MAYO CLINIC

The Shifting Nature of Endothelial Progenitor Cells in Aortic Stenosis

See also page 652

Calcific aortic valve disease (CAVD) is the most prevalent form of heart valve disease in the developed world, with a projected increase in disease burden from 2.5 million individuals in 2000 to 4.5 million in 2030.[1] The disease process in CAVD causes the aortic leaflets to thicken and undergo progressive calcification and fibrosis, resulting in narrowing of the valves and the development of aortic stenosis (AS). The classical symptoms of hemodynamically significant AS (ie, heart failure, syncope, and angina) manifest once the valve narrowing has become severe and indicate a poor prognosis unless an intervention is performed. The most common intervention is still surgical aortic valve replacement (SAVR) with bioprosthetic or mechanical valves.[2] However, the indications for transcatheter aortic valve replacement (TAVR) have been expanding as a less invasive alternative to SAVR, especially in patients with excessive surgical risk.[2] Despite increasing efforts to identify treatment targets, medical therapies that prevent or reverse AS are still lacking.

Large population studies have identified several risk factors for CAVD; the most potent being age, bicuspid valves, male sex, and lipoprotein(a) levels, with more modest influences of hypertension, diabetes, tobacco use, and LDL cholesterol levels.[1, 2] Interestingly, several of the risk factors are common to CAVD and atherosclerosis, but the valvular process appears to be distinct in that cholesterol-lowering and anti-inflammatory agents do not slow the disease process in the same way as in the vasculature.[3]

The calcific process in the diseased valves is a regulated process that involves cells, matrix, and a number of signaling pathways related to osteogenesis.[1, 2] Based on their exposed position, the valve endothelial cells (VECs) are likely to be the first line of defense in responding to procalcific factors influencing the valves. The VECs communicate with the valve interstitial cells (VICs), which are responsible for remodeling and integrity of the extracellular matrix. The VICs assume various phenotypes such as osteoblastlike and myofibroblast phenotypes, which have been associated with calcium deposition and stiffness, respectively. The calcific process in CAVD may be triggered by endothelial dysfunction induced by the response to factors like direct injury, hyperglycemia, hypercholesterolemia, or hemodynamic forces. At later stages of CAVD, the endothelial cells can promote the calcific process through active neoangiogenesis with expression of VEGF and hypoxia inducible factors in stenotic valves.[4] It may also provide insufficient protection due to reduced regenerative capacity and early senescence.[5]

Circulating endothelial progenitor cells (EPCs) were initially described as a population of cells positive for CD34 and the vascular endothelial growth factor 2 (VEGFR2 or KDR) with vascular regenerative capacity.[6] The EPCs were soon considered part of the cardiovascular system, and are noted for their capacity for vascular regeneration and as potential therapies for tissue ischemia.[6] It could therefore be postulated that circulating EPCs with beneficial characteristics might limit CAVD by restoring the valve endothelium. However, an opposing "dark side" of the EPCs could also be postulated, where the EPCs have turned injurious somewhere between release and differentiation in the valves. Indeed, in the current study, Al Hijji et al[7] found that the levels of total EPCs with regular phenotype were reduced in severe AS, but were parallelled by a higher release of EPCs with osteoblastic phenotype. Such osteoblastic EPCs are positive for expression of

CD133 and osteocalcin (OCN), are referred to as EPC-OCN, and are believed to represent an early bone marrow-derived lineage. As the cells mature in the circulation, the expression of CD133 expression disappears while expression of CD34 or KDR appears as a sign of maturity.

Al Hijji et al[7] also extended their study and examined the association between the number of EPC-OCN and echocardiographic parameters. They collected samples from 178 individuals with mild, moderate, or severe aortic stenosis, as determined by echocardiography and analyzed the peripheral blood mononuclear cells for the presence of OCN-positive EPCs. The results revealed that severe AS was associated with an approximate 4-fold increase in the number of total circulating EPC-OCN compared with mild AS, both with and without CD133 expression. A similar association was found between severe and moderate AS but only for the CD133+ EPCs. In addition, there were significant associations between total circulating EPC-OCN and aortic valve (AV) calcification, AV mean gradient, and AV area. The investigators also confirmed the presence of the biomarkers OCN, CD34, KDR, and CD133 in the resected stenotic aortic valves using immunofluorescence.

These interesting results indicate a role for EPC-OCN in the progression of CAVD. Indeed, the EPC-OCN may represent the postulated "shady" side of the EPC-spectrum, and may reflect a shift towards distorted EPC phenotypes that promote rather than prevent calcific disease. Further characterization of the EPC-OCN and similar phenotypes will undoubtedly increase our understanding of the cellular mechanisms driving AS, and potentially be developed as markers of impaired valvular regeneration. This may also have a predictive value.

Important aspects of the capacities of the EPCs are likely to stem from what the cells encounter in the circulation and the cellular milieu of the valves. The local environment of already diseased valves may drive differentiation of the EPCs towards inflammatory phenotypes with less adhesion and endothelial coverage, but with increased senescence and osteogenesis. For example, diabetes is known to affect both the bone marrow and circulating stem cell progenitors, and to induce endothelial inflammation in the vasculature.[8, 9] Thus, the treatment of valve disease would have to target not only the valves but all involved areas where the EPCs circulate. Another intriguing possibility is the potential communication between the bone marrow and the valves. As stated above, at later stages of AS, there is a reduction in the release of healthy EPCs but an increase of osteoblastic EPCs. This could reflect a breakdown in the communication between the bone marrow and the valves. In the end, CAVD may be better understood as a part of a systemic condition, with involvement of at least the bone marrow, circulation, and valves, reflected in the behavior of the EPCs.

The findings of Al Hijji et al[7] raise a number of interesting questions that ultimately need to be resolved. For example, what determines the OCN+ phenotype in EPCs and what triggers the release of EPC-OCN in severe AS? How do the EPC-OCN behave in the diseased valves? Is there a communication between the bone marrow and the aortic valves, and what makes EPC-OCN home to the valves as opposed to other locations? These and other questions will require further mechanistic studies.

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Grant Support: This work was supported in part by the National Institutes of Health/National Heart, Lung, and Blood Institute (HL30568 and HL81397).

Potential Competing Interests: The author reports no competing interests.

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