Letter to the Editor

On the 'cusp' of clinical feasibility: aortic wall shear stress derived non-invasively with 4D flow MRI

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Respond to: Carelli MG, Seco M, Bannon PG, Grieve SM. Is wall shear stress ready to become a prime-time clinical tool?—measurement of post-surgical patterns in patients undergoing aortic valve and thoracic aortic replacement using 4-dimensional flow magnetic resonance imaging. J Thorac Dis 2019;11:S440-2.

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It is with great interest that we read the expert commentary by Carelli *et al.* regarding our recent study in their Editorial entitled "Is wall shear stress ready to become a prime-time clinical tool?—measurement of post-surgical patterns in patients undergoing aortic valve and thoracic aortic replacement using 4-dimensional flow magnetic resonance imaging" (1). We agree with the authors that basic wall shear stress (WSS) measurements are on the cusp of clinical feasibility. We also agree that additional technical developments remain to occur in order to enable more sophisticated, time-resolved WSS measurements—and we continue to work diligently to make these available to the wider community.

Our study used 4-dimensional flow magnetic resonance imaging (4D flow MRI) to quantify pre- and post-surgical aortic WSS in 33 patients with aortopathy, suggesting different outcomes depending on the performed intervention such as aortic root replacement with or without valve repair (2). As Carelli *et al.* mentions, "at-risk" tissue was identified using an atlas of normal WSS values (n=56 healthy control subjects) to identify patient regions that exhibited WSS values outside of the normal measured 95% confidence intervals. This approach is reasonable given that no large cohort data have been reported which establish pathologic WSS thresholds, or their relationship with long-term outcome. Of note, subsequent work by our group has provided further supporting evidence regarding the approach and found significant correlation between WSS magnitude as a continuous variable and medial elastin fiber thinning, as assessed using histopathology in 27 bicuspid aortic valve patients with aortopathy (3). Furthermore, the statistical power of the 'atlas' methodology continues to grow, especially now that larger 4D flow MRI databases on hundreds of age- and sex-matched patients are becoming available (4,5). However, we recognize that long-term outcome data are needed, something that we and the editorialists are diligently working towards. Given the challenge of data collection, and the relative rarity of aortic dissection, we encourage multi-site collaboration to further understand this crucial topic.

As also mentioned by Carelli *et al.*, there are limitations to our study, especially when considering subject numbers and our WSS quantification approach. For example, we chose not to focus on the measurement of low diastolic WSS values, which are particularly challenging to measure with 4D flow MRI due to the presence of noise and its impact on the ability to accurately measure low velocities. Additionally, time-resolved WSS (including derived WSS values such as oscillatory shear index) requires time-resolved segmentation of the aorta for each phase of the cardiac cycle, a time-consuming, manual, and potentially error prone process. Diastolic segmentation errors are

particularly challenging to mitigate, considering that blood-tissue contrast is markedly improved at systole due to inflow enhancement. The corollary of systolic inflow enhancement, is that diastolic flow suffers from poor blood pool and tissue contrast, a factor that will affect both WSS accuracy and repeatability (especially with gradient recalled echo MRI techniques). Ongoing efforts to increase the dynamic range of our measurements using dual-venc encoding, alternative pulse sequence approaches to improve blood/tissue contrast, as well as accelerated artificial intelligence-assisted analysis workflows should yield improvements in the future. The community as a whole, including: us and other research groups, MRI manufacturers, as well as third party software vendors are making significant progress to further reduce 4D flow MRI data acquisition and analysis time to foster larger, multi-center and multi-manufacturer studies.

With these ongoing developments, the increasing interest in 4D flow MRI to study aortopathy (6-8) provides a unique opportunity to build large prospective cohorts with longitudinal follow-up. It is also an opportunity to gather the sufficient evidence needed to show that this non-invasive technique can provide crucial information regarding the success of intervention on patient outcome, and, in the longer term, enable more personalized care. The ultimate goal has always been to make this complex technology robust, repeatable, and clinically feasible; we are on the cusp of this reality. We hope someday that these efforts will enable us to achieve the ultimate goal, that is, to limit unnecessarily aggressive procedures, minimize patient risk and optimize care.

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Footnote

Conflicts of Interest: Michael Markl: Research support: Siemens Healthineers; Research Grant: Cryolife Inc.; Consultant and Research Grant: Circle - Cardiovascular Imaging. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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