**EDITORIAL COMMENT**

**Bicuspid Aortic Valve and Thoracic Aortic Aneurysm**

**Toward a Unified Theory***

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In this issue of the *Journal*, Biner et al. (1) report that a significant number of first-degree relatives of individuals with bicuspid aortic valve (BAV) have more stiff, less distensible, and pathologically enlarged aortas despite their having completely normal aortic valves. That BAV is a familial disease is established (2). The present study is the final word in the debate over the relative insignificance of BAV as a cause of aortic dissection in the heritable aortopathy known as familial thoracic aortic aneurysm and dissection (FTAAD). Indeed, this study and the work of Loscalzo et al. (3), in which BAVs were found among relatives of individuals with tri-leaflet nonstenotic aortic valves and thoracic aortic aneurysms, refute the belief, held closely by some (4), that ascending aortic enlargement in the setting of BAV is caused solely by disturbed flow through an abnormal valve, the so-called post-stenotic dilation. Other corroborative studies fail to show any correlation between the severity of aortic valve stenosis/regurgitation and aortic dimension (5–7). Furthermore, these studies suggest that BAV disease and FTAAD might best be understood as variable expressions of the same disease.

See page 2288

Although Biner et al. (1) rule out the absolute necessity for turbulent flow or high-velocity jets, or the presence of BAV itself in the pathogenesis of aortic aneurysm, others have clearly shown that aortic stenosis is correlated with the growth rate of the aorta (8) and is predictive of clinical outcome (9). These observations should come as no surprise because an interaction between hemodynamic state and the composition of the aortic wall in the pathogenesis of dissecting aortic aneurysm has been recognized for a long time. For example, the eminent cardiac pathologist, Dr. Jesse Edwards, in a landmark 1978 report (10) showing the high incidence of nonobstructive BAV among autopsy cases of aortic dissection, concluded that “dissecting aneurysm of the aorta may be viewed as a complication of disproportion between the strength of the aorta, on one hand, and intraluminal pressure, on the other.” The misapprehension, until now, was the pervasive notion that an acquired injury to the aortic wall caused by disrupted flow through the aortic valve, the stress induced by high blood pressure, and the ravages of aging were primarily or solely responsible for the disease.

We can now be certain that a complete understanding of the pathogenesis of aortic aneurysm will require an elucidation of both the genetic triggers of aortic disease and their downstream molecular targets. A number of researchers, most notably Harry C. Dietz, a Hughes Institute investigator at Johns Hopkins University, have already generated a body of compelling evidence by studying families with aortic disease and mutations in genes that encode either regulatory or structural proteins. The results of these investigations point to the need to understand the complex interactions between signal transduction pathways and structural components of the aorta. This fundamental idea was recently proposed by Dietz (11) as an alternative explanation for the etiology of aortic aneurysm in Marfan syndrome. Previously it was believed that the causative gene defect in Marfan syndrome, mutations in the gene encoding fibrillin-1, acted postnatally to decrease the elastin content of the aorta. Disease progression was thought to result from postnatal hemodynamic stresses that disrupted the internal elastic laminae of the aortic wall, producing the histological finding of cystic medial necrosis.

Dietz’s (11) breakthrough was the observation that in a mouse model of Marfan syndrome, fibrillin-1 is essential to maintain the integrity of the elastin fiber but is not required for generation of elastin prenatally. Most researchers in the field have abandoned the acquired weakness hypothesis based on evidence provided by Dietz and others (12,13) that intracellular signals regulating cell proliferation, migration, or programmed cell death are important. The recognition by Maslen et al. (14), of structural homology between fibrillin-1 and a protein called transforming growth factor (TGF)–β binding protein suggested that there might be an interaction between the cytokine TGF-β signaling pathway and the abnormal fibrillin-1 protein. This hypothesis led to a series of elegant experiments showing that TGF-β neutralizing antibody reverses aortic disease in an engineered mouse model of Marfan syndrome (15). Subsequent demonstration (reported in the same publication) that the angiotensin II receptor blocker, losartan, by inhibiting upstream TGF-β pathways, essentially cured the Marfan mouse of dissecting aortic aneurysm was a scientific tour de force that has been rarely seen in our generation.

Of course the unanswered question is: To what extent can the Marfan–TGF-β story be generalized to other aortopathies? With regard to FTAAD, the responsible genes are
largely unknown. So far, 5 gene loci have been identified (16–21), and at least 1 of them has been associated with mutations in TGF-β receptor signaling (21). Mutations in the gene ACTA2 encoding smooth muscle cell alpha actin accounts for 14% of FTAAD (17) and previously reported mutations in the gene MYH11 (15) (beta myosin heavy chain) suggest that maintenance of contractile function of aortic smooth muscle cells is also important. Whether there will be a sort of unified field theory for the molecular pathways that predispose to aortic aneurysm that ultimately provides clinicians with the tools to intervene at critical points along the path leading to aortic dissection remains an open question.

The good news is that the National Heart, Lung, and Blood Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases have established a registry that is collecting medical data and biological material from patients with genetic conditions that may be related to thoracic aortic aneurysms. This program, called GenTAC (Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions) (22), includes 5 regional centers across the U.S. GenTAC’s goal is to make widely available a bioinformatic infrastructure specifically related to aortic disease. The genius of the GenTAC project is to attract the best and the brightest in the field of aortic disease and to offer them the clinical information and the biological materials to generate and test new hypotheses. If it works, the competition that for too long has hindered many scientific advancements will yield collaborations that effectively move the project forward.

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