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CICLO XX

Natural and Unnatural History of Isolated Ventricular Septal Defects in a Paediatric Population: A Longitudinal Retrospective Study

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Index

The Ventricular Septal Defect

1. Introduction:

The ventricular septal defect (VSD) is a communication at the level of the septum that separates the two ventricular cavities, the right and the left. The defect may be present as an isolated anomaly or in association with other complex malformations: like tetralogy of Fallot; double outlet right ventricle; almost all cases of common truncus arteriosus; atrioventricular canal; transposition of the great arteries; it may be present in pulmonary atresia and coarctation of the aorta syndrome.

VSD is the most common cardiac malformation after the bicuspid aortic valve and mitral prolapse; in the literature it is reported that 4 % of asymptomatic neonates presents small VSD after birth, and it is present in 50% of children with congenital heart disease 1, 2,3,4.

The incidence is increased because of improved diagnostic techniques and neonatal screening, reaching an incidence of 53 per thousand in live neonates 5,6. A revison of the literature has estimated that the median incidence is about 2829 per million in live neonates, with a prevalence in the adult population about 0.3 per thousand 7.

2. Genetic factors:

The formation of the cardiac tube, curving and forming the septum with the constitution of systemic and pulmonary circulation is a very complex process.

Any alteration in any step of this complex process determines a large spectrum of congenital cardiac defects. The responsible genetic factors are classified into three types: chromosomal disorders, single gene alteration, polygene alteration 8.

Chromosome disorders represent 5% to 8 % of congenital heart diseases: they include trisomy 21, 18,13, 22q11.2 deletion (DiGeorge syndrome) and 45x deletion (Turner syndrome) 8.

Monogene disorders are present in 3% of patients with cardiac defect 9. The risk of recurrence is highly elevated in the families of patients with these disorders.

In septation defects the NKX2-5 gene identified in a study about interatrial defects in non-syndromic patients is implicated 9,10,11.

The study of the families of patients affected by Holt-Oram syndrome has shown that mutations of TBX5 may cause interatrial or interventricular defects [11].

Successive studies have shown that alteration of the TBX5, GATA4 and NKX2.5 genes may be responsible for septal defects [12].

Polygene disorders are the result of interaction between ambiental and genetic factors.

The risk of recurrence when the VSD is present in the father of the patient is about 2%, while it is about 6%-10% when the mother is affected [13].

3. Ventricular septal defect embryology [14]

Ventricular septation is a complex process involving different septal structures from various origins and positioned at various planes. These structures eventually meet to complete the separation of the right and left ventricles

Muscular interventricular septum: During the fifth week, around day 30, a muscular fold extending from the anterior wall of the ventricles to the floor appears at the middle of the ventricle near the apex and grows towards the AV valves with a concave ridge. Most of the initial growth is achieved by growth of the two ventricles on each side of the ventricular septum. In addition trabeculations from the inlet region coalesce to form a septum which grows into the ventricular cavity at slightly different plane than the primary septum, this is the inlet interventricular septum, which is at the same plane of that of the atrial septum. The point of contact between these two septa will cause the edge of the primary septum to protrude slightly into the right ventricular cavity forming the trabecular septomarginalis. The fusion of these two septa forms the bulk of the muscular interventricular septum. This septum will then become in contact with the outflow septum.

The interventricular foramen, which is bordered by the concave upper ridge of the muscular interventricular septum and the fused AV canal endocardial tissue, closes at the end of week 7. This is achieved by growth of three structures: the right and left bulbar ridges and the posterior endocardial cushion tissue. This will close the interventricular foramen and connect the ventricular septum to the outflow septum, thus connecting the right ventricle to the pulmonary trunk and the left ventricle to the aortic trunk.

Outflow tract septum: The cardiac outflow tract include the ventricular outflow tract and the aortopulmonary septum. There has been much debate regarding this process, the following is a summary of various theories.

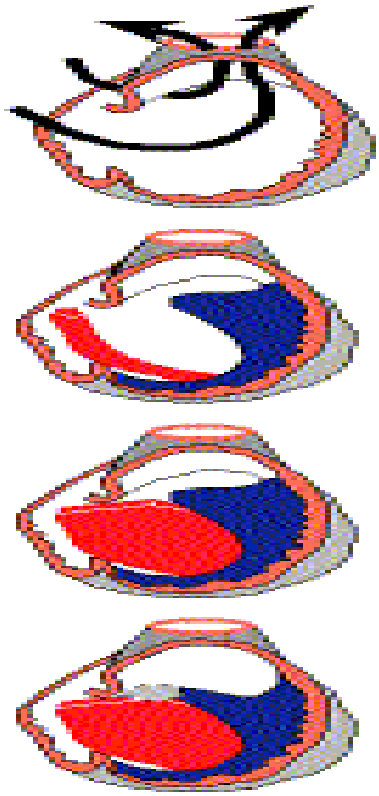


Figure 1. Steps in the embryologic formation of the heart.

Kramer (1942) suggested that there are three embryological areas, the conus, the truncus and the pulmonary arterial segments. Each segment develop two opposing ridges of endocardial tissue, the opposing pair of ridges and those from various segments meet to form the septum separating the two outflow tracts and the aortopulmonary trunks. The aortopulmonary septum is formed by ridges separating the fourth (future aortic arch) and the sixth (future pulmonary arteries) aortic arches. The truncus ridges are formed at the area where the semilunar valves are destined to be formed, therefore forming the septum between the ascending aorta and the main

pulmonary artery. The conus ridges form just below the semilunar valves and from the septation between the right and left ventricular outflow tracts.

Van Mierop (1979), agreed that there are three pairs of ridges forming in the aortopulmonary, truncus and conus regions, however, he stated that the pairs of ridges fuse independently and later on fuse with each other to complete the septation. His theory indicate that the truncus ridges form first, and as they fuse they form a truncal septum which then fuses with the aortopulmonary septum which is formed by invagination of the dorsal wall of the aortic sac between the fourth and the sixth aortic arch arteries.

Asami(1980), followed Van Mierop's theory, however, he stated that these ridge fuse in the opposite direction of what Van Mierop has indicated, i.e. from the outflow tract to the aortopulmonary region.

Pexieder(1978, 1984) and Orts Llorca et al (1982), stated that there are only tow septa, a conotruncal (or bulbar) and an aortopulmonary septum.

Bartlings et al (1989), introduced a new theory. They stated that the septation process of the ventricular outflow tracts, pulmonary and aortic valves and the great vessels is mostly caused by a single septation complex, which they termed aortopulmonary septum. This septation complex develops at the junction of the muscular ventricular outflow tract with the aortopulmonary vessel. This junction has a saddle shape, i.e. not in one plane which would allow the right ventricular outflow tract to be long with a short main pulmonary artery, while the left ventricular outflow tract become short with a long ascending aorta.

The ventricular outflow septation is formed by condensed mesenchyme, embedded in the endocardial cushion tissue just proximal to the level of the aorto-pulmonary valves. The condensed mesenchyme will come in close contact with the outflow tract myocardium, from the area just above the bulboventricular fold, and participate in the septation of the outflow tract by providing an analogue to muscle tissue.

Myocardium in contact with the mesenchymal arch grows rapidly and forms the bulk of the outflow septum and is continuous with the primary fold on the parietal wall of the right ventricle and the myocardium on the right side of the primary septum.

The interventricular foramen, which is bordered by the concave upper ridge of the muscular interventricular septum, the fused atrioventricular canal endocardial tissue, and the outflow tract septation ridges, never actually close. Instead, communication between the left ventricle and the right ventricle is closed at the end of week 7 by growth of three structures—the right and left bulbar ridges and the posterior endocardial cushion tissue—that baffle the left ventricular output through a newly formed left ventricular outflow tract (LVOT). The LVOT is posterior to a right ventricular outflow tract, connecting the right ventricle to the pulmonary trunk.

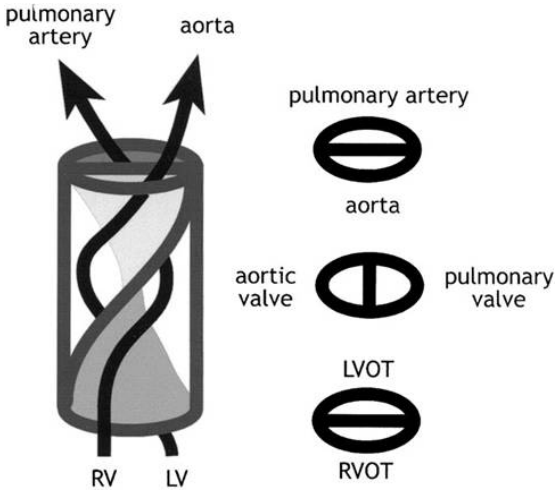


Figure.2 One theory of formation of the outflow tract and vascular septation. LV, left ventricle; LVOT, left ventricular outflow tract; RV, right ventricle; RVOT, right ventricular outflow tract.

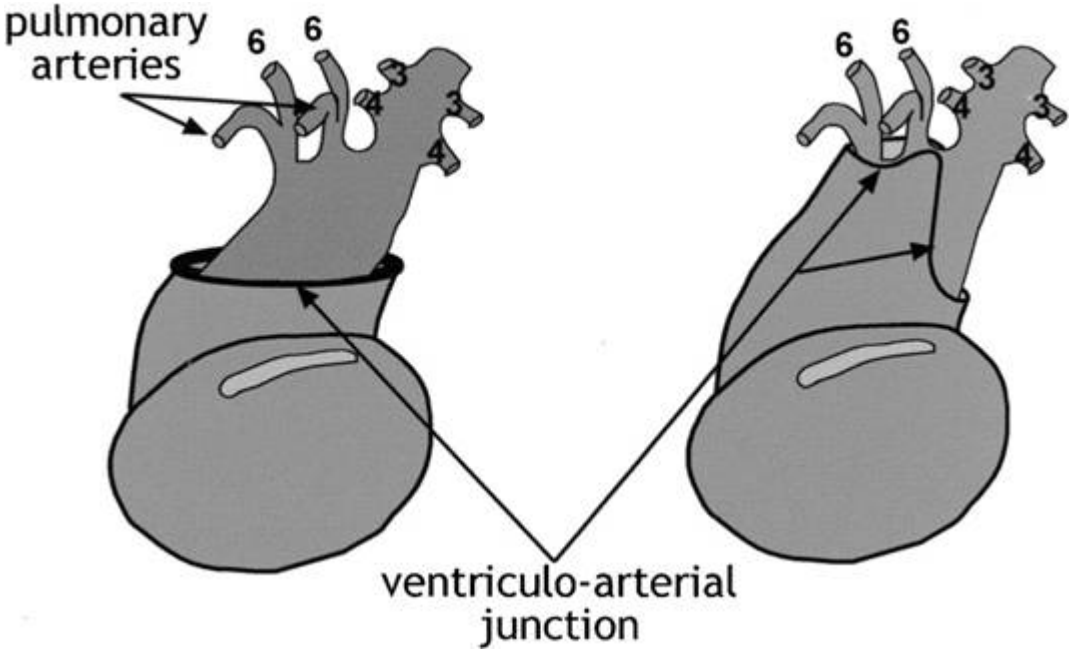


Figure.3 Diagram depicting the theory of ventricular outflow and great vessel septation by Bartlings et al. Numbers indicate specific aortic arch arteries.

4. Anatomy

The septum is formed of a fibrous part (membranous septum) and a muscular part. The membranous part is the smaller and is situated below the plane of the atrioventricular valves between the inflow and outflow portions of the muscular septum, between the non-coronary cuspid and the right cuspid of the aortic valve. The septal cuspid of the tricuspid valve divides the membranous septum into two parts: the atrioventricular and the interventricular.[15-16]

The rest of the septum may be divide into: septal band (septomarginal trabecula) or proximal conal septum, septum of the atrioventricular canal, parietal band (infundibular septum) or conal septum, and muscular septum.[19]

The muscular portion is formed of three parts; the inflow portion that separates the inlet of the two ventricles; the apical trabeculated portion; and the septum of outflow (infundibular septum) between the outlet portion of the two ventricles.

The tricuspidal valve is attached to the atrioventricular septum in a more apical position with respect to that of the mitral valve; in consequence, a part of the septum of inflow is situated between the right atrium and the left ventricle, forming the muscular atrioventricular septum.

A VSD is classified based upon the site of the defect (perimembranous, muscular, sub-pulmonary) and canal type [17-18]

4.a Perimembranous interventricular defect

The perimembranous defect, also known as subaortic, infracristal or membranous, is the most frequent, and represents 75% of all ventricular septal defects when present as an isolated defect [16].

It is localized between the membranous septum and the fibrous trigone of the heart, where the aorta, mitral valve and tricuspidal valve are in fibrous continuity

(Figure 4.5.6).

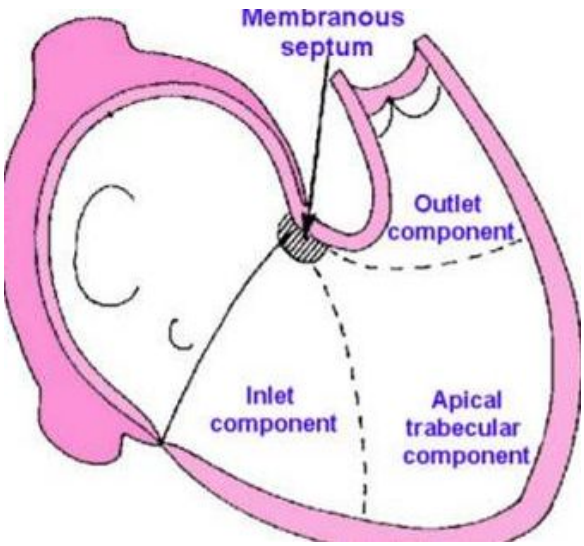


Figure.4 Diagram of various parts of the ventricular septum

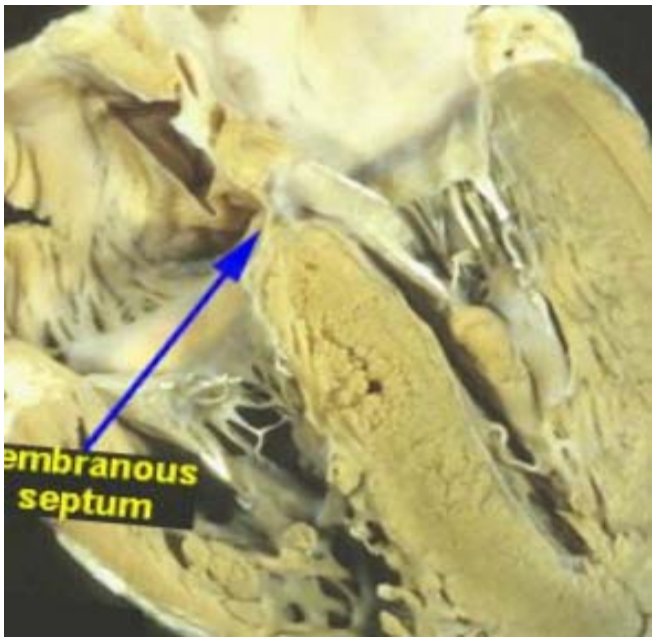
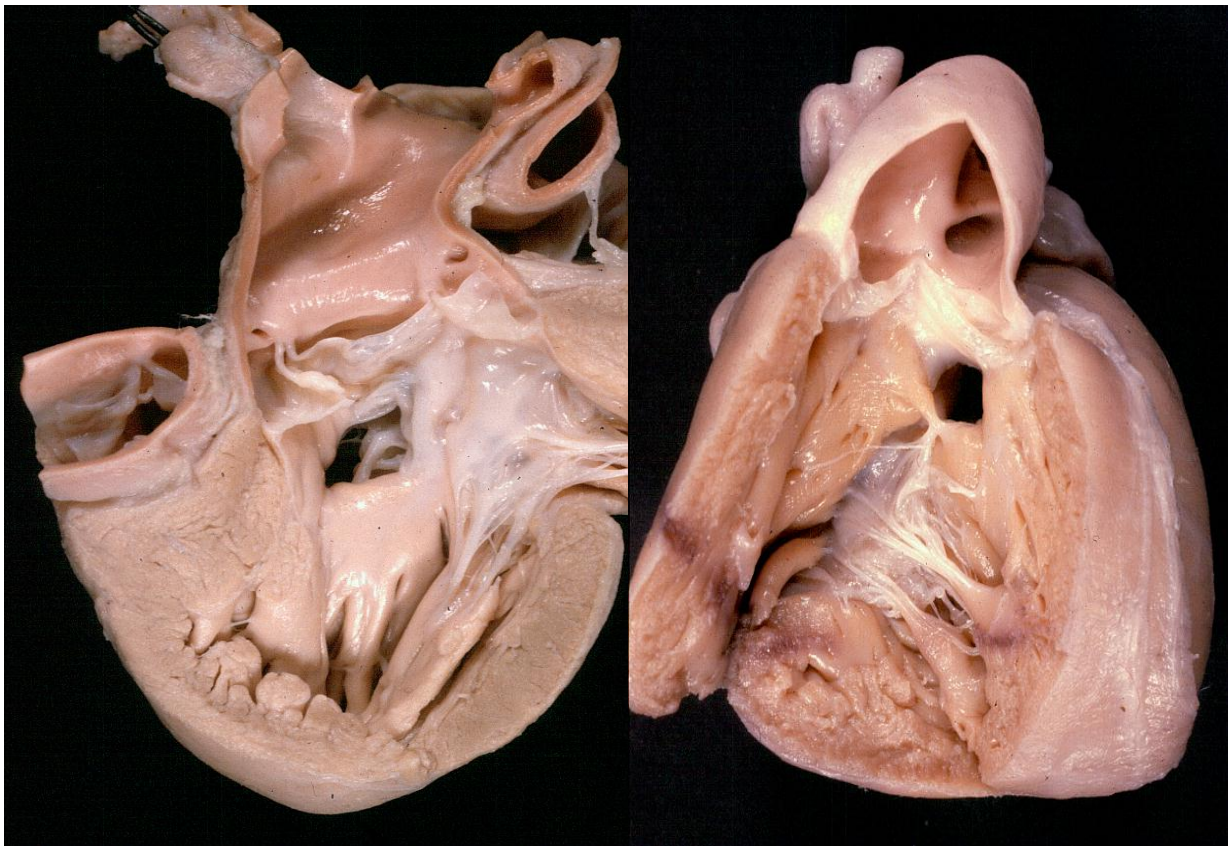


Figure.5: membranous septum



A. **B.**

Figure.6.A perimembranous VSD seen from the left ventricle (the borders of the defect are formed of muscular and fibrous parts in the site of the mitral.aortic.tricuspidal continuity) in this case the aortic valve is bicuspid.

Figure.6.B sub aortic VSD

Favour of Frescura C, Thiene G, Anatomic pathology, university of Padua.

When the defect results from an incorrect alignment of the infundibular septum with the muscular septum (anterior alignment in tetralogy of Fallot, and posterior alignment in interruption of the aortic arch) we speak of malalignment defects.

In these defects, because the ventricular portion of the membranous septum is absent, the superior margin will be delimitated by the non-coronary cuspid valve and the posterior inferior margin will be delimitated of the confluence of the septal and anterior limbs of the tricuspidal valve.

The Lancisi's muscle, with respect to the defect, is normally situated below, and the chordae tendinae of the anterior and septal limbs of the tricuspidal valve are inserted at its base.

Frequently, the septal limb of the tricuspidal valve is inserted at about one third or more of the circumference of the defect, with shorter chordae tendinae contributing partially to obscure it 19.

With 2D echocardiography, it may be visualized in various sections: in parasternal lung and short axis view, and in subxiphoid views, closely below the aortic semilunars.

In these latter sections and in the parasternal short axis, the presence of a fibrous tissue aneurism of the tricuspidal limb may be visualized that reduces the diameter of the defect in direction to the spontaneous closure 20,34

The defect may be visualized with oblique right or left projections, subcostal and parasternal short axis at the level of the tricuspid and aorta. In this last section, the extension of the defect upwards towards the infundibular septum and downwards towards the tricuspidal tissue may be evaluated.

4. B Muscular interventricular septal defect.

Muscular VSD has a variable incidence from 2% to 13% 17, 22, 23. The edges of the defect are completely surrounded by muscular tissue; it may be localized in any part of the trabeculated septum, and it may be multiple (known as Swiss cheese); the size is variable and it take the name from the position occupied in the septum: apical, anterior muscular, or mid muscular 24.

When the defect is large, the presence of gross trabeculated muscles crossing it may give the impression that it is more than one defect. When the defect is inscribed in the apex of the septum it is very difficult to localize, because it is hidden by the trabeculated muscles (numerous in this zone) or by the septal band that crosses in front of it.

Defects of the trbeculated septum are more evident in parasternal or subcostal short axis sections, making a scan from the base to the apex (from the valvular plane to the apex), exploring, in order, the anterior, superior and inferior parts. The colour Doppler helps to visualize small VSDs, not visualized in 2D because of the dimensions or the trabeculated positions, also allowing visualization of the contours of the defect, when it is obliquely and tortuously inside the septum, making the measurement of the gradient less reliable.

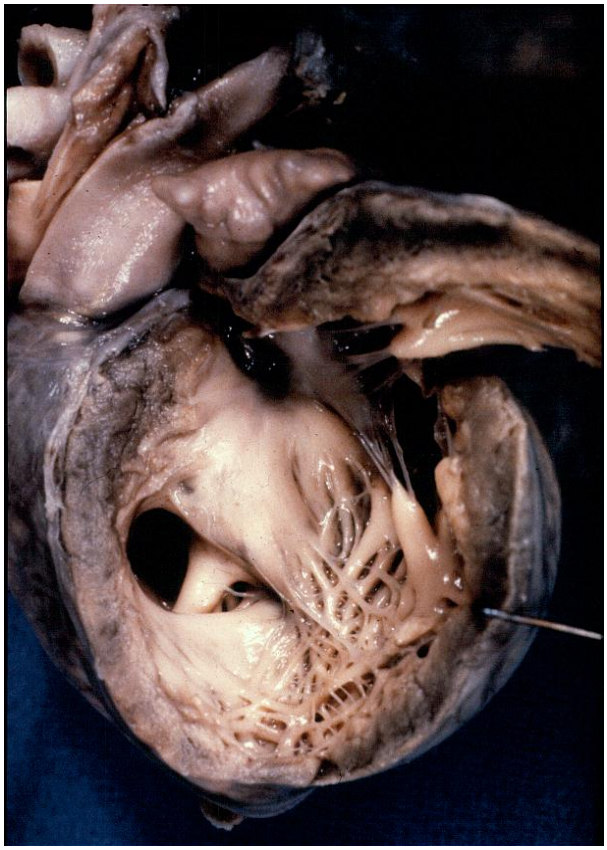


Figure.7: muscular septal defect in the trabeculated portion of the interventricular septum seen from the left, visible a wide defect with borders formed completely of muscular tissue. Deeply, note the trabecola setto-marginalis of the right component. Favour of Frescura C, Thiene G, Anatomic pathology, university of Padua.

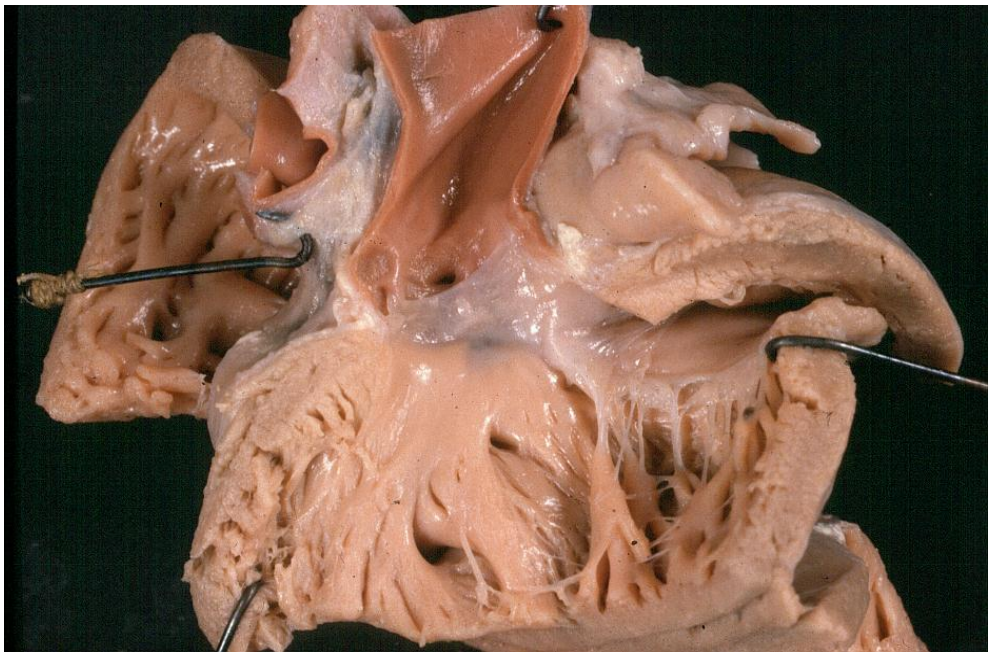


Figure.8: multiple muscular interventricular septum defects (Swiss cheese like VSD). Favour of Frescura C, Thiene G, Anatomic pathology, university of Padua

4-c Subpulmonary conal septum defects

These are often called sub-arterial or doubly committed, and also called supracristal, infundibular, conoseptal, or conal 18.

These are defects that inscribe in the outlet part of the septum, and their superior margins are delimitated by the semilunar leflet of the aortic valve to the left, and the pulmonary valvular annulus to the right. Below and to the left the margin is delimitated by the muscular septum.

The fact that the defect is situated below the annulus of the aorta, the right coronary cusp, means that without annular support it becomes prolapsed, resulting in aortic insufficiency and dilation of the sinus of Valsalva. 25

The VSDs of the infundibulum are studied in the precordial and subcostal short axis and lung axis views.

4. d Ventricular septal defects (canal type)

In the inlet defects, the wall of the atrioventricular canal is totally or partially absent. It represents the more frequent congenital heart disease in Down syndrome.

In canal type defect the malformation involves the atrio-ventricular septum as well as the atrio-ventricular valves: a common atrio-ventricular valve is present, which can or cannot be divided into 2 annuli

The defects of the inflow are better identified with the apical four-chamber and subcostal sections, in which the superior and inferior extensions of the defect are more evident. In these sections, the insertion of the A-V valve and the extension of its leaflets are well studied 5,

5. Physiopathology

Haemodynamics in hearts with VSD involve a passage of blood (shunt) between the two ventricles; the direction of the shunt and its entity depend on two factors: the dimensions of the defect and the resistance of the pulmonary circulation (right ventricle and pulmonary artery pressures). 22,24,25,26

At birth, with the elevated right ventricular pressures, in spite of the presence of large defects, the interventricular shunt may not be present. Within days, the physiologic reduction of pulmonary pressure takes place, with a progressive increase of the pressure gradient between the two ventricles. Then, the left chamber pushes the blood through the defect and the pulmonary artery [26, 27]

A small or restricted defect is defined as when its dimensions offer resistance to the passage of blood. If the defect is restricted and left-to-right shunt is small ([28,29,30]), the pressure in the right ventricle will be normal, and pulmonary blood flow will be only slightly more than the blood flow in the systemic circle (Qp/Qs < 1.5) [30], and the haemodynamic situation will be very like that in a normal heart [31,32,46].

The defect is defined as large or non restrictive when it has a diameter of the same dimensions as the aortic root and does not offer resistance to blood flow; consequently, the pressure in the right ventricle will be similar to that in the left ventricle. The consequence is pulmonary overflow and hypertension, associated with signs of congestive heart failure.

With time, the pulmonary vascular resistance increases, the passage of blood becomes bidirectional, and when the pulmonary vasculopathy becomes clear, the shunt will be from right to left, throughout the cardiac circle [47]. The precise pulmonary resistance values can only be estimated by cardiac catheterization, and its reduction may also be estimated after the use of pharmacologic tests or oxygen.

There are mechanisms of compensation that may occur and limit the right ventricle ejection, reducing the pulmonary overflow Hypertrophy of the sopraventricular crest of the infundibulum or pulmonary stenosis, create an obstacle to the RV outflow, i.e., a gradient from the right ventricle and the pulmonary artery, limiting the pulmonary blood flow. The same mechanism may operate at the level of the outflow tract, pulmonary valve, supravalvular region, or pulmonary branches. [34,35]

In conditions intermediate between the two, mentioned above, we talk about a moderate interventricular defect where the overflow Qp|Qs is between 2 and 3:1

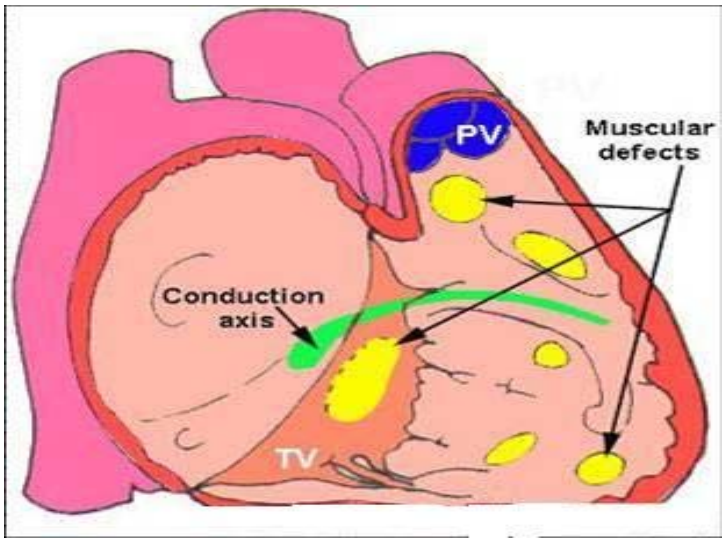


Figure.9 The conduction axis in relation to various types of defects

6. Natural history

The ventricular septal defect may move towards a spontaneous closure through various mechanisms:. the growth of muscles in muscular defects; the formation of aneurism of the septal limb of the tricuspid valve in perimembranous defects; by prolapses of the aortic cusp in infundibular defects, [27,35].

Spontaneous closure of the VSD occurs in 35-45 of cases in the first year of life (it reaches 60% in some studies) and another 8-20% will close in the rest of infancy [36,37,38]. Larger muscular VSDs have a minor tendency to spontaneous closure. Muscular ones tend to close in the first year of life, independently of their location.

Cardiac insufficiency is possible in all ages, although it is frequent in the first months of life, causing difficulties in feeding and failure to thrive [48].

In medium-to-large VSD, because of pulmonary overflow severe pulmonary hypertension develops in about 12% of patients [48,52].

Supracristal VSD, even if small, can be complicated by pulmonary insufficiency.

Fifteen % of patients reach adulthood with the persistence of VSD; amongst these, the major complication is bacterial endocarditis [50].

It is believed that large VSDs operated upon before the second year of life recover normal pulmonary vascular resistance and left ventricle function, while VSDs operated upon after the second year of life will most likely progress into a state of pulmonary arterial ipertension, due to progression of irreversible pulmonary vascular disease [59].

7. Clinical presentation

Clinical presentation, like these patients' haemodynamics, depends on the dimensions of the defect and on the site of the defect [43].

Patients with small VSDs are asymptomatic and present a characteristic heart murmur (the sole abnormality).

Medium-to-large VSDs show heart insufficiency that may manifest itself as difficulties in feeding, growth retardation, reduced tolerance to exercise, cyanosis or clubbing of the fingers when the pulmonary vasculopathy develops [48].

The characteristic VSD murmur is holosystolic, its intensity varies from 3/6 to 5/6, and its location depends on the site of the defect.

The pulmonary component of the second sound is reinforced, only in medium-to-large VSDs with pulmonary overflow and hypertension. If the left-to-right shunt is large, a diastolic rumple at the apex may be heard because of relative stenosis of the mitral valve, due to the overerloading of the left ventricle.

If the VSD is infundibular, it may cause an aortic prolapse with consequent aortic insufficiency, and a decreasing diastolic murmur may be heard at the right upper sternal border .

Perimembranous defects may have an associated systolic snap because of the aneurism of the tricuspidal valve.

The turbulent left-to-tight flow across the VSD causes a palpable precordial fremitus. Large defects involve equal pressures between the two chambers, without any murmur of just an ejective systolic murmur at the left uppee sternal border, due to relative pulmonary stenosis.

Patients with Eisenmenger's syndrome are cyanotic and present finger clubbing; the second tone is reinforced because of the pulmonary component, and a diastolic murmur of pulmonary insufficiency may be present. [46,48]

8. Diagnosis

8. a Electrocardiogram

The electrocardiogram is normal in small defects, but with the increase of the shunt, the volume load of the left ventricle results in hypertrophy, and an enlargement of the left atrium may be present, while in the case of pulmonary hypertension the cardiac axis will be deviated to the right because of the right ventricle hypertrophy [38].

8.b Radiography of the thorax

Small defects do not cause alterations in the chest radiography; in large defects the cardiac shadow shows variable enlargement of the left chambers and pulmonary vascular mark is increased; in Eisenmenger's syndrome pulmonary vascularity is reduced with dilation of the right chambers and of the pulmonary artery [37].

8. c Echocardiography

Echocardiography allows a non-invasive and accurate evaluation of the morphology of the defect and of eventual associated alterations. With an echocardiographic examination we can quantify the haemodynamics of the defect, the pressure in the pulmonary artery, the obstruction of the right ventricular outflow tract, eventual aortic insufficiency or the distortion of the tensor apparatus of the valves.

A m-mode examination is always necessary for evaluation of the parietal thicknesses and the dimensions of the cavities. Integration with the colour Doppler facilitates examination, permitting the visualization of small defects that may be lost with 2D and also permits a more precise evaluation of the dimensions [37, 38, 40].

Echo-Doppler allows the measurement of the pressure gradient between the two ventricles at the level of the defect. When we know the systemic arterial pressure it is possible, subtracting the measure of the gradient, to determine the systolic pressure in the right ventricle, which will be in the absence of obstruction in the right outflow equal to the pressure in the pulmonary artery. A high gradient means a low pressure in the right ventricle, and therefore a medium shunt.

The echocardiographic examination must be completed with the search for associated defects: coarctation of the aorta, interruption of the aortic arch, obstruction of the right outflow (valvular stenosis or infundibular stenosis), patent ductus arteriosus (PDA), interatrial defects (DIA), subaortic stenosis, aortic insufficiency. When the quality of the transthoracic exam is limited because of a bad acoustic window, the trans-oesophageal echo (TEE), may generally be used to study the anatomy and

haemodynamics of the defect. The sensitivity of this method is limited by the performance of sections that do not allow the exploration of all the components of the septum – particularly apical defects. Monitoring with TEE is effectuated through the procedure of closing the defect with devices; the three-dimensional echo (3D) allows a better visualization of the defect and of its relations to the adjacent structures [45, 16].

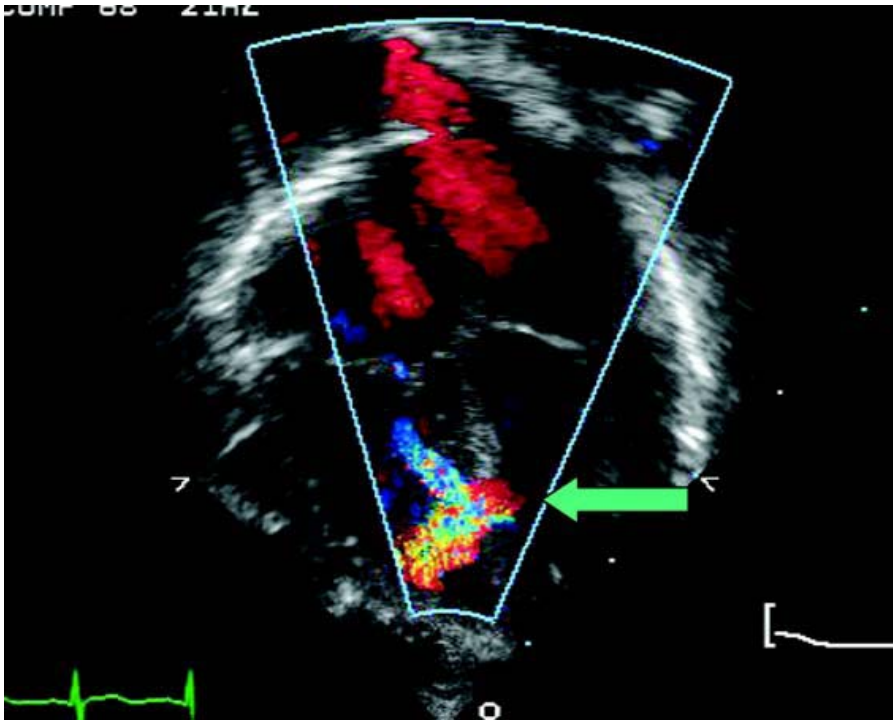


Figure 10 : Echo colour Doppler of a muscular VSD with 4-chamber scan.

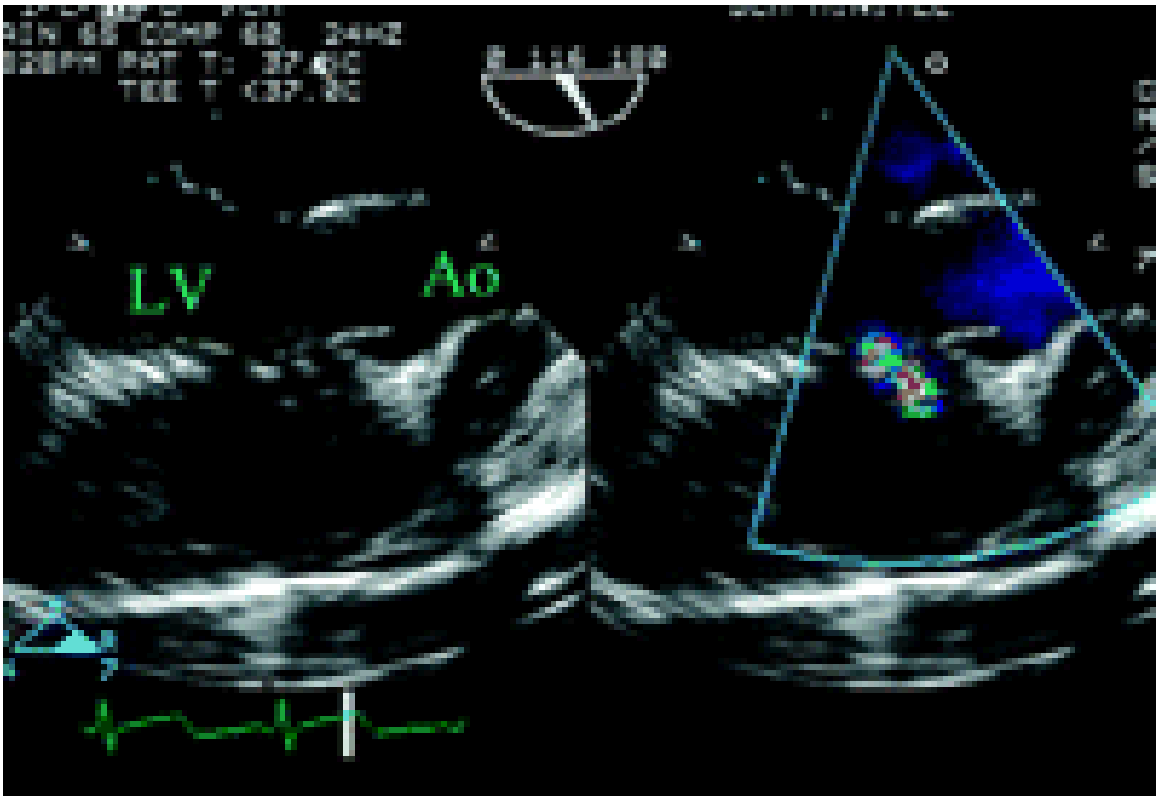


Figure 11: membranous VSD viewed by trans oesophageal echo

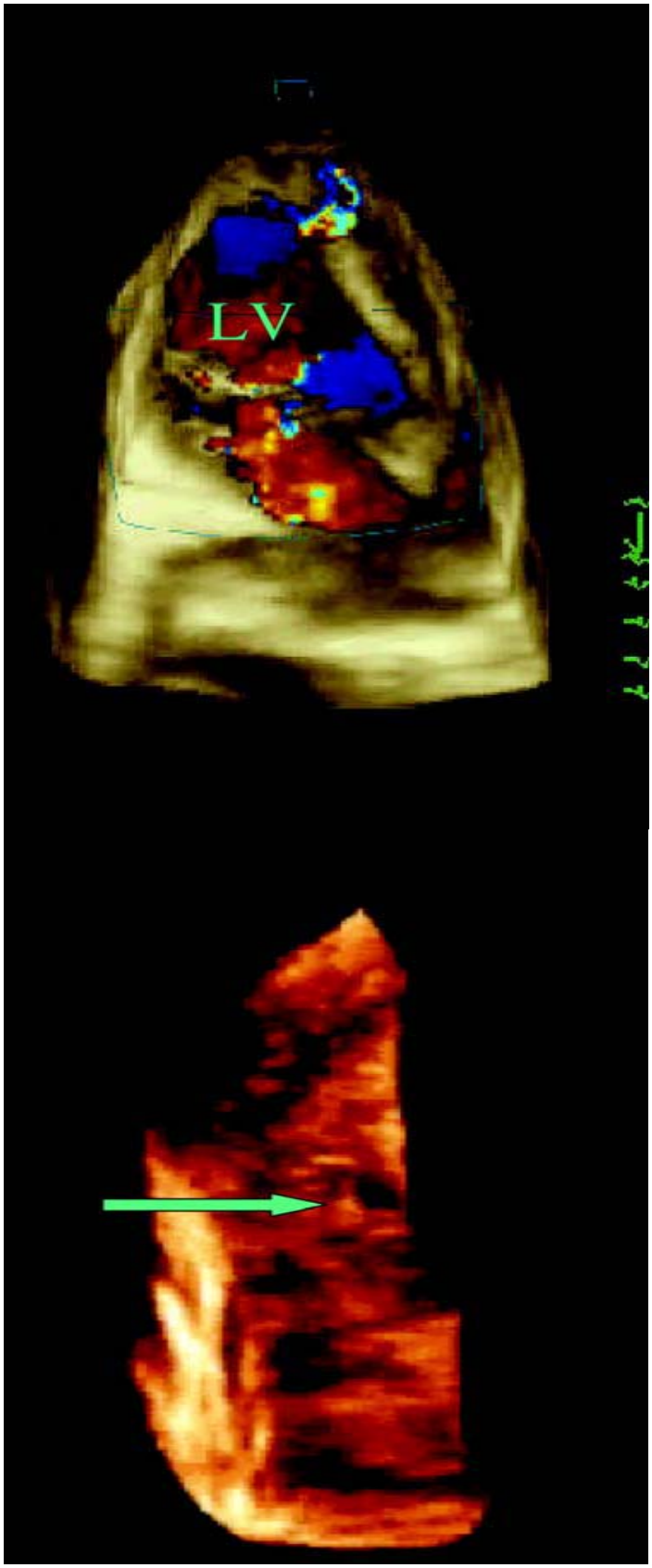


Figure 12 : **Echo 3D. Two images of small muscular VSDs seen from the right ventricle.**

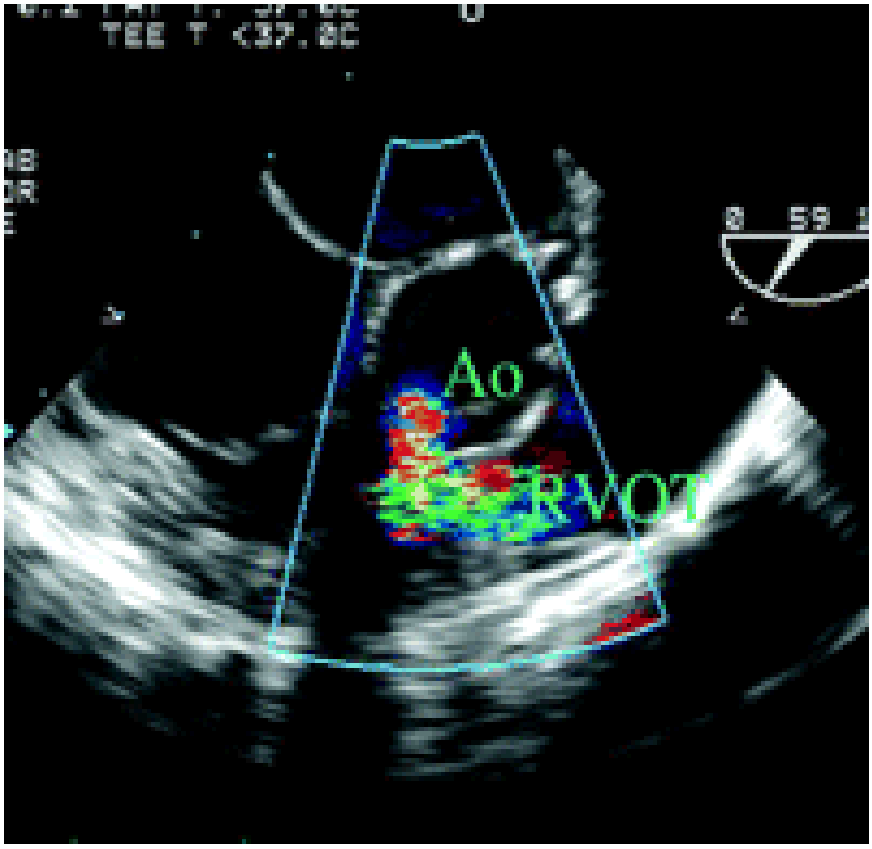


Figure.13 Subaortic high-membranous VSD with flow into the right ventricular outflow tract (RVOT) from interpretative trans-oesophageal echocardiogram. Ao indicates Aorta.

8.d Cardiac nuclear magnetic resonance

The quality of the images obtained with this more expensive method allow better visualization and definition of the defect. It is used in patients with VSDs that are not visualized well by other methods and with VSDs associated with other major defects [44].

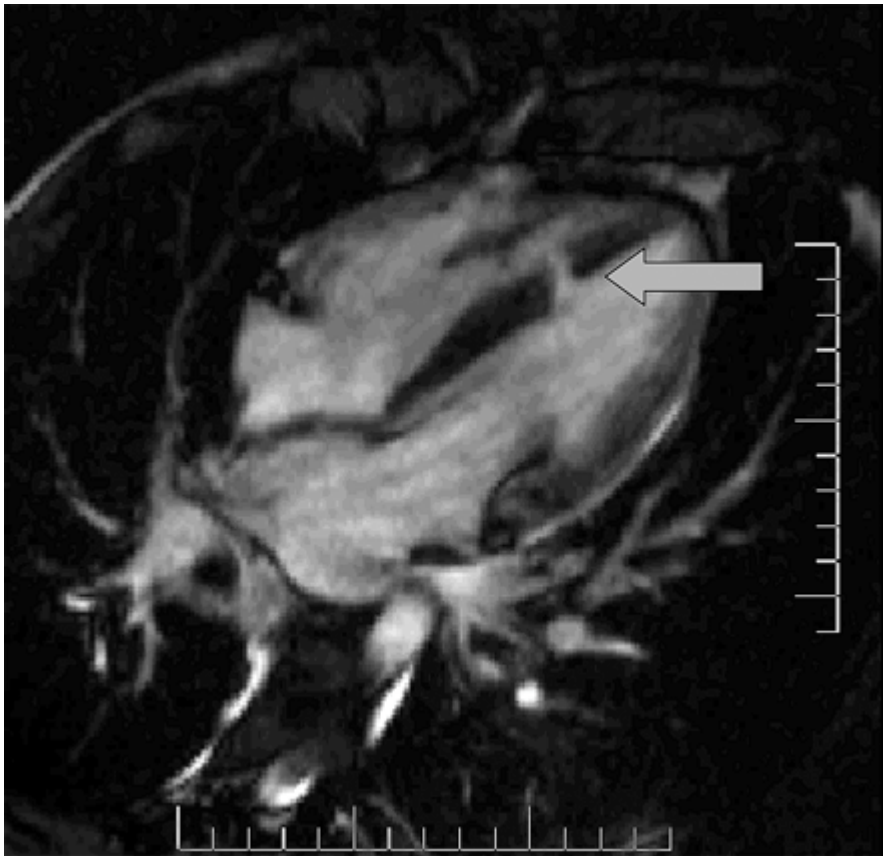


Figure 14: cardiac NMR, 4 Chambers projection, mid muscular VSD.

8.e Cardiac catheterization

With this invasive method we can determine accurately the measure of pulmonary vascular resistance, the response of the pulmonary endothelium to the pharmacological test or to oxygen, and the volume of the shunt. The response to pulmonary vasodilators guides therapeutic choices.

Angiography gives information about the localization of the defect, its size and the grade of aortic insufficiency [47,51].

Cardiac catheterization is performed in case in which a hemodynamic evaluation is mandatory for the decision making or when a transcatheter closure is planned

9. Medical treatment

Therapy depends on the symptoms; small defects do not need any pharmacological treatment, whereas cardiac insufficiency due to overflow needs anti-congestive therapy (digoxine, diuretics, vasodilators) 48,49,51.

Medical therapy in Eisenmenger's syndrome is complex and affected patients must be treated in highly specialized centres 45.

10. Surgical therapy

The decision to proceed with surgical correction must be taken into consideration, although we should bear in mind what has been said about the elevated percentage of spontaneous closure of the defects 41, 53, 55.

The echocrdiographic data that must be considered for the surgical closure are: dimensions and site of the defect, pressures in the pulmonary artery, left ventricular function and geometry.

Large and medium size VSDs need surgical repair in the first six months of life in 30 % of patients if they have caused growth failure or cardiac insufficiency unresponsive to therapy. 54,60.

The presence of a pulmonary systolic pressure superior to 50% of systemic pressures represents an indication of early surgical repair.(from six months to one year), while it is possible to wait until the second year of life if the normalization of the pulmonary pressure and/or a relationship QP/QS < 2/1 is observed 53,60.

The risk of obstructive pulmonary vasculopathy become more evident with age, for which reason the invasive evaluation of pulmonary resistance through cardiac catheterization is necessary for a correct indication of operation in older patients with unrestrictive VSDs.

In the follow-up of patients with VSD the following are fundamental: the serial study of ventricular function and geometry that vary with relation with load and the monitoring of the pulmonary pressures. Follow-up of the associated anomalies are also necessary 55,60.

Early correction leads to a complete recovery, and patients with large VSDs operated later may present, in the post-operative follow-up, anomalies of mass and geometry 56.

After spontaneous or surgical closure of the defect, subaortic stenosis may appear

The exposition of the defect is obtained by an inter-atrial approach, after retraction of the tricuspid valve, or if necessary, temporary detachment of its septal limb.

Malalignment defects and canal-type defects do not have the same possibility of spontaneous closure as other defects, and if they are big enough to require a treatment, there is the indication of selective surgery at the moment of the diagnosis.

Developments in surgical techniques do not seem to have reduced complications of the intervention; a study about corrective intervention in 258 cases 40 years ago demonstrated that 80% had a definitive closure of the defect, 9 patients presented complete atrioventricular blocks, 37 presented transitory a-v blocks, about half presented right branch blocks in the ECG, endocarditis appeared in 9 patients, with an incidence of about 11.4 per 10.000 patients/year [57,58,61].

Another study, published in 2000, demonstrated that in recent surgical interventions too a residual defect is seen in 31 % of patients and a complete a-v block in 3.1%. Furthermore, Kidd's study demonstrated the need for a pacemaker in 908 out of 10000 patients every year, and an incidence of endocarditis of 16.3 per 10000 patients in a year 58.

10.a Pulmonary artery banding

The bandage of the pulmonary artery is a palliative technique that aims to reduce the pulmonary overflow while waiting for the corrective intervention; it is reserved for patients with recurrent pulmonary infections or in the case of patients with very low weight and with multiple defects.

10.b Closure with devices

The closure of the VSD with devices is possible for selected cases or as a hybrid approach in the operating room combining a midline sternotomy with exposure of the heart and a perventricular introduction of a double ombrella device, avoiding the use of cardiopulmonary bypass. The first in this field was Lock and collaborators in 1987, using a device called the Rashkind double umbrella for closure of interventricular defects. Currently exists a specific Amplatzer device for muscular and membranous defects [68]. A study has demonstrated a closure in 96 % of cases at 6 months with a percentage of complications of 8.6 % with the utilization of the Amplatzer membranous device [62].

Arora and collaborators in 2004 published a study showing that the use o Amplatzer muscular VSD closed 100% of single VSDs with follow-up [63,65,66]. However, closure using devices is not without risks and complications, showing temporary a-v blocks in 1.8 % of patients. [63,64,70,71]. In 5% of patients the positioning of the device was not successful because the defect was near the aortic valve [66, 71].

Echocardiography parameters for VSD valuation and indication for non-surgical closure:

1) Site of the defect: muscular and perimembranous

2) Diameter: the width of the defect is defined based on the relationship with aortic diameter:

Large: VSD/aortic diameter >/= 1

Medium: VSD/Ao </= 1\2

Small: VSD/Ao < 1\3

3) Ventricular geometry:

Mass/volume relationship

Index of sphericity

4) Miocardial function :

- Systolic function
- Pump function
- Intrinsic myocardial contractility
- Diastolic function

5) Pulmonary pressure

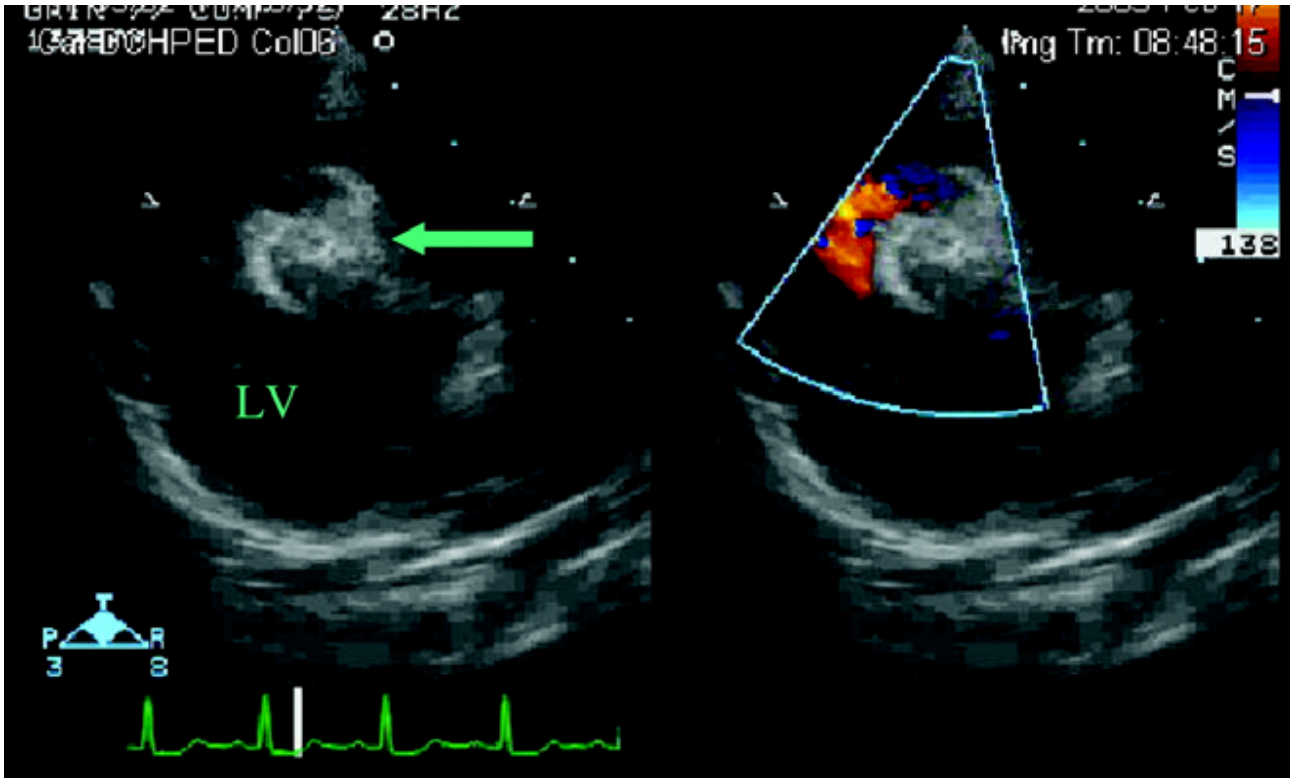


Figure15: **Oblique short axis projection of Amplatzer device; projection for closure of mid-muscular** VSD.

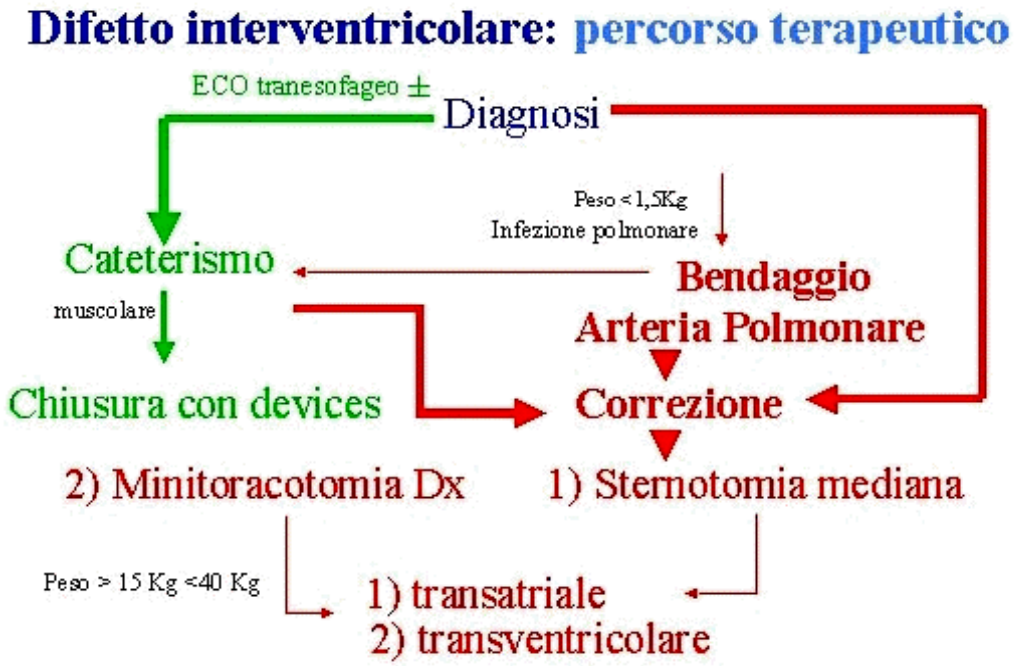


Figure.16: **Treatment of ventricular septal defect**

11. Study

11.a Purpose of the study:

The purpose of our study has been to evaluate the natural and surgical history of isolated ventricular septal defect in pediatric age.

11.b Materials and methods

We have examined the clinical records of the paediatric patients affected by isolated ventricular septal defects, followed in the outpatients clinics of our Paediatric Cardiology Department in the time frame from 1990 to 2006 and followed to 2008.

At every follow-up visit the patients were examined by physical examination, ECG and echocardiography to evaluate cardiac haemodynamics (entity of the shunt), ventricular kinetics (pump function), the existence of pulmonary overflow or pulmonary hypertension, the existence of cardiac insufficiency and the development of complications such as subaortic stenosis, insufficiency of the aortic valve or the spontaneous closure of the defect.

Follow-up of operated VSD included: the development of complications like rhythm disturbances and A-V block; residual VSD; outflow stenosis; kinetics; functioning of the operated ventricles.

Patients with major cardiopathies like tetralogy of Fallot, double outlet right ventricle, complete atrioventricular canals or transposition of great arteries, were excluded from the study.

The echocardiogram was carried out using a or Philips Sonos 5500 or 7500 echocardiography equipped with broad band probes; in all patients a two-dimensional study was carried out in the projections: parasternal long axis, short axis, apical 4 and 5 chambers, and subcostal views. All patients were studied with M-mode, colour-flow Doppler, pulse Doppler and continuous Doppler. All the examinations were recorded on videocassettes for off-line evaluation.

Ventricular septal defects were classified according to their position, perimembranous, muscular, subpulmonary (also called supracristal or doubly committed). The dimensions of the defect ware expressed in relation to the diameter of the aortic annulus: defects ware defined wide when they had a diameter equal or superior to the aortic valve; medium when 2/3 to 1/3 of the aortic valve; small for measurements inferior to 1/3 of the aortic diameter. Were included in the study all the patients followed up with regular check-upsfor whom and at least 2 successive

echocardiography evaluations were available. The presence of signs congestive heart failure (CHF), failure to thrive, anticongestive therapy were also recorded and the patients assigned to either (i) (CHF+) or (ii) (CHF–) groups.

11.c Results

Patients with isolated VSDs who were visited for the first time in the indicated period were about 1100; those who fulfilled the requirement for inclusion (complete data of at least 2 FU visits) were 519.They were 222 males and 297 females; 88% of patients were between 2 and 17 years; median age was 7.7 years.

The first evaluation was made in the neonatal period in 499 patients(97.3%), at an older age in 14 (the murmur was heard occasionally by the paediatrician), and in six cases, all observed in the year 2008, the diagnosis was made prenatally by foetal echocardiography.

In the time frame in study 29% (162) of the children had an age ranging from 2 to 4 years; 41% (203) from 5 to 10 years; 18% (91) from 11 to 15 years; 12%(63) were older than16 years.

Age groups	Number of patients	%
2-4 years	162	29%
5-10 years	203	41%
11-15 years	91	18%
> 16 years	63	12%

Table.1 Age groups in the study

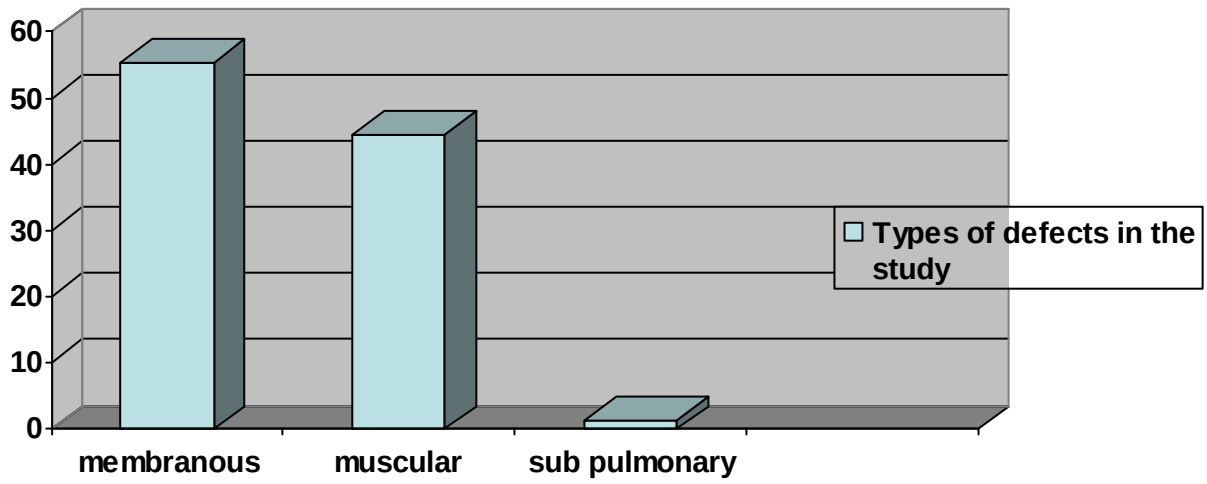


Diagram.1 type of defects in the study

Patients with perimembranous defects were 279 (55.2 %).

Twelve patients had perimembranous and muscular defects at the same time; 232(44.5%) patients had muscular defects.

Eight (1.5%) patients had subpulmonary defects. Defects were single in 487 (93.8%) cases, and multiple muscular or muscular and perimembranous in 32 (6.1%).

Two hundred and seventy seven (53.3%) patients had a small VSD, 102 (19.6%) medium VSD, 140(27.1%) large VSD.

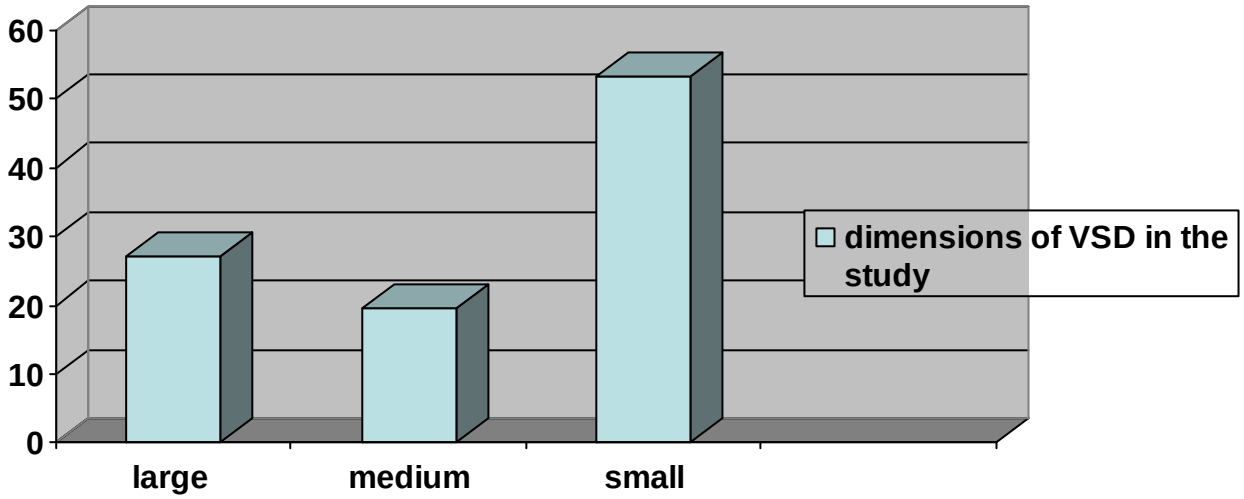


Diagram .2 Dimensions of defects in the study.

In the first visit 426 patients (82%) were without symptoms, while 93 patients (18 %) had symptoms, presenting: congestive heart failure (74 patients, 14%), difficulties in feeding and failure to grow (14 2.6%), moderate pulmonary hypertension (39 7.5%), and recurrent pulmonary infections (4 0.7%). All the children of patients with cardiac insufficiency received pharmacologic therapy, while 45(8,6%) of non-symptomatic patients received preventive therapy. 14 patients with cardiac insufficiency (19 %) received monotherapy with digoxin, while 56 (75%) received double therapy with digoxin and a diuretic, and only 4 patients (5.5%) received digoxin , diuretic and vasodilators.

28 patients (5%) had trisomy 21, one had trisomy 18, one had VATER sequence, one had Holt-Oram syndrome, one Noonan syndrome and one patient with CATH 22. An additional case had a non specified syndrome.

Two patients with large VSDs were first evaluated at our clinics when they already had an Eisenmenger's syndrome. A cardiac catheterization was made in 12 patients,

The follow-up of our patients demonstrated that 185 (35%) of patients needed surgical intervention. Two cases were closed with Amplatzer devices (one by an endovenous approach and the other with a hybrid approach). Forty six children, all affected by small VSDs (9%), were lost at the ultimate follow-up, before the complete closure of the VSD; 247(48%) had spontaneous closure (SC).

SC occurred in 19% of patients by the age of 6 months, and in 50 % by the by the age of 1 to 2 years, and 77% by the age of 2 to 4 years, and 97% by the age of 6 to 10 years.

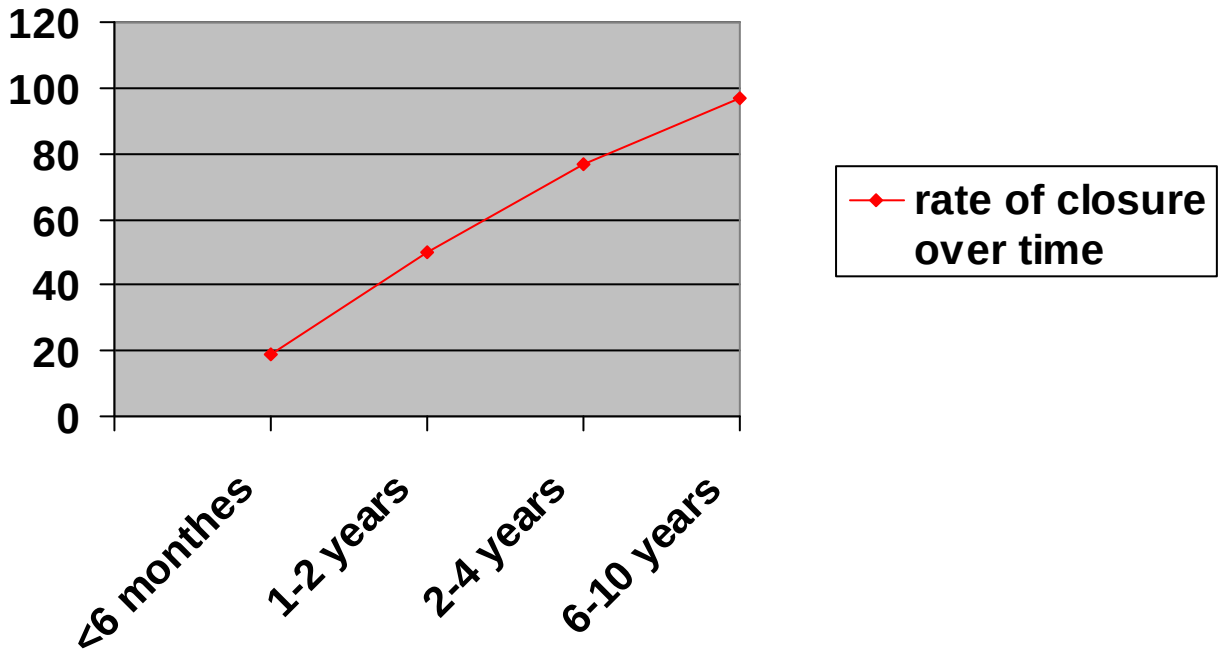


Diagram.3 Rate of closure over time

Ninety three % of SC muscular VSDs were closed by age of 3 years, and 90% of SC perimembranous defects by the age of 6 years.

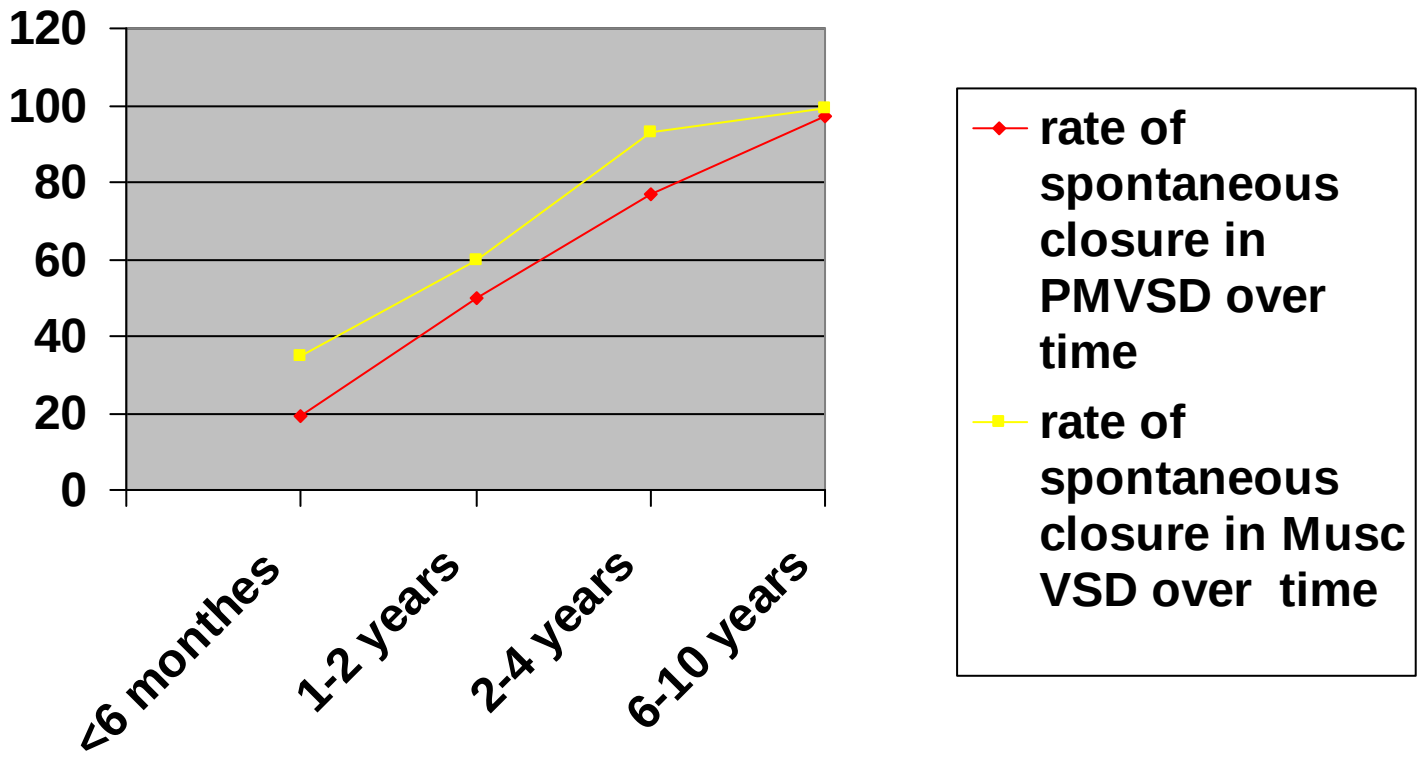


Diagram.4 Rate of closure in muscular and membranous VSDs over time

In patients without CHF, the rate of SC was 50%; SC occurred in only (12/74) 16% of patients with a VSD with CHF.

	Num	%	Spontaneous Closed VSD With CHF	% closed VSD with CHF of all closed	% of closure in CHF	p.value
Spontaneous closure in all VSD	247	48%	12	4.8%	16%	<0.05
Rest of cases	272	52%	62	95,2%	84%	
tot	519	100%	74	100	100	

Table 2: relation between spontaneous closure and congestive heart failure

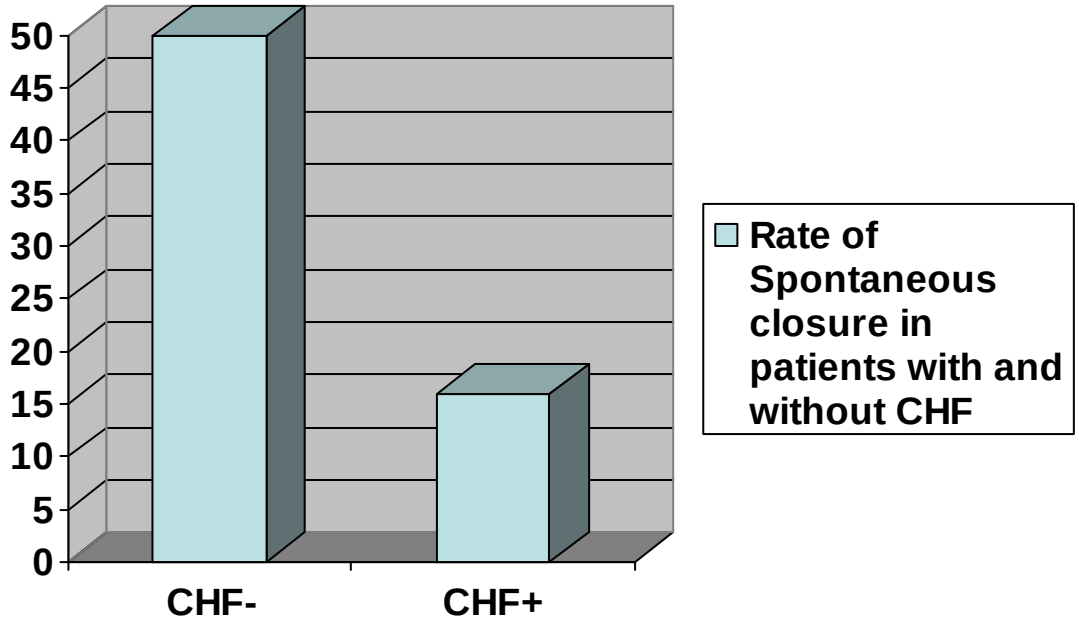


Diagram.5 Rate of closure of VSD with and without CHF

Spontaneous closure was documented in 80% (185/232) of muscular VSD, in 22% (62/279) of perimembranous (pm)VSD, and in one case (1/8, 12%) of subpulmonary (sp) VSD.

	muscular	membranous	subpulmonary
Total number	232	279	8
Spontaneously closed	185	62	1
Rate	80%	22%	12%

Table 3:spontaneous closure rate in various types of the defect

Spontaneous closure was registered in 77 % (240/277) of small defects, in 23% (28/102) of medium defects, and in 5 % (7/140) of VSDs classified as large at the first diagnosis.

Table 4

	Number	%	Spontaneously closed muscular VSD	% of muscular VSD on all closed VSDs	% of closure on all muscular VSDs	p.value
Spontaneous closure in all VSD	247	48%	185	74%	80%	<0.05
Rest of cases	272	52%	47	17,2%	20%	
tot	519	100%	232			

Table 5

	Number	%	Spontaneously closed pmVSD	% of closed pmVSD on all closed	Percent of closure onall pm VSD	p.value
Spontaneous closure in all VSD	247	48%	62	25%	22%	<0.05
Rest of cases	272	52%	217	87%	78%	
tot	519	100%	279			

Table 6

	Number	percent	Spontaneously closed sp VSD	% of closed sp VSD onall closed	% of closure on all spVSD	p.value
Spontaneous closure of all VSD	247	48%	1	0.4%	12.5	0.35
Rest of cases	272	52%	7	2.5%	87.5	
tot	519	100%	8			

Table 4-5-6: Relation between the spontaneous closure and the site of the VSD

We conclude from the tables 4.5.6 that : there is a strong relationship between the site of the defect and the probability of spontaneous closure , and that the results have a strong statistic significance in the membranous and muscular VSD, but not in subpulmonary (because of the small size of the sample).

As we can appreciate in the diagram, a spontaneous closure is much more probable in a muscular VSD than in a perimembranous, although it is quite probable (1/5) also in the latter. Furthermore, a spontaneous closure can happen also in VSD presenting with CHF.

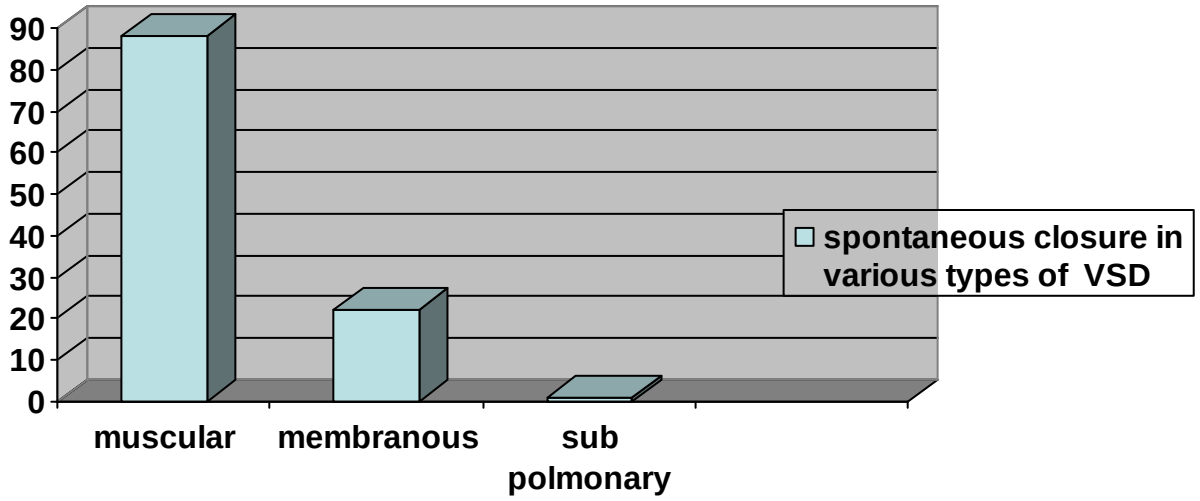


Diagram.6 Relationship between type of defect and spontaneous closure

In contrast, of 185 patients corrected with surgery, 76% (141/185) presented large VSDs while 15% (28/185) presented medium VSDs and 9% (16/185) presented small VSDs; practically all the small VSDs corrected were subaortic VSDs associated with prolapse of an aortic cuspid and were generally corrected in a more advanced age when follow-up had shown the prolaps

Total surgical number	Large VSD	Medium VSD	Small VSD
185	141	28	16
	76%	15%	9%

Table7: rate of surgery according to dimensions of the defect

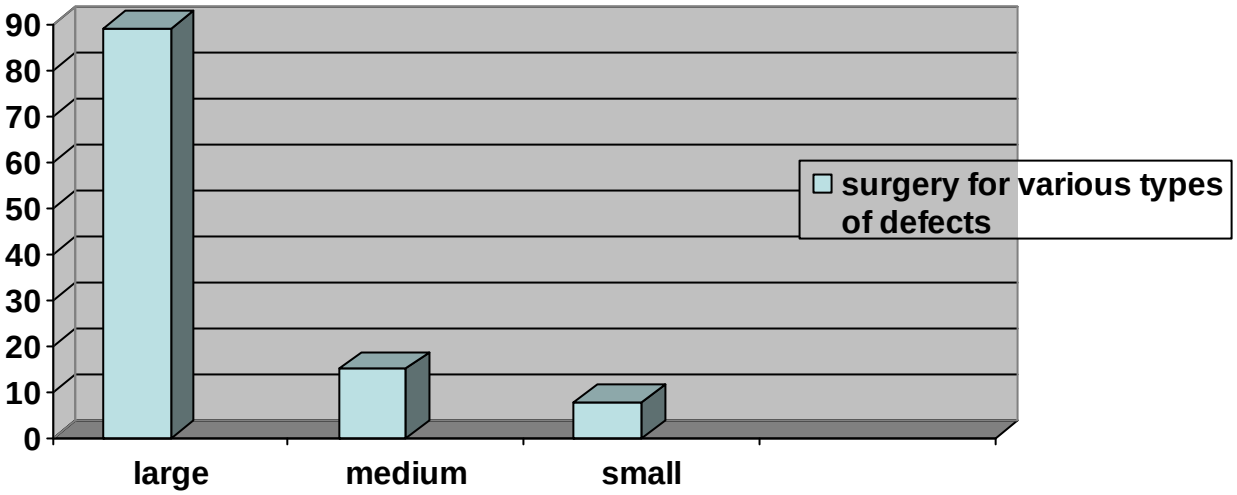


Diagram.7: Rate of surgery according to the dimensions of the defect

Surgical closure was carried out in 185 patients. 87% of whom affected by perimembranous defects, 9.3% muscular, and 3.7 % subpulmonary,

Total	membranous	muscular	infundibular
100%	87%	9.3%	3.7%
185	162	16	7

Table 8: Rate of surgery according to the location of the defect

In total, 57% (162/279) of membranous and 6.9 %(16/232) of muscular and 7 cases out of 8 of subpulmonary VSD required surgical closure. Two cases were closed with Amplatzer devices (one by an endovenous approach and the other with a hybrid approach). Four cases needed a pulmonary banding before the final operation.

Three cases out of 185 (1,6%) required permanent pacemakers because of iatrogenic complete a-v blocks; there were 2 cases of ventricular arrhythmia; 26 cases (14/) with residual VSDs, which required re-operation in one case, and another had successful closure with an Amplazer device.

Aortic insufficiency was evident in 11 cases: in 9 cases it was present preoperatively, while in 2 cases aortic insufficiency developed in spite of surgical closure. The aortic insufficiency that had developed was in cases of perimembranous VSD in 9 cases out of 11 (80%).

Fifty three % presented a right branch block after surgery.

Perioperative complications were relatively few (8%): one case of low cardiac output; two cases of extubation difficulties; 4 cases with pericardial effusion (postcardiectomy syndrome). 3 were resolved by medical treatment and only one case was treated with thoracic drainage.

The defect was not closed at the last check-up in 87 (16.7 %) cases. Of these, 44 were perimembranous and 41 muscular, and there were two cases of non-committed VSD.

Subpulmonary stenosis was evident in 15 patients (2.8%): there were 8 cases in non-operated patients and 7 in operated VSD.

Sub-aortic stenosis was documented in 10 patients (1, 9%): 7 cases in operated patients and 3 in non-operated. In 2 of the 7 patients corrected surgically, stenosis developed after surgery.

Only one patient in the natural history died, at the age of 21 years, due to Eisenmenger's syndrome (delay of diagnosis and follow-up outside of Italy).

11.d Long-term follow-up

During the various years of follow-up (4-15 years) by auscultation, physical examinations. and echo-Doppler, 80% of small VSDs were noted to have closed spontaneously

11.e Conclusions and discussion:

Spontaneous closure was documented in 80% (185/232) of muscular VSD, in 22% (62/278) of membranous VSD, and in one case (1/8) of subpulmonary VSD. Of all cases 247/519 (48%) have a spontaneous closure

In our series we see a low percentage (1.5%) of sub-pulmonary VSD in comparison to the oriental studies (in Japan) [74], in which a 10 % incidence of sub-pulmonary VSDs is reported. This diference is due to genetic factors.

In patients without CHF, the rate of SC was 50%; SC occurred in only 16 % (12/74) of patients with a VSD with CHF.

From the previous table we can see the inverted relation between the probability of heart failure and the probability of spontaneous closure.

This observation suggests that a conservative attitude in the first month of life in patients with VSDs should be maintained, unless pulmonary hypertension is present. Surgery is quite safe (we did not take surgical mortality into account), even though severe complications such as complete or advanced a-v blocks were verified in about 2% of the cases; residual VSDs were present in 14%, requiring reintervention in 1%. We contend that SC probably occurred due to the growth of the muscular septum surrounding the VSD. Muscular VSD spontaneously closed earlier than perimembranous VSD.

In other studies of control, the incidence of spontaneous closure in membranous VSD was more elevated that that of muscular VSD. McCarthy KP, Ho SY, Anderson RH [74] wrote: "The likelihood of spontaneous closure of any ventricular septal defect depends largely on its location. It is usually thought that the majority of defects that close are perimembranous, followed by muscular defects".

In our study, however, spontaneous closure was more elevated in muscular VSD.

This may be because the majority of our patients were neonates at the time of the first diagnosis and it is in the neonatal period that there is a prevalence of muscular VSDs..

We confirm the data obtained: spontaneous closure occurs in more than half the patients, but it was more common in muscular defects. Furthermore, a previous study has shown that 40.2% of asymptomatic VSDs spontaneously closed during a mean follow-up period of 9.5 years. In Krovetz's study, 45% were less than 1 week old when first examined. The cumulative SC rate was 71% and 44% closed when the patient was 12 months or under. The SC rate of patients without CHF was 72% (Krovetz's study [74]).

In the study by Toshiharu Miyake and Tohru Shinohara, [74], the SC rate of VSD by a mean age of 6.9 years was 48%, but it was 72% in patients without CHF. In patients with CHF, SC was seen only in patients with a perimembranous VSD. The rate of SC was 10% in subpulmonary VSD

The observed data evidenced that the dimensions of the defect remain an important factor in predicting the possibility of spontaneous closure, given that spontaneous closure was also found in medium defects (23%), and in 5% of large defects, and even in defects with cardiac insufficiency the possibility of spontaneous closure was 16%. We contend that SC probably occurred due to growth of muscular septum surrounding the VSD. Muscular VSD spontaneously closed earlier than perimembranous VSD. However, large defects found in the apical region of the septum are most likely to remain open. Conversely, spontaneous closure of doubly committed defects is not at all common. When it does occur, it is due to prolapse of the aortic valve leaflets, which is not at all a good thing. In this respect, the timing of surgical or interventional repair to prevent prolapse of the relatively unsupported leaflets of the arterial valves is of paramounting importance. The intense mechanical stress due to a high-pressure environment at the ventriculo-arterial junction greatly increase the risk of prolapse of the leaflets of the aortic valve. The valvular tissues become exposed to increased velocities, and are then subject to progressive mechanical weakness. The uncertain integrity of the arterial valves leads many centres to recommend early surgical treatment of the doubly committed defect. In the extensive study by Tohyama and colleagues, it was noted that seven-tenths of patients aged up to 35 years developed prolapse of the aortic valve, all involving the right coronary leaflet and a third of the total developed overt aortic regurgitation.

Early diagnosis and repair of the doubly committed defect has been suggested in order to prevent the onset of aortic regurgitation. Offsetting of the arterial valves has also been thought to be a factor in the formation of aneurysm of the right coronary sinus of Valsalva.[75]

Intervention was carried out for about one third of patients for large defects or defects that had developed pulmonary hypertension, and in patients with small perimembranous defects that had developed an aortic insufficiency, practically, in a more advanced age and between 10 to 15 years old.

The incidence of valvulopathies was documented in perimembranous defects more than muscular defects, particularly aortic insufficiency.

No cases of bacterial endocarditis were documented. We have not seen any difference in the development of sub-aortic or subpulmonary stenoses in cases of spontaneous or surgical closure. This observation suggests maintaining a conservative attitude in the first month or years of life in patients with VSDs. We contend that SC probably occurred due to the growth of the muscular septum surrounding the VSD. Muscular VSDs spontaneously closed earlier than perimembranous VSDs.

11.f Limits of the study

The incomplete recruitment of the population studied is the principal limit of the study.

Retrospective study using data of clinical files may contain information not always reproducible, because the evaluation of patients was done by different persons in the years of follow-up.

It is known that VSDs spontaneously close during adolescence (26,27). We believe that the frequency of SC will gradually increase on long-term follow-up. About 46 (9 %) cases were lost, but however were closed, because an endocardial tissue developed around the defect. As with those that remained open, only two cases developed sub-aortic stenosis, and there was one case of subaortic spur.

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