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Intrauterine Closure of Membranous Ventricular Septal Defects: Mechanism of Closure in Two Autopsy Specimens

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SUMMARY. **Anatomic evidence of intrauterine closure of ventricular septal defects (VSDs) has been reported rarely. Between 1985 and 1990, 112 autopsies were performed at the Mayo Clinic on third trimester stillborns and infants who died during the first week of life. There were 21 (19%) cases of congenital heart disease. VSD was found in 12 (11%) cases: in eight (7%) as a part of a more complex heart defect and in four (4%) as an isolated lesion. Two cases with membranous VSDs with tricuspid valve tissue partially occluding the ventricular septal defect were found. A 2280-g female infant (case 1) with trisomy 18 died at 4 days of age. Autopsy revealed bilateral superior venae cavae, a large atrial septal defect, cor triatriatum, an atypical tricuspid valve with large septal leaflet partially obstructing a large membranous VSD, a hypoplastic right ventricle, and severe pulmonic stenosis. A 2610-g female infant (case 2), born with congenital heart block died at 4 days of age. Autopsy revealed cor triatriatum dexter obstructing the tricuspid orifice, a large membranous VSD partially obstructed by the septal leaflet of the tricuspid valve, four small muscular VSDs, and pulmonic stenosis. These cases suggest that closure of membranous VSDs may begin in utero and the mechanism of closure is similar to that reported postnatally.**

KEY WORDS: **Ventricular septal defect — Spontaneous closure — Prenatal**

Spontaneous *postnatal* closure of ventricular septal defects (VSDs) is well described [2, 4, 12, 23]. It is believed to occur, in most cases, in the first year of life [13, 16]. The possibility of intrauterine closure of a VSD was suggested in the 1960s [11, 15, 25], but is still subject to debate [16]. It is thought that intrauterine closure of VSDs is accomplished by fusion of myocytes without fibrosis, as happens in the early stages of gestation when many small muscular defects apparently close and disappear [25]. To our knowledge, only three cases of possible intrauterine closure of VSDs have been reported. Nir et al. reported a case of a newborn who died at 5 h of age and had evidence of a muscular VSD closed by fibrotic tissue [17]. In light of this finding, we sought to identify other cases with anatomic evidence of prenatal VSD closure to delineate the mechanism of closure.

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Methods

Hearts from autopsies, performed from 1985–1990 at the Mayo Clinic on third trimester stillborns and infants (who died at 7 days of age or younger), were examined by the authors. The study group included 112 specimens.

Both sides of the ventricular septum were carefully examined for the presence of any depression, a deep cleft, or the presence of fibrosis or adhesions near the membranous septum. Sections perpendicular to the ventricular septum were made at 2-mm intervals, to facilitate the identification of muscular VSDs. Hearts with either a VSD, a septal depression or cleft, or signs of fibrous tissue within the septum, were examined histologically after routine preparation and staining with hematoxylin-eosin and trichrome.

Results

Among 112 autopsies, 57 (51%) were stillborn, 27 (24%) died in the first day of life, and 28 (25%) died at 2–7 days of age. Sixty-seven (60%) cases were premature. Mean gestational age for the whole group was 34 weeks. There were 21 (19%) cases of

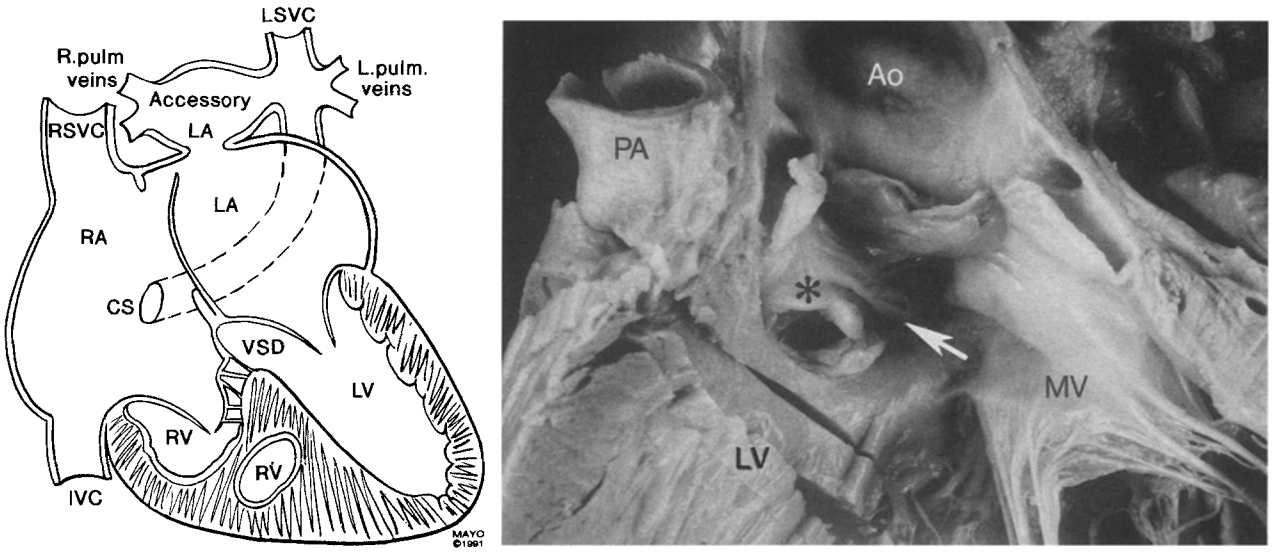

Fig. 1. (**Left**) Schematic representation of the complex heart defect: connection between a persistent left superior vena cava and a single left pulmonary vein, left superior vena cava draining into a dilated coronary sinus, cor triatriatum, atypical tricuspid valve with large septal leaflet, and redundant tissue obstructing a large membranous VSD, and hypoplastic right ventricle. (**Right**) Pathologic specimen showing the LV side with the membranous VSD (*arrow*) partially occluded by the tricuspid valve leaflet (*). *Ao*, aorta; *CS*, coronary sinus; *IVC*, inferior vena cava; *LA*, left atrium; *LSVC*, left superior vena cava; *L. pulm. veins*, left pulmonary veins; *LV*, left ventricle; *MV*, mitral valve; *PA*, pulmonary artery; *RA*, right atrium; *R. pulm. veins*, right pulmonary veins; *RV*, right ventricle; *RSVC*, right superior vena cava.

congenital heart disease and an additional 14 (13%) cases with other somatic anomalies and no heart disease. A VSD was found in 12 (11%) of the patients; in eight (7%) as part of a more complex heart disease and in four (4%) as an isolated cardiac anomaly. Two patients with a membranous VSD had tricuspid valve leaflets that partially occluded the defect and are described in detail.

Case 1

A 2280-g female infant was born at term to a 25-year-old G3P2 mother. The pregnancy was complicated by intrauterine growth retardation. The mother smoked ½ pack of cigarettes per day. A VSD had been suspected using fetal echocardiography. The infant was born vaginally after repeated inductions, with Apgar scores of 1 and 4. The physical examination revealed features of trisomy 18, and a karyotype confirmed the diagnosis. Complex congenital heart disease was found by echocardiography, and the baby died at 4 days of age. Autopsy revealed a connection between a persistent left superior vena cava and a single left pulmonary vein, a left superior vena cava draining into a dilated coronary sinus, a large atrial septal aneurysm, cor triatriatum, atypical tricuspid valve with large septal leaflet, and *redundant tissue partially obstructing a large membranous VSD*, right anterior hypoplastic right ventricle with secondary endocardial fibroelastosis, and severe pulmonary valve stenosis (near atresia) (Fig. 1).

Case 2

A 2610-g female baby was born to a 30-year-old mother at 37 weeks gestation. A persistent low heart rate (in the 60s) was noted the day before delivery. She was delivered by cesarean section following spontaneous rupture of the membranes. Apgar scores were 7 and 7. Echocardiography on day 1 showed complex congenital heart disease and an edematous heart. Congenital heart block was diagnosed and pacing wires were inserted. The baby died at 4 days of age. Autopsy revealed single right and left pulmonary veins, cor triatriatum dexter causing obstruction of tricuspid orifice (Fig. 2), *a large membranous VSD partially obstructed by septal leaflet of the tricuspid valve*, four muscular VSDs 1–2 mm in diameter located in the anteroapical trabecular septum, pulmonary stenosis, and spongy left ventricular myocardium. The echocardiographic findings of this case were reported earlier [1].

Discussion

Postnatal spontaneous closure occurs in about 45% of VSDs [12, 16]. Closure of muscular defects begins with septal muscle adherence, followed by obliteration of the defect by a fibrous tissue plug [5, 23, 25]. In closure of membranous defects, the VSD is "covered" by tricuspid valve tissue [3, 7, 9, 13] (Fig. 3). In the present study two membranous

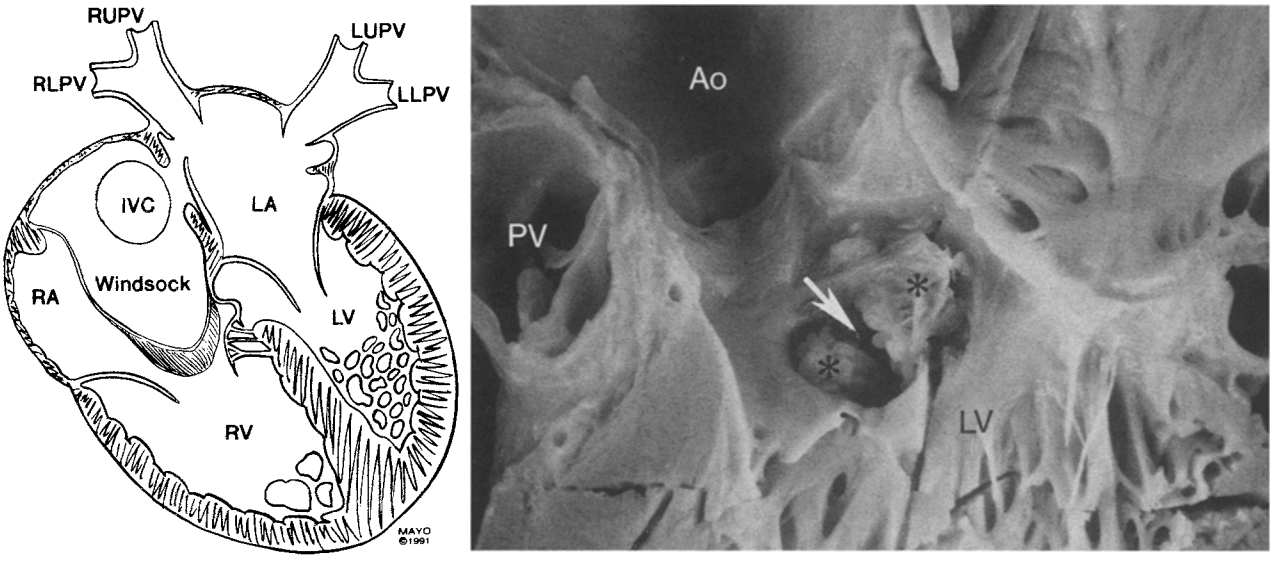

Fig. 2. *Case 2.* (**Left**) Schematic representation of the complex heart defect: single right and left pulmonary veins, patent foramen ovale, cor triatriatum dexter causing obstruction of tricuspid orifice, large membranous VSD partially obstructed by septal leaflet of the tricuspid valve. (**Right**) Pathologic specimen showing the LV side with the membranous VSD (*arrow*) partially occluded by the tricuspid valve leaflet (*). *Ao*, aorta; *IVC*, inferior vena cava; *LA*, left atrium; *LV*, left ventricle; *PV*, pulmonary valve; *RA*, right atrium; *RV*, right ventricle; *LLPV* and *LUPV*, left lower and left upper pulmonary veins; *RLPV* and *RUPV*, right lower and right upper pulmonary veins.

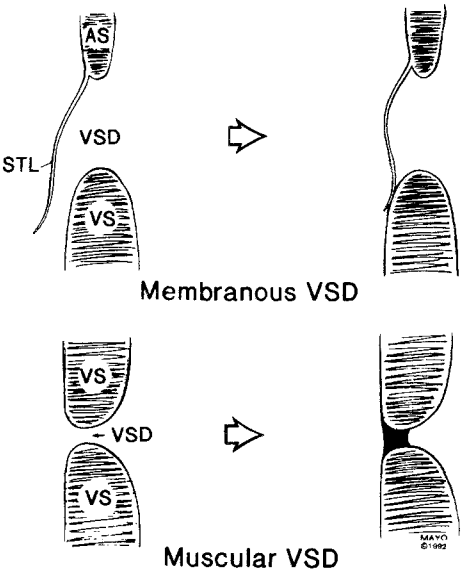

Fig. 3. Schematic representation of the mechanism of spontaneous VSD closure. (**Upper panel**) Membranous VSD closure; (**lower panel**) muscular VSD closure. *AS*, atrial septum; *VS*, ventricular septum; *STL*, septal tricuspid leaflet.

VSDs were partially obstructed by tricuspid valve tissue, indicating an early stage in spontaneous closure of the defects. Because both babies died at only 4 days of age, it is reasonable to assume that the process began prenatally. Two similar cases have been reported. In one case, a muscular VSD was completely closed by fibrosis before birth [17], and in another, a membranous VSD was partially closed by mitral valve tissue in a patient with tricuspid atresia [18].

The possibility of intrauterine closure of a VSD has been suggested in the past [11, 15, 25]. This concept has served to explain the high incidence of VSDs in premature infants. Moe and Guntheroth [16] reported a survey of 222 infants with VSDs, diagnosed and followed by echocardiography. In their report the incidence of VSD in premature infants was 7.06/1000, or twice that observed in full-term infants and about 1.5 times greater than reported previously in premature infants [16]. They found a similar rate of spontaneous closure of VSDs in the two groups and argued that if the hypothesis of intrauterine closure was valid, one should expect to find a higher rate of spontaneous closure in preterm infants. Hoffman and Rudolph [13] suggested that the high incidence of VSDs in preterm infants was due to the fact that they are kept in intensive care units and are examined daily and so nearly no VSD is missed, as opposed to term infants who have small VSDs and are asymptomatic and are either diagnosed late or not at all if their VSD closes. The higher incidence of VSDs in preterm infants in the study by Moe and Guntheroth as compared to the earlier studies could be, in part, related to the

greater number of very small premature babies that survive now in comparison to 25 years ago.

It has been thought that VSDs close in utero by fusion of myocardial fibers without fibrosis, as happens in the early stages of gestation when many small muscular defects disappear [25]. In our study, however, intrauterine closure of membranous VSDs occurred by the same mechanism as described postnatally.

The very intriguing phenomenon of spontaneous closure of physiologically advantageous VSDs, where the VSD is the only route for blood flow to the systemic or the pulmonary circulation, has been studied extensively by Rao and others [8, 14, 18–20]. Both muscular and membranous VSDs have been shown to close spontaneously in these cases. The incidence of VSD closure in cases with tricuspid atresia was found to be 42%, similar to that observed in cases with isolated VSD [18]. Intrauterine closure of physiologically advantageous VSD was suggested as an explanation for the occurrence of rare anomalies like double-outlet right ventricle with intact ventricular septum [4]. In the case reported earlier [17], the VSD that closed completely served as the only outlet from the left ventricle (double-outlet right ventricle). In case 1 in the present study, the VSD was the only outlet of the right ventricle, and in case 2, the VSD served as the only inlet to the right ventricle. Rao [18] reported one case of partial prenatal closure of a membranous VSD in a baby with tricuspid atresia. Also there is one reported case of spontaneous intrauterine closure of a VSD detected echocardiographically in an otherwise normal fetus [22].

In two of the three cases ([17] and case 1), the ventricle with outlet obstruction had endocardial fibroelastosis. Endocardial fibroelastosis develops in ventricles with outlet obstruction and is believed to be caused by endocardial and subendocardial ischemia due to ventricular hypertrophy and high systolic and diastolic pressures [6].

In the three cases it is reasonable to assume a high-pressure gradient between the two ventricles and a high-velocity jet through the defect. In the normal human fetus the pressure in the right and left ventricles is nearly the same [10]. The mechanism of VSD closure is thought to involve endothelial roughening due to a high-velocity jet which leads to accumulation of platelets and production of fibrous tissue. In the membranous VSD it is believed that a high-velocity jet either damages the endothelium on the rim of the VSD or traumatizes the septal leaflet of the tricuspid valve causing it to become "sticky" and adhere to the rim [16, 21, 24].

The fact that there are more reported cases of partial or complete intrauterine closure of VSDs of the physiologically advantageous type could be explained in two ways: (1) these babies had a fatal heart lesion and died early, or (2) the hemodynamics created a high-velocity jet that induced closure of the VSD by adhesion of tricuspid leaflet tissue.

We conclude that the data presented herein provide additional support to the concept that spontaneous closure of VSDs can begin in utero and the mechanism of closure is similar to that seen postnatally.

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