Outcomes and Questions About Discrete Subaortic Stenosis

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Discrete subaortic stenosis (DSS) is a well-described cause of isolated left ventricular outflow tract (LVOT) obstruction in children. The lesion is of obvious hemodynamic significance, but in addition, it is recognized to be the result of a dynamic process that continues and has consequences into adulthood. Consequently, there are questions (including the mechanism of formation, the surgical approaches, the implications for the aortic and mitral valves, and its natural history, as well as the likelihood of recurrence) the answers to which are important to the understanding and treatment of DSS. Despite the many reports on DSS, none of these related questions have been answered completely. The report on surgical outcome of discrete subaortic stenosis in adults by van der Linde et al in the March 19, 2013, issue of *Circulation*, however, adds useful information on the latter questions. This report and others in the literature indicate DSS, even after an apparently successful surgical resection, is a lesion that does not go away easily.

DSS in its discrete form, without a tubular obstruction of the LVOT, is fairly uniform in appearance. For the surgeon, the resection of a DSS is both a “nice case” and one that may prove to be dismaying in the future. DSS is often an essentially circular fibromuscular rim of tissue, with a fibrous inner ring of varying width. The location will vary from just beneath the aortic valve, where occasionally it will be fused with the dependent portion of a cusp, to a position lower down the LVOT with attachments to the anterior leaflet of the mitral valve. This location means that not only will it place a load on the left ventricle (LV), but the resulting turbulence will also affect the aortic valve downstream.

The mechanism for DSS formation has been the subject of debate since its original description. Despite being generally classified as a congenital heart defect and, on rare occasion, appearing in infancy, the general opinion is that DSS is an acquired lesion. There have only been rare reports suggesting a familial occurrence, and overall, there is little evidence that it is a primarily genetic disorder. Although a developmental origin has the most support, it does not appear to completely explain these lesions, and questions remain.

The inciting anatomy and the beginning events may be quite subtle, and early childhood cases have been described in which no apparent echocardiographic abnormality of the LVOT was seen initially; nevertheless, DSS developed later and grew relatively rapidly. The mechanism of DSS formation has not been settled completely; nevertheless, the information available has led to what appears to be a mechanism for its development with implications for longer-term treatment. In children with DSS, a sharper ventricular-aortic angle has been described, and it has been proposed that increased shear forces are generated on the LVOT as the LV output turns the corner and flows out the aortic valve. In addition, an increased separation of the aortic and mitral valves and greater aortic valve overriding of the septum have also been found and may add to the rheological effects that lead to DSS.

The action of the shear forces on the endothelial cell layer of the LVOT could stimulate proliferation of these cells and start the process. A great deal of basic work on biomechanical transduction has shown how similar forces induce cellular growth and division. Furthermore, if shear forces damage the endocardial layer, the cellular injury would attract fibroblasts to begin the repair. Cell injury will also release cytokines and other components of an inflammatory response that stimulate the differentiation of the fibroblasts to contractile and collagen-secreting myofibroblasts. Continued myofibroblast proliferation could lead to further buildup of a fibromuscular layer, producing DSS in the LVOT. A similar process triggered by shear forces generated by flow past anomalous right ventricular muscle bundles would appear responsible for the os infundibulum sometimes seen in patients with tetralogy of Fallot. What produces the flow disturbances that lead to a DSS is more subtle, and after a successful resection, what caused them is usually not apparent looking through the aortic valve. The process is not easily stopped, however, and even after complete operative relief, the recurrence of a DSS a few years later can be disappointing. Remarkably, on reoperation, the DSS often looks pristine, as though there were no previous resection.

A steep ventricular-aortic angle that produces increased shear forces could activate the mechanism for the production of a fibromuscular DSS, but questions remain. A common observation is that the ventricular-aortic angle becomes more acute with age in normal people, and in the elderly, this may be quite pronounced. The initial formation of DSS in the older age group, however, is at best a very rare occurrence. Furthermore, a shear mechanism generally should be operative; nevertheless, DSS occurs in only a small minority (~6%) of children with congenital heart defects such as ventricular septal defect and aortic coarctation that are associated with its formation. In contrast, other shear-associated lesions, such as those that occur in coronary and peripheral arterial disease, occur with a much higher incidence. Although it may be logical that these events would be induced along the aortoventricular angle, they should be less operative on the free wall side of the LVOT. The lesion that forms, however, is
often rather symmetrical and forms as robustly in the outflow track across from the ventricular septum. Finally, patients with idiopathic hypertrophic subaortic stenosis have a marked deviation of the outflow septum into the LV, and despite the severe angulation and resulting shear forces, a DSS-like lesion does not develop. These inconsistencies might suggest that a secondary genetic factor is also necessary for DSS formation.

The surgical resection of a DSS is well understood, as are its pitfalls. Resection of the fibromuscular tissue typically begins below the right coronary ostium and can be carried posteriorly and leftward along the ventricular septum without significantly incurring the risk of heart block. More posteriorly along the septum, the chance of creating a ventricular septal defect will be greater with a deeper resection; however, and not to minimize this complication, it should be apparent and can be repaired at the time. A similar risk exists with vigorous dissection along the free wall of the LV; however, the penalty for excessive resection would be considerably greater. The dissection is continued around the LV wall and then more anteriorly until septum is again reached. From here until reaching the starting point beneath the right coronary ostium, the dissection should not incise the septal tissue, because the conduction bundle may be virtually on the surface.

The debate over whether the resection should be limited to the DSS itself or include more of the hypertrophied LVOT has not been settled. In the present report, a more extended myocardial resection was not advised, because in their patients, it neither provided more complete relief of the obstruction nor reduced the reoperative rate, and it carried an increased risk of heart block. Others, however, including this author, advocate a more generous resection. Given the continuing dynamic nature of the DSS process, a more complete widening of the LVOT that leaves little or no obstruction should reduce or at least slow the redevelopment of a significant gradient. Careful preoperative echocardiographic studies are valuable in providing useful information about the thickness of the septum and LV free wall and will pay dividends in allowing an effective resection without significant complications.

The second major consequence of DSS is damage to the aortic valve from 2 possible causes. Either the aortic or mitral valve, unfortunately, may be caught up in the DSS process and become attached to the fibromuscular shelf. For the aortic valve, separation can often be accomplished without damaging the cusp; however, involvement with the anterior leaflet of the mitral valve may pose a more difficult surgical problem. An intrinsic mitral valve abnormality that includes duplication of part of the leaflet tissue may make it difficult to both remove the obstructing tissue and maintain valve competence. In the large study by van der Linde et al, however, difficulties with the mitral valve were not reported.

More common and usually of much greater long-term significance is damage to the aortic leaflets from the jet effect and turbulence generated by the DSS. Although turbulence is a universal feature of DSS, the amount of aortic regurgitation that results has been variable even over the medium term. Regurgitation results from cusp thickening and retraction, the result of a general response that appears to resemble the formation of a DSS. Certainly, a turbulent jet hitting the undersurface of the aortic valve at the onset of systole might damage the surface layer of the cusp, inciting a fibroblast response and, with more injury, inflammation. The injury pattern, as described previously, stimulates the influx and differentiation of fibroblasts into contractile myofibroblasts, producing thickened, contracted cusps with impaired coaptation.

Medium-term studies have found a significant portion (20% to 40%) of patients with mild or moderate aortic regurgitation. Over the reported study periods, the regurgitation appeared to be only slowly progressive. Small but distinct increases in the number of patients with mild or moderate regurgitation were found, although severe leakage rarely developed. Most of these patients, however, had a relatively short follow-up (a median of 13 years) compared with their presumed life-span of ≥70 years. Once damage has begun, it will probably continue, especially with the likely residual and increasing LVOT obstruction producing turbulence. This important question will require even longer-term studies to answer. Valve dysfunction may become more significant with time, and it may not be wise to discount the old adage that regurgitation begets regurgitation.

Echocardiographic evaluations of DSS lesions also reliably show a fluttering of the aortic leaflets in systole, which is observed as early as there is any LVOT obstruction (personal communication, from a discussion with J. Berry, February 2013). It is possible the abnormal fluttering may also damage the cusp by injuring both the cells and the collagen and elastin strands that provide a sophisticated support network for the leaflets. The fluttering, moreover, is not necessarily symmetrical, which raises the additional question of whether or not the injury would be evenly distributed among the cusps. It remains to be determined whether the fluttering produces valve damage and dysfunction; nevertheless, it is a good marker for the presence of turbulent flow, which does produce injury.

The process that leads to DSS formation and its consequences remains as these patients pass from the pediatric age group into adulthood. Among the many lesions grouped under pediatric heart defects, the mechanism that leads to DSS is perhaps the most persistently active and deserving of continuing follow-up. The multicenter study by van der Linde et al, with its relatively large size, begins to define some of the longer-term issues. The combining of data from multiple institutions will have drawbacks, as has been noted by the authors, but these deficiencies are outweighed by the large size of the resulting group of patients. Certainly, the several centers (and countries) would be expected to have differing indications for treatment, especially with a study period encompassing 30 years. The authors acknowledge that the operative criteria were not uniform during the study, but the indications are not universally agreed on even today.

With a lesion that may recur and valve damage that will likely increase along with the obstruction, we must look to longer-term studies for treatment guidance. There are several important questions to be answered, which include the likelihood of recurrence, the onset and progression of aortic valve regurgitation, the ability of the LV hypertrophy that results from the DSS to regress with successful resection, the possible later onset of LV dilation, and the risk of endocarditis. For answers to these questions, data from patients followed up into adulthood are essential. Among the reports, the study by
van der Linde et al.12 joins those by Oliver et al.,15 Stassano et al.,16 and Vogt et al.17 on patients followed up into early adulthood and, for a few, beyond. The group studied by Vogt et al.17 contains a number of more severe and lengthy LVOT lesions, which makes comparisons with DSS patients difficult. The remaining studies provide information on what might be ahead for the young adult after DSS resection.

From these studies, it can be expected that on average, the degree of LVOT obstruction will slowly progress. For these series, the gradient increased at an average rate of ≥1 to 3 mm Hg per year, although with considerable variation.2,15,16 The results of the first resection appeared to be equally effective whatever the initial gradient, but as might be expected, the rate of increase was greater in patients with more obstruction initially, which suggests a more difficult LVOT. Somewhat surprisingly, the gradient also increased more quickly in females and older patients.2 Taken together, the reoperation rate for DSS was 1.8% per patient-year, or more concretely, 26% of patients had a reoperation within an average of 13 years, very high figures for this relatively short time span. Again these were young adults, and the recurrence number will climb during middle age and probably beyond. Although DSS formation has often been thought to not be very progressive past childhood, the study by van der Linde et al.12 disputes that conclusion and indicates the continuing effects on the myocardium will likely be important. Even longer-term studies will be important to determine the course of the DSS process and its consequences on the aortic valve and myocardium.

The criteria for resection were not firmly set in this multicenter study, and the peak gradient at the time of operation varied from 30 to 100 mm Hg.2 When the initial gradient was ≥80 mm Hg, the results indicated that the DSS would recur more rapidly and the number of patients with aortic regurgitation would increase over a relatively short time span of 10 years. There would likely be widespread agreement that an operation should be performed for a peak gradient of 60 mm Hg or a mean gradient of 40 mm Hg.15,19 For many, the presence of aortic valve dysfunction would lead to a recommendation for resection at an even lower gradient. Finally, the criteria should be similar for initial and subsequent operations, although it may be necessary to consider lowering them if the consequences are becoming worse.

The addition of exercise testing should prove valuable for the evaluation of these patients. For those with a resting gradient of 40 mm Hg, exercise will likely demonstrate that the obstruction is quite significant. Furthermore, echocardiograms and other scans may show significant LV dysfunction. These studies show that with time, it may again become necessary to relieve the effects of a DSS on the LV myocardium and the aortic valve. With continuing ventricular hypertension and the predictable spikes in pressure with daily activities, the possibility of subendocardial ischemia, damage, and fibrosis seems likely. In the series reported by van der Linde et al.,12 a number of patients were hospitalized or died of cardiac failure; no specific causes were given, but certainly this could be a later consequence of DSS.

Valve motion studies may also prove important in the analysis of these patients. If systolic valve flutter can be linked to leaflet damage, this finding may need to be added to the treatment algorithm. Finally, once the process of damage of the aortic cusps, including inflammation and contraction, is under way, the valve will be vulnerable to infection and the development of endocarditis. This well-recognized complication poses a lifelong risk for DSS patients.

The difficulties in analyzing inherently complex clinical problems are obvious; nevertheless, large series do generate valuable information. In this author’s opinion, the trends revealed in the study by van der Linde et al.2 will be useful, if not precise, in considering management strategies. Furthermore, although the data do not answer some of the longer-term questions, they certainly better frame them. The well-recognized tendency of DSS to recur and even occur a third time means these patients should be seen well into adulthood. A DSS also sets in motion consequences for the aortic valve and myocardium, each of varying potential severity for the patient. Neither the DSS nor the potential complications are completely predictable, and these patients should be followed up in clinics for adults with congenital heart disease for years to come.

Disclosures

None.

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