An Individualized Approach to the Ascending Aorta in Bicuspid Aortic Valve (BAV) Disease

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Conflict of interests:
Royalties from Braun Melsungen for vascular prostheses
(Sinus prosthesis, curved prosthesis)
Every BAV patient is genetically different, living in a different environment together resulting in the phenotype

- Thus BAV disease (valve + aorta) is heterogeneous, individually different.
- Optimally, we need an individualized treatment.
- The question here is: What is the best treatment for an individual patient with BAV aortopathy and valve surgery (95% of our BAV surgical workload) weighing risks and benefits to prevent aortic complications (sudden, without symptoms, catastrophic) or reoperation?
- Preferably we would rely on prospective randomized trials for decision making (evidence based medicine) but these are not available. Nevertheless we have to decide.
- We have to rely on clinical experience and scientific knowledge for decision making (ACC/AHA guidelines 2015 – IIa, C-EO: 4.5 cm absolute diameter) with all its shortcomings. (Sundt TM. JTCVS 2015; 149:S6-9)
- These guidelines are mainly based on diameter, vary in relation to period and association, they are very helpful for practical purposes and are also of considerable consequence including medico-legal aspects.
Aortic diameter \( \geq 5.5 \) cm is not a good predictor of type A aortic dissection: Observations from the International Registry of Acute Aortic Dissection (IRAD).


But diameter is not the only predictor for dissection.

40% of patients with dissection had diameters <5 cm and these diameters were measured after dissection!

50% of dissections with normal aortic diameters (<40 mm) had no known risk factor (hypertension, Marfan and BAV).

\[ \text{mean} = 5.31 \text{ cm} \]

\[ \text{uncertainty} \]

\[ \text{4.5 cm} \]

\[ \text{80} \]

\[ \text{60} \]

\[ \text{Count} \]

\[ \text{40} \]

\[ \text{20} \]

\[ \text{0} \]

\[ \leq 2.9 \]

\[ 3.0-3.4 \]

\[ 3.5-3.9 \]

\[ 4.0-4.4 \]

\[ 4.5-4.9 \]

\[ 5.0-5.4 \]

\[ 5.5-5.9 \]

\[ 6.0-6.4 \]

\[ 6.5-6.9 \]

\[ \geq 7.0 \]

\[ \text{Ascending Diameter (cm)} \]


Philadelphia 2016

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How does the ascending aorta geometry change when it dissects?

Diameter after dissection is roughly 13 mm larger compared to pre-dissection state which is the real diameter for risk assessment.

Ascending Aortic Diameter Change After AADA Onset
Blue indicates patients with spontaneous AADA; red, patients with retrograde AADA; and black, the overall median diameter increase. AADA = acute aortic dissection type A.

Rylski B. J Am Coll Cardiol 2014;63:1311-9
How can we understand or even reduce this uncertainty? What do we know for safe about causes of dissection?

**Safe knowledge**

Dissection occurs when **wall stress** (WS, force per unit area) exceeds tensile strength of the material.

The most important determinant of **wall stress** (WS) is the **Law of Laplace**:

$$WS = \frac{\text{diameter} \times \text{pressure}}{\text{wall thickness/quality}}$$
WS = \text{diameter} \times \text{pressure} \\
\text{wall thickness/quality}

\rightarrow \text{95th percentile, } z = 1.63, \text{ generally considered as limit of normal!}

\text{Diameter and diameter is not the same. Diameter depends mainly on age.}

\text{Better to use } z\text{-value (Diameter related to age, BSA, gender)}

\text{\textit{z value} = pathology index}

\text{Diameter 1} = 40 \text{ mm} \rightarrow \text{z} = 6.1
\text{Diameter 2} = 40 \text{ mm but } \text{z} = 0.6
Guidelines threshold for replacement of ascending aorta if valve surgery is performed.

Growth during the expected lifetime of a individual patient is uncertain (0,2-1,9 cm/year\(^1,2\)).

Failure to Prevent Progressive Dilation of Ascending Aorta by Aortic Valve Replacement in Patients With Bicuspid Aortic Valve: Comparison With Tricuspid Aortic Valve

Replacement of the valve doesn’t prevent progressive dilatation of ascending aorta.

Figure 1.
Annual dilation rate in each group.
SV=sinus of Valsalva;
STJ=sinotubular junction;
Prox. Ao=proximal aorta 1 cm above the sinotubular junction. The dilation rate of the BAV-OP patients tended to be faster than that of TAV-OP patients.

The fate of the bicuspid valve aortopathy after aortic valve replacement (Ross operation)

Evolution of absolute (left) and relative (right) ascending aorta diameters in our patient population. The solid lines depict the evolution of a 49-year old male with 1.9 m² BSA and a tricuspid aortic valve (TAV) (blue line) or a bicuspid aortic valve (BAV) (red line).

No difference in the slope of increase of ascending aorta diameters with time could be observed.

Diameter

- Individually different (most significantly related to age, less to BSA and gender)
- Z-value of diameter relates the diameter to age, BSA and gender (pathology index)
- Z-value > 1.6 is more than 95th percentile (normal limit)
- Growth of diameter varies considerably
- AVR is unclear to prevent progressive dilatation
- But diameter is measurable and
- Does not significantly change instantaneously
BP response to weight lifting: Extreme hypertension note the marked elevation in blood pressure (BP) for these 3 scientists as they lift various percentages of their body weight in the bench press.


WS = \frac{\text{diameter} \times \text{pressure}}{\text{wall thickness/quality}}

Blood pressure varies instantaneously, considerably, and unpredictably.

Blood pressure is “the real invisible enemy” Thubrikar 2007

Unreliable predictor
Tensile strength curves (max. wall stress at break in circumferential direction) showing the interplay of diameter, blood pressure and wall thickness provided the quality of tissue is constant.

1. in accordance to Viorp DA et al. Ann Thorac Surg 2003;75:1210-4
Wall thickness was smaller in patients experiencing dissection\(^1\).

Impaired collagen biosynthesis and cross-linking in Aorta of Patients With Bicuspid Aortic Valve

Impaired Collagen Biosynthesis and Cross-linking in Aorta of Patients With Bicuspid Aortic Valve

Dick Wågsäter, PhD;+ Valentina Paloschi, MSc;+ Roeland Hanemaaijer, PhD; Kjell Hultenby, PhD; Ruud A. Bank, PhD; Anders Franco-Cereceda, MD, PhD; Jan H. N. Lindeman, MD, PhD; Per Eriksson, PhD

Background—Patients with bicuspid aortic valve (BAV) have an increased risk of developing ascending aortic aneurysm. In the present study, collagen homeostasis in nondilated and dilated aorta segments from patients with BAV was studied, with normal and dilated aortas from tricuspid aortic valve (TAV) patients as reference.

Methods and Results—Ascending aortas from 56 patients were used for biochemical and morphological analyses of collagen. mRNA expression was analyzed in 109 patients. Collagen turnover rates were similar in nondilated and dilated aortas of BAV patients, showing that aneurysmal formation in BAV is, in contrast to TAV, not associated with an increased collagen turnover. However, BAV in general was associated with an increased aortic collagen turnover compared with nondilated aortas of TAV patients. Importantly, the ratio of hydroxylsyl pyridinoline (HP) to lysyl pyridinoline (LP), 2 distinct forms of collagen cross-linking, was lower in dilated aortas from patients with BAV, which suggests that BAV is associated with a defect in the posttranslational collagen modification. This suggests a deficiency at the level of lysyl hydroxylase (PLOD1), which was confirmed by mRNA and protein analyses that showed reduced PLOD1 expression but normal lysyl oxidase expression in dilated aortas from patients with BAV. This suggests that impaired collagen cross-linking in BAV patients may be attributed to changes in the expression and/or activity of PLOD1.

Conclusions—Our results demonstrate an impaired biosynthesis and posttranslational modification of collagen in aortas of patients with BAV, which may explain the increased aortic aneurysm formation in BAV patients. (J Am Heart Assoc. 2013;2:e000034 doi: 10.1161/JAHA.112.000034)

Key Words: aneurysm • aorta • bicuspid • collagen • valve

Tissue of ascending aorta in BAV patients is not normal

Elastic fiber abnormalities

Frequency of 0 to 1+ and 2+ to 4+ **loss of aortic medial elastic fibers** among the 7 patient groups with aortic stenosis or pure aortic regurgitation.

Plasma levels of soluble receptor for advanced glycation end product (sRAGE) correlate with altered ascending aortic microstructures.

**A**, Ascending aortic diameter measurement by computed tomographic scan (cm), age, and sRAGE concentration (pg/mL) detected in the plasma of the patient nos. 1 to 7.

**B**, Graph representing sRAGE values (bars), proteoglycan deposition (scored from 0 to +3; triangles), and elastin fragmentation (scored from 0 to −3; squares).

**C**, Representative images of modified Movat’s pentachrome staining performed on optimal cutting temperature compound section of ascending aortic tissues excised from patient nos. 1 to 7. Media layer (magnification, ×40). AA indicates ascending aortic replacement.

Quality of aortic wall tissue (genes + WSS)

Seems to be not normal (insufficiency!) even in relatives of BAV patients with TAV$^1$ (elasticity ↓)

- Tissue probably more vulnerable to dissection$^2$ and has
- reduced mechanical properties$^3$

- Are there any other signs in BAV patients associated with connective tissue weakness? (mitral valve$^4$, joints, phenotype, tall, thick, young, nutrition, diabetes, psychological conditions, ...)?

New insights into bicuspid aortic valve disease: the elongated anterior mitral leaflet

Anterior mitral leaflet was 20% more elongated in BAV vs. TAV (p<0.001)

Is there a BAV syndrome?

Fact: We don’t know the real risk of aortic type A dissection in BAV especially not for the individual patient.

Consented risk factors are:

- **Absolute Diameter** (practical, relatively accurate, always achievable)
- **Family history** (genetic background, seldom)
- **Progressive growth** (> 0.5 cm/year?; getting increasing availability)
- **Fragile, thin aortic wall** (only intraoperative)

Keeping these factors in mind we performed BAV operations from 1999 on a more or less heuristic basis and analyzed our strategy retrospectively in 2013 with follow-up till 2016.
Intervention on the ascending aorta in relation to size of aorta

( yellow: intervention  blue: no intervention )

**in favor of aortoplasty (n=172):**
- borderline AA dilatation
- eccentric AA dilatation (FII)
- older age
- „normal“ wall

**in favor of replacement (n=284):**
- larger diameter and/or
- younger age
- small BSA
- fragile and thin AA wall
- family history
  - growth rate > 0,5 cm/year
  - tubular shape of AA (FIII&IV)
  - BAV Type 1 and insufficiency
  - BAV Type 2

**in favor of no intervention (n=906):**
- smaller diameter or
- large BSA
- old patient
- high surgical risk
- severe comorbidities

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**Aortoplasty** preserves Windkessel function

**Replacement** increases up-downstream circulatory stress (dp/dt ↑)

LV diastolic burden ↑

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Cutoff accuracy determination for predicting an aortic intervention

**Asc Ao diameter z-score cutoff**

\[ z = 3.2 \]

**Svensson Cutoff**

\[ 8.4 \]

Aortic cross-sectional area / height ratio
Results

Operative mortality

<table>
<thead>
<tr>
<th></th>
<th>total  (n=1362)</th>
<th>no intervention on AAo (n=906)</th>
<th>aortoplasty (n=172)</th>
<th>replacement (n=284)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality n (%)</td>
<td>12 (0.9)</td>
<td>10 (1.1)</td>
<td>1 (0.6)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

Operative mortality: No difference between groups

Causes of late death (> 30 days)

<table>
<thead>
<tr>
<th>Causes of late death</th>
<th>total  (n=1362)</th>
<th>no intervention on AAo (n=906)</th>
<th>aortoplasty (n=172)</th>
<th>replacement (n=284)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac n (%)</td>
<td>29 (24.6)</td>
<td>24 (27.3)</td>
<td>3 (16.7)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>non-cardiac n (%)</td>
<td>72 (61.0)</td>
<td>52 (59.1)</td>
<td>11 (61.1)</td>
<td>9 (75.0)</td>
</tr>
<tr>
<td>unknown n (%)</td>
<td>17 (14.4)</td>
<td>12 (13.6)</td>
<td>4 (22.2)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>LOR (% / pt-year)</td>
<td>0.40</td>
<td>0.49</td>
<td>0.30</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Late mortality: No difference between groups but no autopsy

“The absence of evidence of impact is not equivalent to the absence of impact”


LOR, linearized annual occurrence rate; Numbers in parentheses are percentages

→ Aortoplasty and especially ascending aorta replacement did not add additional risk to early and late mortality.
Further results:  (BAV phenotype, BAV is a “fish mouth” opening of the aortic valve based on congenital disease)

Significantly more replacements of the ascending aorta in BAV 1 L-R with insufficiency.

Significantly more replacements of the ascending in BAV type 2/unicuspid.

In a recent publication\textsuperscript{1} the authors stated that BAV regurgitation had a 10-fold higher risk of aortic dissection after AVR compared to stenosis and the diameters were smaller in these patients.

\textsuperscript{1} Girdauskas E et al. Aortic Dissection After Previous Aortic Valve Replacement for Bicuspid Aortic Valve Disease. J Am Coll Cardiol. 2015;66:1409-11.
Outcomes after operations for unicuspid aortic valve with or without ascending repair in adults

Kaplan-Meier curves show survival for patients undergoing aortic valve replacement (AVR) and an aortic operation (blue line) and those undergoing AVR alone (red line).


Kaplan-Meier curves show survival for patients undergoing aortic valve replacement (AVR) and an aortic operation (blue line) and those undergoing AVR alone (red line).
### Late reoperations on ascending aorta.
Follow-up mean: 5.8 years (0-14 years, n=1362)

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>N</th>
<th>Reoperation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>no intervention on AAo (n=906)</strong></td>
<td>N=4</td>
<td>• Type A dissection (primary diameter 43 mm, 12y before)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(age 42.1 yrs, BAV type 1 L-R, AV insufficiency)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• False aneurysm at aortotomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(age 69.9 yrs, BAV type 1 R-N, AV stenosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 50 mm diameter (43 mm 2 years before) at bioprosthesis reoperation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(age 56.9 yrs, BAV type 1 R-N, AV stenosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 45 mm diameter (43 mm 3 years before) at bioprosthesis reoperation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(age 52.0 yrs, BAV type 1 L-R, AV stenosis)</td>
</tr>
<tr>
<td><strong>AAo replacement (n=284)</strong></td>
<td>N=0</td>
<td></td>
</tr>
<tr>
<td><strong>Aortoplasty (n=172)</strong></td>
<td>N=5</td>
<td>• Infection of prosthetic material</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dissection type A: thin aortic wall tissue at operation 7 years before</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(age 62.1 yrs, BAV type 1 L-R, AV insufficiency)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• * Reoperation, aneurysm at aortoplasty (type 1 RN, insufficiency)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• * Increase of diameter from 42 mm post operatively to 52 mm after 7.5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• * Increase of diameter from 37 mm post operatively to 50 mm after 11.2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>* between 2013 - 2015</td>
</tr>
</tbody>
</table>
Conclusions from our study for patients with BAV needing valve surgery (our experience)

1. Best results were obtained with replacement of the ascending aorta (no additional operative and late risk, a trend for being even better than no intervention or aortoplasty).

2. Diameter related to age, BSA and gender had greatest influence on decision making (relative diameter, z-score cut-off for intervention: 3.2).

3. The decision making diameter was individually different and was smaller in younger patients.

4. BAV type 1 LR + regurgitation and BAV type 2/unicuspid significantly favoured ascending aorta or root replacement.

5. No intervention and aortoplasty bear the risk of aortic complications

**Consequences:**

- We continue our policy more closely adhering to our results.
- Aortoplasty is less frequently performed, not in insufficiency, replacement is preferred.
- The diameter z-score gets more importance on our decision making.
Our current decision line for management of the ascending aorta in the clinical practice when surgery is performed on the BAV:

**Green area:** Intervention on the ascending aorta (mainly replacement).

**Dark green:** Absolute diameter (4.5 cm)

**Light green:** Relative diameter and/or additional factors.
- Relative diameter: $z$-value $> 3.2$
- Additional factors:
- Family history
- Growth rate
- Thin / fragile aortic wall
- Tubular shape F (III+IV)
- BAV Type 1/LR insufficiency
- BAV Type 2/ unicuspid
- Comorbidities
- Patients wishes
This is only the beginning of the individual treatment journey to reach individual / precision medicine.

New potential risk factors are emerging.
New potential risk factors:

Emotional stress

Does emotional stress lead besides hypertension to vasoconstriction of the media?

Is there something like a Tako-Tsubo Aortopathy (Noradrenalin↑)?

Halsted 1916:
Dilatation may be caused by “paralysis of vasomotor nerves and the occlusion of vasa vasorum”.

New potential risk factors: BAV flow abnormalities increase wall stress

Segmental wall distensibility

BAV type 1 Stenosis

longitudinal wall stress ↑

circumferential wall stress ↑

flow direction

convexity

ORIGINAL ARTICLE

Laminar Shear Stress Stimulates Vascular Smooth Muscle Cell Apoptosis Via the Akt Pathway

TAMARA N. FITZGERALD,1,2 BENJAMIN R. SHEPHERD,1,2 HIDENORI ASADA,1,2 DESAROM TESO,1,3 AKIHITO MUTU,1,2 TIFFANY FANCHER,1,3 JOSE M. PIMENTO,1,3 STEPHEN P. MALONEY,1,3 AND ALAN DARDIK1,2,4,6

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3St Mary’s Hospital, Waterbury, Connecticut
4VA Connecticut Healthcare System, West Haven, Connecticut

New potential risk factors:
Elevated wall shear stress is associated with abnormal wall tissue

New potential risk factors:

Mechanotransduction

New potential risk factors:
Genes and proteins distribution in BAV aortopathy

Immaturity of vessel wall in BAV patients ➔ increased susceptibility to dilatation

New potential risk factors:

BAV PHENOTYPE in relation to ascending aorta phenotype

Mosaic plot of the expected (left) and observed (right) distribution of BAV type, aortic configuration and vHs of our patient population.

E.g. type 1 LR and insufficiency is frequently associated with Fazel type IV (AoR + AAo dilatation, loss of STJ waist).

New potential risk factors: Developmental aspects

Second heart field

Seams are likely locations of dissection and the second seam is the target of the BAV flow jet.

Perspective

A lot of potential risk factors need to be explored to substantiate the individualized approach and end up with precision medicine (Jameson JL, NEJM 2015)

- Genes (transcriptomics, proteomics, metabolomics)
- Exposome (wall shear stress, hypertension, nutrition, smokers)
- Biomarkers
- phenotype and blood flow
- bio-imaging (wall quality, wall perfusion, segmental wall distensibility, molecular imaging)
- psychological background

Surgical goal: Risk of ascending aorta replacement should be near 0% (trainee school)

Perspective: Iterative accumulation of knowledge (randomized, prospective, representative trials, clinical and scientific data, propensity matching, pragmatic trials).

Patients

Surgeon

Consented decision parameter - guidelines 4.5 cm absolute diameter

new results/experience - relative diameter (age, z-value) - BAV-type - insufficiency - aortic phenotype (STJ loss)

new results/experience - elastic prosthesis - Genes - psychology

new results/experience - WSS - Blood pressure - Biomarkers - Imaging (wall quality) - Local imaging - Data sharing - Global data - Drugs

Wishes/fears (Will it break? Can I make sports?) Comorbidities, exercise, lifestyle

local skill, results

adjusted expert decision aid (EDA)

individual medicine (truth)

Philadelphia 2016

Department of Cardiac and Thoracic Vascular Surgery, Luebeck, Germany
Whatever we do, critical follow-up is mandatory.

If you stare (below) at any one of the white circles you will notice black dots appearing and disappearing in some of the surrounding circles. But if you switch your gaze to one of these black dots it immediately turns white again and stays white. You can never catch a black dot in the act. This simple optical illusion shows in a rough way a quantum physics idea: the act of measurement affects a quantum system.


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Logic of research
We want to find the truth

Ideally this would need a prospective randomized trial on the same patient, which is not possible – yet.

Karl Popper (Philosopher of the 20th century):

Safe knowledge of truth is prohibited. The approximation to truth is possible. Our knowledge is critical guesswork, a net of hypotheses and assumptions. This understanding may lead to some intellectual modesty.

Xenophanes (Philosopher of 570 – 475 BC):

The Gods did not reveal, from the beginning, all things to us, but in the course of time through seeking we may learn & know things better. But as for certain truth no man knows it, nor shall he know it, neither of the Gods nor yet of all things that I speak. For even if by chance he were to utter The Final Truth, he would himself not know it: for all is but a woven web of guesses.
Alternative Treatment

We will probably live forever in UNCERTAINTY.
We can only reduce it. Let’s take the challenge!

Al-Khalili J., Quantum Moderne Physik zum Staunen, Elsevier München, 2005
‘A brief moment of wonder’

A new art installation shows the human brain in intricate detail, including this close-up of the cerebellum.

Scientists use environmental DNA to map this salamander’s lairs. The Franklin Institute in Philadelphia, Pennsylvania, is now home to what may be the most detailed piece of brain art ever made.

The image, a 2.4-by-3.7-meter illustration of a slice through the human brain, shows more than 500,000 individual neurons.

Its appearance changes as visitors walk around the installation because microscopic waves etched into the polymer surface, which was then coated with gold leaf, only reflect light from certain angles. An LED light source will illuminate different parts of the image at different times to mimic the flow of electrical activity through the brain.

The permanent installation, which opens 25 June, is the result of a 2-year collaboration between Greg Dunn, a local neuroscientist-turned-artist, and Brian Edwards, an applied physicist at the University of Pennsylvania. The work, funded by a $261,000 grant from the National Science Foundation, is grounded in science, Dunn says.

“But what it’s really about is giving people a brief moment of wonder.”