Increased Vertebral Artery Tortuosity Index Is Associated With Adverse Outcomes in Children and Young Adults With Connective Tissue Disorders

Shaine A. Morris, MD; Darren B. Orbach, MD, PhD; Tal Geva, MD; Michael N. Singh, MD; Kimberlee Gauvreau, ScD; Ronald V. Lacro, MD

Background—Arterial tortuosity is described as a common and distinctive feature of Loeys-Dietz syndrome (LDS), yet reports on arterial tortuosity are based on qualitative observations and none have investigated an association between tortuosity and cardiovascular outcomes in LDS or other connective tissue disorders.

Methods and Results—We performed a retrospective analysis of 90 patients ≤50 years of age with Marfan syndrome, LDS, Ehlers-Danlos syndrome, or nonspecific connective tissue disorder who underwent thoracic contrast-enhanced magnetic resonance angiography. Controls (n = 30) underwent magnetic resonance imaging to exclude arrhythmogenic right ventricular dysplasia. Using a volume-rendered angiogram, vertebral arteries were measured along the curvature of the vessel (actual length) and linearly (straight length), and distance factor was calculated: [(actual/straight length−1)×100]. Each subject’s maximum distance factor was designated the Vertebral Tortuosity Index (VTI). The VTI was compared among diagnostic groups and among patients with cardiac surgery, dissection, and death. Median age at magnetic resonance imaging was 19.6 years (range 0.2 to 50.1). VTI interrater reliability was excellent (intraclass correlation coefficient = 0.987). The VTI was higher in Marfan syndrome (n = 57, median 26; interquartile range 10 to 49) and LDS (n = 13, median 58; interquartile range 18 to 92) compared with controls (median 4.5; interquartile range 3 to 6; P < 0.001 for both). Higher VTI was associated with younger age at surgery even when controlling for root size (adjusted P = 0.002). Vertebral tortuosity index ≥ 50 was associated with earlier age at dissection and death compared with VTI < 50 (P = 0.001 versus P < 0.001). We found no difference in age at surgery, dissection, or death in Marfan syndrome compared with LDS.

Conclusion—Arterial tortuosity measured by magnetic resonance angiography is a reproducible marker of adverse cardiovascular outcomes in connective tissue disorders. (Circulation. 2011;124:00-00.)

Key Words: aorta · genetics · Loeys-Dietz syndrome · magnetic resonance imaging · Marfan syndrome · heart defects, congenital · pediatrics

Arterial tortuosity of the head and neck vessels has been described as a frequent finding in the recently described Loeys-Dietz syndrome (LDS).1–5 Although published reports suggest that tortuosity is present in 84% to 100% of patients with LDS, there is no accepted definition or measure of proximal head and neck arterial tortuosity. In contrast, arterial tortuosity has been described rarely in Marfan syndrome (MS).6–8 Published series also suggest that patients with LDS, as compared to patients with MS, have more rapidly progressing aortic root dilation and may suffer aortic dissection at a smaller aortic root diameter.4 We hypothesized that arterial tortuosity is a marker for vascular fragility and that an objective measure of tortuosity for patients with connective tissue disorders (CTD) could be developed that would be associated with clinical outcomes. Using previously acquired magnetic resonance contrast-enhanced angiographic images, we employed a method of measuring vertebral artery tortuosity using distance factor: [(actual/straight length−1)×100]. Distance factor has been used as a measure of arterial tortuosity in other vascular systems, has been shown to be reproducible, and has been associated with systemic disease.9–11 Using distance factor, we developed a magnetic resonance angiography (MRA) index of vertebral artery tortuosity and evaluated its association with adverse cardiovascular outcomes including dissection, cardiac surgery, and death.

Clinical Perspective on p ·····

Methods

Subjects
Patients were identified by a search of the computer database of the Cardiovascular Program at Children’s Hospital Boston using the
following criteria: (1) Age ≥50 years with MS, LDS, Ehlers-Danlos syndrome (EDS), or nonspecific CTD (NSCTD); and (2) have undergone cardiac magnetic resonance imaging (MRI) with gadolinium-enhanced 3-dimensional (3D) MRA at our institution between January 1997 and May 2010. Patients were included in the NSCTD group if they were given a diagnosis of CTD by a cardiac geneticist at this institution but did not meet criteria for a specific diagnosis. Both the original and the recently revised Ghent criteria were applied for the diagnosis of MS.12-13 According to standard clinical practice, not all MS patients had fibrillin-1 (FBNI) mutation testing. All LDS patients had a documented transforming growth factor β receptor 1 or 2 (TGFBR1/2) mutation as well as clinical characteristics of LDS. Type I/II EDS was clinically diagnosed. Control subjects were patients ≤50 years of age who were referred for cardiac MRI to exclude arrhythmogenic right ventricular dysplasia and were found to have no significant structural heart disease, normal function, no aortic dilation, and no suspicion of CTD.

The medical record numbers of patients and controls were combined and reviewed in random order with all diagnostic information excluded. For each study subject, the most recent cardiac MRI with a technically adequate MRA was reviewed in a blinded fashion by a single observer. The study was approved by the Scientific Review Committee of the Department of Cardiology and by the Children’s Hospital Boston Committee on Clinical Investigation.

Magnetic Resonance Angiography

Cardiac MRI studies were performed using a 1.5-T whole-body scanner (General Electric, Milwaukee, WI; Philips Medical Systems, Best, The Netherlands) using an appropriate coil for patient size. In young patients who could not cooperate with the examination (generally <6 years of age), the study was performed under general anesthesia. After placement of a peripheral intravenous cannula, 0.2 mmol/kg gadopentetate dimeglumine (Magnevist, Berlex Laboratories, Wayne, NJ) was injected at a rate of 2 mL/s. Magnetic resonance angiography image acquisition was initiated using bolus tracker to optimize visualization of the aorta. Images were acquired with the patient holding his or her breath or during suspension of mechanical ventilation, as appropriate. Contrast-enhanced 3D MRA was performed using a commercially available T1-weighted fast field gradient echo sequence with the following representative parameters: field of view 250 to 450 mm (depending on body size), matrix 368×329 reconstructed to 512×512, slice thickness 0.8 to 2.4 mm reconstructed to 0.4 to 1.2 mm, number of slices 100 to 120, echo time 1.4 to 1.7 ms, repetition time 4.5 to 5.5 ms, flip angle 40°, number of acquisitions 2, sensitivity encoding (acceleration) factor 2 to 4, and acquisition time 17 to 25 seconds per acquisition.

Magnetic Resonance Angiography Image Analysis and Calculation of Tortuosity

Using a commercially available computer workstation and software (Extended MR WorkSpace version 2.6, Philips Medical Systems), a 3D volume-rendered angiogram was created from the source gadolinium-enhanced MRA for each patient (Figure 1). Both vertebral arteries in each patient were measured by an investigator who was blinded to the patient’s diagnosis and outcome. The software allows a user to rotate the 3D volume-rendered data set in any arbitrary direction and to simultaneously plot a path that follows the tortuous vessel in 3D space. As the 3D image is rotated, the plotted path rotates with the image and can be adjusted in real time, ensuring that the final measured path either curves with the vessel or follows a straight line, as desired by the user.

The vertebral artery was evaluated from its origin to the superior edge of the MRA acquisition volume or to the vertebral level of C2 if included in the study. The vertebral arteries have a stereotypical posterior turn at C2 and thus have physiological tortuosity that was not included in the calculation of the vertebral tortuosity index (VTI). For both vessels, actual length was measured by tracing the course of the vessel through 3D space from origin to end as described above (Figure 1). Straight distance was calculated for each vessel by measuring the linear distance from the origin to the end of the vessel. Distance factor was calculated for each vessel by the formula: [actual distance/straight line distance]×100. The maximum vertebral artery distance factor for each patient was designated the VTI. Total measurement and calculation time for VTI per patient was ~1 to 2 minutes.

Outcomes

After image analysis was completed, subject diagnosis was unblinded. Descriptive data were collected relative to distribution of
VTI in controls and patients. Medical records were retrospectively reviewed, and information on clinical diagnosis and associated manifestations, genetic studies, serial echocardiographic data, and outcomes was collected. Primary clinical outcomes included cardiac surgery, aortic or neck vessel dissection, and death.

**Aortic Root Size and Rate of Dilation**

In clinical care, factors that frequently contribute to earlier timing of surgery include increased aortic root diameter, increased rate of aortic root growth, and the diagnosis of LDS versus MS. Therefore, we sought to investigate if the role of VTI in timing of surgery continued to be significant when accounting for these factors.

Aortic root measurements were recorded from serial echocardiography reports for each CTD patient up to the time of the first cardiac surgery (if applicable). Aortic root diameter was measured from the parasternal long-axis window, with measurements taken at the level of the sinuses of Valsalva at maximum systolic diameter from inner edge to inner edge as recommended by the American Society of Echocardiography. To account for differences in body size, z-scores were calculated using body surface area (Haycock formula) based on normative data obtained at our institution. To maintain continuity of all indexed measurements, and given that there are no data indicating that the relationship between body surface area and aortic size varies as a function of age in otherwise normal individuals, we applied z-scores to all patients. Recorded aortic root values were inspected for every patient in the context of each patient’s trend to ensure appropriateness of the documented measurements. Using the earliest and latest echocardiograms preceding surgery (if applicable), rate of aortic dilation was measured in 2 ways. The first measure was change in aortic root z-score per year. The second measure was change in aortic root diameter in millimeters per year for all studies performed after age 18 years, to account for differences in body size. For the purposes of the freedom-from-surgery analysis, aortic root z-score was treated conservatively as a stable variable, with the maximum lifetime value assigned to each patient.

Results

**Subjects**

Thirty controls and 90 patients with CTD fulfilled inclusion criteria (Table 1). Of the 57 MS patients, all of whom met original and revised Ghent criteria, 12 had a pathogenic FBN1 mutation, 30 had ectopia lentis (EL), and 40 (70%) had either an FBN1 mutation or EL. Of the 13 patients with LDS, 6 had TGFBR1 mutations and 7 had TGFBR2 mutations. The 2 EDS patients had clinically diagnosed classic EDS (EDS Type I/II). Age at the time of the MRI for controls was not different than that of the LDS patients but was younger than patients with MS and NSCTD (Table 1). There was no significant difference in gender among the groups.

**Descriptive Analysis of Vertebral Tortuosity Index**

The VTI was normally distributed in control patients (mean 4.7±2.5) but not in the CTD patients (Figure 2). Controls had significantly lower VTI than patients (median 4.5; interquartile range [Q1-Q3] 3.0 to 4.5 versus median 15.4 to 16.7; P=0.001; Figure 3). Median VTI in MS patients was 16 (Q1-Q3 10 to 19), with the subgroup of patients with FBN1 mutation having a median VTI of 16 (Q1-Q3 6.5 to 42.5) and the subgroup with a mutation or EL having a median VTI of
28 (Q1-Q3 8 to 49.5; \( P = 0.20 \) and \( P = 0.95 \), respectively, for each compared with all MS). Median VTI in LDS patients was 58 (Q1-Q3 18 to 92). The 2 patients with type I/II EDS had VTIs of 6 and 21. Overall, the NSCTD had values similar to the control group, with the exception of 3 outliers (Figure 2).

Although younger patients had higher VTIs in the patient group as a whole (age at MRI versus VTI: \( r_p = -0.340, P = 0.001 \)), the younger patients referred for MRI likely represent the more severe CTD cases. No correlation between VTI and age was noted when controlling for diagnostic groups (\( r_p = 0.064, P = 0.49 \)). A significant difference was not observed in VTI between the MS and LDS groups either when controlling for age (\( P = 1.00 \)), or when not doing so (\( P = 0.16 \)). There was a trend toward a higher VTI in the \( TGFBR2 \)-mutation group compared with the \( TGFBR1 \) group although the difference did not reach statistical significance (\( TGFBR1 \) median VTI=33.5; Q1-Q3 9 to 58; \( TGFBR2 \) median VTI=88; Q1-Q3 51.5 to 115.5; \( P = 0.065 \)).

Using VTI of 0 to 10 (control mean ±2SD) as the normal reference range, 42 MS patients (74%) and 10 LDS patients (77%) had increased vertebral artery tortuosity. Given that our cohort may represent the more severe end of the spectrum of young MS patients, we also evaluated separately MS patients ≥20 years old who undergo routine MRI at our institution. In MS patients ≥20 years old, 29 of 41 (71%) had increased tortuosity although the VTI was lower than in the LDS group (MS ≥20 years VTI median 20; Q1-Q3 10 to 42; \( P \) versus LDS=0.011).

### Interrater Reliability

The VTI for the 24 subjects (5 controls, 19 patients) chosen randomly for interrater reliability analysis ranged from 2 to 189. Intraclass correlation coefficient for VTI comparison between the 2 observers was 0.987 (\( P<0.001 \)).

### Cardiac Outcomes

#### Cardiac Surgery

A total of 43 CTD patients had undergone 71 cardiac operations at the time of the study. Patient diagnoses were EDS type I/II 1, NSCTD 3, MS 32, and LDS in 7 patients. First surgeries included 35 aortic root replacements (22 of which were valve sparing), 6 root replacements with mitral valvuloplasty or replacement, 1 isolated mitral valvuloplasty, and 1 mitral valve replacement. Total procedures included 47 root replacements, 13 mitral valvuloplasties or replacements, 8 arch repairs, and 6 descending aortic repairs.

Receiver operating characteristics analysis for VTI and cardiac surgery by age 10 years (83 patients were eligible) demonstrated a VTI of 50 to have a sensitivity of 100% and a specificity of 84% (Figure 4). Therefore, analysis was performed for freedom from cardiac surgery with patients stratified by normal VTI (\( \leq 10, n=34 \)), VTI 11 to 49 (\( n=34 \)), and VTI ≥50 (\( n=22 \)) (Figure 5). Each group had successively younger ages at first surgery (VTI ≤10: median 48.2 years; VTI 11 to 49: median 22.2 years; VTI ≥50: median 11.0 years; \( P<0.001 \) for all comparisons).

In addition to earlier age at first surgery, patients with higher VTI also had increased rates of cardiovascular surger-
ies (Table 2). There was no significant difference between rates of surgery in patients with LDS versus MS.

**Contributing Factors**

Maximum unoperated aortic root z-scores were available in 80 patients (34 of whom subsequently underwent surgery). Median largest z-score for patients ultimately undergoing surgery was 6.7 (upper and lower limits 3.2 to 34.1). There was significant correlation between maximum z-score and VTI (r = 0.627, *P* < 0.001). Larger z-scores were associated with earlier age at surgery (*P* < 0.001).

The relationship of VTI to rate of aortic root growth was also investigated, using 2 methods. The first was change in aortic root z-score per year (n = 67 patients). Patients requiring surgery had a median z-score change of 0.09 per year (Q1-Q3 −0.04 to 0.31) compared to 0.01 per year in nonsurgical patients (Q1-Q3 −0.08 to 0.11, *P* = 0.041). There was no significant correlation between VTI and change in z-score over time (r = 0.171, *P* = 0.166). Root dilation was also evaluated using change in millimeters per year after age 18 years (n = 36, median duration between studies 10.5 years, upper and lower limits 1.0 to 27.7 years). Surgical patients had a median dilation rate of 0.7 mm/y (Q1-Q3 0.6 to 1.2) and nonsurgical patients had a median rate of 0.4 mm/y (Q1-Q3 0.1 to 0.6, *P* = 0.002). There was significant correlation between rate of dilation and VTI (r = 0.415, *P* = 0.012). Change in z-score and change in millimeters per year were associated with earlier age at surgery (*P* = 0.001 and *P* = 0.003, respectively). The difference in freedom from surgery between MS and LDS patients in our cohort was not significant (MS versus LDS, *P* = 0.165; MS with FBN1 mutation or EL versus LDS, *P* = 0.22; MS ≥20 years versus LDS, *P* = 0.06).

### Table 2. No. of Cardiac Operations per Patient per Decade

<table>
<thead>
<tr>
<th>VTI</th>
<th>n</th>
<th>Total Operations</th>
<th>Mean Patient Age at Follow-Up, y</th>
<th>Mean No. of Operations per Patient per Decade</th>
<th>95% CI</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10</td>
<td>34</td>
<td>4</td>
<td>29.5</td>
<td>0.04</td>
<td>0.00−0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>11−49</td>
<td>34</td>
<td>33</td>
<td>27.9</td>
<td>0.35</td>
<td>0.21−0.48</td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>22</td>
<td>34</td>
<td>18.8</td>
<td>0.82</td>
<td>0.53−1.11</td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>57</td>
<td>51</td>
<td>28.2</td>
<td>0.32</td>
<td>0.21−0.42</td>
<td>0.59</td>
</tr>
<tr>
<td>LDS</td>
<td>13</td>
<td>11</td>
<td>16.7</td>
<td>0.51</td>
<td>0.09−0.92</td>
<td></td>
</tr>
</tbody>
</table>

VTI indicates vertebral tortuosity index; CI, confidence interval; MS, Marfan syndrome; and LDS, Loeys-Dietz syndrome.

Multivariable analysis for freedom from surgery was then performed initially using stratified VTI, maximum aortic root z-score, change in z-score per year, and MS versus LDS diagnosis (Table 3). Change in z-score and diagnosis were not significant predictors in the final model; high VTI and larger aortic root z-scores remained significantly associated with younger age at surgery.

To further demonstrate the independent association of both VTI and root z-score with surgery, we divided the VTI and z-score values at their medians and assigned our patients into 4 groups: (1) smaller root and lower VTI, (2) smaller root and higher VTI, (3) larger root and lower VTI, and (4) larger root and higher VTI (Figure 6).

Given that LDS patients may have tortuous vertebral arteries and may be referred for surgery at a smaller root diameter than other CTD patients, freedom-from-surgery analysis was repeated excluding LDS patients. Higher VTI again remained significantly associated with younger age at surgery even when controlling for maximum aortic root z-score (z-score: *P* < 0.001, hazard ratio [HR] 1.5, 95% confidence interval [CI] 1.3 to 1.8; VTI 11 to 49: *P* = 0.023, HR 5.8, 95% CI 1.3 to 26.0; VTI ≥50: *P* = 0.007, HR 10.6, 95% CI 1.9 to 59.1).

### Dissection and Death

There were 7 patients with a total of 10 aortic or proximal head and neck vessel dissections. Of those, 5 patients had MS (median age at first dissection 25.1 years, upper and lower limits 15.7 to 40.4 years), 1 patient had LDS (age 14.1 years at dissection), and 1 patient had NSCTD (age 16.4 years at dissection). Median VTI for patients with dissection was 54 (upper and lower limits 18 to 179). Survival analysis for freedom from dissection demonstrated significantly earlier age at dissection with increased tortuosity (*P* = 0.003, Figure...
There was no difference in freedom from dissection in the MS versus LDS groups (all MS versus LDS P=0.43, MS with FBN1 mutation or EL versus LDS P=0.78, MS ≥20 years versus LDS P=0.40). Information on aortic root z-score preceding surgery was only available for 3 of the patients with dissection, precluding analysis of association between dissection and root size.

Five CTD patients in the study died sometime after the cardiac MRI was performed (Table 4). Time to death is shown in Figure 7B. Given the low mortality rate among patients with VTI ≤50 in this cohort, we were unable to discriminate between normal VTI and VTI 11 to 49. However, patients with VTI ≥50 had significantly younger age at death than patients with VTI ≤50 (P<0.001). Four of the patients who died had a VTI ≥100; survival in the group with VTI ≥100 was 0% at age 30. The 2 patients with VTI ≥100 still living at the completion of the study were ages 11.6 and 21.3 years. There was no difference in age at death between patients with MS and LDS in our cohort (P=0.49) although there may have been insufficient number of deaths to detect a difference. Maximum aortic root z-score was only available in 3 patients who died (median 12.2, upper and lower limits 10.6 to 14.1).

Of the 90 study patients, 10 (11%) reached the composite outcome of dissection or death. Higher VTI was associated with younger age at the composite outcome (P<0.001, Figure 7C). There was also a significant association between larger aortic root z-score and younger age at the composite outcome (P=0.014) whereas there was no association with diagnosis of MS versus LDS and the composite outcome (all MS versus LDS P=0.95, MS with FBN1 mutation or EL versus LDS P=0.82, MS ≥20 years versus LDS P=0.76). Only VTI (as a continuous variable) remained significant when VTI and root z-score were placed in a multivariable model (VTI P=0.003, z-score P=0.63).

**Discussion**

This study demonstrates that VTI assessed by MRA is easily measured in a cohort spanning a large age range. Importantly, we found that higher VTI is associated with major adverse clinical outcomes, including more severely dilated aortic root, increased rate of cardiac surgery, and younger age at dissection, cardiac surgery, and death. As previously described, vertebral artery tortuosity was common in our patients with LDS, but in this study tortuosity was a stronger predictor of adverse cardiac outcomes than genetic syndrome diagnosis. Although it is likely that the MS group included in our cohort represents the more severe end of the spectrum of the disorder, it is also possible that early reports of LDS characterized the most severe cases. We attempted to account for this potential bias by repeating analyses using only the subgroup of MS patients who underwent MRI at ≥20 years of age because a baseline MRI is our practice for these patients. Our results, showing no difference in rates of dissection, surgery, or death between MS and LDS, are similar to those published by Attias et al, which described the largest group ever reported of patients with a TGFBR2 mutation (71 LDS-TGFBR2 patients versus 243 MS patients).

Although tortuosity is only rarely described in previous reports of MS, this study demonstrates that vertebral artery tortuosity is common in patients with MS. Tortuosity is probably increased in LDS compared to MS given all comers. In our cohort, VTI was more associated with adverse cardiovascular outcomes than syndrome diagnosis and was additive to aortic root z-score in the predictive model for cardiac surgery. The significant correlation
between vertebral artery tortuosity and cardiac outcome remains unexplained. We hypothesize that arterial wall fragility manifests as tortuosity in the thin-walled vertebral arteries, although this remains speculative. Recent research studies in animals and humans indicate that abnormalities in TGF-β activation account for the clinical manifestations in MS, LDS, and perhaps other CTDs. Inhibition of TGF-β with neutralizing antibody or with angiotensin-II receptor blockers such as losartan reverses the clinical complications in a fibrillin-deficient mouse model. The degree of arterial tortuosity may reflect the degree of abnormality in TGF-β activation though here too the mechanism remains unclear. Future studies may elucidate the mechanism of this association. It would be of interest to investigate whether the degree of arterial tortuosity is affected by TGF-β inhibition with neutralizing antibody or losartan in mouse models of MS and LDS. We did not account for medication in this study given that patients were universally on at least 1 therapy at some point, and it was underpowered to detect a difference between losartan and β-blockers.

Although the measurement of MRI-based VTI may have significant clinical utility in prognostication and decision making relative to frequency of monitoring, lack of access to cardiac MRI may be prohibitive in some centers. In addition, although echocardiography for measurement of aortic root may be performed without sedation and noninvasively, MRA requires the administration of contrast and sedation in younger children. The procedure may, however, be worthwhile given the possible additional prognostic information. In addition, many centers are using MRI/MRA more commonly to follow aortic dimensions in CTD patients, and VTI can be measured from any standard MRA.

**Limitations**

Our study had a retrospective design with inherent limitations leading to potential ascertainment bias, primarily in that the indications for and timing of MRI were not standardized. For example, younger MS patients who underwent MRI were more likely to be more severely affected whereas patients with a confirmed diagnosis of LDS were more likely to undergo MRI regardless of age or severity. To account for this, we performed subanalyses for all outcomes including only MS patients >20 years old and all LDS patients, for whom a cardiac MRI would be standard at our institution. In this subgroup, there was still no difference in timing of cardiovascular outcome based on genetic diagnosis whereas VTI continued to be strongly associated with outcome timing.

In order to explore the interplay between genetic diagnoses, aortic root size, and VTI, we performed several subgroup analyses. Importantly, the results of these analyses must be interpreted with caution given the relatively small number of patients within subgroups and the number of patients reaching the outcome of aortic dissection or death. However, we have included these analyses because this is the first study evaluating the association of arterial

---

**Table 4. Patient Deaths**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>VTI</th>
<th>Prior Surgeries (ages, y)</th>
<th>Age at Death, y</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDS</td>
<td>126</td>
<td>Aortic valve and root replacement (10)</td>
<td>20</td>
<td>Aortic dissection after graft infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aortic arch graft (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Resection of transverse arch aneurysm (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Descending aorta replacement (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>MS FBN1 unk, + EL</td>
<td>175</td>
<td>Aortic root, mitral, tricuspid valve replacement (4)</td>
<td>26</td>
<td>Unk, acute respiratory symptoms preceding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aortic valve, ascending aorta and arch replacement (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aortic arch graft (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MS FBN1 unk, + EL</td>
<td>144</td>
<td>Aortic root replacement, mitral valvuloplasty (0.42*)</td>
<td>0.42*</td>
<td>Late postoperative cardiac arrest</td>
</tr>
<tr>
<td>4</td>
<td>MS FBN1 unk, + EL</td>
<td>17</td>
<td>None</td>
<td>44</td>
<td>Unk, died at home, suspected aortic dissection</td>
</tr>
<tr>
<td>5</td>
<td>NSCTD</td>
<td>179</td>
<td>Aortic root and valve replacement (9)</td>
<td>16</td>
<td>Aortic dissection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ascending aorta and arch replacement (12)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*VTI indicates vertebral tortuosity index; LDS, Loeys-Dietz syndrome; MS, Marfan syndrome; FBN1: Fibrillin-1 gene mutation; unk: unknown; EL: ectopia lentis; and NSCTD, nonspecific connective tissue disorder.

---
tortuosity with cardiovascular outcomes and we felt it was important to explore other known risk factors for adverse cardiovascular outcomes in the CTD population. Despite the small numbers, the majority of comparisons were strongly significant, even when using the Bonferroni correction for multiple tests.

Many MS patients in this study did not have a confirmed molecular diagnosis because it is not routine practice at our institution to pursue mutation analysis for the patient who meets strict Ghent diagnostic criteria and whose history and physical are consistent with MS. To accommodate for possible misdiagnosis, we repeated all analyses using both the entire MS group and using MS patients only with either an \textit{FBN1} mutation or EL (considered to be primarily limited to MS)\textsuperscript{13} and found the comparisons to be similar in all cases.

It is unclear whether VTI changes over time. Given the relatively recent use of cardiac MRI to evaluate CTD patients and the limited number of patients with serial MRA evaluations, we were unable to statistically evaluate if VTI changes over time. There were patients at both ends of the age spectrum with significant tortuosity, including a 4-month-old with VTI of 144 and a 42-year-old with a VTI of 73. No correlation between VTI and age was noted within either the controls or the diagnostic groups. Further studies are needed to investigate the longitudinal trend of VTI although the limited data here suggest that the change is likely not considerable.

Finally, although measurements of vessel diameter on volume-rendered models may vary slightly from measurements performed on other image formats,\textsuperscript{21} measurements of VTI are based on vessel length as opposed to diameter. Although the accuracy of vessel length measurement has not been confirmed against a gold standard, it is important to note that VTI is a ratio comprised of 2 measurements performed using identical technique. Further studies of the accuracy and interstudy reproducibility of this index are warranted.

Conclusions

This study demonstrates that vertebral artery tortuosity as measured by MRA VTI can be measured easily in patients spanning a large age range and that increased VTI is associated with increased aortic root size, increased frequency of surgery, and earlier age at surgery, dissection, and death. Use of this measurement tool may aid in evaluation, prognostication, and development of monitoring plans for children and young adults with various forms of CTD.

Acknowledgments

We thank Emily Harris for the artwork.

Disclosures

None.

References

CLINICAL PERSPECTIVE

Historically, cardiac surgical management of children and young adults with Marfan syndrome and related connective tissue disorders has been based primarily on aortic root size and rate of aortic growth. With the discovery of Loeys-Dietz syndrome and its reported aortic dissection at smaller dimensions and younger age, clinicians have begun to consider underlying genetic diagnosis when making decisions about timing of surgical intervention. We observed vertebral arterial tortuosity in patients with Marfan syndrome and Loeys-Dietz Syndrome and sought to investigate if the degree of arterial tortuosity was related to cardiovascular outcomes. In this study, we developed a vertebral artery tortuosity index based on magnetic resonance angiography to assess arterial tortuosity in both controls and connective tissue disorder patients. The measurement was simple to calculate from standard magnetic resonance angiography, taking 1 to 2 minutes. We found that higher tortuosity is independently associated with earlier cardiac surgery, arterial dissection, and death. In our study, a high vertebral artery tortuosity index was more strongly associated with early adverse outcome than a diagnosis of Loeys-Dietz syndrome compared to Marfan syndrome. The vertebral artery tortuosity index may offer helpful information about prognosis in connective tissue disorder patients and may ultimately play an additive role in surgical decision making.