Connective Tissue Disorders: Aortic Considerations

Identifying factors, unique risks, and therapeutic options for Marfan syndrome and other connective tissue disorders.

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How many times have you seen patients with aneurysmal disease who are younger than usual or lack the typical risk factors? These patients may or may not have a significant family history of aortic aneurysm. In some cases, the difference between these patients and the more commonly seen elderly patients with degenerative disease is so striking that it immediately sets off an alarm—or it should—for physicians. Most often, this alarm may signal you to think Marfan syndrome (MFS) or connective tissue disorders (CTDs) and prompt certain measures including screening for genetic disease, evaluation of family members, reconsideration of the surgical indication criteria, and extra care in the operating room. Moreover, especially in the last few years, this should signal to the physician: "If you're considering an endovascular approach, think again!"

CONNECTIVE TISSUE DISORDERS

A CTD denotes a problem in the extracellular matrix (ECM) of affected patients. Important proteins, such as collagen, fibrillin, fibronectin, and elastin, among others, have biomechanical properties that are critical for connecting, attaching, and retaining tissues and organs. The ECM is therefore an extremely well-organized structure essential for the normal functioning of many organs and systems. Until the last decade, it had been postulated that CTDs jeopardized the structural integrity of the aorta. Accordingly, it was thought that there was not much a physician should do until the CTD ultimately resulted in aneurysmal dilation, dissection, or rupture, unless the aorta was surgically repaired before the event.

More recent studies show that the nature and function of the ECM are much more complex than previously thought and that the related disorders are not simply the result of defects in the quantity or configuration of one of its structural components.[1] Specifically, the newer perspective is that the ECM is an intricate network that, in addition to its structural function, regulates the bioavailability of cytokines and growth factors, such as transforming growth factor beta (TGF-ß), that are involved in cellular proliferation, survival, differentiation, and migration. Consequently, the ECM has important regulatory functions in the development and homeostasis of body organs and tissues, as well as in inflammation, fibrosis, and proteolysis.[2,3]

It now seems more than plausible that TGF-ß signaling is linked to thoracic aortic aneurysms in both syndromic and nonsyndromic disease. The implication is that existing pharmaceuticals may be a reasonable therapeutic approach in cases of deficiency of an ECM component. Because TGF-ß antagonists can attenuate or prevent several CTDs, including MFS, these CTDs are no longer considered "incurable" disorders, and there is hope for the development of new more effective nonsurgical therapies.[4] Several prospective randomized trials are ongoing that involve more than 2,300 MFS patients of various ages and will evaluate the outcomes of angiotensin-receptor blockers, such as losartan, on aortic enlargement via several endpoints.[5-8]

Molecular biology analysis techniques have become more affordable and more widely available, allowing for more extensive analysis. The number of patients screened for CTDs is increasing, and in the near future, a classification system could be proposed based on molecular genetics.[9] However, this might not be enough to stratify the risks related to aortic disease. In fact, intrafamilial variability shows that identical genetic defects may result in different phenotypes and have different clinical consequences.

MARFAN SYNDROME

The differences in the presentation of younger patients with MFS are not always so obvious. For example, your patient may be a middle-aged woman who smokes and happens to be hypertensive, and she does not recall any family history of aneurysmal disease.

In this scenario, a diagnosis of MFS may be quite obvious when some of its key phenotypic characteristics are present. Nevertheless, it is often very challenging because some of its cardiovascular features depend on age, while others (eg, scoliosis; a lean, tall habitus; mitral valve prolapse; and myopia) are also often seen in the general population. It should be clear that the phenotype of MFS patients is quite variable and that many MFS patients do not look at all like an archetypal MFS patient. In addition, MFS has significant overlap with other CTDs.

Although genetic testing can be useful,[10] a diagnosis of MFS should be made according to the revised Ghent criteria.[11,12] As surgeons, we are not highly proficient at this, and the importance of referring patients with a suspicion of CTD to a specialized center cannot be overemphasized. A geneticist might tell us that MFS has high penetrance but variable expressivity or that up to one-third of cases are sporadic and due to de novo mutations.

In any case, we must remember that our patient does not need to have outward signs of being an MFS patient to be one, and we should refer the patient to a center that specializes in MFS. This condition does not disproportionately affect one sex and there is no jump of generation for this autosomal dominant disease. In addition to helping with the diagnosis, the MFS center will be invaluable in following the patient beyond surgery, managing noncardiovascular issues, and offering genetic counseling, family planning assistance, and other supportive services.

SURGERY AND ENDOVASCULAR REPAIR

The role of the surgeon remains crucial for offering patients the best chance of survival, especially those with heritable CTDs and MFS. Earlier and safer aortic root replacements have removed one of the most important causes of early death in patients with MFS. Extended survival also means that the remaining part of the aorta may dilate or dissect in the subsequent years. Therefore, in many patients with MFS who are in their 4th and 5th decades of life, the descending thoracic aorta or the entire thoracoabdominal aorta may become aneurysmal, resulting in a challenging surgical situation. Regrettably, the fragility of the aortic wall in these patients in most instances contraindicates an endovascular approach. Fortunately, surgeons can offer reasonable results even in these extremely demanding operations, thanks to the lessons learned in the past regarding the most appropriate surgical techniques in this subset of patients and the overall improvements in surgery and anesthesiology regarding organ protection during aortic cross-clamping.[13]

Patients who underwent previous aortic surgical repairs and have developed dissection/aneurysm dilatation of the aortic segments that were left behind represent significant exceptions to this general rule. In such cases, the previous surgical grafts may be an ideal landing zone for endografts that can be used safely and successfully. Anecdotal reports of successful treatment of extensive aortic disease in CTD patients with endografts can indeed be found in the literature, although it is still doubtful that these results can be maintained at long-term follow-up. From these experiences, a pattern seems to emerge that favors radical treatment of the entire thoracoabdominal aorta, possibly landing distally in the iliac arteries, to a more limited approach in which the endograft lands distally into the aorta. In such cases, however, a stent graft–induced new entry tear or late aneurysmal degeneration at this site is exceedingly common.

Another area in which an endovascular approach may play an important role could be a life-saving emergency situation, where a stent graft might be used as a bridge to a more definitive open surgical procedure.

CONCLUSION

In recent years, new clinical CTD entities have been recognized, diagnostic criteria have been revised, new therapies continue to be tested including an endovascular approach, and surgery has improved so much that for patients with MFS, "30 years of research equaled 30 years of additional life expectancy."[14] ■

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