

Ventricular Septal Defect and Aortic Valve Regurgitation: Pathophysiology and Indications for Surgery

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As the velocity of a fluid increases a low-pressure zone is created, this is the Venturi effect and it explains the pathogenesis of aortic valve prolapse (AVP) and aortic insufficiency (AI) that is observed in a subset of patients with a ventricular septal defect (VSD). The VSDs complicated by AI are restrictive with high velocity shunting through the VSD, creating a low-pressure zone that impacts the adjacent aortic valve cusp resulting in AVP and subsequent AI. AVP and AI are therefore acquired lesions. AI is absent at birth because the forces necessary to create the low-pressure zone within the restrictive VSD do not exist in utero. The risk of development of AI increases during childhood, peaking at 5 to 10 years of age. VSD closure eliminates the low-pressure zone that is the cause of ongoing aortic valve cusp deformity and, if performed early, prevents development of AI. Patients with a subarterial VSD and AVP should undergo surgery to prevent the development of AI because this complicates about half of subarterial VSDs with AVP and spontaneous closure is rare. Patients with perimembranous VSDs with AVP should be followed with serial echocardiography and undergo VSD closure if more than trivial AI develops.

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A subset of patients with a ventricular septal defect (VSD) will develop aortic insufficiency (AI). These VSDs may be located in the subarterial (also referred to as suprasternal, subpulmonary, doubly committed subarterial, conal septal, or infundibular position), perimembranous (also referred to as subcrystal, conotruncal, or paramembranous position), or outlet muscular positions.¹ AI complicates subarterial VSDs about five times more often than perimembranous VSDs.^{2,3} The aortic cusp adjacent to the VSD has a characteristic deformity in which the nadir of the cusp is elongated and there is associated cusp prolapse with resultant insufficiency. Proposed mechanisms leading to AI in patients with a VSD include a lack of structural support for leaflets adjacent to the VSD, abnormal commissural suspension, lack of appositional

forces, loss of continuity between the aortic media and aortic annulus, and deformity of leaflets adjacent to the defect because of the Venturi effect.⁴⁻⁷ Although several mechanisms may be responsible, a review of literature and natural history observations suggest the Venturi effect is the predominant factor in the development of AI associated with a VSD. Recognition of the Venturi effect as the most important mechanism in the pathogenesis of aortic valve prolapse (AVP) will aid in identification of patients at risk for development of AI, will predict both those patients in whom surgery is indicated as well as the timing of surgical intervention.

The Venturi Effect

Giovanni Battista Venturi (1746–1822) was a professor of physics at the Universities of Modena and Pavia.⁸ His work expanded on Bernoulli's observation that, as the speed of a moving fluid increases, the pressure within the fluid decreases. Venturi's work focused on the application of Bernoulli's principle to fluid passing through smoothly varying constrictions. Fluid passing through conduits of varying diameter will experience changes in velocity and pressure, such

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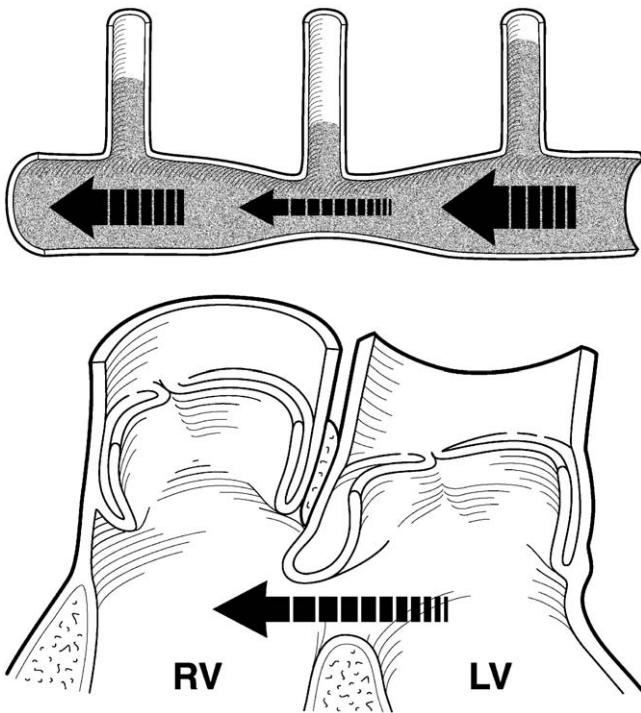


Figure 1 (Top) As a fluid passes through conduits of varying diameter, changes in velocity and pressure will occur, so that as the caliber of the conduit decreases, the fluid velocity will increase and the pressure will decrease. (Bottom) This low-pressure zone within a restrictive VSD can impact the adjacent cusp of the aortic valve.

that as the caliber of the conduit decreases, the fluid velocity will increase and pressure will decrease. One way to gauge the size of a VSD is by the velocity of blood flow through it and this is in part a function of the size of the VSD relative to the aortic root. If there is restriction to flow through the VSD and an aortic valve cusp is adjacent to the defect then the increase in velocity of blood through the defect could adversely affect the adjacent cusp (Fig 1). To function as an effective component of the aortic valve an aortic valve cusp is thin, mobile and sail-like and is therefore especially vulnerable to being drawn into the high-velocity low-pressure jet as blood shunts left to right through a restrictive VSD. Over time this can result in elongation of the nadir of the adjacent aortic valve cusp with progressive AVP and eventually AI (Fig 2). This mechanism was proposed by Tatsuno et al⁷ in 1973. Hypothesizing that the Venturi effect is the mechanism that results in AI, we would predict a number of observations. First, if the velocity of the blood must increase to produce the low-pressure zone that deforms the adjacent aortic cusp, we would anticipate that the VSD must be restrictive. Second, because the left and right ventricular pressures are equal in utero, we would anticipate that the aortic cusp deformity would not be present at birth, but instead would be an acquired lesion. Third, because we are hypothesizing that this is an acquired lesion, we would anticipate that the characteristic cusp deformity would occur in advance of the development of AI. Finally, we would expect that VSDs with override of an adjacent aortic valve cusp would be at greater risk of

development of AI. The observations supporting each of these points will be presented.

The Venturi Effect Is the Predominant Cause of Aortic Valve Cusp Deformity and Subsequent AI

If the Venturi effect explains the development of AI associated with a VSD then the VSD must be restrictive so that the velocity would increase through the defect and result in deforming forces on the adjacent aortic valve cusp. The first evidence indicating that VSDs associated with AI are restrictive is the older age of the patients undergoing surgery for VSD/AI. VSDs that result in congestive heart failure are routinely closed in infancy, whereas those associated with AI are nearly always in older patients and are seldom associated with congestive heart failure. While an occasional infant is included in series of patients with VSD/AI, they are commonly between 5 and 10 years of age.^{2,9-18} Although the role of cardiac catheterization in the assessment of VSDs has been supplanted by echocardiography studies of patients with AI/VSD that include cardiac catheterization data show that these defects are restrictive and the pulmonary artery pressures are usually normal. Chiu et al,¹⁸ from the National Taiwan University, reported a series of 677 patients with subarterial, perimembranous, and outlet muscular VSDs with AVP. They found the pulmonary to systemic flow ratio (Q_p/Q_s) was remarkably similar among patients who developed AVP.¹⁸ In their study, mean Q_p/Q_s was 1.62 ± 0.92 for subarterial VSDs, 1.71 ± 0.77 for perimembranous VSDs, and 1.45 ± 0.64 for muscular outlet VSDs. There was no difference in the Q_p/Q_s associated with AVP among the three types and the average Q_p/Q_s among 373 patients who developed AVP was 1.62 ± 0.83 . Pulmonary artery pressures are at most only mildly elevated. Table 1 summarizes the available cardiac catheterization data. It should be noted that not all studies include all hemodynamic parameters or include catheterization data on all patients; there is some overlap among consecutive series from the same institution. Furthermore, some data is presented as mean \pm standard deviation, whereas in other studies median and range are provided. Nonetheless, a review of the literature indicates that for patients with VSD and AI the VSD is restrictive with a $Q_p/Q_s < 2$ and an absence of pulmonary artery hypertension (Table 1).^{13,17-22} Indeed pulmonary hypertension is not found among patients with VSD and AI and the corollary that patients with a VSD and pulmonary hypertension do not develop AVP and AI is also true.^{6,9,17,22} The fact that pulmonary hypertension and AI are mutually exclusive is further support for the Venturi effect as the predominate mechanism for the development of AI associated with a VSD.

Although VSDs resulting in AI are restrictive among these restrictive VSDs, size remains a factor that can impact the development of AVP and AI. There appears to be a minimum shunt required to produce aortic valve cusp distortion. In a study by Tohyama et al³ among patients greater than 15 years

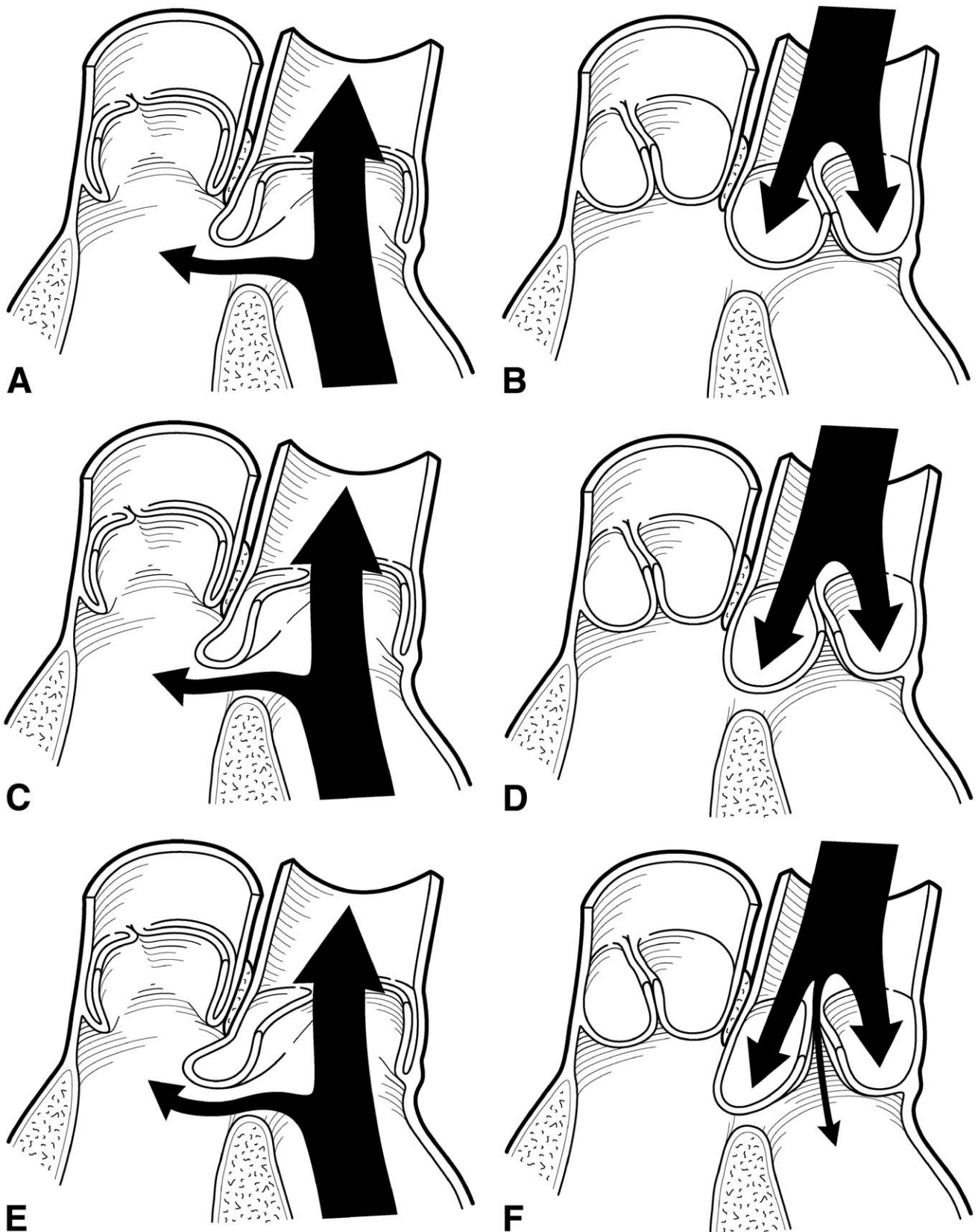


Figure 2 (A, B) Proposed development of AI in a hypothetical patient with restrictive VSD adjacent to a cusp of the aortic valve. In the newborn period the at-risk anatomy can be seen with an aortic valve cusp adjacent to the VSD. At this point the physiologic changes necessary to produce the low-pressure zone adjacent to the aortic valve cusp have been present only since birth and there has been insufficient time for development of aortic valve cusp deformity. The cusp of the aortic valve adjacent to the VSD is drawn into the VSD jet during systole. (C, D) Later in infancy, the low-pressure zone has created a valve cusp windsock deformity with a greater portion of the cusp being pulled across the VSD compared with the newborn period. Although the infant has developed aortic cusp prolapse, AI is not yet present. (E, F) Later in childhood, prolapse has progressed and the cusp is dragged farther into the left ventricle. During diastole the cusps no longer appose and AI has developed.

Table 1 A Summary of Hemodynamic Characteristics of Ventricular Septal Defects With Aortic Valve Prolapse With or Without AI

Study	Year	n Total	VSD Position	No. With AVP With or Without AI	Qp/Qs	PA Pressure (mmHg)	
						Systolic PA Pressure	Mean or Median PA Pressure
Schmidt et al ¹⁹	1988	48	SA	28	Mean, 1.5 ± 0.5	NA	
Rhodes et al ²⁰	1990	92*	PM	62	Median, 1.6	Median, = 15	
			SA	21	Range, 1 – 4	Range, 4 – 36	
Komai et al ¹³	1997	27	SA	12	Mean, 1.44 ± 0.47	Mean, 22.0 ± 16.3	
Sim et al ²¹	1999	128	SA	36	Range, 1.1 – 2.6	NA	
Lun et al ¹⁷	2001	214	SA	102	Mean, 1.6 ± 0.6	Mean, 28.2 ± 11	
Cheung et al ²²	2002	135	SA	56	Mean, 1.7 ± 0.6§	Mean, 30.5 ± 9.5§	
					Mean, 1.8 ± 0.7	Mean, 28.2 ± 5.7	
Chiu et al ¹⁸	2005	677	SA	209	Mean, 1.62 ± 0.92	Mean, 15.7 ± 7.0	
			PM	103	Mean, 1.71 ± 0.77	Mean, 17.1 ± 8.3	
			MO	61	Mean, 1.45 ± 0.64	Mean, 13.4 ± 5.2	

Abbreviations: SA, subarterial; PM, perimembranous; MO, muscular outlet; AVP, aortic valve prolapse; AI, aortic insufficiency.

*Position of VSD unknown in 9 patients.

§Patients with AVP and < moderate AI = 39.

||Patients with AVP and ≥ moderate AI n = 17.

of age with persistent subarterial VSDs without AVP or AI, the highest Qp/Qs was 1.5. Although the high velocity jet produces a drop in pressure, the smallest defects do not have a broad enough column of blood to impact the adjacent aortic valve cusp. Stated another way, the small jet of high velocity blood cannot deform the comparatively larger cusp. Therefore, the VSD must be restrictive but of sufficient size and location to deform the adjacent aortic valve cusp. Conversely, a larger or broader jet through the VSD would expose the adjacent cusp to a great zone of low pressure and would be expected to result in more rapid development of aortic valve deformity. Among patients with a restrictive VSD and AVP, AI developed more rapidly in those with a larger Qp/Qs but it should be emphasized that these VSDs were restrictive with normal pulmonary artery pressure.^{3,18,22} The lower limit of the Qp/Qs associated with the development of AI appears to be approximately 1.5, although the upper limit cannot be defined. In the study by Tohyama et al,³ the highest Qp/Qs among patients with AVP is 2.8; in a series from the Boston Children's Hospital,²⁰ the largest Qp/Qs was 4. These cases are exceptions, because the majority of patients with AI associated with a VSD will have a Qp/Qs of <2.

AI in Association With a VSD is an Acquired Lesion

The diagnosis of VSD is commonly made in the newborn period, but neither AVP nor AI is present at birth. AVP has rarely been identified in infants.^{3,12} Although the at-risk anatomy is present in utero, the physiologic factors do not become extant until after birth with a drop in pulmonary vascular resistance that then results in a high velocity jet across the VSD. AVP precedes the development of AI.^{3,9,13,17,23} Conversely, when associated with a VSD, AI does not occur without the characteristic cusp deformity of windsock elongation and subsequent prolapse.

The nadir of the involved cusp would be expected to reside within the stream of the left-to-right shunt. Particularly in perimembranous VSDs, override of the aortic valve leaflet is observed in patients with AVP and AI. Chiu et al¹⁸ found that

anterior malalignment of the outlet septum among patients with a perimembranous VSD was associated with development of AVP. An echocardiographic study by Eapen et al²⁴ identified aortic cusp override of the VSD as a risk factor for the development of cusp prolapse and subsequent AI.

Does the Venturi Effect Explain All Cases of AI Associated With a VSD?

The absence of muscular septum below the adjacent aortic valve cusp is implicated because this results in unopposed downward force on the cusp during diastole, which would then result in prolapse and AI. Yet larger VSDs, which are bordered by a correspondingly larger portion of the aortic annulus, rarely develop AVP or AI. This suggests that the lack of ventricular septal support alone is an inadequate explanation. If a lack of support were a principle cause of AI than it would follow that larger VSDs would more commonly result in AI. As discussed above, the opposite is true, indicating the predominance of the Venturi effect in the pathogenesis. Abnormal commissural structures have been observed in some cases of AI associated with a VSD.¹² These abnormal commissures take the form of partial fusion of the commissures, resulting in a bicuspid aortic valve. Although these commissural abnormalities undoubtedly contribute to the development of AI when present, they are not a satisfactory explanation for the majority of cases in which the valve is trileaflet. Furthermore, AI can complicate a bicuspid aortic valve in the absence of a VSD, making this an unsatisfactory explanation for the vast majority of cases. A lack of appositional forces has been implicated as a cause of AI in this group of patients.⁴ With progressive cusp deformity, a point is reached where the appositional surfaces of opposing cusps fail to meet. This is the beginning of AI. Although a lack of appositional forces may help explain the progressive nature of AI, it does not

explain the initiation of cusp deformity. Yacoub et al⁵ have implicated a loss of continuity of the media between aorta and valve annulus as the cause of cusp prolapse and subsequent AI. There is no pathologic data to support this theory. Furthermore, it is hard to separate cause from effect. If pathologic evidence of a lack of continuity between the aortic media and annulus was identified in a patient with AI/VSD, it would be impossible to determine if this was the result of progressive cusp deformity or the cause of cusp prolapse. While these mechanisms may contribute to the development of AI associated with a VSD, they do not explain the majority of observations and the Venturi effect remains the most plausible explanation. Two additional factors, drag forces and the differences in anatomy between subarterial and perimembranous VSDs, may play a role in the development of AI.

Drag Forces

The Venturi effect initiates the development of cusp prolapse. As the deformity of the leaflet progresses, windsock elongation of the cusp occurs that may result in substantial amount of aortic valve cusp residing in the VSD during systole. This would permit direct action of the VSD jet on the valve tissue. These are drag forces or direct forces on the cusp rather than a low-pressure zone entraining the lowest portion of the cusp into the VSD jet. These drag forces would come into play after the initiation of cusp deformity. They may contribute to ongoing cusp distortion, prolapse, and the development of AI (even while the elongated distorted cusp itself renders the VSD more restrictive). A similar combination of mechanisms, Venturi and subsequent drag forces, has been proposed for the development of systolic anterior motion of mitral valve and left ventricular outflow obstruction in hypertrophic cardiomyopathy.²⁵

Subarterial Versus Perimembranous VSDs

AI complicates the course of patients with subarterial VSDs five times as often as it does patients with perimembranous VSDs. The fundamental hemodynamic forces at work seem to be similar between the two types of VSD, and therefore other anatomic factors must be modifying the development of AI. The superior border of the subarterial VSD is uniformly adjacent to the hinge point of right coronary cusp and the VSD has a shallow, scooped out or half-moon shape.¹ As a result, the jet of blood through the defect is maximally exposed to the right coronary cusp. In contrast, perimembranous VSDs have a more circular shape and (as noted above) appear to need additional anatomic conditions such as override of the noncoronary cusp for the development of AI.^{18,24} These anatomic factors may account for the difference in the incidence of AI between these two types of VSD. The most concerning anatomy for progressive AVP is when the cusp forms the superior roof of the defect and is exposed to pressure drop and Venturi effect.

Indications for Surgery

Heart failure, a large shunt, poor growth, or elevated pulmonary artery pressure would all be indications for VSD closure regardless of presence of AI.¹⁴ However, as stated above, the

development of AI occurs in the absence of congestive heart failure. In the absence of a hemodynamically significant VSD, the indications for surgery become more complicated. Closure of the VSD, with or without aortic valve repair, is indicated for both perimembranous and subarterial VSDs when more than trivial AI is identified because AI is progressive.¹⁵ For patients with a subarterial VSD and AVP, VSD closure is indicated because of the high likelihood of progression of AVP and development of AI.^{13,17} Lun et al¹⁷ suggested that all subarterial VSDs ≥ 5 mm should be closed regardless of the presence of AVP to prevent the development of AI. Furthermore, there is only a minimal chance for spontaneous closure of a subarterial VSD.²⁶ A lower threshold for closure of subarterial VSDs can be justified because of the increased risk for development of AI, the fact that spontaneous closure is unlikely and defect closure is uncomplicated (the defect is repaired through an incision in the great vessels rather than through an atriotomy and the conduction system is not at risk). Closure of the VSD before development of cusp deformation will prevent the development of AI.^{21,25} For the patient with a hemodynamically insignificant perimembranous VSD with AVP but without AI, indications for surgery are less clear. Progression of AI is variable and spontaneous closure of the VSD can occur. Like subarterial VSDs, closure of the defect eliminates the low-pressure zone deforming the aortic valve cusp and prevents the development of AI. In contrast to the subarterial VSD, surgical closure of perimembranous VSDs places the conduction system at risk and an atriotomy is necessary with the risk, albeit small, of late arrhythmias. Late follow-up of small perimembranous VSDs, without LV enlargement and with normal pulmonary artery pressure, that were not closed shows that patients remained healthy.²⁸ Therefore, in the absence of AI, prophylactic closure of perimembranous VSDs with AVP is probably not justified. Patients with a restrictive perimembranous VSD and AVP should therefore be followed closely with serial echocardiography; surgery is indicated only if AI develops.

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