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REPLY: Final Common Pathway of Aortic Dilation?:

Heterogeneity of Aortic Wall Property Causes the Aneurysmal Change

David G. Guzzardi, BSc, **Alex J. Barker, PhD**, **Michael Markl, PhD**, and **Paul W.M. Fedak, MD, PhD***

Libin Cardiovascular Institute of Alberta, Cumming School of Medicine, University of Calgary and Bluhm Cardiovascular Institute, Northwestern University, C880, 1403-29 Street NW, Calgary, Alberta T2N 2T9, Canada

We thank Dr. Murakami and colleagues for their letter regarding our recently published paper (1) in the *Journal* examining aortic tissue from patients with bicuspid aortic valves following pre-operative 4-dimensional (4D) flow cardiac magnetic resonance imaging. Compared with tissue from regions of normal wall shear stress (WSS), we documented tissue from regions of elevated WSS (in the same bicuspid aortas), exhibiting greater elastic fiber degeneration and content, as well as elevated transforming growth factor β-1 and matrix metalloproteinase concentrations.

Dr. Murakami and colleagues note that tissue from regions of elevated WSS did not always correspond to increased elastic fiber degeneration. This was limited to only 2 of 20 patients, and we observed statistical significance in our patient cohort, suggesting increased aortopathy in regions of elevated WSS. Nonetheless, larger studies are warranted to investigate other clinical characteristics such as patient comorbidities that may account for these differences in regional aortopathy expression. Without question, such work is vital to translate new diagnostic imaging tools such as 4D flow cardiac magnetic resonance imaging to clinical use.

Additionally, Dr. Murakami and colleagues comment that the hemodynamic WSS presented in our work may be representative of “longitudinal stresses” in the vessel wall and request additional details regarding “vertical stresses.” The terms “longitudinal and vertical stress” can be interpreted a number of ways, thus we infer their definitions are based off of the Raaz et al. (2) study referenced in their letter. If this interpretation is correct, we believe this comment is related to a common misunderstanding between 2 important, yet distinct concepts. That is, Raaz et al. (2) explored internal mechanical wall stresses within aortic wall tissue, whereas our study investigated flow-mediated WSS (i.e., the drag force acting on the aortic wall endothelial layer due to blood velocity gradients and viscosity). Wall stress directly quantifies mechanical forces and thus exposure of the aortic wall to potentially disruptive internal stresses. By contrast, WSS quantifies wall shear forces that mediate vascular remodeling through mechanotransduction (i.e., endothelial cells sensing WSS changes) (3). We chose this approach given the WSS alterations previously reported in the

* paul.fedak@gmail.com.

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bicuspid aorta (4), and the challenge to noninvasively obtain in vivo vessel wall thickness and constitutive wall properties (including anisotropic and heterogeneous stiffness properties) needed to compute the internal wall stresses.

In summary, we agree that hemodynamic alterations such as WSS are likely to contribute to the expression of bicuspid aortopathy. However, further study and distinction between other hemodynamic, biomechanical, genetic, and clinical characteristics are required.

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