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Abnormalities of the Left Ventricular Outflow Tract Associated With Discrete Subaortic Stenosis in Children: An Echocardiographic Study

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Objectives. **The purpose of this study was to examine the echocardiographic abnormalities of the left ventricular outflow tract associated with subaortic stenosis in children.**

Background. **Considerable evidence suggests that subaortic stenosis is an acquired and progressive lesion, but the etiology remains unknown. We have proposed a four-stage etiologic process for the development of subaortic stenosis. This report addresses the first stage by defining the morphologic abnormalities of the left ventricular outflow tract present in patients who develop subaortic stenosis.**

Methods. **Two study groups were evaluated—33 patients with isolated subaortic stenosis and 12 patients with perimembranous ventricular septal defect and subaortic stenosis—and were compared with a size- and lesion-matched control group. Subjects ranged in age from 0.05 to 23 years, and body surface area ranged from 0.17 to 2.3 m^2. Two independent observers measured aortoseptal angle, aortic annulus diameter and mitral-aortic separation from previously recorded echocardiographic studies.**

Results. **The aortoseptal angle was steeper in patients with isolated subaortic stenosis than in control subjects ($p < 0.001$). This pattern was also true for patients with ventricular septal defect and subaortic stenosis compared with control subjects ($p < 0.001$). Neither age nor body surface area was correlated with aortoseptal angle. A trend toward smaller aortic annulus diameter indexed to patient size was seen between patients and control subjects but failed to achieve statistical significance ($p = 0.08$). There was an excellent interrater correlation in aortoseptal angle and aortic annulus measurement. The mitral-aortic separation measurement was unreliable. Our results, specifically relating steep aortoseptal angle to subaortic stenosis, confirm the results of other investigators.**

Conclusions. **This study demonstrates that subaortic stenosis is associated with a steepened aortoseptal angle, as defined by two-dimensional echocardiography, and this association holds in patients with and without a ventricular septal defect. A steepened aortoseptal angle may be a risk factor for the development of subaortic stenosis.**

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Subaortic stenosis constitutes up to 20% of all forms of left ventricular outflow obstruction in children (1,2). Subaortic stenosis is commonly subclassified into several different types that are differentiated from idiopathic hypertrophic subaortic stenosis (2). The membranous type, which occurs in 75% to 85% of all patients with subaortic stenosis (3–5), is characterized by a fibrous membrane located just below the aortic valve (6). This membrane may be attached to the anterior leaflet of the mitral valve and encircle the left ventricular outflow tract.

Considerable evidence suggests that subaortic stenosis is an acquired and progressive lesion. It is rarely seen in neonates (7), but frequently develops during the first decade of life (3,8–11). Subaortic stenosis has been associated with other cardiac abnormalities, such as perimembranous ventricular septal defect in up to 35% of cases (11–14), and several other abnormalities of the left ventricular outflow tract, such as small aortic annulus, steep aortoseptal angle and increased mitral-aortic valve separation (12–15). These associated abnormalities in the left ventricular outflow tract suggest not only that subaortic stenosis is an acquired lesion, but also that it requires some preexistent morphologic substrate for development (9,11,16,17). Because altered morphology produces altered flow, a potential connection arises between abnormal fluid dynamics and the development of subaortic stenosis.

We have proposed a four-stage etiologic process for the development of subaortic stenosis (companion report [18]). This study addresses the hypothesis that subtle morphologic abnormalities of the left ventricular outflow tract exist in patients who develop subaortic stenosis (stage I), with or without associated congenital heart defects. If these subtle abnormalities are the primary substrate for the development of subaortic stenosis, it may explain the finding that only one-third of patients with subaortic stenosis have associated congenital heart defects, such as a ventricular septal defect. We addressed this hypothesis by studying the echocardiographic anatomic characteristics of the left ventricular outflow tract in

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children with and without subaortic stenosis. These morphologic abnormalities of the left ventricular outflow tract associated with subaortic stenosis have been previously reported (12–15), but there have been conflicting results (13,14). The finding of a steepened aortoseptal angle, which is particularly interesting from a fluid dynamic viewpoint, has been reported in only one investigation (14). It was therefore especially important to validate this result in an independent study before further investigation.

Methods

Patient group. We reviewed the echocardiograms of all patients with subaortic stenosis diagnosed at our institution between July 1988 and July 1994. Subaortic stenosis was defined as a discrete fibrous membrane or fibromuscular ridge in the left ventricular outflow tract. Patients with complex left ventricular outflow tract obstruction, such as tunnel subaortic narrowing or subaortic stenosis secondary to malalignment of the ventricular septa, either anterior or posterior deviation, were excluded from the analysis. One echocardiographic study per patient was selected on the basis of image quality. The patients were further categorized on the basis of an associated ventricular septal defect. Patients with isolated subaortic stenosis were compared with body surface area–matched control subjects. Patients with subaortic stenosis and a ventricular septal defect were compared with body surface area– and lesion-matched control subjects with respect to ventricular septal defect anatomy. Ventricular septal defects were all located in the perimembranous region of the interventricular septum and ranged in size from 2 to 5 mm, as estimated by two-dimensional echocardiography. All control subjects with an isolated ventricular septal defect have remained free from developing subaortic stenosis at latest follow-up (range 6 to 84 months).

Echocardiographic studies. Studies were performed with three types of cardiac scanners (Acuson 128XP, Hewlett-Packard Sonos 1000 and 1500) and with transducer frequencies appropriate for patient size (2.5 to 7.5 MHz). Studies were recorded on 0.5-in. (1.27-cm) videocassette tape. The studies were reviewed independently by two investigators. Each rater performed all measurements in each patient to provide two complete data sets. Optimal still frames were independently selected by the raters for these measurements.

The following measurements were all performed from the standard parasternal long-axis view, and the average of three values was used in subsequent analysis. *Aortoseptal angle* is the angle formed by the long axis of the ascending aorta and the plane of the ventricular septum (Fig. 1). This measurement was performed in the manner of Fowles et al. (19) at end-diastole, just before aortic valve opening. This long-axis view was the best choice for these measurements because it has consistent landmarks and also places the aortoseptal angle perpendicular to the ultrasound beam, thereby providing the greatest definition of the endocardial surfaces used to perform this measurement. To measure the aortoseptal angle, the midline axis of the aortic root was constructed by bisecting the root at the level of the aortic annulus and above the sinotubular junction. The midline axis of the septum was constructed by bisecting the septum at the level of the mitral leaflet tips and 2 cm apically from that point. The angle between these lines was then measured from hard copies obtained using a Hewlett-Packard 77501A printer. *Aortic annulus diameter* was measured in early systole (at aortic valve opening) from the apparent valve leaflet hinge points.

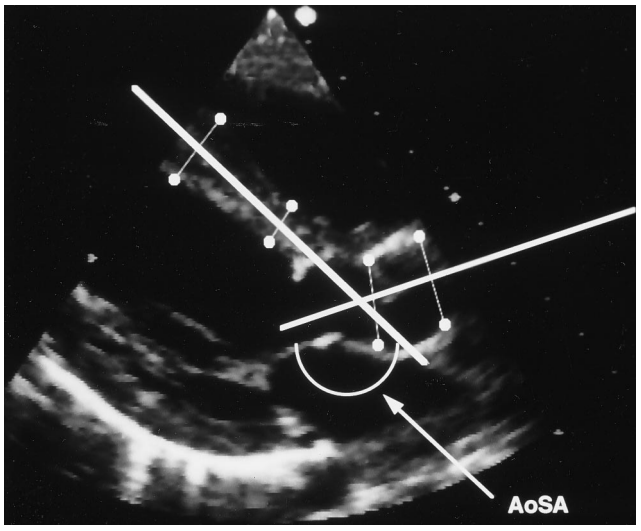


Figure 1. Measurement of the aortoseptal angle (AoSA) from the parasternal long-axis view in early systole (just before aortic valve opening).

Mitral-aortic valve separation was measured from the hinge point of the noncoronary aortic valve leaflet to the hinge point of the anterior mitral valve leaflet. This measurement was performed at end-diastole, at mitral valve closure.

Statistical analysis. All data are expressed as mean value ± SD. For the aforementioned measurements, comparisons between the four groups were performed using the Tukey procedure. The aortic annulus diameter was indexed to the square root of the body surface area, and an independent *t* test for comparison of the mean indexed annulus dimension between patients and control subjects was performed. For all comparisons, $p < 0.05$ indicated a significant intergroup difference. The reliability of the echocardiographic measurements was assessed by evaluating interrater consistency. This was accomplished by using linear regression analysis between two raters for each measurement and calculating the mean difference in measurements.

Results

Patient group. Echocardiographic studies of 90 patients met selection criteria. Of the 45 study patients with subaortic stenosis, 33 patients had isolated subaortic stenosis and 12 had subaortic stenosis associated with a perimembranous ventricular septal defect. Patient age ranged from 0.05 to 23 years (overall mean 8.26 ± 4.76). Patient body surface area ranged

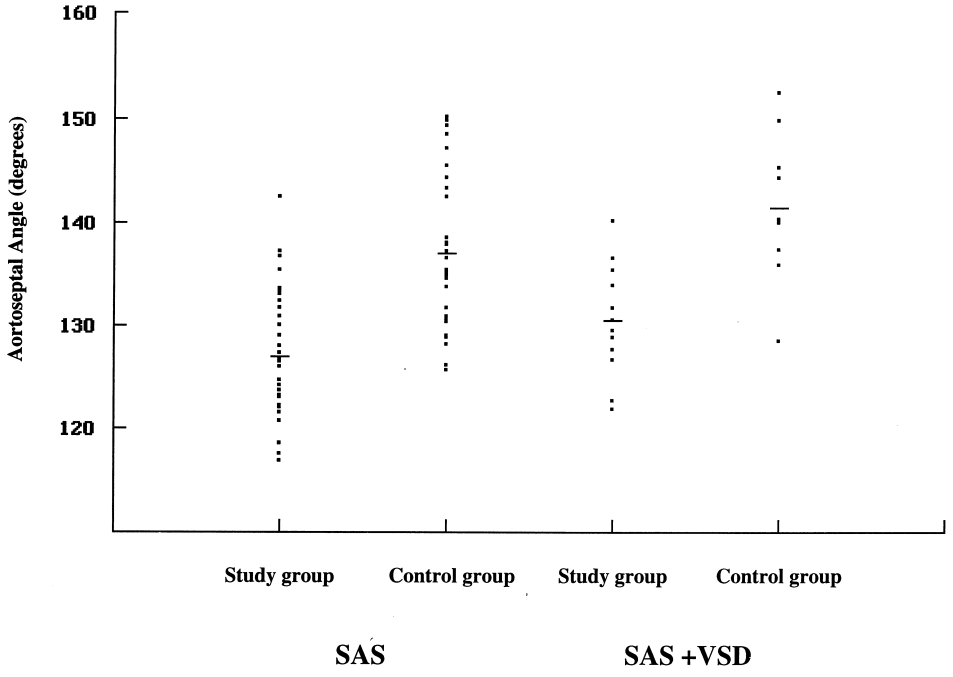


Figure 2. Results of aortoseptal angle measurements in both the study patients and control subjects. SAS = subaortic stenosis; VSD = ventricular septal defect.

from 0.17 to 2.30 m^2 (overall mean 1.04 ± 0.46). For the patients without a ventricular septal defect, there was no significant difference in age (8.6 ± 5.2 vs. 9.0 ± 4.6 years) or body surface area (1.1 ± 0.5 vs. 1.1 ± 0.5 m^2) between patients and control subjects, respectively. There was also no significant difference in age (8.0 ± 4.8 vs. 5.9 ± 3.7 years) or body surface area (0.9 ± 0.4 vs. 0.9 ± 0.4 m^2) between patients and control subjects with a ventricular septal defect, respectively.

Echocardiography. Aortoseptal angle was significantly steeper in patients with isolated subaortic stenosis than in control subjects ($p < 0.001$) (Fig. 2). This was also true for patients with subaortic stenosis and a ventricular septal defect compared with control subjects ($p < 0.001$). The aortoseptal angle was not significantly different between patients with subaortic stenosis and those with subaortic stenosis associated with a ventricular septal defect ($p = 0.4$), nor was this difference significant between control subjects with and without a ventricular septal defect ($p = 0.2$). Neither age ($r = 0.10$) nor body surface area ($r = 0.08$) was correlated with aortoseptal angle. Excellent interrater correlation was found in the aortoseptal angle measurement ($r = 0.997$, mean interrater difference 4.8%).

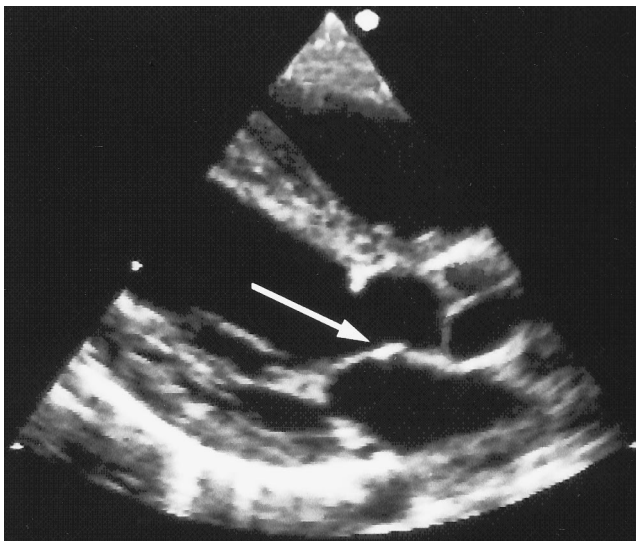
A trend toward smaller aortic annulus diameter indexed to patient size was seen between patients (16.5 ± 2.0 mm/m) and control subjects (17.3 ± 2.1 mm/m), but this failed to achieve statistical significance ($p = 0.08$). Excellent interrater correlation was found in the aortic annulus measurement ($r = 0.994$, mean interrater difference 9.0%).

Measurement of the mitral-aortic valve separation was found to be unreliable in both patients and control subjects, as it was often not possible to consistently determine this separation. In patients with subaortic stenosis, the mitral-aortic valve separation appeared to be secondary to posterior extension of the subaortic membrane onto the anterior leaflet of the mitral valve, resulting in tethering of the anterior mitral valve leaflet and altered mobility (Fig. 3).

Discussion

A steeper aortoseptal angle was consistently associated with subaortic stenosis for all patients studied. The results reported

Figure 3. Two-dimensional echocardiogram of parasternal long-axis view showing posterior extension of the subaortic membrane to the anterior leaflet of the mitral valve, giving the appearance of a hinge point, presumably due to tethering of the mitral leaflet by the membrane.



herein provide independent support for the findings of Kleinert and Geva (14), who demonstrated an association between steeper aortoseptal angle and subaortic stenosis. These findings only suggest that steep aortoseptal angulation may be a risk factor for subaortic stenosis. Fluid modeling studies testing the effect of variable flow angulation have shown that the shear stress on the interventricular septal surface increases with a steeper aortoseptal angle (companion report [18]). Altered fluid shear stress has been shown to induce vascular endothelial cell turnover in vitro and has been connected to the development of vascular obstruction in animal models (20,21). Therefore, the steepened aortoseptal angulation may not only be a risk factor for subaortic stenosis, but may also play a basic role in its development.

Aortoseptal angle predictive value. Figure 2 demonstrates that there is significant overlap in aortoseptal angle between patients and control subjects. This would indicate that the aortoseptal angle measurement is not *specific*. However, it is clear from Figure 2 that a threshold value in aortoseptal angle exists. If a patient has a measured aortoseptal angle steeper than 130° to 135°, the angle is a *sensitive* marker for possible development of subaortic stenosis. The finding of such a critical aortoseptal angle may be of great value in identifying patients at risk for the development of subaortic stenosis.

Effect of other associated abnormalities. Previous investigators have speculated that a ventricular septal defect may cause turbulence in the region of the interventricular septum adjacent to the defect, which may in turn stimulate the development of a subaortic membrane (22–24). Flow modeling studies have supported these speculations by demonstrating increased shear stresses along the interventricular septum in the region adjacent to the ventricular septal defect (companion report). This may explain the association between perimembranous ventricular septal defects and subaortic stenosis development. However, not all patients with a ventricular septal defect develop a subaortic membrane. Our results suggest that a steeper aortoseptal angle may be the most important pathogenic substrate for the development of subaortic stenosis, and may be enhanced by further alterations of shear stress imposed by the presence of a ventricular septal defect.

Our results indicate that there is no difference in aortic annulus dimensions between patients with subaortic stenosis and control subjects. These results are in contrast to the findings from a study of pathologic specimens (13), but agree with the more recent results of other investigations where this association was evaluated by echocardiography (14). More work is required to firmly establish the association of subaortic stenosis with small aortic annulus.

Previous studies (12,15) have reported increased mitral-aortic separation in patients with subaortic stenosis. We found this to be an inconsistent measurement. An abnormal fulcrum for mitral valve movement, as seen from the parasternal long-axis view, could possibly be due to posterior extensions of the subaortic membrane onto the anterior leaflet of the mitral valve. In addition, the dynamic quality of this mitral-aortic valve distance suggests that in some patients, a Venturi effect may contribute to the appearance of mitral-aortic separation.

Study limitations. The left ventricular outflow tract has a dynamic nature, and the measurement of the aortoseptal angle from a still frame at one point in the cardiac cycle is an oversimplification of this complex and changing morphology. However, both the present study and the previous work by Kleinert and Geva (14) have found the steeper aortoseptal angle to be consistently associated with subaortic stenosis when measured in systematic fashion.

This investigation was retrospective, and thus did not establish the preexistence of a steep aortoseptal angle before subaortic stenosis development. A prospective study that identifies individuals with a steep aortoseptal angle and then observes this cohort for a long period will help establish or disprove the fundamental role of steeper aortoseptal angle in the development subaortic stenosis. This study would be feasible in patients who are under care for a ventricular septal defect, because these individuals would routinely undergo an echocardiographic study before subaortic stenosis development.

Conclusions. This study demonstrates that subaortic stenosis is associated with steepened aortoseptal angle, as defined by two-dimensional echocardiography, and that this association holds true in patients with and without a ventricular septal defect. This investigation lays the foundation for flow modeling studies that may provide direct evidence that altered septal shear stresses cause proliferation of endocardial cells in the left ventricular outflow tract, resulting in subaortic obstruction. If the association between steep aortoseptal angulation and subaortic stenosis development can be firmly established, management of those patients identified as being at risk for the development of subaortic stenosis could be altered.

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