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EDITORIAL COMMENT

Beyond Aortic Diameter for the Management of Thoracic Aortic Aneurysm

Multidimensional Data for Multidisciplinary Discussion*

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In 1928, Maude Abbott described in her textbook of congenital heart disease (CHD) that "the presence of a bicuspid aortic valve (BAV) appears to indicate, at least in a portion of the cases in which it occurs, a tendency for spontaneous rapture". BAV is the first nonsyndromic CHD reported for aortic dissection and dilatation.[1] In the early 2000s, Niwa et al reported that progressive aortic root dilatation was relevant in adults late after repair of tetralogy of Fallot,[2] and those aortic medial abnormalities, cystic medial necrosis, are prevalent in a wide variety of CHD with dilated aortic root.[3] After that, aortic aneurysm and dissection resulting from progressive aortic dilatation have been investigated over the past decades in patients with adult congenital heart disease (ACHD) with different underlying cardiac abnormalities and hemodynamics, especially in BAV and syndromic aortic diseases.[4] This pathological concept is known as "aortopathy".

Despite the progress of research thoracic aortic aneurysm (TAA) is still a disease that often remains unnoticed until it ruptures, and type A aortic dissection is a disease with high mortality rates.[4] TAA affects younger individuals, including young children, and has a higher heritability. Approximately 20% to 25% of patients with TAA are estimated to have familial TAA, with up to 25% of the familial cases presenting aortopathy as part of Mendelian connective tissue disease.[5] The most infamous syndromic TAAs are those related to Marfan syndrome (MFS), Loeys-Dietz syndrome, and vascular Ehlers-Danlos syndrom.[6] The prognosis in syndromic TAAs is generally worse than in nonsyndromic cases. This difference is reflected in guideline recommendations for prophylactic aortic surgery at more conservative diameters than the usual 5.0 to 5.5 cm cutoff.[7]

Concerning aortic dissection, the leading risk factor for aortic dissection is the presence of an aortic dilation or aneurysm. Pathological predisposition to the aortic wall can be derived from hypertension, smoking, hypercholesterolemia, aging, valvular dysfunction, and genetic disorders, which interfere with stability.[8] This has particular relevance in patients with MFS, Loeys-Dietz syndrome, and other heritable aortic disorders planning pregnancy, as they may fail to catastrophic events during pregnancy.

Thus, aortic diameter and dimension as anatomical biomarkers, and genetic background are the most accessible risk factors and current guidelines also employ them to indicate surgery. Using aortic diameter and dimension as a surrogate marker has the advantage of a continuous variable and clinically relevant parameters of aortic disease risk. However, a study based on serial imaging studies suggests that an aortic diameter of 55 mm may be an incomplete predictor of aortic rupture.[9]

The reasons for this issue are genetic heterogeneity, regional differences in exposure to mechanical stress, and differences in the molecular and cellular consequences of a given genetic variant. In this

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context, extensive research on biomechanical properties such as shear stress is in progress. Although we cannot see the histological changes in situ before the surgery, some investigations about shear stress correlate with the phenotypic change of elastic fiber suggestive of aortopathy. Previous studies have shown that energy loss correlates with aortic wall shear stress,[10] reduced aortic compliance[11] and wall thinning by 4D magnetic resonance imaging.[12] Previous studies have also shown that energy loss is correlated with stiffness obtained by transesophageal echocardiography strain imaging.[13] They have also been shown to correlate with the collagen-elastin ratio.[14] Concerning pathological changes, previous studies showed the severity of medial degeneration in aortic tissue from people with aortic dilatation was highest in MFS, followed by BAV, while the other CHD groups had a moderate severity.[3] At the same time, dissection was most frequent in Marfan, followed by BAV and other CHD.[15] Therefore, the degree of medial degeneration may predict dissection quite accurately. However, these investigations have the limitation that they cannot directly derive in vivo histological findings or energy losses.

In this context, using deep learning models for ACHD is promising for better shared decision-making.[16] It is essential for those with pregnancy and aortic disease to determine whether to consider conception, appropriate timing for prophylactic aortic repair, and the mode of delivery. For patients with ACHD, the timing and modalities of therapeutic interventions are crucial. However, frequent computed tomography scans carry the risk of radiation exposure, and magnetic resonance imaging scans are also costly. Echo can be performed relatively cheaply and frequently, but as mentioned above, aortic diameter and dimension could be better indicators. Therefore, a machine learning (ML) approach to predict shear stress regarding TAA is a very timely study.

In this issue of *JACC: Advances*, Lauren et al[17] investigated a ML approach to predict aortic biomechanical function, which means an ex vivo measured biomechanical metric of energy loss from the information of a total of 147 patients who underwent elective aortic valve or aortic resection surgery for TAA and 11 healthy controls. Energy loss was significantly positively correlated with age ($r = 0.61$, $P < 0.001$) and ascending aortic (AscAo) diameter ($r = 0.51$, $P < 0.001$). Energy loss also increased above 55 mm compared with below 55 mm (34% ± 5% vs 30% ± 5%, $P < 0.001$).

In the predictive model from clinical data, the Gaussian process regression-based model demonstrated the best performance (mean squared error [MSE] = 8.69, $R^2 = 0.63$) compared to the other ML models, including linear regression, support vector machines, and random forest. For the Gaussian processes-based model, a total of 13 variables were selected, including age, AscAo diameter, AscAo diameter/body surface area (BSA), hypertension, BAV, female sex, BSA, dyslipidemia, sinus of Valsalva diameter, type 2 aneurysm, aortic stenosis, MFS, and heavy weightlifting. Interestingly, using linear regressions and the training data set, these models were found to be surprisingly poor for metrics including AscAo diameter (MSE = 17.5, $R^2 = 0.26$), AscAo diameter/BSA (MSE = 16.3, $R^2 = 0.32$), and AscAo surface area/height (MSE = 16.8, $R^2 = 0.29$).

The results of the Gaussian process regression-based model were further improved when the dataset with cardiac cycle pressure modulus, which means stiffness, was added (MSE = 8.60, $R^2 = 0.62$).

However, this approach also possesses some limitations. As the authors cited in their work, energy loss does not have rigid and direct evidence to relate to the complications of TAA. The limited number of cases also renders it difficult to study differences between BAV and tricuspid aortic valve and differences due to genetic background.

In summary, Lauren et al[16] demonstrated that: 1) age was strongly correlated with energy loss; and 2) acquired comorbidities such as hypertension and dyslipidemia were also strongly correlated with energy loss. These findings suggest the importance of multilayered assessment rather than just aortic diameter, which is applied to risk prediction in the current guidelines. These findings also suggest the future utility of ML-based risk assessment in ACHD patients potentially exposed to aortopathy. Given all these issues, the pathogenesis of aortopathy remains to be elucidated. There is a need for prospective studies to further evaluate the prognosis and genetic underpinnings of this heterogeneous disease, aortopathy, and biomechanical function of the aorta.

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