Bicuspid aortic valve (BAV) is the most common congenital heart defect, occurring in 0.5–2.0% of the general population. A broad spectrum of complications associated with BAV has been described, including aortic valve stenosis (AS) and/or regurgitation, infective endocarditis, and ascending aortic complications, called bicuspid aortopathy.

Although AS is the most common complications of BAV, dilatation of any or all segments of the ascending aorta from the aortic root to the aortic arch is also present in 20–80% of BAV patients (a variation that is mainly caused by differences in study population and aortic-size threshold). A recent paper demonstrated that progression of aortic dilatation in BAV patients is associated with genetic risk factors and altered hemodynamics.
Japanese BAV-AS patients was faster than that of tricuspid aortic valve-AS patients, even after AV replacement. On this basis, guidelines on aortic disease specifically address BAV and generally recommend early surgical intervention (depending on the diameter of the aorta) to the bicuspid aortopathy for prevention of sudden death from aortic dissection or rupture of aneurysm.

The previously reported pathophysiological and histological features of BAV-associated aortic dilatation are cystic medial necrosis, abnormal processing of the extracellular matrix protein fibrillin 1 by vascular smooth muscle cells (VSMCs), increase in the release of matrix metalloproteinases (MMPs), increased apoptosis of VSMCs, and abnormality in the medial layer probably because of the disrupted collagen and elastin (Figure). Many genes have been implicated in the etiology of BAV: NOTCH1 and GATA5 mutations, FBN1, TGFBRII/2, and ACTA2. However, a small proportion of bicuspid aortopathy patients carry such mutations, so it appears to be a polygenic disease and further genetic research is needed to clarify the contribution of genetic factors. Despite the controversy regarding aortic dilatation representing a genetic disease and further genetic research is needed to clarify the contribution of genetic factors. Despite the controversy regarding aortic dilatation representing a genetic preposition vs. being the result of abnormal hemodynamics, there is enough evidence to consider both as culprits in the origin of aortic dilatation in BAV.

In this issue of this Journal, Hirata et al. examine the transcriptome and immunohistochemical analyses of surgically removed ascending aortic specimens from AS patients with and without BAV. They demonstrate the changes in receptor tyrosine kinase (RTK) pathway-related genes in the ascending aorta between BAV-AS patients and tricuspid aortic valve-AS patients. Some of the receptors, ligands, or signal modulators were either induced or suppressed in the BAV aortic samples, though the detailed functional mechanisms were not clarified. Further, immunohistochemical study revealed the increasing phosphorylation of protein kinase B (AKT) in the medial VSMCs of BAV-AS patients, regardless of the size of the ascending aorta. The PI3K/AKT signaling pathway has been shown to play critical roles in cell function (proliferation, cell survival, migration, protein synthesis, and metabolism) in many cells, including VSMCs. Mechanical stretch was shown to increase MMP-2 production in VSMCs via activation of the AKT signaling pathway. Activation of the PI3K/AKT signaling pathway was shown to inhibit VSMC apoptosis. It remains to be clarified whether the finding of activation of the AKT in BAV patients might be the cause of the dilatation (e.g., increase in MMP-2) or compensation (e.g., inhibition of apoptosis) of the fragile VSMCs. Molecular, cellular and hemodynamic mechanisms of BAV-associated aortic dilatation are shown in the Figure, using the authors’ imagination based on previous papers and the present study. Although this study had several limitations (small number of patients, unable to specify the factors that affect AKT phosphorylation, unable to detect functional or phenotypic changes in VSMCs), it indicates for the first time the significant changes in RTK/AKT activation in bicuspid aortopathy. This research result is an important step and offers a key to understanding the mechanisms of BAV-associated aortic dilatation. Further research is required to clarify the mechanisms and apply this notion to the development of diagnostic or therapeutic tools for bicuspid aortopathy.

In summary, bicuspid aortopathy is a multifaceted heterogeneous disease with at least genetic and hemodynamic factors contributing (Figure). Although the usefulness of medical treatment for preventing bicuspid aortopathy (aortic aneurysm formation in BAV) is controversial, more vigorous basic and clinical research attempts like this can lead to the discovery of novel therapeutic interventions and optimum treatments.

Conflict of Interest
None declared.

References