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Arterial Tortuosity in Genetic Arteriopathies

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Abstract

Purpose of Review—Arterial tortuosity is emerging as a common feature in genetically mediated thoracic aortic disease that may be prognostic. This review will summarize recent literature on arterial tortuosity in the setting of genetic arteriopathies.

Recent Findings—While arterial tortuosity has been primarily described in Loeys-Dietz syndrome due to *TGFBR1* and *TGFBR2* mutations and in arterial tortuosity syndrome due to *SLC210A* mutations, recent studies that use quantitative measures of tortuosity suggest that tortuosity is present in many other genetic conditions associated with aortic dilation and dissection. The mechanisms of the development of tortuosity in these disorders are not fully understood, but are founded in the concept that there is abnormal, pathologic arterial lengthening in a fixed space, resulting in more tortuous vessels. Further studies suggest that patients with increased arterial tortuosity are at increased risk of adverse cardiovascular events, including aortic surgery, aortic dissection, and death.

Summary—Arterial tortuosity in commonly present in genetically mediated aortic disease. Given the suboptimal performance of aortic dimension alone in predicting aortic dissection, quantification of tortuosity may augment the current algorithms for determining risk in patients with aortic disease.

Keywords

tortuosity; Marfan; Loeys-Dietz; aortic aneurysm; aortic dissection

Introduction

Arterial tortuosity, defined as the property of the artery having many turns, is becoming more recognized as a common feature in genetic conditions associated with aortic disease. While arterial tortuosity has been most commonly described in Loeys-Dietz syndrome (*TGFBR1/2*)[1] and arterial tortuosity syndrome (*SLC2A10*)[2], it has been observed in multiple other genetic disorders associated with aortic dilation and dissection, including Marfan syndrome (*FBN1*)[3], aneurysms-osteoarthritis syndrome (*SMAD3*)[4,5], and familial thoracic aneurysm and aortic dissection (FTAAD) due to *TGFB2*[6] and *PRKG1* mutations[7]. A limitation of the majority of these reports is the qualitative assessment of tortuosity, which

Conflicts of Interest: None

likely varies significantly between those interpreting radiologic studies, unless severe tortuosity is present. Recent measures to quantify tortuosity have allowed more detailed and rigorous study of tortuosity[3,8]. A study in 2011 demonstrated that increased tortuosity, as measured by the vertebral artery tortuosity index on magnetic resonance angiography (MRA), is associated with earlier adverse cardiovascular outcomes in children and young adults with Marfan syndrome and Loeys-Dietz syndrome (Figures 1 and 2). These findings, along with studies suggesting that aortic dimension alone is a poor predictor of aortic dissection[9,10], have highlighted tortuosity as a potential prognostic indicator to aid in determining risk and appropriate surgical timing.

This review will highlight the recent literature regarding arterial tortuosity, including proposed mechanisms, new descriptions of tortuosity in different genotypes and phenotypes, and the association between arterial tortuosity and cardiovascular outcomes.

Text of Review

Mechanisms of tortuosity

The exact cause and timing of arterial tortuosity in these conditions are unclear, although several mechanisms are postulated. An overarching hypothesis is that there is abnormal gradual lengthening of the arteries in a fixed space, resulting in forced curving and bending of the vessels. This lengthening may be a maladaptation to axial stress along the vessel, as an intrinsic effort to reduce stress along the vessel[11]. Another possibility is that the genetically abnormal vessel wall actually has lower manifest axial tension, which has been shown in manipulated rabbit carotid arteries to result in increased tortuosity[12]. Increased TGFβ activity has also been postulated to affect the degree of arterial tortuosity[13].

Most studies to date have centered on the lengthening and tortuosity observed in with aging, hypertension, and atherosclerosis[14]. Indeed, data on vertebral artery tortuosity by Alicioglu et al suggest again that increased tortuosity is seen in aging[15,16]. It remains unclear if the mechanisms in genetically mediated aortic disease are the same. The study by Franken et al (discussed in more detail below) suggested a small but gradual increase in aortic tortuosity in patients with Marfan syndrome over a three-year period, supporting this hypothesis. Morris et al., however, demonstrated the presence of significant vertebral artery tortuosity at a very young age in some patients with aortopathy, with a decrease and then plateau in tortuosity during adolescence[17]. The cause of the decrease in tortuosity was postulated to be secondary increases in height (resulting in ‘stretching’ of the artery), medical therapy, or changes in vascular signaling with age. Some investigators have proposed that the presence of an aneurysm may be actually reduce a “critical buckling pressure” of the artery, and that buckling may be a mechanism of tortuosity in genetically mediated aortopathy[18]. While there are multiple proposed mechanisms, further work is needed to better delineate etiologies and timing of tortuosity.

Conditions with associated arterial tortuosity

Arterial tortuosity has been previously described in several genetically mediated conditions associated with aortopathy (Table 1). For most of the conditions listed in the table, tortuosity has only been described qualitatively. Reports usually describe tortuosity in the head and

neck vessels, but affected aortas are also described. Conditions in which tortuosity has been described in detail or only recently are detailed below, including recently evaluated conditions: x-linked dominant periventricular heterotopia, type 1b autosomal recessive cutis laxa, occipital horn syndrome, and Turner syndrome.

Loeys-Dietz syndrome due to TGFBR1 and TGFBR2 mutations—The first report of Loeys-Dietz syndrome described diffuse arterial tortuosity, and images included examples of aortic and carotid tortuosity[19]. Rodrigues et al qualitatively evaluated the neurovascular system[26]. All 25 patients evaluated in the study qualitatively had arterial tortuosity present in the neurovascular system, with specific examples of the common and internal carotid arteries given. Kono et all compared the vascular systems in 10 patients Loeys-Dietz syndrome compared to 20 patients with Marfan syndrome[27]. Tortuosity of the vertebral arteries and carotid arteries was graded using a semi-quantitative score ranging from 0–3. The results of the study demonstrated that the vertebral arteries showed the most tortuosity in both conditions, and that vertebral artery tortuosity was greater in Loeys-Dietz syndrome than in Marfan syndrome. Morris et al quantified vertebral artery tortuosity in 13 patients with Loeys-Dietz syndrome and 57 patients with Marfan syndrome, as well as 20 other patients with either Ehlers-Danlos syndrome or a diagnosis of non-specific connective tissue disorder[3]. Using the quantitative measure, the vertebral artery tortuosity index (VTI), they demonstrated significantly increased vertebral artery tortuosity in Loeys-Dietz syndrome and Marfan syndrome compared to controls. Diedrich et al described increased basilar artery and vertebral artery tortuosity in Loeys-Dietz syndrome compared to normal controls using a variation of the quantitative measure distance factor[28].

Marfan syndrome—Tortuosity was only rarely described in confirmed Marfan syndrome until recently. The papers discussed above by Kono and Morris both demonstrated vertebral artery tortuosity in Marfan syndrome[3,27]. Franken et al evaluated aortic tortuosity in 211 patients with Marfan syndrome compared to 20 controls using the aortic tortuosity index (ATI, Figure 3). The ATI was derived from a magnetic resonance angiogram (MRA), defined as the ratio of the length of a centerline through the entire aorta (from annulus to aortic bifurcation) divided by the Cartesian (geometric) distance between aortic valve annulus and aortic bifurcation. The study demonstrated that patients with Marfan syndrome had significantly increased tortuosity compared to controls[29]. Further investigated associations with outcomes are discussed below.

Arterial Tortuosity Syndrome—Given that the predominant feature of arterial tortuosity syndrome (due to a SLC2A10, mutation encoding Glucose Transporter 10) is arterial tortuosity, significant tortuosity has been described since the first description of the syndrome[2]. All reports to date have been qualitative.

X-linked dominant periventricular heterotopia—X-linked dominant periventricular heterotopia is caused by mutations in filamin-A (*FLNA*)[30]. In addition to periventricular nodular heterotopia and epilepsy, vascular features are common, including patent ductus arteriosus, bicuspid aortic valve, and dilation of the sinuses of Valsalva or the thoracic aorta[30]. Reinstein at al. evaluated the vertebral artery tortuosity in a mother and daughter

with periventricular heterotopia caused by a Filamin A mutation (8-bp deletion in exon 6, c. 883_890 that constitutes a null *FLNA* allele). The mother was a 38-year-old female with joint laxity who ultimately had a 5.7 cm thoracic aortic aneurysm. Her 19-year old daughter had diffuse heterotopia and was loose jointed, bruised easily, and had soft skin. The daughter had a 2.7 cm right subclavian aneurysm. The vertebral artery tortuosity index (VTI) was calculated from MRA in both patients, and tortuosity was not increased, despite significant arterial dilation.

Cutis laxa due to FBLN4/EFEMP2 mutations—Severe tortuosity has previously been described in a rare form of cutis laxa caused by a mutation in the gene that encodes fibulin-4 (*FBLN4 also known as EFEMP2)*[20,21,31]. Rajeshkannan at al described in detail the imaging findings in large cohort (n=31) of related patients with a novel fibulin-4 (*FBLN4*) mutation that results in a severe lethal inherited arteriopathy syndrome (homozygous c.608A>C, p.Asp203Ala mutation in exon 7, chromosome 11q13)[32]. Twenty-seven affected children died by age 3 years. Cardiovascular features included aneurysmal dilatation, elongation, tortuosity and narrowing of the aorta, pulmonary artery and their branches. The phenotype included a variable combination of cutis laxa (52%), long philtrum with a thin vermillion (90%), micrognathia (43%), hypertelorism (57%), prominent eyes (43%), sagging cheeks (43%), long slender digits (48%), and visible arterial pulsations (38%). In addition to a high prevalence of both aortic dilation and stenosis, diffuse arterial tortuosity was noted, including in the cerebral vessels, neck vessels including the vertebral arteries, and the aorta. Quantitative measures of tortuosity were not performed.

Aneurysms-osteoarthritis syndrome due to SMAD3 mutations—Arterial tortuosity was discussed in the first paper describing aneurysms-osteoarthritis syndrome[4]. The cardiovascular findings were reviewed in greater detail by van der Lindle et al[5]. They qualitatively describe arterial tortuosity throughout the great vessels of the abdomen and thorax 11 of 23 affected patients with cardiovascular imaging, with specific examples given of splenic artery and internal carotid tortuosity.

Menkes disease/Occipital horn syndrome—Mutations in *ATP7A* cause Menkes disease and occipital horn syndrome, and have been associated with arterial aneurysms[22,33,34]. Two recent papers highlight qualitatively marked cerebrovascular tortuosity seen in this condition[23,24].

Turner syndrome—In a brief report of 26 children and young women with Turner syndrome undergoing cardiac magnetic resonance angiography, mildly increased vertebral artery tortuosity was noted in a subset of patients using VTI, and this was associated with larger aortic dimensions[25].

Tortuosity and outcomes

In addition to the prior study by Morris et al. that demonstrated an association between vertebral artery tortuosity and adverse cardiovascular outcomes, three recent studies support the hypothesis that increased tortuosity is an indicator of poorer prognosis in aortic disease, as previously proposed[3]. Shirali et al investigated whether anatomic measurements from a

CT angiogram could predict Type B aortic dissection in hypertensive adults[8]. Of note, patients with known genetically mediated disease were specifically excluded. While this study did not address genetically mediated aneurysms, it is one of the first to investigate the predictive value of tortuosity. In addition to length, diameter, and volume of the aorta, ascending aortic and thoracic aortic tortuosity were examined, as well as arch vessel angulation in hypertensive adults with and without Type B aortic dissection. Tortuosity of the aorta was defined as the length of the midline within the aorta divided by the linear distance between the aortic root and the iliac bifurcation, and tortuosity of the ascending aorta was defined as the measured length of the ascending aorta divided by the linear distance between the aortic root and left subclavian artery.

Patients with aortic dissection were found to have longer aortas, greater aortic dimension and volume, and greater arch tortuosity. When all the variables were included in a multivariable model, arch tortuosity only added a small amount of predictive power when larger arch diameter, longer arch length, and decreased brachiocephalic artery angle were included. While this study continues to support tortuosity as a prognostic indicator, other anatomic factors may be stronger. In addition, images analyzed in those with dissection were after the dissection, so the anatomic variables studies could have been influenced by presence of the dissection.

Franken et al also examined the tortuosity of the aorta, this time in 211 patients with Marfan syndrome who were enrolled in the Dutch COMPARE trial[13]. For this, they utilized the aortic tortuosity index (ATI, discussed above). The authors demonstrated that there were significant but weak correlations between both baseline larger aortic volume and larger aortic root diameter and higher ATI ($r = 0.280$, $p = 0.001$ and $r = 0.223$, $p = 0.006$, respectively).

In this adult cohort, they demonstrated a slow but nonsignificant increase in ATI over 3 years of follow up. Higher ATI was not associated with faster aortic root growth over the course of the study ($r = 0.043$, $p = 0.63$), but was strongly associated with occurrence of Type B aortic dissection ($p=0.002$) and reaching the combined clinical endpoint (prophylactic aortic surgery, aortic dissection and death, $p=0.015$). In multivariable Cox regression analysis, higher ATI was the only variable associated with earlier aortic dissection, and higher ATI and larger aortic root dimension were independently associated with earlier occurrence of the combined endpoint. The authors found that most discriminating value of ATI for aortic dissection over the three year period was >1.95. Interestingly, Losartan had no effect on ATI over the study, and use of Losartan was not associated with lower occurrence of dissection or the combined endpoint.

In the small study regarding Turner syndrome and vertebral artery tortuosity discussed above, the authors investigated the association between tortuosity (using VTI) and presence of BAV, aortic root z-score, and ascending aortic z-score. No patients in the study of children and young women had aortic dissection. Higher VTI was associated with larger aortic root z-score and larger ascending aortic z-score. VTI did not differ by BAV status or age. In multivariable analysis controlling for age, both BAV and higher VTI remained independently associated with larger ascending aortic z-scores. Of note, patients who had

received growth hormone had lower VTIs and poorer correlation between VTI and aortic dimensions than in patients not receiving growth hormone.

The relationship between dilation, tortuosity, and dissection in terms of cause and effect is still unclear. Authors in the papers by Franken et al and Hatakeyama propose that an altered flow profile through a tortuous aorta may independently lead to a more severe distal aortic phenotype and enhanced susceptibility to aortic dissections. This may be true, although no study investigating causation has been performed. It may be that aortic tortuosity and susceptibility to dissection coexist, and these are secondary to a yet unknown more primary etiology.

In the papers by both Franken and Morris et al., increased tortuosity was associated with adverse events completely independently of aortic dimension[3,13]. This was also previously demonstrated in abdominal aortic aneurysms[35]. Apart from aortic dimensions, quantitative measures to guide prophylactic aortic surgery are rare. Degree of tortuosity may ultimately prove to be a helpful component of the medical or surgical management algorithm.

Conclusions

Arterial tortuosity continues to be recognized as a common feature in genetically mediated aortopathies. The genetic disorders in which tortuosity is seen are not limited to TGF-b signaling pathway genes, but also include genes responsible for extracellular matrix proteins, vascular smooth muscle relaxation, and copper transport. Mild tortuosity is also apparent in Turner syndrome, and was associated with more significant aortopathy. Studies continue to suggest that increased vertebral artery and arch tortuosity are markers for more severe disease and are associated with earlier or more severe outcomes, most recently Type B aortic dissection. Continued work to standardize quantification and study outcomes in larger populations is indicated to determine if tortuosity should be included in decision-making about patients with genetic aortopathies.

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Key points

1. Arterial tortuosity is present in multiple genetic conditions associated with aortopathy.
2. Quantitative measures of arterial tortuosity of the aortic arch and vertebral arteries have been developed, and allow investigation of tortuosity in research studies.
3. The mechanisms of development of tortuosity in genetically mediated aortopathy are not known, but biomechanical studies suggest tortuosity may be secondary to pathologic lengthening of the vessel as an attempt to modify axial stress.
4. Increased arterial tortuosity is associated with earlier and more severe adverse cardiovascular events in Marfan syndrome and Loeys Dietz syndrome.

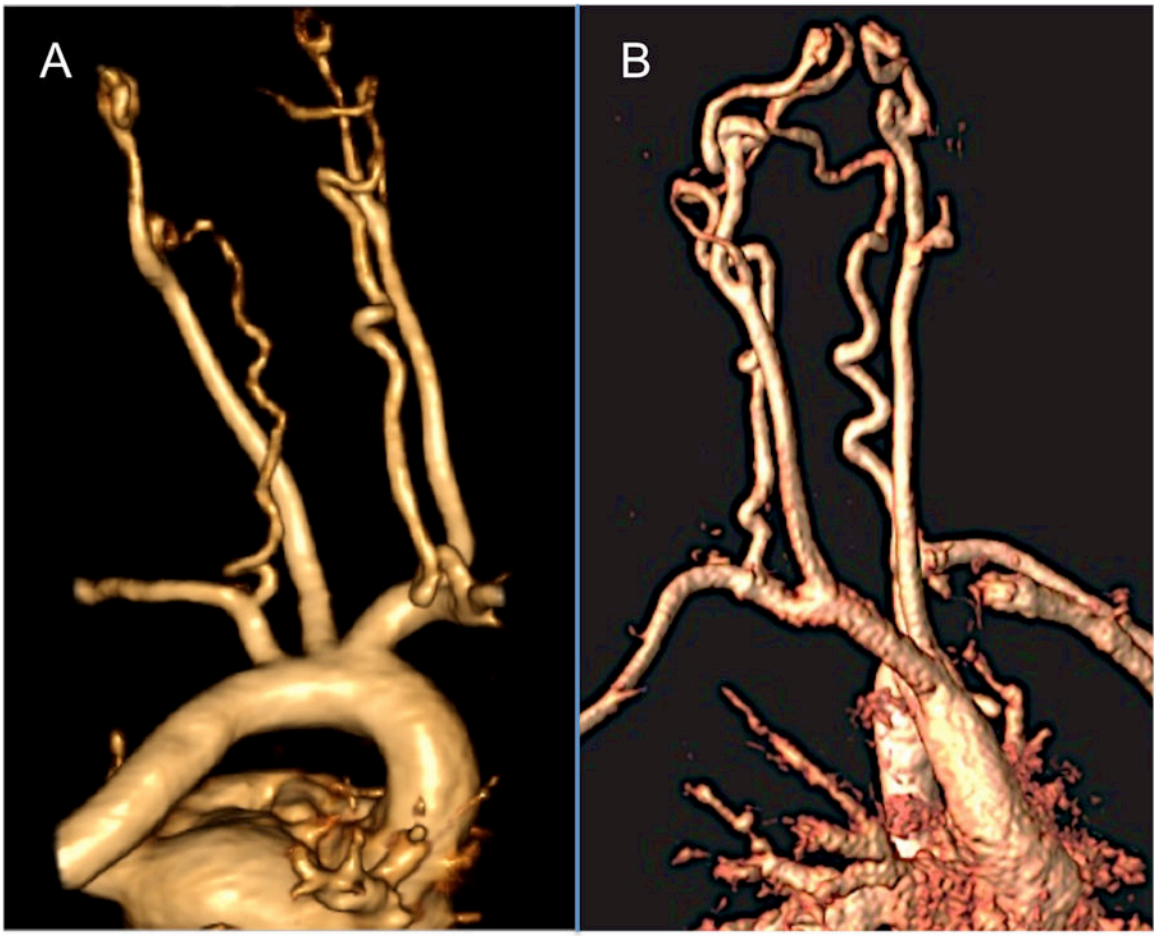

Figure 1.
Examples of vertebral artery tortuosity in Marfan syndrome with *FBN1* mutation (A) and Loeys-Dietz syndrome with a *TGFBR2* mutation (B).

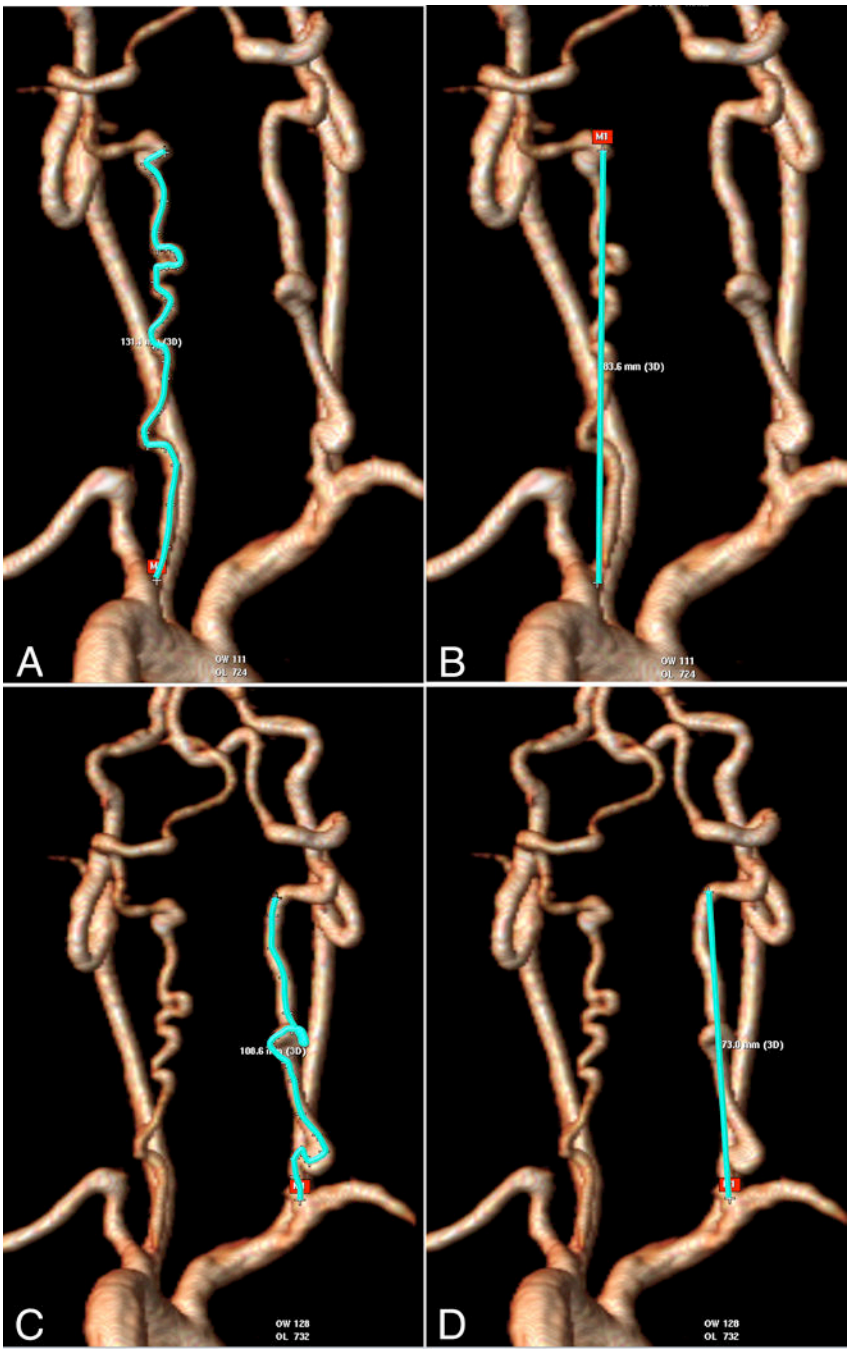

Figure 2.

Calculating the vertebral artery tortuosity index (VTI)[3]. This example uses a volume-rendered 3D magnetic resonance angiogram. Actual length (A and C) and straight length (B and D) of each vertebral artery are measured from the origin of vessel to the vertebral level C2 before the normal posteriolateral bend of the vessel. For both vertebral arteries, the distance factor is calculated: (actual/straight length−1)*100. The maximum distance factor of the two vessels is the VTI. In this example of a patient with Loeys-Dietz syndrome, the left vertebral artery distance factor is ((131.1/83.6)−1)*100=57. This can be thought of as

57% excess length of the vessel. The right distance factor is ((108.6/73.0)−1)*100=49, or 49% excess length. Therefore this patient's VTI is 57%. Images complements of Alex Dodd, Texas Children's Hospital.

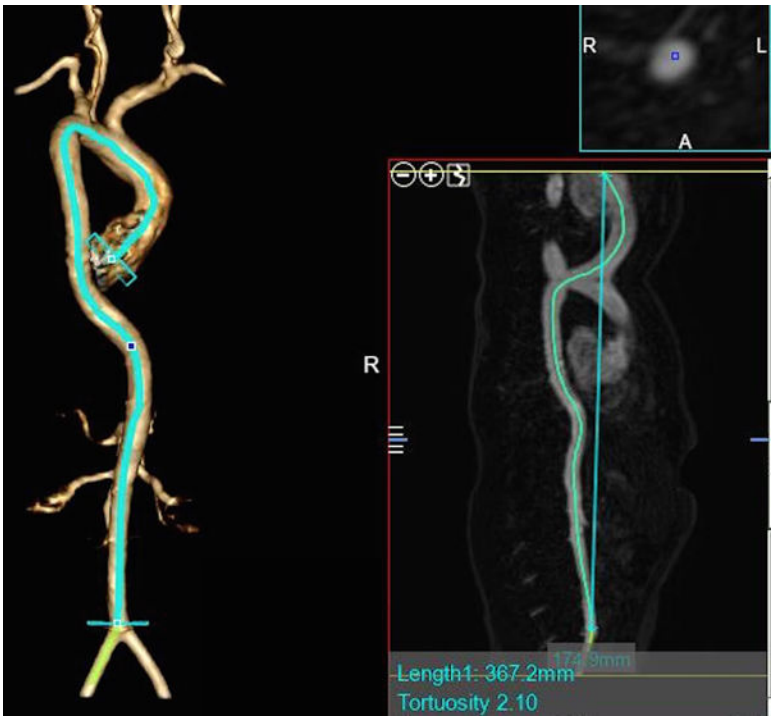

Figure 3.

Calculating the aortic tortuosity index (ATI), per Franken et al., International Journal of Cardiology 2015[29] from a 3D computed tomography angiogram. ATI is calculated as the ratio of aortic length (actual length) to geometric length (straight length). The aortic length (left side of image) was defined as the length of a centerline through the entire aorta (from annulus to aortic bifurcation) created by manually placed seeding points through the lumen of the aorta using post-processing software. Geometric length is the Cartesian distance between its 2 endpoints (added in smaller image on right, overlying the centerline). Aortic tortuosity index (ATI) is measured by dividing aortic length by geometric length. In this example in a patient with significant aortic tortuosity, aortic length = 367.2 mm, geometric length = 174.9 mm, ATI = 2.10. Images complements of Alex Dodd, Texas Children's Hospital.

Table 1

Genetic disorders associated with aortic disease and arterial tortuosity

TGFBR1[1,19]	Loeys-Dietz syndrome or FTAAD
TGFBR2[1,19]	Loeys-Dietz syndrome or FTAAD
FBN1[3]	Marfan syndrome
SMAD3[4,5]	Osteoarthritis-aneurysm syndrome or FTAAD
SLC2A10[2]	Arterial tortuosity syndrome
TGFB2[6]	FTAAD
PRKG1[7]	FTAAD
FBLN4/*EFEMP2*[20,21]	Cutis laxa
ATP7A[22–24]	Occipital horn syndrome/Menkes disease
Monosomy X/mosaic monosomy X[25]	Turner syndrome