EDITORIAL COMMENT

Development of Aortic Valves With 2 and 3 Leaflets*

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In this issue of the Journal, Fernández et al. (1) have extended the studies of the normal and abnormal development of the aortic valve started by their group nearly 2 decades ago (2). In their initial studies, the group from Malaga described the existence of aortic valves with 2 rather than 3 leaflets in an inbred strain of Syrian hamsters. They showed that the abnormality was caused by excessive fusion between the cushions, or ridges, that normally join together to produce a transient septum in the developing outflow tract. With ongoing normal development, this embryonic septum subsequently disappears, so that in the post-natal heart the aortic and pulmonary roots are discrete and separate structures (3). Others (4) subsequently showed that aortic leaflets with 2 leaflets were also a feature of mice lacking endothelial nitric oxide synthase. The investigators reporting the murine findings, however, gave no details on the specific arrangement of the abnormal valvar leaflets. The group from Malaga now shows that in the Syrian hamster, the so-called conjoined valvar leaflet is formed from the leaflets normally arising from the sinuses that give rise to the coronary arteries. In the mice lacking endothelial nitric oxide synthase, in contrast, the conjoined leaflet represents fusion of the noncoronary and right coronary arterial leaflets, with the abnormality resulting from abnormal fusion during development of an outflow cushion and the so-called posterior intercalated cushion.

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Their study has direct translational consequences because these phenotypes of bifoliate aortic valves are also found in humans. It is exceedingly rare in humans with bifoliate aortic valves to find the conjoined leaflet formed from the noncoronary and left coronary aortic leaflets (5). Fernández et al. (1) emphasize that the individuals with the different types of bifoliate aortic valves also have markedly different associated lesions and malformations. Thus, as they state, for appropriate genetic counseling, it is no longer sufficient simply to note the presence of the valve with 2 leaflets, but rather to specify the anatomic location and structure of the conjoined leaflet.

There is also much in their current description that points the way forward for others investigating the normal and abnormal development of the arterial valves. The valvar leaflets and their supporting sinuses are formed within a turret of cardiac muscle, which is part of the initially muscular wall of the entirety of the developing outflow tract (3,6). How the initially muscular walls of the intrapericardial arterial trunks become transformed to arterial structures has yet to be determined, as has the method of separation of the adjacent parts of the aorta and pulmonary trunk (3). The sinusal walls of the arterial roots are also formed of arterial tissues, and as with the intrapericardial arterial trunks, there is a discrete tissue plane post-natally between the aortic root and the freestanding supravalvar infundibulum. Once it is accepted that the aortic valve develops within a myocardial turret, which subsequently disappears (6), it becomes clear why the interleaflet fibrous triangles separating the attachments of the semilunar leaflets of the aortic valve proximal to the sinutubular junctions are interposed between the cavity of the left ventricular outflow tract and the pericardial space, or the tissue plane between the aortic root and the supravalvar infundibulum (7).

The group from Malaga also account for their findings without resorting to descriptions of the mythical aortic annulus. In reality, the most obvious anatomic “little ring” to be found in the arterial valves is at the level of their sinutubular junctions. The zones of apposition of the valvar leaflets are attached at this junction, which should therefore be considered an integral part of the valvar complex, rather than being considered supravalvar (8). The leaflets themselves are then suspended in semilunar fashion from the sinutubular junction, the overall arrangement being tricominate in the normal valve, but more akin to the episcopal mitre in the so-called bicuspid valves. The essential feature of the aortic valve with 2 leaflets, therefore, is the presence of a solitary zone of apposition between the working components of the valvar complex.

The Spanish investigators also emphasize the difference in structure between the valvar leaflets and their supporting arterial sinuses. It is now vital that we determine the molecular biological cascade permitting the developing cushions to excavate so as to form the walls of the sinuses on their mural aspect, yet give rise to the valvar leaflets on their luminal aspect (3). We know that multiple arrays of different genes and proteins are present in these 2 components of the aortic root, and our own ongoing studies have shown that mice deficient in some of these genes develop abnormal aortic valves, with calcification as one of their major features. Clarification of the genetic cascade underscoring normal valvar development may provide crucial information regarding the pathogenesis of calcific aortic ste-

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nosis, known to be a major developing epidemic in the increasingly elderly population.

The other major purpose of the outflow cushions is to fuse so as initially to separate the solitary lumen of the embryonic outflow tract into aortic and pulmonary channels (3). Migration of cells from the neural crest into the cushions is known to be key in this process of normal separation (9). Condensations of extracardiac mesenchyme are formed between the developing arterial valves during septation of the outlet, as seen in the figures shown in the Spanish study (1). Such condensations are also found in chicken, rat, and human embryos (10). The frequent observation of bicuspid aortic valves in the Spanish study (1), along with the occurrence of bicuspid pulmonary valves in the same inbred hamster (11) and the infrequency of doubly bicuspid valves, suggests that the normally central position of the condensed mesenchyme is disturbed in this strain, but perhaps to either side. This might occur through asymmetry within this ephemeral structure, or else could be caused, or accompanied, by perturbation of flow, because aortic coarctation and tetralogy of Fallot, known to produce reduced aortic or pulmonary flow, are associated with bifoliate aortic or pulmonary valves, respectively.

In addition to the cells taking their origin from the neural crest, we now know that normal development and separation of the outflow tract requires additional migrations of cells from the so-called second heart field (12). The precise components of the structures that fuse together initially to divide the common outflow tract, but that then disappear as the aortic and pulmonary pathways achieve their separate walls, have yet to be determined. Recent work has shown, nonetheless, that remodeling of the extracellular matrix may be an important mechanism during valvar development. Members of the family of matrix metalloproteinases (MMPs), and/or the motifs of the A Disintegrin And Metalloproteinase with Thrombospondin (ADAMTS) family, which cleave proteoglycans in the initial matrix, likely contribute to the processes of valvar patterning and maturation. Differential profiles of the MMPs have been found in patients with bicuspid as opposed to degeneratively diseased trifoliate aortic valves (13,14). This differential profile has been shown to correlate with changes in the expression of protein kinase C isoforms (15). A deficiency in Notch1 has also been implicated in the development of bicuspid aortic valves (16), with this activated protein both inducing MMPs (17) and facilitating migration and differentiation of cells derived from the extracardiac neural crest (18). Expression of the MMPs is likely required not only for the removal of proteoglycans, but also for the production of cleaved fragments that may signal changes in the cellular programs that facilitate subsequent valvar maturation (18).

In this respect, excavation of the valves occurs concomitantly with the appearance of an organized fibrillar matrix, including peristin and collagens, in contrast to the proteoglycan-rich matrix found early in development that permits expansion of the endocardial cushions and migration into the outflow tract of populations of extracardiac cells. Remodeling of the extracellular matrix during patterning of the aortic valve, therefore, is a crucial part of overall development of the outflow tract of the heart (18). Many aspects of cardiac development remain to be clarified. The work provided by the group from Malaga (1) shows that we are moving in the appropriate direction, but that there is still much to be done.

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