Through Thick and Thin Collagen Fibrils, Stress, and Aortic Rupture

Another Piece in the Jigsaw

Janet T. Powell, MD, PhD; Toste Länne, MD, PhD

This century has seen a leap forward in both treatment and understanding of the molecular and pathogenetic mechanisms underlying aortic dissection. The advantages of endovascular stenting are becoming obvious, and results from the Investigation of Stent Grafts in Patients With Type B Aortic Dissection (INSTEAD) trial are pending. Molecular and pathogenetic advances include genetic defects mapped to several chromosomes in familial thoracic aortic dissection, including splice and missense mutations in the TGFBR2 gene on chromosome 3 associated with a Marfanoid syndrome. Indeed, evidence is increasing that dysregulated transforming growth factor–β signaling is an underlying mechanism in aneurysm formation. The small leucine-rich proteoglycans, including biglycan, bind transforming growth factor–β and regulate collagen fibrillogenesis in vitro. The current article by Heegaard and colleagues, as well as the recent work of Takaluoma et al, uses mouse models to further our understanding of the weaknesses in collagen fibrils that can provoke the aortic dissection characteristic of Ehlers-Danlos syndrome.

Heegaard et al elegantly demonstrate the altered morphology of aortic collagen fibrils in the absence of bgn, the biglycan core protein gene, which is encoded on the X chromosome in both mice and men. Absence of aortic biglycan leads to smaller collagen fibrils and a reduced resistance of the aorta to passive stress. In particular, the role of the adventitia in resisting passive stress is highlighted. The magnitude of these changes in fibril diameter and resistance to passive stress was much greater in males than in females, and only males were susceptible to death from aortic rupture. The authors speculate about the role of estrogens and the stress response as being responsible for these sex-specific effects. Certainly, evidence is increasing that male rodents are more prone to aortic aneurysm formation in a variety of experimental models. However, other mechanical factors should be considered, particularly because the passive aortic diameters of bgn−/− mice were larger than in wild-type mice. Males have larger aortic diameters than females and seem to have less compensatory aortic wall thickening in response to aortic dilation or increase in blood pressure, which will influence circumferential stress. Hence, female aortas seem to be affected by lower levels of stress than males. Therefore, in patients with Ehlers-Danlos syndrome (vascular), the high stress imposed on the aortic wall in males might be another reason for the tendency to rupture. In addition, some have argued that changes in collagen fibrils can be a response to stress in blood vessels subject to augmented hemodynamic stress.

High wall stress would provide a common mechanism for the contrasting observations of Takaluoma et al, who showed that collagen fibrils had increased diameter in the aorta of Plod1−/− mice (deficient in lysyl hydroxylase isoenzyme LH1) and that these mice also were susceptible to aortic rupture. Rupture usually occurred at night, during periods of maximum activity, and was twice as common in males (17%) as in females (9%), but mechanical properties of the aorta were not measured. However, they also reported degenerative changes in aortic smooth muscle cells, not dissimilar to those observed in fibrillin-1−/− deficient mice. Therefore, either abnormally thick or thin collagen fibrils appear to predispose to aortic rupture in mice: fibril size per se may not be the key issue. The critical regulatory and signaling properties of cell-matrix interactions and hemodynamic factors probably underlie these Ehlers-Danlos syndrome–like syndromes in mice, which can lead to aortic rupture.

Dissecting disease of the aorta may not be a localized disease but rather a general defect of the vasculature, and the mechanical properties of other arteries are impaired, as well as the blood flow regulation of arterioles. It seems reasonable to assume that the altered morphology of collagen fibrils found in the aorta in either bgn−/− or Plod1−/− mice might impose changes in both heart and peripheral vessels of different sizes. Therefore, blood pressure regulation may influence the imposed stress on the aortic wall. Blood pressure regulation and resistance to active stress are of interest for further studies to elucidate structure-function relationships.

Aortic function may be species specific. In humans, the aorta is an elastic artery without contractile smooth muscle cells, whereas the mouse aorta seems to behave more like a muscular artery affected by both sympathetic stimulation and endothelium-derived nitric oxide. Because the regulation of arterial wall stiffness differs between elastic and muscular arteries, the magnitude of these stress changes might impose changes differently in human and mouse vessels.
arteries, it may not be possible to translate the findings of altered aortic wall mechanical properties from mice to humans. In addition, the pathology of these mouse models is very different from the classic cystic medial necrosis and mucoid degeneration (with proteoglycan accumulation) commonly observed in the presentation of idiopathic aortic dissection in humans. Nevertheless, the work of Heegaard et al is a very important step in understanding structure-function relationships in the aorta.

Disclosures

None.

References

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