Pathogenetic Mechanisms of Prolapsing Aortic Valve and Aortic Regurgitation Associated With Ventricular Septal Defect

Anatomical, Angiographic, and Surgical Considerations

By Katsuhiro Tatsuno, M.D., Souji Konno, M.D., Masahiko Ando, M.D., and Shigeru Sakakibara, M.D.

SUMMARY

The developmental mechanisms of prolapse and regurgitation of the aortic valve which complicate ventricular septal defect (VSD) were investigated from the anatomical, angiographic, and surgical viewpoints on the basis of autopsied heart specimens, preoperative thoracic aortography, and surgical records.

Two major, conceptually distinct but functionally interdependent factors contribute to the aortic valve’s prolapse into the VSD. The major feature of the first category is the lack of anatomical support for the valve. In subpulmonary VSD, a regional defect of the conal septal musculature which supports a section of the right coronary sinus and the annulus was observed. In infracristal VSD, a deficiency of the sinus of Valsalva was noted.

The hemodynamic effects, which actually produce prolapse of the anatomically unsupported valve into the VSD, is the second contributing factor. The left-to-right shunt of blood through the VSD during the early systolic phase pulls the sagging aortic valve into the defect. The distinctive feature of the second category is that prolapse of the anatomically unsupported valve is produced by hemodynamic effects. Diastolic aortic pressure does not appear to contribute greatly to bulging of the aortic valve into the right ventricular cavity. However, in the diastolic phase, the closed valve is subject to intra-aortic pressure, causing the free margin of the prolapsed cusps to hang down, to gradually become elongated, and finally to separate from the free margin of the other two cusps, and thus be rendered incompetent.

Additional Indexing Words:
Anatomical factors Hemodynamic factors Conal septal musculature Annulus

Sinus of Valsalva

This study was undertaken to assess the etiological determinants of a prolapsed aortic valve in an associated ventricular septal defect (VSD). Van Praagh and McNamara’s report, based on morphological findings of autopsied heart specimens, is among the most extensive and accurate of those concerning this problem. Additional data resulting from the study of a ruptured aneurysm of the sinus of Valsalva also has previously been described. Two intrinsic factors appear to be involved. The first is the lack of anatomical support for the valve, and the second deals with hemodynamics that may augment prolapse.

In this report the developmental process of prolapse of the aortic valve in patients with a VSD and aortic regurgitation is discussed on the basis of 120 heart specimens with isolated VSD, 112 operated cases with a VSD and aortic regurgitation, and 85 preoperative thoracic aortograms of those surgical instances.

Anatomical Factors

As pointed out in previous reports, in all cases of prolapsing aortic valve and regurgitation, the VSD is adjacent to the annulus of the aortic valve. However, in many cases of isolated VSD, the superior margin of the defect is closely adjacent to the aortic valve annulus. Studies performed on 120
heart specimens with uncomplicated VSD at the Heart Institute of Japan revealed that the VSD was present immediately beneath the aortic valve in 81 cases (table 1), while aortic regurgitation was evident in only six (7%). Thus protrusion of the valve into the VSD must involve a mechanism other than mere adjacency of the VSD and the aortic valve.

As Van Praagh et al. described, deficiency in anatomical structures supporting the aortic valve's annulus and the sinus of Valsalva are highly correlated with the eventual prolapse of the valve through the VSD. Normally, and in many cases of uncomplicated or isolated VSD, the sinus of Valsalva and elements of the annulus are supported by the thick conal septum (parietal band) issuing from the right ventricular side. In some cases of uncomplicated VSD a deficiency of this musculature has been observed. Figure 1 (right panel) is the right ventricular view of an autopsied heart.

Table 1

<table>
<thead>
<tr>
<th>Classification</th>
<th>No. of autopsied cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD contiguous with aortic valve's annulus</td>
<td>81</td>
</tr>
<tr>
<td>Subpulmonary VSD</td>
<td>20</td>
</tr>
<tr>
<td>Infraaristal VSD</td>
<td>50</td>
</tr>
<tr>
<td>Total conal defect</td>
<td>2</td>
</tr>
<tr>
<td>VSD not contiguous with aortic valve's annulus</td>
<td>39</td>
</tr>
</tbody>
</table>

As Van Praagh et al. described, deficiency in anatomical structures supporting the aortic valve's annulus and the sinus of Valsalva are highly correlated with the eventual prolapse of the valve through the VSD. Normally, and in many cases of uncomplicated or isolated VSD, the sinus of Valsalva and elements of the annulus are supported by the thick conal septum (parietal band) issuing from the right ventricular side. In some cases of uncomplicated VSD a deficiency of this musculature has been observed. Figure 1 (right panel) is the right ventricular view of an autopsied heart.

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**Figure 1**

*Left panel* Right ventricular view of an autopsy specimen with isolated conal septal defect, having a denuded aortic valve and sinus of Valsalva. The unsupported aortic valve and sinus (surrounded by dotted line) are exposed in the right ventricular lumen. Right panel Bird's-eye view of the right coronary and noncoronary sinus of Valsalva from an autopsy specimen with isolated infraristal VSD. Semilunar-shaped concave formations are seen at the nadir of the sinuses (marked with arrows). These consist of the same translucent fibrous tissue, as is found in the adjacent valve leaflets. PV = Pulmonary valve; TV = Tricuspid valve; RCS = Right coronary sinus; RCC = Right coronary cusp; NCS = Noncoronary sinus.
with a subpulmonary VSD. The conal muscle between the right superior margin of the VSD and the annulus of the right pulmonary cusp is absent (note the dotted line). The right coronary cusp of the aortic valve and the sinus of Valsalva are exposed in the right ventricular cavity. This type of muscular deficiency was found in six of the 120 autopsied specimens. These anatomical features in subpulmonary VSD are quite similar to those of hearts having prolapse of the aortic valve and regurgitation.

In patients with an infracristal VSD, two anatomical anomalies are felt to contribute to the aortic valve’s prolapse into the VSD. One is the same muscular defect observed in subpulmonary VSD, although the deficient portion of the conal septum is slightly lower. The other is an abnormal development of the sinus of Valsalva. Figure 1 (left panel) is a left ventricular view of an autopsied heart with a membranous VSD located just below the right coronary and noncoronary commissure of the aortic valve. A semilunar region of fibrous tissue can be observed at the lowest margins of the right coronary and noncoronary sinuses of Valsalva (marked with arrows). This type of abnormality was found in five of the autopsied specimens. In all of these hearts, the aortic valve was felt to lose the support of the annulus because of the deficiency in the conal septal musculature and the sinus of Valsalva. The aortic valve may be further traumatized by the surge of blood through the left ventricular outflow tract and become susceptible to sagging and bulging into the right ventricle secondary to the hemodynamic action.

Hemodynamic Factors

Prolapse of the anatomically unsupported aortic valve is influenced by at least two hemodynamic factors. The action of the blood shunting through the VSD in early systole forces the aortic valve to prolapse. The influence of the shunt is greater during the early developmental stages of this disease. In the early phase of left ventricular contraction, when the aortic valve is beginning to open, a small amount of blood from the left ventricle shunts through the VSD into the right ventricle. If the anatomically unsupported valve is sagging over the VSD, the opening becomes narrower and the velocity of the blood shunting through the defect is increased, drawing the aortic cusp into the right ventricular cavity (fig. 2). This can be observed by serial aortography as shown in figure 3. The right coronary cusp bulges slightly in early systole, and even less in diastole. In

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**Figure 2**

Schematized illustrations of the hemodynamic action causing prolapse of the aortic valve and the sinus, and regurgitation. Left) Early systolic phase. The anatomically unsupported aortic valve and sinus are drawn into the right ventricular lumen by the action of shunting blood through the VSD. Center) Mid systolic phase. The blood ejected from the left ventricle pushes the unsupported sinus outward, and makes a large bulge in the sinus of Valsalva, which shows on an aortogram. Right) Diastolic phase. The free margins of the three aortic cusps close and establish competency as a result of intra-aortic pressure. The bulged portion becomes less prominent. However, the free margin of the prolapsed cusp is then forced down and elongated by the intra-aortic pressure, finally separating from the other two cusps, thus resulting in incompetency. LV = Left ventricle, RV = Right ventricle, IVS = Interventricular septum, PA = Pulmonary artery, AI = Aortic incompetency.
midsystole, the bulge cannot be observed. The surgical record of this case indicates that the VSD was located in the infracristal portion, and the posterior part of the right coronary cusp bulged slightly into the right ventricular outflow tract through the VSD.

During ejection of blood into the ascending aorta from the left ventricle, the aortic root and sinus of Valsalva expand outward. The anatomically unsupported aortic valve and the sinus are shifted to the right ventricular side during midsystole (fig. 2, center). This hemodynamic influence is greater in cases having a moderate or large bulge of the aortic valve and the sinus, and in advanced stages of this syndrome. Figure 4 indicates a moderate bulge of the

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**Figure 3**

Three different phases of a serial thoracic aortography of a ten-year-old boy in lateral views from the right side. At left above, early systole, a small bulge is observed at the bottom of the right coronary sinus (marked with an arrow). This bulge disappears in midsystole (right panel above), and is less prominent in diastole (right) than in early systole. The infracristal VSD was closed by direct suture.

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right coronary sinus with no aortic regurgitation. The bulge of the sinus, although observed in all phases, is most prominent during midsystole, less in early systole, and least during diastole.

During diastole, on the other hand, the intraventricular pressure forces the three cusps of the aortic valve to close and become competent. As the annulus of the unsupported cusp is shifted toward the right ventricle, the cusp's free margin is pushed down and gradually elongates. Finally it separates from the other two cusps and incompetency results (fig. 2, lower right panel).

Hemodynamic influences present in both systole and diastole therefore contribute to prolapse of the valve and the subsequent increase in aortic regurgi-

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**Figure 4**

Three different phases from a serial aortography of a seven-year-old girl. Aortogram in left panel, above, is a lateral view in early systole, and to right, above, midsystolic phase is shown. The bulge of the right coronary sinus is more prominent in early and mid systole than in diastole (left). The VSD is located in the subpulmonary conal septum. These features of the conal septum including VSD are quite similar to those shown in figure 1 (left panel).
AORTIC REGURGITATION WITH VSD

The two aortograms shown in figure 5 illustrate the systolic and diastolic phases of a typical case with both the aortic valve and sinus prolapsing into the infarctial VSD. The bulge of the lowest portion of the right coronary sinus to the right ventricular side is greater in systole than in diastole. This mobility of the bulged portion during systole and diastole indicates that the unsupported aortic valve is not complicated by deformities such as severe thickening and loss of flexibility and suppleness through hardening. A moderate degree of aortic regurgitation can be observed.

Indication for Surgical Treatment

Based upon the preceding discussion, clinical classification and criteria for surgical treatment were established.

This syndrome is routinely diagnosed with reference to the following factors: 1) determination of time elapsed since the onset of aortic regurgitation; 2) determination by aortography of the relative mechanical mobility of the bulging portion of the aortic valve and sinus during various phases of the cardiac cycle; and 3) determination of the severity of aortic regurgitation by aortography.

From data specific to the above categories, cases of this syndrome can be divided into four groups. In Group A, the early developmental phase, aortic regurgitation is mild or moderate as assessed by aortography, and typically less than three years have elapsed since its onset. The bulged portion of the sinus retains a high degree of flexibility as determined by its relative physical mobility. Group B includes those cases having relatively longstanding (over three years) aortic regurgitation of moderate or advanced severity and small to moderate prolapse of the sinus with poor mobility. Group C consists of the severest cases with longstanding aortic regurgitation (over six years generally and in many cases more than ten years). A huge aneurysmal bulge of the sinus and complete lack of mobility is present. A fourth classification, Group D, is made up of those cases of VSD in

Figure 5

Lateral view of thoracic aortograms of a four-year-old girl with infrarctial VSD, prolapsing aortic valve, and regurgitation. The left panel shows systolic phase. The bulge is seen at the lowest portion of the right coronary sinus. In the diastolic phase (right panel) the bulge of the sinus becomes less serious. A moderate amount of aortic regurgitation is revealed.

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which aortic regurgitation is present but there is no observable prolapse of the aortic valve.

In the majority of patients in Group A, aortic regurgitation is correctable by simple closure of the VSD after thrusting the prolapsed aortic valve to the left ventricular side of the defect. In 33 patients, aortic regurgitation disappeared completely or became less following closure (table 2). There was one exception which showed no change in the level of aortic regurgitation postoperatively; no explanation for this can be offered. Aortic valvuloplasty was required in five cases. The aortograms in figure 6 represent pre- and postoperative changes in the aortic valvular prolapse and regurgitation level in a six-year-old boy. The preoperatively demonstrated prolapse of the right coronary sinus and moderate aortic regurgitation (left panel) disappeared after closure of VSD (right panel).

In contrast, in patients in group B, C, and D, a decrease in the amount of aortic regurgitation by simple closure of the VSD was rarely achieved. Aortic valvuloplasty or valve replacement with an artificial prosthetic valve is necessary to completely relieve the aortic regurgitation (table 2). It is current practice to perform aortic valvuloplasty as far as is feasible in the young patients of groups B and C. Aortic valve replacement is preferable for the older patients in groups B and D and for all patients in Group C.

Figure 7 shows the aortograms of a four-year-old boy from Group B. Mobility of the prolapsed portion of the right coronary sinus is limited, and

<table>
<thead>
<tr>
<th>Group</th>
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<th>VSD closure and aortic valvuloplasty</th>
<th>VSD closure and aortic valve replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>34 (23)*</td>
<td>5 (4)</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>5 (0)</td>
<td>5 (3)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>C</td>
<td>3 (0)</td>
<td>0</td>
<td>7 (6)</td>
</tr>
<tr>
<td>D</td>
<td>15 (3)</td>
<td>3 (2)</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

*Figure within parentheses represents cases in which aortic regurgitation disappeared or was markedly reduced.

Figure 6
Pre- and postoperative aortograms of a six-year-old boy classified on the basis of level of regurgitation in Group A. Although the protrusion of the right coronary sinus and mild aortic regurgitation were demonstrated before operation (left panel), they are not seen following simple closure of the VSD (right panel).
AORTIC REGURGITATION WITH VSD

Aortic regurgitation is severe for his age. Closure of the VSD and plication of the aortic valve were performed. Postoperatively, aortic regurgitation was reduced. Figure 8 shows pre- and postoperative aortograms of a 16-year-old boy from Group C who underwent closure of a VSD and aortic valve replacement.

Improvement or exacerbation of aortic regurgitation was distinguished by auscultation of the aortic regurgitation murmur as well as measurement of the pulse pressure. Left heart catheterization and aortography performed after the operation in 22 of the 112 patients confirmed these changes in the level of aortic regurgitation.

Discussion

Since Laubry and Pezzi reported the first case of VSD with a prolapsed aortic valve and regurgitation, many papers concerning this syndrome have appeared, some of which have dealt with its etiology primarily from the morphological viewpoint. Nadas et al. divided VSD with aortic regurgitation into Type 1 and Type 2, depending on the location of the VSD. Van Praagh and McNamara found that aortic regurgitation in Type 1 (infracristal VSD with aortic regurgitation) resulted from underdevelopment of the aortic valvular commissure, and in Type 2 (subpulmonary VSD), from deficiency of the conal musculature which usually supports the annulus of the aortic valve and the sinus. We concur with this over-all interpretation.

Considering the pathogenesis of aortic regurgitation associated with a VSD, we found two modes distinguishable both anatomically and by aortography. In the first there is the prolapse of the aortic valve into the VSD. The distinctive anatomic features are a deficiency of the conal musculature (fig. 1, right panel) and congenital defect of the lower margin of the sinus (fig. 1, right panel). The deficiency of the conal musculature is found mainly in patients with subpulmonary VSD, while the congenital defect of the sinus is specific to infracristal VSD. A similar deficiency of the conal septum is revealed only infrequently in cases of infracristal VSD.

The second mode is characterized by the absence of prolapse of the aortic valve. No specific deficiency of the aortic valve and the sinus is found in our series of patients with VSD and aortic regurgitation, except for underdevelopment of the valve commissures, as Van Praagh described. Many

Figure 7

Pre- (left panel) and postoperative (right panel) cineaortograms of a four-year-old boy in Group B. He underwent closure of the VSD and plication of the elongated aortic valve. Postoperatively, aortic regurgitation decreased.

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cases with no valvular prolapse have either the subpulmonary VSD or the infracristal VSD (note table 3). We have not encountered patients with infracristal VSD having a bicuspid aortic valve and regurgitation, although two cases were found of subpulmonary VSD in which aortic regurgitation was caused by a bicuspid aortic valve. We speculate that latent endocarditis or other undetermined factors may contribute to aortic regurgitation in those instances of nonprolapsing aortic valve.

Generally, it appears that subpulmonary VSD tends to be associated with a prolapsing aortic valve as the cause of regurgitation. However, the same mechanism provokes aortic regurgitation in the case of infracristal VSD. Congenital anomalies of the aortic valve can be associated with both subpulmonary and the infracristal VSD resulting in aortic regurgitation.

It was originally felt that the unsupported aortic valve prolapsed and bulged into the right ventricular cavity as a result of aortic pressure during diastole. Recent studies of the thoracic aortograms, however, indicated that the main factor was the ejection of blood from the left ventricle during systole. In diastole, on the other hand, the intra-aortic pressure forces the unsupported valve leaflets down, leading to aortic regurgitation. In general, it

### Table 3

<table>
<thead>
<tr>
<th>Group</th>
<th>Subpulmonary VSD (%)</th>
<th>Infracristal VSD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>34 (88)*</td>
<td>5 (12)</td>
</tr>
<tr>
<td>B</td>
<td>12 (87)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>C</td>
<td>9 (90)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>D</td>
<td>17 (77)</td>
<td>5 (23)</td>
</tr>
</tbody>
</table>

*N* Number within parentheses represents percentage of patients within each group.
AORTIC REGURGITATION WITH VSD

is believed that the prolapsed portion of the aortic valve and the sinus becomes distorted gradually by these hemodynamic influences. This does not necessarily culminate in a huge aneurysmal dilatation as shown in figure 8. Patients with this type of aneurysmal sinus are rather rare. Aortograms of many cases in the later stages of this syndrome show a small or moderate bulge of the sinus but severe aortic regurgitation. The size of the bulge depends largely upon the degree of deficiency in the conal musculature which supports the aortic valve annulus and the sinus of Valsalva.

The final and most important consideration in patients with this syndrome is the choice of the surgical procedure for the correction of the aortic regurgitation. Robinson et al.\textsuperscript{12} reported a patient in whom aortic regurgitation was corrected by simple closure of the VSD. Others,\textsuperscript{8, 11, 13, 14} however, have insisted that direct intervention such as valvuloplasty or valve replacement was necessary, since in many cases the valve had become severely elongated and deformed. From our experience, the aortic regurgitation of patients in the early developmental stages of this syndrome has a good possibility of being lessened or eliminated by simple closure of the VSD after thrusting the bulged aortic valve into the left side. However, if the prolapse and regurgitation of the valve are more severe, direct repair on the deformed valve is necessary to correct regurgitation. We favor very careful diagnosis to detect the syndrome in its early developmental stages. Intervention can then be performed before the aortic valve leaflets become markedly stretched and require replacement.

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