The Marfan Syndrome

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Sir Magdi Yacoub Lecture
MSTCVS 2017
Marfan Syndrome

- Most common inherited connective tissue disorder
- Cardinal features in skeletal, ocular and cardiovascular systems
- Premature mortality due to aortic catastrophe
- Lifespan shortened by one third
Antoine Marfan
Aortic Root Aneurysm in Marfan Syndrome
Marfan Syndrome Shortens Life Expectancy by a Third
There is no disease more conducive to clinical humility than aneurysm of the aorta.

Sir William Osler
“Pre-Bentall” Treatment of Marfan Ascending Aortic Aneurysm

- Usually reserved for emergency rupture or dissection
- Operative mortality > 50%
The Bentall Procedure

A technique for complete replacement of the ascending aorta

HUGH BENTALL AND ANTONY DE BONO
From the Royal Postgraduate Medical School, London, and Hammersmith Hospital

A technique for complete replacement of the aortic valve and ascending aorta in cases of aneurysm of the ascending aorta with aortic valve ectasia is described. The proximal aortic root was too attenuated to afford anchorage to the aortic prosthesis, so this was sutured to the ring of a Starr valve and the prostheses were inserted en bloc. The ostia of the coronary arteries were anastomosed to the side of the aortic prosthesis.

Aneurysmal dilatation of the ascending aorta is often associated with ectasia of the aortic valve ring and presents clinically as aortic incompetence. In Marfan’s syndrome, or cystic medial necrosis, this may develop with dramatic suddenness in an ostensibly healthy individual.

The dilatation of the valve ring makes repair or replacement with other than a prosthesis valve difficult. The aneurysm, which is either a true dilatation or dissection, is best treated by excision and replacement with a tubular prosthesis, as the wall is invariably attenuated. This is not difficult provided that the aorta distal to the aneurysm and proximal to the arch is suitable for anastomosis.

Proximally, in most cases, the aortic prosthesis can be sutured to a rim of aorta, leaving the coronary ostia undisturbed, while a valve prosthesis is placed in the usual sub-coronary position (Cooley, Bloodwell, Beall, Hallman, and De Bakey, 1966).

However, it sometimes happens that the root of the aorta is so involved in the disease process that the wall is too attenuated to be sutured to the proximal end of the aortic prosthesis. In this situation, the management of the coronary ostia is the main concern of the surgeon.

CASE REPORT

A man aged 33 years had been in excellent health until a few months before admission, when his wife noticed a loud cardiac murmur and he developed signs and symptoms of gross aortic regurgitation. Angiocardiography showed a large aneurysmal dilatation of the ascending aorta, not involving the vessels of the arch but associated with free aortic regurgitation. He was in incipient cardiac failure with an effective cardiac output of 1.81/min/m².

Operation A mid-sternal thoracotomy revealed a large globular dilatation of the ascending aorta. Its bulging intimal wall was so thin that blood could be seen eddying within. Figure 1 gives an idea of the attenuation of the wall.

Total cardiopulmonary bypass was established, and after cross-clamping the aorta distal to the aneurysm, the aorta was opened, and the coronary ostia were cannulated and perfused in the usual way. The aortic valve ring was much dilated and the wall was extremely thinned down to the ring.

It was clear that it would not be possible to join the aortic wall above the coronaries to an aortic prosthesis. It was therefore decided to suture the tube prosthesis directly to the ring of a Starr valve. A No. 13 Starr valve was sutured to one end of a crimped Teflon aortic prosthesis, as shown in Figure 2. The aortic cusps having been excised, sutures were placed in the aortic ring and through the Starr valve ring. These were tied, fixing the Starr valve and the attached Teflon tube.

At this stage the coronary cuspae were outside the lumen of the aortic replacement. Holes were cut in the aortic prosthesis at the site of the coronary ostia, which were then re-cannulated, this time through the lumen of the tube (Fig. 3). The aortic wall was sutured to the perimeter of the holes in the Teflon tube, thus reincorporating the coronary ostia within the new aorta.

The distal anastomosis was then completed, leaving a vertical slit (Fig. 3 (5)) through which the coronary cuspae were removed and air was evacuated. This was then closed with a clamp, while the aortic clamp was released and retrograde coronary perfusion was started again without any delay. The wall of the aneurysm was closed over the prosthesis.

The patient made an uneventful recovery and remains well after nine months.
Stigler's Law of Eponymy

"no scientific discovery is named after its original discoverer"

(all eponyms are wrong)
Robert Merton (1910-2003)

- American sociologist at Columbia Univ
- Coined phrases “unintended consequences”, “role model”, “self-fulfilling prophecy”
Helen B. Taussig
(1898 – 1986)

CONGENITAL ANEURYSMAL DILATATION OF THE AORTA ASSOCIATED WITH ARACHNODYSTYLY

RIGDELY W. BAER,1 HELEN B. TAUSSIG AND ELLA H. OPPENHEIMER
From the Departments of Pediatrics and Pathology, Johns Hopkins University
School of Medicine

Received for publication March 30, 1943

Congenital malformations of the heart are known to be of frequent occurrence in persons with arachnodactyly. Ellis (1) estimated that of the patients with this skeletal abnormality one-third had a malformation of the heart. In a previous report one of us (2) discussed the frequency with which interauricular septal defects are found in association with this anomaly. Piper and Irvine-Jones (3) also have emphasized this fact. In the following two cases there was a malformation of an entirely different nature:—there was an extraordinary aneurysmal dilatation of the ascending portion of the aorta proximal to the aortic arch. Histological examination of the aorta showed that the dilatation was caused by a congenital abnormality of the media. Therefore, the two cases are reported in detail.

CASE I
Helen B. Taussig
(1898 – 1986)

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CASE I
Indications for Surgery

- Sinus diameter > 5 cm
- Sinus diameter > 4.5 cm and family history of aortic rupture or dissection
- Dissection (acute or chronic)
- Rapid enlargement (> 0.5 cm/year)
- Progressive AI in moderate aneurysm
Annual Risk of Complications of Aortic Aneurysm

- 3.5 to 3.9 cm: 3.7%
- 4.0 to 4.9 cm: 3.9%
- 5.0 to 5.9 cm: 6.9%
- ≥ 6.0 cm: 11.8%

Outcome:
- Rupture
- Dissection
- Rupture or Dissection
- Death
- Rupture, Dissection or Death

Average Yearly Rate

18%
16%
14%
12%
10%
8%
6%
4%
2%
0%
Rupture
Dissection
Rupture or Dissection
Death
Rupture, Dissection or Death
Modified Bentall Procedure
Valve Sparing Techniques

Remodeling
(David II, Yacoub)
(1993-2002)

Reimplantation
(David I)
(2002-present)
Aortic Root Replacement
In Marfan Syndrome:
The Johns Hopkins Experience

- 490 patients
- September 1976 to March 2016
- Mean age 32.5 years (0.9-73)
- 72% Male
- Children 13%
- Mean aortic diameter 6.0 cm (3-13cm)
Aortic Root Prostheses

- Mechanical: 62%
- Valve-Sparing: 31%, 147 pts
- Bioprosthesis: 7%
## Operative Results with Aortic Root Replacement in the Marfan Syndrome (JHH 1976-2016)

<table>
<thead>
<tr>
<th></th>
<th>Pts</th>
<th>30 Day Mort</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective Repair</td>
<td>438</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Urgent Repair</td>
<td>52</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>490</td>
<td>3</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Actuarial Survival After Root Replacement

Kaplan-Meier Estimates of Mortality

- All Patients
- No Dissection
- Dissection

Survival (%)

Years

Time (years)

70%
50% (all)
30%
# Causes of Late Death

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissection/rupture of residual aorta/iliac artery</td>
<td>10</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>9</td>
</tr>
<tr>
<td>Intracerebral/spinal hemorrhage</td>
<td>4</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>3</td>
</tr>
<tr>
<td>Systemic infection</td>
<td>3</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2</td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
</tr>
<tr>
<td>Drug overdose</td>
<td>2</td>
</tr>
<tr>
<td>Dehiscence of coronary anastomosis</td>
<td>1</td>
</tr>
<tr>
<td>Thrombosis of mechanical valve</td>
<td>1</td>
</tr>
<tr>
<td>Cardiogenic shock (occlusion Cabrol graft to LM coronary)</td>
<td>1</td>
</tr>
<tr>
<td>Complications following surgery for intestinal obstruction</td>
<td>1</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>1</td>
</tr>
<tr>
<td>Motor vehicle accident</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>26</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>74</strong></td>
</tr>
</tbody>
</table>
# Univariate and Multivariate Predictors of Late Mortality

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>P value</td>
<td>Hazard Ratio</td>
<td>P value</td>
</tr>
<tr>
<td>Older Age</td>
<td>1.02</td>
<td>0.007</td>
<td>1.03</td>
<td>0.002</td>
</tr>
<tr>
<td>Mitral valve surgery</td>
<td>1.41</td>
<td>0.227</td>
<td>1.85</td>
<td>0.039</td>
</tr>
<tr>
<td>Preoperative dissection</td>
<td>2.33</td>
<td>0.002</td>
<td>1.90</td>
<td>0.054</td>
</tr>
<tr>
<td>NYHA class III/IV</td>
<td>2.24</td>
<td>0.001</td>
<td>1.61</td>
<td>0.100</td>
</tr>
<tr>
<td>Urgent surgery</td>
<td>2.51</td>
<td>0.003</td>
<td>1.42</td>
<td>0.376</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.34</td>
<td>0.320</td>
<td>1.38</td>
<td>0.288</td>
</tr>
</tbody>
</table>
Late Morbidity among 370 Survivors of Aortic Root Replacement

<table>
<thead>
<tr>
<th>Complication and Outcome</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thromboembolism</strong></td>
<td></td>
</tr>
<tr>
<td>Cerebral emboli – complete recovery</td>
<td>7</td>
</tr>
<tr>
<td>Cerebral emboli – mild incapacity</td>
<td>6</td>
</tr>
<tr>
<td>Cerebral emboli – moderate incapacity</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral emboli – complete recovery</td>
<td>1</td>
</tr>
<tr>
<td>Thrombosis of Bjork-Shiley valve</td>
<td>3</td>
</tr>
<tr>
<td>Thrombosis of St. Jude composite</td>
<td>1</td>
</tr>
<tr>
<td><strong>Endocarditis</strong></td>
<td>18</td>
</tr>
<tr>
<td>Successful treatment</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>10</td>
</tr>
<tr>
<td>Homograft aortic root replacement</td>
<td>5</td>
</tr>
<tr>
<td>Demise</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>2</td>
</tr>
<tr>
<td>Redo aortic root replacement</td>
<td>1</td>
</tr>
<tr>
<td><strong>Coronary Dehiscence</strong></td>
<td>3</td>
</tr>
<tr>
<td>Successful repair</td>
<td>2</td>
</tr>
<tr>
<td>Demise</td>
<td>1</td>
</tr>
</tbody>
</table>
Freedom From Thromboembolism

Time (years)

 (%)
Freedom From Endocarditis

% vs Years
Freedom From Operation on the Distal Aorta

70% at 25 yrs

Freedom From Operation on the Residual Aorta

50%

Time (years)

All Patients
No Dissection
Dissection
The Johns Hopkins Technique for VSRR
Graft size based on optimal sinotubular junction diameter
Management of the prolapsed leaflet

Leaflet plication  Free edge suture
Aortic Root Operations for Marfan Syndrome: A Comparison of the Bentall and Valve-Sparing Procedures

Nishant D. Patel, BA, Eric S. Weiss, MD, Diane E. Alejo, BA, Lois U. Nwakanma, MD, Jason A. Williams, MD, Harry C. Dietz, MD, Philip J. Spevak, MD, Vincent L. Gott, MD, Luca A. Vricella, MD, and Duke E. Cameron, MD

Division of Cardiac Surgery, McKusick-Nathans Institute of Genetic Medicine, and Division of Cardiology, The Johns Hopkins Medical Institutions, Baltimore, Maryland

- 56 Bentalls, 84 VSRRs
- Similar operative risk
- Higher T-E rates in Bentalls
- Higher rates of reoperation in VSRR (6%) versus Bentall (2%)
- Lower late survival after Bentall (? Pt selection)
Valve Sparing Aortic Root Reinforcement: The Florida Sleeve
PEARS
(personalized external aortic root support)
PEARS
(personalized external aortic root support)
New Insights Into Pathogenesis
Mutations in the gene encoding fibrillin-1 (*FBN1*) cause Marfan Syndrome

Discovered in 1991
Microfibrils (fibrillin-1)

Elastic fiber

The dogma: Microfibrils are needed for elastic fiber assembly and therefore Marfan syndrome manifests failed elastogenesis.
How could structural failure of tissues cause bone overgrowth?
Skeletal and Morphologic Features of the Marfan Mouse
Aortic dissection in a mouse model of Marfan syndrome
From Fibrillin Mutation to TGFβ

- Using human genome database, a sequence homology was identified between fibrillin and TGFβ binding protein (Dietz)
- High levels of TGF β seen in Marfan mouse tissues
- Hypothesis: Fibrillin is a regulator of TGFβ; fibrillin mutation leads to excess TGFβ signaling
- In other models, TGFB mutations known to lead to overproduction of collagen and disarray of elastin
- Anti-TGF β antibody given to Marfan mouse prevented aneurysm
Losartan: An angiotensin II R1 receptor blocker that prevents TGFβ signaling

- ACEi 
- Ang 1 
- Ang 2 
- ATII R1 
- ATII R2

Losartan 

↑ TGFβ activation 

↑ TSP-1

↑ Proliferation 

↑ Fibrosis 

↓ Apoptosis 

↓ Proliferation 

↑ Apoptosis 

↓ Fibrosis
Aortic Growth in 2 MFS Children Treated with Losartan

![Graph showing aortic growth comparison between treatments. The left graph shows growth with a β-blocker followed by Losartan, while the right graph shows growth with a β-blocker followed by ACE inhibitor. The graphs illustrate the dimensions over age (months).]
• 608 pts with Marfan syndrome
• Mean age 11 yrs (6 mos - 25 yrs)
• Baseline aortic root Z-score >3
• Randomized to Atenolol versus Losartan
• Both drugs reduced Z-score over 3 years
• No significant difference between Atenolol and Losartan
• ?Equivalent dosing
Mitral Valve Repair in Marfan Syndrome
Did Lincoln have the Marfan syndrome?
Summary

• Prophylactic aortic root replacement has low operative risk and can durably prevent life-threatening aortic catastrophe in Marfan syndrome
• Long term results with composite grafts are excellent
• Valve sparing operations have excellent results but shorter followup; reimplantation technique is preferred
• Late distal aortic dissection and arrhythmia remain challenges to long term survival
• New insights into pathogenesis may lead to novel therapies