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*Editorial Comment*

# The Long and the Short of It: Some Thoughts About the Fixed Forms of Left Ventricular Outflow Tract Obstruction*

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Any number of institutions have demonstrated the progressive nature of the fixed forms of the so-called membranous, discrete or fibromuscular subaortic stenosis and have commented on the secondary changes of the aortic valve that result in aortic insufficiency (1–6). Progression may at times be particularly rapid and egregious, whereas in other patients the obstruction may be mild and relatively quiescent (1,2,7,8). Those factors determining the rate and severity of progression are unknown. Significant and progressive left ventricular outflow tract obstruction promotes left ventricular hypertrophy, myocardial ischemia, secondary damage to the aortic valve with resulting aortic insufficiency and the ever-present risk for infective endocarditis (1,6,9,10). Thus, operative intervention to prevent these consequences is certainly indicated. But what remains both contentious and concerning are the criteria for and timing of intervention and the expectation of recurrence.

In this issue of the Journal, Brauner et al. (11) document the benefits of early surgical repair in a reasonably large cohort with fixed subaortic stenosis. The authors state that "it has been the institutional policy at the University of California Los Angeles since the early 1980s to proceed with resection of subaortic stenosis at the time of patient referral, regardless of the degree of left ventricular outflow tract obstruction or involvement of the aortic valve." Their data seemingly support this policy, showing that surgical intervention before the occurrence of a significant (>40 mm Hg) left ventricular outflow tract gradient significantly reduced the incidence of recurrence, reoperation and progression of secondary aortic valve disease. Surprising? Yes. Specific issues? Some. One cannot dispute their data, but perhaps one should soften their conclusions. The mean age of their patients at operation was 8.6 years (median six). The length of postoperative follow-up was 6.7 ± 0.9 years. This is certainly not long-term follow-up, and I wonder what another 10 to 20 years of follow-up will indicate about this institutional policy. It is of interest that Coleman et al. (12) from Toronto have also addressed the merits of early intervention. A preoperative mean pressure gradient <30 mm Hg was used as indication for surgical intervention. Results from their study indicated that early subaortic resection did not reduce the rate of recurrence but was likely to reduce acquired damage of the aortic valve. A number of reasons could explain the differences between the two institutions, including surgical technique and specific anatomic substrate of the left ventricular outflow tract. In this regard, Brauner et al. (11) characterize the nature of the obstruction in conventional ways. But perhaps more attention to the pathologic substrate would be predictive of a specific subset of patients anticipated not to experience a recurrence or a substrate more at risk. Not all patients with subaortic stenosis demonstrate aortic–mitral fibrous discontinuity (13–17). Some will be identified as having posterior deviation of left ventricular outflow tract septal components with an intact ventricular septum (18–20), and others will have a small aortic annulus (21,22). What is the proximity of the obstructing subaortic tissue to the aortic valve (23)? Some patients will be identified with all or some of these morphologic variables. Are these morphologic features at all predictive of outcome, early as well as truly late? And is there a hierarchy of risk? Thus, despite the seeming simplicity of this disorder, the considerable morphologic heterogeneity of subaortic stenosis, the interface between rheology and altered endothelium, the variable outcome of surgical intervention and the risk for recurrence all underscore the complexity of this disorder (24–31).

Somerville (32) some years ago suggested that the so-called fibrous, diaphragmatic or discrete forms of subaortic stenosis are none of these. In many respects her observations are valid (10,32). Yet her views must be interpreted in terms of her patient clientele: an older and often adult population. We will return to this issue. When one surveys the historical aspects of this disorder, acknowledging that justification is not really required, it is evident why this condition was considered fibrous or diaphragmatic or membranous. The angiocardiographic image in at least some patients was that of a discrete lucency suggestive of a membrane or diaphragm at a variable distance beneath the aortic valve with considerable systolic excursion (15). Furthermore although cross-sectional echocardiographic imaging is certainly diagnostic of this condition, it too often failed to show the true extent of the disorder (16,17,26,33,34). Although able to visualize a circumferential ridge at a variable distance beneath the aortic valve, echocardiographic imaging usually does not provide information about echocardial changes that may be extensive. Yet both surgical or postmortem inspection of the left ventricular outflow tract indicated that in most patients, tissue obstructing the left ventricular outflow tract was considerably more diffuse and less membranous than anticipated.

The so-called short-segment or fixed forms of left ventricular outflow tract obstruction are indeed complex, with considerable heterogeneity in their morphologic expressions. It is

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this heterogeneity that perhaps explains some of the variability in the surgical outcome of these patients (11,12). The so-called fixed or short forms of left ventricular outflow tract obstruction do occur in isolation, but as in the patients studied by Brauner et al. (11) they may be associated with ventricular septal defect, ventricular septal defect and divided right ventricle, atrioventricular septal defect, aortic valvar stenosis, aortic coarctation and patent arterial duct; (1–3,7,11,15,16,19,20,35–39). However, for the purpose of this commentary, my remarks will be largely confined to patients with concordant atrioventricular and ventriculoarterial connections and an intact ventricular septum, although my musings may be germane to more complex forms of left ventricular outflow or systemic outflow tract obstruction as well.

There are any number of peculiarities about the fixed forms of left ventricular outflow tract obstruction. They have features of both congenital and acquired disorders of the heart (1,7,15,30,40,41). The fixed forms of subaortic stenosis are only rarely observed in the fetus, and it is unusual for these forms to be manifest in the neonate and young baby (42–44). One can then ponder whether the fixed forms of left ventricular outflow tract obstruction are indeed congenital abnormalities or are acquired, or both? Data provided by Pyle et al. (45) from observations of the genetically inherited canine form of left ventricular outflow tract obstruction showed that the lesions were not seen in dogs <3 weeks old, and the mildest form was observed only in dogs between 3 and 12 weeks old. Of considerable interest was the variable morphologic expression of left ventricular outflow tract obstruction in this canine model. The mildest form consisted of a variable number of 1- to 2-mm nodules on the endocardial surface of the interventricular septum immediately below the aortic valve, and some nodules were noted on the ventral surface of the aortic valve cusps. This form was neither membranous nor, in its classical sense, diaphragmatic. The most severe form was characterized by a nodular fibrous band, ridge or collar that completely encircled, or nearly so, the left ventricular outflow tract just below the aortic valve. This circumferential nodular ring was raised 1 to 2 mm above the endocardial surface and extended across the interventricular septum beneath the aortic valve cusp and the anterior leaflet of the mitral valve at its base. The ventricular surface of the aortic valve was considerably thickened as well. Pyle et al. (45) also stratified the pathologic features of the left ventricular outflow tract by age. The mildest lesions were never observed in dogs >12 weeks old, and the severest defects were seen predominately in dogs >6 months old. Pyle et al. suggested that the mildest changes in the left ventricular outflow tract represent an early form of the defect, which matures (? progresses) with age. If one tries to extrapolate these canine observations to humans (and that may be inappropriate in view of the different histopathologic features of the canine subaortic stenosis compared with those features in humans [46]), it is possible that the early representation of the defect is more discrete than that observed in the older patient or adult. Nonetheless, despite the absence of subaortic obstruction in the newborn puppy, there is an inherent disposition to this development. What is also unclear from this interesting study is the nature of the left ventricular outflow tract. Is the left ventricular outflow tract longer and narrower in those dogs destined to develop subaortic stenosis compared with those that do not?

For a number of years it has been speculated that the occurrence of subaortic left ventricular outflow tract obstruction results from a specific anatomic substrate promoting abnormal and likely turbulent flow dynamics. The sequela of these abnormal flow patterns is an abnormal fibrous response at the endothelial surface expressed as an excessive growth of fibrous tissue (24–28). The formation, then, of the fixed forms of subaortic stenosis can be related to defined morphologic characteristics of the left ventricular outflow tract. Considered common to almost all forms of fixed subaortic obstruction is an outflow tract that is longer and narrower than "normal" and that it is this abnormal outflow tract that is the rheologic stimulus to the endothelial response (24–28). Fibromuscular obstruction has been attributed to increased aortic–mitral separation according to observations based on the normal extent of aortomitral separation in humans (13,14). Other mechanisms have also been implicated in the morphogenesis of subaortic stenosis, including an intrinsically small aortic outflow tract and a hypoplastic aortic annulus (21,22). Zielinsky et al. (19) suggested that in patients with a ventricular septal defect, malalignment of septal components was one stimulus for the development of subaortic stenosis in this setting. Ozkutlu et al. (18) described posterior deviation of left ventricular outflow tract components but without a ventricular septal defect as the cause of subaortic stenosis. Cape et al. (47) showed that the changes in the aortoseptal angle produces important changes in shear stress and that the levels of stress increase are consistent with cellular flow studies showing stimulation of growth factors and cellular proliferation. They suggest, as have others, that a steepened aortoseptal angle may be a risk factor for the development of subaortic stenosis (18,19,33,47,48). Perhaps the most consistently abnormal left ventricular outflow tract is that of the atrioventricular septal defect. The consequence of deficiency of atrioventricular muscular and membranous septum is that the aorta is unsprung from its normal wedged position between the atrioventricular valves. This results in disproportion between the dimension of the left ventricular inlet and outlet, resulting in an abnormally long and narrow left ventricular outflow tract (15,49,50). But although subaortic stenosis has been adequately documented in patients with the partial or complete form of atrioventricular septal defect, both preoperatively and postoperatively, the overall incidence of this association or sequela remains small (51–55). Similarly, among patients with anatomically corrected malposition of the great arteries and a well defined subaortic left ventricular infundibulum preventing aortomitral continuity, subaortic stenosis, again although well documented is not particularly frequent (56–58).

Thus, as one considers those factors defining the genesis of subaortic obstruction, certainly an intrinsically abnormal left ventricular outflow tract is important. But what sets the stage

for subaortic stenosis when one cannot define a rheologic stimulus? Could specific cells in the left ventricular outflow tract be programmed to an abnormal endothelial response? Speculation for consideration. The observations of Ferrans et al. (46) some years ago may be germane to these comments. They studied the ultrastructure of the fibrous ring in patients with discrete subaortic stenosis excised at operation (note the nosology). Histologic and untrastructural analysis disclosed the presence of five tissue layers in these tissues. These layers included 1) a surface monolayer of endothelial cells; 2) a subendothelial layer rich in acid mucopolysaccharides and basement membrane-like material; 3) a fibroelastic layer containing collagen and small elastic fibers; 4) a layer of smooth muscle cells with thickened basement membranes; and 5) a central fibrous layer with large amounts of collagen and small amounts of elastic fibers. They observed that the connective tissue layers in these collars or rings were discontinuous and that the layered arrangement of these tissues was reminiscent of normal endocardium of the left ventricular outflow tract. If there is escalation of the pathology of the left ventricular outflow tract with age, one should not be surprised that the operative or postmortem findings of the left ventricular outflow tract are diffuse, with a thickened, irregular collar of tissue extending from beneath the aortic valve, from the septal surface to the anterior mitral leaflet and to the ventricular surface of the aortic valve. Finally, subaortic stenosis, like many (?all) forms of congenital heart disease, is a paradigm for education. We continue to be challenged by the clinical management of the fixed forms of subaortic stenosis and desire to understand the more fundamental mechanisms of the mechanical stress–endothelial interface and the genetic regulatory factors that are so persuasive in this form of congenital heart disease (24–28,44,45).

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