3rd International Meeting on Aortic Diseases

New insights into an old problem

October 4-6 2012

Congress Center Liège, Belgium

Biomechanical Implications of Bicuspid Aortic Valve

...and implications of BAV biomechanics

Alessandro Della Corte, MD, PhD

Department of Cardiothoracic Sciences, Second University of Naples

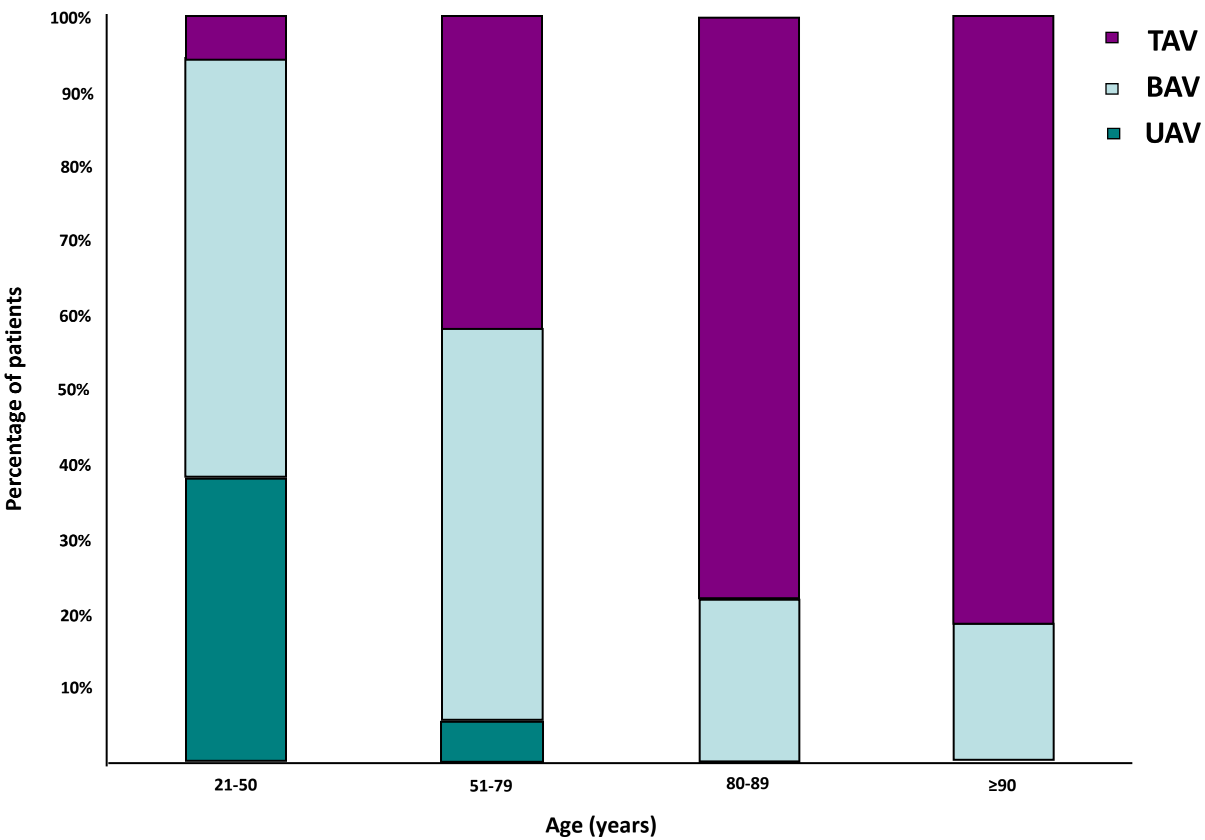
@ Cardiac Surgery Unit, Monaldi Hospital, Naples - Italy

1. Why Biomechanics?

BAV disease: a global public health concern?

Roger VL *et al.*

Circulation 2011



Percentage of aortic valve stenosis patients requiring AVR

Roberts WC *et al.*

Am J Cardiol 2012

Reasearch on BAV disease

Hemodynamics Genetics

Clinical Evidence → Pathogenetic Hypotheses

e.g.

Aortic dilatation occurs even without valve stenosis or regurgitation

e.g.

Hemodynamics do not have a role in the determinism of the dilatation

Hemodynamics → PATHOGENESIS ← Genetics

PATHOGENESIS → **CLINICS**

mechanisms — management

"When the wise man points at the moon, the fool looks at the finger"

Ancient Chinese proverb

Aortic root dilatation in young men with normally functioning bicuspid aortic valves

S Nistri, M D Sorbo, M Marin, M Palisi, R Scognamiglio, G Thiene

Conclusions—**Aortic root enlargement in people with a bicuspid aortic valve occurs independently of haemodynamic abnormalities, age, and body size. However, there appear to be different subgroups of young adults with bicuspid aortic valves, one of which is characterised by aortic dilatation, possibly caused by a congenital abnormality of the aortic wall.**

(*Heart* 1999;**82**:19–22)

ELSEVIER

European Journal of Cardio-thoracic Surgery 31 (2007) 397—405

EUROPEAN JOURNAL OF
CARDIO-THORACIC
SURGERY

www.elsevier.com/locate/ejcts

Predictors of ascending aortic dilatation with bicuspid aortic valve: a wide spectrum of disease expression[☆]

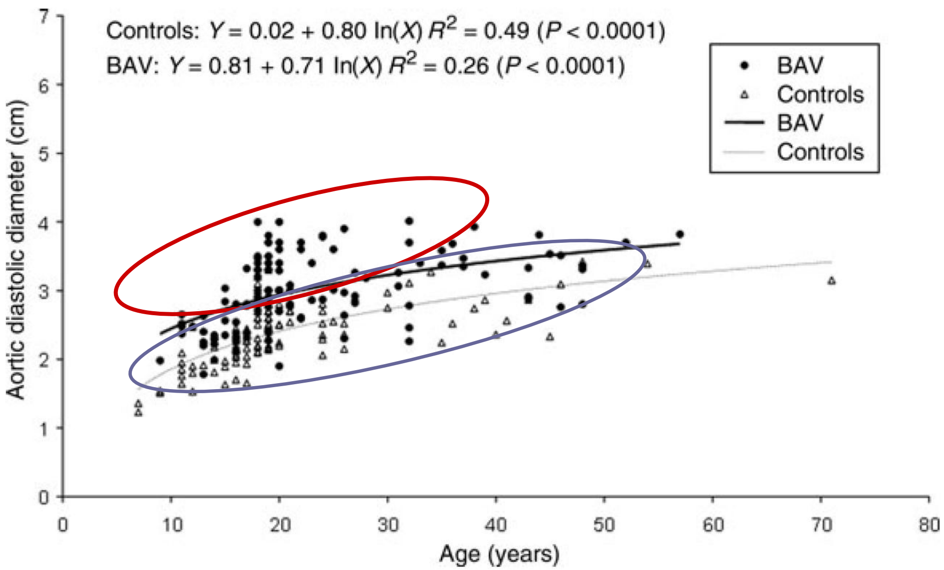
Alessandro Della Corte[*,1], Ciro Bancone, Cesare Quarto, Giovanni Dialetto, Franco E. Covino, Michelangelo Scardone, Giuseppe Caianiello, Maurizio Cotrufo

Department of Cardiothoracic and Respiratory Sciences, Second University of Naples, Department of Cardiovascular Surgery and Transplant, V Monaldi Hospital, via L Bianchi, 80131 Naples, Italy

Conclusions: BAV patients constitute an importantly heterogeneous population in terms of risk and features of aortic disease. The most common condition is an ectasia of the mid-ascending tract, with unaffected or mildly involved root. If further confirmed, this could suggest that surgical approach may spare the root in most BAV patients. Mid-ascending dilatation is proportional to stenosis severity, suggesting a post-stenotic causative mechanism. Root dilatation is rarer, mostly observed in younger men, and unrelated to the presence and severity of stenosis. The two different aortic dilatation phenotypes (mid-ascending and root) may be subtended by different pathogeneses.

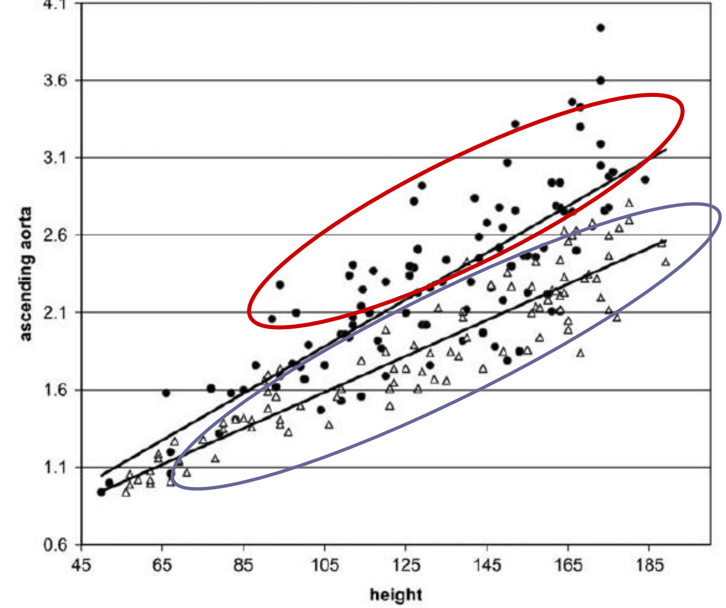
Nistri S *et al*.

Eur Heart J 2008



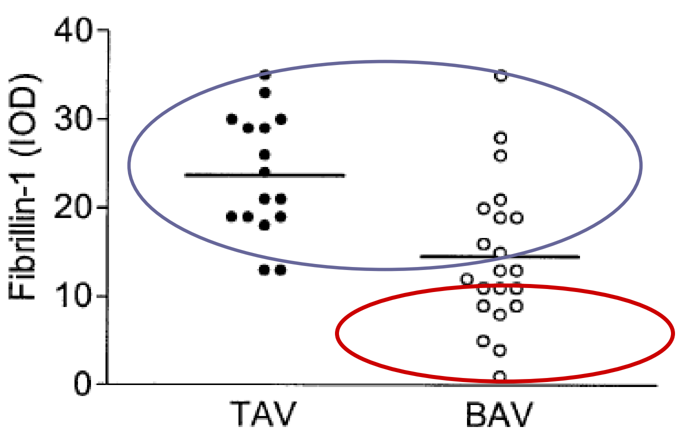
Beroukhim RS *et al*.

Am J Cariol 2006



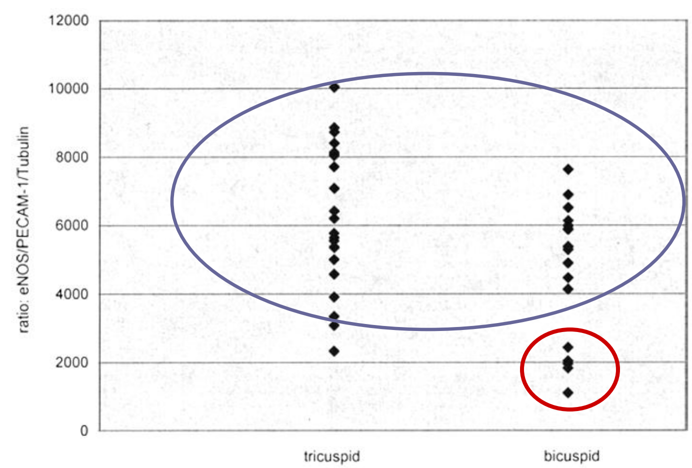
Fedak PWM et al.

J Thorac Cardiovasc Surg 2003



Aicher D et al.

Ann Thorac Surg 2007



Heterogeneity

The "Third Theory"

Phenotypic heterogeneity may result from **quantitatively varying** contributions of either one of the coexisting determinants

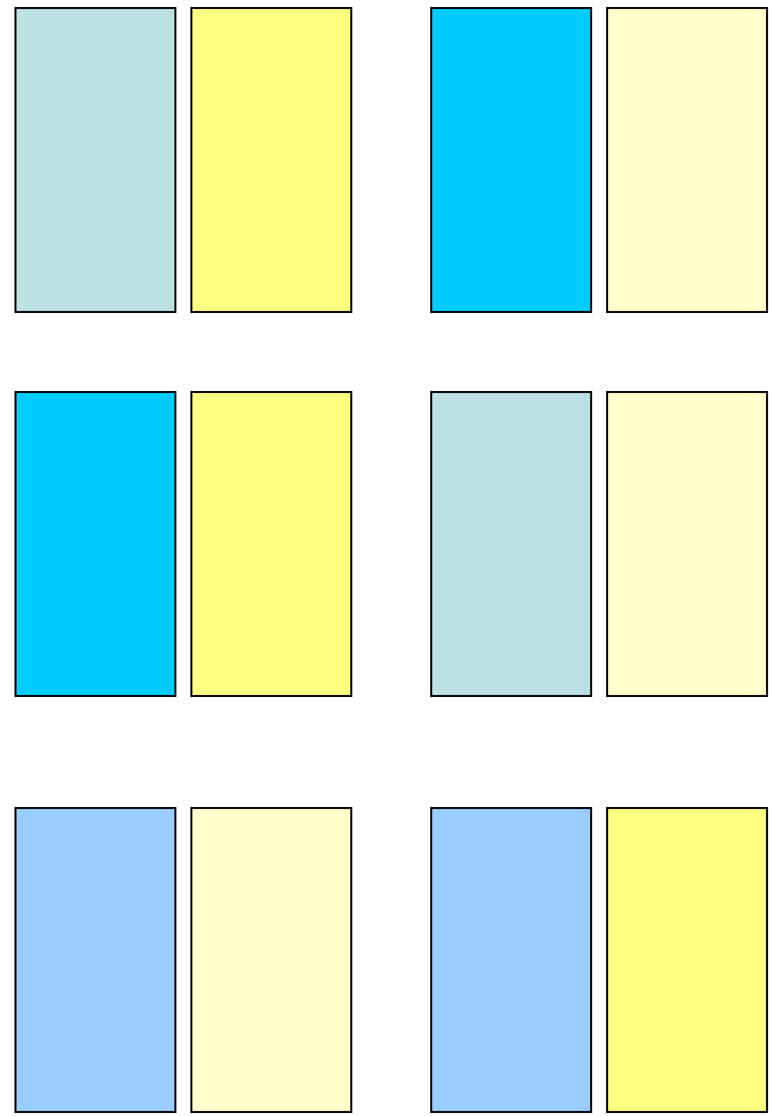
one or more genes

(variable expressivity)

one or more biomechanical stimuli

(variable degree of derangement)

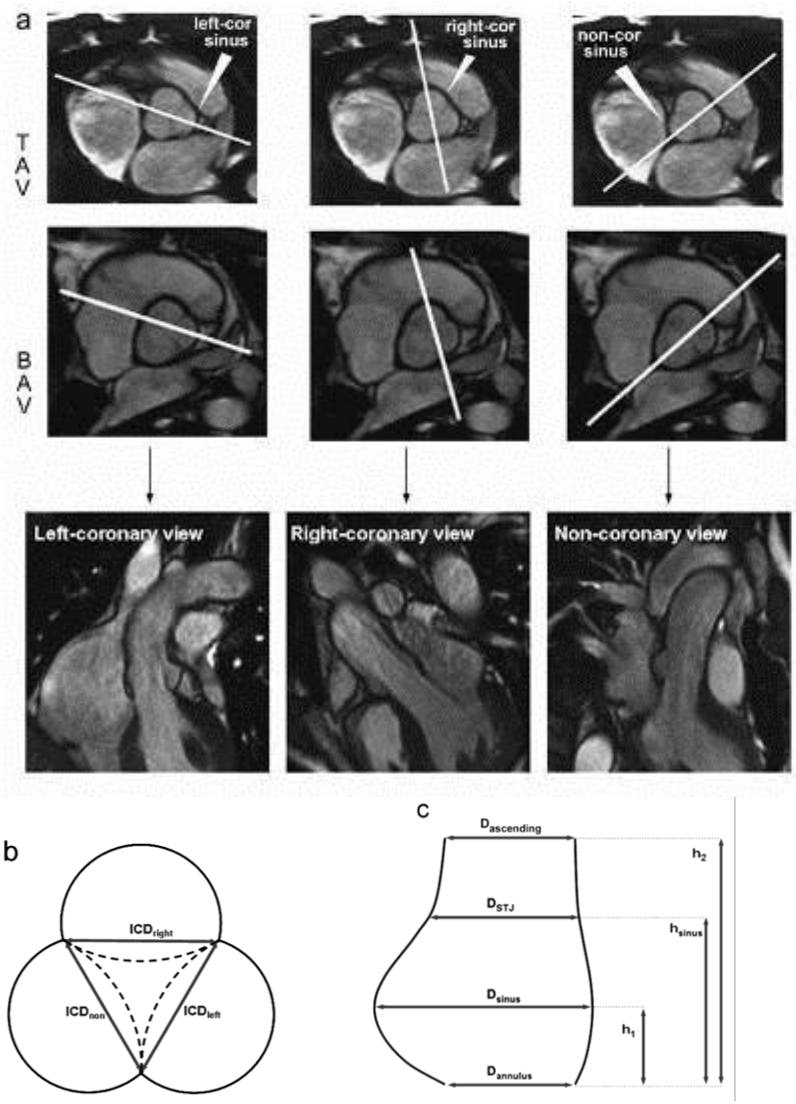
Variable resulting phenotypes



2. Quantifying what's quantifiable

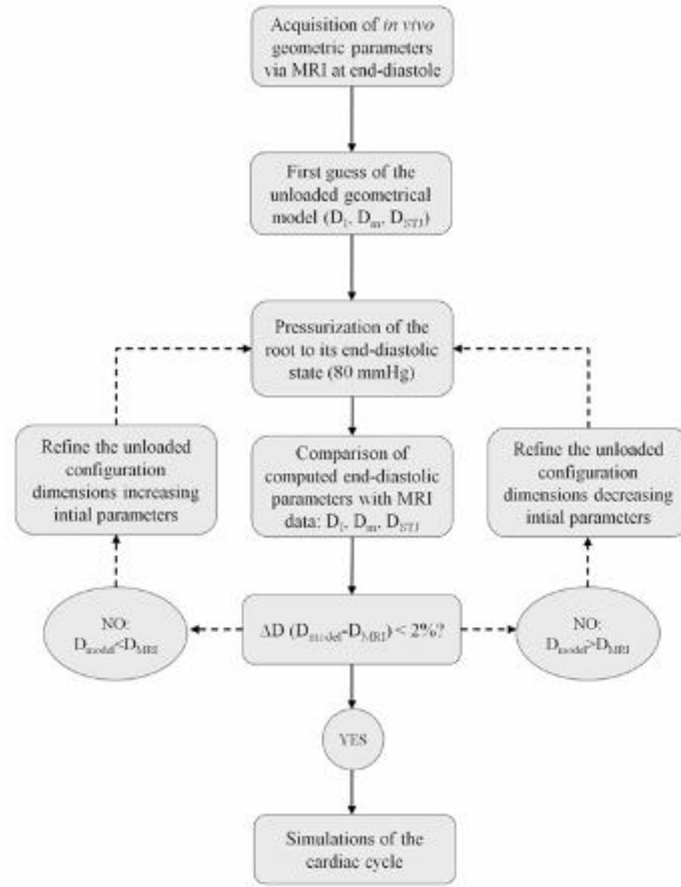
Forces acting on the bicuspid valve and aorta

The aortic root-valve unit: asymmetric anatomy and function



8 healthy BAV subjects

10 healthy TAV volunteers

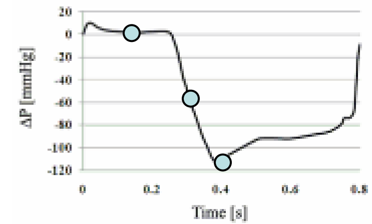


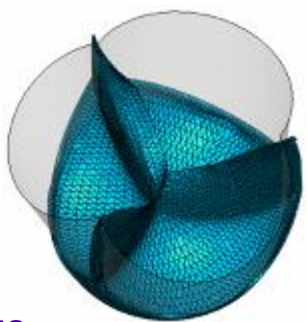
Conti CA *et al*. Med End Phys 2010

Conti CA *et al.* J Thorac Cardiovasc Surg 2011

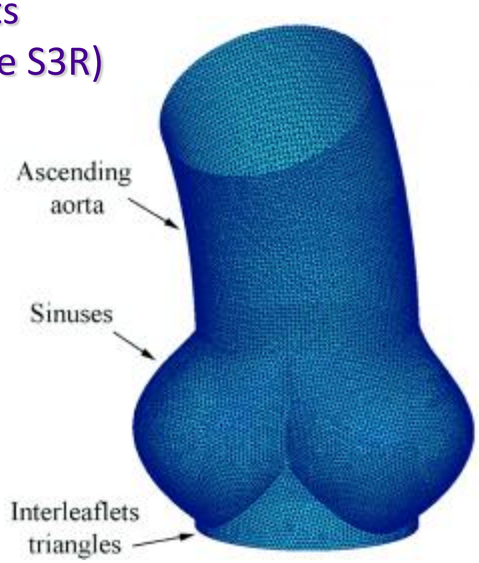
Biomechanical implications of the congenital bicuspid aortic valve: A finite element study of aortic root function from in vivo data

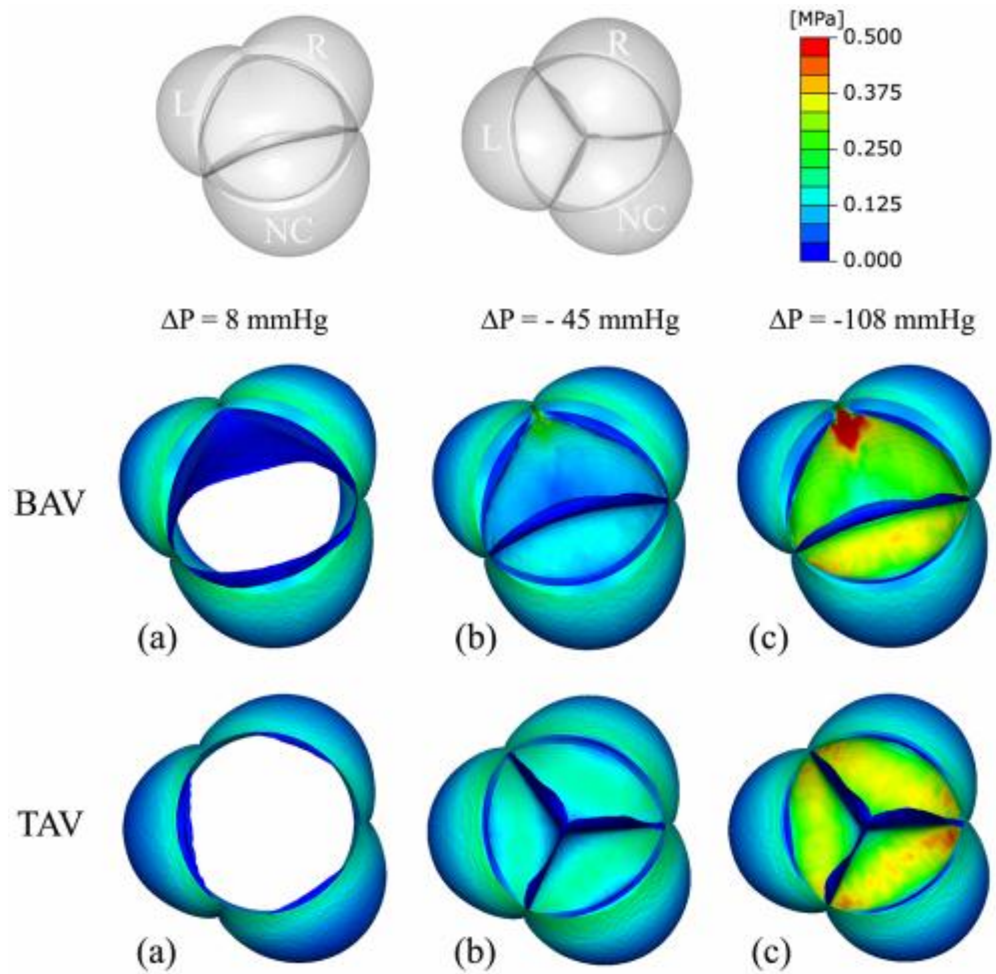
Carlo A. Conti, MD,[a] Alessandro Della Corte, MD, PhD,[b] Emiliano Votta, PhD,[a] Luca Del Viscovo, MD,[c] Ciro Bancone, MD,[b] Luca S. De Santo, MD,[b] and Alberto Redaelli, PhD[a]





The model was discretised in 44,378 shell elements (ABAQUS type S3R)

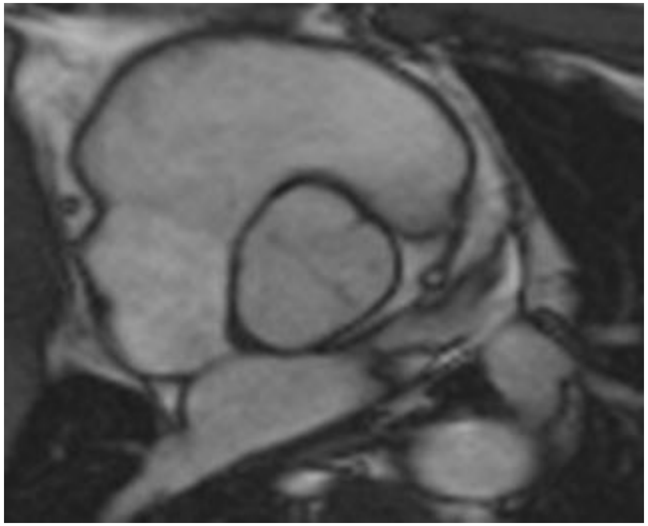


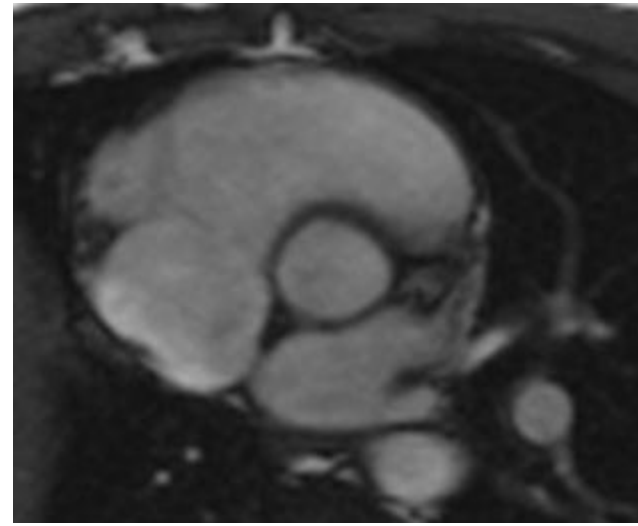


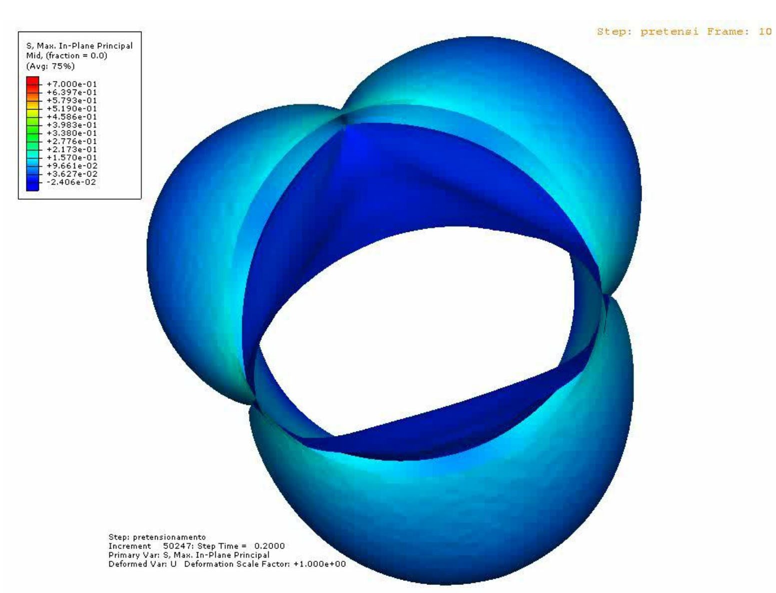
Max principal stresses

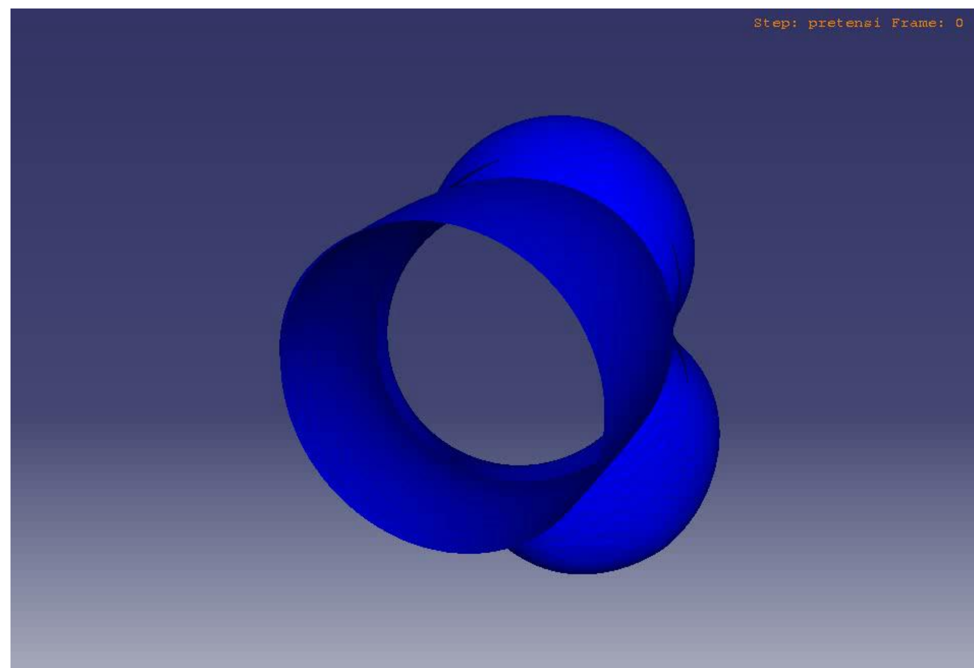
BAV R-L

TAV



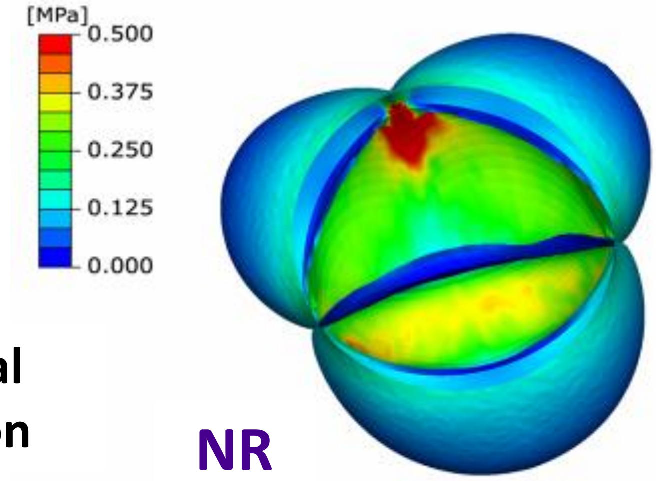




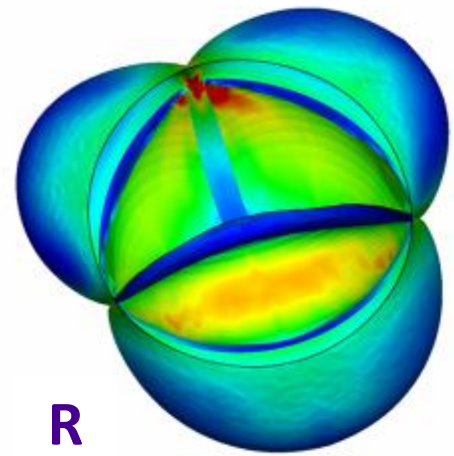


Diverse stress patterns in diastole

Structural simulation



NR



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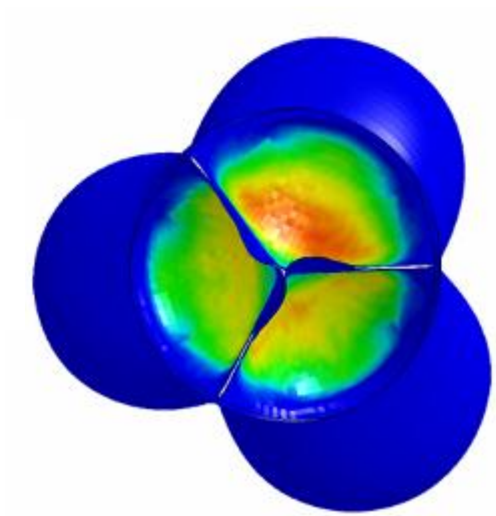
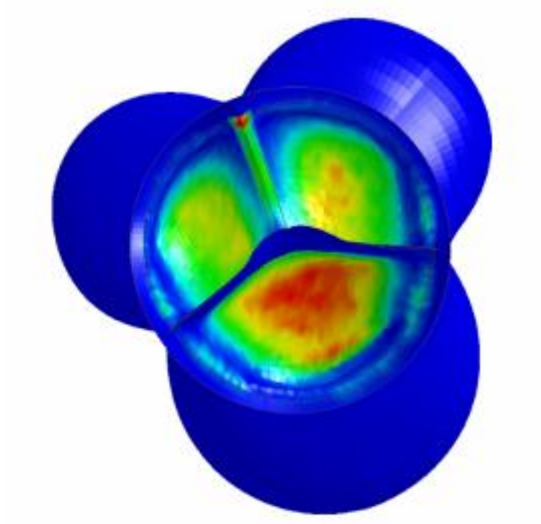
SURGICAL IMPLICATIONS ?

Fluid-structure interaction simulation



TAV



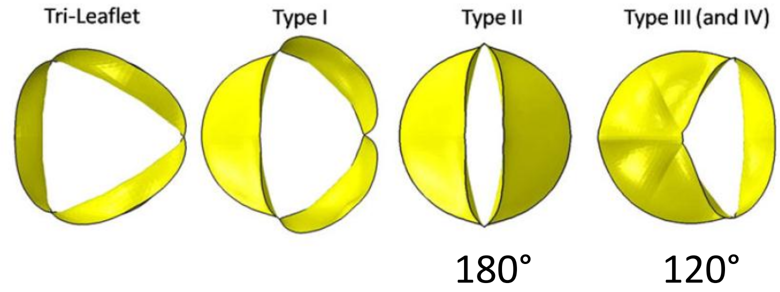
BAV RL (with 3D raphe)

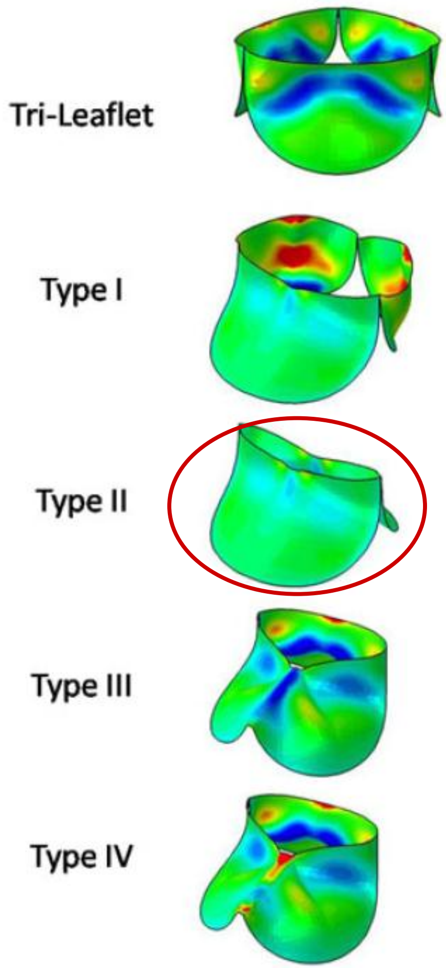
unpublished

Cardiovascular Engineering and Technology, Vol. 2, No. 1, March 2011 (© 2011) pp. 48–56
DOI: 10.1007/s13239-011-0035-9

Effect of Geometry on the Leaflet Stresses in Simulated Models of Congenital Bicuspid Aortic Valves

PAUL N. JERMIHOV,[1] LU JIA,[2] MICHAEL S. SACKS,[3] ROBERT C. GORMAN,[4]
JOSEPH H. GORMAN III,[4] and KRISHNAN B. CHANDRAN[1]





Valve Configuration Determines Long-Term Results After Repair of the Bicuspid Aortic Valve

Diana Aicher, Takashi Kunihara, Omar Abou Issa, Brigitte Brittner, Stefan Gräber and Hans-Joachim Schäfers

Circulation 2011;123;178-185; originally published online Jan 3, 2011;

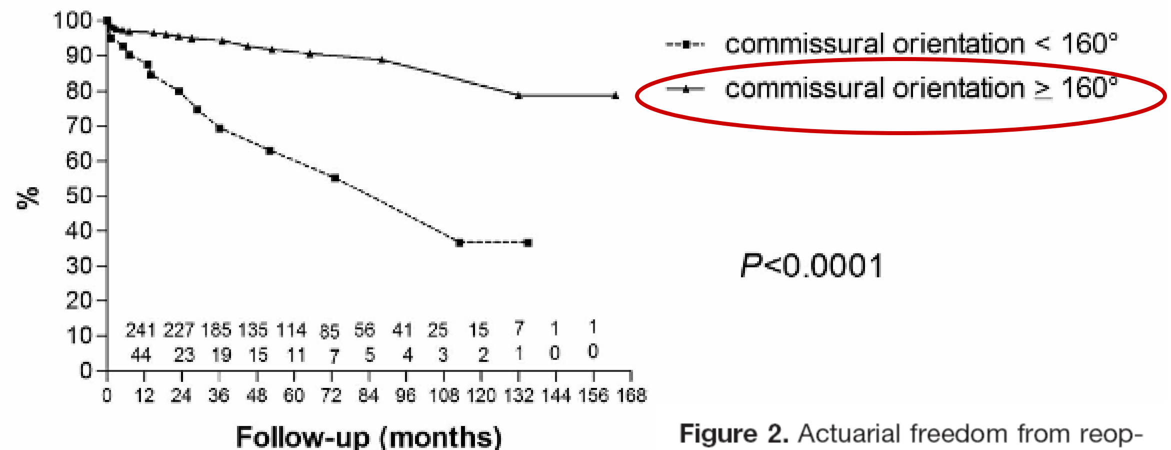
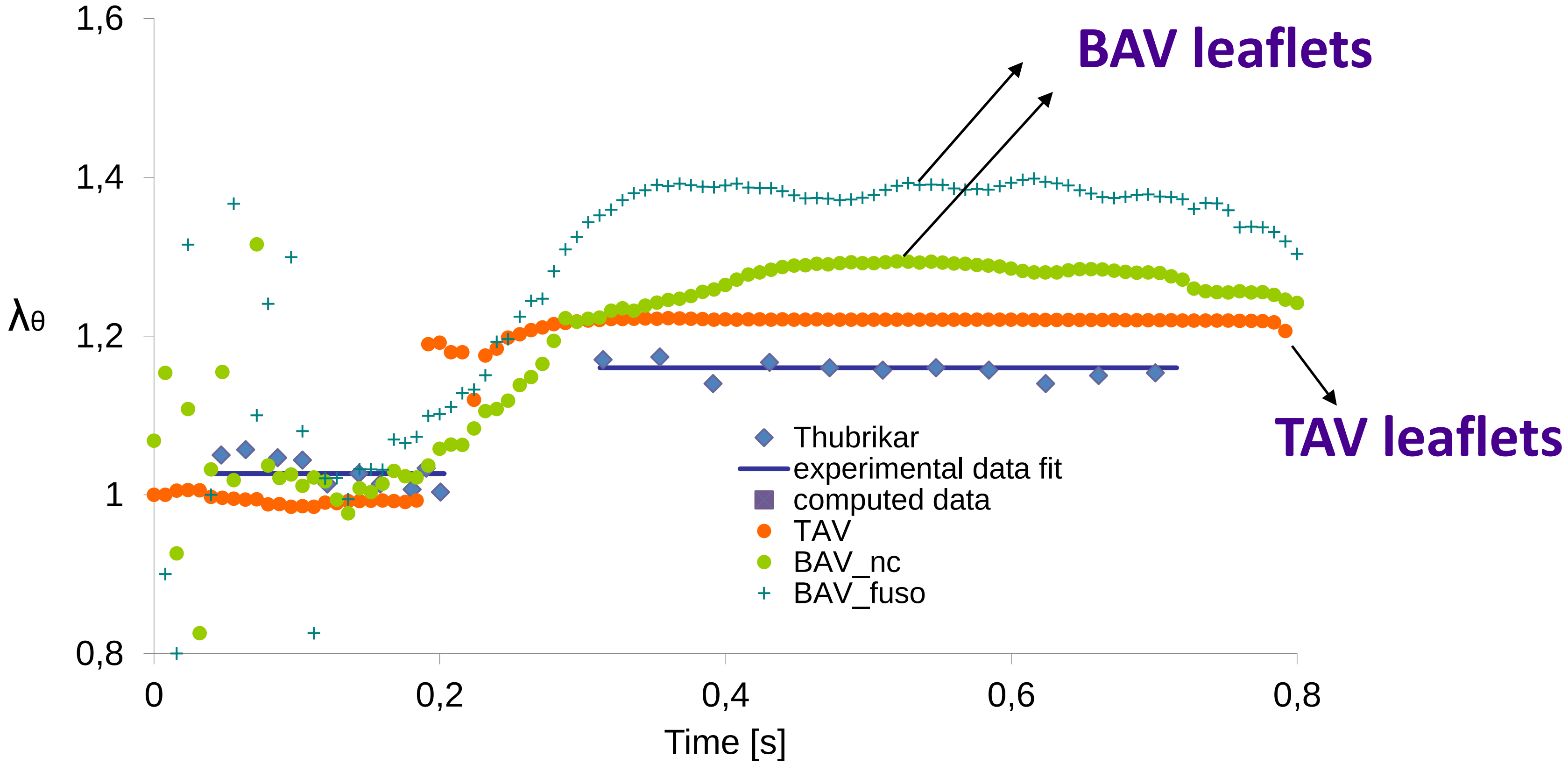


Figure 2. Actuarial freedom from reoperation after aortic valve repair in patients with a BAV depending on the orientation of the 2 normal commissures.

PATHOGENETIC IMPLICATIONS ?

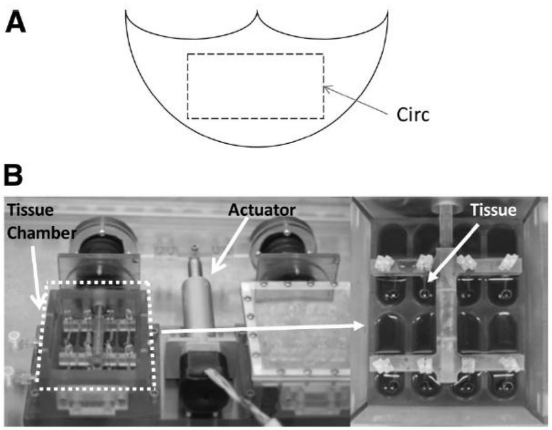
Leaflet stretches:



The American Journal of Pathology, Vol. 177, No. 1, July 2010
Copyright © American Society for Investigative Pathology
DOI: 10.2353/ajpath.2010.090631

Cardiovascular, Pulmonary and Renal Pathology

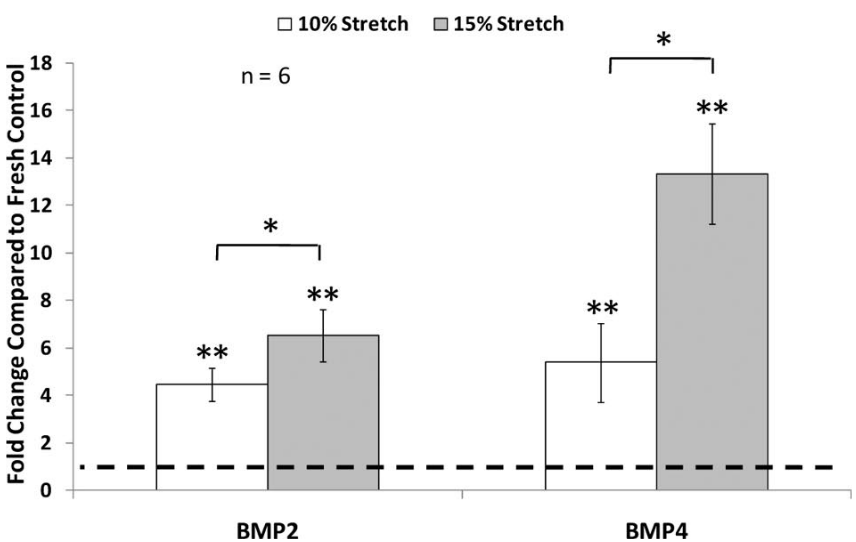
Elevated Cyclic Stretch Induces Aortic Valve Calcification in a Bone Morphogenic Protein-Dependent Manner

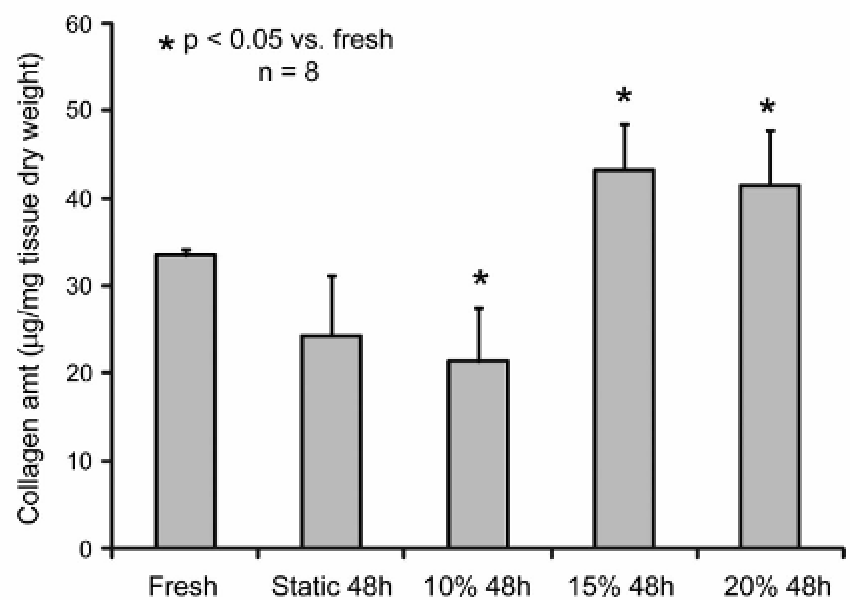


"stretch bioreactor"

Balachandran K *et al*.

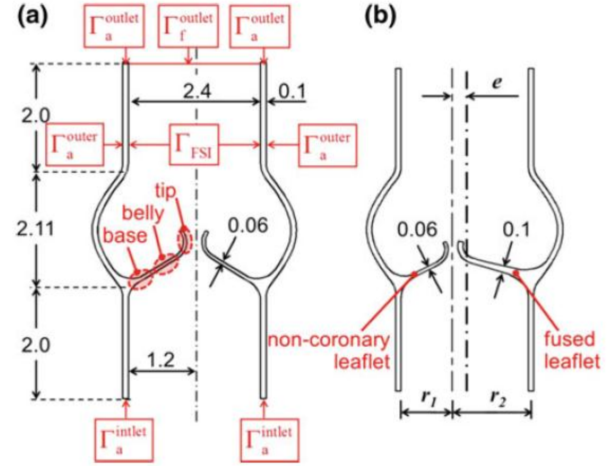
Am J Pathol 2010





Biomech Model Mechanobiol
DOI 10.1007/s10237-012-0375-x

ORIGINAL PAPER

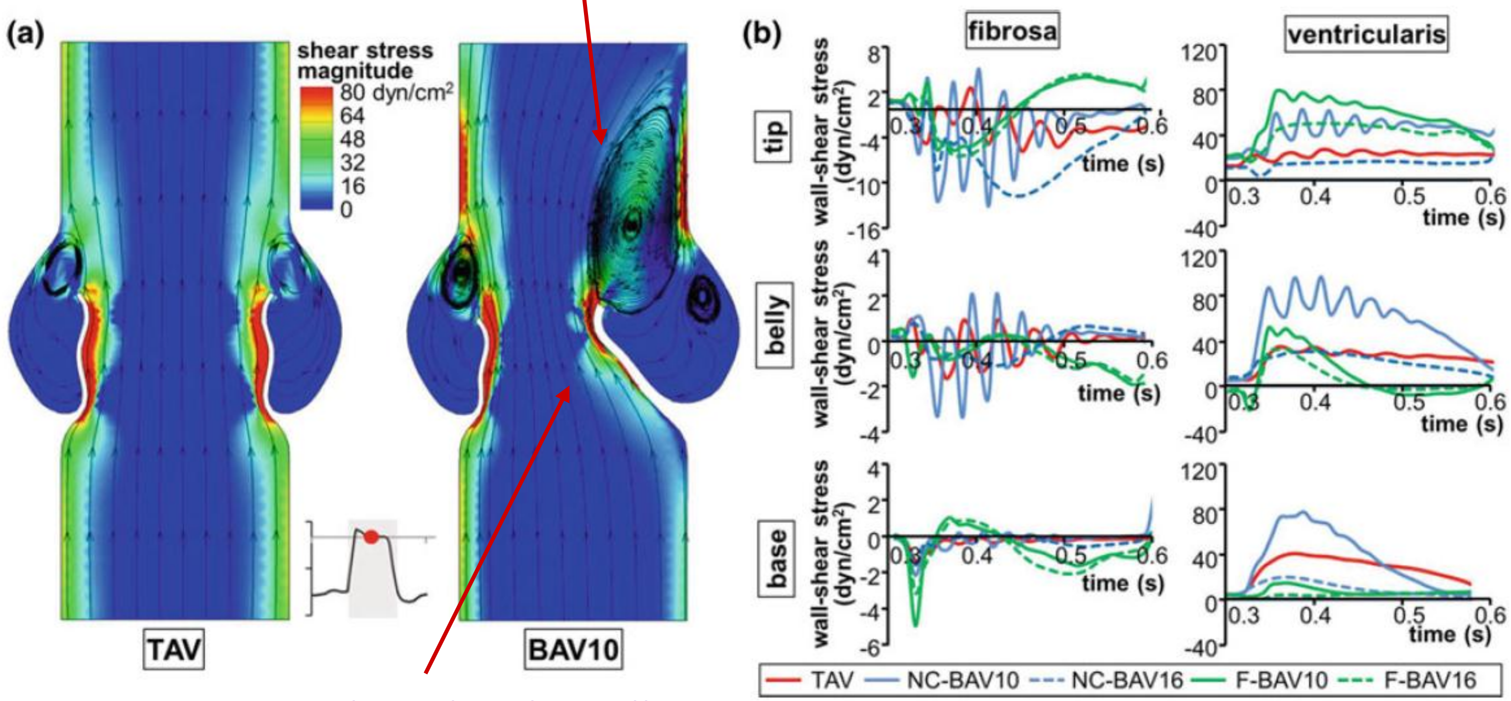


Computational assessment of bicuspid aortic valve wall-shear stress: implications for calcific aortic valve disease

Santanu Chandra · Nalini M. Rajamannan · Philippe Sucosky

Published online: 01 February 2012

Low, oscillatory wall shear stress



High, pulsatile wall shear stress

Ohno M, Cooke JP, Dzau VJ, Gibbons GH (1995) Fluid shear stress induces endothelial transforming growth factor beta-1 transcription and production. Modulation by potassium channel blockade. J Clin Invest 95(3):1363–1369. doi:10.1172/JCI117787

Butcher JT, Penrod AM, Garcia AJ, Nerem RM (2004) Unique morphology and focal adhesion development of valvular endothelial cells in static and fluid flow environments. Arterioscler Thromb Vasc Biol 24:1429–1434

Sucosky P, Balachandran K, Elhammali A, Jo H, Yoganathan AP (2009) Altered shear stress stimulates upregulation of endothelial VCAM-1 and ICAM-1 in a BMP-4- and TGF-beta1-dependent pathway. Arterioscler Thromb Vasc Biol 29:254–260. doi:10.1161/ATVBAHA.108.176347

Clark-Greuel JN, Connolly JM, Sorichillo E, Narula NR, Rapoport HS, Mohler ER, 3rd, Gorman JH, 3rd, Gorman RC, Levy RJ: Transforming growth factor-beta1 mechanisms in aortic valve calcification: increased alkaline phosphatase and related events. Ann Thorac Surg 2007, 83:946–953

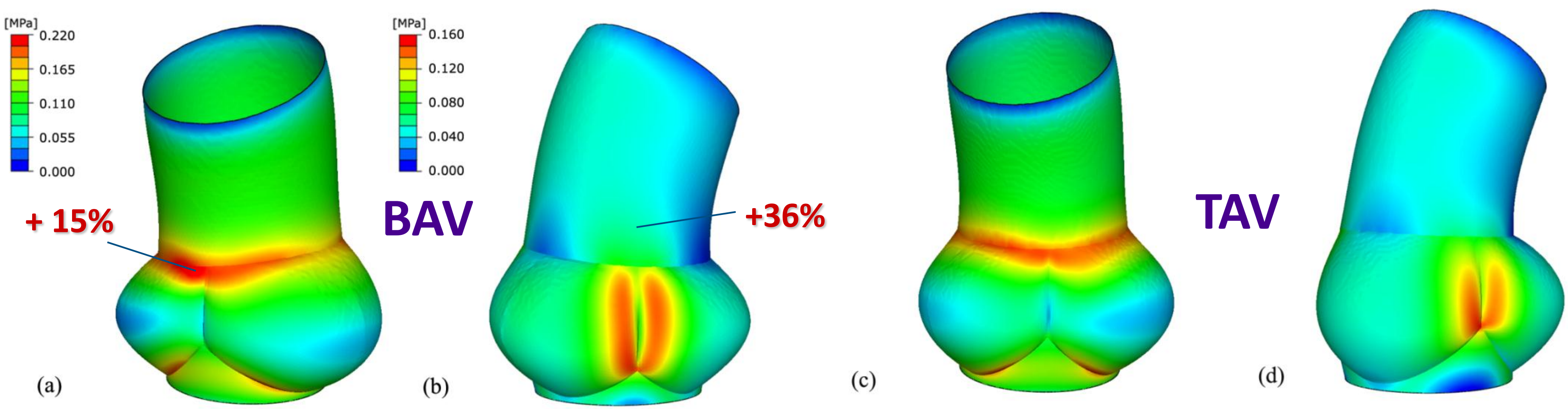
Jian B, Narula N, Li QY, Mohler ER, 3rd, Levy RJ: Progression of aortic valve stenosis: TGF-beta1 is present in calcified aortic valve cusps and promotes aortic valve interstitial cell calcification via apoptosis. Ann Thorac Surg 2003, 75:457–465; discussion 465–466

Biomechanical implications of the congenital bicuspid aortic valve: A finite element study of aortic root function from in vivo data

	Interleaflet Triangles	Left Coronary Sinus	Right Coronary Sinus	Non Coronary Sinus	Ascending Aorta
S11 [kPa]	81 - 182	31 - 234	23 - 220	40 - 223	14 - 225
S22 [kPa]	-25 - 106	19 - 138	31 - 144	19 - 148	4 - 86

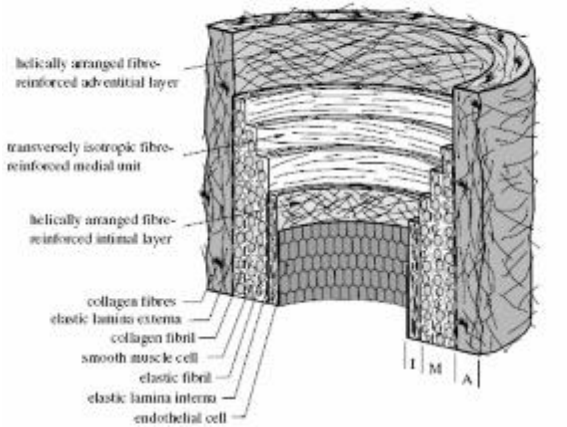
S11 = circumferential stress

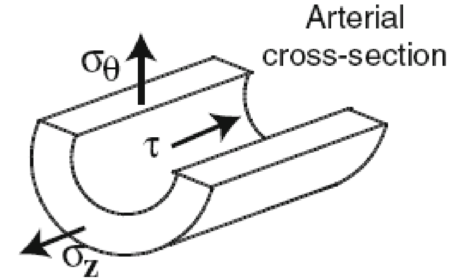
S22 = longitudinal stress

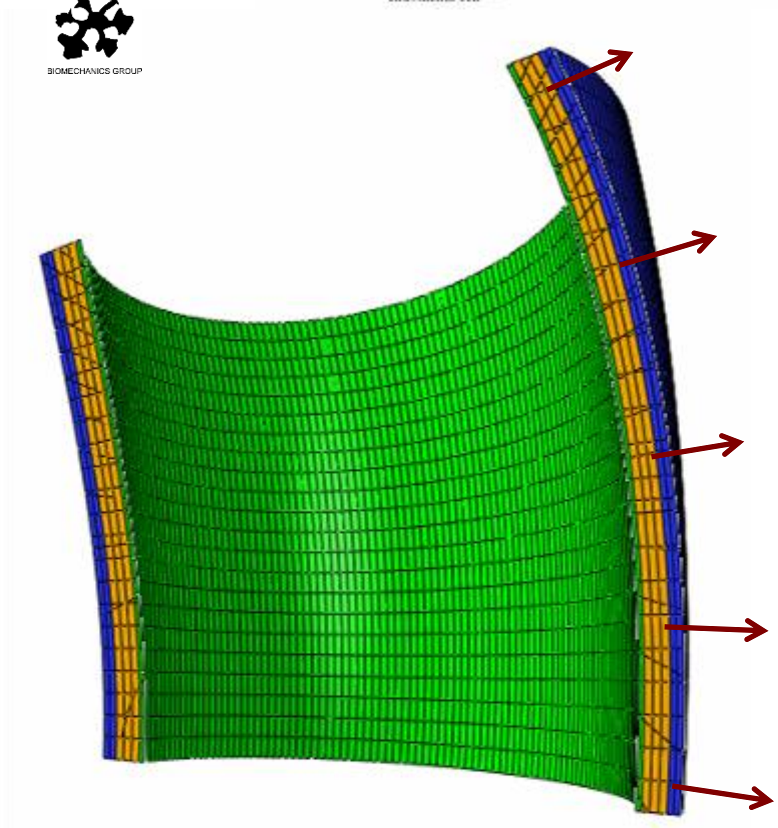


a, c = circumferential stress

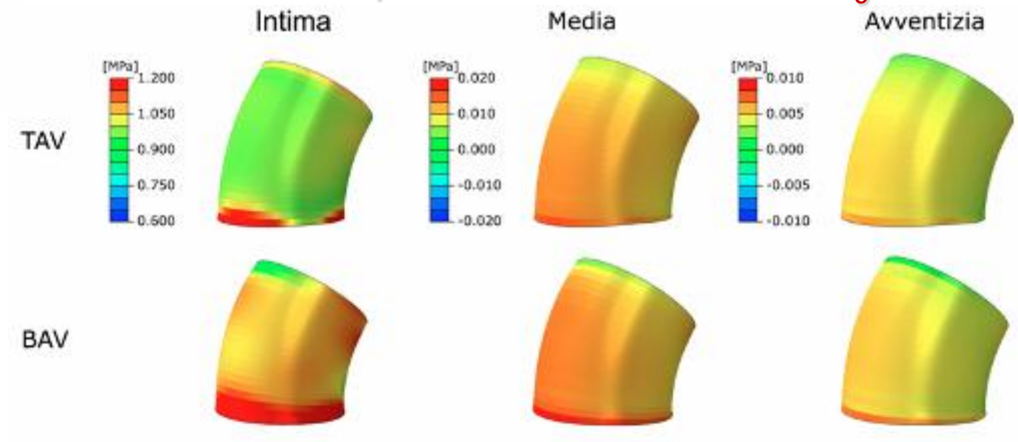
b, d = longitudinal stress



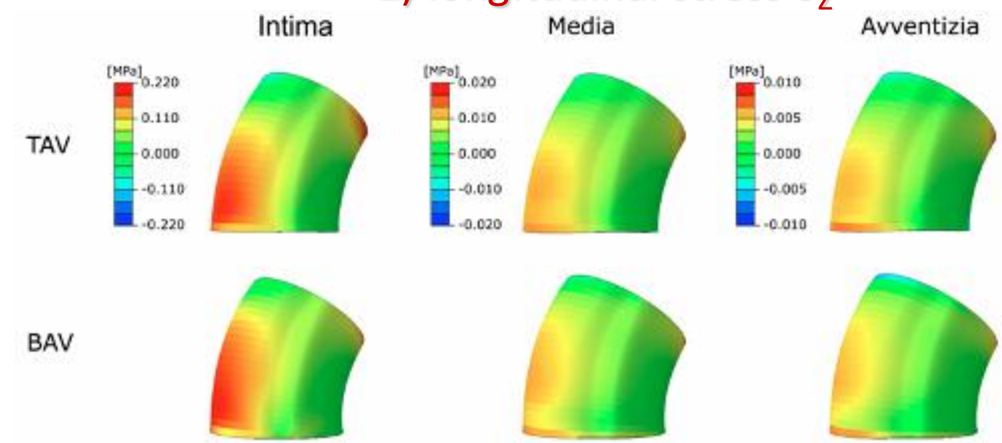




1) circumferential stress σ_θ

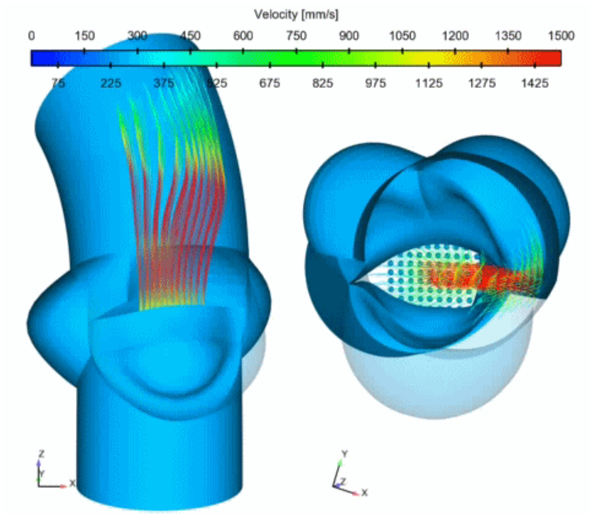


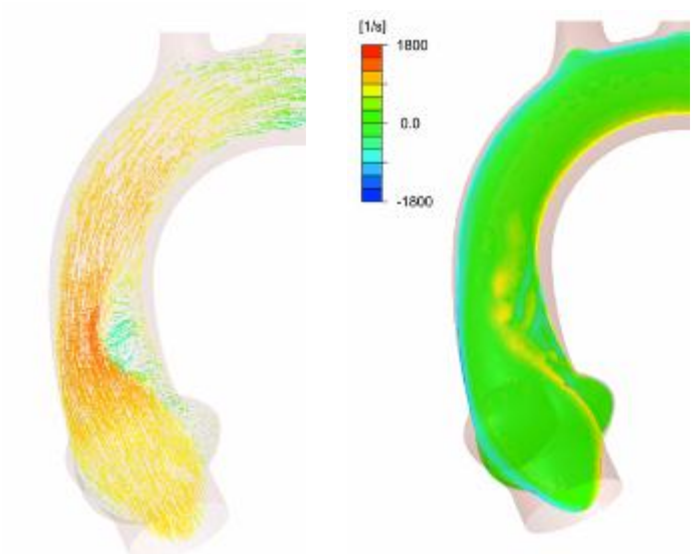
2) longitudinal stress σ_z



unpublished

3) shear stress τ

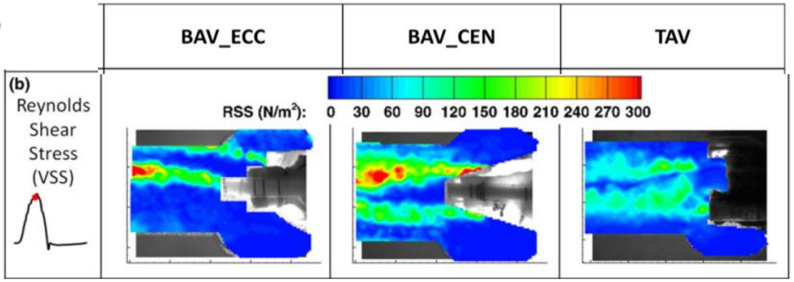




- FSI, Mesh geometry from patients' data, valve included, not patient-specific

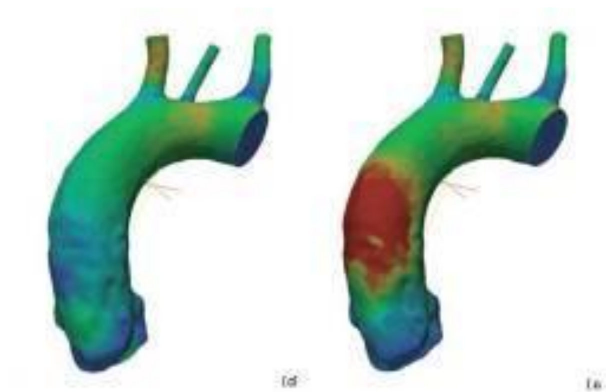
Annals of Biomedical Engineering (© 2012)
DOI: 10.1007/s10439-012-0527-2

- "in-vitro", particle image velocimetry



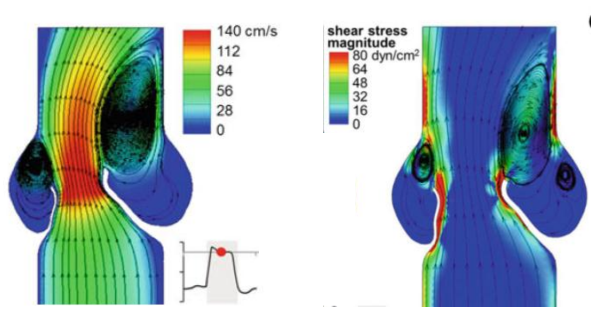
Artificial Organs
34(12):1114–1120, Wiley Periodicals, Inc.

- CFD, mesh from 1 patient, no leaflets



Biomech Model Mechanobiol
DOI 10.1007/s10237-012-0375-x

- Designed geometry, no patient



DIFFERENT METHODS,

HIGHLY CONCORDANT RESULTS

Biomech Model Mechanobiol
DOI 10.1007/s10237-012-0405-8

ORIGINAL PAPER

PATHOGENETIC IMPLICATIONS ?

Extracellular matrix and the mechanics of large artery development

Jeffrey K. Cheng · Jessica E. Wagenseil

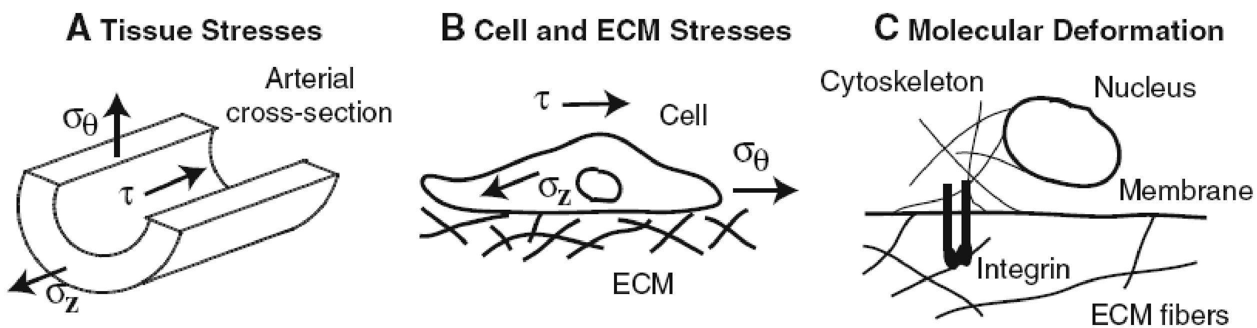


Fig. 5 Different length scales over which stresses and deformations act to stimulate growth and remodeling in developing arteries. Circumferential (σ_θ), axial (σ_z), and shear (τ) stresses depend on the blood pressure, axial tethering forces, and blood flow, respectively, as well as on the arterial wall geometry (Eqs. 1–3). These stresses act on the artery as a whole (**a**), as well as on individual cell and ECM fibers (**b**). Whole cell and ECM deformations cause local deformations in individual ECM fibers and the cell membrane, which are connected to each other through transmembrane proteins, such as integrins. The local deformations trigger signaling cascades due to conformational changes in the transmembrane proteins directly, and through their connections to cytoskeletal proteins that may link all the way to the cell nucleus (**c**)

Which effects can abnormal stresses in the pre-natal period exert on the developing aorta **?**

The bicuspid aortic valve: an integrated phenotypic classification of leaflet morphology and aortic root shape

B M Schaefer, M B Lewin, K K Stout, E Gill, A Prueitt, P H Byers and C M Otto

Heart 2008;94;1634-1638; originally published online 28 Feb 2008;
doi:10.1136/hrt.2007.132092

Association of Bicuspid Aortic Valve Morphology and Aortic Root Dimensions: A Substudy of the Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin (ASTRONOMER) Study

Davinder S. Jassal, M.D., F.R.C.P.C.,*†‡ Kapil M. Bhagirath, M.D., F.R.C.P.C.,*
James W. Tam, M.D., F.R.C.P.C.,* Randall A. Sochowski, M.D., F.R.C.P.C.,§

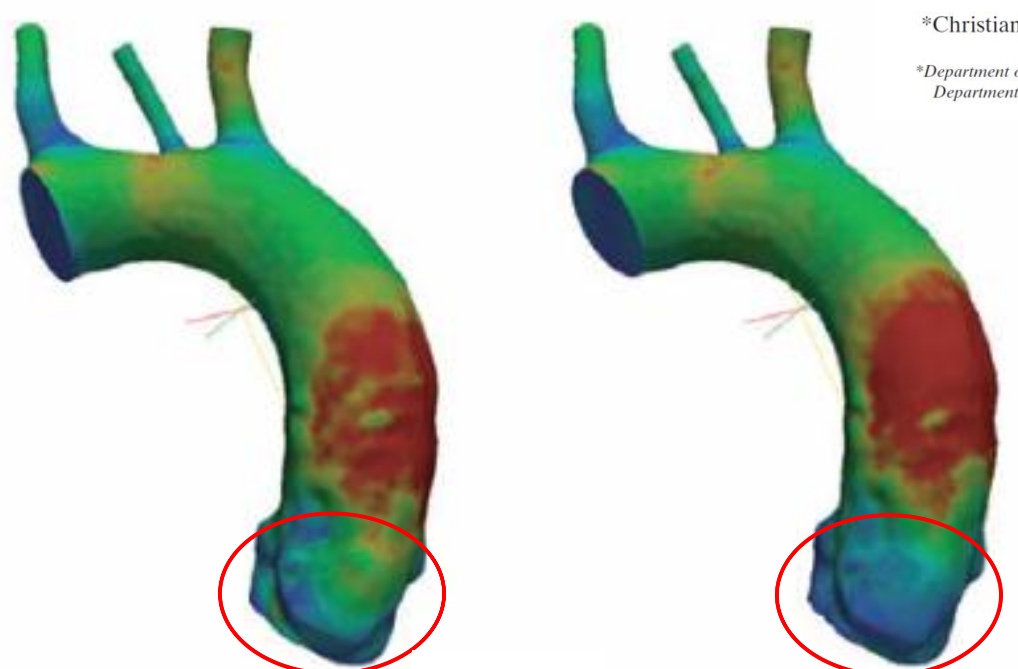
Greater sinus dimensions in RL BAV type than in RN type

Influence of Bicuspid Valve Geometry on Ascending Aortic Fluid Dynamics: A Parametric Study

*Christian Vergara, †Francesca Viscardi, ‡Luca Antiga, and †Giovanni Battista Luciani

*Department of Information Engineering and Mathematical Methods, University of Bergamo; ‡Biomedical Engineering Department, Mario Negri Institute, Bergamo; and †Division of Cardiac Surgery, University of Verona, Verona, Italy

Artificial Organs
34(12):1114–1120, Wiley Periodicals, Inc.



BAV RL

BAV RN

?

3. From Pathogenesis to Risk Stratification

of BAV aortopathy

The PARS-BAV project (2012-2015)

Insights into the **P**athogenesis of the **A**ortopathy for the development of new **R**isk **S**tratification criteria

(Italian Ministry of Health grant n. GR09-1580434)

- New applications of alternative imaging modalities (e.g. MRI, 3D speckle-tracking echo) for assessment of aortic function
- Development and semiautomatization of patient-specific computational models from MRI-derived geometry and flow data
- Biohumoral markers of the BAV aortopathy

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Politecnico di Milano, Milan, Italy

“Federico II” University, Naples, Italy

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ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2009.08.084

STATE-OF-THE-ART PAPER

Thoracic Aortic Aneurysm

Clinically Pertinent Controversies and Uncertainties

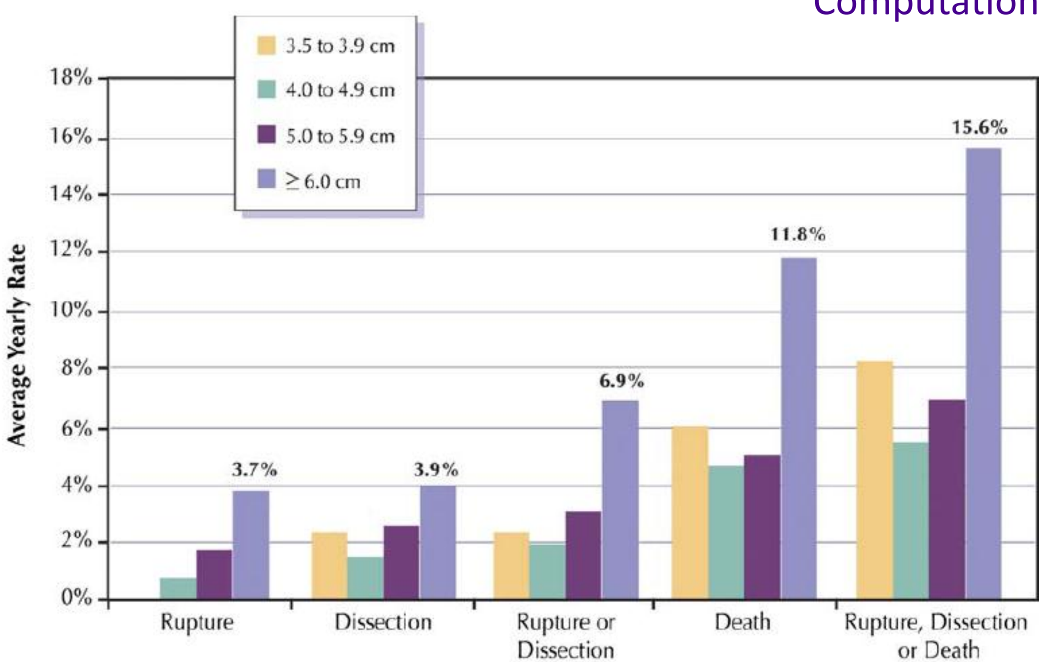
John A. Elefteriades, MD,* Emily A. Farkas, MD†
New Haven, Connecticut; and St. Louis, Missouri

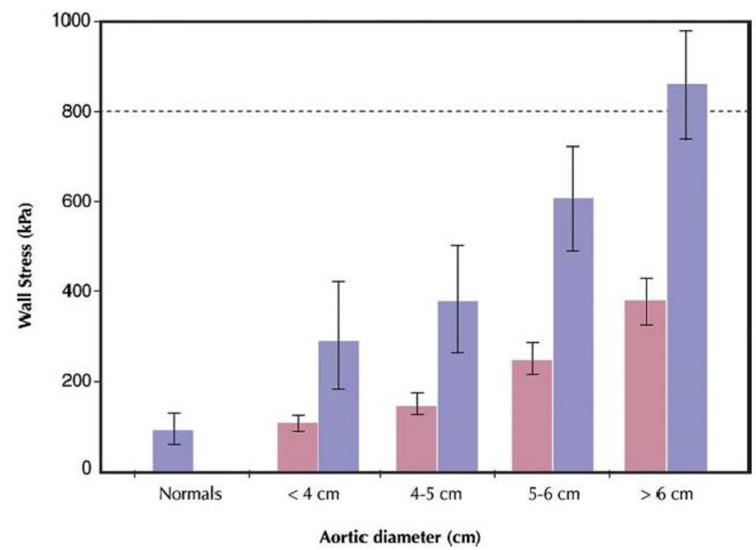
Humoral biomarkers
Molecular Imaging

Functional Imaging

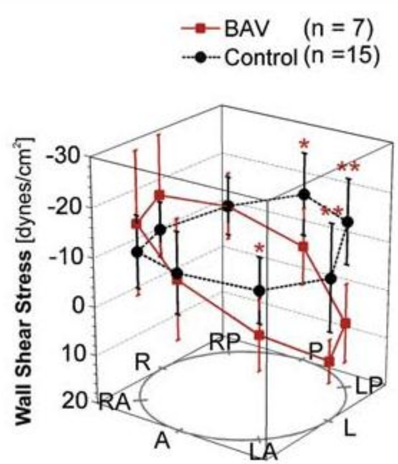
6 cm is the critical dimension for the risk of catastrophic aortic events, because at 6 cm the underlying remodelling has altered the mechanical properties of the aortic wall to the point that wall stress is closer to overcome the maximal tensile strenght

Computational analysis



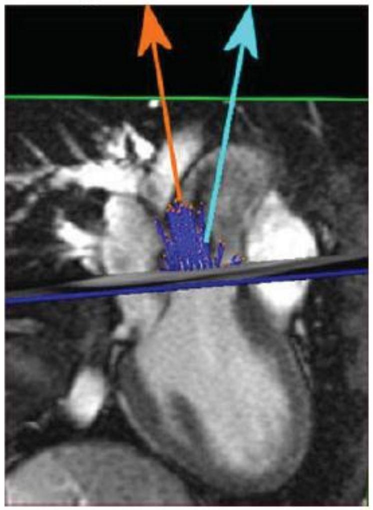


Stratifying for Flow Eccentricity



Barker et al.

Shear range index



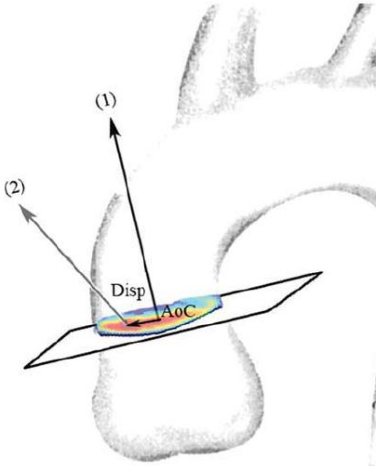
Den Reijer et al.

Flow jet angle

WHICH METHOD ?

Della Corte et al.

Cusp opening angle



Sigovan et al.

Flow displacement

JOURNAL OF MAGNETIC RESONANCE IMAGING 36:505–506 (2012)

Letter to the Editor

Rationale and Methods for Quantifying Ascending Aortic Flow Eccentricity: Back to the Underlying Mechanism?

Alessandro Della Corte, MD, PhD
Marianna Buonocore, MD
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Second University of Naples
Naples, Italy
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Synopsis of Four Recent Studies Investigating Flow Misdirection in Bicuspid Aortic Valve Subjects

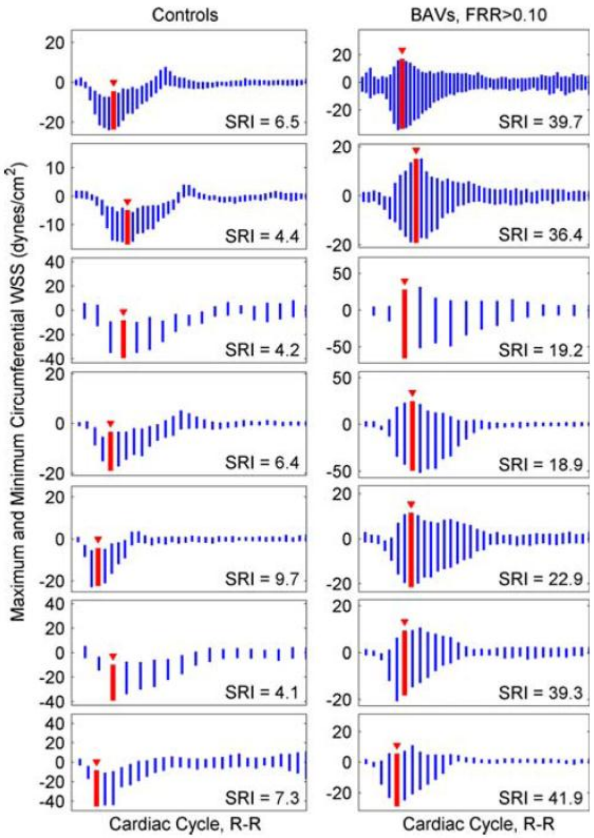
Authors	N of BAV patients	Computed parameters	Proposed metrics	In vivo validation
Sigovan et al (1)	22	Center of velocity	Flow displacement	N/A
Den Rejier et al (4)	18	Mean flow direction vector; LV outflow channel direction	Flow jet angle	Significant correlation with aortic diameter and MMP-2
Barker et al (5)	15	Axial WSS at eight points along the aortic circumference	Shear range index	Significant correlation with aortic diameter
Della Corte et al (6)	36	N/A	Cusp opening angle	Significant independent predictor of aortic diameter and growth rate in the follow-up

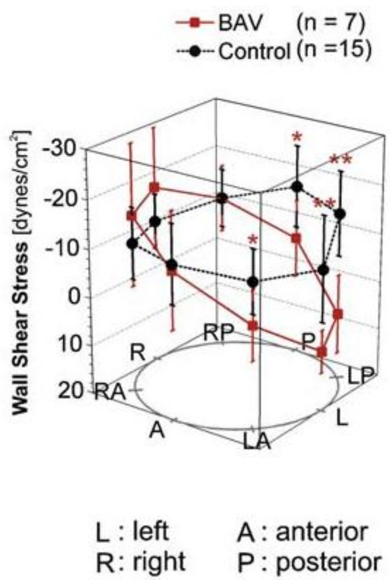
Note: all four methods have shown good reproducibility

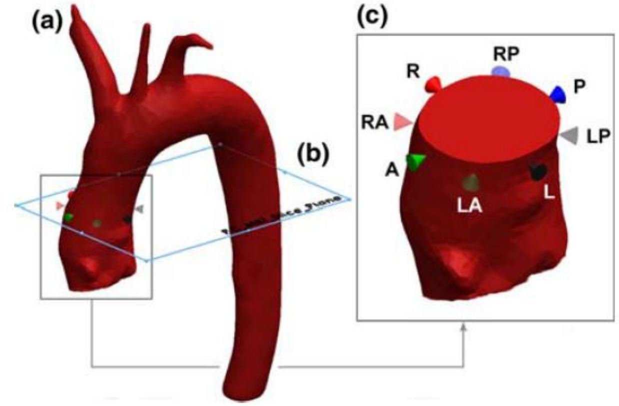
Annals of Biomedical Engineering (© 2009)
DOI: 10.1007/s10439-009-9854-3

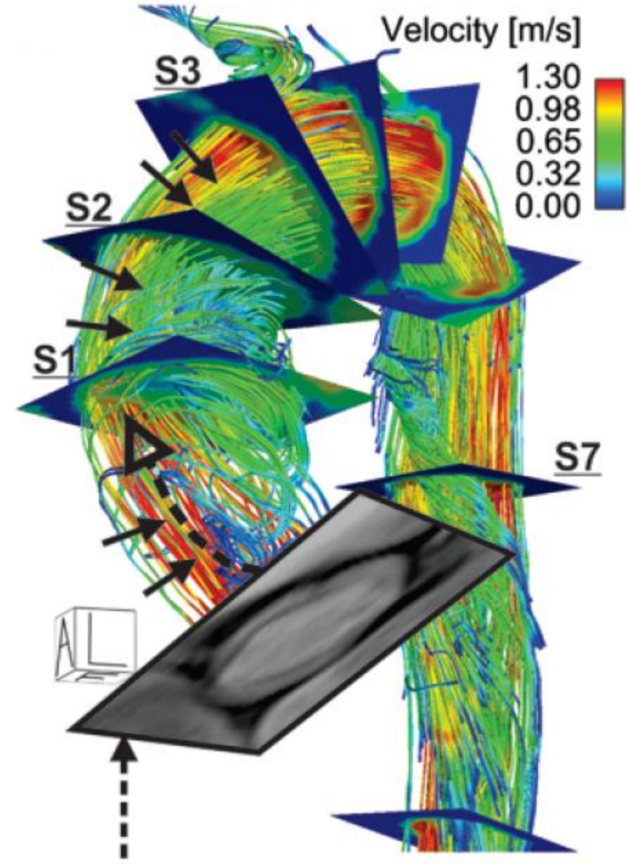
Quantification of Hemodynamic Wall Shear Stress in Patients with Bicuspid Aortic Valve Using Phase-Contrast MRI

Alex J. Barker,[1] Craig Lanning,[2,3] and Robin Shandas[1,2,3]









Bicuspid Aortic Valve Is Associated With Altered Wall Shear Stress in the Ascending Aorta

Alex J. Barker, PhD; Michael Markl, PhD; Jonas Bürk, MD; Ramona Lorenz, MS; Jelena Bock, MS; Simon Bauer, PhD; Jeanette Schulz-Menger, MD; Florian von Knobelsdorff-Brenkenhoff, MD

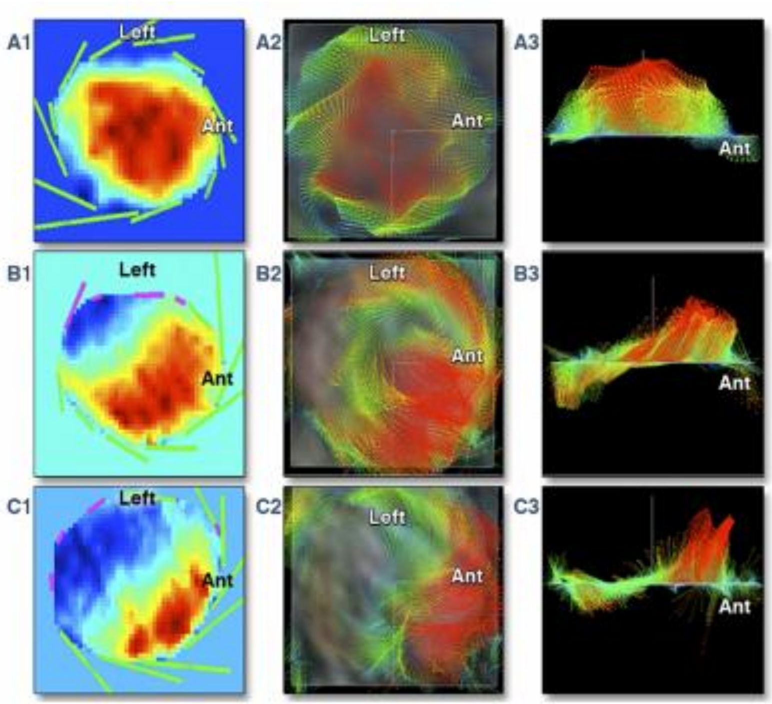
Circ Cardiovasc Imaging. 2012;5:00-00.

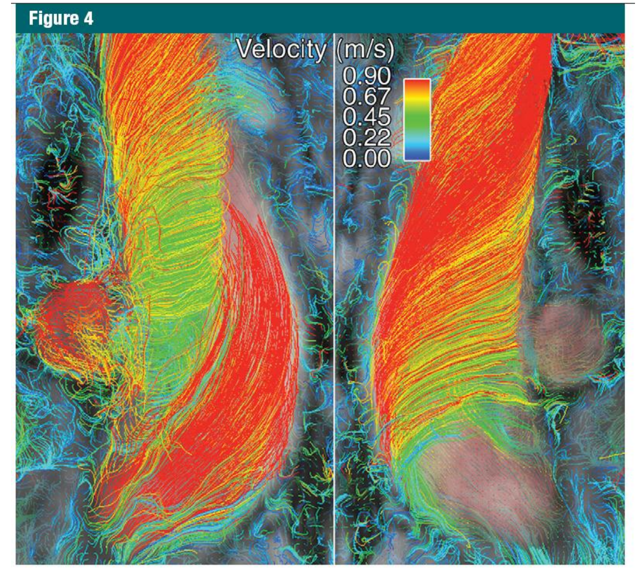
Bicuspid Aortic Valve:

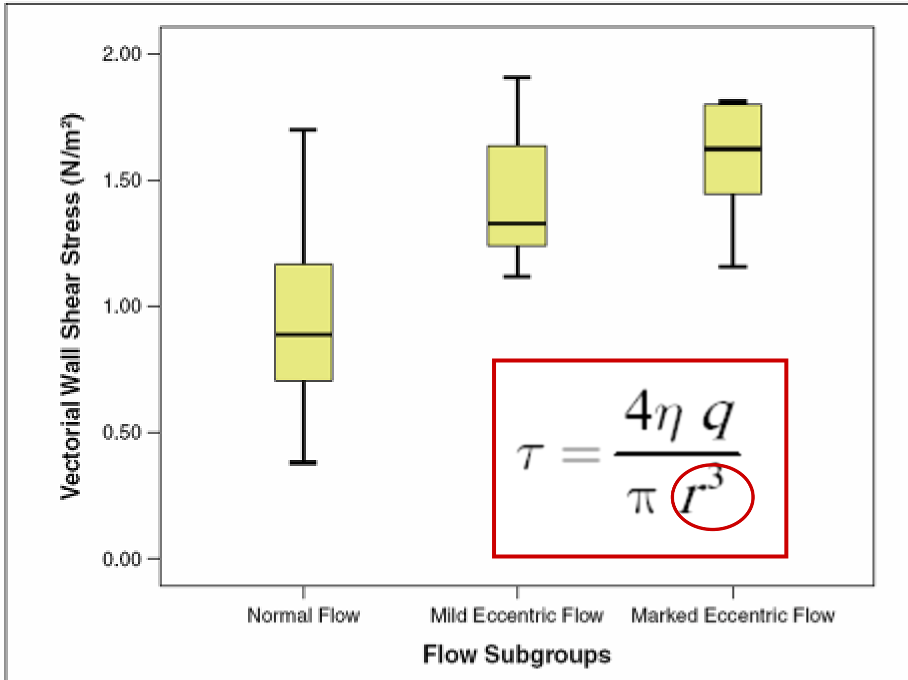
Four-dimensional MR Evaluation of Ascending Aortic Systolic Flow Patterns[1]

Michael D. Hope, MD
Thomas A. Hope, MD
Alison K. Meadows, MD, PhD
Karen G. Ordovas, MD
Thomas H. Urbania, MD
Marcus T. Alley, PhD
Charles B. Higgins, MD

Radiology: Volume 255: Number 1—April 2010







4D Flow CMR in Assessment of Valve-Related Ascending Aortic Disease

Michael D. Hope, MD,* Thomas A. Hope, MD,* Stephen E. S. Crook, BA,* Karen G. Ordovas, MD,* Thomas H. Urbania, MD,* Marc T. Alley, PhD,† Charles B. Higgins, MD*

San Francisco and Stanford, California

den Reijer *et al. Journal of Cardiovascular Magnetic Resonance* 2010, **12**:4
http://www.jcmr-online.com/content/12/1/4

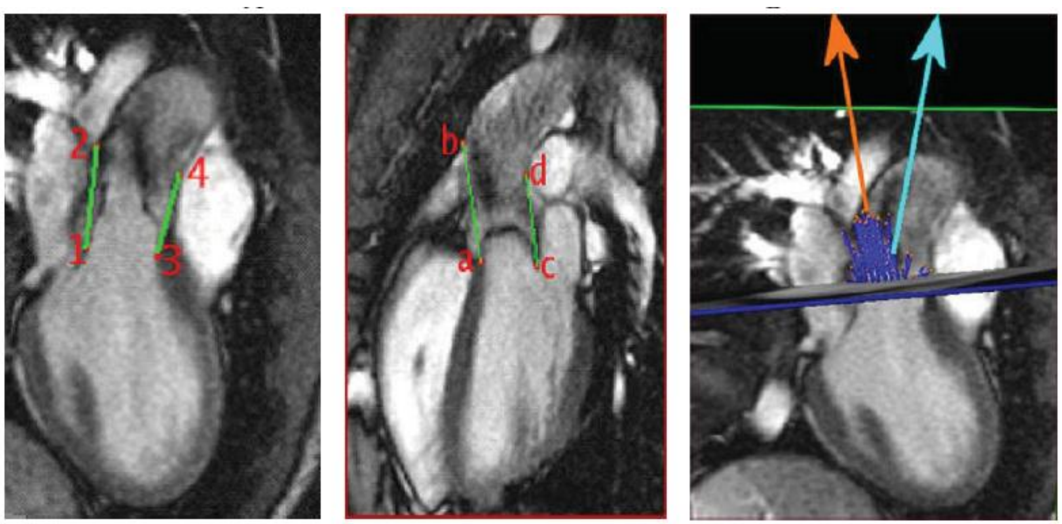
Journal of Cardiovascular Magnetic Resonance

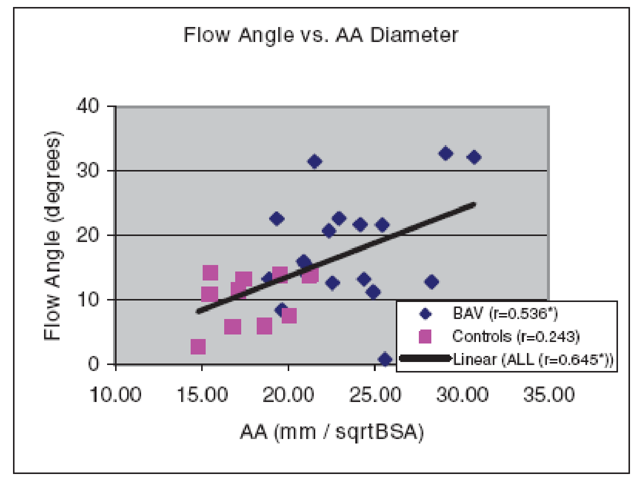
RESEARCH **Open Access**

Hemodynamic predictors of aortic dilatation in bicuspid aortic valve by velocity-encoded cardiovascular magnetic resonance

P Martijn den Reijer[1,4], Denver Sallee III[2,4], Petra van der Velden[1], Eline R Zaaijer[1], W James Parks[2,4], Senthil Ramamurthy[3], Trevor Q Robbie[4], Giorgina Donati[4], Carey Lamphier[4], Rudolf P Beekman[1], Marijn E Brummer[4*]

PC slice flow data. Therefore a 4-D flow scan[38,43] was also acquired on all subjects. However due to ethical concerns no gadolinium contrast was used in this study, and without contrast these scans suffer from poor contrast and SNR. For this reason these data were not used in this study.





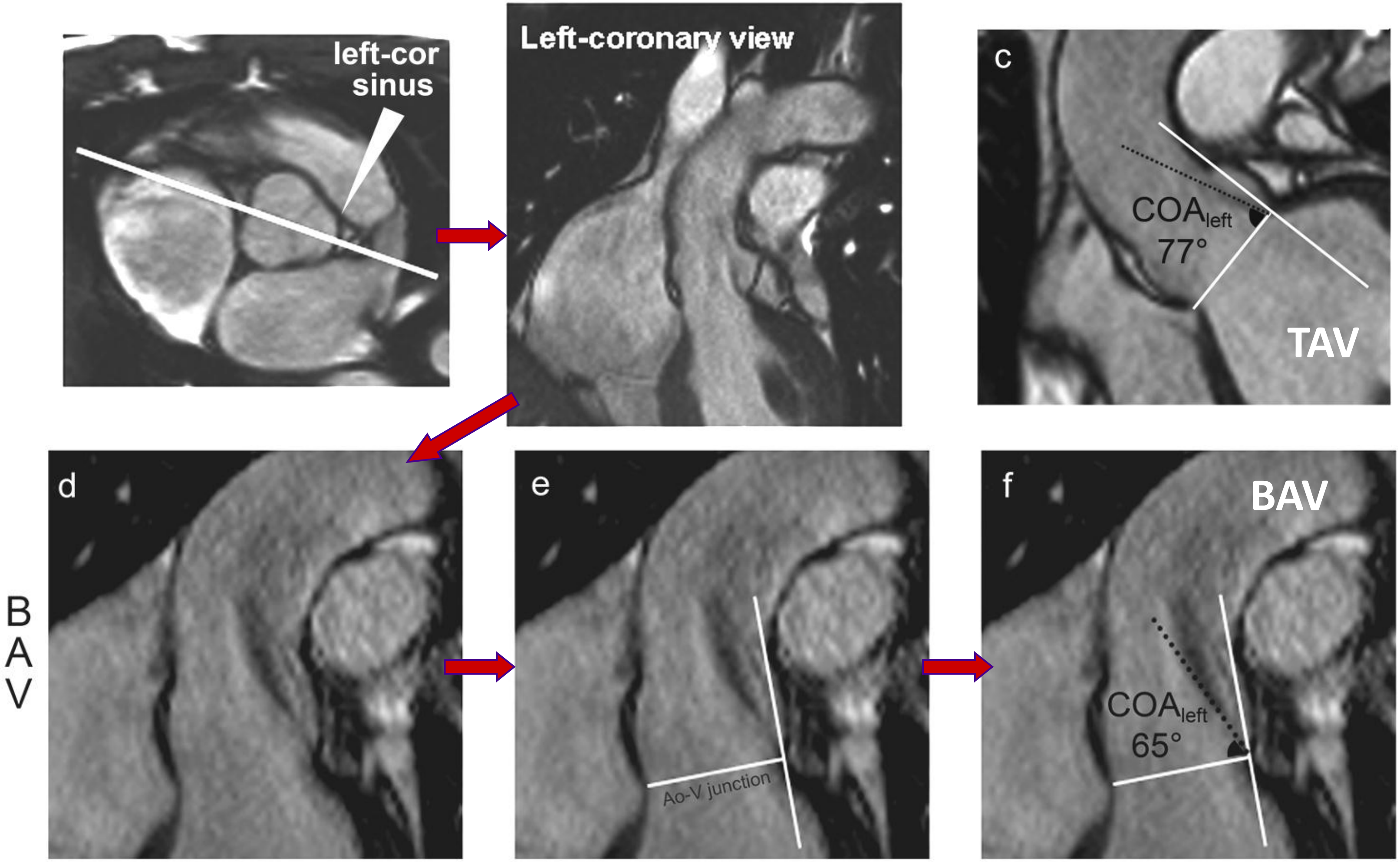
Plasma MMP2 levels were moderately correlated to blood flow jet angle (Spearman r = 0.509, p = 0.044). No significant correlation was observed between blood flow jet angle and MMP9 or TIMP1 and TIMP2 plasma levels.

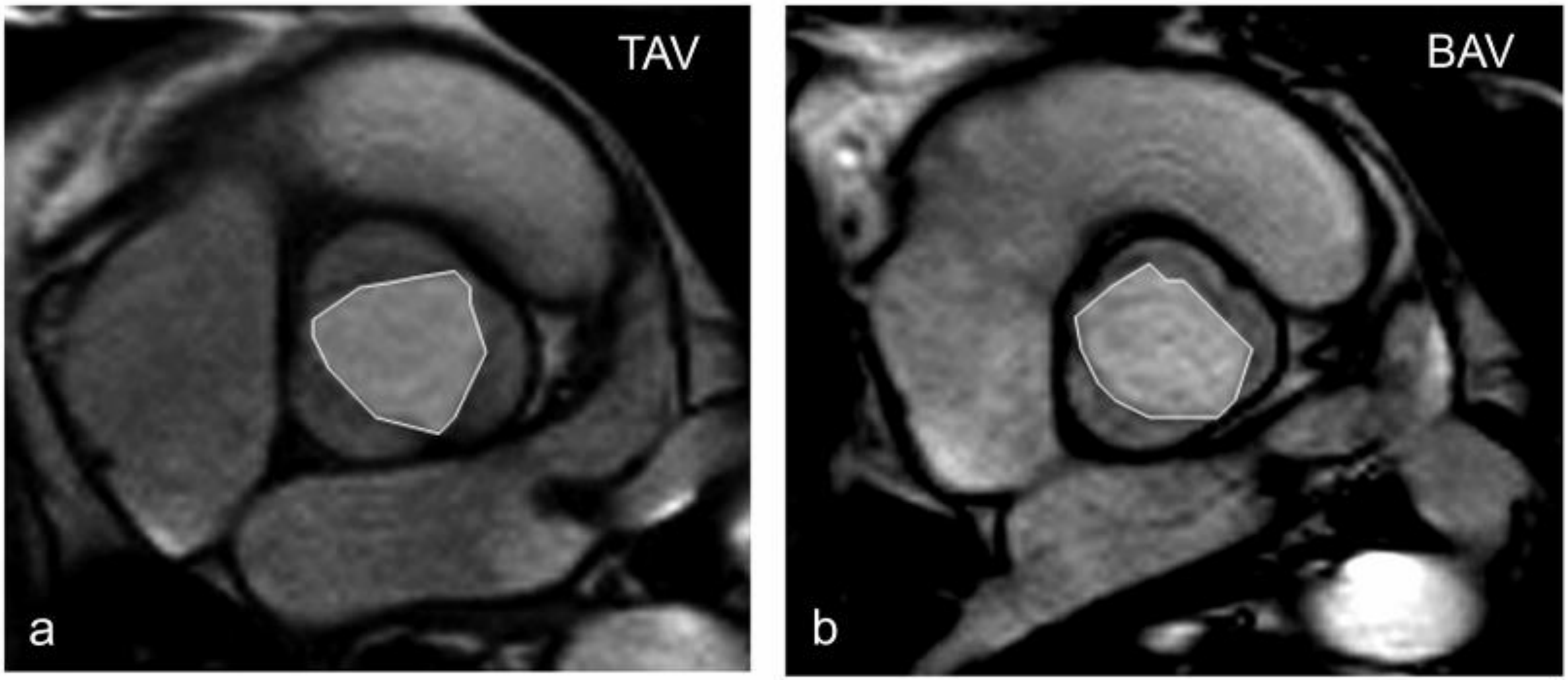
The Journal of
Thoracic and Cardiovascular Surgery

Restricted cusp motion in right-left type of bicuspid aortic valves: A new risk marker for aortopathy

Alessandro Della Corte, Ciro Bancone, Carlo A. Conti, Emiliano Votta, Alberto Redaelli, Luca Del Viscovo and Maurizio Cotrufo

J Thorac Cardiovasc Surg 2012;144:360-3691




TAV
a
BAV
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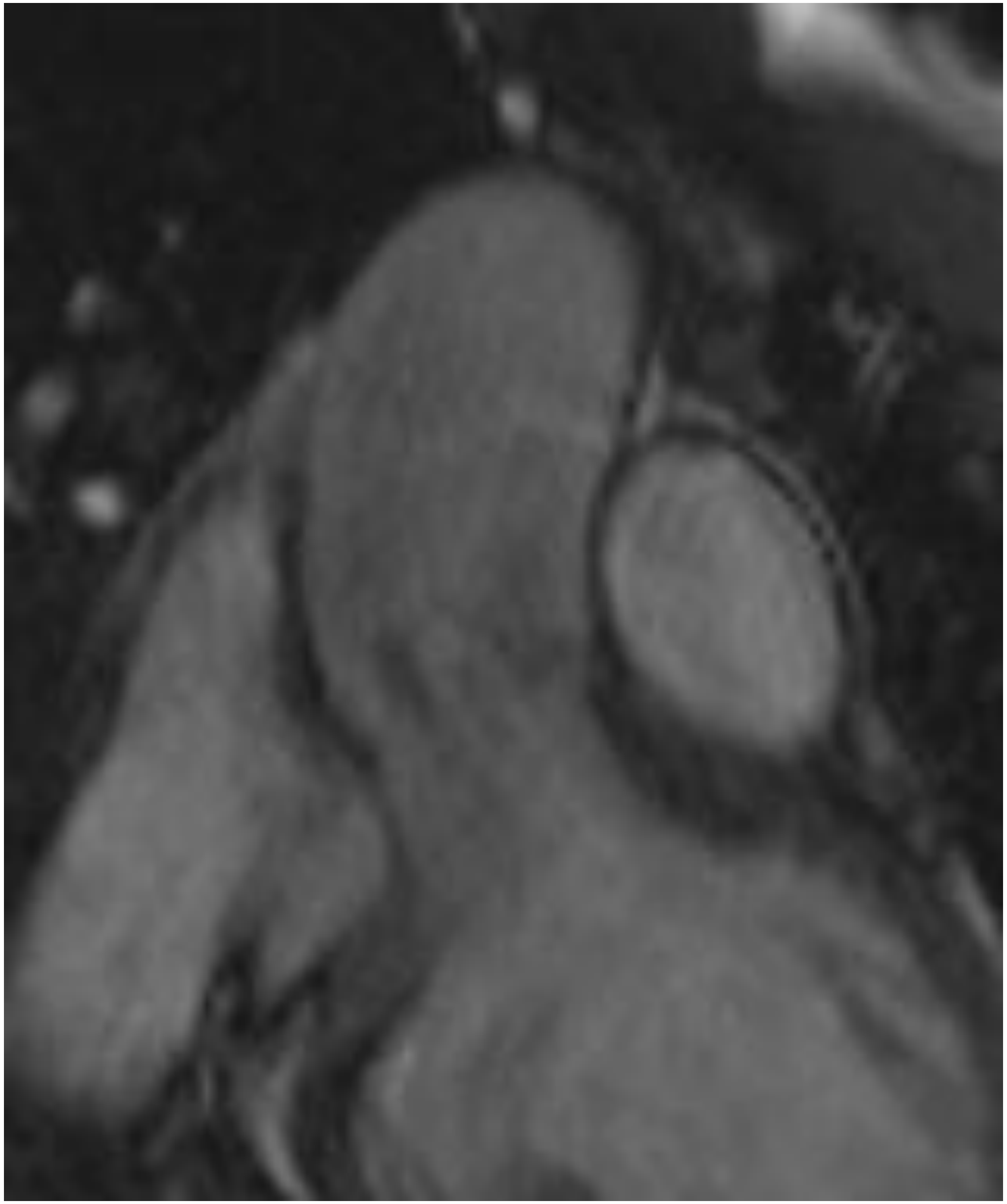
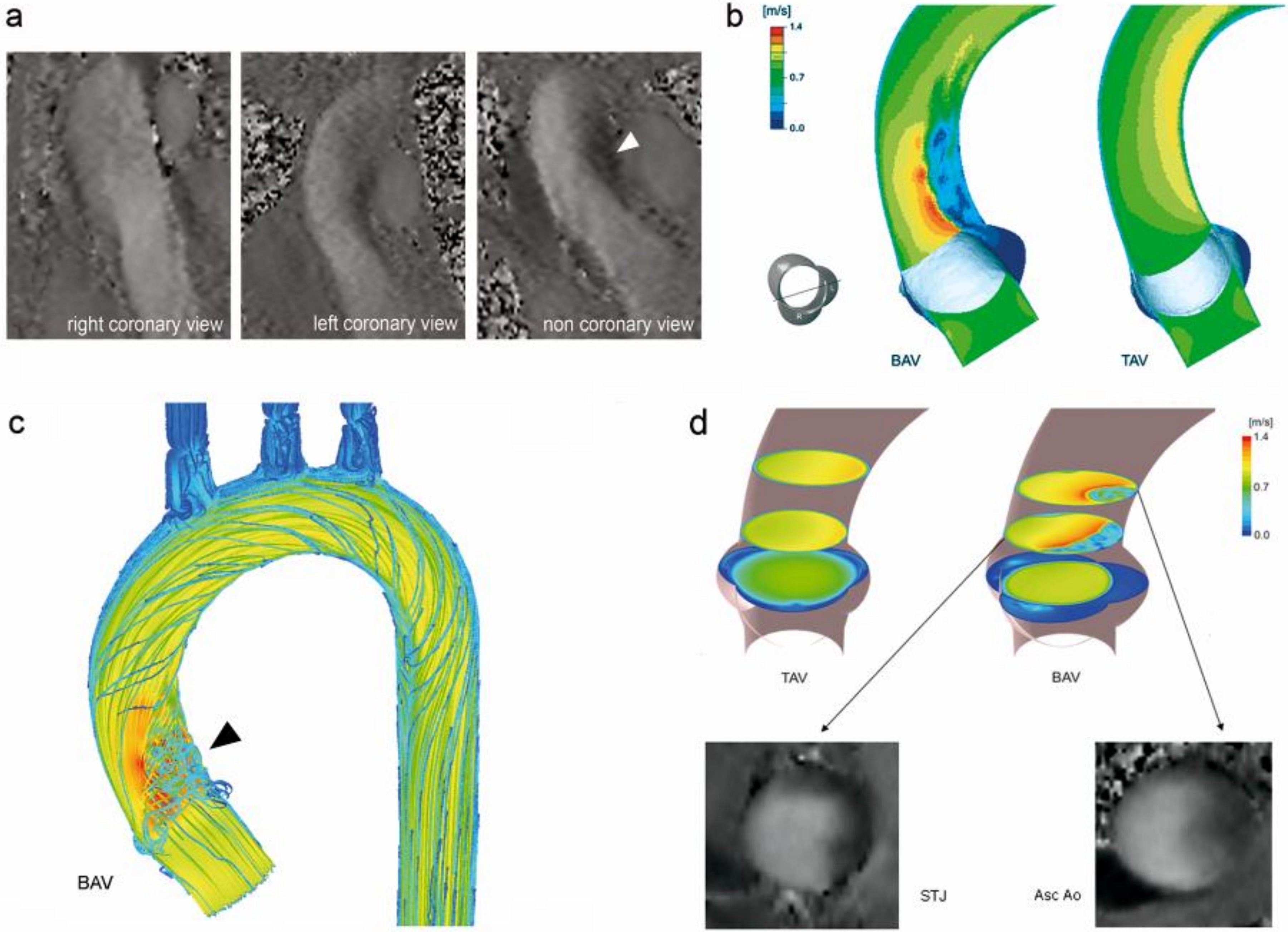
Seconda Università degli Studi di Napoli SUN

POLITECNICO MILANO

BIOMECHANICS GROUP




a
right coronary view
left coronary view
non coronary view
b
[m/s]
1.4
0.7
0.0
BAV
TAV
c
BAV
d
[m/s]
1.4
0.7
0.0
TAV
BAV
STJ
Asc Ao

Restricted cusp motion in right-left type of bicuspid aortic valves: A new risk marker for aortopathy

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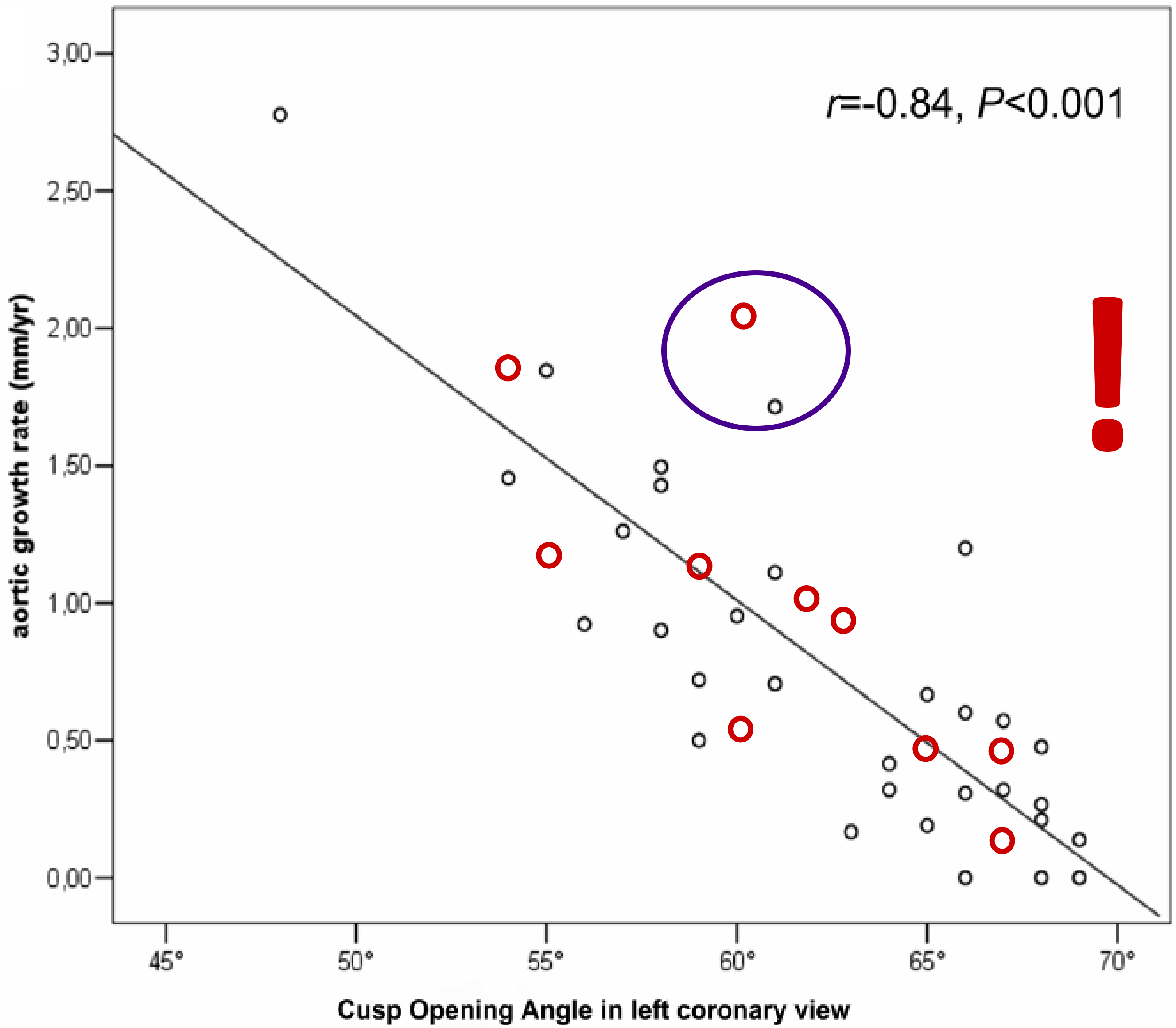


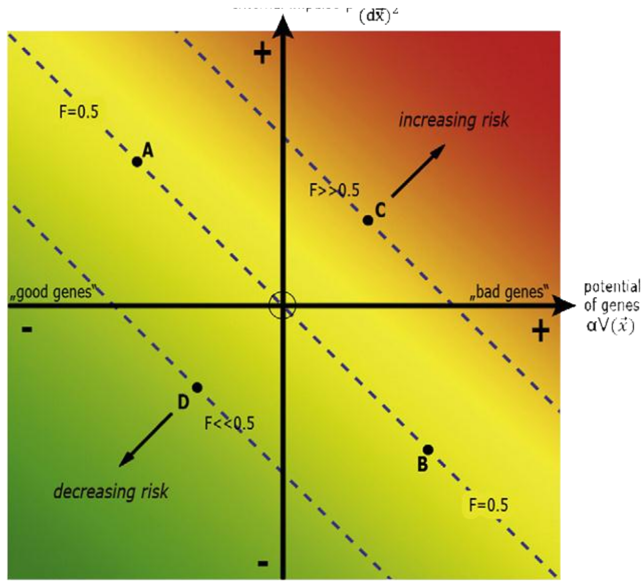
4. Still Misconceptions

after decades of researching!

Sievers HH et al. EJCTS 2011;39:803-804

Editorial

Aortopathy in bicuspid aortic valve disease — genes or hemodynamics? or Scylla and Charybdis?



$$\underbrace{\frac{dF}{dt}(\vec{x},t)}_{1\,\text{total risk}} = \underbrace{\alpha V(\vec{x}) \times F(\vec{x},t)}_{2\,\text{genes-related risk}} + \underbrace{\beta \frac{d^2F}{(d\vec{x})^2}(\vec{x},t) \times F(\vec{x},t)}_{3\,\text{external impulse-related risk}} \qquad (1)$$

where, in general,

(1) the overall change of the probability *(F)* over time to get an aortopathy as a sum of 2 and 3;
(2) genes-related change of *F*; and
(3) influence of external impulse (hypertension, turbulence a.s.o.) on the change of *F*.

"Exact solutions of Eq.(1) can probably not be drawn because **nature is too complex**"

«This is pure physics and hydrodynamic, respectively. […] Whether or not this is enough for dilatation and aneurysm formation remains open. The authors themselves are not fully convinced about the purely hemodynamic theory because they discuss the possibility that the jet and the regionally increased wall stress "could act as a stimulus to the expression of wall remodeling effectors“.

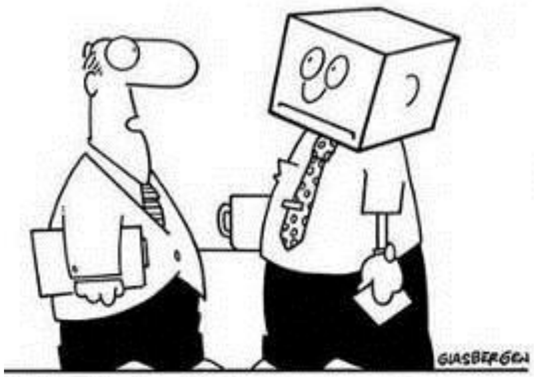
Tissue remodeling ≠ instrinsic disease

[…] still open question whether or not congenital BAV and proximal aortic dilatation and aneurysm formation results from a common genetic defect that would call for a more aggressive treatment or from the altered hemodynamics that can be changed by simple AVR when necessary.»

“Hemodynamic” ≠ “benign”

Anonymous expert, 2011

(a journal reviewer on the manuscript “Restricted cusp motion…”)



“Thinking outside of the box is difficult for some people. Keep trying.”

A little bored?

Do not worry: Conclusions!

To sum up…

- BAV disease is heterogeneous
- Think of causative factors in quantitative terms
- Need for risk stratification
- Aortic function & refined hemodynamics
- Biomarkers
- Biomechanics + Genetics

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