Should the Criterion for Surgical Intervention for Thoracic Aortic Aneurysm be Moved “Leftward” (earlier)?

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Time for a Left-ward Shift in Guidelines?

Aortic Size

4.0 cm  4.5 cm  5.0 cm  5.5 cm  6.0 cm

Current Intervention Criterion

???
Outline: Left-Shift Needed?

1. Earlier hinge points in natural history
2. Diameter change at moment of dissection
3. Advent of automated “Centerline” measurement
4. Advent of genetic testing via Whole Exome Sequencing
5. Safety of aortic surgery in present era
6. Impact of prior dissection in a family member
How big is the normal aorta?

Almost Normal distribution, with wide R tail

Log Normal distribution

3573 Patients with MRIs as part of MESA Study

Min 1.6  Mean 3.2  Max 5.0

ASCENDING AORTA

Hinge Point – Ascending Aorta

Risk of Complications – Height alone suffices


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- Light green area indicates low risk, yellow area indicates moderate risk, orange area indicates high risk, and red area indicates severe risk.
Criteria for Prophylactic Surgical Intervention

APPENDIX

The Yale Center for Thoracic Aortic Disease
Recommended Surgical Intervention Criteria for
Thoracic Aortic Aneurysms

1. Rupture
2. Acute aortic dissection
   a. Ascending requires urgent operation
   b. Descending requires a “complication-specific approach”
3. Symptomatic states
   a. Pain consistent with rupture and unexplained by other causes
   b. Compression of adjacent organs, especially trachea, esophagus, or left main stem bronchus
   c. Significant aortic insufficiency in conjunction with ascending aortic aneurysm
4. Documented enlargement
   a. Growth ≥1 cm/yr or substantial growth and aneurysm is rapidly approaching absolute size criteria
5. Absolute size (cm)

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<th>Marfan's</th>
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<tr>
<td>Descending</td>
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Why is the plot thickening?
1. Yale Natural History Re-analysis

2. Diameter prior to aortic dissection

So, dissections are occurring at smaller size than we thought.

Pre- and Post-Dissection Aortic Diameters

Changes in Aortic Diameters at Dissection

Patient 220

- 8 years: 45 mm
- 7 years: 46 mm
- 6 years: 47 mm
- 5 years: 48 mm
- 4 years: 48 mm
- 3 years: 49 mm
- 2 years: 50 mm
- 1 year: 51 mm
@dissection: 58 mm
3. “Centerline” method confuses criteria

“All tested commercially available software tools systematically underestimated…”


Comparison of Centerline Method to Traditional Measurements

Measurement of thoracic aorta: Traditional CT measurements (2 experts) vs. Centerline CT measurements

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<th>Aortic Root(mm)</th>
<th>Traditional</th>
<th>Centerline</th>
<th>Discrepancy</th>
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Maximum Measurement (mm)

-2.6666667
4. Genetic testing in thoracic aortic aneurysm

Routine Genetic Testing for Thoracic Aortic Aneurysm and Dissection in a Clinical Setting

Bulat A. Ziganshin, MD, Allison E. Bailey, BS, Celine Coons, Daniel Dykas, BS, Paris Charilaou, MD, Lokman H. Tanriverdi, Lucy Liu, BS, Maryann Tranquilli, RN, Allen E. Bale, MD, and John A. Elefteriades, MD

Aortic Institute at Yale-New Haven, and Department of Genetics, Yale University School of Medicine, New Haven, Connecticut

Background. Hereditary factors play an important etiologic role in thoracic aortic aneurysm and dissection (TAAD), with a number of genes proven to predispose to this condition. We initiated a clinical program for routine genetic testing of individuals for TAAD by whole exome sequencing (WES). Here we present our initial results.

Methods. The WES was performed in 102 patients (mean age 56.8 years; range 13 to 88; 70 males [68.6%]) with TAAD. The following 21-gene panel was tested by WES: ACTA2, ADAMTS10, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, ELN, FBLN4, FLNA, FBN1, FBN2, MYH11, MYLK, NOTCH1, PRKG1, SLC2A10, SMAD3, TGFBR2, TGFBR1, TGFBR3.

Results. Seventy-four patients (72.5%) had no medically important genetic alterations. Four patients (3.9%) had a deleterious mutation identified in the FBN1, COL5A1, MYLK, and FLNA genes. Twenty-two (21.6%) previously unreported suspicious variants of unknown significance were identified in 1 or more of the following genes: FBN1 (n = 5); MYH11 (n = 4); ACTA2 (n = 2); COL1A1 (n = 2); TGFBR1 (n = 2); COL5A1 (n = 1); COL5A2 (n = 1); FLNA (n = 1); NOTCH1 (n = 1); PRKG1 (n = 1); and TGFBR3 (n = 1). Identified mutations had implications for clinical management.

Conclusions. Routine genetic screening of patients with TAAD provides information that enables genetically personalized care and permits identification of novel mutations responsible for aortic pathology. Analysis of large data sets of variants of unknown significance that include associated clinical features will help define the mutational spectrum of known genes underlying this phenotype and potentially identify new candidate loci.

Frequency Distribution of Genetic Defects in TAAD-related genes

Surgical criteria for specific genetic mutations

5. Safety of Aortic Surgery

<table>
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<tr>
<th>Location of Surgery</th>
<th>Operative Mortality</th>
<th>Postoperative Stroke</th>
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<tr>
<td>Composite Aortic Root Replacement</td>
<td>1.9%</td>
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<tr>
<td>Root Sparing Ascending Aortic Replacement</td>
<td>0%</td>
<td>1.0%</td>
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<tr>
<td>Aortic Arch Replacement with DHCA</td>
<td>1.4%</td>
<td>1.2%</td>
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6. Powerful impact of prior dissection in family member

1. 5.75 cm
2. 5.25 cm
3. NEW
4. Aneurysm Size (cm)
5. Location of Surgery
   - Composite Aortic Root Replacement: 1.9% Operative Mortality, 1.4% Postoperative Stroke
   - Root Sparing Ascending Aortic Replacement: 0% Operative Mortality, 1.0% Postoperative Stroke
   - Aortic Arch Replacement with DHCA: 1.4% Operative Mortality, 1.2% Postoperative Stroke
6. Type A Dissection: Frequency of absolute diameter
   - Graph showing absolute diameter vs. time.
Time for a Left-ward Shift in Guidelines?

Aortic Size

- 4.0 cm
- 4.5 cm
- 5.0 cm
- 5.5 cm
- 6.0 cm

Current Intervention Criterion

Current Intervention Criterion

???

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