Manuscript Details

Manuscript number	JMCC_2018_372_R1
Title	Computational Modeling of Bicuspid Aortopathy: Towards Personalized Risk Strategies
Article type	Full Length Article

Abstract

This paper describes current advances on the application of in-silico systems for the understanding of bicuspid aortopathy and future perspectives of this technology on routine clinical care. This includes the impact that artificial intelligence can provide to develop computer-based clinical decision support system and that wearable sensors can offer to remotely monitor high-risk bicuspid aortic valve (BAV) patients. First, we discussed the benefit of computational modeling by providing tangible examples of in-silico software products based on computational fluid-dynamic (CFD) and finite-element method (FEM) that are currently transforming the way we diagnose and treat cardiovascular diseases. Then, we presented recent findings on computational hemodynamic and structural mechanics of BAV to highlight the potentiality of patient-specific metrics (not-based on aortic size) to support the clinical-decision making process of BAV-associated aneurysms. Examples of BAV-related personalized healthcare solutions are illustrated.

Keywords	bicuspid aortic valve, computational-fluid dynamic; finite-element analysis
Taxonomy	Medical Imaging, Mathematical Modeling

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Submission Files Included in this PDF

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Reviewer Comment.docx [Response to Reviewers]

Comp Mod of BAV Aortopathy_FC_SP_Rev6_REVISE.docx [Manuscript File]

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Dear Editor,

This manuscript presents a review on the computational modeling of bicuspid aortopathy. The review does not only report the current findings but also show how in-silico can be used to develop clinical decision support system based on artificial intelligence and develop wearable sensors to monitor patient at highest risk of aortic failure.

We declare the following:

- the manuscript is not currently submitted for publication by any other journal,
- none of the manuscript contents or parts have been previously published,
- all authors have read and approved the manuscript
- all authors declare that they have no conflict of interest.

Should you have any questions, please contact our office at +39 091 6657170 or email

Best Regards,

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Editor

All the reviewers' comments should be carefully addressed. Please clarify whether original data are present in the paper. If this is the case, please remove these results or change the format of the paper introducing an extensive methods section also describing statistical analyses. Please also state whether the displayed figures are original or were previously published. In the latter case, please provide the permissions to reproduce such figures.

Reply: As suggested, original data were removed since this paper aimed to review the literature instead of presenting new data. With regards to published figure, we confirm to have permissions from publisher and copyright owners (such as Wiley and Elsevier) to reproduce all figures. For each figure, the text “with permission” was added as specified by Elsevier guidelines. For instance, please find below permission for Figure 1.

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Licensed Content Date	Nov 15, 2015
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Licensed Content Issue	n/a
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Publication new article is in	Journal of Molecular and Cellular Cardiology
Publisher of the new article	Elsevier
Author of new article	Cosentino et al
Expected publication date	Jun 2019
Estimated size of new article (number of pages)	5

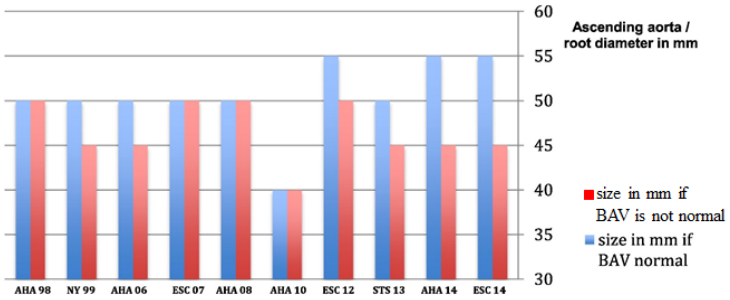
Reviewer #1

We thank the reviewer for his or her valuable consideration about our study. We have taken comments into careful consideration when preparing the revised manuscript and feel that the critiques led directly to an improved submission. We hope that the reviewer agrees. All changes made to the document were highlighted in yellow.

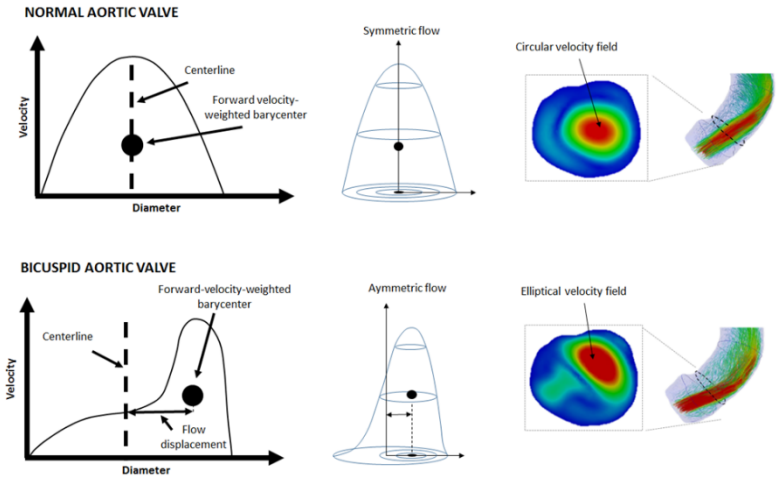
General Comment: This paper reports latest findings about interesting and potentially useful technological applications that could change the way to approach to aortic aneurysm treatment, giving support to prognosis and decision process when surgery is needed. Computer based simulations of blood dynamics, artificial intelligence applied to clinical decisions and development of reliable wearable sensors could be a revolution in every medical field and mostly in vascular medicine. Being Bicuspid Aortic Valve (BAV) one of the major causes of aortic aneurysm that evolves in lethal aortic dissection, it represents one of the natural targets of that innovative approach.
The present paper appears interesting but suffers from some issues that need to be revised.

Comment 1. The Authors have to correct several typos because they make the reading difficult.
Reply: Typos were fixed and the English was polished by our language service at ismett. Please see text highlighted in yellow throughout the text

Comment 2. Figure 1 comes from a paper published by Hardikar et al. As the original figure, the red histogram legend is missing. It is suggested to add it or to rebuild the figure.
Reply: Indeed, the red histogram is missing in the original figure as well. Therefore, the meaning of red and (blue) histogram was written in the figure legend. We fixed the Figure by adding the meaning of red histogram as a follow:



Comment 3. The complex technological approach discussed by the Authors groups together concepts of fluid dynamics, vascular physiology, mathematics and computer programming. Then, figures should strongly support them. The Authors should improve the graphical representation of the paper. Moreover, figure captions should show detailed information.
Reply: We agree with reviewer comment to improve figures and their legends. Thus, Figure 2 was improved and shown below



The legend was rewritten to better explain the meaning of the figure with the following text:

“Flow jet in a morphological normal tricuspid aortic valve (top row) versus that shown by a BAV (bottom row); plots on the left and sketches in the middle show the flow displacement which is the distance between the vessel centerline node and the forwards velocity-weighted center of mass position. The flow displacement is a parameter that quantifies the flow eccentricity in the ascending aorta. Computational modeling allows to evaluate the velocity field (contour map on the right) to show an elliptical flow velocity for BAV as compared to circular flow field shown by a normal aortic valve; figure adapted from Mahadevia et al. [29] and Vergara et al. [32].”

In a similar way, the legend of Figure 3 was improved with the following additional text:

“the “heat” map shows the area where WSS magnitudes are high (red color) and low (blue color); this WSS atlases demonstrate the ability to regionally detect that all BAV patients exhibit significantly elevated WSS compared to healthy volunteers with TAV; with permission from Pim van Ooij et al. [58]”

Figure 4 and the legend were fixed as well:

“Biomechanical stress analysis of a dissected aorta; (A) clinically observed dissection origins were plotted on the aortic models and were subsequently contrasted against (B) intramural stress map along the longitudinal direction of the vessel; (C) dissection patients were found to have increased peak longitudinal stress compared with control patients (ie, non-dissected); (D) there was no significant difference in peak circumferential stress between the dissected and control cohorts; with permission from Emrel et al. [67]”

Figure 5 presenting new data was deleted according to suggestions from Editor and other Reviewers.

Comment 4. The approach proposed has its target in the clinical practice. Aspiring to this, every procedure, practice or manipulation needs to be previously validated and standardized. It is suggested to stress the existence of validated and/or standardized procedures and to highlight the promising works in progress, among those reported. It could offer the reader a clear scheme of the available opportunities and future applications.

Reply: We agree with reviewer that a remarkable validation and standardization process needs to be undertaken before these promising works are applied in the clinical practice. The following text was added in a new section named " Challenge and Limitations" at the end of text:

"**CHALLENGES AND LIMITATIONS**

Although studies here reported demonstrated promising findings, the challenge is the development of relevant standard procedures and validation strategies of presented personalized strategies to manage bicuspid aortopathy. Indeed, a standardized method for calculating hemodynamic and structural parameters needs to be agreed upon to set reference values and enable predictions on disease progression and management. Validation commonly involves comparison with either values measured within an *in-vitro* phantom or acquired during *in-vivo* evaluation. Moreover, diagnostic software is regulated by CE marking and FDA directives, respectively; but there are no standards governing accuracy, reliability or validation of computational modeling approach. Large volumes of clinical data are needed for model development and validation in order to expedite clinical translation. Finally, the next generation of physicians will require training for *in-silico* approaches to understand their principles and limitations for an ideal implementation in the clinical practice."

Reviewer #2

We thank the reviewer for his or her valuable consideration about our study. We have taken comments into careful consideration when preparing the revised manuscript and feel that the critiques led directly to an improved submission. We hope that the reviewer agrees. All changes made to the document were highlighted in yellow.

General Comment: This article provides a comprehensive overview on the current in-silico computational modeling of bicuspid aortopathy. In the specific, authors reported some examples of in-silico tools based on computational fluid-dynamic (CFD) and finite-element method (FEM), highlighting benefits in cardiovascular medicine. They further discussed current knowledge of computational hemodynamic and structural mechanics of BAV. The need to merge mechanical data with biological parameters is also well highlighted. Finally, authors provided some examples of personalized healthcare solutions for BAV individuals.

The work is interesting and well organized. All relevant literature has been nicely covered. Here some comments:

Comment 1: The source of Figures is unclear. Were these figures already published in other papers? If yes, do the authors have permissions for publish these figures or even modify? Please clarify this issue.
Reply: Out of four figures, three were adopted from published paper. In all cases, permissions were obtained from the publisher. For instance, please find below permission to reproduce Figure 1:

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Licensed Content Author	Ashutosh A. Hardikar,Thomas H. Marwick
Licensed Content Date	Nov 15, 2015
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Licensed Content Issue	n/a
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Publication new article is in	Journal of Molecular and Cellular Cardiology
Publisher of the new article	Elsevier
Author of new article	Cosentino et al
Expected publication date	Jun 2019
Estimated size of new article (number of pages)	5

Comment 2: Authors should provide more details in the legend of figure 3 and figure 4.
Reply: More details for Figure 3 and 4 were added in the legend. Figure 2 was fixed as well as it required by other reviewers. Additionally, labels of Figure 4 were fixed. Please find below the text legend of these figures:

"Figure 3: Cohort-specific WSS (unit is N/mm2) atlases of (a) healthy controls with tricuspid valves, (b) BAV patients, (c) BAV patients with aortic dilation, (d) patients with BAV stenosis. The insets show the p-value maps on the shared geometry of the BAV vs. controls (b), BAV with dilation vs. controls (c) and BAV stenosis vs. controls (d) comparison; the "heat" map shows the area where WSS magnitudes are high (red color) and low (blue color); this WSS atlases demonstrate the ability to regionally detect that all BAV patients exhibit significantly elevated WSS compared to healthy volunteers with TAV; with permission from Pim van Ooij et al. [58]

Figure 4: Biomechanical stress analysis of a dissected aorta; (A) clinically observed dissection origins were plotted on the aortic models and were subsequently contrasted against (B) intramural stress map along the longitudinal direction of the vessel; (C) dissection patients were found to have increased peak longitudinal stress compared with control patients (ie, non-dissected); (D) there was no significant difference in peak circumferential stress between the dissected and control cohorts; with permission from Emrel et al. [67]"

Comment 3: Last paragraph: authors should add a schematic representation or a diagram related to the computer-based clinical decision support system (CDSS) in the management of BAV patients.
Reply: if it permitted by the reviewer, we prefer not to add a figure on the CDSS because of the pending patent submission. The patent was cited in Ref 98 so that it can be easily found on internet using the ID number if additional information about this technology are needed. We hope that the reviewer can understand our needs to protect our pending patent.

Comment 4: Please remove original and unpublished data (Figure 5) from this article.
Reply: The original data of Figure 5 and the text were removed from the text. These will be the focus of our next paper.

Computational Modeling of Bicuspid Aortopathy: Towards Personalized Risk Strategies

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Conflict of interest: none

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Abstract: This paper describes current advances on the application of *in-silico* for the understanding of bicuspid aortopathy and future perspectives of this technology on routine clinical care. This includes the impact that artificial intelligence can provide to develop computer-based clinical decision support system and that wearable sensors can offer to remotely monitor high-risk bicuspid aortic valve (BAV) patients. First, we discussed the benefit of computational modeling by providing tangible examples of *in-silico* software products based on computational fluid-dynamic (CFD) and finite-element method (FEM) that are currently transforming the way we diagnose and treat cardiovascular diseases. Then, we presented recent findings on computational hemodynamic and structural mechanics of BAV to highlight the potentiality of patient-specific metrics (not-based on aortic size) to support the clinical-decision making process of BAV-associated aneurysms. Examples of BAV-related personalized healthcare solutions are illustrated.

Keywords: bicuspid aortic valve, computational-fluid dynamic; finite-element analysis

THE CLINICAL DILEMMA

Bicuspid aortic valve disease is the most common congenital heart disorder, being present in 1% to 2% of the general population [1]. Associated aortopathy is a common finding in patients with bicuspid aortic valve (BAV) disease, with thoracic aortic dilations reported in approximately 40% of patients [2]. The risk of adverse events, most commonly aortic dissection, is higher in BAV patients than in the general population with the morphological normal tricuspid aortic valve (TAV) [3]. The precise determination of the optimal timing for surgical intervention is difficult and depends on several risk factors or family history so that the surgical dilemma is still an open debate. Consensus statements and guidelines reported different recommendations on the maximum aortic diameters for elective repair [4] (see Figure 1). In the 1990s and 2000s, more aggressive management was advocated for BAV patients as some suggested that BAV aortopathy was roughly equivalent to Marfan syndrome [5]. Recent studies and observations have led to a more conservative approach, with no distinction in the management of BAV patients versus TAV patients, because the risk of aortic emergencies in BAV was not as high as previously thought [6, 7]. ~~It was emerged that~~ BAV aortopathy is a markedly heterogeneous entity, and this makes surgical-decision particularly challenging. Ascending thoracic aortic aneurysms (ATAA) in BAV may occur in the aortic root, the tubular ascending aorta, the proximal aortic arch, or any contiguous combination of these three [8]. New classification schemes considering BAV morphotypes and patterns of aortic dilatation have been proposed but showed poor prognostic significance [9, 10] . For a compressive review on major aspects of bicuspid aortopathy, we refer to the extended version of the recent consensus statement proposed by Borger and collaborators [11].

Similar obstacles are present for the research community to approach the BAV-associated aneurysm disease. As suggested by Della Corte et al. [12], the research on BAV aortopathy interpreted clinical aspects (eg, rate of progression, relation with severity of valve dysfunction,

risk of dissection) with the aim of drawing inferences on the pathogenesis, that is, alternatively supporting the hemodynamic or the genetic theories. Inconclusive results and increasing awareness of the bicuspid heterogeneity have led to an inversely oriented approach: the contribution of either pathogenetic or genetical factors has to be investigated to identify the respective potential prognostic value of each component. Once such a dichotomy will be addressed, new metrics can be identified to improve management of BAV-associated aneurysms.

BENEFIT OF CARDIOVASCULAR MODELING

For design and analysis, the use of *in-silico* computational modeling is a well-established and essential tool in traditional engineering. Modeling techniques include computational fluid dynamic (CFD) as a specialist area of mathematics and branch of fluid mechanics as well as finite-element method (FEM) for predicting the mechanical response of materials under loading conditions. There exists a third complex technique, integrating both fluid- and structural solvers, named fluid-structure interaction (FSI) analysis. These computational approaches are rapidly emerging in the clinical area because *in-silico* allows to determine patient-specific information at a level of detail otherwise impossible with standard clinical tools. Major evidences are the use of computer simulations for designing ventricular assist devices (VAD) [13, 14] and studying VAD-related complications [15-17], developing heart valves [18], coronary stents [19] and endografts [20, 21].

In the setting of bicuspid aortopathy, computational modeling can be adopted to support the clinical decision-making process by providing patient-specific metrics that are not based on aortic size. A patient-specific approach of bicuspid aortopathy in which the individual's unique anatomy and physiology are simulated to tailor personalized management is advocated. Although *in-silico* is an appealing approach to better understand the risk of a well-functioning

BAV in the setting of a critical aortic size of 4-5cm, clinicians portends towards specific questions that are not yet addressed by our current knowledge of BAV-related mechanics and fluid-dynamic. Is the computed wall shear stress (WSS) sufficient enough to determine aortic dissection? If stress is a better indicator than aortic size, how much is the cut-off of intramural stress (IMS) for the surgical repair of a dilated aorta? Behind these questions, there is a considerable work on the improvement, validation and accuracy of numerical predictions before the application of computational tools for the daily clinical practice. Before reviewing current findings, we would like to highlight the potential of computational modeling by presenting the most recent projects that delivered tools for supporting clinicians in their daily clinical management of cardiovascular diseases and discuss findings as compared to bicuspid aortopathy.

In coronary atherosclerosis, the measurement of fractional flow reserve (FFR), an index of physiological lesion significance as measured with a pressure-sensitive angioplasty guidewire, is the gold standard therapy. Using data from standard CT imaging, the HeartFlow Inc company (https://www.heartflow.com/) generates a personalized 3D model of the coronary arteries and uses CFD to virtually analyze the impact that plaque blockages may have on the circulating coronary blood flow. The HeartFlow's trial demonstrated the performance of virtual FFR using CT coronary angiography versus catheterization (sensitivity 86%, specificity 79% vs invasive FFR) [22]. To all patients with coronary artery disease, this model offers a less invasive approach, neither requires hyperaemic flow induction nor the passage of an intracoronary wire. Numerical simulations of computed coronary flow consist of a color-coded map that aids clinicians in determining, vessel-by-vessel, if the flow reserve is sufficient to reach the heart. This technology proposed by HeartFlow Inc is now FDA approved for use as a class II coronary physiologic simulation software device. However, it should be considered that the impressing technology delivered by HeartFlow Inc is likely due to the fact that FFR is a very accurate

measurement of the coronary plaque risk. For the bicuspid aortopathy, genetic and hemodynamic components play a key role on the ascending aortic dilatation and progression [23]. Indeed, the heterogeneity induced by BAV further complicates the identification of a single risk predictor, taking into account the natural histories of different BAV phenotypes. We envision that not a single predictor but rather a set of new metrics, which quantify the respective contribution of genetic and hemodynamic components, have to be considered to tailor computer-based individual or patient subgroup treatments of BAV-associated aneurysms.

In the field of heart valve diseases, TAVIguide™ (https://www.feops.com/) is a CE-marked product indicated for the structural simulation of transcatheter aortic valve implantation (TAVI) that is based on a preoperative assessment of the interaction between the patient anatomy and the prosthetic heart valve. This simulation tool does not only provide metrics of safety and efficacy of TAVI but can also lead to a new paradigm for which *in-silico* is adopted to reduce time, cost, and risk associated with clinical trials of medical devices. In the setting of BAV, where TAVI is as an off-label application [24], computational tools such as TAVIguide™ are promising in the evaluation of the efficacy of the prosthetic heart valve deployment in the bicuspid annulus, which tends to be less elliptical than the tricuspid one.

Regarding aneurysm disease, Sim&Cure (https://sim-and-cure.com) cleared to the market a patient-specific simulation model for the cerebral aneurysm treatment to predict medical device deployment (eg, flow diverter, intrasaccular device, laser-cuter stent). The computer software provides different scenario for each graft size and type of device according to the patient's unique anatomy to provide essential information prior to intervention. Sim&Cure is also developing CFD to preoperatively provide hemodynamic of cerebral aneurysms. In the last two decades, researchers have been increasingly interested in the understanding of abdominal aortic aneurysms (AAA) using biomechanical principles to develop a new metric called the

rupture potential index (RPI) [25]. This risk parameter is based on computer simulations to determine patient-specific predictions of AAA wall stress [26] and was reported to perform better than aortic diameter for predicting which patients will experience AAA rupture [27]. Using computer simulations, VASCOPS GmbH (http://www.vascops.com) has developed a software product providing a graph plot of the estimated annual risk of rupture versus the RPI parameter as obtained from the ratio of wall stress on the wall strength of an AAA. Indeed, the maximum aortic diameter as standard criterion for both AAAs and ATAAs is a surrogate geometric indicator of the imbalance between biomechanical stress and strength, which is what ultimately determines the rupture of dilated aortas. However, both kinematic and fluid mechanics of AAAs are different from that of ATAAs where the blood flow is highly dynamic and the heart contributes to stretch and twist the vessel during cardiac beating [28]. These differences limit the application of RPI for the risk stratification of bicuspid aortopathy.

These software products based on computer simulations are helpful to understand the potential and limits in the utilization of *in-silico* for personalized medicine of bicuspid aortopathy. To facilitate and regulate *in-silico*, the Avicenna project (http://www.avicenna-isct.org) created a research and technological development roadmap describing how *in-silico* can be introduced into clinical trials. This document provides an overview of how biomedical products including computational solutions are being developed today. Readers can find out where *in-silico* clinical-trials technologies are already being used, and how this area could be extended in the future.

HEMODYNAMIC PARAMETERS AND CLINICAL IMPLICATION OF BICUSPID VALVE

The hemodynamic theory of BAV-associated aneurysms suggests that flow disturbances dictated by the bicuspid phenotype locally increases aortic shear stress, leading to adverse vascular remodeling and weakening of the aortic wall. A bulged dilatation or an ATAAs growing faster than another one are evidence supporting the hemodynamic theory as compared to the

genetic one. For a critical reappraisal of one-sided arguments, we recommend the report of Girdauskas et al. [23]. Table 1 summarizes the definition of potential computational metrics for risk stratification strategies.

Flow patterns in BAV versus TAV

In fluid-dynamic, the visualization of flow patterns is achieved by streamlines, which are tangent to velocity vectors and provide the path travelled by the fluid at each time instant. Flow patterns in the ascending aorta differ significantly according to the aortic valve morphology and have shown correlation with the shape of the dilated aorta [29]. Figure 2 shows how a well-functioning aortic valve produces parallel streamlines broadly centrally distributed in the ascending aorta [30], indicating that the flow is laminar and parallel to the aortic wall [31]. Conversely, in BAVs, the elevated blood flow angle produces an asymmetric outflow pattern [32], with higher velocity shifted towards the aortic wall periphery and disrupting the laminar flow profile.

Flow displacement

Using 4D flow MRI, Garcia et. al.[33] showed altered hemodynamics in BAV patients versus TAV patients matched for the aortic size. Hemodynamic differences were characterized by the flow displacement, defined as the distance between the vessel centerline node and the forward velocity-weighted center of mass position (see Figure 2). Thus, the peak velocity was extracted using the velocity-weighted center of mass location to avoid a single velocity voxel measurement. In a cohort of n.52 subjects with either BAV or TAV, Raghav et al. [34] used normalized flow displacements at sino-tubular junction to assess the relationship between aortic valve phenotype and flow features. They found high values of flow displacement for BAV subjects when compared to size-matched TAV, but the flow angle of BAV did not significantly differ from TAV.

Flow helicity

Helicity is a measure of corkscrew-like motion described by the amount of twisting, writhing, and linking in a fluid. This hemodynamic index can be quantified by the helical flow index (HFI) to consider the forward component (along the longitudinal axis of the aorta) and the rotational component (rotating along the circumferential direction) of the blood flow [35]. HFI was found to be significantly elevated at peak systole in the ascending aorta of stenotic BAV [36]. To elucidate whether flow abnormalities in dilated BAV aortas are due to bicuspid phenotype or to the dilated aorta itself, Cao et al.[37] used CFD to quantify the early impact of different bicuspid morphotypes on the hemodynamic prior to the manifestation of aortic dilatation. Using the ratio of right-handed helical flow to the total helical flow over a section (ie, the positive fraction index, PHF), valvular jet skewness and eccentricity was quantified in term of the flow angle between the direction of the mean flow vector and the unit normal vector to the section of interest. When compared to TAVs, BAV aortas showed increased helicity in the mid ascending aorta (0.86 for BAV and 0.51 for TAV), larger systolic flow skewness (11.2° for BAV and 5.5° for TAV), and flow shift between the center of the section and the centroid of the highest 15% of velocity vector in the same section (6.8mm for BAV and 3.3mm for TAV). The increased flow angle in BAVs was associated to higher rotational flow values, resulting in a larger amount of the jet rotating along the aortic wall and ultimately leading to aortic dilatation [35]. Bissel et al. [35] compared flow patterns over 142 subjects (95 with BAV, 47 healthy volunteers) reporting that the most common flow abnormality in BAVs was an increased right-handed helical flow irrespective of valve morphotype. This finding was associated to large ascending aortic diameters, high rotational flow, and systolic flow angle. In contrast, BAV subjects with aortic diameters and flow angles similar to those of healthy volunteers presented a normal flow characterized by a slight increase in the rotational flow component [35].

Stenotic BAV

The presence of severe aortic stenosis can lead to an accelerated outflow jet, with the increase of the vertical flow component and the prevalence of tubular and transverse BAV dilatations [38]. Youssefi et al. [36] also demonstrated that the greater curvature of bicuspid aorta shows low values of oscillatory shear index (OSI), which is a metric quantifying the changes in the direction and magnitude of WSS over time. This parameter was associated to valvulopathy [39] and aneurysm progression [40, 41]. As the aortic shear stress, OSI is symmetric in healthy individuals, but not in stenotic TAV and BAV patients [42].

Wall Shear Stress

Wall Shear Stress is the frictional force exerted per unit area by the flowing blood on the intimal surface of the aortic wall and plays an important role on vascular homeostasis [31]. In general, bicuspid aortopathy shows more pronounced WSS, even in non-stenotic cases [32] when compared to healthy volunteers [43]. High WSS values are distributed along the greater curvature of the ascending aorta [38, 44-48], which is an area where usually thinning occurs [49]. Several studies reporting WSS magnitudes at several anatomic levels of the ascending aorta demonstrated that BAV patients have higher WSSs in the ascending aorta than those of TAV patients [32, 50, 51].

Although WSS plays a key role on the onset of aortic dissections [52], it is not possible to establish whether acute events occur only due to pronounced shear magnitudes. Since the aorta is not uniform in the thickness and wall strength [53-55], the rupture might not occur in locations of peak WSSs, but rather where the aortic wall is also weak. We recently reported the computational study of a young male patient with a rare unicuspid aortic valve who refused the surgical repair of the large ascending aorta (maximum diameter of 67 mm) [56]. A month later than the computational result was obtained, he had a type A aortic dissection repaired in emergency surgery. Interesting, we found that the site of intimal tear seen at CT scan accurately

corresponded with the region of the aortic wall at highest WSS magnitude, suggesting the potential of this hemodynamic parameter for individual risk stratification.

When comparing the magnitude of WSSs reported by all studies, large discrepancies are observed according to: 1) type of computational tools (CFD vs FSI) and boundary conditions (lumped parameter models vs MRI flow data) [57]; 2) type of techniques (CFD vs 4D Flow MRI) [58]; 3) study design mainly including valve stenosis and cusp fusion patterns [43-45]. The systematic review proposed by Edlin et al [42] summarizes these discrepancies on WSS predictions in BAV-associated aneurysms. The utilization of "aortic atlases" of WSS vectors is an elegant solution for the systematic analysis of WSS differences in large patient cohorts [59] as shown by Figure 3.

CFD versus 4D Flow MRI

CFD analysis requires reconstruction of virtual anatomy and the knowledge of boundary conditions that can be obtained by imaging and outflow analyses. Although rapid and automated tools for virtual anatomic reconstructions can be used [60], the segmentation step of BAV anatomy for CFD analysis can increase the time of the numerical solution. Given the complexity of mathematical equations governing the fluid motion, the use of accurate boundary condition is fundamental to obtain realistic predictions of aneurysm flow [61]. CFD has ideally limitless spatial and temporal resolutions as compared to 4D Flow MRI, which offers the possibility to quantify *in-vivo* fluid-dynamic alterations dictated by BAV. MRI-derived shear stress measures are likely underestimated due temporal and spatial resolution when compared to CFD predictions [58]. We conclude that computational modeling and 4D Flow MRI should be seen as complementary rather than contrasting techniques.

BIOMECHANICAL ANALYSIS OF DILATED AORTA

Aortopathy progression is accompanied by both an increase of wall stress and a decrease in the ability of the aortic wall to withstand this stress condition (ie, decrease in the wall's failure strength). Aortic wall weakening due to BAV-related histopathological changes promotes vessel dilatation. Computational modeling has the potential to non-invasively estimate the distribution of aortic wall stress and strain in virtual anatomic models reconstructed from patients who undergo close monitoring of aneurysm size [62].

Aortic Dissection and Wall stress

Thubrikar et al. [63] first noted that most intimal tears in the circumferential direction of the aorta could be caused by increased longitudinal IMS; however, this study considered an ideally bulged aortic model and uniform material properties. In our opinion, such a mechanism is inadequate because aortic dissection depends on the inhomogeneity and anisotropy (ie, directionally dependent dissection property) of the aorta that locally increase IMS required for tearing the aortic wall as a result of cyclic pulse pressure. Local maxima of IMS on the inner aortic layer were found greater than those of the outer aortic layer, which confirms the increased risk of dissection in BAV-associated aneurysms [64]. Most clinically-relevant studies demonstrated peaks of IMS above sinotubular junction and regional differences in the IMS magnitudes between the ascending and descending aortas [65, 66] and between BAV and TAV patients [67, 68]. This suggests that stress distribution may contribute to the pathogenesis of type A aortic dissection because maxima of IMS were observed above the left and right coronary sinuses of the ascending aorta where dissections are seen clinically. Recently, Emerel et al. [69] demonstrated that ascending aortas of patients who experienced type A aortic dissection at CT scans have decreased aortic wall strain (14.50 ± 1.13% vs 8.49 ± 1.08%; $p < .01$), decreased distensibility (4.26 ± 0.44 vs 2.39 ± 0.33 10-6 $cm^2 \cdot dyne^{-1}$; $p < .01$), increased stiffness (3.84 ± 0.24 vs 7.48 ± 1.05; $p < .001$),and increased longitudinal wall stress (246 ± 22 vs 172 ± 37 kPa; $p < .01$) as shown by Figure 4. These variables may be sufficient to disrupt the

cell-matrix interactions and separate the layered microstructure of the aortic wall, thereby initiating aortic dissection. However, the mechanisms underlying the onset of aortic dissection as intramural hematoma formation are complex and not yet well elucidated by computational simulations.

Rupture potential index of BAV-associated aneurysms

In the last years, several research groups have presented a rupture criterium based on the imbalance between stress and strength to bypass the ‘‘aortic size paradox’’. Using FEM, Martin et al. [70] demonstrated that the aortic size index is sufficient for identifying patients with the lowest risk of rupture, but unsuitable for delineating between patients at moderate and high risk. Later, they elaborated a predictive rupture risk model showing that elevated blood pressure in a stiffer aorta is a risk factor for aneurysm failure [71]. This was also corroborated by other rupture analyses [72-74], suggesting that only a stiffer dilated aorta may have the most altered distribution of wall stress and that an acute change of peripheral vascular resistances induced by increased blood pressure could significantly increase the risk of rupture. Indeed, mean physiological wall stresses exerted on the pathologic aorta are far from rupture, with factors of safety larger than six. There was no difference on the estimated rupture risk between BAV and TAV, supporting that risk of BAVs is not as high as previously thought [6, 7].

Wall stress analysis requires assumptions as the knowledge of aortic wall thickness and biomechanical properties. Conversely, the prognostic significance of strain has been demonstrated for quantifying regional myocardial function [75]. A loss of arterial elasticity (ie, reduced strain) is common in BAV-associated aneurysms as documented by two-dimensional speckle tracking echocardiography [76]. Thus, another equivalent definition of rupture can be stated when the stretch applied to the aortic tissue by hemodynamic and structural loads exceeds its extensibility (ie, stretch at rupture). Duprey et al. [77] proposed a stretch-based

rupture risk criterion and showed correlation with tangent elastic modulus in ATAAs. Several studies proposed a method for the *in-vivo* identification of aortic stiffness based on the determination of volumetric distensibility [72] or the displacement field obtained by the analysis of dynamic CT images [78]. The open issue is that strength has to be determined by *ex-vivo* experimental testing and cannot be evaluated for those patients monitored for aortic size.

MERGING FUNCTIONAL AND MOLECULAR DATA

A mechanistic link occurs between mechanical stimuli and biological processes. Blood vessels are permanently subjected to mechanical forces exerted by the pulsatile nature of blood flow. Histopathologic changes in the aortic media have been well documented and specifically delineated for the bicuspid aortopathy [79-83]. The aortic ECM plays an important role in maintaining the aorta through both the binding/storing secreted proteins and maintaining the structural integrity of the vascular wall [80]. The presence of thin, fragmented elastin fibers, reduced fibrillin-1 content, and decreased types I and III collagen have suggested elevated proteolytic activity [80, 81]. The degradation of ECM is under the balanced control of metalloproteins (MMP) and their associated tissue inhibitors (TIMP), which are secreted by vascular smooth muscle cells, fibroblasts, and endothelial cells. Various studies have shown disturbances in the ECM of surgically resected BAVs with increased activity of MMPs, thereby suggesting an inherent developmental defect underlying dysregulation of ECM in the aortic medial layer as the main cause of the aortic dilatation [82-86].

In the setting of BAV, the longer period of exposure to increased aortic shear stress in patients born with such a congenital malformation, as opposed to acquired disorders such as hypertension or atherosclerosis, is the rationale of the hemodynamic-mediated mechanism of aortic dilatation. Although 4D Flow MRI [35, 45] and computational studies [31, 36, 67] have elucidated that distinct aortic cusp fusion patterns result in specific orientations of eccentric flow

jets, which in turn may lead to differential distributions of aortic WSS, the study of Guzzardi and collaborators [45] is the only report documenting the relationship between altered WSSs and regional aortic tissue remodeling in BAV-associated aneurysms. Elevated aortic WSS generated by disturbed flow due to cusp fusion corresponded to more severe ECM dysregulation than adjacent regions of normal WSS in the same patient's aorta. Characteristic medial degeneration was observed throughout the aorta, but elastic fiber degeneration was more severe in regions of elevated WSSs (less elastin, thinner fibers, and greater distances between laminae), where higher concentrations of mediators of ECM dysregulation (ie, MMP and TGF-b) were observed. ~~In a similar way, our unpublished data correlating computationally-derived WSS with plasma measurements of MMPs confirms that peak-systolic WSS can determine dysregulation of aortic ECM by altering the concentration of MMP-9 in dilated aortas with BAV (see Figure 5).~~ These data implicate valve-related hemodynamics as a contributing factor to bicuspid aortopathy, however their utility in prediction of disease progression awaits careful studies. It has not yet explained whether the WSS-mediated ECM dysregulation is a consequence of the dilatation itself rather than a determinant or risk factor. There is a need for longitudinal study investigating changes of WSS and ECM over time (ie, at in-hospital admission and during patient follow-up).

The ideal biomarker of bicuspid aortopathy should be accurate and noninvasive and have limited correlation with the aortic size to provide additional information for prognostic stratification alongside with other metrics (eg, WSS and IMS). D-dimer has emerged as a potential serum marker for acute dissection (cut-off of 500 ng/mL) [87]. However, as a nonspecific indicator of intravascular coagulation, D-dimer can be elevated in many conditions. Caution should be exercised in the application of D-dimer because 18% of patients with confirmed aortic dissection may have levels D-dimer<400 ng/mL. Similarly, circulating soluble receptors for advanced glycation end products (sRAGE) has been indicated as risk factor of aortic dilatation [88], but not confirmed in another study [89]. Recently, Forte et al. [90]

observed that, for BAV undergoing surgery for aortic valve stenosis, the ratio of serum TGF-β1 to endoglin correlated with the rate of postoperative progression of aortic dilatation over a mean echocardiographic follow-up time of >3 years. Specifically, patients with higher TGF-β1/ENG ratios at baseline showed faster growth of the ascending aorta in the postoperative period. It should be also mentioned that WSS triggers mechano-transduction pathways not only inhibiting ECM pathways but also inducing or silencing the transcription of miR genes or miRs along with their parental genes [91]. Thus, WSS alterations seen in BAVs can affect the circulating level of miRNAs. Several studies have proposed signature of miRs as novel biomarkers of BAV-associated aneurysms but few common miRs were seen in more than one study and, in some cases, the results disagreed even in the direction of the change [92-95]. Such discrepancies among studies are likely caused by study designs as selection bias, number of samples, or incompletely captured confounding variables. Among these studies, Gallo et al. [92] reported a correlation between the increased aortic wall stiffness and the expression of miR-34a in n.84 patients with ATAA, suggesting a mechanistic link between altered biomechanical properties of the aortic wall and disease progression in BAV patients. This was likely modulated by valve-related hemodynamic because the expression level of miR-34a is sensitive to the fluid flow [96] (downregulated by atheroprotective physiological high WSS and upregulated by atheroprone OSI). A greater prognostic armamentarium including several biomarkers and aortic shear stress would support a patient-specific approach to BAV aortopathy, especially in terms of criteria informing surveillance, surgical indications, and follow-up.

PERSONALIZED HEALTHCARE SOLUTIONS

BAV-associated aneurysm management is based on a “one-size-fits-all” approach where all patients are treated at same way while the presence of genetic variants and hemodynamic abnormalities leads to diverse clinical phenotypes with distinct natural histories. It is becoming increasingly clear that traditional prediction and risk-score models (commonly based on a

handful of epidemiological factors) fail to capture important information on the individual's behavior, comorbidities and specific biological profiles. Healthcare is approaching an inflection point towards therapeutic strategies personalized for a patient and subgroups of patients. In the era of artificial intelligence, a key aspect of personalized medicine is the development of computer-based clinical decision support system (CDSS) that can analyze and interpret data using machine learning classifiers in an automated and adaptive fashion, while providing accurate and actionable clinical information. Machine learning refers to methods developed within the fields of statistics and computer science that allow the creation of algorithms, which can learn from and make predictions using multidisciplinary data. Recently, machine learning approaches have been successfully proposed to directly estimate stress distributions of dilated aorta [97], investigate relationships with shape features [98] and stratify patterns of aortic dilatation in BAV [99]. Our group recently patented a system and method combining multidisciplinary data (including computational simulations to determine WSS and IMS, demographic and clinical data, diagnostic imaging and biomarkers such as miRNAs) into a CDSS architecture that interacts with clinicians to undertake the risk estimation of aneurysm failure [100]. Towards on a holistic and personalized decision-making process, the CDSS is based on machine learning to take advantage of data routinely uploaded in the system to refine its predictive efficiency and capability. However, the amount of training data for the development of an efficient machine-learning algorithm is considerable and furtherly complicated by confounding factors and sources of bias that are characteristics of BAV aortopathy. In our hospital institution, bioengineers collaboratively work with clinicians by routinely applying computational modeling on patients with BAV-associated aneurysms to provide additional information on disease progression. In spite of this synergy, it may be necessary to merge large amounts of adequately powered study populations from multicentric studies and different investigators' expertise to develop CDSS for the management of BAV aortopathy.

The application of CDSS for the treatment of bicuspid aortopathy can surely lead to patient-tailored indications but can also improve resource allocations and overall outcomes by refining surveillance imaging regimens, medical management and decisions regarding early intervention for a dilated aorta. However, such a CDSS tool will be likely inadequate to predict the risk in individuals presenting an acute dissection without concomitant aortic dilatation. In such acute events, the patient information and CT data are often limited or not available and cannot be therefore elaborated by a CDSS tool because the dissection is repaired in emergency surgery. Studies at Yale [101] have added another interesting dimension to our understanding of the timing of an aortic dissection. It seems that aortic dissection occurs in circadian and diurnal patterns, with a preponderance of instances in the winter months and in the early morning hours. The reasons behind these patterns are unknown, but these characteristics correlate with the season and time of day when blood pressure is known to be highest. They also found that an acute hypertensive event supervenes, usually emotional or exertional, was recall by many patients treated for aortic dissection. An increase of blood pressure can lead to extremely-high shear and wall stresses exceeding the tensile limit of the aortic wall and ultimately resulting in a catastrophic event.

These aspects let us envisioning on the utilization of wearable sensors for the remote monitoring of blood pressure for those individuals with family history of aortic dissection seen at initial screening as well as for BAV patients showing stable propagation of the aneurysmal ascending aorta during follow-up. Wearable health devices may play a key role in helping people to better monitor their health status during either an activity or for self-health tracking, providing clinicians with prompt alarming information to prevent acute events or for early diagnosis. Wearable devices are growing and promising technologies [102] that enables continuous monitoring of human vital signs during daily life. There is indeed an increasing interest in ambulatory blood pressure monitoring technologies, as blood pressure is a useful

indicator of cardiovascular diseases at large. New wearable technologies based on photoplethysmography are being developed nowadays [103-105], which are capable to measure accurately blood pressure and send measurements and alarms on personal smartphones. This approach can lead to improved therapeutic strategies for the treatment and management of stable BAV-associated aneurysms and individuals with family history of aortic dissection.

CHALLENGES AND LIMITATIONS

Although studies here reported demonstrated promising findings, the challenge is the development of relevant standard procedures and validation strategies of presented personalized strategies to manage bicuspid aortopathy. Indeed, a standardized method for calculating hemodynamic and structural parameters needs to be agreed upon to set reference values and enable predictions on disease progression and management. Validation commonly involves comparison with either values measured within an *in-vitro* phantom or acquired during *in-vivo* evaluation. Moreover, diagnostic software is regulated by CE marking and FDA directives, respectively; but there are no standards governing accuracy, reliability or validation of computational modeling approach. Large volumes of clinical data are needed for model development and validation in order to expedite clinical translation. Finally, the next generation of physicians will require training for *in-silico* approaches to understand their principles and limitations for an ideal implementation in the clinical practice.

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Figure Legends

Figure 1: Recommendations for aortic surgery in patients with BAV aortopathy. Different criteria are used if the patient is undergoing surgery for aortic valve disease (red) or there are no surgical indications for the aortic valve (blue); with permission from Hardikar et al [4]

Figure 2: Flow jet in a morphological normal tricuspid aortic valve (top row) versus that shown by a BAV (bottom row); plots on the left and sketches in the middle show the flow displacement which is the distance between the vessel centerline node and the forwards velocity-weighted center of mass position. The flow displacement is a parameter that quantifies the flow eccentricity in the ascending aorta. Computational modeling allows to evaluate the velocity field (contour map on the right) to show an elliptical flow velocity for BAV as compared to circular flow field shown by a normal aortic valve; figure adapted from Mahadevia et al. [29] and Vergara et al. [32]

Figure 3: Cohort-specific WSS (unit is N/mm^2) atlases of (a) healthy controls with tricuspid valves, (b) BAV patients, (c) BAV patients with aortic dilation, (d) patients with BAV stenosis. The insets show the p-value maps on the shared geometry of the BAV vs. controls (b), BAV with dilation vs. controls (c) and BAV stenosis vs. controls (d) comparison; the “heat” map shows the area where WSS magnitudes are high (red color) and low (blue color); this WSS atlases demonstrate the ability to regionally detect that all BAV patients exhibit significantly elevated WSS compared to healthy volunteers with TAV; with permission from Pim van Ooij et al. [59]

Figure 4: Biomechanical stress analysis of a dissected aorta; (A) clinically observed dissection origins were plotted on the aortic models and were subsequently contrasted against (B) intramural stress map along the longitudinal direction of the vessel; (C) dissection patients were found to have increased peak longitudinal stress compared with control patients (ie, non-dissected); (D) there was no significant difference in peak circumferential stress between the dissected and control cohorts; with permission from Emrel et al. [67]

Table 1: Parameters and definitions of hemodynamic and biomechanical variables

Parameter	Formula	Description
Helical flow index	$HFI = \frac{1}{N_j}\sum_{i}^{N_j}\psi_i$	Quantify helical and global organization of blood flow. Ψ provides local values of the cosine of the angle between velocity and vorticity vectors. (ψ= 0: steady Poiseuille flow; ψ= 1: purely helical flow)
WSS [N/m^2]	$WSS = \mu \left.\frac{\partial u}{\partial y}\right\|_{y=0}$	Force per unit of area exerted by a moving fluid in the direction of the local tangent on the tubular surface
OSI	$OSI_i = \frac{1}{2}\left(1 - \frac{\left\|\int_0^T \tau_i\, dt\right\|}{\int_0^T \|\tau_i\|\, dt}\right)$	Characterizes the oscillatory nature of the WSS signal (OSI=0: Purely unidirectional WSS; OSI=0.5: purely oscillatory bidirectional WSS)
Angular dispersion index	$D_\alpha = [\overline{cos^2}\alpha + \overline{sin^2}\alpha\,]^{1/2}$	Measure the uniformity of the angular distribution of the WSS (D_α=0: equi-angular spaced WSS; D_α=1: WSS concentration in a single direction)

Figure 1

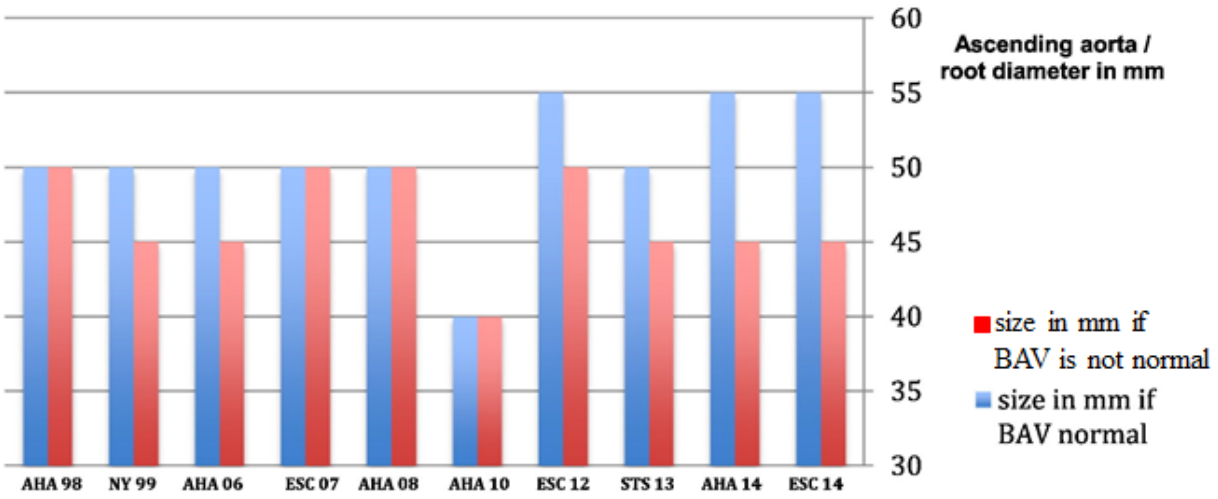

60
55
50
45
40
35
30
Ascending aorta / root diameter in mm
AHA 98
NY 99
AHA 06
ESC 07
AHA 08
AHA 10
ESC 12
STS 13
AHA 14
ESC 14
size in mm if BAV is not normal
size in mm if BAV normal

Figure 2

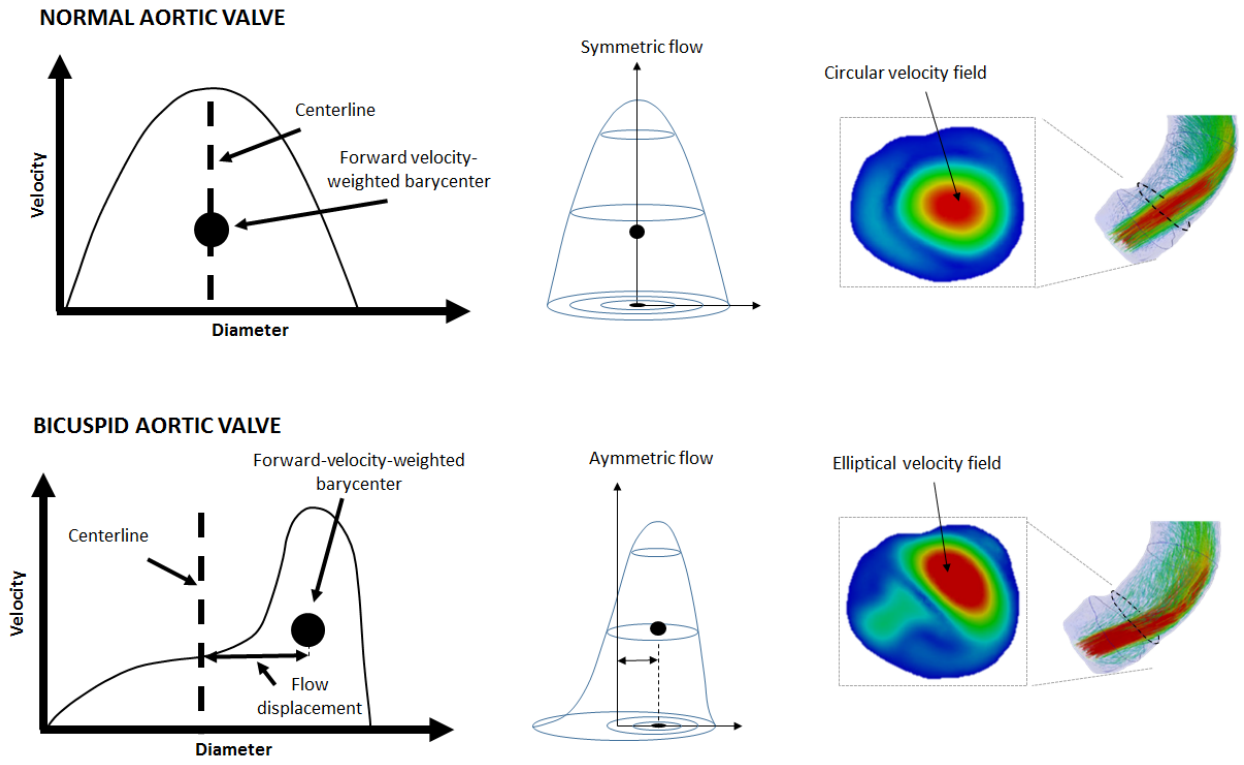

NORMAL AORTIC VALVE
Velocity
Centerline
Forward velocity-weighted barycenter
Diameter
Symmetric flow
Circular velocity field
BICUSPID AORTIC VALVE
Forward-velocity-weighted barycenter
Centerline
Velocity
Flow displacement
Diameter
Aymmetric flow
Elliptical velocity field

Figure 3

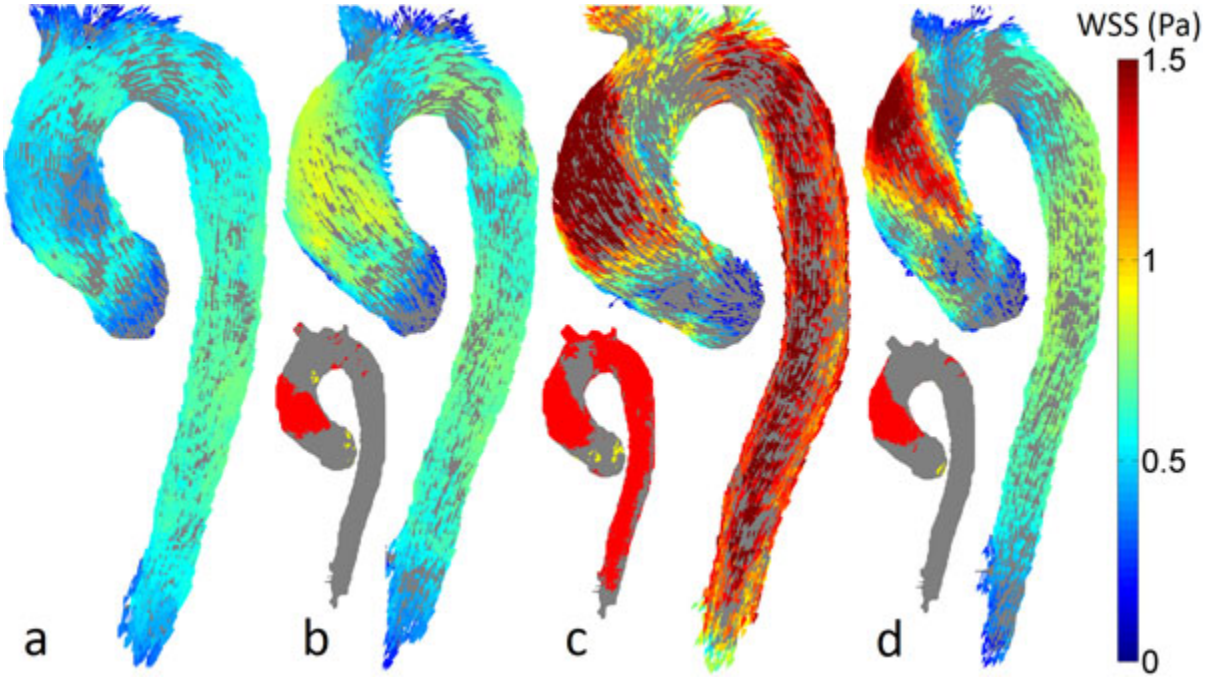
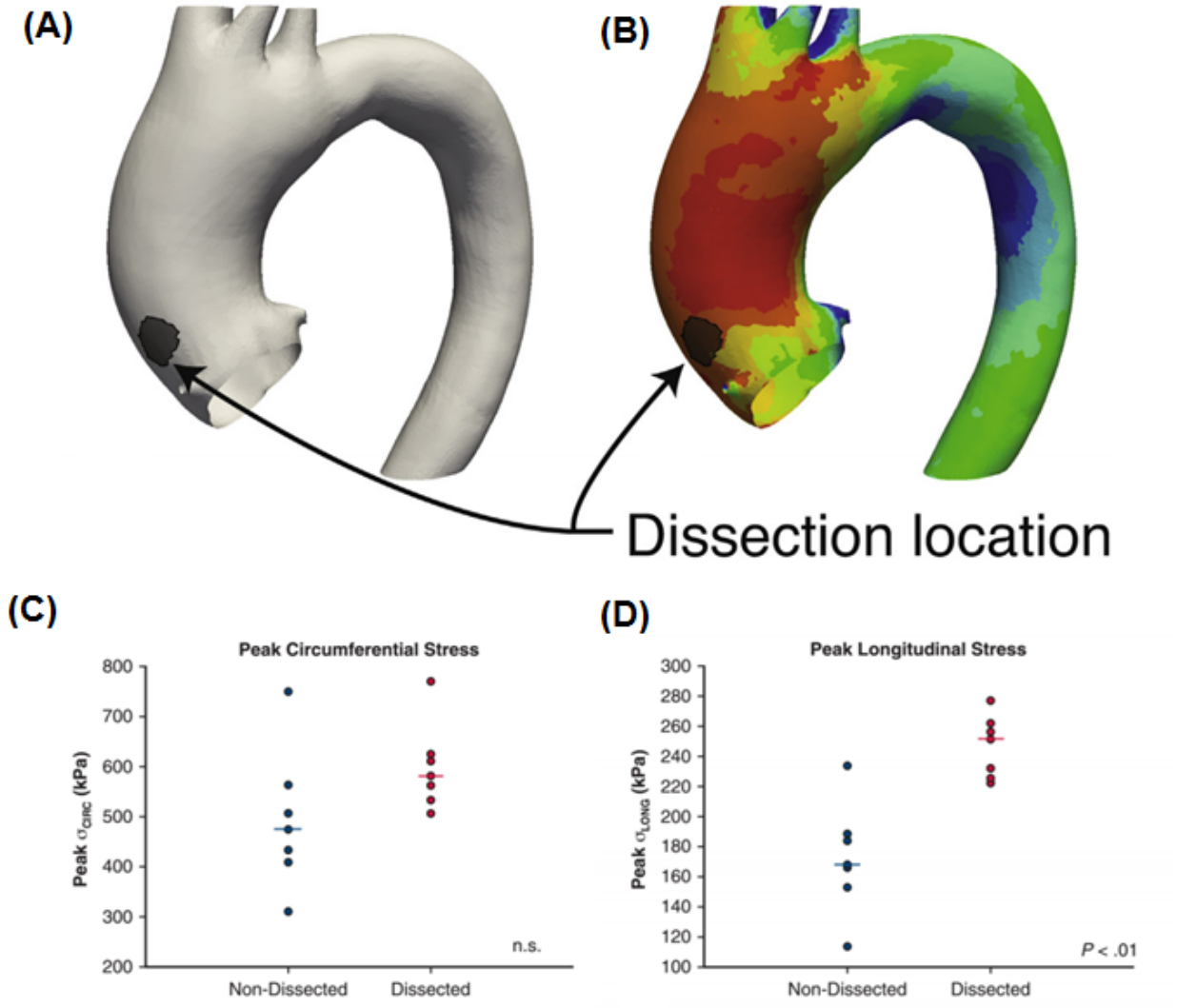


Figure 4


(A)
(B)
Dissection location
(C)
Peak Circumferential Stress
Peak σ_{CIRC} (kPa)
800
700
600
500
400
300
200
n.s.
Non-Dissected
Dissected
(D)
Peak Longitudinal Stress
Peak σ_{LONG} (kPa)
300
280
260
240
220
200
180
160
140
120
100
P < .01
Non-Dissected
Dissected