THE AORTA IN TURNER SYNDROME

Dr. L. Demulier
Annual meeting of the BWGACHD
March 11th 2016
TURNER SYNDROME: INTRODUCTION

- Prevalence = 1/2000 life born girls
- Partial/complete deletion X-chromosome
- Multiple karyotypes ± cell line mosaicism
- Small stature / estrogen deficiency / infertility
- Dysmorphic features
- Highly variable phenotype (diagnostic delay)
- Multisystemic manifestations
- Congenital / acquired CV disease

Mortensen et al. Endocrine Reviews 2012
EXCESS PREMATURE MORTALITY & MORBIDITY

- Risk of premature death x 3:
  - CVD = n° 1
- Life expectancy: – 10y
- 50% of morbidity = CVD
- High early life disease burden
IMPORTANCE OF ACQUIRED CV DISEASE

Mortensen et al. Endocrine Reviews 2012
CARDIOVASCULAR ANOMALIES: CONGENITAL AND ACQUIRED

Aberrant right subclavian artery
SVC
Aortic dissection
Aortic dilatation
PAPVR
Coronary sinus
Bovine aorta
Left SVC
Aortic coarctation
Left ventricular hypertrophy

PAPVR, partial anomalous pulmonary venous return;
SVC, superior vena cava

Normal (tricuspid) aortic valves
Abnormal (bicuspid) aortic valves

Mortensen et al. Endocrine Reviews 2012
CONGENITAL HD: BICUSPID AORTIC VALVE (15-30%)

- Echo ± MRI NIH study in 253 asy TS pts (7-67y)
- 95% Type 1 BAV (vs 60-70%)
- 45% AR - 15% moderate-severe; AS rare
- Diagnosis: 89% echo / 99% MRI
- Association with webbed neck (45%), aortic coarctation (22%), 45 X0

Sachdev et al. Jacc 2008
BAV AND AORTIC DILATION

ARD: BAV 25% - TAV 5%

Sachdev et al. Jacc 2008

Riti Mahadevia et al. Circulation. 2014
PARTIAL CUSP FUSION AND AORTIC DILATION IN TS

Olivieri et al. Circ Cardiovasc Imaging 2013
CONGENITAL HD: THORACIC VASCULAR ABNO

- ELONGATION TRANVERSE ARCH (49%)
- COARCTATION (up to 17%)
  - Association with BAV
  - Need for repair +/- 50%
  - Frequent association with ETA
- KINKING ARCH
- LUSORIAN ARTERY (8%)
- PERSISTENT LEFT SCV (8-13%)
- PAPVR (13-15%)

Associated with:
- Karyotype 45,X
- Neck webbing
- ‘Shield like’ chest

Mortensen et al. Endocrine Reviews 2012
Ho et al. Circulation 2004

24y TS (45,X)
HD EFFECTS OF ALTERED ARCH GEOMETRY: CFD

(a) Descending aorta (J)

(d) TAWSS [Pa]

(b) 

(c) Brachiocephalic branch (C)

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Graphs showing flow rates (Q) over time (t/T) for different conditions:

- TS normal
- TS dilated
- TS constriction
- TS eta
- Inflow
Abnormal aortic arch morphology in Turner syndrome patients is a risk factor for hypertension

Katya De Groote · Daniël Devos · Koen Van Herck ·
Laurent Demulier · Wesley Buysse ·
Jean De Schepper · Daniël De Wolf
HEMODYNAMIC CASE STUDY: ♀ 19y TS

CFD ANALYSE - courtesy of J. Bols

4D FLOW - courtesy of D. Devos
Radiology Dept UZG
ACQUIRED CARDIOVASCULAR ANOMALIES

Aberrant right subclavian artery

SVC
Aortic dissection

Aortic dilatation
PAPVR
Coronary sinus

Mortensen et al. Endocrine Reviews 2012
IS THIS ASCENDING AORTA DILATED?
ABSOLUTE VERSUS BSA-INDEXED AORTIC DIAMETER

♀ 48y - mosaic TS

Ascending aorta diameter = 28 mm

Never GH treatment
132 cm – 47 kg
BSA 1.27 m²

Aortic size index (ASI) = 22 mm/m²
IMPORTANCE OF PROPORTIONS
ABSOLUTE DIAMETER = BAD DISCRIMINATOR IN TS

Fig. 1. The distribution of absolute ARdm on echocardiography (A) and AAdm on MRI (B) with age (subject with aortic dissection excluded). ●, TS; ○, controls. Lines represent the linear regression plot with 95% prediction lines for the distribution. Solid lines, TS; dashed lines, controls.
CAREFUL WITH GUIDELINE EXTRAPOLATIONS
DEFINITION OF AORTIC DILATION

**TABLE 3. Maximum aortic diameter in TS using cardiac magnetic resonance**

| First author (Ref.) | Age (yr) | n | Assessed | Aortic diameter in comparison with controls | Aortic dilation: TS | Association
|
|---------------------|----------|---|----------|---------------------------------------------|---------------------|----------------|
| Cleemann (78)       | <24      | 41| 9 positions | Absolute: smaller in TS except for similar in proximal descending compared to controls (n = 50); BSA-indexed: similar except for arch, isthmus, and descending where smaller in TS | 15%, total<sup>b</sup> | BSA, +; CoA, − |
| Hjerrild (81)       | >18      | 97| 8 positions | Absolute: comparable in TS to controls (n = 24) for all, except smaller at distal arch and isthmus | 23%, total<sup>c</sup> | BSA, +; BAV, +; blood pressure, +; age, + |
| Ostberg (75)        | >18      | 128| 2 positions | Absolute: mid-ascending and mid-descending in TS comparable to controls (n = 36); height-indexed: both aforementioned positions enlarged after adjustment for height and BSA | 16%, mid-ascending<sup>b</sup> | BAV, +; age, + |
| Matura (289)        | >18      | 166| 2 positions | Absolute: mid-ascending similar and mid-descending smaller compared to controls (n = 26); BSA-indexed, larger mid-ascending aorta in TS and similar descending aorta | 24%, mid-ascending<sup>c</sup> | BSA, +; BAV, +; ETA, +; karyotype, + |
| Kim (92)            | <26      | 50| 9 positions | 2–30%, all positions, highest for aortic sinus and sinotubular junction<sup>d</sup> | 2–30%, all positions, highest for aortic sinus and sinotubular junction<sup>d</sup> | Age, +; PAPVR, −; ETA, + |
| Dawson-Falk (80)    | <35      | 40| 1 position | 13%: ascending aorta | 13%: ascending aorta | |

☑ comparison to age-matched controls (> 95th percentile)
☑ correction for BSA or height

Mortensen et al. Endocrine Reviews 2012
BSA corrected reference z-scores for echo measurements

481 ‘healthy’ TS pts (age 2-70 ; av 25)

Excl : BAV / dissection / operation / cath interv / sev AR /AS

Quezada et al. Am J Med Genet Part A
<table>
<thead>
<tr>
<th>Variable position</th>
<th>COARC</th>
<th>Age</th>
<th>Antihypertensive treatment</th>
<th>Diastolic ABP</th>
<th>BSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic sinus</td>
<td>4.42</td>
<td>0.30</td>
<td>-4.02</td>
<td>-0.62</td>
<td>1.62</td>
</tr>
<tr>
<td>Sinotubular junction</td>
<td>-1.54</td>
<td>0.31</td>
<td>-0.74</td>
<td>-0.53</td>
<td>0.54</td>
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<tr>
<td>Mid-ascending aorta</td>
<td>-5.81</td>
<td>0.60</td>
<td>-0.99</td>
<td>0.78</td>
<td>0.52</td>
</tr>
<tr>
<td>Distal ascending aorta</td>
<td>-3.10</td>
<td>0.45</td>
<td>0.31</td>
<td>0.84</td>
<td>0.96</td>
</tr>
<tr>
<td>Proximal aortic arch</td>
<td>-6.73</td>
<td>0.34</td>
<td>-1.15</td>
<td>0.10</td>
<td>1.68</td>
</tr>
<tr>
<td>Mid aortic arch</td>
<td>-5.66</td>
<td>0.09</td>
<td>-0.77</td>
<td>0.86</td>
<td>1.49</td>
</tr>
<tr>
<td>Distal transverse aortic arch</td>
<td>-1.70</td>
<td>0.26</td>
<td>0.55</td>
<td>1.64</td>
<td>1.81</td>
</tr>
<tr>
<td>Proximal descending</td>
<td>23.40</td>
<td>0.07</td>
<td>-1.39</td>
<td>0.86</td>
<td>1.14</td>
</tr>
<tr>
<td>Distal descending aorta</td>
<td>14.43</td>
<td>0.34</td>
<td>1.00</td>
<td>1.37</td>
<td>1.94</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0004</td>
<td>0.005</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

Mortensen et al. JCMR 2013
AORTIC DIAMETER PREDICTION MODEL

INPUT

<table>
<thead>
<tr>
<th>RISK FACTORS</th>
<th>Values</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive treatment (yes/no)</td>
<td>1 (0/1)</td>
<td>No antihypertensive treatment = 0</td>
</tr>
<tr>
<td>Coarctation of the aorta (yes/no)</td>
<td>0 (0/1)</td>
<td>No aortic coarctation = 0</td>
</tr>
<tr>
<td>Aortic valve morphology</td>
<td>1 (0/1)</td>
<td>Tricuspid aortic valves = 0</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1,5</td>
<td>Body surface area = 0.007184 * (weight)0.425 * (height)0.725</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>

Predicted diameter of the thoracic aorta in Turner syndrome, at 9 separate positions from aortic sinuses to distal descending thoracic aorta

Mean predicted diameter (mm) with 95% prediction limits, and please see above for measurement positions.

Mortensen et al. JCMR 2013 (www.biostat.au.dk/MERL/Aorta_Prediction_model.htm)
Prediction of aortic dilation in Turner syndrome - enhancing the use of serial cardiovascular magnetic resonance

Kristian H Mortensen, Mogens Erlandsen, Niels H Andersen and Claus H Gravholt

0.2 – 0.38 mm/y (0.07 mm/y)
BAV: 0.64 mm/y (sinus)

Figure 1: Aortic growth rates (mean and 95% confidence intervals) during 4.8 ± 0.5 years of CMR in Turner syndrome (n = 78). * P < 0.05 when comparing baseline to follow-up using Student's t-test.
ACQUIRED CARDIOVASCULAR ANOMALIES

- Aberrant right subclavian artery
- SVC
- Aortic dissection
- Aortic dilatation
- PAPVR
- Coronary sinus

Mortensen et al. Endocrine Reviews 2012
♀ 50j TS (iso X) - BAV - AHT - AoC - syncope & acute abdo pain
Type A dissection R/ Bentall procedure & aortic arch replacement
ACQUIRED HD : AORTIC DISSECTION

- Lifelong risk ~ 1.4%
- Median age 35y (18-61y)

Figure 1.
The incidence of aortic dissection per 100,000 years in women with Turner's syndrome and in the general population. Gray bars illustrate females with Turner's syndrome in different age groups, and the dark gray bar indicates the total incidence rate for the entire background population.14,15

Gravholt et al. Cardiol Young 2006
Retrospective study Denmark/Sweden (33y)
IS THERE A CRITICAL DIAMETER?
Aortic Dilatation and Dissection in Turner Syndrome

Lea Ann Matura, PhD; Vincent B. Ho, MD; Douglas R. Rosing, MD; Carolyn A. Bondy, MD

- PROSPECTIVE NIH study – FU period 3y
- 166 adult TS – 26 healthy age matched control volunteers (≥ 18y)
- MRI assessment ascending/descending aortic diameter (AD at RPA)
- 95th percentile AD controls : 3,4 cm – aortic size index 2,0 cm/m² (BSA)
- 3 aortic dissections
  - ASI > 2,5 cm/m² (99th percentile) ; BAV ⅔ ; ETA
  - ⅓ TS pts with ASI > 2,5 cm/m² developped aortic dissection / 3y
- ASI > 2,5 cm/m² = cut off for extreme dilation – for intervention?

Matura et al. Circulation 2007
Surgery for Aortic Dilatation in Patients With Bicuspid Aortic Valves

1. Operative intervention to repair or replace the aortic root (sinuses) or replace the ascending aorta is reasonable in asymptomatic patients with BAV if the diameter of the aortic root or ascending aorta is 5.0 cm or greater and an additional risk factor for dissection is present (e.g., family history of aortic dissection or aortic growth rate ≥0.5 cm per year) or if the patient is at low surgical risk and the surgery is performed by an experienced aortic surgical team in a center with established expertise in these procedures (2,7-9).

In shortstatured patients with Turner syndrome and BAV, absolute measurement of aortic root or ascending aortic diameter may not predict the risk of aortic dissection as well as aortic diameter index ≥2.5 cm/m² (11,12). In

2014 ESC Guidelines on the diagnosis and treatment of aortic diseases

operation. In patients with small body size, in particular in patients with Turner syndrome, an indexed aortic diameter of 27.5 mm/m² body surface area should be considered.³²³ Lower thresholds of aortic dia-
Novel Measurement of Relative Aortic Size Predicts Rupture of Thoracic Aortic Aneurysms

Ryan R. Davies, MD, Amy Gallo, MD, Michael A. Coady, MD, MPH, George Tellides, MD, PhD, Donald M. Botta, MD, Brendan Burke, BS, Marcus P. Coe, BA, Gary S. Kopf, MD, and John A. Elefteriades, MD

Section of Cardiothoracic Surgery, Yale University School of Medicine, New Haven, Connecticut

**Background.** Optimal operative decision making in thoracic aortic aneurysms requires accurate information on the risk of complications during expectant management. Cumulative and yearly risks of rupture, dissection, and death before operative repair increase with increasing aortic size, but previous work has not addressed the impact of relative aortic size on complication rates.

**Methods.** Our institutional database contains data on 805 patients followed up serially with thoracic aortic aneurysms. Body surface area information was obtained on 410 patients (257 male, 153 female). We calculated a new measure of relative aortic size, the “aortic size index,” and examined its ability to predict complications in these patients.

**Results.** Increasing aortic size index was a significant predictor of increasing rates of rupture ($p = 0.0014$) as well as the combined endpoint of rupture, death, or dissection ($p < 0.0001$). Using aortic size index, patients were stratified into three risk groups: less than 2.75 cm/m$^2$ are at low risk (approximately 4% per year), 2.75 to 4.24 cm/m$^2$ are at moderate risk (approximately 8% per year), and those above 4.25 cm/m$^2$ are at high risk (approximately 20% per year).

**Conclusions.** This study confirms that (1) thoracic aortic aneurysm is a lethal disease, (2) relative aortic size is more important than absolute aortic size in predicting complications, and (3) a novel measurement of relative aortic size allows for the stratification of patients into three levels of risk, enabling appropriate surgical decision-making.


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Median age 65 y; 67% hypertension; 36% smokers

Exclusion criteria: coarctation
FOCUS ON MULTIPLE RISK FACTORS IN TS
Unreliability of aortic size index to predict risk of aortic dissection in a patient with Turner syndrome

Literature review (1961-2006) : 85 cases
Poorly documented !
80% 45,X – 20% Mosaic (49 karyotypes)
69% CHD (out of 87%) – 47% coarctation
6/85 AD after ART

RISK MARKERS FOR AORTIC DISSECTION

- Age
- Hypertension
- Aortic dilation
- BAV
- Coarctation/obstr ao arch
- Karyotype 45,X
- Pregnancy
- Aortic interventions

Carlson M, Silberbach M. J Med Genet 2007
Mortensen et al. Endocrine Reviews 2012
• Prospective study in 49 TS pts compared to lean and obese controls

• Major finding: childhood-onset increased vessel stiffness (as early as 9y)

• Increased risk for aortic dilation / dissection?
International TS Aortic Dissection Registry (ITSAD registry)

- 20 aortic dissections
  - 1 coarc stent
  - 19 spont
    - 18 BAV
    - 5 obst arch
    - 1 no CHD
    - 1 pregnancy (ART)

- Mean age 31.5y
- Ao diameters in 15/19
- 17/20 Type A
- Mean ASI 2.7 cm/m²
- ASI > 2.5 cm/m²: cut off intervention?

Carlson et al. Circulation 2012
Increased maternal cardiovascular mortality associated with pregnancy in women with Turner syndrome

Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

| TABLE 2. Maternal complications during pregnancy after OD in TS recipients |
|-----------------------------------------------|-----------------|
| Mean ± sp (range) or n (%)                  |                 |
| PAHD                                         | 31/82 (37.8)    |
| PIH                                          | 14/82 (17.1)    |
| PE                                           | 17/82 (20.7)    |
| Maternal death by aortic root rupture        | 2/93 (2.2)      |
## CASE REPORTS OF AORTIC DISSECTION DURING PREGNANCY

<table>
<thead>
<tr>
<th>Reference (country, year of publication)</th>
<th>Age (yr)</th>
<th>Number of fetuses</th>
<th>Heart disease</th>
<th>Hypertension</th>
<th>Karyotype</th>
<th>Time of dissection</th>
<th>Location of dissection</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 (United States, 1997)</td>
<td>NR</td>
<td>1</td>
<td>Mild aortic root dilatation</td>
<td>Yes</td>
<td>NR</td>
<td>Third trimester of pregnancy</td>
<td>NR</td>
<td>Deceased</td>
</tr>
<tr>
<td>26 (United States, 1997)</td>
<td>NR</td>
<td>1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Third trimester of pregnancy</td>
<td>NR</td>
<td>Deceased</td>
</tr>
<tr>
<td>53 (United States, 1998)</td>
<td>33</td>
<td>1</td>
<td>Mild AoC</td>
<td>Yes</td>
<td>NR</td>
<td>27 wg 2 wk after cesarean section for eclampsia</td>
<td>Proximal Distal</td>
<td>Deceased</td>
</tr>
<tr>
<td>54 (Belgium, 2000)</td>
<td>38</td>
<td>1</td>
<td>No</td>
<td>Yes</td>
<td>45 X0, 46 XX</td>
<td>1 wk after cesarean section</td>
<td>Proximal</td>
<td>Alive</td>
</tr>
<tr>
<td>55 (United States, 2001)</td>
<td>30</td>
<td>2</td>
<td>AoC Bicuspid aortic valve</td>
<td>No</td>
<td>NR</td>
<td>36 wg</td>
<td>Proximal</td>
<td>Deceased</td>
</tr>
<tr>
<td>56 (Sweden, 2004)</td>
<td>39</td>
<td>1 (spontaneous pregnancy)</td>
<td>No</td>
<td>Yes</td>
<td>45 X0, 46 XY, 47 XYY</td>
<td>Month 7 of pregnancy</td>
<td>Proximal</td>
<td>Alive</td>
</tr>
<tr>
<td>35 (France, 2008)</td>
<td>33</td>
<td>1</td>
<td>Aortic insufficiency, aortic root dilatation</td>
<td>No</td>
<td>45 X0</td>
<td>1 wk after cesarean section</td>
<td>Proximal</td>
<td>Deceased</td>
</tr>
<tr>
<td>33 (France, 2009)</td>
<td>33</td>
<td>1</td>
<td>Bicuspid aortic valve, mild aortic root dilatation</td>
<td>No</td>
<td>45 X0, 46 XX, 46 XY</td>
<td>37 wg</td>
<td>Proximal</td>
<td>Deceased</td>
</tr>
</tbody>
</table>

AoC, Aortic coarctation; NR, not reported; wg, week of gestation.

MATERNAL MORTALITY 75%

Chevalier et al. JCEM 2011
ESC Guidelines on the management of cardiovascular diseases during pregnancy

- Increased risk of aortic dissection in TS patients
- Risk ↑ with BAV – coarctation – AHT
- highest risk if aortic dilation (index voor BSA !)
- aortic diameter ≥ 27 mm/m² : consider prophylactic surgery
CONTRA-INDICATIONS FOR PREGNANCY

- aortic diameter > 35 mm
- aortic diameter > 25 mm/m²
- progression ao diam > 10%/y
- coarctation aorta
- uncontrolled AHT
- history of aortic surgery
- history of aortic dissection
- BAV = risk factor (no CI)

ABSOLUTE
- aortic diameter > 20 mm/m²
- significant CV anomaly on cardiac MRI

RELATIVE
- Turner syndrome

Chevalier et al. JCEM 2011
ASRM Practice Committee. Fertil Steril 2012
- TS frequently associated with congenital / acquired CV disease
- Aortic disease is an important cause of early excess mortality
- Aortic diameters should be corrected for BSA
- Echocardiography and MRI are mandatory in every patient
- Increased risk of aortic dissection – especially during pregnancy
- Further research is needed to determine who is at highest risk
- Multidisciplinary FU in a specialized Turner clinic is recommended
THANK YOU FOR YOUR ATTENTION!