Distal Aortic and Peripheral Arterial Aneurysms in Patients With Marfan Syndrome

To the Editor: The mainstay of clinical surveillance for the unoperated patient with Marfan syndrome (MFS) is echocardiography. Because the aorta is not routinely imaged beyond its ascending component, the overall incidence of distal or peripheral arterial disease in MFS is unknown. We sought to determine the incidence of such disease in adults (age >18 years) with MFS.

Patients were diagnosed in accordance with established clinical criteria (1), had been receiving routine cardiac care in a regional aortopathy clinic during 2000 to 2010 for >3 months, and underwent >1 magnetic resonance angiography (MRA)/computed tomography angiography (CTA) evaluation of the aorta from the skull base to iliac bifurcation per our routine clinical protocol. Additional imaging of cerebral vessels was performed at the ordering cardiologist’s discretion in a subset of patients with nonfocal neurological symptoms or when disease of the cervicocephalic vessels was noted. Genetic testing for TGFBR1/TGFBR2 mutations was performed in all patients with distal disease without lens subluxation, to rule out Loeys-Dietz syndrome, a related aortopathy with diffuse arterial involvement (1).

Clinical data in those with and without distal disease were compared. Nominal data were analyzed with a chi-square test or Fisher exact test. Continuous variables were analyzed with a Mann Whitney U test as their distributions were found to be non-normal. Relative risk ratios with 95% confidence intervals (CIs) were calculated. Logistic regression was used to control for potential confounders using the backward conditional approach for removal of variables from the model. Analyses were performed using SPSS version 18.0 (SPSS Inc, Chicago, Illinois). Data are presented as means with SDs or medians with ranges as appropriate.

MRA/CTA of the thoraco-abdominal aorta was performed in all 140 adults with MFS who met inclusion criteria. Previous aortic root replacement had been performed in 73 (52%) patients at a median age of 24 (11 to 59) years. Surgery was elective in 62 patients (85%). Of the remaining 11 patients with prior dissection, 2 had residual dissection of the thoraco-abdominal aorta, which was not addressed initially. Of the patients undergoing elective repair, 43% underwent a valve-sparing procedure. Patients were followed up for up to 20 years after aortic root replacement.

MRA/CTA imaging was used to identify 47 distal or peripheral aneurysms in 44 of 140 (31%) patients. Fourteen patients (10%) underwent additional imaging of the intracranial vessels. Aneurysms were noted in the native ascending aorta contiguous with the prior aortic graft in 5 patients, aortic arch in 4, carotid in 6, subclavian artery in 4, descending thoracic aorta in 13, abdominal aorta or branch vessels in 3, iliac arteries in 2, and cerebral vessels in 5. Dissection of the distal/peripheral aneurysm occurred in 32 of 47 aneurysms (68%) and was fatal in 6. During routine follow-up, 13 patients (9%) sought emergent care for symptomatic distal dissection in the face of an aortic root diameter, which had not yet attained surgical criteria (median aortic root diameter: 38 [33 to 45] mm).

Patients with distal/peripheral aneurysms were older (35.5 [18 to 71] years vs. 30 [18 to 64] years; p = 0.04) and were more likely to have undergone prior aortic root replacement (Table 1). Distal disease was, however, present in approximately one-quarter of patients who had not had prior aortic root surgery and did not meet surgical criteria for such. Despite the greater likelihood of having had prior aortic replacement, the maximal attained aortic root diameter did not relate to the presence of distal disease. Although there was no difference between groups when assessing for the use of any antihypertensive agent, those patients with distal/peripheral aneurysms were less likely to be receiving an angiotensin-converting enzyme (ACE) inhibitor at the time of confirmatory MRA/CTA. There was no relationship between ACE inhibitor use and age, previous surgery, or other clinical variables. Patients with distal/peripheral aneurysms had a greater number of risk factors for acquired heart disease and were 14.9 times (95% CI: 1.75 to 127.21; p = 0.01) more likely to die than those without such aneurysms when controlling for smoking (odds ratio: 5.09 [95% CI: 1.07 to 24.31]; p = 0.04). After controlling for the presence of a distal/peripheral aneurysm, other variables (including age, family history of dissection, hypertension, hyperlipidemia, prior aortic surgery, and prior ascending aortic dissection) did not contribute to the model significantly and were removed. No patient died secondary to complications related to the ascending aorta. Treatments used for distal aneurysms varied according to aneurysm site. In general, aneurysms were observed serially, and if progressive in size, symptomatic, or if published surgical size criteria were met (2), surgical or percutaneous intervention was used. Of the 47 aneurysms noted, 26 (55%) required intervention.

This study demonstrated distal/peripheral arterial aneurysms in approximately one-third of adults with MFS. In keeping with prior publications (2), smoking, hypertension, and hyperlipidemia correlated with a greater likelihood of distal/peripheral aortic disease. Given the study sample size, the multivariate model may be limited by overfitting.

The incidence of cerebrovascular aneurysms was high at 36% in a select cohort of patients who underwent cerebral imaging. Although aneurysms of carotid arteries have been described in patients with TGFBR1/TGFBR2 defects, they have not been previously noted in association with isolated FBN-1 mutations. An unexpected finding in our study was the significantly lower incidence of distal/peripheral disease in patients undergoing ACE inhibitor therapy. Previous studies have demonstrated a lack of protective effect of beta-blockade on the development of distal disease in patients with MFS (3), but to date, no other medical therapies have been studied.
This study highlights the changing clinical picture of MFS. Although the literature still notes dissection of the ascending aorta to be the primary cause of death in patients with MFS (4), our data would suggest that those patients with a known diagnosis who receive routine cardiac care do not succumb to complications related to the ascending aorta but rather face ongoing morbidity and mortality related to distal or peripheral arterial disease. Surveillance of the distal aorta and branches is warranted in all adults with MFS.

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Letters to the Editor

Cerebrovascular Atherosclerosis and Stroke in Patients After Coronary Artery Bypass Graft Surgery

We read with interest the paper by Lee et al. (1) on the influence of cerebral atherosclerosis and stroke after coronary artery bypass surgery (CABG). Interestingly, they demonstrated that two-thirds of the patients undergoing CABG (65.4%) had steno-occlusive lesions in the intracranial and/or extracranial cerebral arteries. Thus, the issue of cerebrovascular disease and postoperative neurological complications is very important in these patients, and awareness is mandatory for the cardiac surgeons. At our institution, we perform ultrasound of the carotid arteries as a routine checkup before CABG surgery. If we have evidence of neurovascular disease, we modify the anesthesiological management (e.g., keep mean arterial pressure higher during extracorporeal circulation), the patient monitoring (cerebral near-infrared spectrometry), and surgical management (e.g., epiaortic ultrasound, aortic “no-touch” techniques). Our first question for the authors is: Was the perioperative management adapted in patients with (more severe) cerebrovascular disease?

In one of our studies, we found that atherosclerosis of the ascending aorta, as determined by intraoperative epiaortic ultrasound, was a risk factor for strokes and during mid-term follow-up of CABG patients (2). Furthermore, ascending aortic atherosclerosis adversely affected long-term survival after CABG (3). Our second question for the authors is: Did (severe) atherosclerosis of the aortic arch and/or the ascending aorta have an impact on post-CABG strokes?

Table 1 Clinical Factors Associated With Distal Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Distal Disease (n = 44)</th>
<th>No Distal Disease (n = 96)</th>
<th>p Value</th>
<th>Multivariate Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (%)</td>
<td>9 (21)</td>
<td>6 (6)</td>
<td>0.04</td>
<td>1.95 (1.19–3.21)</td>
</tr>
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<td>Hypertension (%)</td>
<td>18 (41)</td>
<td>11 (11)</td>
<td>&lt;0.001</td>
<td>2.39 (1.54–3.69)</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>14 (32)</td>
<td>9 (9)</td>
<td>0.002</td>
<td>2.15 (1.38–3.36)</td>
</tr>
<tr>
<td>Not receiving an ACE inhibitor (%)</td>
<td>43 (98)</td>
<td>47 (49)</td>
<td>&lt;0.001</td>
<td>23.06 (3.28–161.80)</td>
</tr>
<tr>
<td>Maximal aortic root size on echocardiogram (mm)</td>
<td>47 (32–71)</td>
<td>44 (31–90)</td>
<td>0.23</td>
<td>NA</td>
</tr>
<tr>
<td>Prior aortic root replacement (%)</td>
<td>30 (68)</td>
<td>43 (45)</td>
<td>0.03</td>
<td>1.75 (1.03–2.98)</td>
</tr>
<tr>
<td>Time from root replacement (yrs)</td>
<td>8 (1–22)</td>
<td>3 (1–20)</td>
<td>0.003</td>
<td>NA</td>
</tr>
<tr>
<td>Distal dissection (%)</td>
<td>32 (71)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>Death (%)</td>
<td>6 (14)</td>
<td>1 (0.96)</td>
<td>0.001</td>
<td>2.96 (2.07–4.24)</td>
</tr>
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Values are n (%) or median (range), unless otherwise indicated.

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