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Circulation 2006;114;2190-2197
DOI: 10.1161/CIRCULATIONAHA.106.618124
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

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Abstract—Ventricular septal defects are the most common congenital heart defect. They vary greatly in location, clinical presentation, associated lesions, and natural history. The present article describes the clinical aspects of ventricular septal defects and current management strategies. **(*Circulation*. 2006;114:2190-2197.)**

Key Words: echocardiography ■ heart defects, congenital ■ heart diseases ■ heart septal defects ■ imaging ■ pediatrics ■ shunts

Ventricular septal defect (VSD) is a common congenital heart defect in both children and adults. Management of this lesion has changed dramatically in the last 50 years. Catheter-based therapy for VSD closure, now in the clinical trial phase, is another step in the evolution of treatment for this disorder. Despite these advances, many patients with small VSDs require only subacute bacterial endocarditis prophylaxis. This article addresses the basic concepts of isolated VSDs.

Nomenclature

VSDs are openings in the ventricular septum and are classified according to their location. The terminology for the ventricular septum commonly used is that of Soto et al.[1] The ventricular septum can be divided into 2 morphological components, the membranous septum and the muscular septum (Figure 1).

The membranous septum is small and is located at the base of the heart between the inlet and outlet components of the muscular septum and below the right and noncoronary cusps of the aortic valve. The septal leaflet of the tricuspid valve divides the membranous septum into 2 components, the pars atrioventricularis and the pars interventricularis.[1] Tricuspid, aortic, and mitral continuity is via this central fibrous body. True defects of the membranous septum are surrounded by fibrous tissue without extension into adjacent muscular septum. Defects that involve the membranous septum and extend into 1 of the 3 muscular components are called perimembranous, paramembranous, or infracristal.

The muscular septum is a nonplanar structure that can be divided into inlet, trabecular, and infundibular components. The inlet portion is inferioposterior to the membranous septum. It begins at the level of the atrioventricular valves and ends at their chordal attachments apically. An inlet VSD has no muscular rim between the defect and the atrioventricular valve annulus. Defects in the inlet muscular septum are called inlet VSDs. Another classification scheme divides the inlet septum into the atrioventricular septum and the inlet septum.[2] Defects in the inlet septum can include abnormalities of the tricuspid and mitral valves that are called common atrioventricular canal defect.

The trabecular septum is the largest part of the interventricular septum. It extends from the membranous septum to the apex and superiorly to the infundibular septum. A defect in the trabecular septum is called muscular VSD if the defect is completely rimmed by muscle. The location of defects in the trabecular septum can be classified as anterior, midmuscular, apical, and posterior, as proposed by Kirklin et al.[3] An anterior muscular defect is anterior to the septal band. A midmuscular defect is posterior to the septal band. Apical defects are inferior to the moderator band. Posterior defects are beneath the septal leaflet of the tricuspid valve.

The infundibular septum separates the right and left ventricular outflow tracts. On the right side, it is bordered by the line from the membranous septum to the papillary muscle of the conus inferiorly and the semilunar valves superiorly. The right side of the infundibular septum is more extensive. Defects in the infundibulum are called infundibular, outlet, supracristal, conal, conoventricular, subpulmonary, or doubly committed subarterial defects. A deficient infundibular septum may be present with corresponding degrees of malalignment.

All defects should be assessed for location, size, and multiplicity. The relationship of the defect to the atrioventricular valves, infundibular septum, and great arteries should be noted.

Many defects involve >1 component of the ventricular septum. Perimembranous defects extend into the adjacent muscular septum and have been called perimembranous inlet, perimembranous muscular, and perimembranous outlet on the basis of the extension.[4] Abnormalities of the tricuspid valve adjacent to these defects can be in the form of an aneurysm partially or completely occluding the defect (Figure 2). The tricuspid valve can have perforations, clefts, or commissural abnormalities.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.106.618124**

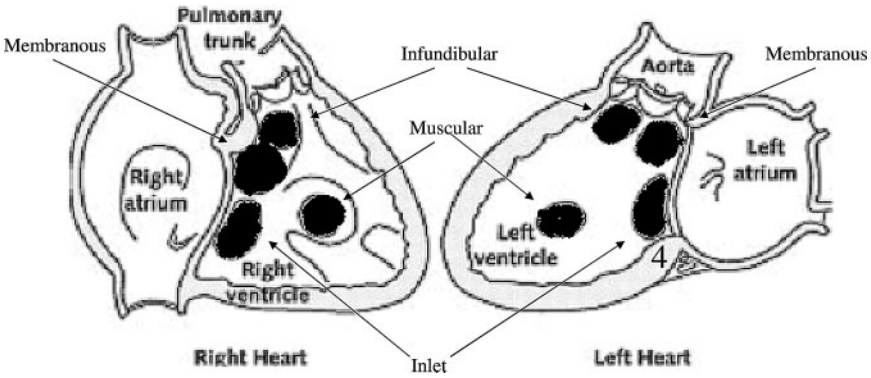

Figure 1. Locations of VSDs seen from the right and left ventricular aspects.

Infundibular and perimembranous defects can be associated with various degrees of malalignment of the infundibulum septum and the remainder of the ventricular septum. This can be anterior, posterior, or rotational and may result in overriding of a semilunar valve. Although this defect exists in isolation, it is most frequently associated with other defects, eg, tetralogy of Fallot.

There can be straddling of the mitral valve in the presence of infundibular defects. Inlet defects can involve malalignment of the atrial and ventricular septa. Naturally, this will result in annular overriding of one of the atrioventricular valves. There also may be various degrees of straddling of the chordal attachments of the tricuspid valve in some cases.

A VSD can therefore be classified according to location, size, and the presence or absence of any of the aforementioned factors (Figures 3 through 9).

Prevalence

The most common form of congenital heart disease in childhood is the VSD, occurring in 50% of all children with congenital heart disease[5] and in 20% as an isolated lesion.[6] The incidence of VSDs, which has increased dramatically with advances in imaging and screening of infants, ranges from 1.56 to 53.2 per 1000 live births.[7–9] The ease of detection of small muscular VSDs is reflected in the higher incidence rates. A large review of the literature estimated the median incidence of VSDs at 2829 per 1 million live births.[10] In the adult population, VSDs are the most common congenital heart defect excluding the bicuspid aortic valve.[11] Task Force 1[12] estimated the prevalence of simple VSDs in the adult population as 0.3 per 1000. The number of adults in the United States with simple congenital heart lesions was estimated to be 368 800.[12] Another study by Hoffman et al[13] also estimated the number of surviving adults by decade with either small or large VSDs.

Genetic Factors

The developmental biology of the heart is a large field of study. Formation of the heart tube, looping, septation, and resultant systemic and pulmonary circulations is a complex process. Disruption at any point during primary morphogenesis results in the large spectrum of congenital heart defects being treated today. Genetic disorders responsible for these alterations can be classified into 3 types: chromosomal disorders, single-gene disorders, and polygenic disorders.[7]

Chromosomal disorders caused by absent or duplicated chromosomes include trisomy 21 (Down syndrome), 22q11 deletion (DiGeorge syndrome), and 45X deletion (Turner syndrome). From 5% to 8% of congenital heart disease patients have a chromosomal disorder.[14] Recurrence risk in an offspring is that of the chromosomal disorder.

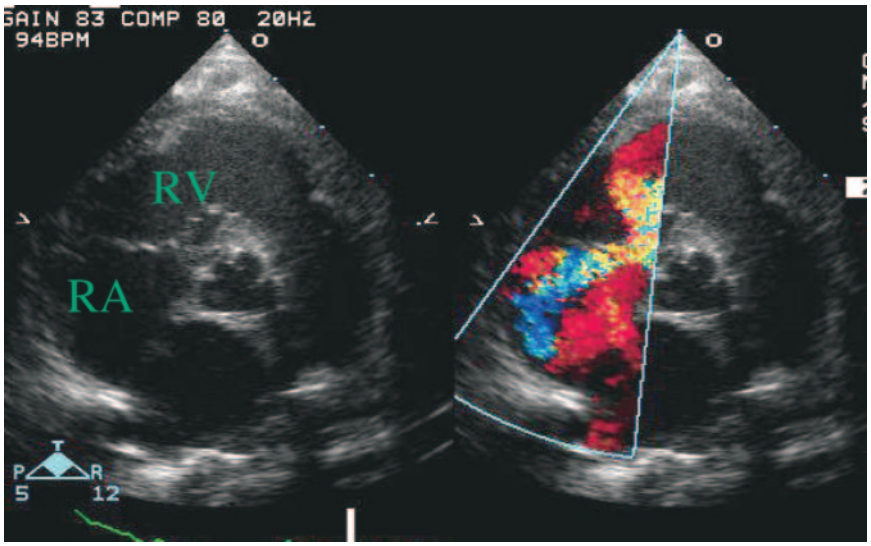

Figure 2. Oblique short-axis view of perimembranous VSD shows resulting color Doppler jet flows of VSD and tricuspid regurgitation. RV indicates right ventricle; RA, right atrium.

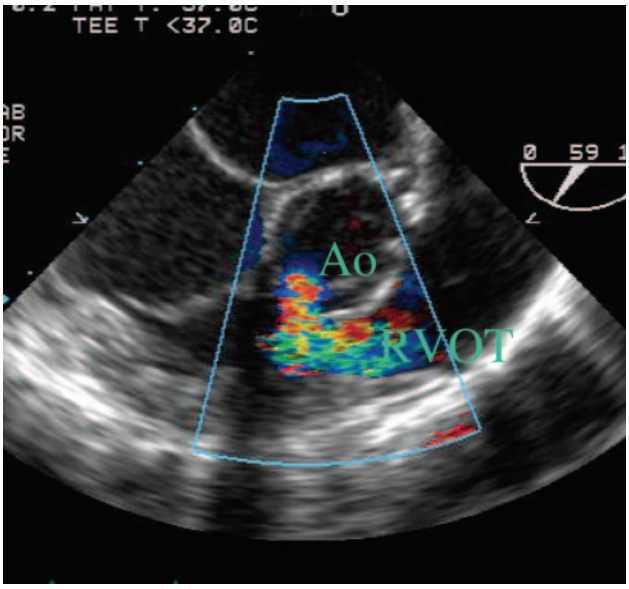

Figure 3. Subaortic high-membranous VSD with flow into the right ventricular outflow tract (RVOT) on intraoperative transesophageal echocardiogram. Ao indicates Aorta.

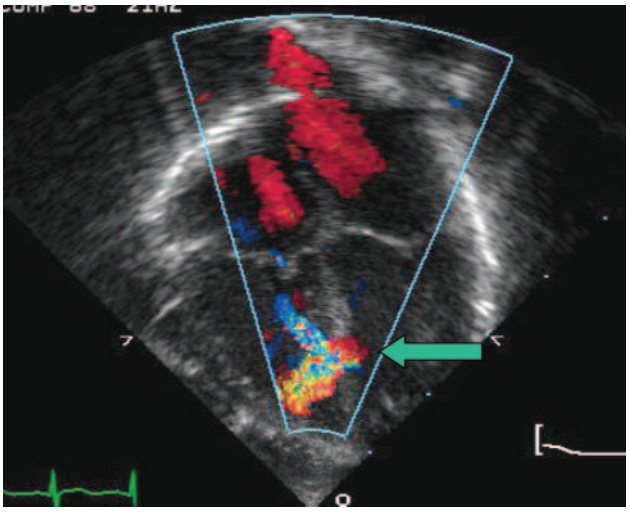

Figure 5. Ultrasound color Doppler 4-chamber view of midmuscular VSD (arrow).

Single-gene disorders are caused by deletions, missense mutations and duplications within a gene. These disorders follow autosomal-dominant, autosomal-recessive, or X-linked inheritance patterns. Some examples are Holt-Oram syndrome, atrial septal defect with conduction defect, and supravalvular aortic stenosis.[7] Three percent of patients with congenital heart disease have a single-gene disorder.[14] Recurrence risk is high in first-degree relatives of patients with these disorders.

Septation defects have recently been the subject of molecular studies, with the identification of the *NKX2.5* gene implicated in nonsyndromic atrial septal defects.[15] Studies of families with Holt-Oram syndrome resulted in the elucidation of the *TBX5* mutation causing atrial septal defects and VSDs.[16,17] Further studies have shown an interaction between *TBX5*, *GATA4*, and *NKX2.5*, suggesting that transcriptional activation may be responsible for septal defects.[18]

Polygenic disorders encompass many congenital heart defects. They result from environmental and genetic factors.

Although there is not direct genetic testing at this time for VSDs not associated with chromosomal disorders or single-gene disorders, recurrence risk can be used for counseling reproductive adults. With paternal VSDs, the recurrence risk in an offspring is 2%. Maternal VSDs have a recurrence risk of 6% to 10%.[19]

Pathological Anatomy and Physiology

The size of the VSD, the pressure in the right and left ventricular chambers, and pulmonary resistance are factors that influence the hemodynamic significance of VSDs. A VSD may not be apparent at birth because of the nearly equal pressures in the right and left ventricles and a lack of shunting. With increasing shunt corresponding to the increas-

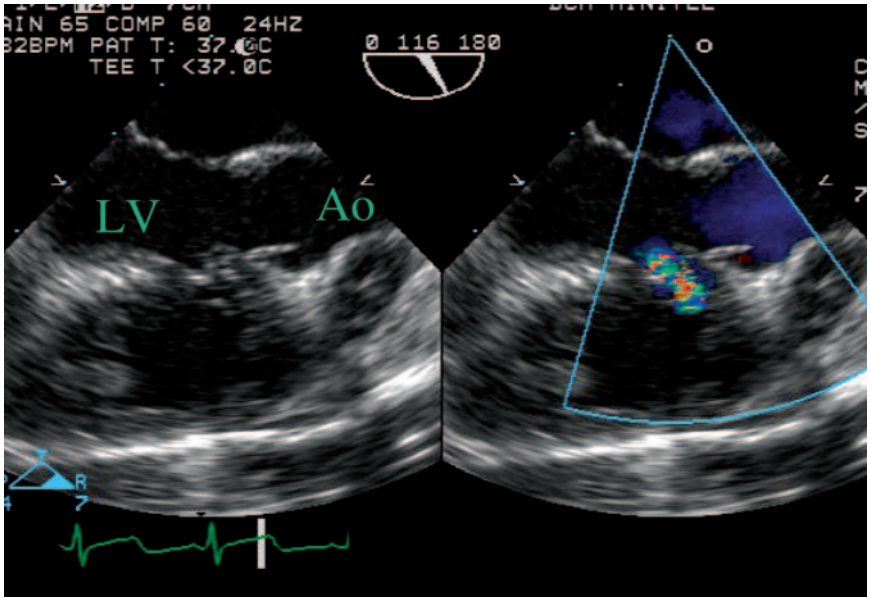

Figure 4. Small perimembranous VSD with ventricular septal aneurysm on transesophageal echocardiographic examination. LV indicates left ventricle; Ao, aorta.

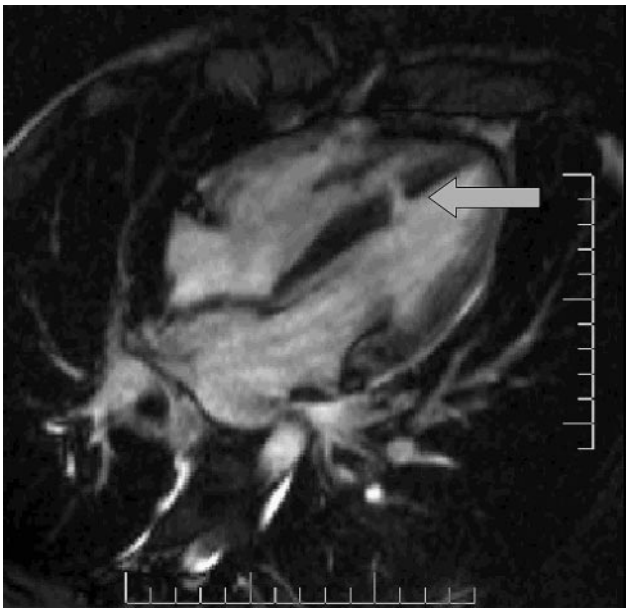

Figure 6. Four-chamber-view cine MRI image of midmuscular VSD (arrow).

ing pressure difference between the ventricles, these defects become clinically apparent. Exceptions to this rule are patients with Down syndrome who may not undergo the natural drop in pulmonary resistance and do not manifest signs of a VSD. Routine screening of all Down syndrome patients is the standard of care.

The shunt volume in a VSD is determined largely by the size of the defect and the pulmonary vascular resistance. Without pulmonary hypertension or obstruction to the right ventricle, the direction of shunt is left to right, with corresponding pulmonary artery, left atrial, and left ventricular volume overload. In the setting of elevated pulmonary vascular resistance, right ventricular obstruction resulting from muscle bundles, or pulmonary stenosis, the shunt volume is limited and may be right to left, depending on the difference in pressure. Eisenmenger syndrome results from long-term left-to-right shunt, usually at higher shunt volumes. The elevated pulmonary artery pressure is irreversible and leads to a reversal in the ventricular level shunt, desaturation, cyanosis, and secondary erythrocytosis.

Muscular VSDs can undergo spontaneous closure as a result of muscular occlusion. Perimembranous defects can close by tricuspid valve aneurysm formation. Infundibular defects can close by prolapse of the right aortic cusp. A reduction in the size of the defect by any of these mechanisms results in changes in the hemodynamic significance of the defect.

The integrity of structures immediately adjacent to ventricular defects is a concern. For example, the development of aortic insufficiency in the case of infundibular defects is a result of the deficiency of the support apparatus of the aortic valve and results in damage to the aortic valve leaflets.

Clinical Features

VSDs can be detected by auscultation. The murmurs are typically described as holosystolic or pansystolic. The grade

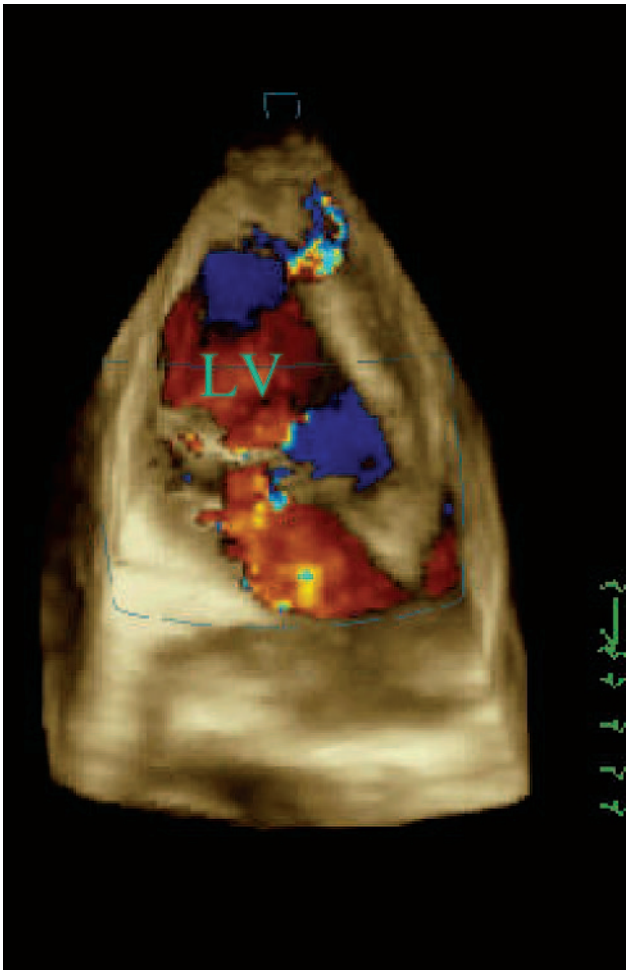

Figure 7. Small apical muscular VSD on 3-dimensional echocardiographic image. LV indicates left ventricle.

of murmur depends on the velocity of flow; the location of murmur is dependent on the location of the defect. Smaller defects are loudest and may have a thrill. Muscular defects can be heard along the lower left sternal border and may vary in intensity as the defect size changes with muscular contraction throughout systole. Infundibular defects shunt close to the pulmonary valve and can be heard best at the left upper sternal border. Perimembranous defects may have an associated systolic click of a tricuspid valve aneurysm.

In the setting of low pulmonary vascular resistance, larger defects have murmurs of constant quality that vary little throughout the cardiac cycle and less commonly have an associated thrill. These defects will have a corresponding increase in mitral flow, resulting in a diastolic rumble at the apex. There may be evidence of left ventricular volume overload on palpation of the precordium with a laterally displaced impulse. Elevated pulmonary pressure causes an increase in the pulmonary component of the second heart sound. Large defects with no shunt and defects with Eisenmenger physiology and right-to-left shunt often do not have a VSD murmur.

Defects that contribute to or are associated with tricuspid regurgitation have a systolic murmur at the left lower or right lower sternal border. Defects with aortic insufficiency have a

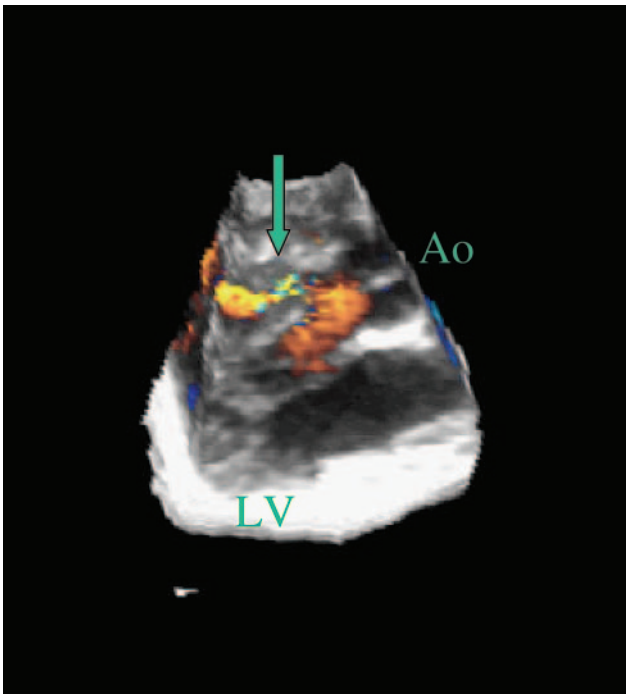

Figure 8. A 3-dimensional echocardiographic image shows flow from small muscular VSD (arrow) tunneling through the septum.

diastolic decrescendo murmur along the left sternal border with the patient sitting and leaning forward. A widened pulse pressure may be present.

Patients with Eisenmenger syndrome often are cyanotic with clubbing. They have a right ventricular heave on palpation of the precordium and a loud pulmonary component of the second heart sound. A VSD murmur may not be present.

Diagnostic Evaluation

Electrocardiography

The ECG is most likely normal in patients with small VSDs. With increasing shunt, there may be evidence of left ventricular volume load and hypertrophy. Left atrial enlargement may be present. In cases of elevated pulmonary artery pressure, right axis deviation, right ventricular hypertrophy, and right atrial enlargement may be evident on ECG.

Chest Radiography

Small defects have no apparent radiographic abnormality. With larger defects, chamber enlargement is present to various degrees, depending on the volume of the shunt. Increased pulmonary vascularity is present. As patients develop Eisenmenger syndrome or increasing pulmonary resistance, there is loss of pulmonary vascularity and pruning of the vasculature. In these patients, there is evidence of right heart enlargement and a dilated main pulmonary artery.

Echocardiography

Echocardiographic evaluation of VSDs is a noninvasive tool that accurately delineates the morphology and associated defects. Hemodynamic evaluation of the defect, the presence of elevated pulmonary artery pressure, obstruction of the right ventricular outflow tract (double chamber physiology), insufficiency of the aortic valve, and distortion of the valve apparatus are all evaluated by echocardiography. When limitations in image quality of transthoracic echocardiography prevent evaluation of these aspects of the cardiovascular physiology, transesophageal imaging can be performed. Three-dimensional echocardiography has proved accurate for quantifying shunt[20] and can provide accurate visualization of defects that otherwise are difficult to evaluate by 2-dimensional imaging alone.[21]

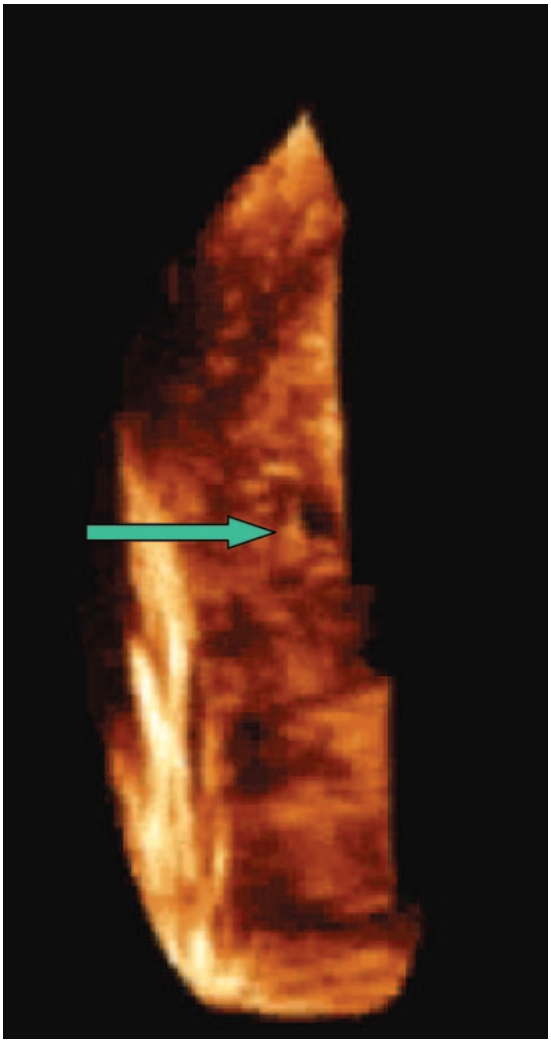

Figure 9. En face view of the left ventricular septal surface showing midmuscular VSD (arrow).

Magnetic Resonance Imaging

Magnetic resonance imaging can be used to delineate VSDs in patients with complex associated lesions.

Cardiac Catheterization

Catheterization can give accurate measurements of pulmonary vascular resistance, pulmonary reactivity, and volume of shunting. Response to pulmonary vasodilators can be determined and can guide therapy. Angiography can provide information on the location of a defect, number of defects,

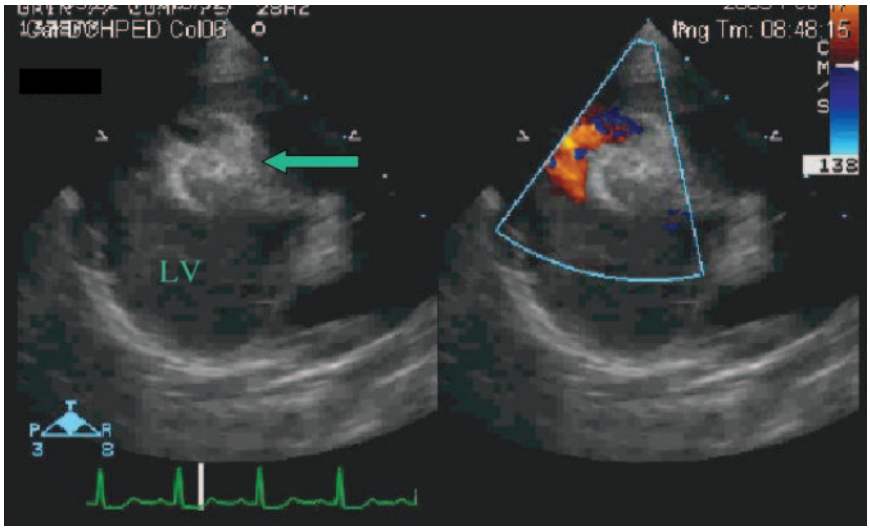

Figure 10. Oblique short-axis view shows Amplatzer device (arrow) placed to close a midmuscular VSD. LV indicates left ventricle.

and the degree of aortic insufficiency. The aortic valve can be inspected for integrity.

Management

Medical Management

The management in the infant and child depends on symptoms. A small defect does not require medical management or likely require any intervention. The medium and larger defects require various degrees of medical management and eventual surgical closure. Congestive heart failure in the infant is treated with diuretics, digoxin, and afterload reduction at times.[22,23]

The adult with an unrepaired VSD in the current era likely has a small defect without evidence of left ventricular volume overload or alterations in the adjacent structures. Those with evidence of left ventricular volume overload or progressive aortic valve disease in most institutions are referred for closure.

The adult who has had VSD repair needs surveillance for aortic valve dysfunction. Those adults with residual defects need continued monitoring and consideration for reoperation if there is left ventricular volume overload or progressive aortic valve dysfunction.

The patient with Eisenmenger syndrome needs very specialized care at centers, with trained personnel capable of managing myriad medical problems. Arrhythmias, endocarditis, gallstones, gouty arthritis, hemoptysis, pulmonary artery thrombosis, and symptomatic hypertrophic osteoarthropathy are frequently seen.[24] Pregnancy is poorly tolerated and many believe contraindicated in this disorder. Echocardiography and magnetic resonance imaging are used to evaluate right ventricular function. Cardiac catheterization is reserved for cases in which surgical or device closure is a question. Vasodilator therapy is an important adjunct to management and can provide functional improvement. Changes in $\dot{V}O_2$ with exercise or Qp:Qs from magnetic resonance imaging–derived cardiac output can be determined but are not generally used to guide therapy.

Endocarditis is a lifelong risk in unoperated patients (18.7 per 10 000 patient-years)[25] and those with residual defects. Proper prophylaxis and periodic follow-up are indicated.

Surgical Closure

Location has been used as an indication for surgical closure regardless of the need for medical management in the case of infundibular defects.[26] Chamber enlargement is another measure of the degree of shunting and may indicate the need for closure. Catheterization can be used in some individuals to determine Qp:Qs and pulmonary artery pressure and resistance to help guide clinicians. Generally, a Qp:Qs of 1.5:1 to 2:1[27] or evidence of increased pulmonary arteriolar resistance is an indication for closure. Multiple "Swiss cheese" defects refractory to medical management may require a palliative pulmonary artery band procedure.

Advances in surgical and bypass techniques and timing of surgical repair have decreased the morbidity associated with surgical closure. The early era of repair showed an 80% closure rate in catheterized patients at long-term follow-up.[28] In that study, 9 of 258 patients had complete heart block, 37 had transient heart block, and 168 had right bundle-branch block. Endocarditis occurred in 9 patients (11.4 of 10 000 patient-years).[28]

More recent studies have shown residual defects in 31% of patients and an incidence of complete heart block of 3.1%.[29] Another natural history study showed occurrence rates for pacemaker placement of 9.8 per 10 000 patient-years and occurrence rates for endocarditis of 16.3 per 10 000 patient-years in operated patients.[30]

Catheter Closure

Advancements in catheter techniques and devices are leading us into the era of percutaneous closure of VSDs. The benefits of avoiding bypass are intuitive, and the relative ease of placement makes this procedure ultimately attractive. Currently, these devices are in the investigational stage. In 1987, Lock and colleagues[31] used the Rashkind double-umbrella device to close VSDs. The defects closed in that study included congenital, postoperative congenital, and post–myo-

cardial infarction VSDs. The Amplatzer VSD occluder, of which there are the muscular and perimembranous types (AGA Medical Corp, Golden Valley, Minn), is another investigational devices. A phase 1 clinical trial for the Amplatzer membranous device showed a 96% complete closure rate at 6 months with a serious adverse event rate of 8.6%.[32] Likewise, there was 100% occlusion of single defects at 3 to 96 months of follow-up with the Amplatzer muscular VSD occluder.[33] Using the device for iatrogenic defects after aortic valve replacement has also been successful.[34]

Imaging during deployment traditionally has been transesophageal echocardiography. Intracardiac echocardiography can now be used with accurate measurements and safety similar to that with transesophageal echocardiography.[35]

Device placement is not without its own risks and potential long-term complications. Complete heart block has been observed as a temporary complication in 1.07% to 1.9% of patients.[36,37] There was also transient bundle-branch block in 2.8%.[37] There was no late development of complete heart block. Tricuspid stenosis was seen in 1 patient requiring ballooning of the valve as a result of hemodynamic instability, after which the stenosis was reduced and remained stable. Tricuspid regurgitation developed in 1 patient (0.7%).[37] Placement failure was experienced by 5.1% of patients as a result of proximity to the aortic valve and acute insufficiency, chordae of the tricuspid valve, and inability to pass the delivery sheath.[37]

Studies using an open chest animal model and perventricular technique for device deployment have been successful for perimembranous defects.[38] A similar technique has been used for muscular or multiple muscular defects (Figure 10).[39] This provides a further reduction in the invasiveness of closure and could allow therapy for those with contraindications to bypass in the future.

Disclosures

None.

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Correction

In the article "Ventricular Septal Defects," by Minette and Sahn that appeared in the November 14, 2006, issue (*Circulation*. 2006;114:2190–2197), the legend to Figure 6 was incorrect. The figure was reproduced with the kind permission of *Circulation* and the authors, Franck Thuny, Alexis Jacquier, Alberto Riberi, Jean-François Avierinos, Sébastien Renard, Frédéric Collart, Xavier Luanika, Jean-Michel Bartoli, Dominique Métras and Gilbert Habib, from "Ventricular Septal Rupture After a Nonpenetrating Chest Trauma: Findings From Real-Time Three-Dimensional Echocardiography and Cardiac Magnetic Resonance" (*Circulation*. 2005;112:e339–e340). Although it shows the general anatomy of a mid-muscular VSD on MRI, the example is not of a congenital defect, as judged especially by the concordant interruption of the right ventricular wall in conjunction with the nonpenetrating traumatic origin of this defect.

The authors regret this error.

DOI: 10.1161/CIRCULATIONAHA.107.181352

(***Circulation.*** **2007;115:e205.**)