Discrete Subvalvular Aortic Stenosis: Is the Presence of Upstream Complex Blood Flow Disturbances an Important Pathogenic Factor?*

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Background. Discrete fixed subvalvular aortic stenosis can occur as an isolated abnormality or in association with other cardiac anomalies, especially ventricular septal defect, persistent patent ductus arteriosus or coarctation of the aorta (1-4). It most often presents as a crescent-shaped ridge of fibroelastic tissue protruding from the left septal surface into the subaortic region or as a ring with extensions to the septum and anterior leaflet of the mitral valve (4,5). Although there is no evidence that these abnormalities are present at birth, they usually become evident during the 1st decade of life. This observation has led to the suggestion that discrete fixed subvalvular aortic stenosis is an acquired lesion whose hemodynamic severity can progress with time (1-4,6). An alternative interpretation is that the development of subaortic stenosis requires the changes in pressure and flow associated with birth or growth, or both, to establish the conditions that would generate the septal tissue reaction. By this view the lesion is "acquired," yet still "congenital," because the underlying predisposing abnormality is waiting for the necessary conditions to become manifest. Numerous studies (6,7) have shown that redevelopment of the obstruction is common even after successful surgical resection of the obstructing tissue and can occur as long as 17 years after the initial procedure (7). There are many theories to explain the pathogenesis and natural history of discrete subvalvular aortic stenosis in humans including:

1. Polygenic inheritance. Although an animal model for the congenital development of subvalvular aortic stenosis exists, no human equivalent or underlying predisposing structural variation has been described (8).

2. The presence of an intrinsically long and narrowed left ventricular outflow tract resulting in alterations in blood flow patterns within the heart during early embryogenesis and leading to the accumulation of cells near the crest of the ventricular septum (9). These cells would later differentiate into fibromuscular tissue that obstructs the subaortic region. Although this scenario would explain the delayed appearance of subaortic stenosis, there are few histologic data to support the existence of residual embryonic tissue within the upper portion of the interventricular septum.

3. Recurrence due to scar formation in the subvalvular region or failure to adequately resect all of the tissue that led to the initial obstruction (7,10). Although these explanations could account for the redevelopment of subvalvular aortic stenosis, they cannot explain the process that initiated the original hemodynamic problem.

The present study. It is evident that there is no unanimity of opinion regarding the pathogenesis of discrete subvalvular aortic stenosis nor is it clear if the high recurrence rate after surgical resection reflects a failure to alter the inciting pathologic process itself. The study by Gewillig and coworkers (11) in this issue of the Journal attempts to address both of these clinically relevant issues. These investigators hypothesized that blood flow disturbance upstream from (that is, proximal to) the region of subsequent outflow tract obstruction can be an important pathogenic factor in this condition. Furthermore, if abnormal flow patterns are responsible for the subsequent subvalvular stenosis, these abnormalities may not be altered by surgical resection of the obstruction, thereby laying the foundation for recurrence of the lesion. To test this hypothesis, 26 patients were studied with use of ultrasound imaging and Doppler color flow techniques a minimum of 6 months after operation for isolated discrete subvalvular aortic stenosis. Only limited preoperative data were available on the patients. Color flow variance was used as a marker for turbulent blood flow within the left ventricular outflow tract. Postoperatively, the patients with subvalvular aortic stenosis tended to have narrower and longer left ventricular outflow tract dimensions than were noted in 58 similarly aged normal subjects. Twenty of the 26 patients with subaortic stenosis had turbulence adhering to the left septal surface with its origin "well below the site" of the previous surgical resection. In 16 patients a ridge was noted 13 to 23 mm from the insertion of the aortic valve. In the other four patients the crest of the muscular septum protruded into the left ventricular outflow tract because of a displacement of the membranous septum 15 to 26 mm from its usual insertion site at the crest of the muscular septum. The authors concluded that 1) in most patients, even after surgical removal of the subvalvular obstruction, abnormal flow patterns are present when the blood reaches the subaortic area; and 2) this chronic turbulence may be the stimulus for the development of subvalvular aortic stenosis and its recurrence.

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**Methodologic considerations.** To appropriately interpret the data of Gewillig et al. (11), it is necessary to assess critically the experimental methods used in the study. It is important to understand that turbulent blood flow is characterized by a multitude of flow velocities occurring in random directions. Instead of laminar flow, there may be vortices and eddies created with regions of flow acceleration and deceleration (12). The authors (11) tracked, in a nonquantitative manner, the presence of disturbed blood flow in the left ventricular outflow tract using Doppler color flow mapping of flow velocity variance. These maps are based on calculations of flow velocity variability around the determined mean velocity for flow toward or away from the interrogating transducer (13). By using an instrument-specific algorithm to encode variance (that is, broad velocity spectrum), the data are color coded and superimposed on the traditional two-dimensional echocardiographic image. The equating of variance with turbulence, as was done by Gewillig et al. (11), has potential problems because the determination of variance by Doppler color flow imaging is greatly influenced by instrument gain, transducer frequency, encoding algorithm and pulse repetition frequency (14,15). Additional confounding variables include the wall filter settings and the rate of flow acceleration. If the latter is high enough that rapidly changing flow velocities are detected during the data sampling time, the Doppler color map can show "statistical" variance without true hydrodynamic turbulence (13). Thus, the mere detection of variance by Doppler color flow mapping does not necessarily mean that hemodynamically important complex blood flow was present in the left ventricular outflow tract of patients after resection of the subvalvular aortic stenosis. If no significant flow disturbance was present, then the basic hypothesis presented by Gewillig et al. (11) would be difficult to accept as the explanation for the development and subsequent recurrence of discrete fixed subvalvular aortic stenosis in humans.

**Possible importance of upstream complex blood flow.** On the positive side, if significant upstream complex flow is present, how could it result in discrete outflow tract obstruction? It is known that various mechanical factors can generate intracellular signals that turn on localized cell growth (16). The concept of regional hypertrophy as an adaptive response to chronic transmural wall stress (17) does not appear to apply in this case because the area of stenosis is not subjected initially to increased intracavitary pressure, large radius of curvature or excessive wall thinning. Whether the configuration of the septum upstream from the subaortic area has a direct impact on myocardial infrastructure and the subsequent development of other regions of hypertrophy is unknown. Perhaps the explanation lies in a conceptual parallel between complex blood flow in arteries (analogous to the left ventricular outflow tract) and the propensity for vascular wall intimal thickening (analogous to the subendothelial endocardium in subvalvular aortic stenosis). It has been postulated that departures from unidirectional laminar blood flow occurring at branch points or around projecting ridges can lead to high frequency fluctuations in flow velocities and rapidly changing directions of wall shear (that is, the force that tends to displace the endothelium or endocardium in the direction of blood flow) (18,19). The low and oscillating shear that is often associated with flow velocity variance has been shown in an experimental model to induce cell turnover and deoxyribonucleic acid (DNA) synthesis (18). An additional possibility is that local flow abnormalities at the blood-wall interface lead to elaboration of an as yet unidentified growth factor resulting in regional proliferation of cells and localized obstruction. If turbulence (or more generalized forms of complex flow disturbances) are really the key pathophysiologic stimuli for subvalvular aortic stenosis, then surgical resection must include both the area of obstruction and the more apically positioned inciting region.

Clearly, long-term serial ultrasound evaluations are required in patients at risk for developing discrete subvalvular aortic stenosis to more fully test the hypothesis that the presence of an upstream blood flow abnormality is an important pathogenic factor in this form of left ventricular outflow tract obstruction. If this proves to be the case, it will be another example (20,21) of how localized intracardiac flow abnormalities can have a significant impact on ventricular form and function.

**References**


