JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.
VOL. 66, NO. 8, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.06.1310

Valve-Related Hemodynamics Mediate Human Bicuspid Aortopathy

Insights From Wall Shear Stress Mapping

David G. Guzzardi, BSc,* Alex J. Barker, PhD,† Pim van Ooij, PhD,†‡ S. Chris Malaisrie, MD,§ Jyothy J. Puthumana, MD,‖ Darrell D. Belke, PhD,* Holly E.M. Mewhort, MD,* Daniyil A. Svystonyuk, BSc,* Sean Kang, BSc,* Subodh Verma, MD, PhD,¶ Jeremy Collins, MD,† James Carr, MD,† Robert O. Bonow, MD,‖ Michael Markl, PhD,†# James D. Thomas, MD,‖ Patrick M. McCarthy, MD,§# Paul W.M. Fedak, MD, PhD*§

ABSTRACT

BACKGROUND Suspected genetic causes for extracellular matrix (ECM) dysregulation in the ascending aorta in patients with bicuspid aortic valves (BAV) have influenced strategies and thresholds for surgical resection of BAV aortopathy. Using 4-dimensional (4D) flow cardiac magnetic resonance imaging (CMR), we have documented increased regional wall shear stress (WSS) in the ascending aorta of BAV patients.

OBJECTIVES This study assessed the relationship between WSS and regional aortic tissue remodeling in BAV patients to determine the influence of regional WSS on the expression of ECM dysregulation.

METHODS BAV patients (n = 20) undergoing ascending aortic resection underwent pre-operative 4D flow CMR to regionally map WSS. Paired aortic wall samples (i.e., within-patient samples obtained from regions of elevated and normal WSS) were collected and compared for medial elastin degeneration by histology and ECM regulation by protein expression.

RESULTS Regions of increased WSS showed greater medial elastin degradation compared to adjacent areas with normal WSS: decreased total elastin ($p = 0.01$) with thinner fibers ($p = 0.00007$) that were farther apart ($p = 0.001$). Multiplex protein analyses of ECM regulatory molecules revealed an increase in transforming growth factor β-1 ($p = 0.04$), matrix metalloproteinase (MMP)-1 ($p = 0.03$), MMP-2 ($p = 0.06$), MMP-3 ($p = 0.02$), and tissue inhibitor of metalloproteinase-1 ($p = 0.04$) in elevated WSS regions, indicating ECM dysregulation in regions of high WSS.

CONCLUSIONS Regions of increased WSS correspond with ECM dysregulation and elastic fiber degeneration in the ascending aorta of BAV patients, implicating valve-related hemodynamics as a contributing factor in the development of aortopathy. Further study to validate the use of 4D flow CMR as a noninvasive biomarker of disease progression and its ability to individualize resection strategies is warranted. (J Am Coll Cardiol 2015;66:892–900) © 2015 by the American College of Cardiology Foundation.

From the *Department of Cardiac Sciences, Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Canada; †Department of Radiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; ‡Department of Radiology, Academic Medical Center, Amsterdam, the Netherlands; §Division of Cardiac Surgery, Department of Surgery, Bluhm Cardiovascular Institute, Northwestern University, Chicago, Illinois; ‖Division of Cardiology, Department of Medicine, Bluhm Cardiovascular Institute, Northwestern University, Chicago, Illinois; ¶Division of Cardiac Surgery, Li Ka Shing Knowledge Institute of St. Michael's Hospital, University of Toronto, Toronto, Canada; and the #Department of Biomedical Engineering, McCormick School of Engineering, Northwestern University, Chicago, Illinois. Funded by Melman Bicuspid Aortic Valve Program, Bluhm Cardiovascular Institute (Dr. Fedak), American Heart Association grant 14POST20460151 (Dr. van Ooij), National Institutes of Health (NIH) grant K25HL119608 (Dr. Barker), and NIH grant R01HL115828 (Dr. Markl). Dr. Carr has a research agreement with Siemens. Dr. Thomas is a consultant for Abbott; and has received honoraria from Edwards Lifesciences, GE, and Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Manuscript received April 16, 2015; revised manuscript received June 8, 2015, accepted June 12, 2015.

Bicuspid aortic valves (BAVs) are associated with an increased predisposition towards dilation of the ascending aorta that could increase the rates of aortic complications such as aortic dissection, rupture, and/or sudden death (1,2). Although several dilation patterns have been proposed (2), considerable debate remains as to whether they are due to an inherent aortic wall defect (i.e., genetic aortopathy) or are secondary to valve-related changes in regional hemodynamics and shear stress

SEE PAGE 901

(i.e., acquired etiology). A genetic etiology for BAV aortopathy is widely accepted and may prompt aggressive resection strategies to remove diseased tissues at risk of future complications (3,4). Increasingly, valve-related hemodynamics are believed to contribute to disease progression (5). Greater understanding of the pathophysiology of BAV aortopathy may facilitate improved surgical resection strategies, development of best practices and effective clinical guidelines, and in so doing, optimize clinical outcomes (6).

Flow-sensitive cardiac magnetic resonance imaging (CMR) with full volumetric coverage of the ascending aorta (4-dimensional [4D] flow CMR) can measure and visualize complex aortic 3-dimensional (3D) blood flow patterns, such as flow jets, vortices, and helical flow. Using 4D flow CMR, we previously observed that normally functioning BAVs are associated with disturbed flow patterns in the ascending aorta, with regional increases in wall shear stress (WSS) (7), a parameter known to be associated with vessel wall remodeling (8). We further established that the location of BAV cusp fusion is associated with different patterns of ascending aorta dilation (9). Recent studies have provided significant associative evidence that the pattern of cusp fusion corresponds with the expression of aortopathy (10,11), thus aligning with previous imaging findings implicating altered outflow patterns and the regional expression of elevated WSS with BAV morphology. To further investigate these findings, in this study, we measured aortic WSS by 4D flow CMR in healthy normal volunteers and BAV patients to detect non-physiological values, and for the first time, correlated valve-related changes in WSS to regional tissue architecture and remodeling in paired BAV aortic wall tissue samples.

METHODS

With internal review board approval and informed consent, 20 BAV patients referred for ascending aortic surgery were enrolled. Patients with previous ascending aortic surgery or evidence of other forms of connective tissue disease were excluded. Healthy age-matched controls (n = 10) with tricuspid aortic valves were enrolled to compute regionally resolved 95% confidence interval values for physiologically normal aortic WSS (12); these controls had no evidence of cardiovascular disease and did not undergo surgery. The degree of aortic stenosis was graded based on absolute systolic peak velocity by continuous-wave Doppler ultrasound (mild: 2 to 3 m/s; moderate/severe: ≥3 m/s), and aortic regurgitation was graded based on regurgitant fraction (mild: <30%; moderate/severe: ≥30%) (13).

Participants received pre-operative CMR at 1.5-T or 3-T (Magnetom Aera, Espree, Avanto, Skyra, Siemens Healthcare, Erlangen, Germany) to assess presence and significance of suspected BAV. 4D flow CMR provided complete volumetric coverage of the thoracic aorta for quantification of temporally resolved 3D blood flow velocities. Data were acquired during free breathing using respiratory and prospective electrocardiographic gating (14), with imaging parameters as described previously (12). Velocity encoding ranged from 150 to 400 cm/s based on the severity of valve stenosis. If the glomerular filtration rate was >30 ml/min, gadopentetate dimeglumine, gadofosveset trisodium, or gadobenate dimeglumine was administered intravenously, and the flip angle was set to 15°; otherwise, 7° was used. Patient-specific WSS heat maps of the BAV aorta were computed relative to a map of the population average for healthy age-matched controls as described in detail previously (12,15,16). WSS regions outside the healthy 95% confidence intervals were classified as abnormal. Intra-aortic regions of normal, depressed, and elevated WSS were mapped onto 3D visualizations of patient-specific aortas (**Figure 1**).

Aortic wall samples were collected as permitted by the extent of ascending aorta resection; surgeons were blinded to WSS heat maps. Samples were labeled according to pre-operative zonal designations relative to the position of the right pulmonary artery (zones 1, 2, and 3 correspond to regions proximal, adjacent, and distal to the right pulmonary artery, respectively) (**Figure 1**), and according to circumferential location (greater curvature, lesser curvature, anterior or posterior wall). Tissue samples were divided in 2 for histology and protein analysis, flash-frozen in optimal cutting temperature freezing compound (VWR International, Radnor, Pennsylvania)

ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional
4D = 4-dimensional
BAV = bicuspid aortic valve
CMR = cardiac magnetic resonance imaging
ECM = extracellular matrix
IQR = interquartile range
MMP = matrix metalloproteinase
TGF = transforming growth factor
TIMP = tissue inhibitor of matrix metalloproteinase
WSS = wall shear stress