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DNA methylation in bicuspid aortic valve aortopathy: potential contribution of oscillatory flow to an epithelial-to-mesenchymal transition signature

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Background: Bicuspid aortic valve (BAV) occurs in 1-2% of the population, making it the most common congenital heart malformation. Compared with individuals having a normal tricuspid aortic valve (TAV), BAV patients are at increased risk of ascending aortic dilatation and dissection. Disturbed hemodynamics, characterized by high shear stress and flow reversal has been described in the BAV ascending aorta and suggested to aggravate aneurysm development in BAV individuals. Aberrant DNA methylation has been described in various human diseases, and we have previously shown that key enzymes of the methylation machinery are differentially expressed in the aorta of BAV and TAV patients. Lately, several studies have demonstrated the importance of hemodynamics in the regulation of DNA methylation.

Purpose: The purpose of the study was to combined global DNA methylation analysis with in vitro studies of flow-sensitive methylation to identify biological processes associated with BAV-aortopathy, and delineate the potential contribution of flow.

Methods: Biopsies from non-dilated and dilated ascending aortas and internal thoracic arteries were collected from BAV (n=21) and TAV (n=23) patients. DNA methylation was measured in aortic intima-media, as well as in EA.hy926 cells and BAV and TAV primary aortic ECs exposed to oscillatory (±12 dynes/cm²) or laminar (12 dynes/cm²) flow, using Illumina 450k array. Gene expression was determined by Affymetrix HTA.

Results: We show an epithelial-mesenchymal-transition (EMT) DNA methylation signature in the non-dilated BAV aorta, associated with an oscillatory flow profile. The flow-related DNA methylation in non-dilated BAV was specifically related to endocytosis, and the EMT-related methylation signature was more pronounced in dilated BAV aortas compared with TAV. The potential influence of perturbed flow was further verified in EA.hy926 cells and primary aortic ECs on both methylation and expression level.

Conclusion: Aberrant EMT in the aortic wall could contribute to increased aneurysm susceptibility of BAV patients, and may be due to exposure to disturbed hemodynamics. Perturbations during the spatiotemporally related embryonic development of ascending aorta and semilunar valves can however not be excluded.