relaxation,[40] Takotsubo cardiomyopathy,[41] and dementia.[42,43]

Inherited Arteriopathies Associated With Arterial Tortuosity

In this section, we review the main genetic syndromes associated with arterial tortuosity. The mode of inheritance and causative genes are summarized in Table 2.

Marfan Syndrome

The best-known genetic aortopathy is Marfan syndrome, an autosomal dominant connective tissue disorder first described by Antoine Marfan in 1896 and characterized by manifestations in the cardiovascular, skeletal, ocular, and other organ systems.[54] Although tortuosity is not a classical feature of Marfan syndrome, vertebral artery TI measured on magnetic resonance angiography scans is significantly higher in Marfan and LDS compared with controls (median 26 and 58 versus 4.5; $P<0.001$ for both). In Marfan syndrome, a higher vertebral artery TI was associated with earlier age at first cardiovascular surgery and increased rate of surgical interventions.[3,55]

Furthermore, 211 Marfan patients were evaluated for tortuosity of the aorta using the aortic TI (ATI) on magnetic resonance imaging. ATI was slightly lower in controls versus sex-, age- and height-matched Marfan patients (1.82±0.1 versus 1.92±0.2; $P=0.048$). Patients who developed aortic dissection or required aortic surgery during the 4 years of follow-up had a significantly higher ATI at baseline (1.98±0.2 versus 1.86±0.2; $P=0.002$). A moderate but statistically significant correlation has been noted between ATI and age ($r=0.281$; $P<0.001$), aortic root diameter ($r=0.223$; $P=0.006$), and aortic volume expansion rate ($r=0.177$; $P=0.026$). Patients with an ATI >1.95 had a 13-fold higher probability of aortic dissection or aortic surgery ($P<0.001$) and a 12-fold higher probability of developing an aortic dissection ($P=0.003$) compared with patients with an ATI <1.95. During follow-up, ATI was the single predictor of aortic dissection ($P=0.039$).[6]

Loeys-Dietz Syndrome

The diagnosis of LDS classically relies on a triad of clinical findings, arterial tortuosity, and aneurysms being distinctive

features of this syndrome, together with hypertelorism and bifid uvula. All 11 princeps cases presented arterial tortuosity.[56] Although the classical description includes widespread aortic and arterial tortuosity, the head and neck arteries seem to be predominantly affected.[44] All genetically confirmed LDS patients in a series (n=25) displayed head and neck vessel tortuosity on computed tomography angiography or magnetic resonance imaging.[45] Similarly, in a review of published cases, arterial tortuosity was frequently found in the head and neck (carotid 55%, vertebral 56%, intracranial 37%), whereas tortuosity of the aorta or of the other vessels was only reported in 5% to 10% of the cases.[46] A recent retrospective study analyzing computed tomography angiography of 54 patients with LDS showed that patients with higher carotid TI were more likely to require aortic root replacement ($P<0.001$).[7] Since the initial discovery of mutations in the genes encoding the transforming growth factor beta receptors (*TGFBR1, TGFBR2*) as causal LDS genes, 4 additional genes (*TGFB2*, *TGFB3*, *SMAD2,* and *SMAD3*) have been identified. The degree of vascular involvement, including arterial tortuosity, is most prominent in patients with *TGFBR1/2* or *SMAD3* mutations. Aortic tortuosity was identified as a prognostic marker for aortic aneurysm/dissection development in 214 patients with *TGFBR1/2* mutations.[5]

Aneurysms Osteoarthritis Syndrome

Aneurysms osteoarthritis syndrome, caused by *SMAD3* mutations, is a rare disease first described by van de Laar et al[47] in 2011 and is considered a variant of LDS. In a Dutch family consisting of 22 patients with aneurysms-osteoarthritis syndrome, arterial tortuosity was documented in 53% of cases in the cerebral, thoracic, or abdominal beds.[47] Patients present marked arterial tortuosity and earlier dissections occurring at smaller diameters. In 7 families with a pathogenic *SMAD3* variant including 44 aneurysms-osteoarthritis syndrome patients, arterial tortuosity was found in the large vessels of the abdomen and thorax (48% of cases) as well as in the brachiocephalic and intracranial vessels (50% of cases).[49] In another study involving 45 patients with this syndrome, aortic tortuosity was found in 38% of cases, tortuosity of other thoracic and abdominal arteries in 38%, and tortuosity of the cerebral arteries in 50% of patients.[48]

Autosomal Recessive Cutis Laxa Type 1

Although categorized as cutis laxa subtype, this connective tissue disorder is mainly characterized by vascular anomalies, with less common lung emphysema and diverticulae of the urinary and gastrointestinal tract.[57,58] In a study including 39 patients, the predominant vascular findings were aortic aneurysms, arterial tortuosity, and stenosis.[50] Autosomal recessive cutis laxa 1 was described as a syndrome with lethal outcome in 24 infants (13 males, 11 females), involving arterial dilatation and tortuosity of the neck and cerebral vessels, related to a novel mutation in the *FBLN4* gene.[51] Arterial tortuosity in AR-cutis laxa type 1 is more generalized than in LDS.

Arterial Tortuosity Syndrome

Arterial tortuosity syndrome is an autosomal recessive disorder described typically in children, characterized by tortuosity, elongation, stenosis, and aneurysm formation in the major arteries because of disruption of elastic fibers in the medial layer of the arterial wall, first described in 1967.[59] It shares common clinical features with LDS and recessive cutis laxa, such as hyperextensible skin, arterial aneurysms, and arterial tortuosity. Fifty new arterial tortuosity syndrome patients were recently described. As with autosomal recessive cutis laxa type 1, tortuosity of the aorta and medium-size arteries was a constant finding (90%), mostly affecting the head, neck, and pulmonary arteries (48%).[52] Only a few cases have been reported in adults, with marked tortuosity of the aorta, pulmonary arteries, and most middle arteries.[60–62] Typically, the disease is also associated with pulmonary artery stenosis (57%).

Menkes Disease

First described in 1962, Menkes syndrome is an X-linked, neurodegenerative disorder resulting from deficient activity of copper-dependent enzymes, which classically affects males, characterized by hypotonia, developmental delay, seizures, skin and joint laxity, and twisted hair.[63] Tortuosity of intracranial arteries has been occasionally reported.[53,64]

Other

Other connective tissue disorders that have occasionally been associated with arterial tortuosity are autosomal dominant cutis laxa due to elastin mutations[65] and X-linked periventricular nodular heterotopia—related to *FLNA* mutations.[66] Arterial tortuosity is also identified in nonsyndromic form of thoracic aortic aneurysm caused by *PRKG1* mutations[67] and in Turner syndrome.[68]

Finally, arterial tortuosity restricted to the retinal vessels has been described in William Beuren syndrome,[69] Familial Retinal Arteriolar Tortuosity,[70] Hereditary Angiopathy, Nephropathy, Aneurysms, and Muscle Cramps Syndrome,[71] and Fabry disease.[72]

Table 3. Standardized Measurement and Reporting of Arterial Tortuosity: a Proposal

Conduct all measurements of length and angle in 3-dimensions
Define the fixed anatomic points within which tortuosity is to be measured
State the proximal and distal vessel diameter (or cross-sectional area)
Measure the minimum distance between the fixed anatomic points and the maximal arterial midline true path length
Record the number of inflection points between the fixed anatomic points (inflections at branching points should also be recorded)
Measure the angle at all points of inflection between the fixed anatomic points such that the recorded angle at each point is the maximum 2-dimensional angle achieved in any 3-dimensional plane.
These elements can be used to assess
The tortuosity index, which gives a measure of vessel redundancy per unit length
The no. of inflections exceeding a defined threshold angle (>30°, >60°, and >90°) indexed to vessel length
The sum of angles >30° at all points of inflection indexed to vessel length
Any comparison should be limited to vessel segments of equivalent diameter (data on proximal and distal diameters should always be reported).

Arterial Tortuosity, SCAD, and FMD

In the recent European Society of Cardiology Position Paper[73] and the American Heart Association Scientific Statement on SCAD,[74] coronary tortuosity is listed among the possible angiographic findings in patients with SCAD.

The link between SCAD and arterial tortuosity was first studied in a large angiographic series including 246 patients with SCAD.[4] Coronary artery tortuosity (defined as the presence of ≥3 consecutive curvatures of 90° to 180° in end-diastole in a major epicardial coronary artery ≥2 mm in diameter) was 4-fold more common in patients with SCAD compared with controls (78% versus 17%, $P<0.0001$). Tortuosity features, such as the symmetrical tortuosity sign, multivessel symmetry sign, or corkscrew sign (Table 1) were also significantly more frequent in patients with SCAD (50% versus 14%, $P<0.001$; 24% versus 11%, $P<0.001$; 37% versus 4%, $P<0.001$, respectively). Severe coronary artery tortuosity, defined as ≥2 consecutive curvatures of ≥180° in a major coronary artery ≥2 mm in diameter, was associated with a trend towards recurrent SCAD events, with dissections occurring mostly within the tortuous segments (80%). Furthermore, extracoronary FMD was associated with a higher coronary tortuosity score (4.76±1.63 versus 3.82±1.95; $P=0.008$) and higher prevalence of the angiographic corkscrew and multivessel symmetry signs (44% versus 20%, $P=0.009$; 27% versus 10%, $P=0.03$, respectively). Notably, the frequency of marked extracoronary tortuosity was low, at least for the carotid artery (5%). However, as only 112 out of 246 patients (45%) were explored for extracoronary vascular abnormalities, this prevalence may be underestimated.[4]

In the case of 39 SCAD patients (97% women) followed at the Mayo Clinic, the prevalence of extracoronary FMD

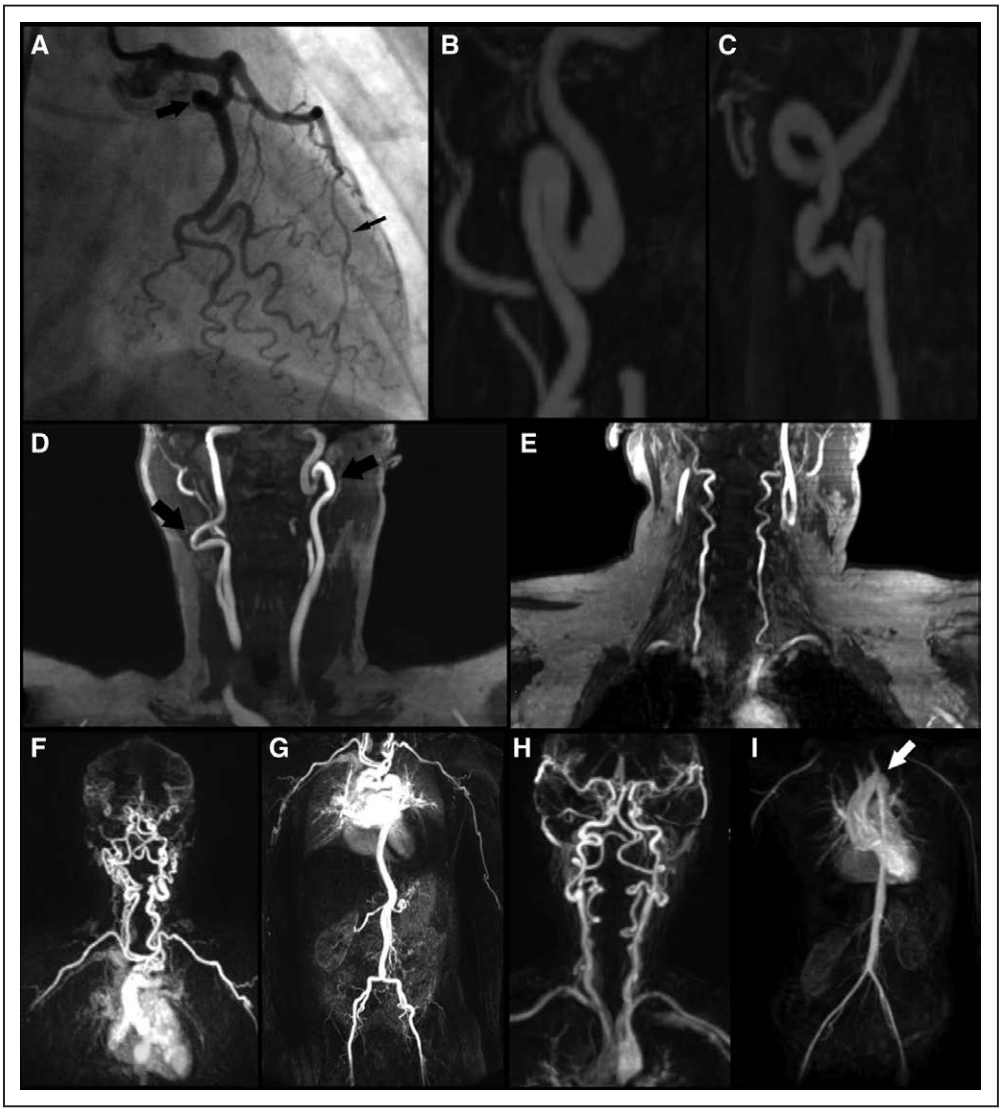


Figure 3. Examples of arterial tortuosity in various clinical contexts. **A**, Tortuous circumflex coronary artery with a proximal spiral loop (thick arrow) and multiple terminal loops in a patient with spontaneous coronary artery dissection (SCAD). Note dissection of left anterior descending artery (thin arrow). **B**, S-shaped tortuosity of the right internal carotid artery in a patient with fibromuscular dysplasia. **C**, Right vertebral artery loops in the same patient. **D**, bilateral carotid loops (arrows) in a patient with SCAD. **E**, Bilateral vertebral artery tortuosity in another SCAD patient. **F** and **G**, Extreme widespread aortic and arterial tortuosity in an 8-y-old male patient with arterial tortuosity syndrome. **H** and **I**, Aortic root aneurysm and arterial tortuosity, most pronounced in the vertebral and carotid arteries in an 8-y-old female patient with Loeys-Dietz syndrome. Please also note the elongated aortic arch (white arrow).

lesions was 69%. Aortic tortuosity and common iliac artery tortuosity were each present in 10% of patients.[75] In addition, in another report from the same group, involving 115 SCAD patients who underwent computed tomography angiography of the head, neck, chest, abdomen, and pelvis, 45% met the diagnostic criteria for extracoronary FMD. Aortic undulation was present in 3% of patients, carotid loops in 3%, and vertebral tortuosity in 1%, whereas intracranial vessel tortuosity was detected in 5% of patients (2 out of 40 patients screened).[76]

Notably, in these different studies, the definition and methods used for assessing extracoronary tortuosity were not described, and the other recent series of patients with SCAD[77–80] did not report the prevalence of extracoronary arterial tortuosity.

Finally, a recent case-control study including 102 patients with spontaneous cervical artery dissection using vertebral artery TI calculated on magnetic resonance angiography images found increased tortuosity in affected patients (median 7.3 versus 3.4; $P \leq 0.001$).[81]

Along with dissections and aneurysms, arterial tortuosity is also part of the vascular spectrum of FMD, although its presence is not deemed sufficient to establish the diagnosis, in the absence of focal or multifocal stenosis.[74,82] In a case-control study including 116 patients with FMD, an association between a tortuosity pattern of the internal carotid artery named the S curve (Table 1) and FMD was shown.[12] The S curve was 10× more frequent in patients with FMD versus age- and sex-matched controls (32% versus 2.7%; $P<0.0001$). Along the same lines, van Twist et al[83] reported 5 patients with resistant hypertension and chest pain. Coronary angiographies showed no significant coronary stenosis but marked coronary tortuosity in all cases. Further renal or carotid artery imaging prompted by the presence of coronary tortuosity led to the diagnosis of FMD in the corresponding arterial beds. The prevalence of coronary and extracoronary tortuosity needs to be studied in larger cohorts of patients with FMD.

Conclusions and Future Directions

Incidental finding of marked arterial tortuosity should prompt a search for predisposing factors or associated clinical conditions (Figures 2 and 3), with possible substantial impact for the patient and their family.

There is growing evidence that arterial tortuosity has considerable potential clinical and research utility as a biomarker for both rare (eg, genetic, SCAD, FMD) and more frequent arterial diseases. However, its incorporation requires adoption of a standardized approach to measurement, terminology, and reporting. We therefore propose:

1. A uniform recommended terminology for describing tortuosity with definitions (Table 1).
2. A common approach to measurement and reporting of tortuous vessels (Table 3).

Adoption of this approach will allow detailed cross-comparison between different studies. Further research will then be required to work towards age and gender-specific normal ranges for tortuosity indices in different vascular beds.

Other research directions may include:

- Development of an evidence-based algorithm to look for the underlying causes of arterial tortuosity
- Establishment of national and international registries enrolling patients with marked idiopathic arterial tortuosity
- Prospective studies aiming at unraveling the natural history and prognostic value of various forms of arterial tortuosity
- Creation of associated biobanks of tissue specimens aiming at determining the pathological abnormalities underlying arterial tortuosity
- Identification of susceptibility genes associated with idiopathic arterial tortuosity

To meet these objectives, the authors make a plea for the establishment of an international multidisciplinary initiative on arterial tortuosity involving vascular geneticists, experts in FMD and SCAD, radiologists, bioengineers, and basic scientists.

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