Circulating microRNAs in bicuspid aortopathy

Evaldas Girdauskas

Department of Cardiovascular Surgery, University Heart Center Hamburg
Disclosure of Interest

Speaker name: Evaldas Girdauskas

- I do not have any potential conflict of interest
Background

- Limitations of aortic size-based parameters to predict aortic events

Modeling of predissection aortic size in acute type A dissection: More than 90% fail to meet the guidelines for elective ascending replacement

Bartosz Rylski, MD, Emanuela Branchetti, PhD, Joseph E. Bavaria, MD, Prashanth Vallabhajosyula, MD, Wilson Y. Szeto, MD, Rita K. Milewski, MD, PhD, and Nimesh D. Desai, MD, PhD

JTCVS 2014;148:944-948

Most aortic events occur in patients with aortic diameters below 50mm

- Serologic biomarkers for size-independent prediction of aortic events?
  - MicroRNAs: miR-17-associated miRNAs have been demonstrated to impact progressive aortic dilatation (Wu, J et al. J Am Coll Cardiol. 2016;67:2965-77.)

HYPOTHESIS: specific circulating microRNAs might be useful as size-independent predictors of aortic events in BAV patients presenting with distinct valvulo-aortic phenotypes
### BAV database / University Hamburg

**Prospective BAV surgery database (2015 – 2018) (n=310)**

- aortic imaging
- blood samples
- aortic tissue collection
- follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>BAV-AR (n=63)</th>
<th>BAV-AS (n=32)</th>
<th>TAV-AS (n=50)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.3 ± 11.3</td>
<td>58.7 ± 10.5</td>
<td>66.5 ± 14.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>58 (92)</td>
<td>24 (73)</td>
<td>27 (55)</td>
<td>0.01</td>
</tr>
<tr>
<td>Proximal aorta (mm)</td>
<td>47.4 ± 10.2</td>
<td>38.3 ± 8.5</td>
<td>38.1 ± 7.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Aortic surgery</td>
<td>34 (54)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

63 patients with BAV-AR + root dilatation

32 patients BAV-AS w/o aortopathy

50 patients TAV-AS w/o aortopathy
Methods

Literature-based selection of 11 microRNAs associated with aortopathies: 
(miR-1, miR-17, miR-18a, miR-19a, miR-20a, miR-21, miR-29b, miR-106a, 
miR-133a, miR-143, miR-145)

• Isolation of total RNA in 145 patients (PaxGene Blood miRNA kit)

• Analysis of specific miRNAs (TaqMan Advanced miRNA System)

Study endpoints:

(1) Correlation between circulating miRNAs and the severity of aortopathy (n=145)

(2) Expression patterns of circulating miRNAs in BAV-AR vs. BAV-AS vs. TAV-AS
Results

Correlation of circulating microRNA’s and aortopathy in the whole study cohort (n=145)

- All 7 microRNAs showed inverse correlation with the proximal aortic diameter
- The strongest correlation was found for miR-17, miR-20a and miR-106a
**Results**

<table>
<thead>
<tr>
<th>Phenotype of bicuspid aortic valve stenosis</th>
<th>Root phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="#">Image A</a> Aneurysm of the ascending aorta</td>
<td><a href="#">Image B</a> Sinus of Valsalva aneurysm</td>
</tr>
<tr>
<td>BAV stenosis</td>
<td>BAV regurgitation</td>
</tr>
</tbody>
</table>

*Images showing anatomical and ultrasound images corresponding to the phenotypes.*
Results

Circulating microRNAs in BAV-AR (n=63) vs. BAV-AS w/o aortopathy (n=32)

- Circulating microRNAs were significantly downregulated in a subgroup of patients with BAV regurgitation (BAV-AR) vs. BAV stenosis (BAV-AS)
Results

Circulating microRNAs in BAV w/o aortopathy (n=32) vs. TAV w/o aortopathy (n=50)

- Circulating microRNAs were differentially expressed in BAV w/o aortopathy vs. TAV w/o aortopathy. This difference persisted after normalization to miR-16.
NOTCH1 variants & circulating miR-145

Aortopathy gene panel and circulating microRNAs in BAV-AR (n=63)

Girdauskas et al. PLOS One 2018
NOTCH1 variants & circulating miR-145

Aortopathy gene panel and circulating microRNAs in BAV-AR (n=63)

• Potential mechanistic linkage between NOTCH1 variants, miR-145 expression and bicuspid aortopathy

Girdauskas et al. PLOS One 2018
Conclusion

- Circulating microRNAs showed a significant inverse linear correlation with aortic diameter in the whole study cohort.
- Circulating microRNAs were significantly down-regulated in BAV-AR vs. BAV-AS patients.
- Expression patterns of circulating microRNAs were significantly different in BAV vs. TAV patients with normally sized proximal aorta.
- Larger prospective patients’ cohorts and longitudinal population-based data are required to define the value of circulating microRNAs in the risk prediction of aortopathy.
Thank you!

e.girdauskas@uke.de