Preventative medicine: The next revolution in the treatment of aortic stenosis

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Central Message

Insight into a molecular pathway involved in aortic valve calcification moves physicians a step closer to aortic stenosis prevention.

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Calcific aortic stenosis (AS) has been the most common indication for surgical valve replacement in the developed world for decades.¹ The pathophysiology of aortic valve (AV) calcification is driven by 3 interrelated mechanisms²: (1) classical cardiovascular risk factors,³ (2) genetic factors,⁴ and (3) valve cellular biology.⁵ Although AV calcification was long believed to be a passive process (“degenerative” valve disease), a growing body of literature has demonstrated that the progression of calcification on the AV is actively regulated.⁶

The natural progression of calcific AV disease was first described by Otto and colleagues.⁷ The initial stage of AV calcification, called *valve sclerosis*, is associated with focal leaflet thickening that leads to calcification without hemodynamic consequences.⁸ Eventually leaflet thickening and calcification obstruct the left ventricular outflow tract, causing hemodynamic changes and a resulting diagnosis of AS. Notably, aortic sclerosis is slow to progress to AS,⁹ which is the primary reason AS is typically considered a disease of the elderly. AS ultimately leads to heart failure, and the major predictor of mortality for this pathology is the onset of associated symptoms, left ventricular dysfunction, or both.¹⁰ Despite the rapid growth in our understanding of the etiology of AV calcification, no preventive strategy for AS is currently available.

Currently, there are an estimated 500,000 elderly people (age ≥ 75 years) with severe symptomatic AS living in the United States, a number that is expected to triple by 2050.¹¹ For many years, the only available therapy for calcific AS was surgical AV replacement (SAVR).¹² SAVR has been demonstrated to be effective in reducing symptoms and increasing survival,¹³ with low operative mortality in select patients.¹⁴ As many as 30% of patients with severe symptomatic AS, however, are not offered surgical intervention because of their high surgical risk as a result of advanced age, left ventricular dysfunction,

or problematic comorbidities.¹⁵ During the last decade, transcatheter AV replacement (TAVR) has become increasingly available for patients with severe AS who are not surgical candidates or are at believed to be at too-high risk to undergo SAVR.^{16,17} Despite the rightful enthusiasm surrounding the ascent of TAVR, however, a strategy to prevent the development of AS would be even more revolutionary.

In this issue of the *Journal*, Wang and colleagues¹⁸ present work that further elucidates the molecular signaling pathways regulating AV calcium deposition. Wang and colleagues¹⁸ hypothesized that high-mobility group box-1 protein (HMGB1), a molecule that has been implicated in the pathogenesis of vascular atherosclerosis and inflammatory changes,¹⁹ may also be involved in AV calcification. HMGB1 is a key agonist of Toll-like receptor 4 (TLR4),²⁰ which is known to stimulate osteoblastic differentiation of valvular interstitial cells.²¹ Pro-osteogenic differentiation of these cells is believed to promote calcium deposition on the AV, so Wang and colleagues¹⁸ attempted to delineate the relationship of HMGB1 and TLR4 with AV calcification.

Wang and colleagues¹⁸ collected calcified AV leaflets from 15 patients undergoing SAVR because of severe AS and “normal” AV leaflets from 10 patients undergoing a Bentall procedure for acute aortic dissection. First, through immunohistochemical staining of these samples, they found that both HMGB1 and TLR4 expressions were increased in the calcific AVs. Then, by conducting a series of experiments, Wang and colleagues¹⁸ were able to outline several

steps in a HMGB1/TLR4 pathway that ultimately promoted osteoblastic differentiation, inflammation, and calcification in cultured valvular interstitial cells. In their study, Wang and colleagues¹⁸ did not identify the source of the HMGB1 during the development of AV calcification, nor could they confirm that the pathway of interest is the sole mechanism through which HMGB1 affects this disease process. Nevertheless, their work indeed does implicate HMGB1 in the pathogenesis of calcific AV disease.

By furthering our understanding of the molecular pathways promoting the calcification of AV leaflets, Wang and colleagues¹⁸ have moved medicine a step closer to the next revolution in the treatment of AS—its prevention. Future work stemming from this report should attempt to gain additional insights into the molecular mechanisms of AV calcification. Eventually, these molecular pathways can be traced back to genetic factors that place certain patients at increased risk for the eventual development of AS. By identifying susceptible patients early and targeting the HMGB1/TLR4 pathway or some other pathway with preventative therapy, physicians could begin to eliminate the burden of AS altogether.

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