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EDITORIAL COMMENT

Anemia, Increased Shear Stress, and the Progression of Aortic Stenosis*

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Calcific aortic stenosis is increasingly prevalent and found at echocardiography in up to 2% of asymptomatic subjects older than 65 years of age.[1] The rate at which aortic stenosis progresses in severity over time is highly variable and difficult to predict. Despite great interest in disease prevention, medical interventions such as statin therapy and bisphosphonates have not been shown to modify disease progression as compared with untreated controls. Thus, our current approach to manage asymptomatic patients with aortic stenosis uses close medical follow-up for the development of symptoms coupled with serial echocardiography at selected intervals to quantify aortic valve area and aortic outflow pressure gradients to identify the rate of change of aortic valve area as an index of the individual rate of progression of disease.

Anemia is common in patients with aortic stenosis, and it increases in severity as a function of age. A hemoglobin level of <10.9 g/dL is found in almost 40% of subjects with severe aortic stenosis.[2] Anemia negatively impacts aortic stenosis in a variety of ways. First, it contributes to symptoms of myocardial ischemia due to reduced oxygen-carrying capacity, which can arise from pressure overload and left ventricular hypertrophy in the setting of normal coronary arteries.[3] Second, it accentuates the pressure gradient associated with any aortic valve area because a higher cardiac output is required to meet systemic oxygen delivery at rest as well as increases during exercise. In addition to these physiological effects, anemia also increases the local shear stress on the stenotic aortic valve itself, which, as discussed later in this article, activates a number of shear-dependent molecular pathways.

The most widely studied consequence of increased aortic valve shear stress is the development of an acquired form of von Willebrand Disease (VWD), which mimics congenital VWD in many aspects. In this regard, congenital VWD is a family of disorders that arise from mutations to the large multimeric blood glycoprotein von Willebrand factor (VWF), whose function is highly regulated by hydrodynamic shear stress.[4] In a VWD variant, called VWD Type 2A, there is decreased affinity of the VWF protein for the platelet receptor GpIbα, often due to exacerbated proteolysis of the VWF-A2 domain by a blood metalloprotease called ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13). ADAMTS13 activity on VWF is highly shear-dependent and augmented when VWF binds to vascular endothelial cells as well as after shear-driven VWF self-association. These processes reduce the multimer distribution of VWF and impair hemostasis leading to enhanced mucocutaneous bleeding. This is commonly in the gastrointestinal (GI) tract and is frequently a consequence of angiodysplasia in the intestines of patients with VWD. Acquired von Willebrand disease (AVWD) exhibits a bleeding phenotype similar to congenital VWD except that high shear forces are the primary drivers of the loss of VWF function and GI angiodysplasia. This commonly occurs with severe aortic stenosis, and also on implantation of prosthetic devices that result in abnormally high flow, like left ventricular assist devices. The importance of shear stress and AVWD in patients with aortic stenosis is confirmed by subjects undergoing surgical or transcatheter aortic valve replacement

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who rapidly restore their preoperative loss of high-molecular mass VWF with normalization of the bleeding tendency. In the absence of intervention, increasing levels of aortic valve shear stress can lead to a vicious cycle of progressively impaired coagulation, GI blood loss, and more severe anemia.

In this issue of *JACC: Basic to Translational Science*, Subramani et al[5] provide important new insight into an additional mechanism through which elevated shear stress may accelerate the anatomical progression of aortic stenosis. Previous work by this group demonstrated that the transformation of the secreted, latent form of transforming growth factor (TGF)-β1 into its active form is shear-dependent, with a Cys33Ser mutation in murine latency-associated peptide preventing its activation.[6] In the present study, the authors employed a translational approach using both clinical observations in patients along with a murine model of aortic stenosis to examine the relationship between TGF-β1 and progression of aortic valve disease. They observed that elderly aortic stenosis patients had higher TGF-β1 levels (1.74 ng/mL) compared with controls (1.4 ng/mL). This was inversely related to hemoglobin levels in aortic stenosis patients that were older than 75 years of age. They went on to study this relationship in the LA100 mouse, which spontaneously develops aortic stenosis with aging. The development of aortic stenosis in these mice was associated with higher levels of TGF-β1 (4.4 ng/mL vs 2.5 ng/mL) along with a reduction in hemoglobin levels, much like elderly humans with aortic stenosis. Interestingly, the induction of more severe anemia in mice with aortic stenosis, using a low-iron diet and high-volume phlebotomy, resulted in further elevation in TGF-β1 levels, a loss of high-molecular mass VWF consistent with AVWD and a more rapid progression in the severity of aortic stenosis. This was quantified using anatomical cardiac measurements available in the mouse such as reduced fractional valve opening from echocardiography and aortic valve thickness at pathology. Using similar methodology, they went on to show that the targeted inactivation of TGF-β1 in platelets attenuated the progression in aortic stenosis and as a result lowered shear stress despite a similar reduction in hemoglobin. Although one would predict that the less severe aortic stenosis would also improve the AVWD, VWF multimers were not assessed in these experiments. An additional limitation of the study is that while Doppler velocities were used to calculate aortic shear stress, in vivo Doppler-derived hemodynamic parameters like those used to assess aortic stenosis clinically (or left ventricular hemodynamics at the end of the studies) were not systematically reported. Nevertheless, the limited data provided shows reasonable correlation for the direct valve area measurements and Doppler-derived area. These data raise the possibility that processes thought to be sequelae of aortic stenosis like AVWF and anemia from GI blood loss may also provide a positive feedback mechanism where the anemia from chronic blood loss also accelerates the progression of aortic stenosis through shear-dependent TGF-β1 release.

The results of this study suggest that the effects of anemia on aortic stenosis may extend well beyond simply increasing symptoms of myocardial ischemia. There are several translational implications and directions for future work. One is that assessing serial circulating levels of TGF-β1 and VWF multimers in asymptomatic patients may provide biomarkers to identify the progression of disease and need for earlier intervention strategies for individual patients. A corollary to this is that it may become feasible to use a molecular approach to prevent the progression of moderate aortic stenosis using pharmacologic interventions to block TGF-β1 for example. The second more intriguing possibility is that anemia may be a modifiable risk factor contributing to the variability in the rate of aortic stenosis progression. In conjunction with the known frequency of anemia in aortic stenosis and its deleterious impact on prognosis, the results suggest that it may be time to consider a clinical trial targeting anemia in asymptomatic patients to prevent the progression from moderate to severe aortic stenosis. Although speculative, implementing more aggressive therapeutic approaches to treat anemia could result in a straightforward approach to reduce shear stress and the frequency and severity of bleeding from AVWD as well as aortic stenosis progression from TGF-β1 release.

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