Korean Circ J. 2026 Jan;56(1):97-99
https://doi.org/10.4070/kcj.2025.0325
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Editorial

Proteomic Dissection of Aortic Stenosis: Distinct VIC Signatures and the Role of Aging in Valve Remodeling

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▸ See the article "Characterization of Proteome Features in Patients With Aortic Stenosis Using Data-Independent Acquisition-Based Proteomic Analysis" in volume 56 on page 80.

Received: Jul 28, 2025
Revised: Aug 5, 2025
Accepted: Aug 6, 2025
Published online: Aug 28, 2025

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Funding
The author received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest
The author has no financial conflicts of interest.

Aortic stenosis (AS), the most prevalent valvular heart disease in aging populations, presents a pressing clinical challenge due to its progressive and often asymptomatic course. Despite advances in transcatheter aortic valve replacement and surgical techniques, no medical therapies exist to alter the natural history of AS. This reflects our limited understanding of its underlying molecular mechanisms, particularly the cellular and subtype-specific drivers of AS. Of particular interest is the dichotomy between patients with tricuspid aortic valves (TAVs) and those with congenital bicuspid aortic valves (BAVs), the latter often displaying earlier and more aggressive calcification.[1] Molecular stratification of AS patients based on their valve morphology and proteomic landscape could therefore inform novel strategies for early diagnosis and intervention.

In this issue of the *Korean Circulation Journal*, Lee et al.[2] present an in-depth proteomic analysis of valve interstitial cells (VICs) derived from patients with AS and morphologically normal aortic valve from recipient's heart. By applying data-independent acquisition-based proteome analysis, they profile protein expression in VICs isolated from TAV-AS, BAV-AS, and control valves. Their findings delineate shared and subtype-specific differentially expressed proteins (DEPs), providing mechanistic insights into AS pathogenesis and suggesting potential molecular targets.

The strength of this study lies in its methodological rigor and cell-type specificity. By isolating VICs—rather than analyzing whole valve tissue—the authors focus on the principal effector cells in valve remodeling. Moreover, construction of a customized spectral library from fractionated peptides ensures high-resolution detection of proteins, minimizing batch effects and maximizing quantification depth. The use of matched normal TAV samples from transplant patients adds further strength by enabling subtype comparisons that are internally controlled.

Among the 39 DEPs identified, several protein groups stand out. Structural proteins such as keratins (KRT7, KRT18), COL5A1, and SYNPO were upregulated in AS VICs, reflecting cytoskeletal remodeling and possible myofibroblast transformation. Notably, transcriptional regulators like DNA methyltransferase 1 (DNMT1) and oxidative stress markers such as superoxide dismutase 2 (SOD2) and sulfide:quinone oxidoreductase (SQOR) were also differentially expressed. These observations align with prior studies highlighting the role of

Data Sharing Statement

The data generated in this study is available from the corresponding author upon reasonable request.

The contents of the report are the author's own views and do not necessarily reflect the views of the *Korean Circulation Journal*.

epigenetic modulation, oxidative stress, and mitochondrial dysfunction in AS.[3-5] The authors validated the expression of key candidates including DNMT1, secreted protein, acidic, and rich in cysteine (SPARC), and prothymosin alpha (PTMA) through immunohistochemistry, strengthening the translational relevance of the proteomic findings.

Importantly, the comparative analysis between BAV-AS and TAV-AS VICs revealed subtype-specific proteomic signatures. SPARC and PTMA were preferentially upregulated in BAV-AS, suggesting more pronounced matrix remodeling and calcific potential in these patients. Conversely, KRT family proteins and oxidoreductase-related molecules were predominantly altered in TAV-AS. These differences support the hypothesis that BAV and TAV-AS are not merely a phenotypic variant but a biologically distinct entity. Identifying such distinctions could pave the way for molecular phenotyping of AS and tailored therapeutic approaches.

Beyond structural remodeling, this study also touches on metabolism and mitochondrial function in VICs. The downregulation of SOD2 and SQOR—both critical to reactive oxygen species (ROS) detoxification and mitochondrial redox balance—underscores the vulnerability of mitochondrial homeostasis in AS progression. Prior research has shown that impairment of these enzymes in VICs accelerates osteogenic transdifferentiation and extracellular matrix (ECM) calcification.[4] Thus, targeting mitochondrial stress responses may offer novel avenues for delaying disease progression.

Interestingly, several proteins identified in this study have also been implicated in aging-related cardiovascular remodeling. Some of these proteomic changes may reflect overlapping mechanisms of both AS pathology and physiological aging, although disentangling these processes remains challenging. For instance, SOD2 and SQOR are consistently downregulated in aged tissues, contributing to ROS accumulation, impaired oxidative phosphorylation, and eventual cellular senescence.[6] Likewise, SPARC, a matricellular protein involved in collagen binding and matrix regulation, is known to increase with age, promoting ECM stiffening and fibrosis. These findings suggest that some of the proteomic alterations observed in AS VICs may reflect not only disease-specific mechanisms but also age-associated degenerative remodeling. Given that AS primarily affects elderly individuals, the overlap between aging and disease pathophysiology highlights the importance of studying shared pathways. Future investigations should clarify the causal relationship between senescence-driven metabolic dysregulation and fibrocalcific remodeling in VICs, and evaluate whether anti-aging strategies, such as senolytics or mitochondrial-targeted therapies, can be leveraged to delay or reverse AS progression.

Despite these promising findings, several challenges remain. First, the sample size, while reasonable for a proteomic study, limits generalizability. Only 10 patients were analyzed per AS group, and potential confounders such as statin use or comorbidities were not fully adjusted. Second, while protein-level changes were clearly demonstrated, the study did not integrate transcriptomic or functional readouts, which would be essential for confirming the causal role of DEPs. Third, the focus on VICs, while valuable, omits contributions from other key players in valvular pathology such as endothelial cells, immune cells, and fibroblasts. To gain a more comprehensive understanding of AS pathogenesis, future research should incorporate multi-omics datasets—including transcriptomics, epigenomics, and metabolomics—combined with single-cell and spatial profiling techniques. Such integrative approaches will enable dissection of cell-type specific contributions (e.g., from endothelial, immune, and stromal populations) and their interactions, ultimately facilitating systems-level insights into disease progression and heterogeneity.

https://doi.org/10.4070/kcj.2025.0325

Translationally, the study lays a foundation for biomarker discovery in AS. Proteins like SPARC, PTMA, and SQOR—if detectable in plasma or exosomes—may serve as non-invasive markers of disease subtype or progression. Additionally, therapeutic targeting of epigenetic regulators like DNMT1 or mitochondrial enzymes such as SQOR could offer new strategies beyond mechanical valve replacement. Indeed, early pharmacologic modulation of these targets may hold promise for halting or reversing the fibrocalcific cascade before irreversible damage occurs.

In conclusion, the study by Lee et al.[2] provides a valuable proteomic roadmap of VICs in AS, revealing shared and unique signatures across BAV and TAV subtypes. Their work reinforces the concept of AS as a heterogeneous disease and underscores the need for molecular classification to guide precision therapies. Given the overlap between aging and AS-related molecular changes, future strategies should also consider targeting senescence-related mechanisms as a novel approach for disease modification. As we move toward a future of personalized cardiovascular care, such high-resolution molecular profiling will be indispensable. Successful clinical translation of these findings will require validation in larger, diverse patient cohorts and development of standardized protocols for integrating proteomic biomarkers into diagnostic and risk stratification workflows.

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