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Correlating Intramural Biochemistry and Elasticity in Patients With Ascending Aortic Aneurysms

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The natural history of an ascending thoracic aortic aneurysm is expansion resulting from hemodynamic factors acting in accordance to LaPlace's Law and progressive arterial wall weakening. An aneurysmal expansion to 6 cm is associated with a 14.1% per year risk of rupture, dissection or death [1]. However, the presence, and subsequent expansion, of the aneurysm rarely produces symptoms until catastrophic complications ensue. Once the complications are diagnosed, 24.8% of patients with a Stanford type A dissection die prior to hospital presentation, 14.5% die within 6 hours of hospital arrival, 28.9% within 24 hours, and 56.6% within 30 days [2]. Although current guidelines suggest surgical repair when the aortic diameter reaches 4.5-5.0 cm, aortic complications can occur at even smaller diameters [3]. Hence, early diagnosis of those aneurysms with a subsequent increased risk of a calamitous complication, regardless of diameter, would be of considerable clinical benefit.

Aortic distensibility is directly related to collagen and elastin content, and ascending aortic aneurysms are pathologically characterized by destruction of the extracellular matrix, specifically collagen and elastin. Atherosclerosis is rare. The balance between matrix metalloproteinases (MMPs), which play an important role in degradation of the extracellular matrix, cell proliferation and migration, and tissue inhibitors of metalloproteinases (TIMPs) has been implicated to play a major role in aneurysm formation given their role in connective tissue homeostasis.

As the aneurysmal aorta enlarges, mechanical properties deteriorate and aortic distensibility decreases. For example, distensibility in aneurysms <4 cm in diameter is 3.02 +/- 0.595/mmHg, decreasing to 1.45 +/- 0.38/mmHg in those >5 cm in diameter, while wall stress increases from 108.5 +/- 12.72 to 245 +/- 63.4 kPAa and stress/strain decreases from 0.908 +/- 0.16 to 3.56 +/-0.88 MPa as determined by peri-aortic echocardiography [4].

In this issue of *Cardiovascular Revascularization Medicine*, Khanafer et al. [5] describe preliminary studies designed to examine a potential relationship between elastic moduli of the ascending aortic wall and biological levels of MMPs and TIMPs obtained from patients undergoing surgical repair of ascending aortic aneurysms. The tested proteinases MMP-1 and MMP-8 are collagenases, MMP-3 is a stromelysin, while MMP-2 and MMP-9 are gelatinases. TIMP-1 and TIMP-2 inhibit all MMPs. Circumferential aneurysmal samples from the greater curvature were obtained, and mechanical tissue testing was evaluated using a tensile testing machine. The maximal elastic modulus, a quantity that measures an object's resistance to elastic deformation when a stress is applied to it, was ascertained from the maximum slope of the stress/strain curve. MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, and TIMP-1 and TIMP-2 were quantified densitometrically. Aortic tissue was obtained from 12 patients, although the MMP/TIMP assays were negative in 2 patients, resulting in 10 data points.

The results showed an inverse relationship between MMP-3, MMP-8, and MMP-9 and aortic wall elasticity; an association between MMP-2 levels and elasticity; and no association between MMP-1 and elastic modulus. An association between MMP-9 and TIMP-1 was also observed. The inverse relationship between MMP-9 and aortic wall elasticity, albeit weak, is of interest in that MMP-9, in concert with MMP-2, has been shown in a mouse model to play a role in the aneurysm development [6]. A recent meta-analysis showed an increase in MMP-9 in aortic aneurysm tissue; however, unlike in the current study, there was a reduction in TIMP-1 and TIMP-2 [7]. From a clinical perspective, this preliminary and hypothesis-generating study correlating intramural biochemistry with elastic moduli of an aneurysmal aortic wall demonstrates a potential approach to investigate the potential future growth of ascending aneurysms by non-invasive means, i.e., computed tomography or magnetic resonance imaging.

Insofar that aortic aneurysm progression is complex and dynamic, assessment of potential roles of MMPs and TIMPs in the aneurysmal progression remains challenging. As such, a limitation of the current study is the small sample size, which is especially important given the differing roles that MMPs may play in aortic aneurysm development in the setting of bicuspid or trileaflet aortic valves because of differing

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pathophysiology and hemodynamics. Lemaire et al. [8] showed that patients with bicuspid valves had elevated MMP-2 and normal MMP-9 expression in the setting of elastin content preservation, while patients with trileaflet aortic valves had increased MMP-9 expression, normal MMP-2 levels, and diminished elastin content. A meta-analysis [9] examining MMP expression in aortic aneurysm patients with or without a bicuspid valve also showed that in patients with bicuspid valves, there was a significant increase in MMP-2 but not MMP-9, as well as a significant decrease in TIMP-1 but not TIMP-2 or TIMP-3, in comparison with trileaflet patients. In trileaflet patients, there was a significant increase in MMP-9, but not in MMP-2, in comparison with the control group, and a significant reduction in TIMP-1 and TIMP-2, resulting in a 3.5-fold greater MMP-9 to TIMP-1 or TIMP-2 ratio. With regard to MMP-2, Shen et al. [10] demonstrated two opposing roles for MMP-2 in aortic wall remodeling, contributing to both the production and the degradation of extracellular matrix proteins. Trscheuschier et al. [11] assessed serum and aortic tissues from 24 patients with ascending aortic aneurysms and identified Pro-MMP-2 and active MMP-2 in all tissue samples; however, no correlation could be ascertained between total tissue MMP-2 or Pro-MMP-2, or between tissue and serum MMP-2. In addition, there was no correlation between MMP-2 isoforms and aortic diameter. Surprisingly, serum MMP-2 levels were higher in healthy controls than in patients.

In summary, ascending aortic aneurysms are not a homogeneous lot, and the identification of a specific MMP and/or TIMP may be of importance only in a subset of aneurysms. The data presented by Khanafer et al. offer very preliminary evidence. If confirmed in larger studies assessing aortic aneurysm patients with and without bicuspid aortic valves and showing that elastic moduli determined non-invasively can predict progression of disease, in one or both subsets, it would be an important step in the development of a personalized approach to the care and treatment of patients with ascending aneurysms.

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