REVIEW

Rheology of discrete subaortic stenosis

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The discrete form of subaortic stenosis is thought to be an acquired lesion, the aetiology of which may be a combination of factors which include an underlying genetic predisposition, turbulence in the left ventricular outflow tract, and various geometric and anatomical variations of the left ventricular outflow tract. A review of hypotheses relating to its aetiology is provided

Rheology, as the science of flow and deformation of matter, would seem to apply to the discrete form of fixed subaortic stenosis, the development of which is poorly understood. It has become apparent in recent years that this is an acquired lesion that is rarely seen in the newborn or neonatal period.^{1–4} Recent theories about the pathophysiological mechanism of its formation suggest an abnormal underlying endothelial substrate that is stimulated to undergo proliferation by sheer stresses caused by abnormal flow patterns and chronic turbulence. The lesion increases in severity, and progression of obstruction occurs if the initially discrete obstruction is not adequately relieved at an early age. Ultimately, increasing left ventricular outflow obstruction will lead to concentric left ventricular hypertrophy with the potential for diffuse ischaemic myocardial damage and rhythm disturbances in the long term, to aortic valve insufficiency, and to bacterial endocarditis.⁵

ANATOMICAL SITES AND COMMON ASSOCIATIONS

Subvalvar subaortic stenosis is a relatively uncommon type of left ventricular outflow obstruction and accounts for approximately 8–30% of subaortic obstruction.^{6,7} Most commonly, a discrete fibrous membrane or fibromuscular collar encircles the left ventricular outflow tract just below the aortic valve. Rarely, a long diffuse fibromuscular narrowing obstructs the left ventricular outflow tract for several centimetres.⁸ Associated cardiac malformations—especially coarctation of the aorta and ventricular septal defect (VSD)—occur in approximately 65% of patients.^{1,7} As many as 51% of patients with a VSD and discrete subaortic stenosis have been found to have deviation of the outlet septum. It is thought that deviation of the interventricular septum (anterior or posterior) results in the development of a fibrous shelf which contributes to the development of subaortic stenosis because the deviated septum causes a disturbance of the flow pattern in the left ventricular outflow tract.⁹

RECENT AETIOLOGICAL THEORIES

The following series of hypotheses on the aetiology of this lesion were preceded by earlier observations by Rosenquist and colleagues¹⁰ and Somerville and associates,¹¹ who concluded that fixed subaortic stenosis is a lesion that is acquired because of a flow disturbance in the left ventricular outflow tract.

Turbulence theory

The fact that discrete subaortic stenosis can recur after surgical removal led to the supposition that the lesion occurs as a result of a pathological process that was left unaltered by the surgery. An echocardiographic study by Gewillig and colleagues in 1992¹² showed that abnormal flow patterns are present in patients with discrete subaortic stenosis and that chronic flow disturbances are the cause of the development of the stenosis and its recurrence. Causes of chronic flow disturbances that may stimulate the endothelium to undergo transformation are mainly anatomical. They are as follows:

- apically situated muscular ventricular bands that reach the outflow tract, causing disturbance of flow in the subaortic area
- a septal ridge, which is an offshoot of a muscular band situated more apically in the outflow tract, causing turbulence that reaches the subaortic region
- malalignment of the interventricular septum, resulting in protrusion of the septum into the left ventricular outflow tract, so causing flow disturbances
- a long left ventricular outflow tract associated with increased mitral–aortic separation, resulting in an enhanced flow disturbance in the left ventricular outflow tract.

Geometric theory

In 1987, Zielinsky and colleagues found that most patients who developed subaortic stenosis had a malaligned VSD with anterior deviation of the infundibular septum,¹³ while Rosenquist and associates showed a twofold increase in mitral–aortic separation compared with normal hearts.¹⁰ In 1993, Kleinert and Geva confirmed the above findings but also showed that there was exaggerated aortic override in patients with subaortic stenosis and an intact interventricular septum.¹⁴ An aortoseptal angle (defined as the angle formed by the long axis of the ascending aorta and the plane of the ventricular septum) of $< 130^\circ$ was a prominent feature in their group of patients with subaortic stenosis (fig 1). The steeper angle results in a flow disturbance in the left ventricular outflow tract. The turbulent flow produced by the angle may induce an abnormal

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Figure 1 An illustration of the long axis of the heart showing the aortoseptal angle between the long axis of the aortic root and the proximal ascending aorta and the midline of the interventricular septum. An angle of $< 130^\circ$ is thought to contribute to increased turbulence in the subaortic area, resulting in the development of a subaortic ridge. Drawing reproduced from Kleinart and Geva¹⁴ with permission.

proliferative response at the site of high shear stress. The presence of a VSD will add to the increased shear stresses produced by an acute aortoseptal angle. Subsequent investigators have also demonstrated a steepened aortoseptal angle in association with discrete subaortic stenosis, with and without a VSD.¹⁵

Mechanical stress and genetics theory

More recent data from Cape and colleagues¹⁶ highlight the effects of mechanical stress on endothelial cells and the later development of fixed subaortic stenosis. Mechanical stresses alter the structural and functional properties of cells by mechanotransduction. The stresses are converted to electrophysiological and biochemical responses in the sensing cells, and this is followed by adaptation of the cells to external forces by altered gene expression.¹⁷

A four stage aetiology for the development and progression of discrete subaortic stenosis has been proposed, based on Cape's hypothesis.¹⁶ The procession of events begins with an underlying morphological abnormality, such as a steep aortoseptal angle, which is associated with a genetic predisposition and results in cellular proliferation when exposed to altered septal shear stresses. A genetic predisposition to the development of subaortic stenosis has been documented in Newfoundland dogs,¹⁸ while a familial occurrence of subaortic stenosis has been reported in humans.^{19,20} Other evidence for cellular proliferation related to abnormal shear stresses has been obtained in studies of atherogenesis,²¹ where obstruction to flow has been shown to develop after exposure to abnormal stresses in subjects with a predisposition to circulatory vascular disease.

UNUSUAL ASSOCIATIONS WITH DISCRETE SUBAORTIC STENOSIS

Bilateral fibrous ridges have been noted in patients with a doubly committed VSD. Turbulence is maximal in the area of the subpulmonary and subaortic ridges, and the histopathological similarities suggest a common mechanism for the development of fibrous ridges in patients with this type of VSD.²² The increased flow across the left ventricular outflow tract in patients with a patent arterial duct²³ may be the stimulant for membrane development, while the haemodynamic changes accompanying pulmonary artery banding²⁴ have been implicated in the development of subaortic stenosis related to a secondary leftward shift of the conal septum. A further intriguing association is the trilogy of double chambered right ventricle with subaortic narrowing. The

severity or progression of the subpulmonary obstruction and any relation to the severity of subaortic narrowing is unclear.²⁵

CONCLUSIONS

The pathophysiology of discrete, fixed subaortic stenosis is now closer to being understood. The definitive answer may evolve with further cellular biological research. Studies on endothelial and other growth factors may eventually provide the means of preventing and treating this intriguing heart lesion.

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