Commentary: Why do some patients with hypoplastic left heart syndrome have endocardial fibroelastosis?

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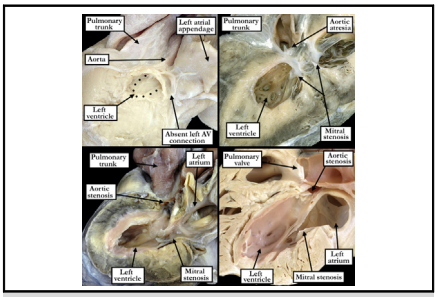

The images show the phenotypic variants of HLHS with mitral or aortic atresia or stenosis.

Central Message

The presence of flow-related fibroelastosis shows that the variant of hypoplastic left heart syndrome with mitral stenosis rather than atresia is an acquired disease of fetal life.

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Those who treat patients diagnosed with so-called hypoplastic left heart syndrome are well aware that the syndrome is made up of several phenotypic entities.[1] This important fact, however, is not always appreciated by those seeking to establish the genetic cues predisposing toward development of the lesion.[2] If we are to establish the reasons that some infants are born with the syndrome, it will be optimal if we can agree on the phenotypic variables to be included. In this regard, at least in the clinical setting, there is now agreement that one of the required features is the integrity of the ventricular septum, and the presence of concordant ventriculoarterial connections.[3] Within this basic definition, we can then separate out those infants with mitral and aortic atresia from those with mitral stenosis (Figure 1, *A* and *B*). Within the second category, we can then identify those who have aortic stenosis as opposed to aortic atresia (Figure 1, *C* vs *B*). The remaining conundrum to be faced when assessing the patients with aortic stenosis is the cutoff between those deemed to have so-called critical stenosis, who can be referred for a therapeutic strategy culminating in biventricular circulations, as opposed to those included within the syndrome, and thus likely referred for functionally univentricular repair (Figure 1, *C*). When hearts from such problematic patients are assessed in the autopsy suite, the presence of fibroelastosis has proved to be a helpful indicator for those considered properly to belong in the syndrome. This, however, has not always helped in determining which infants might have had small left ventricles in keeping in size with miniaturized aortic and mitral valves, the pattern that has been identified as the hypoplastic left heart complex (Figure 1, *D*).

In the current issue of the *Journal*, Weixler and colleagues,[4] writing for the group from Boston Children's Hospital, describe their findings regarding the potential origin of the fibroelastotic lining, the feature that morphologists expect to be universally present when hearts are correctly assessed as having the variant of the syndrome characterized by mitral stenosis rather than atresia. Weixler and colleagues[4] provide strong evidence that the fibroelastosis is caused by abnormal flow through the cavity of the left ventricle. Such flow self-evidently can only occur when there is mitral stenosis, rather than mitral atresia. They have used sophisticated techniques to show that the fibroelastotic lining is produced from the endothelial lining of the left ventricle by the process known as endothelial-to-mesenchymal transformation.[5] The notion that the fibroelastotic layer originated from the endocardium had, in fact, been promoted much earlier by Lurie.[6] Making use of their elegant techniques, the Boston group now emphasize the relationship to the process initially observed as part of the production of the endocardial cushions that are essential for normal cardiac septation. Their findings are convincing, although they concede that surgical resection of the fibrotic layer is unlikely to provide a therapeutic panacea for those seeking to convert more patients to biventricular circulations.

By demonstrating the causal relationship between abnormal flow and development of the fibrotic layer, they nonetheless have now shown that the variant of hypoplastic left heart syndrome associated with mitral stenosis is an acquired disease of fetal life.[7] This should be of obvious interest to those seeking to establish the genetic background

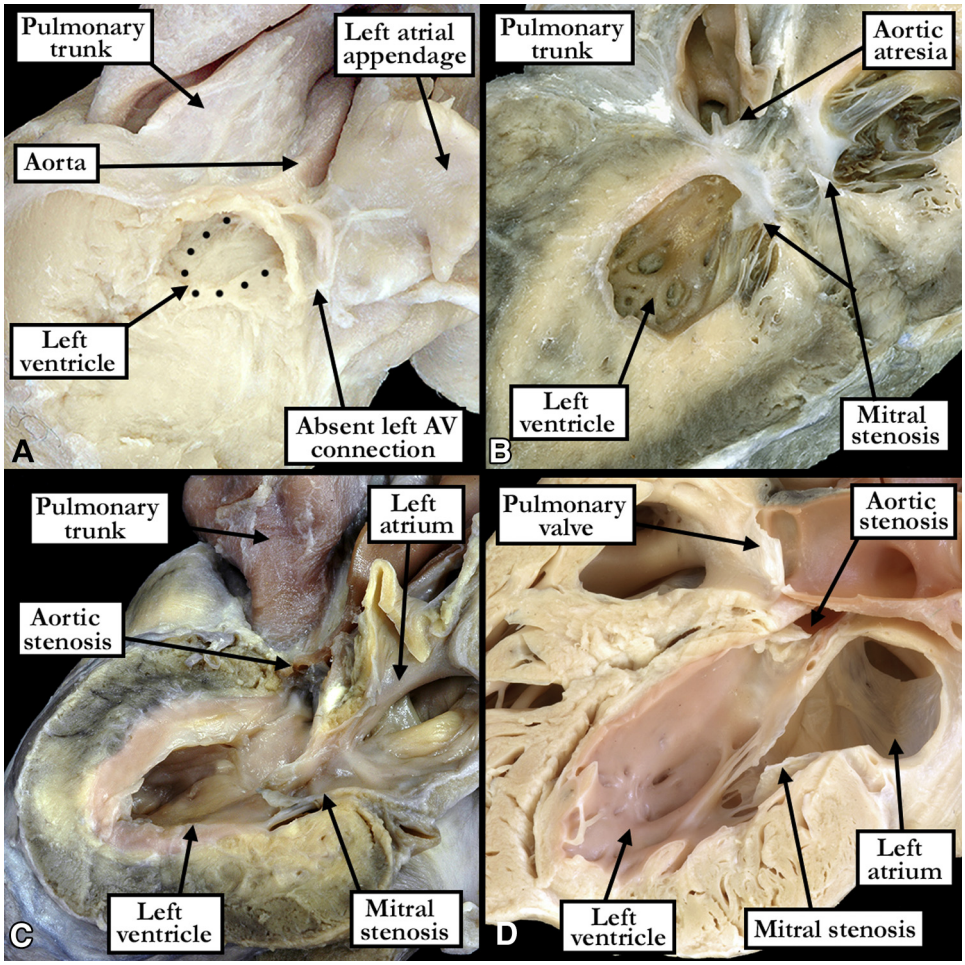

FIGURE 1. The images show the phenotypic variants of hypoplastic left heart syndromes with mitral or aortic atresia or stenosis. *AV*, Atrioventricular.

to the syndrome. This is because it is surely reasonable to presume that the disease itself did not begin to manifest until the completion of cardiac septation, calling into question the suggestion that the genetic background can be resolved by evaluation of animals models characterized by the presence of double-outlet right ventricle or atrioventricular septal defect.[2] It remains the case that, unfortunately, we still do not have a good animal model for the patients who have the variant of hypoplastic left heart syndrome used in the current investigation of the Boston group.[4] As Weixler and colleagues[4] state, their own investigations continue, not least to assess whether they can establish a better means of combatting the problems produced by the presence of the fibroelastotic layer as they seek to treat more patients by using an algorithm leading to eventual biventricular repair. This is also of interest to those performing fetal interventions as to whether we can prevent or mitigate the development of fibroelastosis by improving flow during fetal life. Their findings of fibroelastotic lesions related to abnormal flow could also be relevant to those seeking to identify patients with the so-called hypoplastic left heart complex.[3] Our own ongoing morphologic studies suggest that patchy areas of fibroelastosis are to be found in stored archival hearts from those who might have had this variant of the overall syndrome (Figure 1, *D*). We, along with surgeons and pediatric cardiologists, will be waiting with increasing interest for the future investigations as promised by the Boston group. Weixler and colleagues[4] have pointed out that recurrence is a major problem. Prevention of recurrences should be a focus of future studies.

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