JACC Vol. 19, No. 4
March 15, 1992:818–24

PEDIATRIC CARDIOLOGY

Rheologic Genesis of Discrete Subvalvular Aortic Stenosis: A Doppler Echocardiographic Study

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To determine whether morphologic structures or abnormal flow patterns predispose to pathologic proliferation of subvalvular tissue, 26 patients (mean age 19.8 ± 10.3 years) were studied ≥6 months after operation for isolated discrete subvalvular aortic stenosis. The aortic root diameter and the mitral-aortic separation were measured with sector echocardiography. Flow patterns in the left ventricular outflow tract of these patients and control subjects were evaluated with a color flow mapping system optimized for the detection of turbulence.

All control subjects had laminar flow throughout systole in the left ventricular outflow tract. By contrast, turbulence originating well below the site where the shelf had previously been resected was observed in 20 (77%) of the 26 patients. In 16 of these 20 patients turbulence was caused by a ridge, which in 13 patients could be identified as the offshoot of a ventricular band. In four patients the turbulence was caused by malalignment of the muscular and membranous septum, resulting in protrusion of the muscular septum into the outflow tract. Except for the latter four patients, the aortic root diameter was 84 ± 10% of values predicted by body surface area, with values in six patients falling below the third percentile ($p < 0.01$). The mitral-aortic separation was 9.7 ± 3.5 mm, values in 21 patients falling above the 97th percentile ($p < 0.001$).

These data support the theory that discrete subvalvular aortic stenosis may be caused by a chronic flow disturbance, preferably in a small and long outflow tract. Left ventricular bands, if reaching the outflow tract, may be a factor. Because recurrence of subaortic stenosis is a frequent problem, these findings argue for careful echocardiographic and surgical exploration of the outflow tract well below the subvalvular stenosis to detect and resect structures that cause turbulence.

(J Am Coll Cardiol 1992;19:818–24)

There is clinical and experimental evidence that discrete subvalvular aortic stenosis is an acquired lesion. However, the substrate of the postnatal development of this malformation is poorly understood. Morphologic abnormalities of the outflow tract (1), persistent embryonic endocardial cushion tissue with residual proliferative capacity (2,3) and abnormal flow patterns and turbulence have been suggested to lead to proliferation of subvalvular tissue. Flow patterns can currently be assessed by Doppler color flow mapping. In this study we investigated whether morphologic abnormalities or abnormal flow patterns in the left ventricular outflow tract can be identified in patients with subvalvular aortic stenosis.

In a preliminary study we evaluated flow patterns in patients with isolated subvalvular aortic stenosis before operation. The subvalvular obstruction itself caused considerable turbulence. Moreover, a significant acceleration of the blood was identified across the obstruction, starting well below the lesion. This acceleration was believed to obscure any turbulence that might originate below the subaortic stenosis. Interpretation of flow patterns in these circumstances would be speculative. We therefore chose to evaluate patients after surgical resection of the subvalvular stenosis. We speculated that if abnormal flow patterns did induce the subvalvular obstruction, these flow abnormalities originated upstream from an area that was likely to be left unaltered by the operation.

Methods

Study patients. We studied electively 26 patients, 16 male and 10 female, with a mean age (± SD) of 19.8 ± 10.3 years (range 3.4 to 53) ≥6 months after operation for isolated discrete subvalvular aortic stenosis. The mean age at operation was 13.4 ± 9.1 years (range 2.8 to 46) and the mean time since operation 6.4 ± 4.4 years (range 0.6 to 15). Patients with a long tunnel type of stenosis were excluded from this study. No patient had marked aortic valve disease at the time of operation for subaortic stenosis (gradient <25 mm Hg or no more than mild stenosis at surgical inspection, regurgitation grade ≤2/4 on aortography). During infancy one patient underwent closure of a patent ductus arteriosus and three patients underwent repair of coarctation of the aorta with good hemodynamic result. Six patients had

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Manuscript received June 19, 1991; revised manuscript received October 3, 1991, accepted October 15, 1991.

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0735-1097/92/$5.00

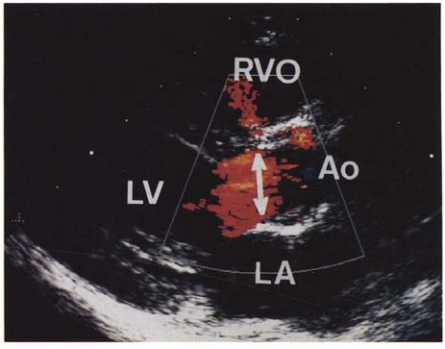

Figure 1. Long-axis systolic flow map of a normal left ventricular (LV) outflow tract. Note the complete absence of variance below the insertion of the aortic valve (arrow). Variance in this and subsequent color maps is displayed in green. Ao = aorta; LA = left atrium; RVO = right ventricular outflow tract.

an asymmetric or bicuspid aortic valve without a significant pressure gradient (<25 mm Hg).

The preoperative subvalvular peak to peak gradient at cardiac catheterization was 81 ± 28 mm Hg (range 40 to 140). In 9 patients the surgeon described the lesion as a crescent-shaped, fibrous curtain adhering to the septal surface, and in 17 a ring was found with adhesions to both the septum and the anterior mitral valve leaflet. The obstruction was peeled with blunt dissection in 14 patients and resected in the remaining 12. An additional myomectomy was performed in 12 patients.

Fifty-eight normal control subjects, 36 male and 22 female, were studied; their age ranged from 0.83 to 56 years (mean 17.2 ± 13.1).

Echocardiography. The study protocol was approved by the Ethical Committee on Human Research. Informed consent was obtained from the patient or the parent where appropriate. The subaortic area was visualized from different angles and flow patterns were identified throughout the outflow tract with a color flow mapping system (Acuson 128). The system was optimized for detection of variance. Care was taken to use the lower frequencies of the transducers (3 or 2 MHz), to select the appropriate Doppler color scales and to avoid oversaturation of the Doppler color level. Variance in these conditions was considered to display true turbulent blood flow. By determining flow patterns throughout the outflow tract, flow separation could be excluded or identified in all subjects. No attempt was made to quantify the degree or extent of turbulence. Aortic regurgitation was quantified as proposed by Perry et al. (4). From a standard left parasternal long-axis view the aortic root was measured at the site of insertion of the aortic valve cusps at end-diastole. Data were expressed as a percent of the normal value predicted by body surface area (5). Similarly, the mitral-aortic separation was measured in early diastole from the site of insertion of the noncoronary cusp to the base of the anterior mitral leaflet. All data are expressed as mean values ± SD.

Results

Flow patterns in the left ventricular outflow tract. Aortic regurgitation was observed in 18 patients. When quantified as proposed by Perry et al. (4), aortic regurgitation was found to be mild in eight patients, moderate in nine and moderately severe in one patient. In most patients there was no significant increase from the preoperative level.

During systole all control subjects had laminar blood flow in the left ventricular outflow tract (Fig. 1). By contrast, turbulence originating well below the site of the previous subvalvular stenosis was observed in 20 (77%) of the 26 patients. Longitudinal and transverse echocardiographic sections showed the turbulence to adhere to the septal surface, reaching the subaortic area where the subvalvular shelf had been resected (Fig. 2).

Two types of anatomic abnormality could be identified as causing the turbulence. In 16 of the 20 patients the turbulence was caused by a ridge that rose 17 ± 4 mm (range 13 to 23) from insertion of the aortic valve (Fig. 3 to 5). This ridge could be identified in 13 patients as the offshoot of a ventricular band that originated more apically in the ventricle. In four patients the turbulence was caused by protrusion of the crest of the muscular septum into the outflow tract. This protrusion resulted from malalignment of the muscular and membranous septum. The membranous septum did not join the muscular septum at its crest but inserted 15 to 26 mm more apically on the right ventricular side of the septum (Fig. 6).

Six of the 26 postoperative patients had normal laminar blood flow in the ventricular outflow tract. In five of them

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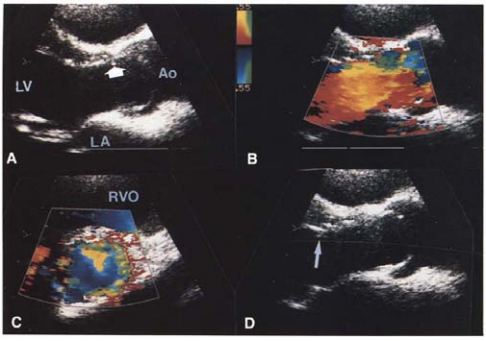


Figure 2. Echocardiograms of the left ventricular (LV) outflow tract 5 years after resection of a crescent-like subaortic obstruction. **A,** There is a mild recurrence of the discrete subaortic stenosis (**arrow**). **B,** Color flow map showing flow separation with variance (**green**) anterior in the outflow tract, originating well below the region of the subaortic obstruction. **C,** Color map of the outflow tract in the short-axis view shows the cloud of turbulent flow to adhere to the septum where previously a crescent-like obstruction had been resected. **D,** The cause of the turbulence could be identified as a small ridge (**arrow**), which was the offshoot of a spiral ventricular band. Other abbreviations as in Figure 1.

echocardiographic examination of the left ventricle demonstrated a muscular band that fused at an obtuse angle with the interventricular septum 15 to 24 mm below the aortic valve. In these patients we were unable to identify turbulent flow reaching the subaortic region.

Left ventricular outflow tract dimensions. The size of the aortic root in the control subjects was 98 ± 6% of values predicted by body surface area (p = NS) (5). The four patients with malalignment of the ventricular and membranous septum had a normal aortic root size (88%, 92%, 98% and 127%, respectively, of values predicted by body surface area). In contrast, the aortic root diameter in the remaining 22 patients was 84 ± 10% of values predicted by body surface area, with values in 6 patients below the third percentile ($p < 0.01$) (Fig. 7). The mitral-aortic separation was 9.7 ± 3.5 mm with values in 21 of the 26 patients above the 97th percentile ($p < 0.001$) (Fig. 8). Thus, although some

Figure 3. Long-axis systolic flow map of the left ventricular (LV) outflow tract after resection of a discrete subaortic crescent just below the aortic (Ao) valve. There is flow separation with marked turbulence (**green**) caused by a ridge (**large arrow**) that was the offshoot of a spiral ventricular band. **Thin arrow** = insertion of the right coronary aortic cusp. Other abbreviation as in Figure 1.

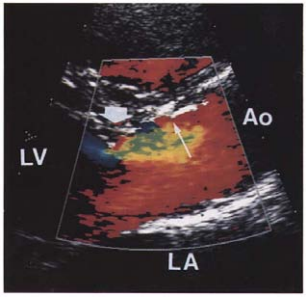
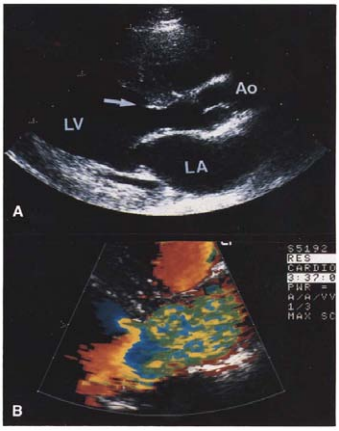


Figure 4. **A,** Long-axis echocardiogram of the left ventricle (LV). The **arrow** points to the insertion of a longitudinal ventricular band. **B,** Color flow map showing turbulence throughout the subaortic region. A ringlike obstruction had previously been resected in this patient. Other abbreviations as in **Figure 1.**



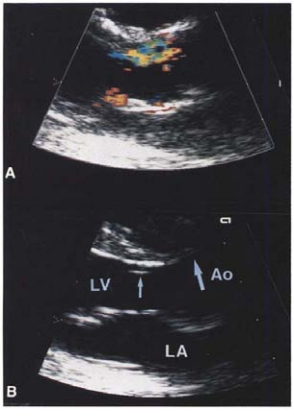


Figure 5. **A,** Systolic color flow map shows variance in the anterior part of the subaortic region. Flow in the posterior part was mapped from more obtuse angles and found to be laminar. **B,** The two-dimensional echocardiogram identifies a small ridge (**small arrow**) as a cause of the flow separation. In this patient no ventricular band could be related to the ridge. **Large arrow** = insertion of the right coronary aortic (Ao) cusp. Other abbreviations as in Figure 1.

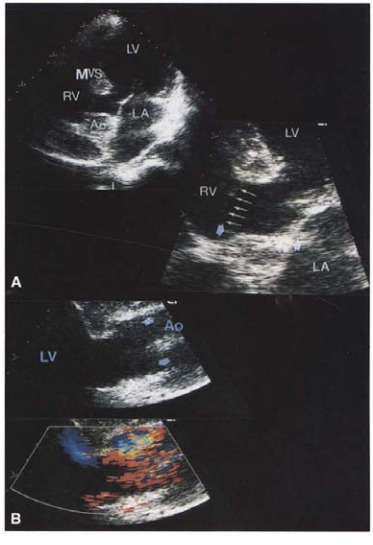


Figure 6. **A,** Apical five-chamber view at **left** demonstrates malalignment of the muscular (M) and membranous ventricular septum (VS). **At right,** magnification of the left ventricular (LV) outflow tract shows a huge membranous septum (26 mm, **small arrows**) inserting not on the crest of the muscular ventricular septum but on the right ventricular side. **B,** This causes the muscular septum to protrude into the outflow tract without causing an obstruction (parasternal long-axis, view **top**). However, the systolic color flow map (**bottom**) shows turbulence in the region where the surgeon had previously resected a subvalvular aortic stenosis. **Large arrowheads** = aortic valve anulus. RV = right ventricle; other abbreviations as in **Figure 1.**

patients had normal left ventricular outflow tract dimensions, the majority had an outflow tract that was narrower and longer than normal.

Discussion

For years cardiologists have been intrigued by the pathogenesis of subvalvular aortic stenosis. In some children with no evidence of any obstruction to left ventricular ejection subvalvular stenosis can develop for no apparent reason. The progression to stenosis can occur at any age and its speed is variable (6–8), but it appears to occur more rapidly in young patients, patients with associated aortic valve stenosis and patients with the tunnel type of subaortic narrowing. Even after surgical removal of the subvalvular crescent or ring, the stenosis may recur in a significant proportion of these patients. This observation suggests that the lesion is the result of a pathologic process that was left unaltered by the operation. Some high risk groups have been described, such as patients with a ventricular septal defect, coarctation of the aorta, patent ductus arteriosus, left superior vena cava and aortic valve stenosis (6,9), but the pathologic substrate has not been clearly defined. Lack of understanding of the pathophysiologic mechanism makes it difficult to provide medical and surgical management for these patients or any person at risk for subaortic obstruction.

With the development of color flow mapping systems with high spatial and temporal resolution, it became possible to evaluate the hypothesis that a discrete subvalvular aortic stenosis is caused by chronic flow disturbance. Our study demonstrates that in most patients, even after surgical removal of the subvalvular obstruction, abnormal flow patterns are present when the blood flow reaches the subaortic area. These data support the hypothesis that chronic turbulence may be the pathophysiologic mechanism for the development of subvalvular aortic stenosis and its recurrence.

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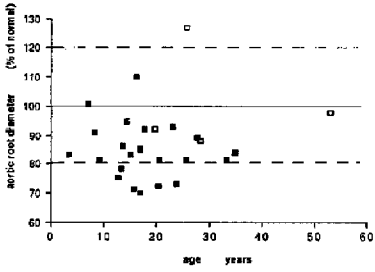
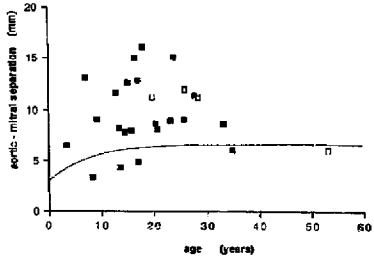


Figure 7. Scattergram of the aortic root dimension in 26 patients expressed according to age as a percent of normal for body surface area (mean values ± 2 SD are represented). The **open squares** represent the four patients with malalignment of the muscular and membranous septum.

Causes of turbulence. *A septal ridge more apical in the outflow tract.* Two anatomic substrates caused turbulence in the left ventricular outflow tract. In the majority of patients a ridge could be identified that was more apical in the outflow tract. Color flow mapping clearly demonstrated this ridge to cause a cloud of turbulence adhering to the septal surface, reaching the subaortic region where previously a crescent-like stenosis had been surgically removed. This ridge was unlikely to be a surgical artifact; its site was more apical than the site where the obstruction had been resected, and in the majority of patients this ridge was the offshoot of a ventricular band. In some patients these bands had been observed during previous echocardiograms. However, most of these bands had an oblique course and therefore were not evident on routine echocardiographic views. With Doppler color flow studies, attention was focused on turbulence. Then, by determining the cause of turbulence, the septal ridge was found. This ridge was frequently not seen on standard (orthogonal) views. Only ridges in the anterior position will be seen routinely; all others will be missed. Patients with these findings also had a small aortic root, a feature reported in other series (1,5,10). A narrow outflow tract may predispose to the onset of subaortic stenosis, because it contributes to the development of turbulence and may augment the rheologic impact on the endothelium of the heart or vessels. In our laboratory, flow mapping of the outflow tract of patients with a tunnel-like stenosis, the most severe type of subaortic stenosis, shows an enormous amount of turbulence throughout the tunnel, even after surgical relief of the gradient. This may explain why surgical treatment in these patients is almost invariably complicated by recurrence of the obstruction.

Figure 8. Scattergram of the aortic-mitral separation in 26 patients. The **open squares** represent the four patients with malalignment of the muscular and membranous septum. The 97th percentile for normal hearts is represented (**solid line**).



Malalignment of the interventricular septum. In a smaller subgroup, turbulence was caused by the crest of the interventricular septum, which protruded into the outflow tract because of malalignment of the membranous and muscular septum. The membranous septum, normally a very small structure, was significantly enlarged and could measure up to 26 mm; in each of these patients it could be differentiated from the septal leaflet of the tricuspid valve. None of these patients was ever known to have had a ventricular septal defect. A similar anatomic situation is created when the surgeon closes a relatively large perimembranous ventricular septal defect, especially when it is associated with malalignment and mild aortic override. To avoid the conduction system, the patch is sewn on the right ventricular side of the interventricular septum, which causes the crest of the septum to protrude into the left ventricular outflow tract. Zielinski et al. (11) demonstrated that a malalignment type of ventricular septal defect is a constant feature in patients who develop preoperative or postoperative discrete subaortic stenosis with ventricular septal defect.

A longer outflow tract. The mitral-aortic separation corresponds to the aortic-mitral fibrous continuity (12) and forms with the anterior mitral leaflet the base of the left ventricular outflow tract. This distance was increased in the current and previous series (1,13). However, it is not known whether this morphologic feature is present before subaortic stenosis develops or is secondary to the crescent-like stenosis that often extends from the septum onto the anterior mitral leaflet and may remodel the base of the outflow tract. A longer outflow tract enhances flow separation and may therefore predispose to occurrence (or recurrence) of discrete subvalvular aortic stenosis.

Small outflow tract. Only laminar flow throughout systole was observed in the left ventricular outflow tract of normal subjects over a wide age range. However, normal blood flow is close to turbulence as the Reynolds number (14) reaches critical values, especially in infants and small children. The slightest irregularity may destabilize the brittle laminar flow in these small outflow tracts, resulting in a significant amount

of turbulence that in time may induce growth of subvalvular tissue. The likelihood of turbulent flow decreases as the heart grows: the acceleration of blood and flow velocities decreases, and the outflow tract becomes bigger, especially in relation to any protrusion that might cause turbulence.

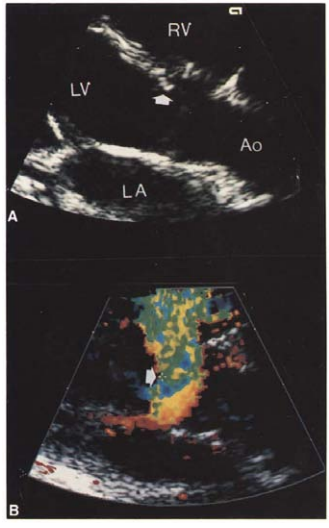
Apical muscular band. Six patients had normal laminar systolic flow throughout the left ventricular outflow tract after surgical resection of a discrete subvalvular stenosis. In five of the six a muscular band was found more apically. At the time of study these bands did not cause turbulence reaching the subaortic area. It may be hypothesized that at an earlier age and in a smaller heart these bands extended closer to the aortic valve, possibly at a more acute angle. In such circumstances these bands may have caused turbulence in the subaortic region and induced the subaortic stenosis. Left ventricular bands have been described in normal hearts (15). However, our study suggests that if these bands reach the left ventricular outflow tract, they may be less innocent than generally thought.

Turbulence and remodeling of pathways. In this study turbulence appears to be the common pathway in the development of subaortic stenosis. Turbulent blood flow may damage the endothelium and thereby initiate the formation of platelet and fibrin deposition. Turbulent fluid shear stress has been demonstrated to increase endothelium cell turnover (16). This sequence of events is similar to that seen in the course of primary plug formation with vascular injury (17) and has been suggested as a possible cause for the late development of aortic coarctation (18,19). Langdon et al. (20) studied an elegant model and demonstrated that rheologic factors can cause remodeling and narrowing of paths. They created a mild coarctation by placing a braided Dacron ligature around the aorta in 4- to 7-day old puppies. In 3 of the 18 animals a second new coarctation was evident 1 cm distal to the surgically induced narrowing on reevaluation at age 18 months. It consisted of a diaphragmatic structure with a central opening. The extent of the diaphragm was determined by local rheologic factors, particularly the origin of intercostal arteries. The investigators (20) concluded that the second coarctation was produced by the effects of abnormal blood flow in the developing aorta. Microscopic examination of these diaphragms disclosed an amorphous ground substance with scanty cellularity. Few smooth muscle cells were surrounded by elastic lamellae and the lumen surfaces were covered by endothelial cells. Subaortic shelves have a very similar aspect on microscopic examination (21).

Recurrence of discrete subvalvular aortic stenosis. Several mechanisms for recurrence of subvalvular aortic stenosis have been suggested. On the basis of our echocardiographic and Doppler ultrasound findings, we suggest that the surgeon, by resecting the subvalvular obstruction, only removes the end product of a rheologic disturbance but leaves the underlying cause unaltered. Thus, if the predisposing factors are not critically modified by another process, subaortic stenosis is likely to recur. Such processes may include growth of the outflow tract, slowing of blood acceleration and peak velocities (22,23), decreasing endogenous levels of catecholamines and changes in reactivity of blood platelets (24), leukocytes (25) or the endothelium. A better understanding of the pathophysiology of the development of discrete subvalvular aortic stenosis will influence the management of patients with this condition. Surgery should not only aim at relief of the obstruction, but also streamline the outflow tract by removing protrusions that create turbulence. If the link between turbulence and proliferation is better understood (26–29), drug treatment may both help prevent recurrence of stenosis after incomplete relief of turbulence and limit progression of a discrete stenosis or even tunnel stenosis.

Some investigators (30) hypothesize that the cause of recurrent stenosis is related to scar formation in the subvalvular area as it heals, thus fixing the size of the left ventricular outflow tract. Within the growing heart, a fixed outflow tract would result in recurrent stenosis even in the absence of further narrowing. However, this mechanism is

Figure 9. Parasternal long-axis two-dimensional echocardiogram (A) and color flow map (B) of the left ventricular outflow tract of a patient with a ventricular septal defect and a small subaortic shelf (arrow). Blood accelerates from the middle of the outflow tract toward the septal defect, hitting the crest of the ventricular septum at the site where the shelf is formed. Other abbreviations as in Figures 1 and 6.



unlikely to account for the majority of restenoses, which consist of a new crescentlike structure.

Ventricular septal defect and subaortic stenosis. Turbulence may also be the critical link between a ventricular septal defect and the frequent occurrence of discrete subvalvular aortic stenosis. Figure 9 shows a systolic flow map perpendicular to the left ventricular outflow tract in a patient with a small ventricular septal defect and a mild discrete subaortic stenosis. Blood accelerates from the middle of the outflow tract toward the septal defect, hitting the crest of the ventricular septum at the site where the shelf is formed.

The incidence rate of bacterial endocarditis in discrete subvalvular aortic stenosis, which may be as high as 13% to 25% as assessed at operation (31,32), is fully 10 times greater than the rate in any other congenital heart malformation. Damaged endothelium, which may be caused by chronic turbulence, is a superior predisposing factor for infective endocarditis (33).

Conclusions: clinical implications. These data support the hypothesis that discrete subvalvular aortic stenosis may be the result of a chronic flow disturbance. Left ventricular bands, seen in a large proportion of patients with this condition, may be less benign than is generally thought because they may cause flow separation. Because subaortic stenosis frequently recurs, these findings argue for careful echocardiographic and surgical exploration of the left ventricular outflow tract well below the subvalvular stenosis to detect and, if possible, resect structures that cause turbulence.

We gratefully acknowledge the critical and constructive comments of Prof. ir. J. Mewis and ir. P. Moldenaers of the Laboratory of Applied Rheology.

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