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Chapter 6

Congenital Heart Disease in Down Syndrome

Margaret Louise Morrison and Colin J. McMahon

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Abstract

Down syndrome remains the most common chromosomal abnormality in live-born infants in the world today. The association between Down syndrome and congenital heart disease (CHD) is well known, and it is widely recognized that CHD contributes significantly to the morbidity of children with Down syndrome. The reported incidence of CHD in Down syndrome patients is between 40 and 60%. The most commonly described defect is complete atrioventricular septal defect (AVSD), which comprises 30–40% of all cardiac defects. Complex genetic factors are involved. Routine cardiac screening of all newborn babies with Down syndrome is recommended. Expert groups suggest that the cardiac status of all children with Down syndrome should be established by 6 weeks of age to permit appropriate and timely treatment avoiding the establishment of irreversible pulmonary vascular disease that would make corrective surgery impossible.

Keywords: Down syndrome, congenital heart disease, screening, AVSD, pulmonary hypertension

1. Introduction

Down syndrome remains the most common chromosomal abnormality in live-born infants in the world today [1]. The association between Down syndrome and congenital heart disease (CHD) is well known. It is widely recognized that CHD contributes significantly to the morbidity and mortality of children with Down syndrome. Despite this there continues to be reports of children with Down syndrome who present with serious CHD too late for the best chance of a good cardiac outcome [2]. Early recognition of lesions is pivotal to obtain the best possible outcome, and education is still needed. In this chapter, we discuss the incidence and main types of CHD occurring in the setting of Down syndrome. We focus mainly on atrioventricular septal defect (AVSD), which accounts for 30–40% of all cardiac defects in Down syndrome patients. We review genetic consideration and also discuss the principles of surveillance for cardiac disease in this population.

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2. Prevalence and genetics

Prevalence of Down syndrome is estimated to be around 1–2 per 1000 live births [1]. The reported incidence of CHD in Down syndrome patients is between 40 and 60% [1–3]. The most commonly described defect is complete AVSD which comprises 30–40% of all cardiac defects. The types of CHD described in Down syndrome do seem to follow a fixed pattern; there are high numbers of septal defects in general; tetralogy of Fallot is described, but there are lower rates of other conotruncal defects like transposition or conditions such as coarctation [4]. Prevalence of individual lesions is given later in **Table 1**.

Obviously the triplication of chromosome 21 suggests that genes located in this area are likely to play an important role in the development of CHD. However the fact that Down syndrome is not invariably accompanied by CHD implies that more complex genetic factors are involved. No single gene candidate has been identified yet [1]. Recent research implicates Hsa21-encoded genes in the development of CHD [5]. Genes for several matrix-related proteins COL-α1 and COL-α2 and Down syndrome cell adhesion molecule (DSCM) are located in chromosome 21. Overexpression of these genes for collagen matrix-related proteins has been associated with development of AVSD [4]. However not all AVSDs are associated with trisomy 21. Other genes not located on chromosome 21 and environmental factors may play a role [1, 5].

Mutations in the cell adhesion molecule cysteine-rich epidermal growth factor-like domain (CRELD) 1 on chromosome 3 have also been implicated in the genetics of CHD in Down syndrome and correspond to one of the specific genetic loci identified for AVSD [6]. This molecule is thought to be essential to the process of cellular adhesion and formation of the endocardial cushions. Overexpression of the junction adhesion molecule (JAM) 2 has also been shown to potentiate CHD in mice that already have CRELD1 mutation [7]. Undoubtedly the genetic influence of chromosome 21 on CHD is complex and yet to be fully understood.

There is evidence to suggest that sex and ethnic differences do exist in the incidence of CHD in Down syndrome, particularly among those with AVSD. There is a predominance of female infants

	Percentage of Down syndrome patients affected by study			
	Tubman et al. [3]	**Frid et al. [17]**	**Freeman et al. [8]**	**Stoll et al. [18]**
AVSD	38%	47%	39%	30%
VSD	15%	33%	43%	22%
ASD	21%	8%	42%	25%
Tetralogy of Fallot	—	2%	6%	3%
Coarctation	—	1%	—	5%
TGA	—	—	—	—
Patent ductus	18%	9%	—	5%

Table 1. Percentage of patients with Down syndrome affected by congenital heart disease by defect.

affected by AVSD and VSD [8]. Black infants with Down syndrome appear to have around twice the risk of AVSD as white infants, whereas Hispanic infants have a much smaller risk than white infants [8]. The type of lesion is thought to vary according to geographical area. For example, in Brazil the most frequently described defect is an atrial septal defect (ASD) [9, 10]. In Asia the most common lesion is a ventricular septal defect (VSD) [11]. A group in Sweden reports AVSD as the most frequent lesion like other Western European countries and the USA. Interestingly they also note a decreasing frequency of complex CHD in Down syndrome; such a trend could be explained by selective termination of fetuses with Down syndrome in some areas [12].

3. Surveillance and screening

The American Academy of Pediatrics recommends routine cardiac screening of all newborn babies with Down syndrome [13]. This statement is echoed by the Down Syndrome Medical Interest group (DSMIG UK). They recommend that the cardiac status of all children with Down syndrome should be established by 6 weeks of age [2]. Age at evaluation is an important factor for reduction in morbidity and mortality rates. Failure to recognize cardiac defects early in life can have serious consequences including establishment of irreversible pulmonary vascular disease that makes corrective surgery impossible [3]. The fact that children still occasionally present to pediatric cardiology clinics in this fashion indicates that the importance of early detection is not fully acknowledged, even in the present era [9, 14]. Neonatal and infant mortality in patients with Down syndrome remains higher than in the general population, primarily due to CHD [1].

Clinical examination alone remains insufficient to reliably diagnose CHD in Down syndrome with only around 40% of newborns having a cardiovascular abnormality detected based solely on clinical findings [3, 15]. An ECG is likely to be abnormal, particularly in the setting of AVSD, and an abnormal ECG has been shown to have a high positive predictive value for congenital heart disease [3]. Taken together clinical examination and ECG are more powerful than either individually [3].

Echocardiography is undoubtedly the most effective single diagnostic test however even it is not 100% effective in identifying lesions in the neonatal period. Authors acknowledge that echocardiography should only be carried out by pediatric cardiologists or experienced pediatricians with special interest in cardiology that have access to the necessary equipment and technical skills [3, 15]. There should be a low threshold for repeating the investigation if symptoms or signs of cardiac disease present at any age, even with a history of previously normal echocardiogram [2]. Diagnosis of purely physiological shunts such a PFO or PDA may cause unnecessary worry for some parents.

The DSMIG suggest that all babies with a diagnosis of Down syndrome should have a thorough clinical examination and ECG performed shortly after diagnosis and that the urgency of their assessment by a pediatric cardiologist should be determined on the basis of these investigations, such that those with abnormal signs or abnormal ECG be seen within 2 weeks for echocardiogram and those felt to be at lower risk based on the initial tests be seen within 6 weeks from birth [2].

4. Common cardiac defects occurring in Down syndrome

The major types of congenital heart defect occurring in Down syndrome are listed in **Table 1**. As noted earlier the most common defect is AVSD, which can affect up to 40% of patients [1]. Conversely around 80% of all AVSDs occur in children with Down syndrome [16]. We describe the morphology and pathophysiology of some of the major types of CHD associated with Down syndrome.

AVSD, atrioventricular septal defect; VSD, ventricular septal defect; ASD, atrial septal defect; TGA, transposition of the great arteries.

4.1. Atrioventricular septal defect (AVSD)

The term AVSD covers a broad spectrum of CHD characterized by a common atrioventricular junction with coexisting deficiency in the atrioventricular septum. AVSD comprises around 7% of all CHD and is also referred to as an endocardial cushion defect [19].

The common atrioventricular junction is usually ovoid with unwedging of the left ventricular outflow tract from the usual position between mitral and tricuspid valves. Instead of separate inlet valves, the AV junction is guarded by a common valve, which often is comprised of five leaflets, two of which are bridging leaflets across the crest of the interventricular septum (**Figure 1**). These are termed superior and inferior bridging leaflets, respectively. There is also a left lateral (mural) leaflet, right anterosuperior leaflet, and a right inferior leaflet [16, 19].

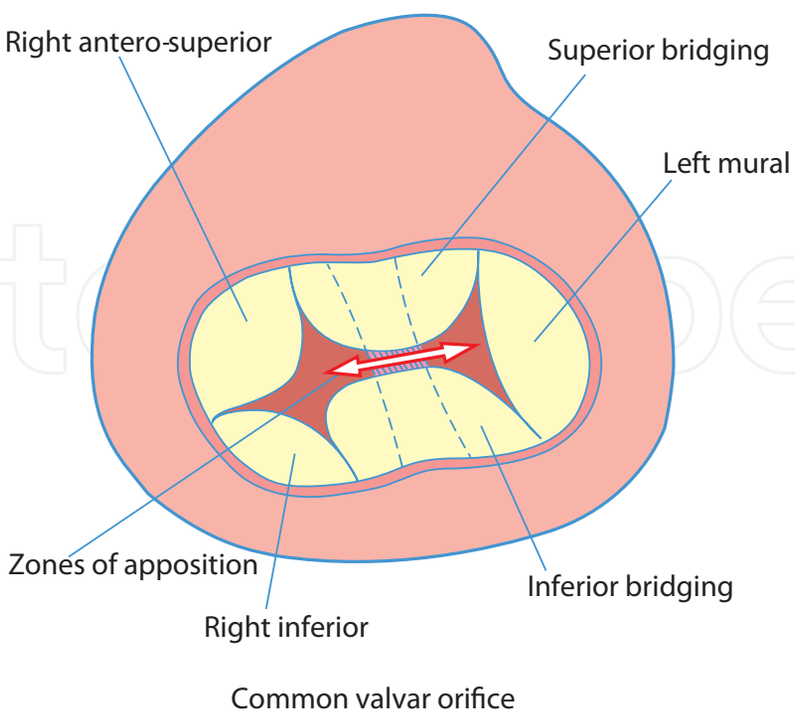


Figure 1. The arrangement of the common atrioventricular valve leaflets in complete AVSD.

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The Rastelli classification from 1966 divides complete AVSD into three subgroups on the basis of the anatomy of the superior bridging leaflet and its chordal attachments (**Figure 2**). In Rastelli type A, the superior bridging leaflet is divided at the level of the ventricular septum; in Rastelli type B, the division of the superior bridging leaflet occurs to a right ventricular papillary muscle; and in Rastelli type C, the superior bridging leaflet is undivided or free floating. Rastelli type C is the most common arrangement found in Down syndrome [20].

In complete AVSD, shunting occurs at both atrial and ventricular levels; however, attachment of the bridging leaflets to the crest of ventricular septum results in an exclusively atrial shunt through a primum ASD, also called a partial AVSD (see later), whereas attachment of the bridging leaflet to the atrial septum results in exclusively ventricular shunting (**Figure 3**).

Other congenital heart defects commonly associated with AVSD include left ventricular outflow tract obstruction especially in the setting of a Rastelli type A superior bridging leaflet as there is extreme unwedging of the aorta from its usual position and consequent elongation of the outflow tract. Ventricular hypoplasia and atrial isomerism are also described although infrequently with Down syndrome. Tetralogy of Fallot is the most commonly observed association and is seen in up to 6.7% cases of AVSD [20]. There is a high incidence of associated other extra cardiac abnormalities. One study of 87 patients with Tetralogy and AVSD reported that 67% of these patients had Down syndrome [21].

Clinical presentation relates to the morphology of the AVSD and any associated defects. If the ventricular component is large, left to right shunting occurs after the first few weeks of life as the pulmonary vascular resistance falls, and the infant will develop signs of congestive heart failure.

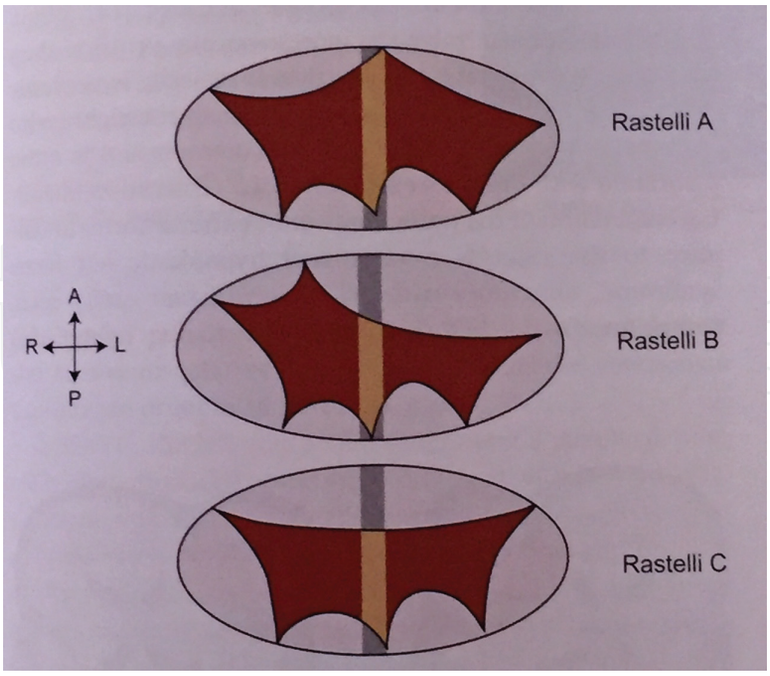


Figure 2. Rastelli classification. Type a (top): The superior bridging leaflet is divided at the ventricular septum. Type B (middle): The division occurs to a right ventricular papillary muscle. Type C (bottom): The superior bridging leaflet is undivided.

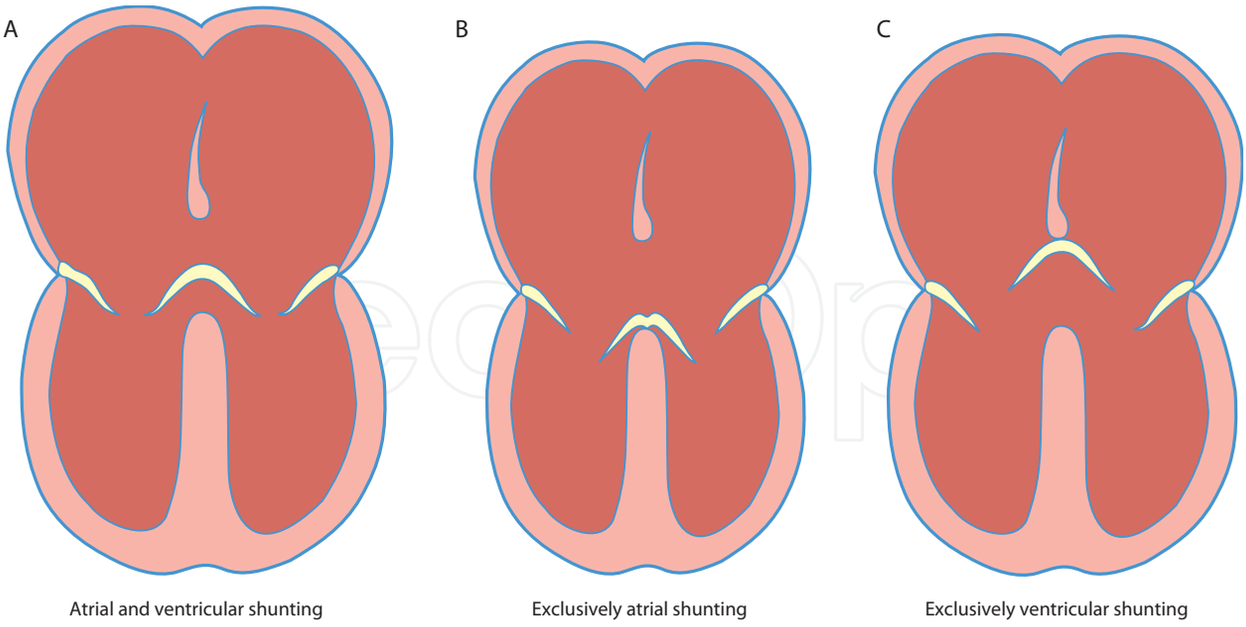


Figure 3. Resultant shunting in complete AVSD depends on the arrangement of the bridging leaflets with the atrial and ventricular septum. (A) atrial and ventricular shunting, (B) exclusively atrial shunting, (C) exclusively ventricular shunting.

If there is associated significant AV valve regurgitation, ventricular imbalance or coarctation signs of cardiac failure will occur much earlier [16, 20]. There is a small subgroup of patients with complete AVSD who do not develop signs of cardiac failure despite a significant ventricular component. In these individuals there is persistent elevation of pulmonary vascular resistance [20].

In the present era, medical treatment is aimed at optimizing the patient's condition to get to corrective surgery. This includes maximizing fluids and calorie intake, often with supplemental nasogastric tube feeding to promote good nutrition. Symptomatic management of congestive heart failure is with diuretics and ACE inhibitor therapy. The aim of surgery is to completely close the septal defects and repair the AV valve. Today surgery is offered to all Down syndrome patients with CHD although this was not always the case. Surgical results are good, and there is believed to be no extra risk from the concomitant presence of Down syndrome [22, 23]. Surgical repair is aimed in the first few months of life and certainly before 6 months old as irreversible pulmonary vascular disease is more likely to develop quickly in patients with Down syndrome and AVSD. Surgery is usually successful with low operative mortality. The most recent statistics from National Institute for Cardiovascular Outcomes Research (NICOR) suggest that survival following complete AVSD repair is 99.5% at 30 days post-op and 91.9% at 1 year [24]. Without corrective surgery many patients with complete AVSD will die in infancy, with only 4% surviving beyond 5 years old [25]. Those who survive will develop pulmonary vascular disease and eventual reversal of the systemic to pulmonary shunt with accompanying cyanosis or Eisenmenger's syndrome.

Postoperative complications following surgical repair of complete AVSD are listed in **Table 2**. Those seen most commonly are left ventricular outflow tract obstruction and left AV valve regurgitation. Left AV valve regurgitation forms the most common reason for reoperation in

• Left atrioventricular valve regurgitation
• Left ventricular outflow tract obstruction
• Late-onset complete heart block
• Pulmonary vascular disease
• Atrial or ventricular rhythm problems
• Left atrioventricular valve stenosis
• Right atrioventricular valve stenosis or regurgitation
• Residual ventricular septal defect
• Aortic incompetence

Table 2. Long-term complications following repair of complete AVSD [16, 19].

most surgical series [26]. Interestingly, the morphology of the AV valve most associated with Down syndrome, Rastelli type C, may actually be more favorable for surgical repair as there is often extensive bridging of both superior and inferior bridging leaflets resulting in less left AV valve regurgitation. Surgical series demonstrate that patients with Down syndrome experience greater freedom from reoperation for left AV valve regurgitation than those without Down syndrome [27].

4.2. Primum atrial septal defect/partial AVSD

In an isolated primum ASD or partial AVSD, the AV junction is a common structure; however, there are separate right and left AV valve orifices as a band of valve tissue joins the superior and inferior bridging leaflets. The AV valves appear at the same level, and there may be regurgitation through the zone of opposition or "cleft" in the left AV valve (**Figure 4**). Timing of surgery in this case is less crucial especially if there is minimal AV valve regurgitation. Repair is often carried out in late infancy or early childhood. Isolated primum ASD unrepaired carries 50% mortality before the age of 20 years [16]. Surgical results are good, and 30-day and 1-year survival are 98.8 and 98.7%, respectively [24]. Long-term complications are similar to those described following AVSD repair with the most common reason for reoperation being left AV valve regurgitation followed by left ventricular outflow tract obstruction [26].

4.3. Tetralogy of Fallot

Tetralogy of Fallot is a conotruncal defect caused by the anterior and cephalad deviation of the infundibular septum, which leads to the development of the four characteristic components: ventricular septal defect, overriding aorta, right ventricular outflow tract obstruction, and right ventricular hypertrophy (**Figure 5**). Tetralogy of Fallot occurs in around 6% of patients with Down syndrome and is the most common cyanotic heart defect to present in this patient group. Conversely around 8% of patients with Tetralogy of Fallot have Down syndrome, although this is slightly higher in fetal series [28].

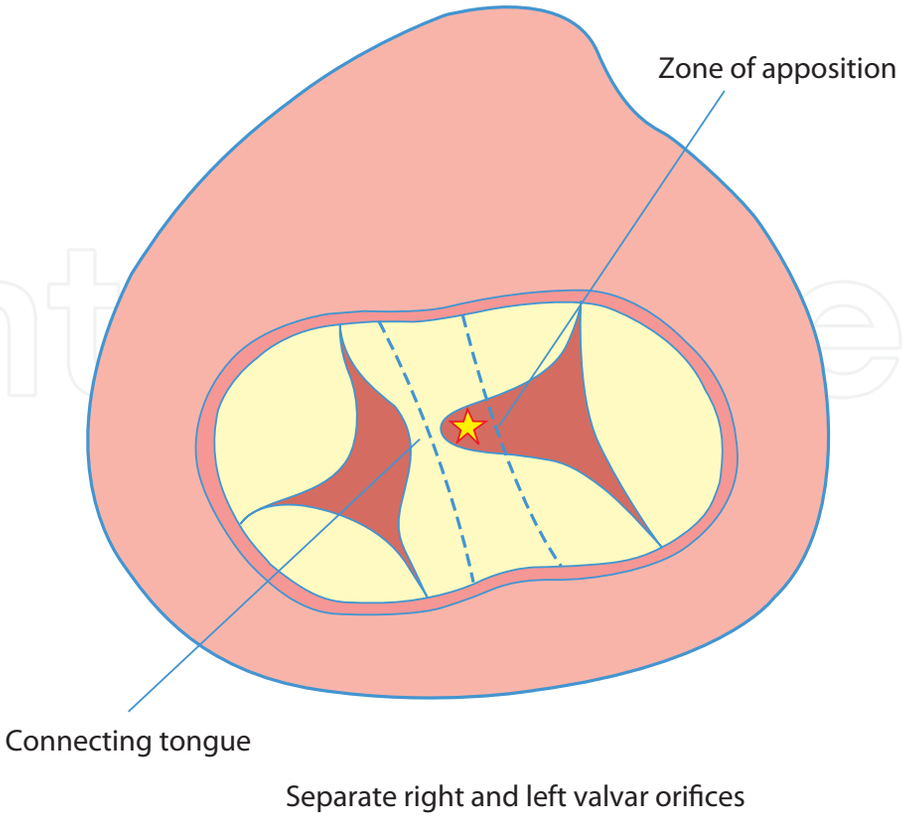


Figure 4. Arrangement of the common atrioventricular valve leaflets in primum ASD.

Clinical presentation of tetralogy of Fallot depends very much on the degree of outflow tract obstruction present. Patients may present with profound central cyanosis in the neonatal period if the obstruction is severe and may actually be duct dependent, i.e., there is insufficient pulmonary blood flow once the ductus arteriosus closes. These patients require palliation with a Blalock-Taussig shunt or ductal stent to secure pulmonary blood flow and permit growth for corrective surgery. If there is little outflow tract obstruction, the patient may exhibit signs and symptoms of congestive cardiac failure as there will be a large left to right shunt through the VSD; in this case there will be little or no cyanosis.

Most commonly, patients fall somewhere in between and have a degree of outflow tract obstruction often presenting with an ejection systolic murmur and some cyanosis [28]. The degree of cyanosis is often variable, and patients may have cyanotic spells, which result from an acute increase in right to left shunting due to spasm of the muscular infundibular region. Patients with cyanosis or frequent spells that cannot be managed with beta blocker therapy may require a RVOT stent. Corrective surgery is performed at around 6–8 months of age. Outcomes are good, and survival following tetralogy repair is 99.7% at 30 days and 97.8% at 1 year [24]. Common long-term complications are listed in **Table 3**.

The relief of right ventricular outflow tract obstruction during tetralogy of Fallot repair results in chronic pulmonary regurgitation, which subsequently leads to right ventricular dilatation

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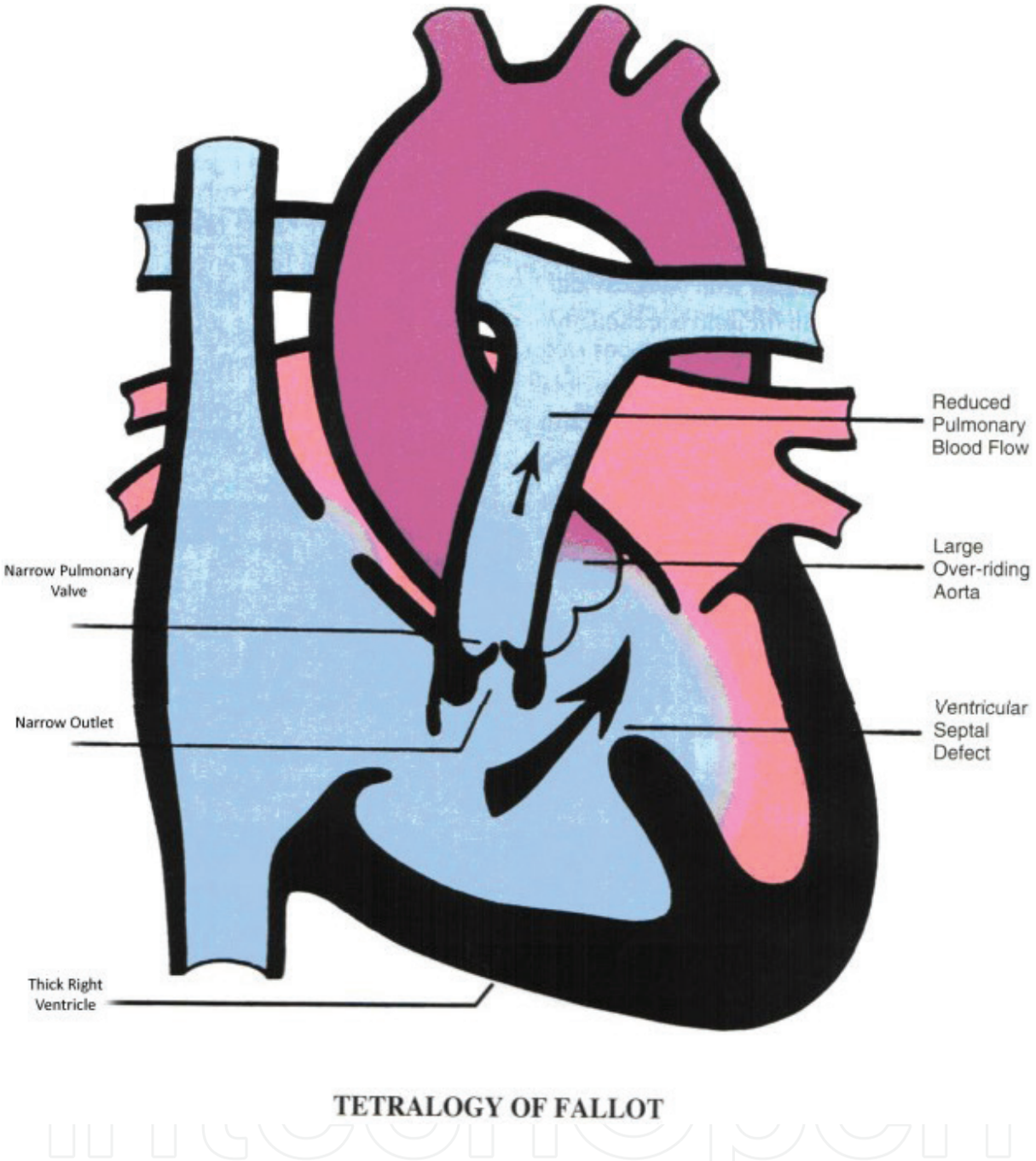


Figure 5. Diagrammatic representation of tetralogy of Fallot.

necessitating interventions. The most frequent reason for reoperation in this patient group is to replace the pulmonary valve either surgically or percutaneously [28, 29]. There is evidence to suggest that patients with Down syndrome who have undergone tetralogy of Fallot repair come to pulmonary valve replacement more frequently than patients without Down syndrome. This is felt to be due to the presence of pulmonary arterial hypertension, also common in Down syndrome, which contributes to more severe pulmonary regurgitation and earlier RV dilatation [30].

• Pulmonary regurgitation
• Right ventricular dilatation and dysfunction
• Residual right ventricular outflow tract obstruction
• Branch pulmonary stenosis
• Rhythm problems
• Aortic incompetence
• Aortic root dilatation

Table 3. Long-term complications following tetralogy of Fallot repair [29].

4.4. Ventricular septal defect (VSD)

A ventricular septal defect is defined as a hole between the right and left ventricles. In most series it is the second most common form of CHD described in Down syndrome (**Table 1**). VSDs are generally classified depending on what portion of the ventricular septum they span, illustrated in **Figure 6**. In Down syndrome VSDs often occur in the inlet septum [31]. In a large series of patients with Down syndrome, inlet VSD was one of the most frequently reported subtypes. Muscular and subarterial VSDs were not described [32]. Inlet VSD is associated with abnormalities of the left AV valve with straddling chordal and papillary muscle attachments [31]. In the setting of Down syndrome, these defects likely form part of the AVSD complex described earlier [32].

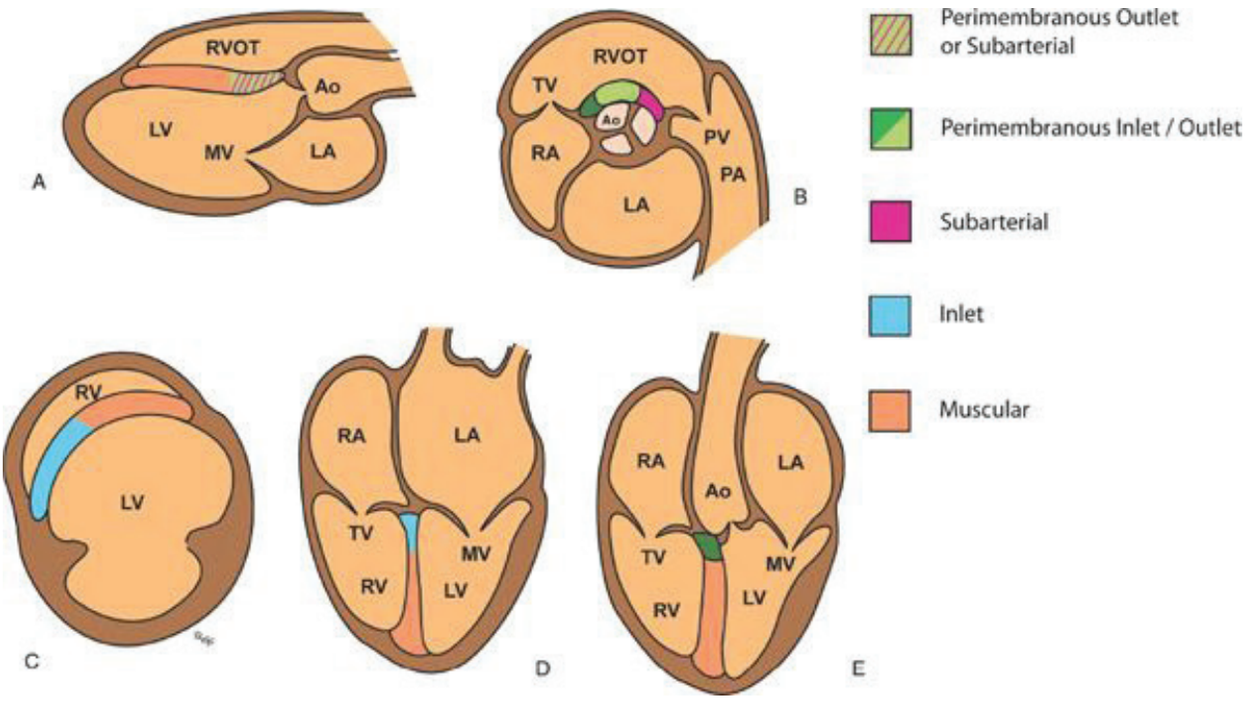


Figure 6. Diagrammatic representation of possible VSD locations on standard echo views. (A) long axis view, (B) short axis view at aortic valve level, (C) short axis view through ventricles, (D) four chamber view, (E) left ventricular outflow tract view.

Similarly to AVSD, a VSD results in a left to right shunt with extra pulmonary blood flow, the magnitude of which depends on both the size of the defect and the patient's pulmonary vascular resistance. Hemodynamically significant defects are repaired before 6 months of age. Like AVSD uncorrected lesions will lead to the development of pulmonary vascular disease and Eisenmenger's syndrome [31].

4.5. Other lesions

From late adolescence there is evidence of an increased incidence of asymptomatic mitral valve prolapse (MVP) and aortic incompetence in children with Down syndrome. These are often asymptomatic; however, the MVP in particular can progress to symptomatic mitral regurgitation, and it is recommended that auscultation continues to be part of surveillance for individuals with Down syndrome in adult life [2].

5. Pulmonary hypertension in Down syndrome

Patients with Down syndrome are considered to be at higher risk of pulmonary arterial hypertension both with and without CHD. This is likely to be multifactorial, but the high incidence of CHD and airway problems undoubtedly plays a pivotal role in its development [33]. Down syndrome patients have a high incidence of gastroesophageal reflux with micro-aspiration, recurrent respiratory infections, and sleep apnea. They may experience chronic hypoxia from upper airway obstruction in the form of tracheobronchomalacia, stenosis, or subglottic compromise [33]. There is a high prevalence of persistent pulmonary hypertension of the newborn in infants with Down syndrome, and as discussed earlier, there is a small subset of Down syndrome CHD patients who continue to have elevated pulmonary vascular resistance beyond the newborn period [16].

In the setting of a significant left to right shunt, intrinsic lung abnormalities such as abnormal pulmonary arterioles, a smaller number of alveoli, and impaired endothelial function contribute to the development of pulmonary arterial hypertension in association with CHD [34]. As observed earlier, timely corrective surgery will prevent irreversible lung damage and development of Eisenmenger's syndrome. Despite this move to early surgery, there remain a significant number of Down syndrome patients with Eisenmenger's syndrome among the adult congenital heart disease population. Some studies estimate that as many as 50% of the total population of Eisenmenger's patients have Down syndrome; there is also evidence to suggest that this group receives significantly less therapy and is often under-managed [35].

6. Conclusions

Congenital heart disease is one of the most frequent associations with Down syndrome and remains a major cause of morbidity and mortality among patients. Over half of Down syndrome patients have CHD the most common form being complete AVSD. Ethnic and

geographical variations among lesions have been described. Early recognition of lesions is paramount to permit appropriate and timely treatment. To this end, cardiac screening should be undertaken in all newborn infants with Down syndrome.

Author details

Margaret Louise Morrison and Colin J. McMahon*

*Address all correspondence to: cmcmahon992004@yahoo.com

Department of Paediatric Cardiology, Our Lady's Hospital for Sick Children, Crumlin, Dublin, Ireland

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