Atrioventricular Septal Defect Associated with Pulmonary Artery Hypertension

[1] Saeed Mohamed Morsy, [1] Mohamed AbdelsalamGomaa, [2] Hanan Samir Ahmed, [1] Waleed TeganyMohamed Elhafez
[1] Pediatrics Department, Faculty of Medicine Zagazig University
[2] Clinical pathology Department, Faculty of Medicine, Zagazig University
Corresponding author: Waleed Tegany Mohamed Elhafez
Email: w.hafez95@gmail.com, **Mobile:** 01003645838

Abstract

Atrioventricular septal defects are a common congenital heart defect. The majority of patient with AVSD often follow an uncomplicated course of events. However, a proportion of patients with ASDs, may have their condition complicated by pulmonary hypertension (PH), with a subsequent significant impact on management, morbidity and mortality. The presence of PH, influences the suitability for defect closure.

KeyWords:AVSD, CHD, ASD.

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Introduction.

Atrioventricular septal defects (AVSD) account for ~4–5% of congenital heart disease (CHD), with a prevalence of about 1 per 4500 live births **(1)**.

AVSD are also termed atrioventricular canal defects or, in reference to the embryologic etiology, endocardial cushion defects. They result from abnormal development of the endocardial cushion at the crux of the heart, resulting in the absence of the atrial and ventricular septum at the crux, and abnormalities of the atrioventricular (AV) valves **(Figure 1)**. Out of convention, the AV valves are termed right and left AV valves instead of the tricuspid and mitral valves, in the presence of an AVSD **(2)**.

Features shared by all forms of AVSD:

- A septum primum atrial septal defect (ASD).
- AV valve leaflets insert at the same level at the cardiac crux as opposed to the normal relationship where the tricuspid valve inserts more apically in the interventricular septum **(Figure 2)**.
- Elongated left ventricular (LV) outflow tract with anterior displacement of the aortic valve, often referred to as “goose necking” of the LV outflow tract **(**
- **Figure 3)**.
- Counterclockwise rotation of the LV papillary muscles.
- Cleft left AV valve component, directed toward the ventricular septum **(3)**.

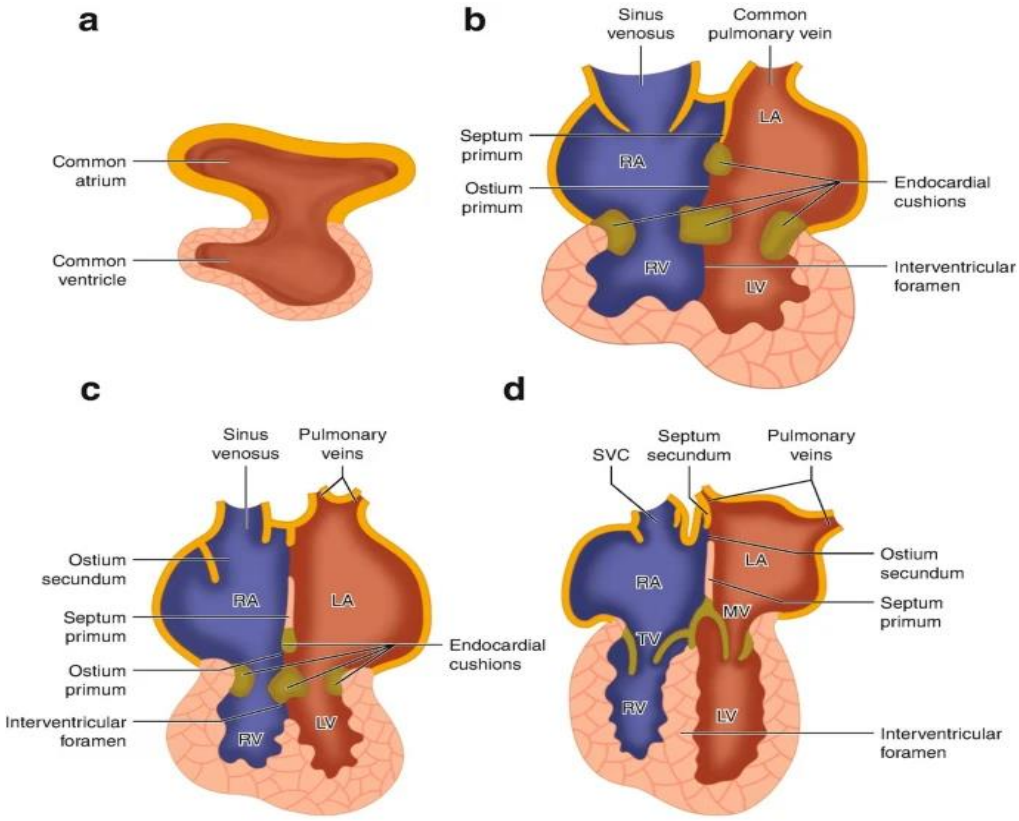

Figure 1: Normal fetal cardiac development: (a) the primitive common atrium and ventricle. (b) the four endocardial cushions form at the crux of the heart. (c) the endocardial cushions grow toward each other, contributing to the development of the atrial and ventricular septa and to the separate atrioventricular valves. (d) the normal fetal heart. Green colored areas represent anatomic structures formed by the endocardial cushions that are susceptible to malformation in atrioventricular septal defects (1)

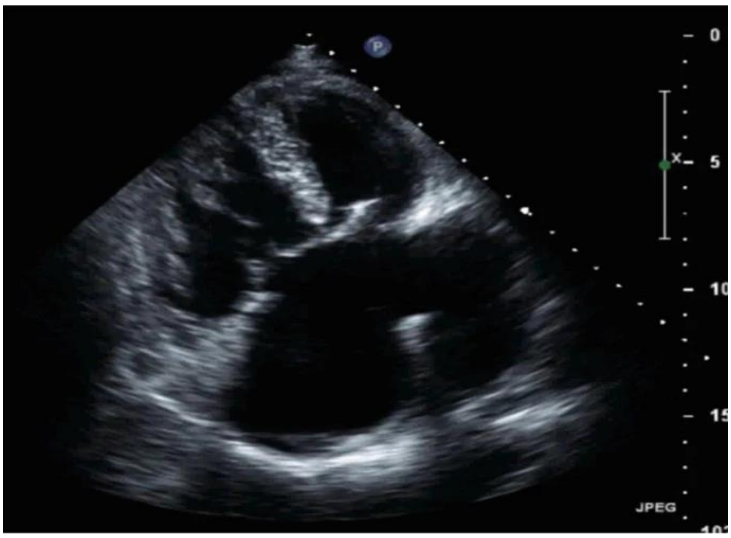

Figure 2: Four-chamber view (apex up) of a patient with an uncorrected AVSD demonstrating a large primum atrial septal defect and equiplanar AV valves (1)

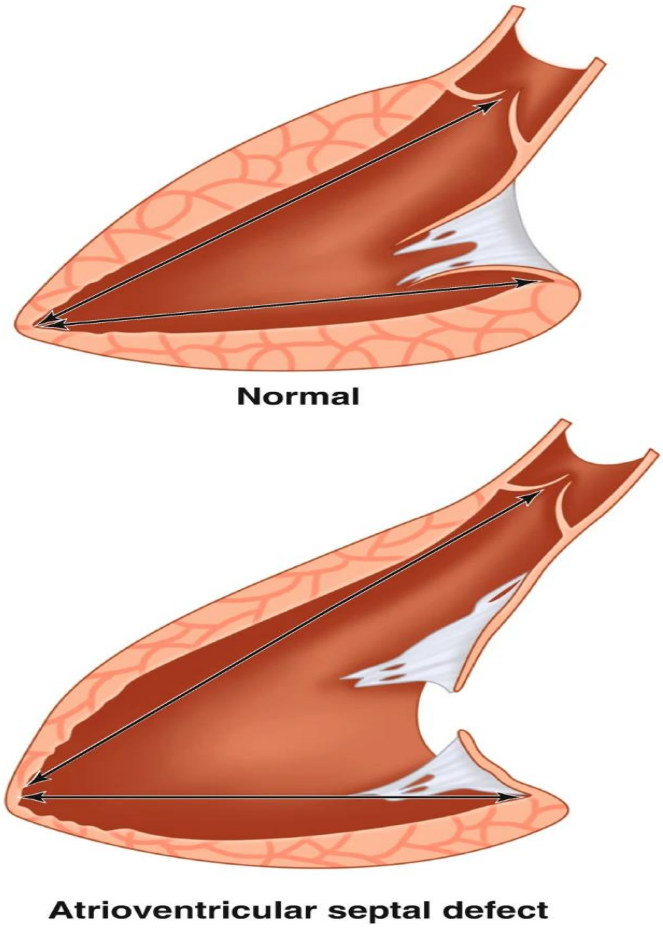

Figure 3: Left ventricular outflow elongation with anterior displacement of the aorta, commonly seen in patients with AVSD (1)

AVSD lie along a continuum with isolated septum primum ASDs that do not involve the AV valves or ventricular septum. AV valve involvement results in a common AV valve annulus that spans across both ventricles. The size of the associated inlet interventricular defect can vary **(4)**:

- **Partial AVSD:** Primum ASD with a cleft left AV valve, with the cleft directed toward the ventricular septum; distinct right and left AV valve annuli remain, and a ventricular septal defect (VSD) is not present.
- **Transitional AVSD:** Primum ASD with a cleft left AV valve. A common AV valve is divided by a tongue of tissue into right and left orifices. An inlet VSD is usually small and covered by aneurysmal membranous septal tissue.
- **Intermediate AVSD:** Primum ASD, a common AV valve divided by a tongue of tissue into right and left orifices, and a large hemodynamically significant VSD.
- **Complete AVSD:** Primum ASD, a common AV valve without dividing tissue, and large hemodynamically significant VSD **(4)**.

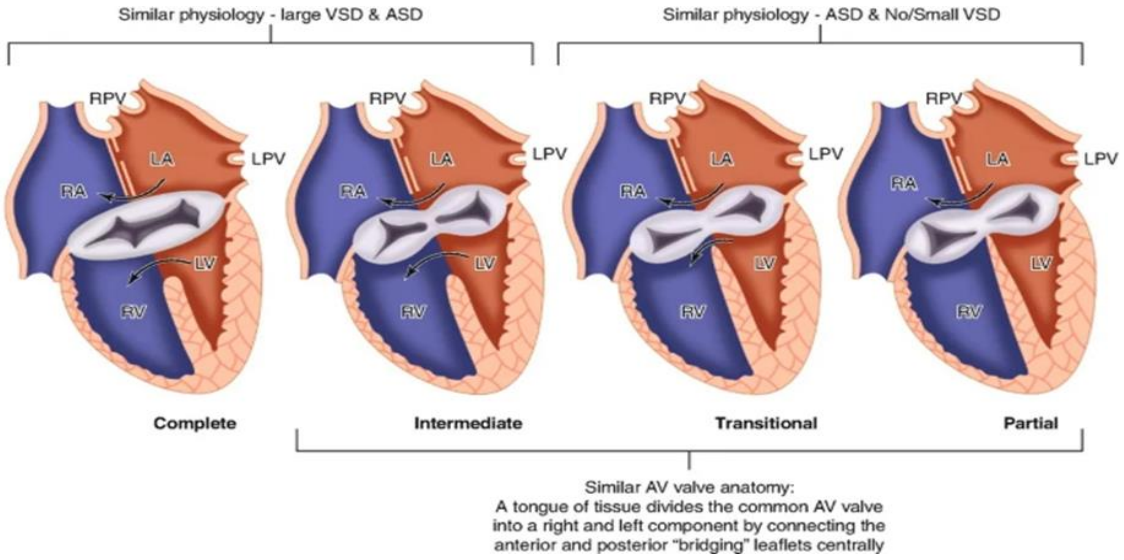

Figure 4: Schematic of the subtypes of atrioventricular septal defects (1)

In addition to left AV valve cleft, patients may have a double-orifice left AV valve, due to additional tissue that subdivides the left AV valve orifice. This results in decreased valve area, and mitral stenosis physiology **(Figure 5)**. The common AV valve is composed of five leaflets: three free-wall leaflets (two right-sided, one left-sided) and two bridging leaflets, with five associated papillary muscles. The LV papillary muscles are rotated counterclockwise and sit closer together than in the usual anatomic relationship, sometimes forming a "parachute" left AV valve with a single LV papillary muscle **(5)**.

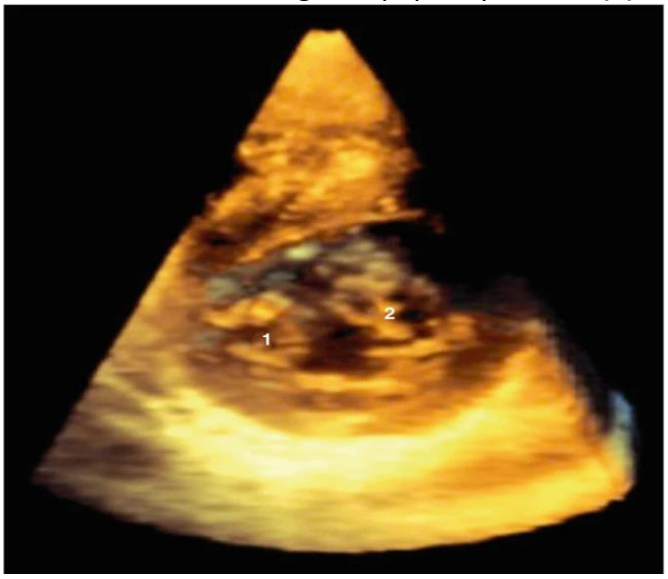

Figure 5: Parasternal short axis of 3D echocardiogram image from a patient with a transitional atrioventricular canal defect and a double-orifice left AV valve, with number marking each orifice (1)

There can be variability in the anterior bridging leaflet, which is often defined using the Rastelli classification. Rastelli type A: divided and attached to the crest of the ventricular septum with multiple chordae. Rastelli type B: Partly divided; not attached to the crest of the septum. Chordae attach to the right ventricular (RV) papillary muscle. Rastelli type C: Not divided and not attached to the crest of the septum ("free floating"). Chordae attach to the RV papillary muscle **(6)**

Unbalanced AVSD, the AV valve inflow may be malaligned over the ventricular septum, which results in underdevelopment of either the RV or LV **(7)**.

- **Physiology**

A. Partial AVSD

It is defined by a large left-to-right atrial shunt with progressive RV volume and subsequently pressure overload. Patients may also have significant left AV valvular regurgitation as a result of cleft left AV valve **(8)**.

B. Transitional AVSD

It is defined by a large left-to-right atrial shunt and a smaller, usually restricted, left-to-right VSD. As in a partial AVSD, the hemodynamics are driven primarily by the atrial level shunt, with progressive RV volume and subsequently pressure overload **(9)**.

C. Intermediate or complete AVSD

Large left-to-right atrial and ventricular shunts quickly progress to pulmonary hypertension and congestive biventricular heart failure, usually requiring repair early in infancy**(10)**.

- **Associated defects**

Partial AVSD is associated with persistent left superior vena cava, Coarctation of the aorta and patent ductus arteriosus. Complete AVSD is associated with tetralogy of Fallot, double outlet right ventricle and Ebstein's anomaly. LV outflow tract obstruction is associated with more common in patients with partial AVSD, can be due to the anteriorly displaced, elongated, and narrowed LV outflow tract, due to subaortic membrane and left AV valve chordal insertion to the ventricular septum can result in flow acceleration across the LV outflow tract, but significant obstruction from this defect is uncommon and Heterotaxy syndromes **(1)**.

- **Genetic or maternal factors**

AVSD is seen in patients with trisomy 21 (Down's syndrome). Most complete AVSD are seen in patients with Down's syndrome (>75%). Most partial AVSD occur in patients without Down's syndrome (>90%) **(11)**.

Childhood repairs

- **Pulmonary artery banding**

In this procedure, a band is placed around the pulmonary artery to introduce resistance to pulmonary blood flow. Left-to-right shunting is reduced, and the pulmonary vascular remodeling that occurs with excessive pulmonary blood flow is limited. Pulmonary artery banding is a palliative procedure that has been employed with decreasing frequency in recent decades in lieu of primary repair. In rare circumstances when an infant is very ill or has a large, complex defect that is technically difficult to surgically repair, a pulmonary artery band may be placed until the child grows and primary repair can be performed **(12)**.

- **Surgical repair of AVSD**

The primary repair consists of patch repair of the central AVSD and subdivision of the AV septal bridging leaflet with approximation of the cleft in the left AV valve using either a one-patch or two-patch technique **(Figure 6)(13)**.

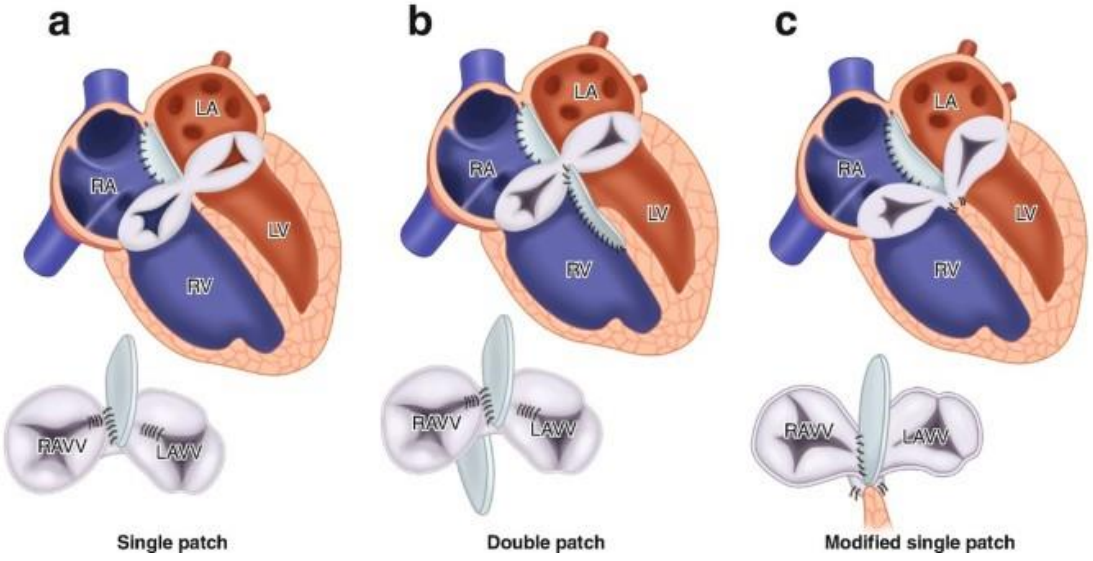

Figure 6: Schematic of the surgical techniques for AVSD repair: (a) The Single-Patch technique: a single prosthetic patch is used to close both atrial and ventricular septal defects, with the divided AV valve sutured to the patch. (b) The Double-Patch techinque: Individual patches are used to close the atrial and ventricular septal defects, with the divided AV valves sutured to each patch individually. (c) The Modified Single-Patch technique: The divided AV valve is pulled down and sutured to the crest of the ventricular septum, and a patch is used to close the remaining defect (1)

Diagnosis

- **Physical examination**

1. Repaired patient

Exam should be normal. Listen for systolic murmurs associated with residual left AV valve regurgitation or left ventricular outflow tract obstruction. Listen for diastolic rumbling murmur that may be indicative of left AV valve stenosis. Right bundle branch block is common, so wide split S2 may be heard **(14)**.

2. Unrepaired adult

- ASD: may result in a fixed and split S2 due to delayed closure of the pulmonary valve that does not vary with inspiration. A pulmonary flow murmur may be heard over the left

upper sternal border due to increased flow over the pulmonary valve. With very large shunts, a diastolic flow murmur may be heard across the tricuspid valve. RV heave.

- VSD: Small restrictive VSD; loud, holosystolic, high-pitched murmur; augments with isometric maneuvers due to increased systemic afterload and subsequent increased shunt. Large, unrestrictive VSD; there may be no murmur associated with the VSD. As the RV pressure increases with progression of disease, the duration of the murmur decreases and the pitch drops.
- AV valve regurgitation or stenosis: Holosystolic blowing murmur best heard at the apex and left lower sternal base. Diastolic rumbling murmur that may be indicative of left AV valve stenosis.
- LV outflow tract obstruction: Systolic crescendo-decrescendo murmur.
- Severe pulmonary arterial hypertension with Eisenmenger syndrome **(13)**.

- **Electrocardiogram**

In AVSD, the AV node is inferiorly and posteriorly displaced to where the posterior rims of the atrial and ventricular septae unite. The His bundle extends along the lower rim of the ventricular septum and the left anterior fascicle is hypoplastic, resulting in a left axis deviation with a superior QRS axis. Right bundle branch block morphology is classically seen, though this is thought to reflect aberrant conduction along a longer-than-normal right bundle branch that comes off of the inferiorly displaced His bundle. First-degree AV block is found in >50% of patients, due to progressive conduction disease or postoperative injury, right ventricular volume and pressure overload, right atrial enlargement and RV hypertrophy **(15)**

- **Chest radiography**

Cardiomegaly, pulmonary hypertension (prominent main pulmonary artery segments and distal pruning of pulmonary vessels) **(16)**.

- **Echocardiography**

Transthoracic echocardiography is the gold standard for evaluation of patients with repaired or unrepaired AVSD **(17)**.

- **Cardiac catheterization**

Cardiac catheterization serves a limited role in AVSD. In select cases, preoperative right heart catheterization with inhaled nitric oxide (iNO) may be useful to assess for reversibility of severe pulmonary hypertension. A coronary evaluation is reasonable in patients with planned operative management who have risk of coronary disease because of age or other risk factors **(18)**.

- **Advanced imaging techniques**

Cardiac MRI and CT can be useful for evaluation of associated vascular lesions. 3D images may be useful for delineating leaflet morphology if echocardiographic images are equivocal.

Pulmonary hypertension related to CHD

Pulmonary hypertension (PH) is a clinical disorder, incited by an extensive heterogeneous number of pathophysiological triggers, resulting in a rise in pulmonary arterial pressures, PVR, subsequent right heart failure and premature death **(19)**.

The hemodynamic definition of PH is a mean pulmonary arterial pressure (mPAP) of ≥25 mmHg at rest by means of right heart catheterization. More specifically, the definition of PAH, which describes a small proportion of patients displaying hemodynamic evidence of pre-capillary PH, whom, along with a mPAP ≥25 mmHg have the additional requisite of a pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg, and a PVR of >3 Wood units **(20)**.

The incidence of PAH related to CHD (PAH-CHD) varies geographically, but a consensus of registries globally estimates that up to 10% of adults with CHD develop PAH **(21)**.

The pathophysiology in CHD, results from progressive vascular remodeling by a range of mechanisms depending on the underlying lesion. In PAH-CHD, often this is due to a defect with a left-to-right shunt large enough to allow sufficiently increased pulmonary blood flow to trigger a pathological mechanism whereby there is increased shear stress, endothelial dysfunction, smooth muscle hypertrophy, proliferation and progressive distortion of the pulmonary vasculature, thus contributing to the development of PAH **(Figure 7)**. As the disease progresses, there is a consequent rise in the PVR, and if on right heart catheterization, this satisfies the hemodynamic definition of PAH, then the disease is established and irreversible, in most cases **(20)**.

The extreme of this is when a significant left-to-right shunt continues to elevate the PVR to reach systemic levels; the shunt then reverses to a right-to-left or bi-directional status, thus leading to clinical cyanosis and the development of the Eisenmenger syndrome (ES). Importantly, with advances in antenatal care and fetal screening, increasingly children are born into a prepared environment allowing for optimal timing of surgical intervention or are diagnosed at routine neonatal screening. Consequently, the pulmonary vasculature is protected from developing ES and the prevalence is reducing **(19)**.

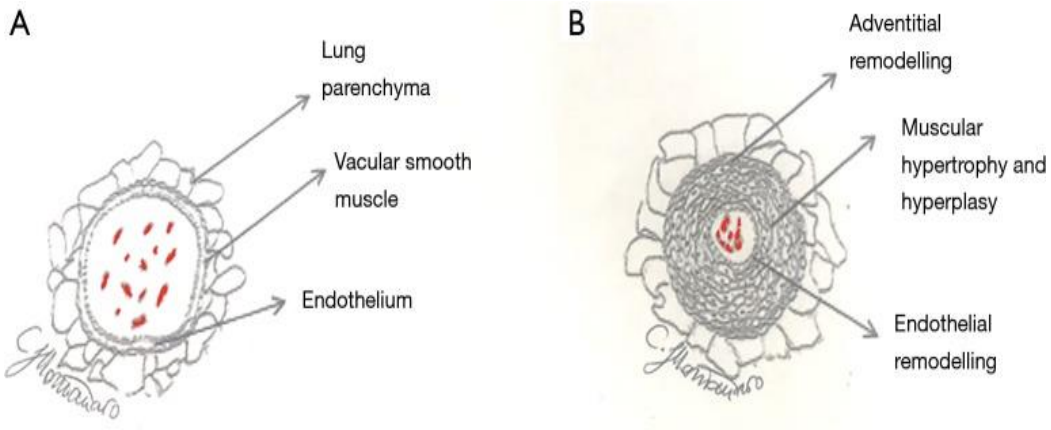

Figure 7: Illustrates the microstructural changes, of smooth muscle hypertrophy and proliferation, implicated in the development of pulmonary vascular disease. (A) Demonstrates the normal anatomy of a pulmonary artery embedded within lung parenchyma. (B) Demonstrates in contrast the hypertrophy and fibrosis, resulting in vasoconstriction (22)

- **Classification of PAH-CHD**

The current classification system in use was finalized at the fifth World Health Organization (WHO) meeting in 2013 and comprises of five groups. Group 1 is distinctly termed as PAH. PAH-CHD is categorized in Group 1, sharing hemodynamic features similar to idiopathic PAH, heritable PAH, PAH associated with other pathologies such as connective tissue disease, infections and drug-induced PAH. Furthermore, PAH-CHD is further described by two classification systems, one being a clinical classification system and the other is the anatomic-pathophysiological system **(23)**.

The clinical classification system divides the patients into four groups. Group 1 is patients with ES, characterized by a right-to-left shunt through a defect at any level, a significant

elevation in PVR and cyanosis. ES is much less common in patients with an ASD than with a ventricular septal defect (VSD), nevertheless it is commonly seen due to the higher prevalence of ASDs. Group 2 are patients characterized by a left-to-right shunt through a moderate-to-large defect with a 'mild-to-moderate' elevation in PVR and cyanosis is not a feature **(24)**.

ASDs are the commonest in this group and although defect repair is often not suitable, evidence to guide the management in this group is limited. Group 3 are the PAH patients with a small/coincidental defect. These patients have a marked elevation in PVR, in the presence of an ASD <2 cm (or VSD <1 cm) which does not account for the development of the PAH. Often the clinical course and prognosis is similar to patients with idiopathic PAH and closure of the defect is contra-indicated. Group 4 is PAH after correction of the defect, either surgical or percutaneous. In these cases, the PAH either persists immediately after correction or develops months or years after the correction in the absence of a residual shunt. Often, the prognosis in this group is poorer after closure than if the lesion was left uncorrected **(23)**.

The other classification system used in PAH-CHD is the anatomic-pathophysiologic classification. This system categorizes lesions according to their anatomic location in relation to the tricuspid valve or complex anatomy. Pre-tricuspid defects include ASDs and anomalous pulmonary venous connections. Post-tricuspid lesions include VSDs and patent ductus arteriosus falls into this category. Lastly, complex defects include AVSDs, single ventricle physiology and some patients with large pre- and post-tricuspid defects **(24)**.

In practice both systems are used by clinicians to differentiate patients with PAH-CHD. One study investigating the use of both classification schemes, showed that the anatomic-pathophysiologic classification was significantly better at differentiating survival compared to the clinical classification **(25)**. This is further supported by other studies, which have shown that there is an adverse prognosis and outcome with pre-tricuspid lesions over post-tricuspid lesions **(26)**.

It has been implicated that in some pre-tricuspid lesions that are found in patients with PAH, may have a genetic disposition additional to their hemodynamic lesion further contributing to the pulmonary vascular remodeling and hence more aggressive disease, and may encourage more aggressive management of these patients. Nonetheless, CHD comprises of a very heterogeneous composition of patients, and some do not fit into a specific category, due to anatomical complexity **(27)**.

Children with AV canal defect presents with various degrees of symptoms such as tachypnoea, recurrent respiratory tract infections, poor feeding, and failure to thrive. These symptoms are usually present by 6–8 weeks due to a fall in pulmonary vascular resistance and blood flow through the large interventricular communication with or without incompetence of the common atrioventricular valve. Pulmonary hypertension occurs from excessive pulmonary flow and elevated pulmonary artery pressure via a large ventricular septal defect (VSD). Irreversible pulmonary vascular disease could occur by 2 years of age or earlier in infants with Down syndrome **(28)**.

In children with complete AV canal defect and a small interventricular component, or with ostium primum ASD where atrioventricular valve regurgitation is minimal, cardiac failure is rare and pulmonary hypertension may be minimal or absent in infancy and childhood. Without surgery, however, there is considerable longer-term morbidity and mortality with only 25% survival beyond 40 years of age **(29)**.

Pulmonary hypertension is one of the most dangerous signs in children with AV canal defect with a very high morbidity and mortality. This can lead to increased pulmonary vascular resistance, increase remodeling, heart failure and death. The mechanism of pulmonary hypertension in AV canal defect could be explained by progressive vascular remodeling arising from a left-to-right shunt. If the shunt lesion is large, there will be increase pulmonary blood flow to trigger a pathological mechanism with resultant endothelial dysfunction, hypertrophy of the smooth muscle, with attendant progressive distortion and proliferation of the pulmonary vasculature. If the disease progresses, there will be consequential increase in the pulmonary vascular resistance which could be irreversible, in most cases **(20)**.

It was showed a very high risk of pulmonary hypertension and higher odds of developing clinical symptoms among children with AV canal defect when compared with children with other forms of congenital heart disease. Though all large, unrestrictive shunt defects may be associated with PAH and elaboration of clinical symptoms; early development of severe clinical symptoms and pulmonary vasculopathy is particularly frequent in complete atrioventricular septal defects. Nearly 100% of un-operated patients with these anomalies will develop PAH. This is not so with other congenital heart defect. For instance, un-operated children with large, unrestrictive VSDs or ASDs are also at risk of developing pulmonary hypertension and clinical symptoms **(30)**.

It was reported that few children who presented with AV canal and obstructive outflow lesion like pulmonary hypertension did not present with pulmonary hypertension, nor did they show any serious risk of worsening clinical symptoms. This could be explained by the protective effects offered by the lungs by the obstructive pulmonary valve **(28)**.

There was positive correlation between pulmonary hypertension and size of VSD and ASD. This was also corroborated in some studies. For instance, it is noted that the risk of developing pulmonary hypertension is not only associated with the size of the atrial septal defect (ASD) but also dependent on the compliance of the right ventricle, i.e., magnitude of the left-to-right shunt. The volume load of the pulmonary circulation will be strongly influenced by additional left heart lesions and left ventricular dysfunction **(28)**.

Children with AV canal defect had higher odds of developing most clinical symptoms and pulmonary hypertension than children with other congenital heart disease and this is statistically significant. This could also be explained by the fact that post-tricuspid lesions with left-to-right shunts especially AV canal defect are usually at a high-pressure level, which may lead to volume overload on the left ventricle and pulmonary over- circulation. If the post-tricuspid defects are large enough, pulmonary hypertension ensues and this occurs within two years of life compared to other types of post-tricuspid shunt lesion which occur a bit later **(31)**.

In fact, if worsening clinical symptoms caused by pulmonary hypertension is not addressed, about 50% of children with AV canal defect will develop supra-systemic PVR with shunt reversal, the so-called Eisenmenger complex. It is documented that children with pulmonary hypertension from AV canal defect have a 5-year mortality that is comparable to those with idiopathic/heritable PAH (29% vs 25%)**(32)**.

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