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Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC-Arrhythmia Working Group joint consensus statement

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In children with structurally normal hearts, the mechanisms of arrhythmias are usually the same as in the adult patient. Some arrhythmias are particularly associated with young age and very rarely seen in adult patients. Arrhythmias in structural heart disease may be associated either with the underlying abnormality or result from surgical intervention. Chronic haemodynamic stress of congenital heart disease (CHD) might create an electrophysiological and anatomic substrate highly favourable for re-entrant arrhythmias.

As a general rule, prescription of antiarrhythmic drugs requires a clear diagnosis with electrocardiographic documentation of a given arrhythmia. Risk–benefit analysis of drug therapy should be considered when facing an arrhythmia in a child. Prophylactic antiarrhythmic drug therapy is given only to protect the child from recurrent supraventricular tachycardia during this time span until the disease will eventually cease spontaneously. In the last decades, radiofrequency catheter ablation is progressively used as curative therapy for tachyarrhythmias in children and patients with or without CHD. Even in young children, procedures can be performed with high success rates and low complication rates as shown by several retrospective and prospective paediatric multi-centre studies. Three-dimensional mapping and non-fluoroscopic navigation techniques and enhanced catheter technology have further improved safety and efficacy even in CHD patients with complex arrhythmias.

During last decades, cardiac devices (pacemakers and implantable cardiac defibrillator) have developed rapidly. The pacing generator size has diminished and the pacing leads have become progressively thinner. These developments have made application of cardiac pacing in children easier although no dedicated paediatric pacing systems exist.

Keywords Paediatrics • Arrhythmias • Antiarrhythmic drugs • Radiofrequency ablation • Electrical devices

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Anatomy of the conduction system of the heart

Conduction system in normally structured hearts

The sinus node is usually located immediately subepicardially in the terminal groove (sulcus terminalis) on the lateral margin of the junction between the superior caval vein and the right atrium (*Figure 1A*). It is spindle-shaped, with a tapering tail in the majority of hearts. In about one-tenth of individuals, it is shaped like a horseshoe and straddles the crest of the right atrial appendage. At the borders, the nodal cells are adjacent to working myocytes in places and short tongues of transitional cells inter-digitate with ordinary musculature in others. The tail of the sinus node penetrates postero-inferiorly into the musculature of the terminal crest to varying distances. Apart from the occasionally long tail, and the tongues of transitional cells, no histologically specialized pathways are seen in the internodal musculature.

In the normal heart, the atrial musculature constitutes a separate myocardial mass relative to the ventricular musculature apart from one muscular connection—the bundle of His. The areas of contiguity at the atrioventricular (AV) junctions around the orifices of the AV valves provide the separation.

The triangle of Koch is the gross landmark to the position of the AV node (*Figure 1B*). Viewed from the right atrial aspect, the triangle is delimited posteriorly by the continuation of the attachment of the Eustachian valve, the tendon of Todaro, into the sinus septum (also known as the Eustachian ridge). The anterior border of the triangle is the hingeline (annulus) of the septal leaflet of the tricuspid valve. The mouth of the coronary sinus is usually taken as the base of the triangle, with the AV node located at the apex where the tendon of Todaro inserts into the central fibrous body. On one side, the compact AV node lies against the central fibrous body whereas on the other side it has an interface of transitional cells with atrial myocardium. The extension of the node into the central fibrous body, the penetrating bundle of His, is then completely encased within fibrous tissues. The AV conduction bundle, still within a fibrous sheath, continues to a short non-branching portion before it becomes the branching bundle. Although sandwiched between the membranous septum and the muscular ventricular septum, the branching bundle is disposed towards the left in many hearts (*Figure 1*), resulting in the cord-like right bundle branch passing through the septum before emerging in the subendocardium on the right ventricular (RV) side. The left bundle branch descends in the subendocardium of the ventricular septum. Having descended the septum as bundles of conduction tissue surrounded by fibrous tissue sheaths, the bundle branches then continue into the so-called Purkinje network that allow interface with ventricular myocardium.

Congenital heart block

Congenital complete heart block can occur in congenitally malformed hearts or in otherwise normal hearts.[1] Complete block associated with a cardiac defect is most frequently seen in the anomaly of congenitally corrected transposition, isomeric arrangement of the atrial appendages, and in some AV septal defects. When occurring in a structurally normal heart, the pattern of the cardiac conduction system can take one of three anatomic forms: atrial-axis discontinuity, nodal-ventricular discontinuity, or intraventricular discontinuity (*Figure 1C*). The last form is extremely rare. The association of congenital complete heart block with maternal connective tissue disease is well documented. Most commonly, the AV node was lacking and there was associated fibrosis of the sinus node in several cases.[2,3]

Accessory atrioventricular connections

Accessory AV connections have been located both in structurally normal hearts and in hearts with congenital malformations. These anomalous muscle strands breach the separation of atrial from ventricular myocardium at any point around the AV junctions (*Figure 2*). The majority of left-sided parietal pathways run close to the epicardial aspect of the fibrous hinge of the mitral valve. In contrast, accessory pathways along the right parietal junction either cross an area of deficiency in the fibrofatty tissues or traverse more peripherally though the fatty tissues of the AV groove. Some right-sided pathways may arise from a node-like structure (node of Kent) at its atrial origin. 'Mahaim physiology' can be produced by such histologically specialized right-sided pathways that connect with the AV conduction system via a bundle that descends in the right parietal wall. The pathways are hence described as 'atriofascicular' connections. Such a sling of histologically specialized conduction tissue, with its various appellations, should be distinguished from the classic 'Mahaim fibre'. The latter directly connects the AV node or bundle to the ventricular septum. Descriptively, they are better labelled nodoventricular and fasciculoventricular accessory connections, respectively, highlighting their connection with the conduction tissues (*Figure 2*). These fibres are regularly found in normal hearts, especially in neonates. So-called septal accessory connections are between atrial and ventricular myocardium at the offset attachments of the leaflets of mitral and tricuspid valves. A further subset of accessory pathways has been described as being located close to the penetrating bundle ('intermediate septal' or para-Hisian pathways). Another type, atrio-Hisian connections (originally designated as 'atriofascicular') traverse through the central fibrous body, connecting atrial myocardium with the node-bundle axis distal to the nodal region.

Further variants of accessory connections are those related to coronary venous structures instead of being related to the insertions of the AV valves or the conduction system. For example, they are associated with aneurysmal dilation of the coronary sinus or aneurysmal formation of the anterior cardiac vein, where broad bands of muscular connections surround the mouth of the aneurysm.

Conduction system in congenitally malformed hearts

Sinus node

The majority of malformed hearts have the atrial chambers in their usual position (situs solitus) with a regular location of the sinus node. Abnormal positions of the sinus node have been found in

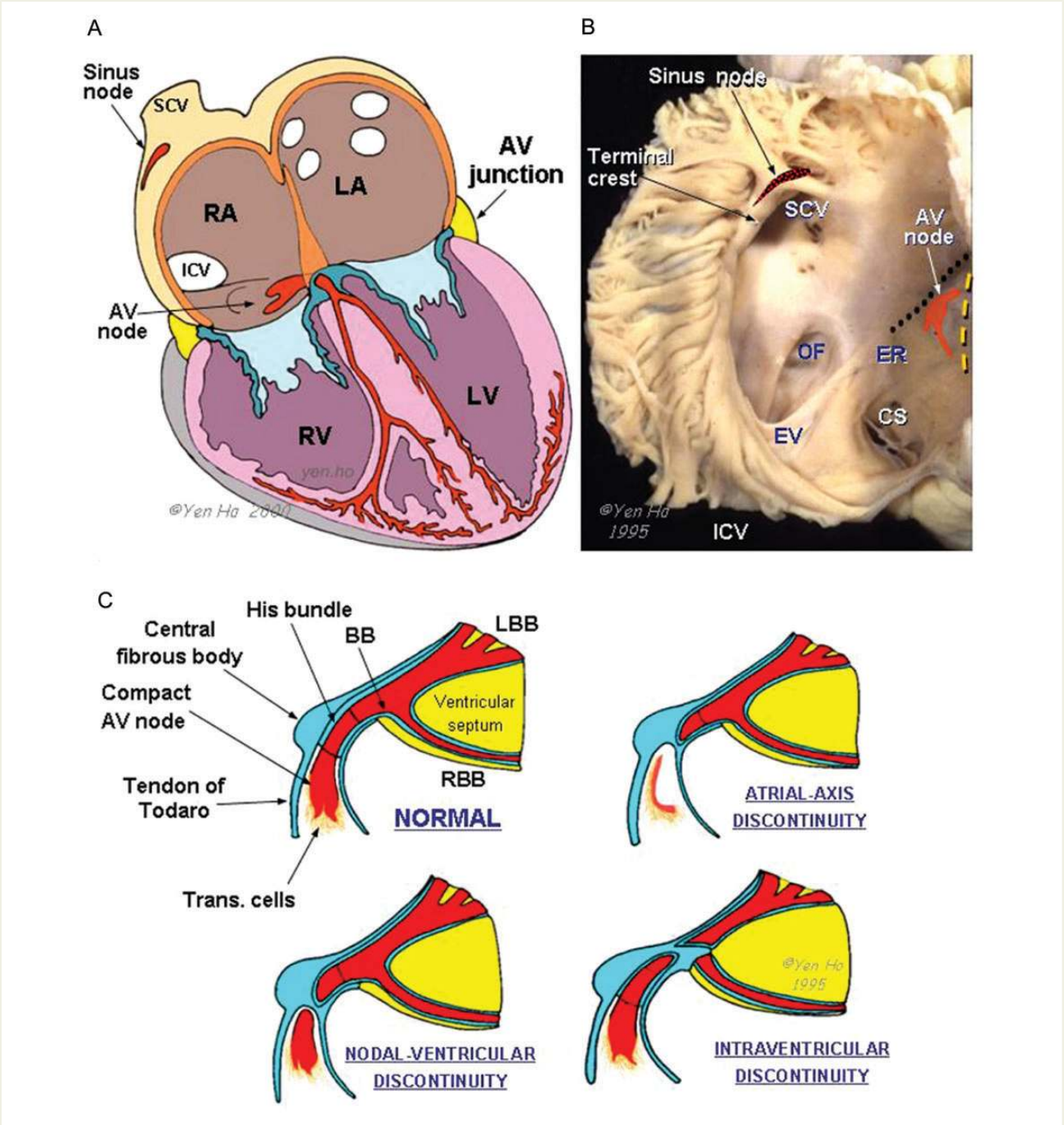

Figure 1 (*A*) Diagram of the cardiac conduction system. (*B*) The right atrium is opened to show the triangle of Koch delimited by the hinge line of the tricuspid valve anteriorly (broken line), the tendon of Todaro (dotted line) posteriorly, and the coronary sinus (CS) inferiorly. The sinus node lies in the terminal crest at its antero-lateral junction with the superior caval vein (SCV). (*C*) These four panels depict the normal components of the atrioventricular conduction system and the variants of interruption that are the anatomic substrates of congenital heart block. AV, atrioventricular; BB, branching bundle; LBB, left bundle branch; ER, Eustachian ridge; EV, Eustachian valve; ICV, inferior caval vein; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; Trans., transitional.

hearts with juxtaposition of the atrial appendages and in hearts with an atrial arrangement other than the usual. Left juxtaposition in which the right atrial appendage lies alongside the left atrial appendage to the left side of the arterial pedicle has an anteriorly displaced sinus node owing to the distortion of the atrial anatomy that deviates the terminal crest.[4] Right juxtaposition is much rarer but does not affect the location of the sinus node.

Abnormal arrangement of the atrial chambers themselves also affects the location of the sinus node. When the atria are arranged in mirror image of normal (situs inversus), the right atrium and the

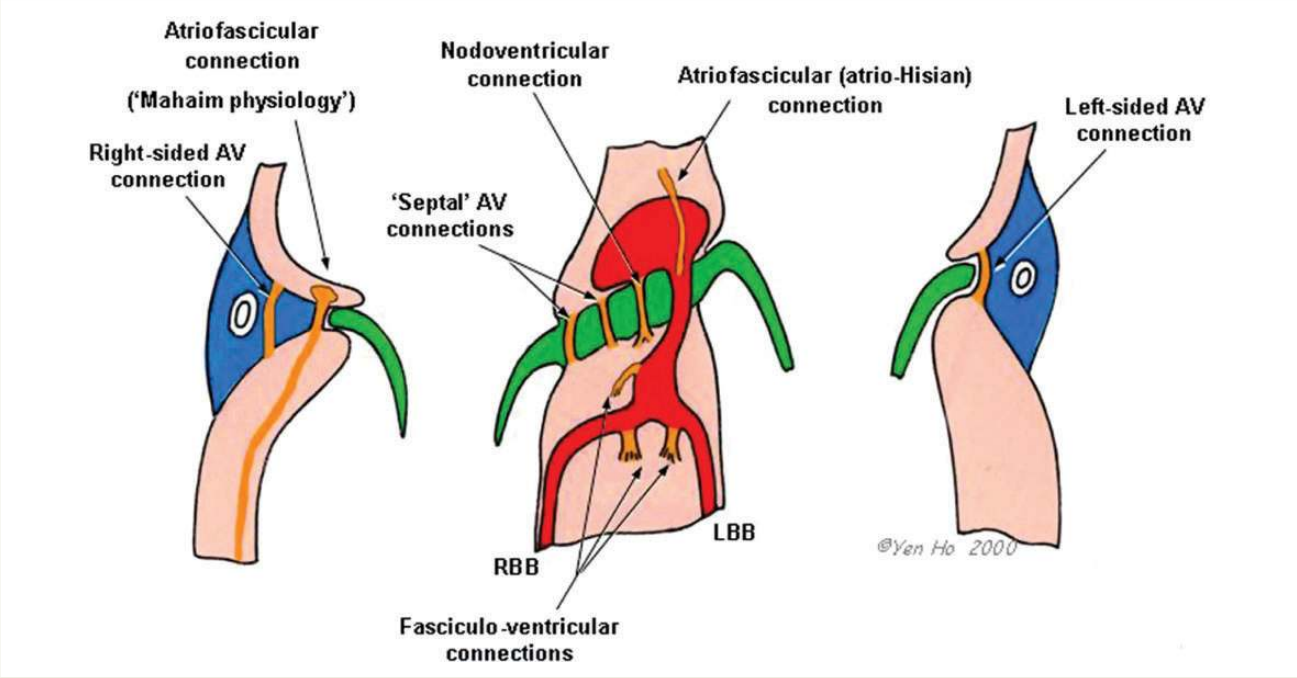

Figure 2 Diagram of the AV junctions depicting various types of accessory connections. AV, atrioventricular; LBB, left bundle branch; RBB, right bundle branch.

sinus node are on the left side of the patient. In hearts with isomeric arrangement of the morphologically right atrial appendages ('asplenia'), there are bilateral terminal crests and, correspondingly, bilateral sinus nodes.[2] Terminal crests, however, are lacking in hearts with isomeric arrangement of the morphologically left atrial appendages ('polysplenia'). Although in this group bilateral superior caval veins can be present, usually the sinus node is not found in its anticipated position. In some hearts a remnant of specialized tissue is found in the inferior atrial wall near the AV junction while in other hearts such tissue cannot be identified.

Atrioventricular conduction system

Most congenital heart lesions are simple holes in the cardiac septum or abnormal ventricular origins of the great arteries. These malformations have little effect on the proper alignment of atrial and ventricular septal structures and, generally, a regular posteriorly situated AV conduction system is to be expected. The key prerequisite to a regular system is concordant connection at the AV level (i.e. the morphologically right atrium connects to the morphologically RV and the morphologically left atrium connects to the morphologically left ventricle (LV). When associated with mirror-imaged arrangement of the atrial appendages (situs inversus), these hearts have mirror-imaged distribution of the AV conduction axis.

Heart defects with normally aligned septal structure

The more common malformations in this group are hearts with an isolated ventricular septal defect, with AV septal defect, and with tetralogy of Fallot. Except for those hearts with AV septal defect, the triangle of Koch remains a good landmark for the location of the AV node.[5]

The distribution of the AV conduction axis in hearts with tetralogy of Fallot is directly comparable with hearts with isolated ventricular septal defect because a defect in the ventricular septum is a cardinal feature of tetralogy of Fallot. Most ventricular septal defects, whether in isolation or otherwise, are located in the environs of the membranous septum. These are termed *perimembranous defects* since they have a fibrous component or remnant of the membranous septum at their posteroinferior border that contains the AV conduction bundle (*Figure 3A*). The non-branching bundle is longer than in normal hearts and the normal leftward shift of the bundle still brings it into the LV outflow tract making this part of the defect the most critical area for avoiding injury to the conduction system.[5]

Defects with completely muscular borders, termed *muscular defects*, have varying relationships with the conduction axis depending on their location within the septum (*Figure 3A*). Those situated between the ventricular outlets are remote from the conduction axis, whereas defects in the apical trabecular part are in the environs of the ramifications of the bundle branches. Defects opening to the inlet part of the RV need to be distinguished from those perimembranous defects that have an extensive posteroinferior incursion. The conduction axis runs in the anterosuperior quadrant of the margin of a muscular inlet defect, in stark contrast to the posteroinferior location found with a perimembranous inlet defect. When both a perimembranous defect and a muscular inlet defect exist in the same heart, the conduction axis traverses the muscular bridge separating the defects.

Defects situated immediately beneath both arterial valves (*doubly committed and juxta-arterial defects*) have a varying relationship to the conduction system depending on its posteroinferior

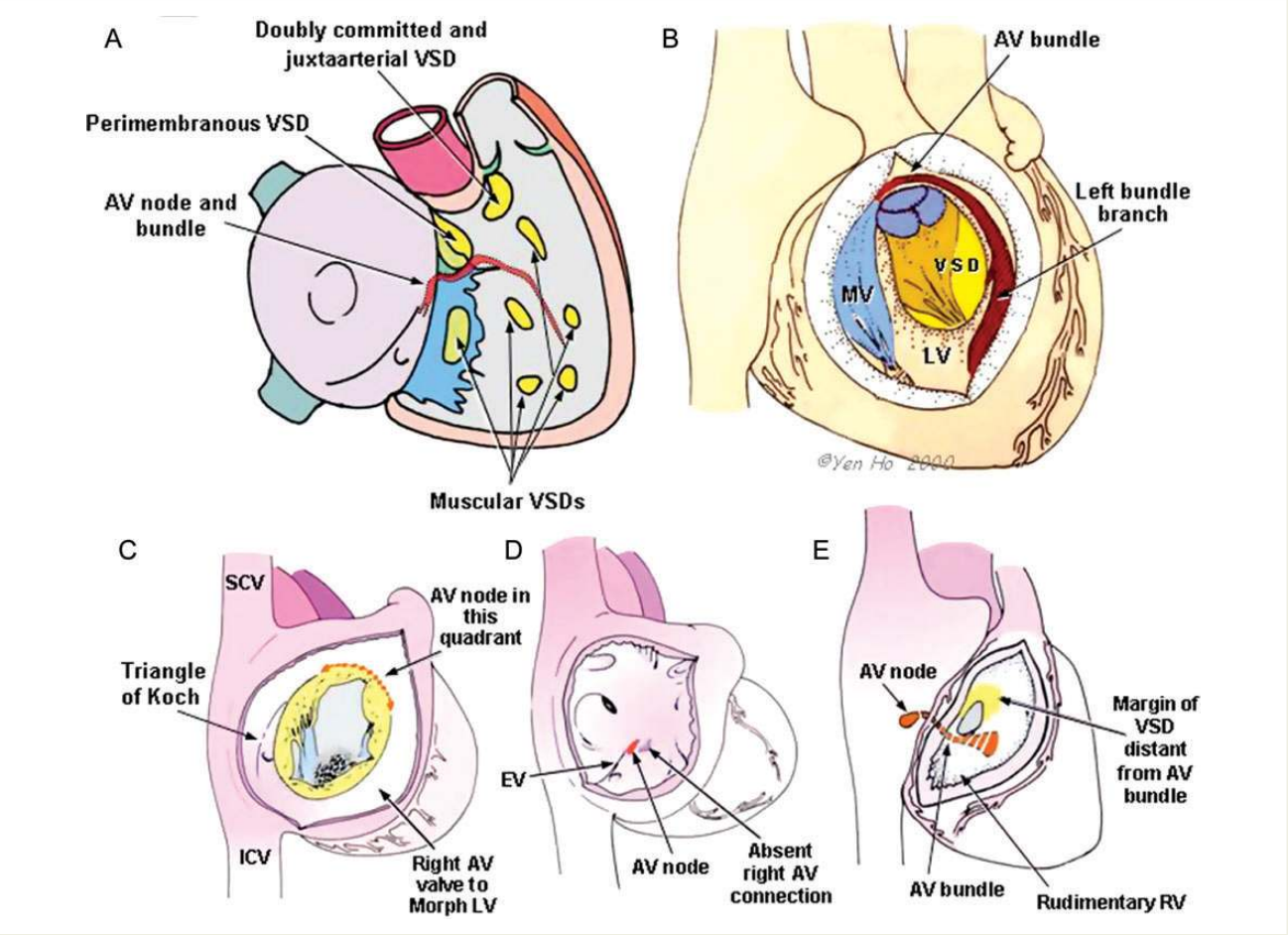

Figure 3 (*A*) Diagram showing the septal aspect of the right atrium and ventricle. The types of VSD (yellow shapes) are shown in relation to the course of the AV conduction tissues. The fibrous tissue (green) at the postero-inferior margin of the perimebranous VSD abuts the AV conduction bundle. (*B*) This diagram shows usual atrial arrangement with discordant AV connections with the morphologically LV opened. The AV conduction bundle passes antero-superior to the LV outlet and descends along the anterior margin of VSD. (*C*) The AV node is abnormally located. (*D*) The AV node is located in the muscular floor of the right atrium in hearts with 'tricuspid atresia' where there is absence of the right AV connection. (*E*) When viewed from the aspect of the rudimentary RV, the AV conduction bundle passes along the margin of the ventricular septal defect (VSD) that is nearest to the acute cardiac margin. AV, atrioventricular; VSD, ventricular septal defect; RV, right ventricle; LV, left ventricle; SCV, superior caval vein; ICV, inferior caval vein; MV, mitral valve.

margin. If the posteroinferior rim is muscular, the conduction axis is protected by the muscle but it is vulnerable in the area of fibrous continuity between arterial and AV valves in the perimembranous type.

Hearts with AV septal defect usually have a wide separation between atrial and ventricular septal structures. The landmarks of the triangle of Koch no longer delineate the position of the connecting AV node.[5] Instead, the connecting AV ventricular node is displaced posteroinferiorly at the atrial side of the junction between atrial and ventricular septa (*Figure 3B*). The penetrating bundle pierces through the conjoined valvar attachment at the cardiac crux. The non-branching bundle is long and runs on the crest of the ventricular septum.

Heart defects with malalignement of the septal structures

These include hearts with straddling tricuspid valve, hearts with discordant AV connection in the setting of lateralized atrial arrangement, hearts with left-hand topology in the setting of isomeric atrial appendages and some varieties of hearts with univentricular AV connection.

Hearts with straddling of the tricuspid valve have the posteroinferior part of the ventricular septum deviated to the right of the cardiac crux. The connecting AV node is situated posteroinferiorly but is displaced to a position of the atrial wall that is nearest the point at which the ventricular septum rises to meet the tricuspid orifice at the AV junction.[5] The penetrating bundle passes through the hinge of the tricuspid valve in this region and continues to a long non-branching segment before dividing into the bundle branches.

Hearts with usual atrial arrangement and discordant AV connections (such as *congenitally corrected transposition*) have a ventricular arrangement similar to those with isomeric arrangement of the atrial appendages in association with left-hand ventricular topology.

The distribution of the conduction system is also similar.[5] In these hearts, the anterosuperior and right-sided ventricular chamber is a morphologically LV (*Figure 3B*). The connecting AV node is located in the atrial wall related to the anterolateral quadrant of the mitral valve (*Figure 3C*). The penetrating bundle runs in the region of fibrous continuity between the mitral valve and the valve of the posterior great artery. A long, non-branching bundle then courses anterior to the outflow tract of the posterior great artery before descending along the anterosuperior margin of a ventricular septal defect to branch into the bundle branches with the left bundle branch descending down the right aspect of the ventricular septum, whereas the right bundle branch penetrates the septum to emerge on the left side (*Figure 3B*). Occasionally, a second AV node is present. This is the regular node within the triangle of Koch. A sling of conduction tissues may sometimes be formed when the regular node also connects with the ventricular bundle branches. Rarely, only the regularly situated node makes the connection with the ventricles.

Hearts with univentricular AV connection include those with double-inlet connection, together with those having absence of either the right or left AV connections. Those that are significant in having an abnormal disposition of the conduction axis are hearts with the atria connected to a dominant LV and those with a solitary indeterminate ventricle.[5] Essentially, hearts with dominant LV usually have an anteriorly located ventricular septum. Thus, hearts with double-inlet connection have a connecting AV node at the acute marginal position of the right AV orifice. From here, the bundle perforates the valvar attachment to enter the ventricular septum. When the right AV connection is absent (tricuspid atresia) and the dominant ventricle is of left morphology, the AV node is found in the muscular floor of the right atrium (*Figure 3D*). In both settings, the descending bundle passes to the border of the septal defect that is nearest the acute cardiac margin, irrespective of the location of rudimentary RV (*Figure 3E*). Hence, the ventricular course of the conduction axis in double-inlet LV and in 'tricuspid atresia' is comparable.

In summary, the cardiac conduction system both in structurally normal hearts and in malformed hearts shows variability that can account for some of the rhythm abnormalities. Cardiac surgeons, electrophysiologists, and other interventionists should be knowledgeable of the locations of the specialized conduction system whether in repairing the cardiac malformations or in modifying the sinus or AV nodes.

Pathophysiology and epidemiology of arrhythmias in children

In children with structurally normal hearts the mechanisms of arrhythmias are usually the same as that in the adult patient, although certain arrhythmias are particularly associated with young age and very rarely seen in adult patients. However, accessory pathways, atrial foci, and dual AV nodal physiology represent the substrate of the vast majority of paediatric arrhythmias in normal hearts. Arrhythmias in structural heart disease may be associated either with the underlying abnormality, or result from surgical intervention and the chronic haemodynamic stress of congenital heart disease (CHD) that in combination create an electrophysiological and anatomic substrate highly favourable for reentrant arrhythmias.

Epidemiology and pathophysiology of arrhythmias in structurally normal heart

Supraventricular arrhythmias

Population-based study reported a prevalence of supraventricular arrhythmia (SVA) of 2.25/1000 persons with an annual incidence in children <19 years of age of 13/100 000. This may underestimate the true frequency due to the sporadic nature of symptoms in many patients, and spontaneous resolution of symptoms in infants never diagnosed as supraventricular tachycardia (SVT). In infancy, SVT results predominantly from accessory pathways and a small number of ectopic atrial tachycardia. In teenage life, there is a significant increase in the prevalence of atrioventricular nodal reentry tachycardia (AVNRT) particularly in females.

Atrioventricular reentry tachycardia

Atrioventricular reentry tachycardia (AVRT) is facilitated by a muscular accessory pathway(s) spanning the fibrous AV junction and providing continuity between atrial and ventricular myocardium, at a site electrophysiologically distinct from the AV node and proximal His–Purkinje system (AVN/His). Such connections have been described in the developing human heart, normally regressing by 20 weeks gestation. It has been inferred that failure of these pathways to regress forms the substrate for accessory pathways.[6] Spontaneous regression of pathway function in infancy is well documented, although in what proportion of patients symptoms redevelop later in life remains uncertain.

The exact epidemiology of accessory pathways (APs) can best be appreciated by assessment of patients undergoing electrophysiology study and radiofrequency ablation (EPS/RFA).[7,8] Between 55 and 60% of AP(s) will be manifest on the surface electrocardiogram (ECG) as varying degrees of ventricular pre-excitation,[8] the Wolff–Parkinson–White (WPW) ECG pattern or WPW syndrome in symptomatic individuals. The degree of pre-excitation is dependent on multiple factors: the anterograde conduction velocity of the pathway relative to the AVN/His; the position of the AP atrial insertion relative to the sinus and AV nodes; intra-atrial conduction time and refractoriness and the quality of input and output of the AP ultimately dependent on the spatial-geometric arrangement between the atria and ventricles.

In 10 583 children undergoing EPS/RFA reported by the Paediatric Electrophysiology Society (www.paces.org) between 1991 and 2003,[7] AVRT was the mechanism in 67%, of which ~50% of pathways were located on the left free wall, 30% on the septum and 20% on the right free wall. Pre-excited tachycardia may occur during antidromic AVRT but also during AVNRT, atrial flutter (AFL) or atrial fibrillation (AF) where the AP is a bystander not essential to the arrhythmia mechanism.

Atrial fibrillation in association with accessory pathways

Atrial fibrillation occurs more frequently in patients with manifest pre-excitation than those with concealed APs. The most common mechanism of AF initiation is degeneration from AVRT. The importance of AF in association with pre-excitation is the potential

for rapid anterograde conduction via an AP with a short refractory period initiating ventricular fibrillation (VF). However, sudden cardiac death (SCD) secondary to pre-excited AF remains rare. Detailed analysis of 184 asymptomatic children with WPW ECG pattern after baseline EPS and a median follow-up of 57 months, found life-threatening arrhythmias (documented pre-excited AF with shortest pre-excited R–R interval $<$250 ms) in 19 (10.3%), of whom the majority reported atypical or minimal symptoms. An AP effective refractory period (ERP) of $\leq$240 ms and multiple pathways identified those at highest risk.[9]

Accessory pathways with unique electrophysiological properties

Atriofascicular (Mahaim) accessory pathways. Atriofascicular pathways (AFP) are considered a duplicate of the normal conduction system, with an atrial insertion point on the lateral tricuspid annulus and distal insertion point at the terminal end of the right-sided conducting system (fascicle). These pathways exhibit slow, decremental anterograde conduction, such that pre-excitation may be minimal or absent during sinus rhythm but becomes evident during atrial pacing or AVRT. The QRS morphology during tachycardia is broad due to anterograde conduction exclusively via the AFP and retrograde conduction via the true AVN/His or rarely via a second pathway.

Permanent junctional reciprocating tachycardia. Permanent junctional reciprocating tachycardia (PJRT) represents a small proportion of AVRT (2) facilitated by an AP that typically demonstrates only retrograde, decremental conduction. The AP is most commonly located in the posteroseptal region close to the coronary sinus ostium, although may be found at other sites. In tachycardia anterograde conduction is via the AVN/His producing a narrow QRS complex on the surface ECG, with the retrograde P-wave immediately preceding the following QRS due to slow conduction within the AP (long RP tachycardia). Due to the incessant nature of PJRT particularly in infants and young children, severe LV dysfunction may be present at diagnosis, which typically resolves with suppression of pathway activity. Spontaneous AP regression has been documented in over 20% of children with PJRT.

Atrioventricular nodal reentry tachycardia

The substrate for AVNRT is two electrophysiologically distinct pathways (dual AV nodal physiology) within the triangle of Koch; a superiorly and posteriorly located 'fast' pathway which demonstrates rapid impulse conduction but a long ERP and a 'slow' pathway located more inferiorly and anteriorly with slower impulse conduction but shorter ERP.

The most common mechanism of AVNRT in children is anterograde slow pathway activation followed by retrograde activation of the atria via the fast pathway (slow–fast) and anterograde ventricular activation occurring shortly after via the His–Purkinje system. This produces a narrow complex QRS tachycardia with P-waves visible as a discrete deflection in the terminal portion of the QRS complex in lead V1, and a short interval ($<$70 ms) between the earliest ventricular and atrial signals at EPS. In the less common atypical AVNRT (fast–slow) the circuit is reversed and earliest atrial activation seen in the low right atrium, producing a long RP tachycardia on the surface ECG with an inverted P-wave shortly before the following QRS complex.

Atrioventricular nodal reentry tachycardia associated with 2 : 1 transient conduction block is present in 17% of children during EPS, a much greater proportion than seen in adults (9%).

Ectopic atrial tachycardia

Ectopic atrial tachycardia is a rare cause of SVT in children accounting for 3.7–5.7% undergoing EPS,[7,8] although may be more common in infants. Atrial tachycardia in children is typically automatic in nature, displaying enhanced phase 4 automaticity and 'warm up/cool down' behaviour often with wide fluctuations in atrial rate secondary to autonomic tone.[10] The mechanism is typically one of centrifugal atrial activation away from a single source, although multifocal atrial tachycardia (MAT)/chaotic atrial rhythm is well recognized and may have the ECG appearance of different P-wave morphologies or may be indistinguishable from AF. The site of origin is varied including right and left atrial appendages, pulmonary vein ostia and crista terminalis. Due to their incessant nature, LV dysfunction, potentially severe in nature, is frequently seen. Spontaneous resolution is common in those presenting $<$3 years of age (78%), but much less in older children and adolescents (16%).[10,11]

Junctional ectopic tachycardia

Congenital junctional ectopic tachycardia (JET) is believed to result from abnormal automaticity at, or close to, the His bundle, and may accelerate or decelerate in response to automatic tone. An incessant pattern and faster junctional rates are more commonly seen in those presenting $<$6 months of age. The ECG typically shows a rather narrow complex QRS with variable RR intervals, and either ventriculoatrial (VA) dissociation or less commonly 1 : 1 VA conduction. Rarely, JET may be associated with AV block, and a potential role for maternal anti-SSA/anti-SSB has been suggested. Left ventricular dysfunction was reported in 15 of 94 (16%) children with JET, with fatality seen in 4 patients.[12]

Atrial flutter

Atrial flutter in children is rare and most frequently seen in the neonatal period. The ECG appearance of tricuspide isthmus-dependant flutter is similar to that seen in the adult, with a baseline of continuous regular atrial activity and morphology suggesting either clockwise or counter clockwise rotation around the tricuspid annulus.

Atrial fibrillation

Atrial fibrillation is extremely rare in children and adolescents with structurally normal hearts and its presence should immediately warn about the possibility of a genetic origin. It is most typically associated with organized SVT such as AVRT or AVNRT degenerating into AF. Similar to other incessant arrhythmias, persistent AF in adolescents may lead to LV dysfunction. Rapidly firing atrial foci (often multiple) located during EPS at the pulmonary veins, crista terminalis and left atrium have been shown to initiate paroxysms of irregular atrial tachycardia indistinguishable from AF on the surface ECG. Irregular atrial tachycardia appears less likely to degenerate into AF in adolescents compared to adults probably due to age-related differences in atrial fibrosis and refractoriness.[13]

Ventricular arrhythmias

Ventricular tachycardia (VT) is rare in children representing only 1.8% of children undergoing EPS.[8] Ventricular tachycardia in children is typically associated with a structurally normal heart, although those presenting with VT require careful evaluation for early manifestations of underlying cardiac disease.

Ventricular tachycardia is well described in infancy, and although symptoms are less common compared to older children (22 vs. 34%), and may be incessant leading to ventricular dysfunction. Infantile VT demonstrates a left bundle morphology suggesting a RV origin in 86% of cases, and shows a high rate of spontaneous resolution (89%).

Ventricular outflow tract ventricular tachycardia

Outflow tract VT most frequently originates from the RV outflow tract, and less commonly the left (including the sinuses of Valsalva), and represents a clinical spectrum from regular ectopy to non-sustained and sustained VT. The mechanism is usually adrenergically mediated triggered activity caused by cyclic adenosine monophosphate (cAMP) induced after depolarizations that are sensitive to fluxes in intracellular calcium. Due to antagonism of cAMP by adenosine, outflow tract VT is typically adenosine-sensitive. Symptoms range from absent to severe including syncope and ventricular dysfunction.[14] The 12-lead ECG in VT typically shows a left (or right) bundle branch pattern and inferiorly directed axis; the QRS morphology may predict the exact site of origin, and intracardiac mapping demonstrates a centrifugal pattern of activation consistent with a focal mechanism. A site of origin close to the perimembranous septum and electrophysiologically and anatomically distinct from the His bundle has been reported in 29% of children with RV VT undergoing EPS. These types of RV Outflow tract VT should be differentiated from those seen in arrhythmogenic right ventricular cardiomyopathy (ARVC), which may at times be difficult.

Fascicular ventricular tachycardia

Fascicular VT is a reentrant arrhythmia that involves the left fascicles (typically posterior, but in rare cases anterior) producing right bundle branch block (RBBB) QRS morphology and left, superior or right, inferior axis during VT, respectively. Fascicular VT is highly sensitive to verapamil (but not adenosine), one of the identifying characteristics of this arrhythmia, suggesting a calcium-dependent mechanism. Similar to outflow tract VT, symptoms in children may be absent or include syncope and tachycardia induced ventricular dysfunction.

Torsade des pointes

Torsade des pointes (TdP) is a polymorphic VT characterized by a QRS morphology that appears to rotate around an imaginary baseline, and is typically associated with congenital long QT syndrome (LQTS) in children. Torsade is initiated by subendocardial focal activity commonly manifest as a short-long-short RR pattern on the surface ECG, followed by successive reentrant excitation of ventricular myocardium with the classical ECG appearance secondary to the bifurcation of the rotating wave front as a result of localized functional conduction block.[15] Torsade frequently terminates spontaneously either due to the development of further functional conduction block or wave front collision within ventricular myocardium.

Bidirectional ventricular tachycardia

Bidirectional ventricular tachycardia is the hallmark arrhythmia of catecholaminergic polymorphic ventricular tachycardia (CPVT), although may also be seen in Andersen–Tawil syndrome and digitalis toxicity. Bidirectional ventricular tachycardia results from delayed after depolarization induced triggered activity occurring alternatively in the Purkinje fibres of the right and left bundle branches.[16] The surface ECG displays a characteristic pattern beat-to-beat 180° alteration in QRS polarity consistent with the alternate sites of Purkinje fibre activation.

Foetal arrhythmias

Many different arrhythmia mechanisms may be identified in the foetus including AVRT, atrial and JET and TdP secondary to QT prolongation. Poor rate control precipitates cardiac failure and hydrops fetalis, frequently associated with a poor prognosis.

Epidemiology and pathophysiology of arrhythmias in congenital heart disease

Junctional ectopic tachycardia

Junctional ectopic tachycardia is a malignant tachyarrhythmia that most commonly occurs after surgical correction of congenital heart defects, although a congenital variant also exists (see above). It is associated with numerous variables including age less than 1 month, history of cardiac failure, higher body temperature, longer cardiopulmonary bypass time, type of cardioplegia, higher levels of post-operative troponin T or creatine kinase, longer ventilatory support and high inotropic requirement. Post-surgical JET may occur after any kind of surgery for congenital heart defects; however, is most frequently observed after closure of a ventricular septal defect (4%), AV septal defect repair (2%), and complete repair of tetralogy of Fallot (22%).[17]

Post-surgical JET is most likely due to enhanced automaticity in the bundle of His, and several potential aetiologies have been proposed, including (1) placement of suture lines in the area of the AV node giving rise to haemorrhage, oedema or an inflammatory response, (2) direct damage to the AV node itself, or (3) longitudinal stretch of the AV node area caused by cardiac surgery during exposure of a ventricular septal defect and/or resection of muscle bundles to relieve RV outflow-tract obstruction.

Post-operative atrial arrhythmia in congenital heart disease

Early post-operative arrhythmia

Tachycardias arising after surgical repair of congenital heart defects are caused by electro-pathological alterations secondary to the congenital defect, a consequence of cardiac surgery, or the result of haemodynamic abnormalities in the post-operative period. In a large cohort of children ($N = 580$) undergoing paediatric surgery for CHD, early post-operative arrhythmias occurred in 51,[18] including SVT ($N = 21$), JET ($N = 12$), complete atrioventricular block ($N = 10$), VT ($N = 3$) and AF ($N = 5$). Death occurred in 15 of them. The most important risk factor for

development of early post-operative tachycardias in this population was the type of surgical procedure.

Late post-operative arrhythmia

Late post-operative tachycardias are mainly atrial arrhythmias including AFL and intra-atrial reentrant tachycardia, which may arise months to years after cardiac surgery. They are most often observed after Fontan, Mustard, and Senning procedure or repair of tetralogy of Fallot. Atrial reentrant tachycardias also develop in patients with ventricular septal defect, most likely as a result of atrial enlargement. Development of late post-operative atrial tachycardia is additionally influenced by various patient- and procedure-related variables including the complexity of congenital heart defects, the number of surgical procedures performed, haemodynamic status, and time after cardiac surgery. Atrial tachycardia presenting late after surgical repair in this patient group are typically reentrant in the majority of cases around surgical scars. Precipitating factors for development of atrial tachycardias in the setting of congenital heart defects are the presence of prosthetic materials and electro-pathological alterations of the atrial architecture.

Arrhythmias in Fontan circulation

The Fontan procedure is aimed at re-directing systemic venous blood directly into the pulmonary circulation without passing through the subpulmonary ventricle. This is accomplished by anastomosing the right atrium to the pulmonary artery, either directly or using a conduit. Early tachyarrhythmias (most typically AFL), arising during the first 30 days after cardiac surgery are more common in older patients undergoing surgery.

The most frequent complication observed late after the Fontan procedure is atrial reentrant tachycardia (AFL, AF, and intra-atrial reentrant tachycardia). Risk factors for atrial reentrant tachycardias in patients with Fontan circulation include right atrial enlargement, elevated atrial pressure, dispersion of atrial refractoriness, sinus node dysfunction, older age at the time of cardiac surgery, elevation of pulmonary pressure, low oxygen saturation, preoperative arrhythmias, and a longer time after cardiac surgery. As time after cardiac surgery passes by, there is an increase in arrhythmia propensity; an incidence of 21% has been reported during a follow-up period of 15 years after the Fontan surgery.[19]

The presence of conduits, long sutures lines or scar tissue increase the likelihood of development of intra-atrial reentrant tachycardias as they can serve as barriers of the reentrant circuits.

Arrhythmias in transposition of the great arteries

Before surgery, a variety of abnormalities in cardiac rhythm have been observed in children with transposition of the great arteries including sinus bradycardia, sinoatrial block, sinoatrial Wenckebach block, junctional escape rhythms, and premature atrial depolarizations. In 1964, the Mustard procedure was introduced as physiologic correction of the transposition of the great arteries. This surgical baffle procedure is extensive and requires long intra-atrial suture lines. The reported incidence of both bradyarrhythmia and tachyarrhythmia after this surgical procedure was high (30–100%). The incidence of SCD was also considerable high, ranging from 2 to 8%. Post-operative tachycardias commonly observed in this patient group were AFL, AF or ectopic atrial rhythms and are most likely the result of damage to the (i) sinus node and its blood supply, (ii) interatrial conduction pathways, (iii) AV node and its blood supply, and (iv) atrial muscle, caused by the extensiveness of the surgical procedure.

The frequency of sinus node dysfunction and atrial tachycardias after the Senning procedure was comparable with the Mustard procedure. Nowadays, the atrial redirection procedure has been replaced by an arterial switch operation (Jatene procedure). Follow-up studies have demonstrated that this surgical technique is associated with a lower incidence of atrial tachyarrhythmias (5%) and preserved sinus node function. This may be due to the fact that the Jatene procedure requires limited operation in the atria. In addition, the operation is also performed in the neonatal period and it is therefore less likely that the patient has had a prior surgical atrial septectomy requiring atrial sutures which may damage the sinus node or its blood supply.

Arrhythmias in atrial septal defect

Pre-operative atrial tachycardias in children with ostium secundum atrial septal defects are uncommon. Development of these tachycardias is associated with older age, shunt size, and severity of pulmonary hypertension. Pre-operative EPSs performed in children with ostium secundum atrial septal defects revealed sinus node dysfunction, AV node dysfunction, abnormalities in atrial conduction, and refractoriness. These electropathological alterations facilitate development of reentrant tachyarrhythmias and are most likely the result of atrial stretch caused by right-sided volume overload.[20] Early surgery may prevent the occurrence of tachyarrhythmias as it has been shown that electropathological alterations are partly reversible after surgical repair of the atrial septal defect.

Atrial tachyarrhythmias after surgical repair of atrial septal defects are frequently encountered complications. In addition to pre-existing electropathological alterations, damage to atrial muscle bundles caused by the atrial incisions further facilitates development of atrial tachycardias. The incidence of late post-operative tachycardias in children with ostium secundum atrial septal defects is variable, ranging from 8 to 71%. It is more frequently observed in patients who also had tachycardias pre-operatively. Atrial flutter and AF are the most frequently occurring arrhythmias. Late post-operative tachycardias are more common in patients who also have an abnormal pulmonary venous drainage. The occurrence of post-operative arrhythmias is also influenced by the surgical procedure; a lower incidence of tachyarrhythmias has been reported after conversion of the cannulation technique from cannulation through the right atrial appendage to direct cannulation of the superior caval vein. Arrhythmogenecity of cardiac surgery is supported by studies demonstrating that tachyarrhythmias in children after transcatheter closure of atrial septal defect are uncommon.

Arrhythmias in tetralogy of Fallot

Surgical repair of tetralogy of Fallot can be performed through either a transatrial or transventricular approach. The transatrial approach is nowadays preferably used because it is associated to a reduced risk of ventricular arryhthmias. In the post-operative period, SVTs are an important cause of morbidity. They have

been reported after both transventricular and transatrial repairs of tetralogy of Fallot. The incidence of SVTs is associated with pulmonary regurgitation, atrial volume overload, and older age at the time of surgery or previous palliation with a Waterston or Potts anastomosis.

Ventricular tachycardias may be the cause of SCD, which occurs in 1–3% in the operated Fallot patients. Risk factors for development of post-operative VTs include older age at intracardiac repair, longer interval after cardiac surgery, increased RV systolic pressure, and moderate to severe pulmonary regurgitation or ventricular dysfunction. The ventricular septal defect, ventriculotomy scar and outflow patch are often part of the reentrant circuit of ventricular tachyarrhythmias in this patient group.

Post-operative ventricular arrhythmias in congenital heart disease

Isolated ventricular premature beats frequently occur in the early period after cardiac surgery and they are often the result of hypokalemia. Sustained VTs are rare and they commonly arise in the setting of myocardial ischaemia or myocardial infarction. Development of VTs are facilitated by disruption of the ventricular myocardium caused by (1) areas of scar due to the ventriculotomy, (2) fibrotic tissue as a result of long-lasting cyanosis, or (3) valvular regurgitation causing ventricular dilatation. Ventricular tachycardias are mainly observed after correction of tetralogy of Fallot and LV outflow tract defects but they also arise in other type of congenital defects such as transposition of the great arteries, univentricular hearts, double-outlet RV, and ventricular septal defects. The reentrant circuits of late post-operative VTs involve ventriculotomy scars or prosthetic materials like patches and conduits. Risk factors for developing sustained VT are older age at the time of surgery, longer duration of post-surgical follow-up, poor haemodynamic status, and prolongation of the QRS complex. Ventricular tachycardias are assumed to be the main cause of SCD observed in patients with congenital heart defects.

Genetics in paediatric arrhythmias

The role of inheritance in arrhythmias has been largely demonstrated in genetic as well as in epidemiological studies. Genetic research has shown that inherited arrhythmias can be caused by mutations in genes mainly encoding four types of proteins: sarcomeric, which cause mainly hypertrophic cardiomyopathy (HCM); cytoskeletal, which cause mainly dilated cardiomyopathy (DCM); desmosomal, which cause mainly ARVC; and ion channels, which cause electrical diseases (or channelopathies). This last group includes LQTS, Brugada syndrome (BrS), short QT syndrome (SQTS), CPVT, and AF. Several of these diseases are highly lethal in the early years. The use of genetics enables the identification of mutations responsible for these phenotypes.[21–24]

Cardiomyopathies

Cardiomyopathies are heart diseases induced by mutations in genes that encode contractile and structural proteins as well as proteins for cardiac energy production. They are responsible for lethal arrhythmogenic disorders in pediatric population, mainly HCM and arrhythmogenic cardiomyopathy (ARVC).[25]

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is one of the most common genetic cardiovascular disorders, affecting 1 in 500 people in the general population. Hypertrophic cardiomyopathy is defined by the presence of asymmetric LV hypertrophy and myocyte disarray usually affecting the septum. However, HCM is a disease of variable penetrance and expressivity, and the disease pattern can range from severe hypertrophy and disarray to minimal changes, from septal hypertrophy to other less common forms (apical) and from SCD to asymptomatic individuals. Nevertheless, HCM is the most common cause of premature SCD in the young, especially in the young athlete.[26] The disease is considered inherited in 90% of the cases, generally with an autosomal dominant pattern of transmission, except for cases with mutations in mitochondrial DNA (mtDNA), which have a maternal transmission.[27,28]

Mutations have been described in several genes encoding essential sarcomeric proteins, heavy chain β-myosin (*MYH7*) and myosin-binding protein C (*MYBPC3*), heavy chain α-myosin (*MYH6*), troponin I (*TNNI3*), troponin T (*TNNT2*), α-tropomyosin (*TPM1*), essential myosin light chains (*MYL3*), regulatory light chain (*MYL2*), titin (*TTN*), and α-actin (*ACTC*).[29] Mutations have also been detected in genes implicated in the metabolism of the heme and Fe^{2+} group, and in genes involved in mitochondrial bioenergetics. Genetic studies of families with LV hypertrophy have shown metabolic cardiomyopathies with mutations in the *PRKAG2* and *LAMP2* genes. Recently, missense mutations that cause defective interaction between nexilin and α-actin have been described in HCM. Nexilin (*NEXN*) is a cardiac Z-disc protein that has a crucial function to protect cardiac Z-discs from forces generated within the sarcomere.[30]

Up until present, mutations have not been thought to predict the severity of the phenotype because individuals with different degrees of hypertrophy or with a greater predisposition to sudden death (SD) may be present in the same family despite carrying the same mutation. This is due to the intervention of modifying genes and polymorphisms, which require more exhaustive studies to achieve a full understanding. It is assumed that interruption of mitochondrial energy metabolism in the heart is the cause of HCM in patients with sarcomeric contraction disruption; this sheds some light on several clinical observations such as heterogeneity, variability in clinical presentation, and asymmetry in hypertrophy.

Risk stratification for SCD in HCM patients remains at the forefront of clinical research. Left ventricle wall thickness *z*-score >6 and an abnormal blood pressure response to exercise are considered clinical factors for SD in children. Differentiating HCM from 'athlete's heart' remains a challenge for an important percentage of cases. Electrocardiogram criteria, echocardiography, and genetic analysis as well as detraining can successfully resolve some of these cases.[31]

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy is an inherited cardiomyopathy characterized by RV dysfunction and ventricular arrhythmias. Patients with ARVC show fibrofatty replacement of RV wall. However, ARVC may involve both ventricles and in very isolated cases only the LV. This pathological alteration is progressive and will generate RV dysfunction and ventricular arrhythmias, including SCD. The diagnosis of ARVD is based on a series of

criteria (imaging, electrocardiographic, family history, genetic, and histological) which define the probability of the individual being affected.[32]

About 50% of ARVC cases are familiar with variable penetrance. It affects ~1/5000 individuals although the prevalence is higher in men (80%), particularly young athletes. Most cases are diagnosed before the age of 40. Usually, the individuals affected have symptomatic ventricular arrhythmias that originate in the RV, with syncope and a high risk of SD. This entity is responsible for 5% of all SCD.

The disease has two different patterns of transmission: autosomal dominant pattern (the most common) and an autosomal recessive pattern. The recessive pattern has been reported on the Greek island (Naxos), giving rise to the Naxos syndrome. This syndrome comprises ARVC, palmoplantar keratoderma and typically curly hair. To date, several genes are described as capable of inducing disease (http://www.arvcdatabase.info/). Most cases involve genes encoding proteins responsible for the junctions of intercalated discs, especially in desmosome, which led to the appointment of ARVC as a desmosomal disease with a disorder of the connections between myocytes.[33]

The clinical picture may include (i) a subclinical stage hidden structural defects, during which the affected person may have a cardiac arrest/SCD as the first manifestation of the disease, (ii) an electrical disorder with palpitations and syncope tachyarrhythmias arising the RV, often triggered during stress, and (iii) the failure of the pump of the RV, sometimes severe enough to require a heart transplant.[34] Studies have shown that up to 20% of SCDs may be attributed to ARVD, and it is common in athletes who die suddenly, so strenuous exercise is contraindicated.[35]

Channelopathies

Channelopathies are heart diseases induced by mutations in genes encoding cardiac ion channels. They are not associated with structural cardiac abnormalities and their first manifestation may be SCD. Moreover, some of these diseases are not accompanied by changes in the ECG, which makes the diagnosis more difficult. Given that these diseases are determined by a genetic defect, it is hoped that genetic testing can contribute substantially to the diagnosis, prevention and treatment.

In 1976, the first association between SIDS and a cardiac disorder, the LQTS was published.[36,37] Since this association, genetic and/or clinical correlations between channelopathies and SIDS have been found in several studies. To date, up to 35% of cases of SCD in young people may be caused by a genetic mutation in ion channels.[38,39]

Long QT syndrome

Long QT syndrome is a cardiac channelopathy characterized by a prolongation of the QT interval. Long QT syndrome is responsible for ventricular tachyarrhythmias, episodes of syncope, and SD. Long QT syndrome is one of the leading causes of SD among young people. It can be congenital or acquired, generally in association with drugs and electrolyte imbalance (hypokalaemia, hypocalcaemia, and hypomagnesaemia). The clinical presentation can be variable, ranging from asymptomatic patients to episodes of syncope and SD due to ventricular tachyarrhythmias (TdP) in a structurally normal heart. Prolongation of the QT interval may arise due to a decrease in the K+ repolarization currents or to an inappropriate delay in the closing of the Na+ channel of the myocyte.[40]

Inheritance of LQTS can follow an autosomal dominant (Romano–Ward syndrome) or recessive (Jervell and Lange–Nielsen syndrome) transmission pattern. To date, more than 600 mutations and splice-site altering mutations have been identified in 14 LQTS-susceptibility or LQTS overlap-susceptibility genes.[41] Approximately a 75% of clinically definite LQTS are caused by mutations in three genes: *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3). The remaining 25% have been identified in a variety of ion channels or channel-interacting proteins.[42] The most common form, LQTS type 1, caused by mutations in *KCNQ1* is responsible for 40–50% of the cases of prolonged QT interval.[43,44]

The second most common gene is *KCNH2* (*HERG*, *human-ether-a-go-go-related*), that codifies the α-subunit of Ikr. The mutations in this gene suppose a 35–45% of cases (LQTS type 2)[45,46] The β-subunit is codified by *KCNE2* (MiRP1 protein); the mutations in *KCNE2* gene induce LQTS type 6, a rare type (<1%) that also induce a loss of function. *KCNE1*, responsible for 2–5% of cases (LQTS type 5) can alter both iks and ikr.[47] The *KCNJ2* gene is also implicated in LQTS. It codifies Kir2.1 protein; the mutations are associated to loss of function (LQTS type 7 or Anderson–Tawil syndrome). The incidence is very low and infrequently is associated to SCD.[48]

Recently,[49–51] it has been associated *KCNJ5* gene (Kir3.4 – also named GIRK4-) to LQTS (LQTS type 13). The mutation induces a loss of function.[52] Mutations in the LQTS give rise especially to a gain of function in the sodium current (inappropriate prolonged entry of Na^+ into the myocyte), by mutations in *SCN5A* (LQTS type 3), the third gene most prevalent in LQTS.[53,54]

Mutations in this gene induce gain of function. The LQTS type 10 is caused by mutations in *SCN4B* that codifies for β-subunit of sodium cannel (NaVβ4). The β-subunit plays a key role both in the kinetic regulation and in the α-subunit expression of the sodium channel[55] In 2008, mutations in *SNTA-1* gene were associated to LQT (type12) thought a gain of function of the fast sodium channel.[56,57] It encodes α1-syntrophin protein. The LQTS type 9 is caused by mutations in *CAV3* gene.[58] Mutations in this gene induce gain of function of sodium channels, similar as LQTS type3. Calcium channels are also associated to LQTS. Type 8 LQTS (Timothy syndrome) has been described with a mutation in the *CACNA1C* gene that encodes the pore (Cav1.2) of the L-type cardiac calcium channel. This type of LQTS is uncommon, but it has the highest associated mortality. The mutation induces an enhanced function with Ica abnormality, and loss of the channel dependent voltage, leading to a prolongation of the action potential.[59,60] This gives rise to an ECG with an extremely long QT interval. Recently, a long QT interval was also associated with a patient that showed a mutation in the cardiac ryanodine receptor gene *RYR2*;[61] however, further studies were required in order to clarify this case report. The type 11 LQT is a disorder of the QT interval caused by a mutation in *AKAP9* gene, which encodes the protein kinase-A anchor protein-9. The severity of this type of QT may vary; the most common symptoms are angina, partial or total loss of consciousness and in some cases the SCD.[62] There are other genes as *ANK2*, which is involved in type 4 LQT syndrome. Although not specific to a channel is included in the group of

channelopathies. This gene encodes the protein ankyrin-B which is to adapt different structures in the cell membrane as the Na/K ATPase, Na/Ca and inositol triphosphate receptor. A decrease in the role of ankyrin-B alters calcium homeostasis prolonging repolarization and fatal ventricular arrhythmias generated.[49–51]The syntrophins are cytoplasmic proteins that are part of the protein complex associated with dystrophin.

Short QT syndrome

The SQTS—first described in 2000[63]—is a highly malignant condition characterized by a short QT interval (<330 ms), with a high sharp T-wave and a short interval between the peak and the end of the T-wave, leading some clinical manifestations from lack of symptoms to recurrent syncope, and high risk of SCD.[64–66] because of ventricular arrhythmias, but AF is also commonly seen in patients with SQTS.[67,68] Clinical manifestations may appear as early as childhood, and so it is considered a possible cause of SD in nursing infants.[69,70]

The genetic origin of this condition has been reported recently, with an autosomal dominant pattern of transmission and a high penetrance. The mutations that induce this syndrome are located on six genes, of which three (*KCNQ1*, *KCNJ2*, and *KCNH2*) encode potassium channels, with enhanced function and, therefore, shortened repolarization. The origin of this entity has been recently described, with autosomal dominant inheritance pattern and high penetrance. The SQT syndrome type 1 has been associated with two mutations in *KCNH2* (hERG protein) that induce a rapid activation of potassium currents, with a gain of function of IKr and a shortening of ventricular action potentials. Generally, cardiac events are associated with adrenergic in situations such as noise or exercise, but also occurred at rest.[71]

The SQT syndrome has been associated with AF in some families.[72] The SQT syndrome type 2 has been associated with two mutations in the gene *KCNQ1* (KvLQT1 protein) which leads to a gain of potassium channel function, leading to a shortening of action potential with AF. There is a particular entity, by affecting the same gene that is expressed *in uterus* in the form of bradycardia in the neonatal period was diagnosed as AF and SQTS.[73] The SQTS type 3 has been associated with a mutation in the gene *KCNJ2* (Kir2.1 protein) located on chromosome 17, involving a speeding of phase 3 of action potential, resulting in a gain of function.[74] Recently, it has been published a relation between *CACNA2D1* and SQTS.[75] However, more studies must be performed to establish a clear clinical-genetic association.

Brugada syndrome

Brugada syndrome is a hereditary disease responsible for VF and SCD in the young. The disease is characterized by the presence of RV conduction abnormalities and coved-type ST-segment elevation in the anterior precordial leads (V1 to V3). Brugada syndrome has a structurally normal heart, although minor structural alterations have been described in some cases. The prevalence of BrS is estimated at around 35/100 000 person/year. Although the mean age of onset of events is ~40 years, SCD can affect individuals of any age, particularly men (75%). In fact, the first two patients ever described with the syndrome were children aged 2 years old. Of those patients affected, 20–50% have a family history of SCD.[76,77]

To date, 12 genes have been associated to BrS. Approximately 20–30% of patients with BrS have a mutation in the *SCN5A* gene, classified as BrS type 1. The *SCN5A* gene (α-subunit of the cardiac sodium channel) is responsible for the phase 0 of the cardiac action potential, a key player in the cardiac electrical activity. Mutations in *SCN5A* result in 'loss of function' of the sodium channel.[78] Another sodium channel that has been reported to induce BrS is *GPD1-L* gene. It has been shown that mutation of the *GPD1-L* gene reduces the surface membrane expression and reduces the inward sodium current. In addition, *GPD1-L* has been shown to be the cause of some of the SCD in nursing infants.[79,80] In addition, it has been published mutations in *SCN1B* (sodium channel β-1 subunit) and *SCN3B* (sodium channel β-3 subunit) also associated to BrS.[81,82]

In the heart, β1-subunit modifies Nav1.5 increasing $I_{Na.}$ The mutation described in *SCN3B* alters Nav1.5 trafficking, decreasing I_{Na}. Other gene associated to BrS is *KCNE3* that codify MiRP2 protein (β-subunit that regulates the potassium channel I_{to}). The KCNE peptides modulate some potassium currents in the heart. The *KCNE3* gene encodes the regulatory subunit of the potassium channel I_{to}. The relationship between mutations in this gene and the BrS were detected in a Danish family.[83]

Mutation in the *CACNA1C* gene is responsible for a defective a unit of the type-L calcium channels. This induces a loss of channel function, linked to the combination of BrS with shorter QT interval. Transmission follows an autosomal dominant pattern. With the same phenotype, mutation of the *CACNB2B* gene leads to a defect in the L-type calcium channel, giving rise to a combination of BrS and shorter QT interval. In 2009 was associated BrS to *HCN4* gene,[84] that codifies for HCN4 channel or If channel. The HCN4 channel controls the heart rate, and its mutations also predispose to inherited sick sinus syndrome and LQTS associated with bradycardia. Another gene described associated to BrS is *KCNJ8*, also previously related to early repolarization syndrome (ERS).[85] The report implicate *KCNJ8* as a novel J-wave syndrome susceptibility gene and a marker gain of function in the cardiac $K_{(ATP)}$ Kir6.1 channel.[86] Recently, Kattygnarath *et al.*,[87] published a study supporting that *MOG1* gene can impair the trafficking of Nav1.5 to the membrane, leading to I_{Na} reduction and clinical manifestation of BrS. Also in 2011, Giudicessi *et al.* provide the first molecular and functional evidence implicating novel *KCND3* gain-of-function mutations (Kir4.3 protein) in the pathogenesis and phenotypic expression of BrS, with the potential for a lethal arrhythmia being precipitated by a genetically enhanced I_{to} current gradient within the RV where *KCND3* gene expression is the highest. Finally, and also in 2011, it is published a study recommending *KCNE5* gene screening for BrS or Idiopathic ventricular fibrillation (IVF)-affected patients. Therefore, *KCNE5* gene modulates I_{to} and its novel variants appeared to cause IVF especially BrS in male patients through gain-of-function effects on I_{to}.[88]

Catecholaminergic polymorphic ventricular tachycardia

In 1975, CPVT was first reported.[89] Catecholaminergic polymorphic ventricular tachycardia is a heritable arrhythmia syndrome triggered by adrenergic stimulus and mainly expressed during exertion, extreme stress or emotion. It occurs mainly in children and adolescents and is increasingly recognized as a

cause of unexplained SCD in young individuals in the absence of any other structural heart disease, predominately in young males. Diagnosing CPVT can be difficult especially in young children. When presumptive symptoms are encountered, an exercise ECG, and 24 h Holter monitoring can be very useful in young, physically active children since CPVT cannot be diagnosed by a resting ECG or other cardiologic studies. Catecholaminergic polymorphic ventricular tachycardia is associated with a completely normal resting ECG and is electrocardiographically suspected by significant ventricular ectopy following either exercise or catecholamine stress testing. It was once thought to manifest only during childhood (from 7 to 9 years), but more recent studies have suggested that the age of first presentation can vary from infancy to 40 years of age.[40,90]

Three genetic variants have been identified, an autosomal dominant one caused by mutation in the gene encoding the ryanodine receptor *RYR2* and a recessive one, caused by mutation in the calciquestrin isoform gene (*CASQ2*.[55,91]). Both genes are implicated in regulating intracellular calcium and both types of defect lead to increased function of these proteins, and so outflow of calcium from the sarcoplasmatic reticulum is increased. This excess calcium is associated with abnormalities in the sarcolemmal membrane potential, leading to late depolarizations that cause a predisposition to arrhythmias. Similarly, some patients diagnosed with CPVT type 3 on the basis of the presence of bidirectional VT on exercise have been identified as possessing *KCNJ2* mutations, which are associated with the rarely lethal Andersen–Tawil syndrome (ATS1, LQT7).[92] The misdiagnosis of Andersen–Tawil syndrome as the potentially lethal disorder CPVT may lead to a more aggressive prophylactic therapy [i.e. implantation of an implantable cardioverter defibrillator (ICD)] than necessary. Genetic testing may provide a clear differential diagnosis between atypical LQT1 and CPVT and between CPVT and ATS1.[93]

In the absence of treatment, the mortality rate in CPVT is very high, reaching 30–50% by the age of 20–30 years. The earlier the episodes appear, the poorer the prognosis and there is a correlation between the age at which the first syncope occurs and the severity of the disease.

Atrial fibrillation

Atrial fibrillationAF is the most common arrhythmia encountered in the adult population. However, in the young, AF is rare, and usually associated with CHD. There is a small subgroup of the population who may present with lone AF at a very young age. In this subset of patients, a genetic cause should be suspected. Most of the genes associated with familial AF are ion cannels, especially potassium channels (*KCNQ1*, *KCNH2*, *KCNJ2*, *KCNE2*, *KCNE3*, and *KCNE5*), sodium current-related channels (*SCN5A*, *SCN1B*, *SCN2B*, and *SCN3B*) and connexions (*GJA5*). These mutations will alter current generation and transmission and will potentiate the development of reentrant circuits at the atrial level.[94,95]

Idiopathic ventricular fibrillation

Idiopathic ventricular fibrillation (IVF)—spontaneous VF without identifiable structural or electrical heart disease—may account for up to 10% of SD in the young.[96–98]

Haplotype-sharing analysis has identified a genetic basis for IVF.[99] The shared chromosomal segment contained the *DPP6* gene, which encodes a putative regulator of the transient outward Ito current. DPP6 mRNA levels were increased 20-fold in hearts of human carriers in one study.[100] To date, this seems to be a founder risk locus, but nonetheless it suggests that an increase in DPP6 imparts a higher risk for VF. Furthermore, previously thought to be a benign and common ECG finding present in up to 5% of the population, three separate case–control studies.[101–103] suggest that 'J-point elevation' (manifested either as terminal QRS slurring or notching, or ST-segment elevation with upper concavity and prominent T-waves in inferolateral leads) is significantly more prevalent (16–60%) in patients with IVF. Mutations in genes encoding subunits of the L-type Ca2 channel (*CACNA1C*, *CACNB2*, and *CACNA2D1*)[104] and a subunit of the KATP channel encoded by *KCNJ8* have been implicated in this new 'J-wave syndrome' or ERS.[105]

Lev–Lenègre syndrome

Lev–Lenègre syndrome [also called progressive cardiac conduction disease (PCCD)] is a rare entity characterized by disruption of the conduction system, in which a block gradually develops, resulting in ventricular arrhythmias or asystolia.[106,107] The amount of sodium and the speed with which it enters the cell determine the velocity of conduction of the electric impulse through the sodium-dependent cells (muscle cells of the ventricle and atrium and cells of the His–Purkinje system). If a mutation leads to a reduction in the quantity of sodium that enters the cell, the velocity of conduction of the impulse is reduced resulting in a loss of function in phase 0 of the action potential (channel opening). In 1995, chromosomal abnormalities (19q13.2–13.3) associated with bundle branch block were reported.[108] In 1999 the first mutation was described, located on the *SCN5A* gene.[109,110] In addition, it has been described two loss-of-function mutations in *SCN1B*[81] and mutations in *NKX2.5* gene (5q35) that codify the transcription factor NKX2.5 (also named CSX)[111] The conduction block is due to a congenital heart defect. Recently, it has also been described a mutation in *TRPM4* gene (19q).[112] The *TRPM4* gene is a causative gene in isolated cardiac conduction disease with mutations resulting in a gain of function and TRPM4 channel being highly expressed in cardiac Purkinje fibres.

Sick sinus syndrome

Sick sinus syndrome (SSS) encompasses various forms of arrhythmia that result from sinoatrial node dysfunction. Patients may suffer from syncope and require lifelong pacemaker therapy. Heritable SSS is associated with loss-of-function mutations in *SCN5A*, and often linked to compound heterozygous mutations in patients with severe symptoms at relatively young age.[113] Not surprisingly, SSS may manifest concomitantly with other phenotypes that are linked to *SCN5A* loss-of-function mutations (i.e. BrS and PCCD)[114–116] Interestingly, LQT-3 patients with *SCN5A* gain-of-function mutations may also suffer from sinus bradycardia and sinus arrest.[117]

Pacemaker cells in the sinoatrial node reach the voltage range for the sodium window current during action potential phase 4. In addition to their contribution to cardiac pacemaker activity,

sodium channels also play an essential role in the propagation of action potentials from the central area of the sinoatrial node through its peripheral regions to the surrounding atrial muscle.[118]

Wolf–Parkinson–White syndrome

The WPW syndrome is characterized by a double excitation of the heart induced by pre-excitation (antesystole) along existing accessory excitation pathways bypassing the normal, i.e. orthodromic, AV conduction pathway. The additional AV connection fulfils the anatomic and functional requirements for movement or reentry. Clinically, this usually takes the form of (supraventricular) reentry tachycardia via the atrium, AV node, ventricle, accessory bundle, and atrium. Each case of WPW is highly individual and can have a variety of manifestations.

The WPW syndrome is the second most common cause of SVAs in the Western world. Familial appearance of WPW syndrome is rare and displays an autosomal dominant inheritance associated with HCM. Several mutations in *PRKAG2* have been identified.[119] Recently, it has been reported a novel genomic disorder with WPW associated with a deletion of *BMP2* gene.[120]

Pharmacological treatment

Antiarrhythmic drug therapy in children without documented arrhythmias

As a general rule, the prescription of antiarrhythmic drugs requires a clear diagnosis with electrocardiographic documentation of a given arrhythmia. Thus the sole complaint of palpitations or other symptoms evoking the suspicion of a possible underlying arrhythmia is not a sufficient reason to give antiarrhythmic drugs. Risk–benefit analysis of drug therapy is not possible in case of undocumented rhythm disorder, and no situation can be imagined where diagnosis cannot be clearly made by any of the currently available event recording systems in a patient with symptoms occurring frequently enough to consider drug therapy.

Antiarrhythmic drug therapy in children with documented narrow QRS tachycardia

Acute treatment of narrow QRS tachycardia

Diagnosis of the underlying pathophysiologic mechanism of the tachycardia is important for therapeutic decisions. Thus a 12-lead ECG must be obtained prior to therapy. Except for some very rare exceptions of narrow QRS VT in infancy, the overwhelming majority of regular narrow QRS tachycardias are of supraventricular origin, less frequently junctional. The vast majority of these tachycardias are AVRTs with a large predominance of accessory pathway-mediated tachycardias in infancy and early childhood, with increasing incidence of AV nodal tachycardias at later stages of paediatric age groups.[121] The differential diagnosis to other tachycardia mechanisms can be established by identifying the P-wave and its relationship to the QRS.[122]

The recommendation for acute termination of narrow complex tachycardia in the stable patient is to first use vagal manoeuvres (e.g. ice immersion, gastric tube insertion in infants, Valsalva, and head stand in older children) prior to the administration of antiarrhythmic drugs, as it is effective in a considerable proportion of patients. In case of failure intravenous adenosine would be the drug of choice.[123] In some instances transoesophageal atrial overdrive pacing may be used, while the use of synchronized electrical cardioversion should be limited to the critically ill haemodynamically compromised patient (*Table 1*). The efficacy of adenosine is dose-dependent and lower starting doses than indicated in *Table 1* have been shown to result in an insufficient rate of successful tachycardia termination.[124] Due to its short half-life, adenosine may only cause a short interruption of tachycardia with rapid recurrence, in which case adenosine may be repeated or an

Table 1 Recommendations for acute treatment of haemodynamically stable regular narrow QRS tachycardia in infants and children

Drug/intervention	Dosage (iv)	Class	Level
Vagal manoeuvres	Ice immersion, gastric tube insertion in infants,	I	B
Transoesophageal atrial overdrive pacing[a]	Valsalva, and head stand in older children	I	B
Adenosine	Rapid bolus starting dosages:		B
	For infants: 0.15 mg/kg.	I	
	For >1 year of age: 0.1 mg/kg	I	
	Increasing dosage up to 0.3 mg/kg.		
Verapamil[b,c]	0.1 mg/kg slowly over 2 min	I	B
Flecainide[b]	1.5–2 mg/kg over 5 min	IIa	B
Propafenone[b]	Loading: 2 mg/kg over 2 h	IIa	B
	Maintenance: 4–7 μg/kg/min		
Amiodarone	Loading: 5–10 mg/kg over 60 min.	IIb	B
	Maintenance infusion:5–15 μg/kg/min		

iv, intravenously; Class, recommendation class; Level, level of evidence.
[a]Most effective if AV reentrant tachycardias or atrial flutter.
[b]Myocardial depressant effect.
[c]Contraindicated in infants <1 year of age.

antiarrhythmic drug with longer half-life should be used. Induction of AF with rapid conduction to the ventricles related to enhanced accessory pathway conduction may occur after administration of adenosine,[125] thus appropriate monitoring and precautions to treat such complications in an adequate setting are mandatory. Intravenous drugs alternative to adenosine for immediate tachycardia termination are flecainide, propafenone, and procainamide. Especially in infancy, amiodarone is also used for termination, although it may take hours until successful conversion to sinus rhythm occurs and is therefore mostly used as a last resort medication.[126] Verapamil may be given in older children but is contraindicated in infants <1 year of age as it has been described that this may lead to cardiovascular collapse.[127] Dosing recommendations of these drugs are shown in *Table 1*.

Prophylactic antiarrhythmic drug treatment of narrow QRS tachycardia

In the paediatric population, the highest incidence of SVT is in newborns and young infants. Long-term treatment has to take into account that a majority of these patients will have only a few episodes of SVT with a 'growing out' during the spontaneous course of the disease, and invasive therapy is thus limited to the rare patient with drug-refractory disease and life-threatening conditions. Prophylactic antiarrhythmic drug therapy is given only to protect the child from recurrent SVT during this time span until the disease will eventually cease spontaneously, usually early in the first year of life. Most clinicians have adopted a strategy of giving prophylactic antiarrhythmic drugs during the first 6–12 months of life,[128,129] without clear evidence for which could be the optimal approach.

Almost all antiarrhythmic drugs have been tried for the prophylactic treatment of SVT in infants, but the evidence for efficacy and safety is based on observational studies only and are mostly retrospective in nature. In recent years, the management for the prevention of SVT recurrences has shifted towards the use of Class III antiarrhythmic drugs (sotalol and amiodarone) or Class IC drugs (flecainide and propafenone), with comparable success rates as with digoxin and beta-blocking agents (propranolol), but with proarrhythmic effects mainly observed for flecainide and sotalol. Various combinations of the aforementioned drugs have been documented to be effective in the therapy of SVT refractory to a single-drug management.[130] Drug interactions have to be considered in case of antiarrhythmic drug combinations. *Table 3* gives an overview of drugs used for the prophylactic management of paediatric SVT.

For patients with SVT episodes recurring after 1 year of age or with the first manifestations beyond infancy,[131] 'growing out' of SVT will become much less likely and a long-term management strategy has to be individualized for the patients according to the severity of symptoms and frequency of episodes. No treatment is justified in case of rare and short events with good clinical tolerance, lack of pre-excitation and a normal structured heart. All patients should be instructed how to terminate their SVT episode using a Valsalva manoeuvre. Periodic treatment ('pill-in-pocket approach') is an option for rare but well tolerated and long-lasting episodes of SVT, such as AVNRT, and has been adopted with limited data supporting its efficacy.[132] A single oral dose of a drug that has a short time to take effect is administered only during an episode of tachycardia for its termination when vagal manoeuvres alone are not effective. Patients should be free of significant LV dysfunction, sinus bradycardia, or preexcitation.

Table 2 Recommendations for acute treatment of wide QRS tachycardia in infants and children

Wide QRS tachycardia	Drug/intervention (dosages see *Table 1*).	Class	Level
Wide QRS tachycardia of unknown mechanism	Electrical cardioversion	I	C
	Lidocaine iv bolus starting at 1 mg/kg (up to 3 doses in 10 min interval); followed by infusion of 20–50 μg/kg/min	IIa	C
	Amiodarone iv loading: 5–10 mg/kg over 60 min, followed by maintenance infusion of 10 mg/kg/day (5–15 μg/kg/min).	IIb	
	Procainaimide iv	IIb	
	Esmolol iv bolus 500 μg/kg	IIb	
	Magnesium sulphate iv	IIb	
Antidromic tachycardia, pre-excited AF	Electrical cardioversion	I	B
	Flecainide iv	IIa	C
SVT with bundle branch block	See table for acute treatment of SVT		
Monomorphic ventricular tachycardia	Electrical cardioversion	I	C
	Propranolol iv	IIb	C
	Lidocaine iv		
	Sotalol iv		
Polymorphic ventricular tachycardia	Electrical cardioversion	I	C
	Propranolol iv	IIb	C
	Deep sedation or general anesthesia	IIb	C
	Potassium and magnesium iv.	IIb	C

iv, intravenously; Class, recommendation class; Level, level of evidence; AF, atrial fibrillation; SVT, supraventricular tachycardia.

Table 3 Suggested doses and main side effects/precautions for commonly used oral prophylactic antiarrhythmic drugs for SVT and VT in infants and children

Drug	Total daily dosage per body weight divided in × doses	Main contraindications and precautions	Features prompting lower dose or discontinuation	AV nodal slowing
Digoxine			Bradycardia	Moderate
Propranolol	1–3 mg/kg in 3× daily	Asthma bronchiale	Bradycardia	Moderate
Atenolol	0.3–1.3 mg/kg in 1× daily	Asthma bronchiale	Bradycardia	Moderate
Verapamil	4–8 mg/kg in 3× daily	Myocardial depressant effect	Bradycardia	Marked
Flecainide	2–7 mg/kg in 2× daily	Contraindicated if creatinine clearance <50 mg/mL or reduced LVEF. Caution if conduction system disease.	QRS duration increase >25% above baseline	None
Propafenone	200–600 mg/m^2 or 10–15 mg/kg in 3× daily	Contraindicated if reduced LVEF. Caution if conduction system disease and renal impairment.	QRS duration increase >25% above baseline	Slight
Sotalol	2–8 mg/kg in 2× daily	Contraindicated if significant LV hypertrophy, systolic HF, pre-existing QT prolongation, hypokalaemia, creatinine clearance <50 mg/mL and asthma bronchiale. Moderate renal dysfunction requires careful adaptation of dose	QT interval >500 ms	Similar to high-dose beta-blockers
Amiodarone	Loading: 10 mg/kg for 10 days. Maintenance: 5 mg/kg in 1× daily	Caution when using concomitant therapy with QT-prolonging drugs, HF. Dose of vitamin K antagonists and of digitoxin/digoxin should be reduced.	QT interval >500 ms	Slight

LVEF, left ventricular ejection fraction; HF, heart failure.

A single oral dose of diltiazem (120 mg) plus propranolol (80 mg) was superior to both placebo and flecainide (~3 mg/kg) in sequential testing in 33 adolescents and young adults with paroxysmal SVT, in terms of acute conversion to sinus rhythm.[132] Favourable results using single oral dose of sotalol has also been reported.[84] Beta-blocking agents, combined with a Class III antiarrhythmic effect, such as sotalol or the Ca channel blocking agent, verapamil are the most widely used drugs for this strategy (*Table 3*).

Chronic treatment is to be considered in the first few years of life in case of poorly tolerated symptoms and frequent attacks until the patient reaches the age at which nowadays elective invasive and curative treatment with ablation can be recommended (*Table 4*). In children >5 years of age, with a long-lasting history of SVT episodes, invasive curative treatment may be preferred over chronic antiarrhythmic medication, given safety and efficacy of ablation in the current era (*Tables 3* and *4*). The choice between drugs and ablation relates to the location of the arrhythmia to be treated, and the body weight of the patient.

Antiarrhythmic drug therapy in children with documented wide QRS tachycardia

Ventricular tachycardia affects all age groups, including newborns and small children. Potentially detrimental, VT should always be considered when facing any wide QRS tachycardia and treatment should be directed as for VT unless proven otherwise, as the potential harm of treating an SVT as a VT is very little compared with the converse.

Acute treatment of wide QRS tachycardia

Sustained wide QRS tachycardia requires immediate treatment. If the patient is haemodynamically unstable, electric cardioversion is always the first therapeutic option, at a starting energy of 1–2 J/kg body weight. The energy should be doubled for each attempt if electric cardioversion is unsuccessful.

If the patient is stable, pharmacological treatment can be tried, starting with a bolus injection of lidocaine followed by an infusion (*Table 2*). If ineffective, mostly in reentrant VTs, the next step is a loading dose of amiodarone, followed by an infusion. As an alternative to amiodarone one may try esmolol in bolus together with magnesium sulphate provided that antidromic conduction through an accessory AV pathway has been excluded. Electrical cardioversion should always be considered even in stable patients.

Prophylactic antiarrhythmic drug treatment of wide QRS tachycardia

Prophylactic antiarrhythmic treatment of a wide QRS tachycardia should be directed to the specific diagnosis.

Acute and prophylactic antiarrhythmic drug therapy of supraventricular tachyarrhythmias

Sinus tachycardia

Inappropriate sinus tachycardia

Inappropriate sinus tachycardia (IST), defined as a heart rate out of proportion to physiological need and after exclusion of other primary disease states leading to sinus tachycardia (e.g. thyroid dysfunction, cardiac dysfunction, anaemia, infection, pheochromocytoma and others) is a very rare disease in children and adults. The 12-lead ECG shows P-waves identical to the ones observed in sinus rhythm. Whereas in adults there are heart rate cut-off values for IST,[133] no such values exist in the growing child. Current understanding of this condition is incomplete and treatment usually consists of a beta-blocking agent, and more recently in adults good results were achieved with ivabradine. There is

Table 4 Indications for catheter ablation and oral prophylactic antiarrhythmic drugs for recurrent SVT or VT

Clinical situation	Recommendation	Class	Level	Reference
WPW syndrome and episode of aborted SCD	Catheter ablation	I	C	
WPW syndrome and syncope combined with preexcited RR interval during AF <250 ms or antegrade APERP during PES <250 ms	Catheter ablation	I	C	
Incessant or recurrent SVT associated with ventricular dysfunction	Catheter ablation	I	C	
Recurrent monomorphic VT with haemodynamic compromise and amenable to catheter ablation	Catheter ablation	I	C	
WPW syndrome and recurrent and/or symptomatic SVT and age >5 years	Catheter ablation	I	C	
	Flecainide, propafenone	I		
	Sotalol	I		
	Amiodarone	IIb		
WPW syndrome and recurrent and/or symptomatic SVT and age <5 years	Flecainide, propafenone	I	C	
	Sotalol	IIa		
	Catheter ablation	IIb		
	Amiodarone	IIb		
WPW syndrome and palpitations with inducible sustained SVT during EP test, age >5 years	Catheter ablation	I	C	
	Flecainide, propafenone	I		
	Sotalol	I		
	Amiodarone	IIb		
Single or infrequent SVT (no pre-excitation), age >5 years	None	I	C	
	Valsalva maneuver	I		
	'Pill-in-Pocket':[a] Flecainide (3 mg/kg), Diltiazem (120 mg) + Propranolol (80 mg) Sotalol	IIa		
	Beta-blocking agents	I		
	Catheter ablation	IIb		
SVT, age >5 years, chronic AA therapy has been effective in control of the arrhythmia	Catheter ablation	IIa	C	
SVT, age <5 years (including infants), when AA medications, including Classes I and III are not effective or associated with intolerable side effects	Catheter ablation	IIa	C	
Asymptomatic preexcitation, age >5 years, no recognized tachycardia, risks and benefits of procedure and arrhythmia clearly explained	Catheter ablation	IIb	C	
	Any AA drug	III		
Asymptomatic preexcitation, age <5 years	Catheter ablation	III	C	
	Any AA drug	III		
SVT controlled with conventional AA medications, age <5 years	Catheter ablation	III	C	
Idiopathic monomorphic ventricular tachycardia	Propranolol Sotalol	IIb	C	167,170
	Flecainide, propafenona Verapamil Procainamida Amiodarone	IIa	C	

WPW, Wolff–Parkinson–White; SVT, supraventricular tachycardia; LV, left ventricular; SCD, sudden cardiac death; AF, atrial fibrillation; APERP, accessory pathway effective refractory period; PES, programmed electrical stimulation; EP, electrophysiological; AA, antiarrhythmic; level, level of Evidence; Class, recommendation classification.
[a]Patients should be free of significant LV dysfunction, sinus bradycardia, or pre-excitation.

almost a complete lack of data (except for anecdotic) with regard to treatment in the paediatric age group.

Sinus node reentry tachycardia

Sinus node reentrant tachycardia (SNRT) is exceedingly rare in paediatrics and then mostly occurring in patients with structural heart disease.[134] It is characterized by an inappropriate tachycardia with a P-wave axis and morphology identical to that seen during sinus rhythm. Digoxin has been reported to be effective in treating SNRT,[134] but data to support clear treatment recommendations of SNRT in childhood is lacking.

Atrioventricular nodal reentrant tachycardia

Atrioventricular nodal reentry tachycardia most often presents after 5 years of age with a gradual increase in frequency with advancing age,[121] whereas it is an uncommon (10%) arrhythmia in infants.[135]

The decision to choose drug therapy or to proceed with ablation as initial therapy is related to the patient's age, frequency

and duration of tachycardia, tolerance of symptoms, effectiveness and tolerance of antiarrhythmic drugs, and the presence of concomitant structural heart disease. Patients who successfully can terminate their tachycardia using vagal manoeuvres and experience infrequent minimally symptomatic tachycardia episodes can preferably remain off drugs.

For patients with frequent, recurrent sustained episodes of AVNRT there is a spectrum of antiarrhythmic agents available. Standard therapy includes non-dihydropyridine calcium-channel blockers and beta-blocking agents although multicentre, randomized, placebo-controlled studies of long-term efficacy of antiarrhythmic agents are lacking. In a long-term prospective study, once-a-day oral atenolol started as a mono-therapy in 22 children <18 years of age with clinical SVT was effective in 59% of patients.[136] In patients who do not respond to AV-nodal-blocking agents and who do not have structural heart disease, the Class IC drugs flecainide and propafenone are the preferred choices (*Tables 3* and *4*). Class IC drugs should be combined with a beta-blocking agent to enhance efficacy and reduce the risk of one-to-one conduction over the AV node if AFL occurs. In most cases, Class III drugs, such as sotalol or amiodarone, are unnecessary.

Because drug efficacy is in the range of 30 to 50%, catheter ablation may be offered as the first-line therapy for older children with frequent episodes of tachycardia and low risk of AV block or in case treatment with AV nodal blocking agents fails. The decision is mainly related to patient preference, likely affected by lifestyle issues (competitive athlete), aversions with regard to an invasive procedure or the need for lifelong drug therapy.

Junctional tachycardias

Junctional ectopic tachycardia

Junctional ectopic tachycardia in children is mainly seen in the early post-operative period after surgery for CHD, preferentially in infants, and is then a self-limiting arrhythmia with resolution within a few days but requiring aggressive management due to the haemodynamically unstable condition of the patient. A large spectrum of antiarrhythmic drugs has been tried among which amiodarone is preferred because of its good efficacy in slowing of the heart rate during JET. Noteworthy, 62% of patients in that study required drug combination therapy to successfully slow JET, and conversion to sinus rhythm was achieved in only 11% by drugs alone. Mortality was 4% and was only observed among infants,[12] which however compares very favourably with the reported 35% mortality in the pre-amiodarone era.[137] Final cure was achieved with ablation which was required in a substantial number of patients. Amiodarone, given intravenous or orally according to severity of symptoms, is therefore recommended as the first line therapy for JET. In case of unsatisfactory response, a combined therapy with digoxin, beta-blocking agent or flecainide is recommended (Class I, Level B).

Permanent junctional reciprocating tachycardia

Permanent junctional reciprocating tachycardia is caused by a rare form of accessory pathway with decremental conduction properties and located in the posteroseptal region. It is a long R-P tachycardia with typical deep inverted retrograde P-waves in the inferior leads II, III, and aVF. Spontaneous resolution of PJRT has been observed but occurs infrequently. Several retrospective multicenter studies have evaluated the efficacy of medical therapy which varied considerably and ranged between 40 and 85% with best response to amiodarone and verapamil (both eventually combined with digoxin) and to Class IC drugs flecainide and propafenone with partial or total response to treatment in 60 and 66%, respectively. The studies are difficult to compare related to variation in the definition of treatment success or partial response. Of note is that a considerable proportion of patients finally required an invasive ablation procedure to control the tachycardia.[138] As this form of tachycardia frequently leads to tachycardia-induced cardiomyopathy, once diagnosed, the medical treatment should be initiated without delay using any of the aforementioned drugs as first choice (Class I, Level B).[139,140]

Accessory pathway-mediated tachycardias

Atrioventricular reentrant tachycardia, using an accessory pathway, often presents during the first year of life with subsequent peaks of presentation near the end of the first decade and in the mid-teen years. Over 90% of patients with Wolff–Parkinson–White syndrome diagnosed in infancy have remission of tachycardia episodes by 18 months of age with tachycardia recurrence later in life.[141,142] The SVTs presenting after the age of 5 years tend to persist with recurrence of tachycardia episodes.[143]

If an accessory pathway has a short anterograde refractory period, a rapid conduction to the ventricles may occur during AF resulting in subsequent degeneration into VF. Atrial fibrillation can thus be a potentially life-threatening arrhythmia in patients with WPW syndrome. The incidence of sudden death in a cohort of paediatric and adult WPW patients from a community-based local population was for symptomatic patients, asymptomatic patients, and the overall group, respectively, 0.0025, 0.0000, and 0.0015 per patient-year.[144] No sudden death occurred in patients asymptomatic at diagnosis. Higher death rates have been reported by others, which however, may have been limited by selection biases.[9] The role of digoxin as a contributor to sudden death associated with pre-excitation is still unclear, particularly in the paediatric population.

Acute management of accessory pathway-mediated tachycardias is shown in *Tables 1* and *2*.

All patients with the WPW syndrome (i.e. pre-excitation combined with tachycardia) should be referred for further evaluation because of the potential for lethal arrhythmias, which can occur in all age groups.[144,145] Even a history of paroxysmal regular palpitations in a patient with pre-excitation on the resting ECG is sufficient for referral to an arrhythmia specialist without prior attempts to record spontaneous episodes of tachycardia. Moreover, irregular and paroxysmal palpitations in a patient with pre-excitation on the resting ECG warrant immediate electrophysiological evaluation since it strongly suggests episodes of AF.

Since most typical SVT episodes presenting in infancy resolve spontaneously, a pharmacological therapeutic strategy is favoured rather than an ablative approach, which in this young age group may result in damage to adjacent structures, such as the AV node and the coronary arteries and out-weight the benefits.

Registry data has consistently demonstrated that age <4 years or weight <15 kg are independent risk factors for complications associated with the procedure.[146] Therefore, even in children less than 5 years of age, drug treatment is recommended as initial management of recurrent AVRT, due to the age related increased risk of catheter ablation and considering the natural course with spontaneous remissions of AVRT (*Tables 3* and *4*). Even though serial data derived from registries have demonstrated that ablation is increasingly performed in children as an alternative to chronic antiarrhythmic drug therapy,[147] there have been no randomized trials of drug prophylaxis versus ablation involving children with AVRT. Results from the voluntary registry of paediatric ablation indicate that the incidence of major complications has decreased ranging from 1.4[134,148,149] to 3.8%.[9,150] The mortality rate related to complications of ablation was 0.117% for patients, which should be compared with the 0.0025 risk per patient-year of follow-up of sudden death with a diagnosis of WPW.[144] Given the potential for SCD related to rapidly conducting pre-excited AF in patients with the WPW syndrome, even the low annual incidence of sudden death is of concern and supports the concept of in general liberal indications for catheter ablation. Catheter ablation is thus recommended as first-line therapy for older children with WPW syndrome (*Tables 3* and *4*). The clinical situations in which prophylactic antiarrhythmic drug therapy is recommended in these patients are mainly patient preference, prophylactic therapy while waiting for ablation, failed ablation, and whenever catheter ablation is judged to be associated with too high risks for complications (see ablation section).

Several small, non-randomized and retrospective trials have reported the safety and efficacy of oral antiarrhythmic drugs in children and infants with SVAs, but the large variations in dosages, presence of structural heart disease, and patient age have precluded a direct comparison of efficacy between these drugs. The preferential antiarrhythmic drugs for management of arrhythmias in children with the WPW syndrome, particularly when there is a short anterograde refractory period of the accessory pathway, are those that slow the conduction through the atrium or accessory pathway, i.e. Classes IA and IC drugs (disopyramide, flecainide, and propafenone), and Class III antiarrhythmic drugs (sotalol and amiodarone) (*Tables 3* and *4*). Amiodarone should only be used if other drugs fail to control the arrhythmia and catheter ablation is not an option.

Non-comparative studies of *propafenone* confirmed a good efficacy and tolerability in long-term management of paediatric SVT.[151–154] *Flecainide* has also proven to be effective in controlling SVT in children, even infants, used as single agent or in combination with other antiarrhythmic drugs[155,156]. In the most recent study of 22 children with WPW syndrome and without structural heart disease, 13 of 18 symptomatic children received oral flecainide (2–5 mg/kg/day twice daily), which was effective in all patients followed for mean 3.4 years until ablation.[156] In a review of all published experience with flecainide, including a total of 704 cases with SVT (infants, children, and foetuses) the drug appeared effective (73 to 100% depending on arrhythmia) and safe since there were no deaths and less than 1% serious proarrhythmia.[155] Neither propafenone nor flecainide should be used in children with structural heart disease related to their myocardial depressant effects and the risk for proarrhythmias. Serial monitoring of PR intervals and QRS complex duration is recommended for dosage adjustment, whereas serum levels are seldom of use.

A third option for control of AVRT is *sotalol*, a non-selective beta-blocking agent with Class III effect. Controlled and retrospective studies have reported efficacy rates ranging between 64–80%[8,90]. In a case controlled study of 71 children, of whom 33 had AVRT, 94% responded to oral sotalol (starting dose 2 mg/kg body weight/day divided in three doses).[157] Proarrhythmia occurred in 10%, including sino-atrial block, high-grade AV block, and TTdP. In another study, paediatric patients aged from 0.03 to 17 years, were treated for SVT with varying oral sotalol dosages.[158] Dosing recommendations for different age groups derived were a starting dose and target dose of 2–4 mg/kg/day for neonates and children >6 years, and 3–6 mg/kg/day for infants and children <6 years (*Table 3*). Related to the risk of proarrhythmia, Class I antiarrhythmic drugs and sotalol treatment should be initiated in-hospital. Relatively few studies have evaluated the efficacy and safety of *amiodarone* for treatment of children with accessory pathway-mediated tachycardias.[159] No studies have demonstrated that amiodarone is superior to Class IC antiarrhythmic agents or sotalol. It has substantial cardiac and non-cardiac adverse effects, which may partly be avoided with close monitoring. As a result of the well-recognized organ toxicity associated with amiodarone and the high rate of discontinuation, it is generally not warranted for treatment of patients with accessory pathways. Since amiodarone usually does not exacerbate heart failure and is rarely proarrhythmic, it is suitable for children with structural heart disease, who are not candidates for catheter ablation. No studies have determined the short- or long-term efficacy of *procainamide* or *quinidine* in the treatment of AVRT.

Antiarrhythmic drugs that primarily block conduction through the AV node (digoxin, verapamil, diltiazem, and beta-blockers), although frequently used by many general practitioners in infants and children with WPW, are contraindicated in patients with pre-excitation.

Patients with symptomatic episodes of SVT, but without pre-excitation on resting ECG (concealed accessory pathways) can be managed as patients with AVNRT. If these patients experience infrequent, minimally symptomatic episodes of SVT, they can remain off antiarrhythmic drugs and be instructed to terminate the SVT episodes using valsalva manoeuvres. Should antiarrhythmic drug therapy be preferred by the patient, AV nodal blocking agents are the drugs of first choice (*Tables 3* and *4*). Flecainide, propafenone or sotalol should follow in case of treatment failures in resistant cases.

Management of patients with asymptomatic accessory pathways

There are no circumstances that could motivate treatment with antiarrhythmic drugs in patients with an ECG pattern of pre-excitation in a subject who has no symptoms of arrhythmia (see section on catheter ablation).

Atrial tachycardias

Focal atrial tachycardia

Focal atrial tachycardia (FAT) is a common cause of SVT in childhood and the underlying substrate is a distinct autonomic focus

anywhere in the atria. Clinically, the tachycardia may manifest either as sporadic or permanent. In the latter case progression to congestive heart failure and cardiomyopathy may occur. Spontaneous resolution is frequent in case the arrhythmia manifests in infancy,[11,160] while spontaneous resolution is infrequent in older children.[11] Focal atrial tachycardia was controlled by medical therapy in most infants when using digoxin and/or propafenone with the addition of amiodarone in patients who failed, resulting in a 95% of arrhythmia conversion to sinus rhythm.[160] A conversion rate to sinus rhythm was achieved in 91% in another study starting with digoxin and adding a beta-blocking agent and flecainide in case of failure.[11] A more recent series of neonatal FAT achieved a 100% response rate using Class IC (propafenone) and Class III (amiodarone and sotalol) antiarrhythmic drugs.[161] Response to medical therapy is clearly worst for patients beyond infancy.[11] Based on these data, digoxin is recommended as the first-line therapy, adding a Class IC drug in case of failure, and using amiodarone as a second- or third-line drug. For older children, catheter ablation should be considered early in the management, if FAT is not controlled by drugs (Class I, Level B).

Multifocal atrial tachycardia

Multifocal atrial tachycardia, also known as chaotic atrial tachycardia, is rare during childhood and in the vast majority it affects infants. Its ECG characteristics are quite peculiar with a markedly irregular ventricular rate, multiple P-wave morphologies and irregular P–P intervals. The literature on MAT is scarce, except for some anecdotal reports, and data on the clinical course and treatment are derived mainly from one recent multicentre observational, retrospective analysis.[159] The main finding was that MAT is self-limiting with restoration of sinus rhythm usually after a few months with no late recurrences. As MAT cannot be acutely converted to sinus rhythm, the treatment goal is to achieve adequate rate control of the tachycardia. At presentation, ventricular dysfunction is frequently seen, thus treatment should start rapidly. Most antiarrhythmic drugs have been tried in MAT with varying results. Digoxin has been most frequently used, but usually in combination with a Class III or IC drug. One study observed a good response (83%) to propafenone in six patients,[162] which, together with amiodarone seemed to be the most promising management approach. The recommendation for infants with MAT is that antiarrhythmic drugs are usually indicated, starting with digoxin together with a Class IC drug (flecainide and propafenone), then using amiodarone as second option (Class I, Level B).

Macro-reentrant atrial tachycardia: atrial flutter

Atrial flutter is rarely seen in childhood. Either AFL occurs as a late complication after surgical treatment of CHD or in patients with structural normal hearts, among which the overwhelming majority are newborns, with often already foetal manifestation of AFL. Transplacental intrauterine treatment of foetal AFL is described in another section of this report. Although overall being a rare arrhythmia, neonatal AFL nowadays is well characterized as for treatment and for outcome.[163] Although conversion to sinus rhythm by antiarrhythmic drugs has been observed, available studies with an adequate number of patients, concluded that synchronized electrical cardioversion was the most straightforward procedure to rapidly establish sinus rhythm with a response rate of 87%.[163,164] Transoesophageal overdrive pacing had moderate success rates of 60–70% in the same populations studied. It was concluded that once in sinus rhythm and in the absence of concomitant arrhythmias, recurrences were unlikely to occur and long-term prophylactic antiarrhythmic drug therapy was unnecessary.[163] The recommended therapy for a newborn with AFL (stable as well as unstable) is either transoesophageal atrial overdrive pacing if available or synchronized electrical cardioversion (Class I, Level B). In a stable newborn pharmacologic treatment may be tried but may take some time before sinus rhythm is achieved. The recommended drugs are digoxin with addition of flecainide or amiodarone in case of failure (Class IIa, Level B). Ibutilide was successful during its first-ever administration in 12 of 19 (63%) patients (aged 6 months to 34 years). Two patients developed proarrhythmias.

Acute and prophylactic antiarrhythmic drug therapy of ventricular tachyarrhythmias

Idiopathic ventricular tachycardia

Idiopathic ventricular extra beats are very common in children, with a bimodal peak in neonates and adolescents. These extra beats are considered benign if they disappear with exercise. When they are symptomatic, they can be controlled with beta-blockers (propranolol 1 mg/kg/day) or in severely symptomatic cases flecainide 2–4 mg/kg/day and eventually ablation. Sustained VT is very rare in normal hearts. Thus, deep research has to be made in order to rule out the underlying cause.

Right ventricular outflow tract tachycardia and fascicular left ventricular ventricular tachycardia

The right ventricular outflow tract (RVOT) is the most common VT in young normal hearts, but it is necessary to discard arrhythmogenic RV cardiomyopathy. When symptomatic, beta-blocking agents are normally sufficient to control the arrhythmia. Ablation should be considered in case of failure to control symptoms. Fascicular tachycardia is rare and can be controlled in some cases by using betablockers, verapamil (except in infants), and amiodarone. If uncontrolled, catheter ablation is a very successful alternative.

Channelopathies

Long QT syndrome

Therapeutic strategies for LQTS primary focus on the prevention and treatment of life-threatening ventricular arrhythmias. Life-long beta-blocking agents in all patients (symptomatic and asymptomatic) has showed to be effective in reducing fatal cardiac events,[165] mostly in LQT type 1 and to a lesser extent in type 2[16,166]. However, beta-blocking agents may even be pro-arrhythmic in LQT type 3, for which mexiletine or flecainide may be of particular use.[167,168] Patients who remain symptomatic despite treatment with beta-blockers should be considered for more invasive therapies. Implantable cardioverter defibrillator placement in these patients is further discussed.

Short QT syndrome

Little is known concerning short QT syndrome. Implantable cardioverter defibrillator is the only proven treatment to prevent sudden death. Hydroquinidine and propafenone have been reported to be effective agents to postpone implantation in young children.[169]

Brugada syndrome

Children with type I Brugada ECG and symptoms are at risk of VT and sudden death. Implantable cardioverter defibrillator is the only treatment having a proven effect on the prevention of sudden death. However, complications are frequent in implanted children. Treatment with hydroquinidine could postpone implantation.[137]

Catecholaminergic ventricular tachycardia

Beta-blocking agents at high doses decrease the risk of VT and sudden death in these patients. When non-sustained repetitive VT appears, intravenous beta-blockers are recommended. If VT is poorly tolerated, electric shock should be delivered. If repetitive VT persists, deep sedation or even general anaesthesia may be required during the electrical storm.[170] Flecainide has been proposed recently in cases not adequately controlled with beta-blockers.[171]

Ventricular tachycardia in congenital heart disease

Mitral valve prolapse

Ventricular arrhythmias are more prevalent in patients with mitral valve prolapse but, except for Marfan's disease, it has not been related to increased risk for SCD, thus treatment with beta-blocking agents will only be indicated in symptomatic patients.[172]

Hypertrophic cardiomyopathy

Regular clinical risk stratification for SCD is mandatory for the prevention of sudden death in young patients. The risk factors for sudden death include familial history of sudden death at a young age, LV hypertrophy >3 cm, unexplained syncope, non-sustained VT, and abnormal blood pressure response during exercise. Patients having two or more risk factors are at high risk. Primary prevention of sudden death in patients considered to be at high risk should also include management of obvious arrhythmogenic mechanisms such as paroxysmal AF, accessory pathway, myocardial ischaemia, apart from the prevention, and/or management of ventricular tachyarrhythmias with amiodarone and/or ICD implantation, respectively. The choice of treatment in children is mainly influenced by the age at which ICD implantation is feasible. Beta-blockers and amiodarone could be used as a bridge in children at high risk, until their physical growth permits ICD implantation as long-term therapy.

Arrhythmogenic right ventricular cardiomyopathy

The increased risk for SCD is related to presence of sustained VT, LV involvement, extensive RV disease, and sudden death in family members with ARVC. The primary and secondary preventive strategy in children is mainly influenced by the age at which ICD devices can be implanted. Antiarrhythmic drugs can only be recommended as adjunctive therapy to ICD. A beta-blocking agent could be used as a bridge in children at high risk.

Special circumstances

Arrhythmias in patients with congenital heart disease

Due to haemodynamic alterations and/or surgical scars, tachyarrhythmia early or late after cardiac corrective surgery is still one of the most frequently observed complication after such procedure. Supraventricular and ventricular tachyarrhythmias may co-exist in the same patient; as exemplified by repaired tetrallogy of Fallot patients, in whom VT predominates but with a relatively high rate of AFL (10%),[173] and by Senning/Mustard corrective operation for transposition of the great arteries, with a high incidence of atrial tachyarrhythmias (44%) but also a significant rate of VT (9%).[174]

Atrial tachyarrhythmias

As an atriotomy scar is part of most procedures in congenital heart surgery, AFL is one of the most frequent and typical late complications. Once the arrhythmia has become manifest, it is not self-limiting but rather a long-term management problem, limiting the pharmacological management options in favour of curative catheter ablation of the underlying substrate.[175] Experience with long-term management of these arrhythmias using pharmacologic treatment has been disappointing,[176] and when potent drugs (amiodarone) are used, the burden of side effects is considerable (slowing of atrial rate making 1 : 1 conduction more likely) with still moderate success in arrhythmia control. Sotalol as an alternative has been found to be of some value with a 78% success rate in suppressing AFL in a small population of long-term post-operative paediatric patients,[109] but recurrence rate remains high and catheter ablation may therefore be required.

Ventricular tachyarrhythmias

In the paediatric age group, life-threatening VT are rare among patients with CHD either prior to or after surgery. Yet, the incidence of post-operative VT will increase with increasing age of the patient to reach significant numbers in the adult population with corrected heart surgery. The prototype for studying post-operative VT has been repaired tetralogy of Fallot,[173] which on long-term suffers from VT in up to 12% of patients and with a sudden death rate of nearly 8% at 21 years of follow-up.[177] As the repair of tetralogy of Fallot implies surgical incisions and haemodynamic changes, an ideal substrate for arrhythmias is created. Monomorphic and polymorphic VTs are often seen. Minimally symptomatic ventricular extra beats should be treated with beta-blockers. Severely symptomatic patients and/or inducible VT are considered for ablation with good results[178,179]. Management strategies rely on retrospective observational studies with limited number of patients. Antiarrhythmic drugs with a low risk for proarrhythmias (amiodarone) may be indicated for the prevention of arrhythmia recurrence following catheter ablation or as an adjunctive treatment to ICD.

Foetal arrhythmias

Foetal rhythm abnormalities occur in up to 2% of pregnancies, mostly detected after 20 weeks gestation. The majority are isolated premature atrial contractions and only 10% of rhythm abnormalities are clinically significant.

Assessment of foetal rhythm can be challenging and, up to date, the most feasible technique is echocardiography using M mode, pulse, and tissue Doppler to study the relationship between atrial and ventricular contractions. Simultaneous superior vena cava and ascending aorta Doppler[180] allows for defining the relation between atrial and ventricular contractions and atrio ventricular and ventricular atrial intervals, enhancing the differential diagnosis of various tachycardias.

Extrasystoles

Isolated premature beats are frequently detected in the foetus, and atrial premature beats are generally benign. When accompanied by cardiomegaly, ventricular dysfunction, or hydrops, attention must be paid as they may suggest episodes of SVT. If ventricular premature beats are present, myocardial disease should be excluded. Serial follow-up and post-natal evaluation will exclude serious pathology.

Foetal tachyarrhythmias

A heart rate above 180 b.p.m. is considered abnormal. Defining AV relationship will allow specific treatment:

- A short ventricular–atrial (VA) interval suggests an accessory pathway-mediated tachycardia, at a rate of 230–280 b.p.m., with a 1 : 1 conduction.
- A long V–A interval is consistent with: sinus tachycardia, FAT, and PJRT.
- If the V and A waves are superimposed: JET may be present, very rare as prenatal diagnostic.
- Atrial reentrant tachycardias: AFL, which are rare, usually at a rate of 300–500 b.p.m. with variable ventricular response.

Treatment is reserved for foetuses at risk of heart failure (incessant tachycardia, onset of the tachycardia before 32nd week of gestation and structurally abnormal heart) and should be focused on the type of arrhythmia. Several considerations have to be made when treating foetal arrhythmias, such as first-line treatment, mode of medication delivery (maternal oral administration with risk for inadequate absorption), hydrops obstructing drug absorption, and the variable drug responses among foetuses [108–110]. Transplacental digoxin, flecainide, and sotalol are the most commonly used first-line drugs. A recent multicentre study showed that digoxin and flecainide were superior to sotalol in converting AVRT to sinus rhythm or maintaining rate control.[125]

Recommendations for medical treatment of foetal tachycardias are as follows:

- Short V–A interval tachycardia and AFL:
  - if hydrops is absent: digoxin is first choice in most centres (Class I, Level C);
  - if hydrops is established; maternal medication with flecainide or sotalol is started as first line and digoxin can be added (Class I, Level C). If no response; intraumbilical administration of adenosine, digoxin or amiodarone can be tried, but mortality rates are high (Class I, Level C).
- In Long V–A interval tachycardias: maternal medication with flecainide or sotalol can be used in association if needed with digoxin (Class I, Level C).

Ventricular tachycardia is very rare but when present, myocardial disease should be excluded. In foetuses with structurally normal hearts long QT should be suspected. Beta-blockade, lidocaine, or amiodarone may be needed if incessant VT is present.

It has been stated that prematurity associated complications would be more harmful than the risk of treating the foetuses in uterus. When uncontrolled tachycardia leads to severe hydrops, birth can be attempted in order to treat the newborn directly. Radiofrequency ablation of a preterm hydropic newborn has been successfully attempted.[64]

Foetal bradyarrhythmias

A heart rate below 110 b.p.m. is considered pathological. *Sinus bradycardia* is the most common cause, being most of the time benign. Special consideration should be paid as bradycardia can be a sign of LQTS in a foetus, especially when associated with 2 : 1 AV block and normal A–V conduction. *Foetal AV block*, such as complete or second-degree block is in half of the cases associated with immunological maternal pathologies, and commonly associates foetal myocardial disease. Reversibility of complete AV block, when immune, is rare, even under corticoid treatment. However, dexamethasone may reduce the risk for progression.[181,182]

Antiarrhythmic drugs

Drug effects, side effects, and contraindications

Not only should the efficacy of potent antiarrhythmic drugs be addressed, but as important is the safety of the prescribed treatment.[160] Generally, in-hospital treatment initiation is warranted for most antiarrhythmic agents, except for beta-blockers and amiodarone.[183]

Class I antiarrhythmic drugs

Class I antiarrhythmic agents interfere to varying degrees with the sodium channel with different effects on action potential duration. These agents have been studied extensively and considered to be both effective and safe when appropriately prescribed.[151,155,160] Class I antiarrhythmic drugs are not recommended in the setting of structural heart disease and/or systolic ventricular dysfunction because of their negative inotropic effect[155,162,184,185] and the risk for proarrhythmia. Most Class I agents are metabolized in the liver, excreted in the urine, and have different protein binding profiles, all varying with age. Serial monitoring of QRS complex duration and PR interval is more helpful for proper dosage adjustments than determinations of serum drug concentration.[153]

Class IB agents (lidocaine and mexiletine) are mostly effective in myocardial ischaemia and rarely used in children.

Special attention should be given to QT interval duration before and after the introduction of Class IA drugs (quinidine, procainamide, and disopyramide) since syncope related to TdP may occur in up to 20% of children. Because of a marked anticholinergic effect (especially with disopyramide) and a prolongation of the cycle length during AFL, a paradoxical increase in the ventricular rate may occur with a 1 : 1 AV conduction, as a consequence to the antiarrhythmic drug therapy, resulting in a potential cardiovascular compromise.[186,187]

The effects of Class IC drugs (flecainide and propafenone), include conduction disorders with prolonged PR interval and

QRS complex duration, as well as a Brugada-type ECG pattern.[155,185,188,189] Thus serial monitoring of PR intervals and QRS complex duration may be used for dosage adjustment. Despite proarrhythmic fears concerning Class IC drugs in adults, this appears less relevant among children. *Propafenone* is an agent that combines sodium channel-blocking effects with beta-blocking capacity and a weak calcium antagonism. Side effects of oral propafenone analysed in a retrospective study of 772 paediatric patients with SVT or ventricular arrhythmias,[151] included significant electrophysiological effects and proarrhythmias in 1.9% of patients, including cardiac arrest or sudden death in 0.6%, of which 2/5 had WPW syndrome and 3/5 patients had structural heart disease. Structural heart disease was present in 32.3%. Overall, adverse cardiac events were more common in the presence (4.8%) than in the absence (1.5%) of structural heart disease.[151] Thus, propafenone is a relatively safe drug for the treatment of paediatric arrhythmias, but should not be used in patients with structural heart disease. Of note is that some children with ventricular preexcitation may developed incessant reciprocating tachycardia during initiation of flecainide.[190] Except for ventricular events, minor side effects may include blurred vision, irritability, and hyperactivity.[190]

Class II antiarrhythmic drugs

These agents indirectly affect the cardiac ionic currents primarily by inhibiting sympathetic activity through beta-adrenergic blockade, preventing refractoriness shortening and blocking adrenergic activation of calcium channels.[191] Some beta-blocking agents, such as pindolol and acebutolol, exhibit intrinsic sympathomimetic activity that may be useful in children who develop significant bradycardia with other beta-blockers. Many of the side effects are related to their cardiac mechanisms and include bradycardia, reduced exercise capacity, heart failure, hypotension, AV nodal conduction block, and bronchobstruction.[192] Propranolol and bisoprolol cross the blood–brain barrier and have been associated with mental changes in patients. Finally, esmolol, an ultrashort acting beta-blocking agent, may be administered intravenously and be useful for the acute control of arrhythmias in selected cases.

Class III antiarrhythmic drugs

Class III antiarrhythmic drugs are potassium channel blockers that prolong repolarization leading to increased QT interval with the potential risk for TdP. Generally they do not affect contractility.[193]

Oral sotalol, which also has beta-blocking properties, has been increasingly used for treatment of paediatric dysrhythmias.[194] Because it is primarily excreted unchanged in the urine, dose adjustment is needed in patients with renal insufficiency.[194] The beta-blocking effects of the drug are weak when compared with standard beta-blocking agents, such as propranolol.[194]

Although amiodarone is classified as a Class III agent, it has properties of all four Classes of Vaughan–Williams Classification. Amiodarone is stored in fat and other tissues (with a very long half life of more than 50 days), metabolized in the liver and excreted via the biliary and intestinal tracts. The QT interval prolongation achieved with amiodarone rarely leads to TdP.[195] Amiodarone treatment may lead to a slight increase in the QRS duration and may have more profound effect on the sinus node and the AV conduction. Intravenous use implies continuous cardiac monitoring, since cardiovascular collapse has been described.[196] Unfortunately, amiodarone is associated with a high incidence of severe extracardiac side effects, including thyroid, pulmonary, liver, skin, ocular, and neurologic toxicities, largely due to iodine in the amiodarone molecule.[197,198] Patient thyroid function indices, liver function tests, pulmonary, and neurologic status should be followed every 6 months in children and adolescents receiving amiodarone on long term. Systemic adverse effects of the drug, which are of considerable concern in long-term treatment in adults, seem to be less pronounced in children.[199,200] A similar drug as amiodarone but free of iodine has recently been developed, i.e. dronedarone.[201] More evidence regarding its use in infancy and childhood are warranted, as well as information about the use of other new Class III agents in children, such as azimilide, dofetilide, ibutilide, and vernakalant.

Class IV antiarrhythmic drugs

The non-dihydropyridine calcium channel blockers verapamil and diltiazem affect calcium-dependent slow action potentials in the sinus and AV nodes. These agents slow diastolic depolarization in both nodes, and therefore slow the pacemaker rate. They also prolong the refractory period of the AV node, slowing the ventricular rate during AF. Verapamil and diltiazem may cause peripheral vasodilatation, which may partially offset their sinus and AV nodal slowing effects. The use of intravenous verapamil is not recommended in children with compromised cardiac function or in those receiving long-term treatment with beta-blocking agents.[127] Calcium channel blocking agents are therefore considered contraindicated in newborns or infants less than 1 year.[202] Diltiazem mainly undergoes hepatic metabolism with a large first-pass effect that may differ from patient to patient. About 35 and 70% of an administered dose of diltiazem and verapamil is excreted as metabolites in the urine, respectively.

Other antiarrhythmic drugs

Adenosine. Rapid intravenous injection of adenosine has negative dromotropic and chronotropic effects mainly on the sinus and AV nodes, and its use requires continuous cardiac monitoring.[123,203] It is rapidly metabolized (half-life less than 10 s) by red blood cells and vascular endothelial cells and is therefore a short-acting drug. Bronchospasm has been reported occasionally following the use of adenosine in children and is contraindicated in children with history of asthma.[204]

Digitalis. Digitalis enhances vagal activity and thus slows sinus node automaticity and prolongs AV nodal conduction and refractoriness.[205] In its therapeutic dose, side effects are few and predictable but overdose is not uncommon and can be fatal, addressing the need to verify renal function. Compared with adults, digitalis may be less effective in young patients who present with higher sympathetic tone. Although digoxin is contraindicated in children with the WPW syndrome who are >1 year old, it is still not established whether there is a substantial risk for VF during oral digoxin therapy in infants <1 year old.[206]

Catheter ablation in the paediatric population

In the last decades radiofrequency catheter ablation (RFCA) is progressively used as curative therapy for tachyarrhythmias in children and patients with CHD. Even in young children, procedures can be performed with high success rates and low complication rates as shown by several retrospective and prospective paediatric multicentre studies. Three-dimensional (3D) mapping and non-fluoroscopic navigation techniques and enhanced catheter technology have further improved safety and efficacy even in CHD patients with complex arrhythmias. Furthermore, cryoablation is emerging in the paediatric population as safe alternative technique for arrhythmogenic substrates near the AV node. This chapter aims to review indications, results, and techniques of catheter ablation in this young population.

Radiofrequency catheter ablation for supraventricular tachycardia and ventricular tachycardia in structurally normal hearts

Radiofrequency catheter ablation of supraventricular tachycardias in children with a structurally normal heart

Accessory pathways including Wolff–Parkinson–White syndrome

Accessory AV pathway-mediated SVT are the most frequent form of symptomatic tachycardias in young patients with a structurally normal heart. In symptomatic children >15 kg of body weight, RFCA of accessory pathways is today a well established intervention. It is performed with high success in all age groups.[7,207] The success is higher for left-sided pathways than for right-sided and septal pathways which may in part be explained by impaired catheter stability and the lack of a venous structure like the coronary sinus to facilitate detailed mapping along the tricuspid valve annulus.[8]

The aim of the electrophysiological procedure is the localization of the accessory pathway at the tricuspid or mitral valve annulus and the permanent interruption by radiofrequency current delivered directly at the atrial or ventricular insertion of the pathway. In patients with overt pre-excitation location of the pathway may be assessed with the help of algorithms derived from the delta wave polarity on surface ECG.[208] Several parameters have been described as prerequisites for a successful ablation including recording of an accessory pathway potential and a qs-pattern of the local unipolar electrogram.[209] In some centres, the transseptal approach for mapping and ablation of the atrial insertion of left-sided pathways is used with the support of preshaped long sheaths in order to facilitate manipulation of the tip of the mapping and ablation catheter along the mitral valve annulus.[210] Radiofrequency catheter ablation of anteroseptal and midseptal accessory pathways carries a high risk of AV node–His bundle injury and thus should be reserved for patients with refractory or life-threatening SVT.[211] Posteroseptal accessory pathways can be challenging to identify precisely and to eliminate due to the large posteroseptal space.

Studies from individual centres have shown an overall high efficacy and safety of ablation therapy of accessory pathways in young patients. With growing experience, success rates >90% could be achieved with the need of a fluoroscopy time <40 min and an overall procedure time <240 min. The Paediatric Radiofrequency Ablation Registry reported an acute success rate for ablation of accessory pathways for all locations of 94.4%.[7,8] The use of the non-fluoroscopic navigation systems allows for significant reduction of fluoroscopy in this situation.[212]

In general, there is a risk of late SVT recurrence of 5 to 10% probably due to heating of the pathway with transient loss of conduction without complete destruction.[8]

Permanent junctional reciprocating tachycardia

The anatomical substrate of PJRT is an accessory pathway with solely retrograde conduction and, like the AV node, decremental conduction properties. The majority of these pathways are located in the posteroseptal space. Permanent junctional reciprocating tachycardia is often associated with tachycardia-induced cardiomyopathy which generally resolves within a few weeks after successful ablation. Results of RFCA are favourable with a success rate >90%.[213,214]

Atrioventricular nodal reentrant tachycardia

Atrioventricular nodal reentrant tachycardia is based on dual, anatomically separated AV nodal pathways. Modification/ablation of the slow pathway is the treatment of choice using a combined anatomical/electrophysiological approach.[215]

Results of RFCA in paediatric patients are favourable and comparable to those achieved in adult patients. Success rates varied between 95 and 99%, the risk of AV block was ~1–3%, and recurrence rates were in the range between 3 and 5%.[7,8]

In general, duration of the procedures and fluoroscopy times have been shorter and the number of radiofrequency applications have been lower than during ablation procedures of accessory pathways.[7]

Focal atrial tachycardia

Focal atrial tachycardia is often incessant and may, as in PJRT, result in a tachycardia-induced cardiomyopathy. The aim of endocardial mapping during FAT is to record early local atrial electrograms in relation to the onset of the tachycardia P-wave on surface ECG. Typical locations of the ectopic foci are along the crista terminalis and the entrance into the right atrial appendage as well as the orifices of the pulmonary veins in the left atrium. Success of ablation procedures for FAT is comparable with the other forms of SVT in children reaching ~90%.[7,146]

Radiofrequency catheter ablation of ventricular tachycardias in children with a structurally normal heart

Idiopathic VT occurs in children with a structurally normal heart and a normal QT-interval and may originate from the right and LV myocardium, respectively. Prognosis seems to be excellent as in a significant number of paediatric patients spontaneous cessation of the tachycardia has been noted. Degeneration of idiopathic VT into VF or sudden death essentially does not occur but certain patients may suffer from syncope or heart failure. Accordingly, therapy is only indicated in symptomatic patients.[216]

The electrophysiological substrate of VT from the LV is mainly a reentrant circuit involving the left posterior fascicle. A successful ablation may be performed in >85% of the patients. No serious complications have been reported so far and VT recurrence was rare. The non-contact mapping system has been demonstrated to be helpful to localize the tachycardia origin in selected patients and to improve success rate.[14,217]

Ventricular tachycardia originating from the RV outflow tract are mainly focal tachycardias. These tachycardias are often exercise induced. Mapping may be impaired due to suppressed ventricular ectopy during sedation. In symptomatic patients, EPS is successfully performed with the aim of localization and ablation of the focus in the RV outflow tract guided by prematurity and pacemapping.[14] It is of note that a considerable part of VT with left bundle branch block pattern and inferior axis may originate from the left aortic sinus cusp in adults and children.[218] As in LV VT, the use of the modern mapping systems has proven to be helpful to localize the focus.[217]

Complications related to radiofrequency current delivery in young patients

Radiofrequency catheter ablation can be performed safely and with high success in children. Data from the Paediatric Radiofrequency Ablation Registry and the study for Prospective Assessment after Paediatric Cardiac Ablation (PAPCA) revealed a complication rate ranging from 3 to 4.2%. Most common complications included 2° and/or 3° AV block, perforation and pericardial effusion, and thrombembolism. The risk of serious injury to cardiac valves due to RFA is very low.[7,8,219]

Death

Death has been reported in four patients after a total of 7600 ablation procedures for SVT which was related to respiratory arrest, intractable heart failure, thrombembolism, and coronary artery injury. Schaffer *et al.*[149] reported on seven fatal events in 4651 procedures focussing on a different population whereas no fatal complication was noted in the PAPCA study.[7,8,219]

Atrioventricular block

The most frequent major complication related to radiofrequency current delivery in young patients is inadvertent complete AV block requiring lifelong pacing. Risk of complete AV block has been reported ranging from 1 to 2%. Data from the PAPCA study revealed an AV block risk for AVNRT in 2.1% and for anteroseptal and midseptal pathways in 3.0%. Operator experience has a major impact in this issue. Particularly in substrates with a significant risk for AV block, cryoablation, although still associated with lower success than radiofrequency current, will perhaps become the energy source of choice in the future.[7,8,219,220]

Thromboembolic complications

An overall incidence of thromboembolic complications due to RFCA therapy of 0.6% in all age groups with a higher risk in left heart procedures (1.8 to 2%) has been reported. Heparin did not protect completely against thromboembolic events. Data from the Paediatric Radiofrequency Ablation Registry demonstrated an occurrence of thromboembolic complications in 0.18 to 0.37% of the procedures.[7,221]

Coronary artery damage

Possible damage to the coronary arteries after radiofrequency current delivery has been demonstrated in experimental setting and in children, thus special care should be taken when applications are performed near to a possible site with a coronary artery.[222,223]

Radiation exposure

Prolonged radiation exposure is of particular concern in children. Fortunately, a significant decrease of overall fluoroscopy time for all paediatric paroxysmal SVT procedures from 50.9 ± 39.9 min in 1990–1994 to 40.1 ± 35.1 min in 1995–1999 has been reported from the paediatric US registry. With the use of the modern non-fluoroscopic mapping and catheter navigation systems, a further significant reduction of radiation exposure can be achieved. At the present time, the risk of radiation exposure seems to be low considering the advantages of the procedure resulting in definite cure. This needs to be compared with an expected life-long antiarrhythmic medication including its incomplete safety and potential side effects.[7,212]

Special issues in infants and small children

Patient size <15 kg has been reported to be associated with a higher rate of major complications after RFA therapy when compared with older children. This is in contrast to a study revealing no differences concerning success and major complications between infants (<18 months) and non-infants. Up to now, data are still limited concerning the long-term consequences of radiofrequency current application at growing myocardium. Experience derived from animal studies should be taken into account when an ablation procedure in infants and small children is considered.[134,148,176,210,222,224]

Radiofrequency catheter ablation of supraventricular tachycardia and ventricular tachycardia in congenital heart disease

Preparation for catheter ablation

Prior to an invasive study, a preliminary estimation about mechanism and substrate of the tachyarrhythmia is mandatory using relevant clinical data, ECGs, description of the congenital defect, and all relevant surgical and catheter interventions. Patients with CHD often have a wide QRS complex during normal sinus rhythm, either due to congenital myocardial conduction delay (i.e. Ebstein's disease) or post-surgical myocardial scarring (i.e. tetralogy of Fallot). For these patients a comparison of width and axis of a QRS-complex in the 12-lead ECG during sinus rhythm and tachycardia is mandatory to distinguish between an 'individual normal QRS' and an 'altered QRS' during tachycardia. P-wave axis and morphology also might be influenced by disease, atrial surgery or by heterogeneous sites or even absence of the sinus node region (i.e. heterotaxy syndromes). Further ECG-interpretation of documented tachyarrhythmias can be performed according to general algorithms used in patients with normal cardiac anatomy. These include verification of numeric AV relationship

and regularity or irregularity of R–R intervals, initiation and termination of tachyarrhythmia, efficacy of vagal manoeuvres, and signs of pre-excitation during normal sinus rhythm.

Furthermore, careful evaluation of the actual haemodynamic and anatomical status of the heart is required. Information should be obtained from all available reports from surgical procedures, cardiac catheterizations, catheter interventions, angiographic or non-invasive imaging studies, like computed tomography (CT) or magnetic resonance imaging (MRI) scans as well as echocardiographic evaluations. Finally, it is useful to screen peripheral and central veins and arteries for potential occlusions.

The synopsis of the collected information generates the basis to assess chances, risks and limitations of an electrophysiological procedure in each individual patient. An important risk factor is the sometimes unpredictable course of the specific conduction system. In case of an accidental complete AV-block haemodynamic consequences of ventricular pacing cannot be forecasted, especially if systemic ventricular dysfunction pre-exists.[225] In complex malformed hearts after univentricular palliation or in case of shunt related cyanosis an epicardial pacemaker implantation is mandatory requiring another thoracotomy with a significant risk of surgical complications. Patients need to be frankly informed about the acute success rate, risks of the procedure and the chances of recurrences.

Catheter ablation of atrioventricular reentrant tachycardia in CHD

In the paediatric population ventricular pre-excitation is associated with CHD in 20–32%, whereas for AVNRT only up to 7% of children show any type of congenital cardiac anomaly.[141,143,226]

Ebstein's disease

Ventricular pre-excitation and AVRT occur in 20–30% of patients with Ebstein's malformation of the tricuspid valve apparatus. Accessory pathways are located around the tricuspid annulus, including the more rare Mahaim fibres. In Ebstein's malformation lack of the typical RBBB can be a sign of ventricular preexcitation causing pseudo-normalized ventricular activation. Radiofrequency catheter ablation in Ebstein's anomaly can be technically challenging due to the enlarged right atrium, the fragmented electrograms from the atrialized RV as well as the presence of multiple pathways in up to 50% of patients. Special long sheaths are often required for catheter stability and different techniques can be used to visualize the true electrical right AV junction, including fluoroscopic identification of the AV junctional fat pad, selective angiography of the right coronary artery, or intracoronary mapping of the right coronary artery. In addition, the use of 3D navigational tools or visualization with transoesophageal or intracardiac echocardiographic guidance may be helpful in selected complex cases. In Ebstein's malformation RFCA has an increased risk of a coronary injury because of the thin atrialized portion of the RV adjacent to the AV groove. The use of cryoenergy may lower this risk and also has advantages regarding catheter stability due to the cryoadherence of the ablation catheter tip.[134–143]

Congenitally corrected transposition of the great arteries

Accessory pathways are found in 2–5% of patients with congenitally corrected transposition of the great arteries (ccTGA), and are typically located along the left-sided AV valve annulus which is the anatomical tricuspid valve. If Ebstein's disease is associated additionally there is a tendency towards multiple accessory connections. During the procedure the coronary sinus serves as an important anatomical landmark for the orientation of the left-sided (tricuspid) AV valve. Since the origin and anatomy can be highly variable it is advisable to first visualize the coronary sinus system either by direct selective dye injections or coronary angiograms with recording of the late venous phase as well as by cardiac CT or MRI scan prior to the procedure. When using the transseptal route the course of the coronary sinus is again very helpful for the anatomical orientation and it is important to acknowledge that the fossa ovalis is located more posteriorly towards the posterior left atrial free wall carrying an increased risk for perforation. In ccTGA the position of the compact AV-node is typically located anteriorly at the junction of mitral annulus and the right atrium. A noteworthy exception is seen in cases of ccTGA combined with pulmonary hypoplasia or atresia because then the AV node is located in a 'normal' position. In the rare case of typical AVNRT catheter ablation should be restricted to patients with drug-refractory tachycardia because the risk of AV block is considerable and the individual location of the area of slow conduction of the AV node can only be speculated. In this situation cryoablation is likely to be the safest option.[227,228]

Inter-atrioventricular node reentrant tachycardia

A special form of AVRT can occur in patients with ccTGA, AV septal defect, and heterotaxy syndrome mediated by a twin specific conduction system which consists of an anterior AV node and His bundle at the right atrial–mitral annulus junction and a second posterior AV node and His bundle close to the remnant of the inferior interatrial septum. Diagnosis can be suspected if spontaneous alternations of a superior and inferior QRS-axis are notified during basic rhythm. During an EPS pacing from different atrial sites, programmed ventricular stimulation during AV tachycardia and careful mapping of the entire AV groove can be utilized to objectivate two distinct and separate areas with His bundle signals. The AV nodal system with the reduced conduction capacity typically served as the retrograde limb of the inter-AV nodal reentry tachycardia and was targeted in most cases.[228]

Results of catheter ablation of atrioventricular reentrant tachycardia and atrioventricular nodal reentry tachycardia in congenital heart disease patients

There are only few published reports on catheter ablation of AVRT and AVNRT in CHD patients. A large single-centre study of 83 patients, including 17 patients with single ventricles, reports an acute success rate of 80, 82% for left- and 70% for right-sided accessory pathways. There were two major complications, including one death. Most other data are available from patients with Ebstein's disease. In this group, overall acute success rates are slightly less as compared to patients with normal hearts and range between 76 and 83% in the largest

series. The reported rate of recurrences is up to 25% of patients with a tendency to be increased in smaller patients, in cases with multiple accessory connections or in a more complex anatomy. Furthermore, these factors are associated with a higher complication rate. Reported is one patient out of 59 in the registry for a procedure-related complete AV block with need for a permanent pacemaker and two children with Ebstein's disease with coronary artery occlusions. Ineffective ablation procedures are predominantly seen in small children with complex cardiac malformations or in cases with a close spacial relation of the accessory pathway to the AV node. Especially in these constellations the use of cryoablation may be of help to increase the safety margin of such intervention. Catheter ablation of accessory pathways can become very difficult and less successful following surgical interventions, such as the Fontan operation or AV valve replacement. Therefore, ablation of an accessory pathway should be considered prior to a surgical intervention even in asymptomatic patients.[229–233]

Catheter ablation of atrial tachycardia in congenital heart disease

Atrial tachycardia represents the predominant cause of SVT in CHD patients, in particular after having undergone surgical repair or palliation on the atrial level or with a transatrial route.

Heterogeneous surgical procedures and post-surgical electro-anatomical situations can create almost any kind of macro-reentrant circuits. This challenges the electrophysiologists particular understanding of the congenital anatomy, the variations of surgical and interventional procedures.

Atrial tachycardia in simple congenital heart disease after transatrial surgical approach

In simple congenital heart defects with normal AV connections and dimensions, normal position of the AV valves and regular venous return (i.e. atrial or ventricular septal defects) atrial macro-reentry tachycardia is expected to travel through the cavo tricuspid isthmus (CTI) or along the inferolateral free right atrial wall between the caudal end of the atriotomy scar and the orifice of the inferior caval vein in the vast majority of cases. Myocardial scars resulting from cannulation, atriotomy, and septal patches are typical electrical obstacles that may collaborate with natural barriers of conduction to perpetuate myocardial reentry circuits in the post-operative situation.[234]

Atrial tachycardia in complex congenital heart disease after extended surgery on the atrial level

In complex CHD a more complex surgery on atrial level can be expected. Therefore, close look into surgical reports is mandatory as well as detailed knowledge about the individual characteristics of the CHD and associated anomalies. Post-operative electro-anatomy in these hearts bears potential for more complex and multiple macro-reentrant circuits. Typical representatives are patients with complete transposition (d-transposition of great arteries) after atrial redirection surgery of the Senning or Mustard type as well as univentricular hearts after Fontan-type palliations.[126,235–237]

Atrial tachycardia after Mustard/Senning operations

The task list of an electrophysiological procedure in a patient after an atrial switch operation consists of programmed atrial and ventricular stimulation to inspect AV nodal and Hisian conduction properties, responses of the sinus node, exclusion of an accessory AV connection, and finally to induce atrial reentrant tachycardias. The course of any sustained atrial tachycardia should be reconstructed. With the help of entrainment stimulation the critical zones of each tachycardia can be identified within the 3D map. After successful termination of each tachycardia the completeness of the electrical dissection of the targeted channel needs to be verified by further reconstructions of the activation spread during stimulation at each of its poles.[71] If an atrial tachycardia has been documented in a Mustard or Senning patient but is not inducible during the EP procedure, a general strategy to lower the burden of these arrhythmias with their high clinical impact should be discussed by targeting the CTI because of its predominant involvement in atrial reentry loops. As in the majority of cases the most relevant portion of the CTI is expected to be assorted towards the pulmonary venous isthmus, a crucial part of the procedure is to approach such target site either via a retrograde, transaortic route or preferably with a direct trans-baffle access.[65,66,72,73]

Atrial tachycardia after Fontan operations

Typical for these patients are multiple atrial macro-reentrant circuits sometimes utilizing a myocardial area as a common link for figure of an 'eight reentry loop' or even more complex circuits. In addition, non-automatic foci and micro-reentry mechanisms are frequently seen causing problems in understanding the electrophysiological data particularly if different loops or mechanisms switch over to each other showing just subtle changes in cycle length or electric markers.

An impression of the individual anatomic situation can be provided by imaging of the right atrium (MRI or CT scans). Incorporation of such data into modern 3D navigational tools can aid the electrophysiological procedure as well as selective right atrial angiographies. The initial step of the electrophysiological procedure is focused on localization of the sinus node region and the His bundle signal aiming to minimize the risk of inadvertent damage to the normal conduction tissues.[238] During sinus or basic rhythm as well as while atrial pacing the gross activation spread over the enlarged atrial myocardium needs to be recognized with special attention to regions of electrical silence, areas of slowed conduction with fragmentation of local electrograms and potential myocardial channels bordered by acquired or natural barriers of electrical conduction.

Each atrial tachycardia needs to be reconstructed in order to identify its particular course within the right atrium. Entrainment pacing and mapping of mid-diastolic and fragmented local signals help to identify critical regions for the maintenance of the tachycardia in case of a macro-reentry. Typical sites for successful ablation are the inferior (caudal) pole of the atriotomy scar in close proximity to the inferior caval vein, the CTI, if an imperforate or surgically closed tricuspid valve annulus is present, the cranial connection of the right atrium towards the pulmonary trunk and the circumference of the dilated inferior vein cava.

If a spread of activation suggests a focal automaticity or micro-reentry as the underlying substrate for tachycardia mapping manoeuvres concentrate on identification of the site of earliest local activation in comparison to the onset of the P-wave in the surface ECG-recording.

In classical Fontan patients, ablation success is most frequently hindered by multiplicity of mechanisms and substrate sites as well as by limited lesion formation due to the thickened right atrial myocardium. This limitation often requires creativity in selecting alternative ablation sites and routes towards more reactive myocardial regions. The use of irrigated ablation as well as large-tip catheters with high-output radiofrequency generators are an option, but the application of higher amounts of energy has to be carried out in secure distances to all parts of the specific conduction system.[239,240]

Modern, tunnel type of Fontan operations

Due to less extended atrial surgery and the lower mean patient population age with less alterations on the myocardial level, we are thus facing less complex atrial tachycardias in these patients. However, the vast majority of atrial arrhythmias is generated within the atrial level of the functionally pulmonary venous site. Therefore, the leading problem for catheter ablation in these conditions is to find or create a safe access route to the pulmonary venous atrium and other intraatrial structures. Successful entries are via surgically preformed leaks or by trans-baffle puncture in cases of intracardiac tunnels. Furthermore, a hybrid procedure can be discussed if no transvenous or arterial access is possible. In highly specialized centres a trans-thoracic access is provided by the surgeon allowing the electrophysiologist to create a trans-myocardial direct entrance into the pulmonary venous atrium.[78]

Results of catheter ablation of atrial tachycardia in congenital heart disease patients

In recent years, the results of catheter ablation have improved with success rate between 80 and 90%. This is the result of both improved understanding of tachycardia mechanisms and reentry courses by using 3D mapping systems and enhanced lesion generation by new ablation catheter technology.[70] In patients after classical Fontan surgery success rates are significantly lower due to the multiplicity of substrates and current limitations regarding lesion formation in the extremely thickened right atrial myocardial walls. The recurrence rate ranges between 20 and 30% for the first 3 years after ablation, resulting from partial recreation of targeted tissue or creation of a new tachycardia substrate.[79] Usable data about complications are lacking in the literature. The list of potential complications includes accidental damage to sinus node or AV nodal tissue, myocardial perforations related to transseptal or trans-baffle punctures, occlusion or damage of peripheral veins or arteries, and thrombembolism from the pulmonary venous atrial level particularly after ablation. To lower the risk of the latter complication systemic anticoagulation is advisable for a period of 3–6 months for any 'left-sided' pulmonary venous lesions after radiofrequency current ablation.

Catheter ablation of ventricular tachycardia in congenital heart disease

Ventricular tachyarrhythmias typically occur after cardiac surgery with ventriculotomies or ventricular muscular resections. Most data are reported about patients after corrective surgery for tetralogy of Fallot followed by more anecdotal data from patients after surgery for double-outlet RV, ventricular septal defect (VSD) closures, and Rastelli procedures. Comparable with the findings on the atrial level in patients with any type of CHD the predominant mechanism for the VTs is a macro-reentry circuit rather than focal automaticity. Reentry loops are channelled around natural electrical obstacles in collaboration with closely related acquired post-surgical barriers.

With the use of programmed ventricular stimulation macro re-entrant tachycardias can often be induced and mapped utilizing the same algorithms as described for the atrial level if sustained and tolerated by the patient. In case of non-inducibility or haemodynamic intolerance, a pure substrate mapping can be performed with identification and topographical recognition of scars, natural electrical barriers, areas of slowed and inhomogeneous conduction, and apparently healthy myocardium. Together with the implementation of modern 3D electro-anatomical navigational systems the accumulated data may guide catheter ablation independently of the inducibility or tolerance of a VT. Reports about catheter ablation of VT in patients with congenital heart defects are rare and most anecdotal. The largest series summarize 11[14] and 14[179] consecutive patients with ablation attempts for VT predominantly in patients after surgery for tetralogy of Fallot. Acute success rates range from 50 to 100%, rates of recurrence from 9 to 40% in a mean follow-up period from 30.4 to 45.6 months.

Despite improved electrophysiological understanding with the use of 3D electroanatomical tools, improved ablation technology and facing the present limitations regarding efficacy and reliability of lesion generation in thickened and fibrotic ventricular myocardium, respectively, VT catheter ablation can only be seen as a standalone therapy in patients with haemodynamic well tolerated monomorphic VT with good systemic ventricular function,

In cases of rapid VT with clinically proven or indicative serious consequences the role of catheter ablation is focused to reduce the arrhythmia burden in patients who are already protected by an implantable cardioverter/defibrillator.

Three-dimensional mapping and non-fluoroscopic navigation

Non-fluoroscopic navigation

Progress in computer technology has helped to overcome at least some problems encountered during mapping and ablation of paediatric arrhythmias. One aspect of concern is still the considerable radiation exposure during ablation procedures for our small patients as well for the physicians and staff working in the electrophysiological laboratory. As the main purpose of radiation is the control of the positions of the electrode catheters, especially the mapping and ablation catheter, non-fluoroscopic 3D catheter navigation systems have been developed. The LocaLisa® system (Medtronic) has been upgraded to NavX® system (St Jude Medical). Both systems have been reported to increase efficacy and to reduce significantly fluoroscopy exposure and total procedure time for ablation of SVT in patients with normal cardiac anatomy. The NavX® system even allows integration of CT or MRI scans of the cardiac chambers.[175,212,241–243]

Three-dimensional mapping

The electroanatomical mapping system (CARTO®, Biosense Webster) and the non-contact mapping system (NavX®/Ensite 3000®, St Jude Medical) permit construction of a virtual 3D map of the selected chamber and direct association of electrical activity at a particular location of myocardium with the corresponding anatomical structures. The tip of the mapping and ablation catheter is displayed on the computer screen, allowing catheter manipulation without fluoroscopy and therefore significant reduction of radiation. Anatomical landmarks, areas of electrical isolation, double potentials, and scar tissue as well as ablation lesions can be labelled in the reconstructed anatomy. These systems, although based on completely different technologies, allow precise assessment of propagation of the cardiac activation wavefront during sinus rhythm and atrial and ventricular reentrant tachycardia and identification of the critical areas of the reentrant circuit, the prerequisite for targeting effective radiofrequency energy delivery.

Remote magnetic catheter navigation has recently been introduced into clinical practice. In combination with a non-fluoroscopic mapping system, the technology allows precise catheter navigation with a low radiation exposure for the patient and nearly no radiation exposure for the staff.[244,245]

Transcatheter cryoablation

The use of cryoenergy in the treatment of cardiac disease was firstly described by Harrison *et al.* in 1977 as a new method of producing AV block. After that, Klein *et al.* reported the use of cryotherapy in ablation of AV node to treat a recurrent SVT followed by implantation of a cardiac pacemaker.[246]

Cryoenergy produces a permanent lesion due to cell necrosis, caused by application of very low-temperature freezing the tip of special ablation catheters placed against the area of the heart causing arrhythmia. The benefit of this system over RFA is its ability to find the most suitable site for ablation through transitory electrical paralysis of the heart tissue in contact with the catheter tip, frozen to $-30^{\circ}C$ (*cryomapping*). If the site is suitable, the tissue causing the arrhythmia loses its excitability. A permanent lesion is created only subsequently, with further freezing to even lower temperatures (*cryoablation*). Both beneficial and any unwanted effects can thus be assessed in the cryomapping stage or during the initial part of cryoablation, and, if necessary, cryoenergy application can be stopped before any permanent damage is caused.

Cryoablation has been used in different substrates including accessory pathways, and in these preliminary experiences, an acute success rate ranging from 62 to 92% was reported.[247–249] Unfortunately, a high recurrence rate (7–29%) was also described.[250]

The first data about the use of cryoablation in *AVNRT* showed an acute success rate ranging from 83 to 96%. Unfortunately, also in this case, a high recurrence rate (7–29%) was also reported.[247–249,251,252]

In order to achieve acute and long-term success rate various type of ablation strategy has been proposed. These are: the use of prolonged cryoablation (until 8 min) followed by a bonus cryoapplication to consolidate the lesion,[253] the use a larger tip of the cryocatheter (6–8 mm), and linear lesion cryoablation to extent the lesion.[254–256] Using these types of ablation strategy, the results of cryoablation in children with AVNRT are getting comparable with RFCA.[8,149,176,215,257]

Cryoablation of FAT, often performed with the help of the non-fluoroscopic navigation system, has been reported with a success rate ranging between 0 and 100%.

Cryoablation is to be recommended as an effective and very safe alternative of RFCA in definitive resolution of JET because of the preservation of AV nodal function.[12,248–250]

Very few studies in the literature reported the efficacy and safety of transcatheter cryoablation in resolution of VT in children.[248] Therefore, in this particular situation, cryoablation cannot be yet considered an alternative to RFCA.

With respect to complications of transcatheter cryotherapy, no permanent AV block in the acute phase or subsequently—nor any other major complication—has been reported in any caseload.

Indications for catheter ablation in the paediatric population

Catheter ablation is increasingly used in children as an alternative to antiarrhythmic drug treatment. In experienced centres paediatric catheter ablations can be performed safely and effectively even in young children with outcomes comparable to adult studies. However, major complications, especially inadvertent AV block requiring lifelong pacemaker therapy and the potential risks of radiation exposure in a young individual should be carefully weighed against the natural history of the arrhythmia and the risks and side effects of medication. Guidelines for indications for catheter ablation and antiarrhythmic drug therapy for ventricular and SVTs in children are shown in *Table 4*. The indications for catheter ablation are based mainly on the results of the large retrospective and prospective multicenter paediatric RFCA studies from the USA, smaller single-centre experiences, and previously published guidelines for adults and children Although RFCA procedures can be performed safely in infants and young children most studies report a higher rate of severe complications in this age group. Furthermore, there are still limited data on the long-term effects of radiofrequency lesions on the immature myocardium. It is therefore recommended to consider RFCA in infants and young children only when all antiarrhythmic therapies have failed, including Class I and III antiarrhythmic drugs and drug combinations.[6,7,47,61,62,90,125,132,135–137,145,172,173]

These guidelines aim to be helpful as a practical outline for the management of arrhythmia in children with and without CHD, but it is emphasized that individual decision making remains of utmost importance especially in young children. It is acknowledged that antiarrhythmic drug therapy can be evenly effective and may be preferred in specific circumstances especially in the younger age group.

Ablation procedure in children

Equipment and personnel

Paediatric catheter ablation procedures should be performed in specialized centres by paediatric electrophysiologists or by adult electrophysiologists experienced in paediatric ablations in collaboration with paediatric cardiologists. Furthermore, catheter ablations in young children should be performed in institutions with

the facility to treat children including paediatric cardiac surgery and anaesthesia. The cardiac catheterization laboratory has to be operational for paediatric catheterizations as well as for EPSs and catheter ablation procedures, regarding materials, equipment, and nursing staff. Although most operators prefer biplane fluoroscopy this is not obligatory. Minimization of radiation exposure is of great importance in young patients. This can be achieved by the use of up to date fluoroscopy equipment, operators aiming at low fluoroscopy time in every single procedure. Nowadays, the use of 3D mapping and non-fluoroscopic navigation has become indispensible for more complex arrhythmias, including those in young patients with CHD.[148,175]

Sedation

The majority of paediatric patients undergoing catheter ablation will require some form of sedation to ensure the child's comfort. In older children procedures can be safely performed under conscious or deep sedation. In addition to local anaesthesia commonly used intravenous drugs for deep sedation are midazolam, ketamine, fentanyl, and propofol. If procedures are performed under deep sedation careful monitoring of heart rate, respiratory rate, blood pressure, and oxygen saturation is mandatory as well as close observation of the patient by one of the nursing staff. In younger patients under the age of 10 to 12 years, procedure are mostly performed under general anaesthesia. Although general anaesthesia for paediatric ablations obviously has some clear advantages for both patient and medical team, anaesthetic drugs can sometimes negatively influence inducibility of tachycardias, especially in those tachycardias with automatic mechanisms.

Catheter ablation

Catheter ablation in small children may require specific modifications to potentially lower the risk of vascular or cardiac complications. In infants and young children these modifications may include the use of 5F RFA catheters and single diagnostic EP catheters for both atria and ventricular pacing and recording. Reduced power and temperature setting and the use of short test lesions potentially reduce the risk for coronary and myocardial damage.[134,224] In recent years cryoablation has been increasingly used as therapy for paediatric SVT. In the majority of centres performing paediatric ablation, cryoablation has become the treatment of choice for AVNRT and AVRT caused by para-Hisian, anteroseptal and right midseptal accessory pathways in school-age children. Presently, cryoablation is still less suitable for infants due to the relatively large size and stiffness of the catheter. Radiofrequency catheter ablation is still the preferred method in all other cases.

Electrical devices in children

Antibradycardia pacing

Current evidence-based knowledge

During last decades pacemaker technology has developed rapidly. Pacing generator size has diminished and pacing leads have become progressively thinner. These developments have made application of cardiac pacing in children easier although no dedicated paediatric pacing systems exist.

The rate of lead-related problems in paediatric patients is high. In the largest paediatric study on pacing system survival a total of 1007 leads were implanted in 497 patients. Lead failure occurred in 155 leads (15%), and 115 patients (23%), with 28% of patients experiencing multiple failures. Predictors of lead failure included younger age at implant, CHD, and epicardial lead placement. Epicardial leads were more likely to fail due to fracture or exit block, while transvenous leads failed more due to insulation breaks or dislodgements.[258] The survival of modern steroid eluting epicardial leads is good and can be considered almost equivalent to that of endocardial pacing leads with lead survival at 2 and 5 years of 99 and 94% for atrial leads and 96 and 85% for ventricular leads, respectively, while the electrical performance of the leads remains stable.[259]

Endocardial lead placement in infants and small children is one of the most contentious issues in paediatric pacing. While many reports have shown the feasibility of this approach, it has not become generally accepted. In experienced hands it may, however, provide an acceptable alternative to epicardial pacemaker implantation, although many patients need lead or generator interventions before battery depletion, and long-term lead survival may be decreased compared to epicardial lead placement.[260,261]

The early complications of transvenous electrical device implantation include lead dislodgement, pocket haematoma or bleeding, pneumothorax, heart perforation, cardiac tamponade, device-related infection, and venous thrombosis. In children, the complication rate is probably increased compared with adult patients, although no data on implantation complications in the recent era are available.[262]

Epicardial pacemaker implantation carries the risks associated with thoracic surgery, including bleeding and post-pericardiotomy syndrome. Also, cardiac strangulation by the epicardial leads has been reported as a rare complication. Acute exit block and lead fracture continue to occur even with steroid eluting epicardial leads and may give rise to loss of pacing function.[263]

A legitimate concern for patency of the venous system of endocardially paced very small children remains, given the fact that the venous occlusion/stenosis rate may be as high as 25% in unselected pediatric transvenously paced patients >3 years of age. Although venous obstruction is almost always silent due to collateral formation, problems with vascular access can arise at the time of pacing system upgrade or revision.

Perhaps the most difficult complication of cardiac pacing in all age groups is pacing system infection. Its incidence, risk factors and aetiology are reviewed in a recent North American scientific statement, which also gives recommendations on infection prophylaxis and treatment of infected pacing systems.[264]

Pacemaker infections occur more frequently in paediatric population with infection rates between 1 and 8%. Patients with endocardial leads have composed two-thirds of reported cases, but no clear differences in rates of epicardial and transvenous pacemaker infections have been recognized in most of the studies. In the largest paediatric survey, 385 pacemaker procedures over a 20-year period were analysed. Thirty infections (7.8%) were identified. Of these infections, 19 (4.9%) were superficial and were treated successfully with antibiotics only, whereas 9 (2.3%) were

deep pocket infections that required removal of the generator and leads. Two (0.5%) infections were recognized based on isolated positive blood cultures. The only risk factors for infection in multivariate analysis were the presence of Down syndrome and reintervention for revision of the pacing system. Subpectoral placement of a device may have a reduced infection risk compared with a prepectoral location.[265]

A retrospective multicentre cohort study evaluated the incidence of paradoxical thromboembolic events in patients with intracardiac shunts at the time of device implantation. The study cohort consisted of 202 adult patients with CHD: 64 patients with endocardial and 56 with epicardial pacing systems, and 82 patients with right-to-left intracardiac shunts without a pacemaker. Over the follow-up period of the study (overall median follow-up of 11.8 years) there were 10 (15.6%) embolic events in the endocardial lead group, 5 (8.9%) events in the epicardial lead group, and 9 (10.8%) events in the group without a pacemaker. In multivariate analysis endocardial leads were an independent risk factor for these events.[266]

Long-term pacing studies in adults have revealed that pacing the apical RV can have deleterious effects on LV function.[267] This has also been shown in smaller studies of young patients with complete AV-block. In a study of 24 patients RV apical pacing led to LV dysfunction. Both LV systolic and diastolic function indexes were impaired, when compared with controls. Paced QRS duration had a significant influence on LV contraction.[268] Another group studied 23 patients with congenital complete AV block at least 5 years (mean 9.7 years) after DDD pacemaker implantation. When compared with healthy control individuals, the patients had significantly higher values of pathologic LV remodelling, dilatation, and hypertrophy together with intraventricular dyssynchrony and decreased exercise capacity.[269] In a cohort study of 63 patients with complete congenital AV block and normal ventricular function at the time of pacemaker implantation, 4 patients (6%) developed LV dysfunction after an average of 15.1 years of chronic RV pacing. The cumulative survival free of LV dysfunction at 20 years was 92%. Right ventricular apical pacing and prolonged QRS duration predicted decreased LV systolic function. Pacing the RV free wall increases the risk of developing LV dysfunction, with an odds ratio of 14.3 compared with other RV pacing sites. Also, histological changes have been reported in endomyocardial biopsies after median 5.5 years (3–12 years) of RV apical pacing for congenital complete AV block.[270–272]

The importance of avoiding these long-term deleterious effects is self-evident in paediatric patients in need of many decades of pacing. The potential of RV pacing to cause irreversible damage to cardiac function has led to search of alternative sites of ventricular stimulation that would better preserve LV function. The proposed sites have included alternative RV sites (RV outflow tract, RV septal pacing and His bundle/para-His pacing), as well as the LV. The various studies are summarized in a recent review.[13] Although the study results on the effects of RV septal or RVOT pacing are conflicting, it seems that the RV mid-septal area may provide the shortest QRS duration and may better maintain LV systolic function. Further studies with common nomenclature for different RV pacing sites are needed.[267]

Recently, great interest has been focused on LV as an alternative pacing site. Based on animal studies and acute post-operative experiments in children it seems that LV apical pacing provides better LV haemodynamics compared to RV pacing sites.[273,274] In a study of 32 children with complete non-surgical or surgical AV block, LV ejection fraction, septal to posterior wall motion delay, and septal to lateral mechanical delay were better preserved in patients with LV apical pacing compared with both RV apical and RV free wall pacing.[275] Another study investigating 25 paediatric patients with normal cardiac anatomy and single-site epicardial RV apical pacing or LV free wall pacing for complete heart block showed better LV performance in those paced in the LV.[276]

Automatic threshold measurement and pacing output adjustment algorithms are a standard feature in modern pacemakers. They have been designed to provide increased safety in pacemaker-dependent patients and prolong battery life by allowing lower pacing output safety margin. These algorithms work well also in children, both in ventricular and atrial leads.[277–279]

Indications for cardiac pacing

The most common indications for pacing in paediatric patients are complete heart block, either congenital or post-operative, and sinus node dysfunction after surgery for CHD. The indications

Table 5 The consensus panel recommendations on preferred pacemaker implantation access, pacing modes, and ventricular lead placement in pediatric patients with AV block, systemic LV, and absence of intracardiac shunts

Patient size (kg)	Access	Pacing mode	Ventricular lead placement
<10	Epicardial Endocardial—in specific situations (failed epicardial, centre preference)	VVIR DDD(R)—in case of a specific haemodynamic indication	LV apex RV septum
10–20	Epicardial Endocardial	VVIR DDD(R) – in case of a specific haemodynamic indication	LV apex RV septum
>20	Endocardial Epicardial—in specific situations (e.g. concomitant with other cardiac surgery)	DDD(R) VVIR	RV septum LV apex or free wall—based on surgical feasibility

AV, atrioventricular; LV, left ventricle; RV, right ventricle

have been addressed in both North American device therapy guidelines and European pacing and cardiac resynchronization therapy guidelines and will be summarized below.[280,281] See also *Table 5*.

Disorders of atrioventricular conduction
Complete congenital atrioventricular block
Class I

(1) Complete congenital atrioventricular block in a newborn or an infant with a ventricular rate <55 b.p.m. or with CHD and a ventricular rate <70 b.p.m. (C)
(2) Complete congenital atrioventricular block with a wide complex escape rhythm, complex ventricular ectopy, or ventricular dysfunction. (B)
(3) Complete congenital atrioventricular block beyond first year of life with an average heart rate <50 bpm, abrupt pauses in ventricular rate 2–3× basic cycle length, or associated with symptoms of chronotropic incompetence. (B)

Class II

(1) Complete congenital atrioventricular block in asymptomatic children and adolescents with an acceptable rate, a narrow QRS complex and normal ventricular function. (C)

Other non-surgical atrioventricular block
Class I

(1) Advanced second- or third-degree AV block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output. (C)

Post-operative atrioventricular block
Class I

1. Post-operative advanced second- or third-degree AV block not expected to resolve or persisting at least 7 days after cardiac surgery. (B)

Class IIb

1. Transient post-operative third-degree AV block with residual bifascicular block. (C)

Sinus node dysfunction
Class I

(1) Sinus node dysfunction with correlation of symptoms during age-inappropriate bradycardia. (B)

Class IIa

1. Asymptomatic sinus bradycardia in children and CHD with resting rate <40 b.p.m. or pauses in ventricular rate >3 s. (C)
2. Sinus node dysfunction with intra-atrial reentrant tachycardia with the need for antiarrhythmics when other therapeutic options, such as catheter ablation, are not possible. (C)
3. Congenital heart disease and impaired haemodynamics due to sinus bradycardia or loss of AV synchrony. (C)

Class IIb

(1) Asymptomatic sinus bradycardia in the adolescent with CHD with resting rate <40 bpm or pauses in ventricular rate >3 s. (C)

Other indications. Neuromuscular disease associated with AV conduction disease [e.g. myotonic muscular dystrophy, Kearns–Sayre syndrome, Erb dystrophy (limb girdle), peroneal muscular atrophy etc].
Class I

(1) Third-degree or advanced second-degree AV block with or without symptoms. (B)

Class IIb

(1) Any degree of AV block, because the progression of the conduction disease may be unpredictable. (B)

Neurocardiogenic syncope
Class IIb

(1) Significantly symptomatic patients in who prolonged asystole can be demonstrated spontaneously or at tilt-table testing. (C)

System choice
It seems that in small children with complete AV block the advantages of AV synchrony compared with asynchronous ventricular pacing remain small or non-existent. Therefore, it is reasonable to implant them with a single-lead VVIR pacemaker and to upgrade to a dual chamber device later, at the time of the first or second generator exchange.[282,283] In a child with CHD and/or systemic ventricular dysfunction dual chamber pacing should be considered as the initial pacing mode. The use of VDD pacing is possible also in growing individuals with complete AV block, and would theoretically make possible atrial synchronous ventricular pacing with a single pass lead.[284] Its appropriate use can, however, be problematic if atrial pacing becomes necessary and it is rarely used in children now. In patients with sinus node dysfunction and intact or adequate AV node conduction unnecessary ventricular pacing should be avoided and atrial pacing used to maintain heart rate. Alternatively, the use of pacing modes and algorithms that promote intrinsic AV conduction will decrease the amount of ventricular pacing in patients with dual chamber systems.

One of the most important technical challenges in paediatric pacing is the need for life-long pacing. Repeated generator changes and increased frequency of lead problems highlight the need to preserve the patency of the venous system. In neonates, infants, and small children, most centres use epicardial lead implantation.[285] The choice between epicardial and endocardial implantation technique in these patients depends also on centre and operator experience, as good long-term results have been obtained with endocardial lead placement. In bigger children and teenagers, endocardial lead placement is the standard procedure. The presence of intracardiac shunts may increase the risk of systemic emboli after endocardial pacemaker implantation. In such cases the shunts should be closed before or at the time of the pacemaker implantation, if feasible. Otherwise, epicardial approach should be contemplated. Epicardial pacing is also needed in patients with CHD with no venous access to the heart, especially in patients with univentricular hearts.

It is well established that long-term RV apical pacing is a risk factor for LV dysfunction. Therefore, in children and young individuals in need for life-long pacing alternative pacing sites should be considered—even in the absence of long-term studies confirming a better outcome at these sites. In patients in whom epicardial pacing system implantation is planned, the panel recommends LV apical lead placement to preserve LV systolic function. When endocardial lead placement is considered, the preferred implantation site is the interventricular septum.

Technical implantation issues

Epicardial pacemaker lead implantation can occur via a subxiphoid incision, partial sternotomy or left anterolateral thoracotomy, or at the time of other cardiac surgery. The leads are tunnelled from the thoracic cavity into an abdominal or prepectoral subcutaneous pocket. Excessive redundant intrapericardial loop may lead to cardiac strangulation.

The preferred route for venous access at implantation of endocardial pacing leads is the axillary vein. This approach avoids traversing the costoclavicular membrane as happens with the direct subclavian puncture, and thus diminishes the risk for lead crushing. An appropriate loop of lead is left in the right atrium to allow for the growth of the child. The loop should not be too excessive to avoid the adhering of the lead to the tricuspid valve or the atrial wall, or prolapse of the redundant loop into the RV. The leads are fixed at the site of vessel entry onto a suture sleeve to protect the lead. Although there are no systematic studies, absorbable sutures may prevent excessive fixation that could cause fracture or insulation defect during growth and also allow easier mobilization during extraction than non-absorbable sutures.

Pacemaker pocket is usually dissected prepectorally between the subcutaneous tissue and pectoral fascial plane. In small patients and in patients with very thin subcutaneous tissue, creation of a subpectoral pocket yields better cosmetic result and helps to avoid skin erosion issues and, possibly, infection problems.

In children and young patients active fixation pacing leads should be used. These leads provide reliable sensing and pacing characteristics, allow for selecting the desired pacing site and are easier to extract.

Extraction of old pacing leads is a demanding procedure that carries a risk of serious complications. These procedures should be restricted to hospitals with immediately available cardiothoracic surgical back-up. In the adult population the leads can be extracted with up to 95% success. Significant complications occur in 1–2%, and mortality rate is 0.1–0.4%. The difficulty and risk profile of lead extraction is proportional to the duration of implantation. Some leads can be removed with simple traction, but with increasing implant duration special extraction equipment is usually needed, including mechanical dissection sheaths with locking stylets, and special sheaths using radiofrequency or laser energy to dissect the endovascular fibrous tissue adhesions. The use of power sheaths facilitates the procedure but does not diminish the complication risks. All aspects of lead extraction procedures including the indications, facilities, training, and patient management are reviewed in a previous consensus document.[286]

The most common and compelling indication for lead extraction in general pacemaker population is infection of the pacing system, whereas in paediatric and adolescent patients the most common indication is lead fracture or malfunction.[287–289] In young patients without infection undergoing revision of endocardial pacing leads the need and possibilities for lead extraction vs. abandonment should be considered individually taking into account the complication risks. The acute risks of the procedure should be assessed against the decreased success rate and increased procedural risks if the lead is abandoned and a later extraction is needed. Also, removal of leads when there are multiple leads implanted is more difficult and more dangerous. The removal of redundant non-functioning leads in young patients in need of life-long pacing is a reasonable goal to maintain patency of the endovascular space when the institutional and operator experience is extensive enough to minimize complications.

A recent single-centre cohort study with paediatric and CHD patients described lead extraction procedures involving 144 patients and 203 leads. Of these patients, 86 (60%) had structural heart disease. Successful simple extraction, requiring the use of only a non-locking stylet, was achieved in 59 (29%) leads. Of the remaining leads, 35 were abandoned and 109 underwent complex extraction techniques. Successful extraction was achieved in 80% of all leads and in 94% of leads undergoing a complex extraction. Older lead age, ventricular lead position and polyurethane insulation were associated with a decreased likelihood of simple extraction. There were four major and four minor procedural complications in eight patients. No procedure-related deaths occurred. Lead age was the only recognized factor associated with procedural complications.[290]

Implantable cardioverter defibrillator

Large studies of ICDs in adults have shown clinical effectiveness and ICDs are now implanted in children and CHD patients.[291–294] The lower incidence of sudden death in the paediatric population—estimated to be ~1.3–8.5 per 100 000 patient-years—has limited the number of device implants.[295] Nevertheless, the experience with these devices is increasing and when appropriately used is of life-saving benefit. Guidelines for device implantation from the adult population have been extrapolated to children and CHD patients.[280,296] The differences in patient size and cardiac anatomy of this population, however, lead to unique technical implant challenges, more frequent complications and the need for modifications to program settings.

Current evidence-based knowledge

There are no randomized trials of ICD implantation in children and CHD patients similar to those performed in large adult studies with hundreds of patients with sustained follow-up.[291–294] It is unlikely that with current systems these will be undertaken. The largest observational study to date in children and CHD patients is of 443 patients with ICDs implanted at four North American centres over a 12-year period.[297] During a similar time frame, the total number of ICDs implanted in children under 18 years in the five paediatric cardiology centres in the whole of Holland numbered 45 over an 11-year period.[298]

Efficacy in primary and secondary prevention

Implantation of an ICD after a cardiac arrest (secondary prevention) produced a survival benefit in adult survivors of cardiac

arrest when randomized to ICD or no ICD.[291] Small paediatric observational studies have also shown benefit.[299–301] Large randomized primary prevention trials in adults with heart failure also showed a survival benefit from ICD implantation.[292–294] Guidelines for primary prevention in children and CHD patients (see below) are currently in a rudimentary state due to the absence of any randomized trials or large observational series in well-defined subpopulations. Published studies use different definitions of 'paediatric' with an age ranging from 18 to 21 years, may include older adults with CHD and rarely concentrate on a specific subpopulation (due to small numbers). During follow-up, appropriate shocks have been reported in as many as 40–67% when the device has been implanted for secondary prevention. In mixed series and when used as primary prophylaxis, the incidence of an appropriate shock ranges from 10 to 26%.[159,297–304]

Complications of implantation

The complications associated with ICD implantation are similar to those of pacemaker implantation. The larger generator size increases the risk of local complications (including infection) with subcutaneous placement and submuscular implantation is therefore preferred where it is also cosmetically more acceptable and more protected against trauma. Modern lead sizes are only marginally larger than pacemaker leads and access and placement is similar as is long-term stability. Epicardial placement of patches is associated with a post-pericardiotomy syndrome and migration of the patches during growth. A specific early complication is electromechanical dissociation requiring cardiopulmonary resuscitation during induction of VF for threshold testing in the setting of poor ventricular function.[305]

Lead complications and system survival

Children are more active than adults and this may explain the increased incidence of lead malfunction. Lead fractures and insulation breaks are associated with inappropriate shocks and failure of the device to be effective during an episode of VF. The incidence in adults is 20% at 10 years whereas in children it may approach 7–30% by 2 years in some series.[297,305–308] Late rises in defibrillation thresholds have also been reported to be more frequent in children requiring system revision when reprogramming a higher output is ineffective.[306,307] This is a particular problem associated with coils implanted subcutaneously or in the pericardium; system survival for transvenous systems was 75% at 40 months but fell to 50% for non-transvenous leads.[304]

Inappropriate therapy. In almost all series reported, the incidence of inappropriate shocks is only slightly lower than the incidence of appropriate shocks ranging from 17 to 23% for primary prevention and up to 30% for secondary prevention.[297,298,300–303] Causes of inappropriate shocks are sinus tachycardia, SVAs, T-wave oversensing and lead malfunction.

The higher heart rate achieved by children when exercising is a common cause for delivery of an inappropriate shock. Avoidance of this is by documenting the upper heart rate achieved on exercise – ideally prior to device implantation, the use of beta-blockers to reduce the upper heart rate and programming a high enough rates to avoid triggering a shock during sinus tachycardia. Other reasons for an inappropriate shock include atrial tachycardias and AF which may be preventable using atrial therapies in dual chamber devices or amenable to ablation. Despite use of dual chamber devices to try to discriminate SVAs from VF this remains a problem. In one study of 168 patients, the rate of inappropriate shocks was only 13% in the patients with a single chamber device compared with 24% in those with a dual chamber device.[302] It is not clear whether this was by chance or due to paying more attention to beta-blockade and rate programming in single-chamber devices while relying on discriminating algorithms in the dual chamber devices. T-wave oversensing requires a reduction in ventricular sensing while avoiding undersensing of VF. It is a particular concern with HCM and LV non-compaction. The increased activity levels in this population produce more frequent lead malfunction which can cause oversensing and induction of a shock. It usually requires lead replacement—see following section.

Arrhythmia storm. An infrequent but important complication is the development of an arrhythmia storm. In this situation, an appropriate shock causes pain and sympathetic stimulation leading to further ventricular arrhythmia followed by another shock. This sequence can be repeated continuously until either spontaneous cessation, medical attention is obtained and the device is inactivated while antiarrhythmic therapy is delivered or electromechanical dissociation and death.[297,298] It is particularly of concern in patients with the LQTS and CPVT where brief ventricular arrhythmias that might not have been clinically noticed trigger an initial discharge followed by this potentially fatal sequence. Prolonging the detection time is a means to delay the onset of a shock, which may then be avoided in self-limiting arrhythmias.

Indications according to available guidelines

Indications for ICD implantation for the paediatric and CHD patient group have been addressed in the North American device therapy and North American and European ventricular arrhythmia guidelines.[280,296] The American guidelines state that the indications for implantation are broadly similar to those used in adults.

Class I indications:

- Secondary prophylaxis after cardiac arrest where no reversible cause has been found including patients with a structurally normal heart, CHD, cardiomyopathies, and channelopathies. (B)
- Symptomatic sustained VT in patients with CHD. Full haemodynamic and anatomical assessment should be undertaken so that surgery or catheter intervention can be performed if appropriate. In some RFA my also avoid the need for an ICD implant. (C)
- Symptomatic sustained VT in patients with cardiomyopathies and significant LV dysfunction. (A)

Class II indications:

- Congenital heart disease patients with recurrent syncope and ventricular dysfunction or inducible ventricular arrhythmias. (B)
- Recurrent syncope in LQTS and CPVT patients on full doses of beta-blockers. (B/C)
- Long QT syndrome and medication non-compliance, intolerance to medication. or a family history of sudden death (see comment below). (C)
- HCM with 1 or more major risk factors who are receiving chronic optimal medical therapy [family history of sudden

death; ≥1 episode of unexplained, recent syncope; massive LV hypertrophy (thickness ≥30 mm) in adolescents and older; hypotensive or attenuated blood pressure response to exercise, non-sustained VT on serial ambulatory 24-h Holter ECGs]. (C)
- Arrhythmogenic right ventricular cardiomyopathy with extensive disease, including those with LV involvement, family history of sudden death, or undiagnosed syncope when VT or VF has not been excluded as the cause of syncope. (C)

In the congenital LQTS ICD implantation has been recommended for a family history of sudden death. A more recent report from the International Long QT Registry has shown that family history of sudden death is a poor predictor of events.[309] Patients with long QT3 have more prolonged QT intervals and in some a lower response to beta-blockers. In these ICDs are often implanted on a prophylactic basis.

Strong arguments have been marshalled for using the adult study-derived indication of an ejection fraction below 30–35% as an indication for ICD implantation in CHD patients.[310] Equally strong arguments have been made that these criteria should not be applied rigidly to this population.[311] Given the differences in the underlying conditions and the better prognosis of heart failure in younger patients, an individualized approach is recommended. A combination of poor ventricular function and arrhythmia burden and especially in combination with symptoms, together with the patient's attitude may all be used to weigh up the course of action in any individual.

Technical implantation issues*****

In adult practice, modern ICDs are easily implanted in the subcutaneous or submuscular position in the chest using local anaesthetic and sedation. Commonly, they will be combined with dual- or triple-chamber function with all the leads implanted transvenously. In children above 20–25 kg, small ICDs can also be implanted in a similar fashion under general anaesthesia. Single-chamber devices in smaller children are often used to prevent venous obstruction. A loop of ICD lead in the right atrium allows somatic growth of the child without displacement of the lead or the need for lead advancement. When choosing an ICD lead, there is a balance between the lower defibrillation thresholds obtained with dual coil leads and the need to avoid the second coil lying in the subclavian vein or pocket in smaller children where it may become adherent with a risk of lead disruption during growth. Transvenous placement into hearts with right to left shunts or into the systemic ventricle is possible but has to be accompanied with long-term anticoagulation.

In children between 10 and 20kg, abdominal positioning of the device is usually required due to its size with transvenous leads tunnelled from the subclavian vein to the pocket. In children less than 10 kg, placement of the generator is usually possible in the abdomen although epicardial placement of the pacing leads and defibrillator patches or coils is required.

In patients with CHD who do not have access to cardiac chambers or to avoid implantation into a systemic chamber or in any size patient where vascular access is no longer available or where a multi lead system [e.g. when additional cardiac resynchronization therapy (CRT) is required] will occlude the subclavian vein, epicardial systems are required.

In order to avoid the use of epicardial defibrillator patches, with their longevity problems, novel placement of defibrillator coils have been used with encouraging results. Subcutaneous, pericardial and pleural placement of defibrillator coils have all been used with good effect although the longevity of these systems is less than with transvenous coils.[304] On occasion a hybrid approach with one or more leads placed via a transvenous route and one or more via an epicardial or subcutaneous approach is necessary. This requires co-operation between implanters and surgeons.

A 'leadless' ICD is now available that has the generator placed subcutaneously in the left anterior chest together with a parasternal subcutaneous lead that allows both defibrillation and back up post-shock pacing. The current system is suitable for adults and children over 40Kg only.[312,313] It needs to be combined with an additional conventional pacemaker if constant pacing is required. With continued miniaturization of the device, together with the ability to implant without intravascular or intrathoracic leads, the prospect of liberalizing the indications for ICD implantation may allow randomized studies to be possible in the not too distant future.

Implantable cardioverter defibrillator lead extraction is similar to that of pacing leads.

Psychological and lifestyle issues

In children who have an ICD after an out of hospital cardiac arrest, the psychological issues include adjustment to any cerebral dysfunction from the arrest itself, the life style changes of the newly imposed medical condition, the need for medication and the presence of the ICD itself and the possibility of receiving a shock. Many children appear to be little affected and counselling is not required in all patients.[314] Counselling should be offered at the time of the arrest and remain available during follow up. When an ICD is used for primary prophylaxis, the topic will usually have been discussed on several occasions and the need for counselling is likely to be less but should always be considered. Medicine non-compliance in adolescents is also an area where counselling should be considered. The occurrence of an electrical storm, however, is often followed by extreme psychological stress and fear of further shocks and counselling will usually be needed.

Implantation of an ICD in patients with the LQTS to enable competitive sport may be requested by patients keen to continue these activities. It remains a contentious issue with no guidelines recommending this approach.[315] Patients with ICDs, however, are commonly allowed to partake in non-competitive, non-contact sports.[316–318] The type of sport will depend on the underlying cardiac status as well as the presence of the ICD. Not all 'non-contact' sport is safe; however, golf carries a significant risk to damaging the lead due to the bidirectional swinging motion, as well as weight lifting.

Summary of implantable cardioverter defibrillators in paediatrics and congenital heart disease

Implantable cardioverter defibrillators are of benefit to survivors of cardiac arrest and can be recommended in the absence of a clearly reversible cause.

Implantable cardioverter defibrillator implantation is technically more challenging, requiring use of both the transvenous and epicardial route. Size of the patient, the underlying anatomy, venous patency, and the experience in each unit will dictate the approach in any individual patient. Hybrid implants and novel coil placement also may be required.

Complications from ICD implantation are more frequent due to the increased heart rates and activity of the population so that particular attention to programming and concomitant medication is required as well as surveillance of the system.

Primary implantation indications from the adult population cannot be directly extrapolated due to the heterogeneity of the paediatric and CHD population but can influence the decision when applied on an individual basis.

Entirely subcutaneous systems without the need for thoracotomy or transvenous access may lower the threshold for ICD implantation in this population when the devices become small enough. These devices may prove to be an opportunity for trials that will influence clinical decision making regarding primary implantation.

Cardiac resynchronization therapy

Over the last decade CRT has evolved to a powerful treatment option of systolic heart failure associated with LV mechanical dyssynchrony. According to studies in adult patients with idiopathic and ischaemic cardiomyopathy CRT leads to restoration of LV contraction efficiency, reverse structural and cellular remodelling, functional improvement and decrease in heart failure-associated morbidity and mortality.[319–322] Despite a much more heterogeneous structural and functional substrate, limited evidence has so far shown similar effects of CRT in paediatric and CHD.[323–325]

Available paediatric efficacy data

Efficacy of CRT may obviously vary with the underlying structural and functional substrate like anatomy of the systemic ventricle (left, right, or single), presence and degree of structural systemic AV valve regurgitation, presence of primary myocardial disease, or scaring and type of electrical conduction delay. Two multicentre surveys[323,324] and one larger retrospective single-centre study[325] have mapped response to CRT in a total of 272 paediatric and CHD patients and the results are summarized as follows:

- Conventional single-site ventricular pacing was the most prevalent (63%) cause of systemic ventricular dyssynchrony.
- The majority of the patients reported (58%) were categorized as New York Heart Association (NYHA) Class II reflecting a more liberal and pro-active approach to CRT as compared with adult guidelines at the time of the recruitment period.
- An increase of the systemic ventricular ejection fraction by 6–14% has been reported after CRT.
- Presence of a systemic LV was an independent predictor of better improvement of systolic ventricular function.[324]
- Best response to CRT with almost complete reverse remodelling has been observed in patients with a systemic LV who were upgraded to CRT from conventional RV pacing.[326]
- Cardiac resynchronization therapy was effective in combination with other corrective or palliative cardiac surgery, in particular when aimed at decrease in systemic AV valve function regurgitation.[324,327]
- The proportion of CRT-D systems was low (18–25%).
- Almost 40% of the heart transplant candidates referred to CRT could be de-listed suggesting that young patients awaiting heart transplant should be specifically screened for the presence of mechanical dyssynchrony as a potential substrate for improvement by resynchronization.[326]
- The proportion of non-responders to CRT (14%) was lower than in the prospective adult trials reflecting; however, rather the retrospective nature of the paediatric studies and soft response definition than higher efficacy.
- The presence of primary DCM and a high NYHA class seemed to predict non-response to CRT.[324]

Indications for cardiac resynchronization therapy in paediatric and congenital heart disease

Indications for CRT have so far not been specifically stated for the paediatric and CHD patient group in the European or North American heart failure and device therapy guidelines. Thus current adult CRT indications for patients with idiopathic and ischaemic cardiomyopathy will be used and adapted for this purpose. These state:[281]

Cardiac resynchronization therapy by biventricular pacemaker (CRT-P) or biventricular pacemaker combined with an ICD (CRT-D) is indicated for the following patients who remain symptomatic in NYHA Classes III–IV despite optimal medical therapy, with an LV ejection fraction $\leq$35%, LV dilatation, and a wide QRS complex ($\geq$120 ms) with the following options:

- Implantation of a CRT-P device to reduce morbidity and mortality. Class I: level of evidence A.
- CRT-D is an acceptable option for patients who have expectancy of survival with a good functional status for more than 1 year; Class I: level of evidence B.
- Primary implantation of a biventricular pacemaker or upgrade of conventional pacemaker in heart failure patients with concomitant indication for permanent pacing. Class IIa: level of evidence C.
- Implantation of a CRT-D system in heart failure patients with primary preventive indication for an implantable cardioverter defibrillator. Class I: level of evidence B.
- Implantation of a biventricular pacemaker in heart failure patients with permanent AF and indication for AV junctional ablation. Class IIa: level of evidence C.

Recently, CRT preferentially by CRT-D has also been recommended to reduce morbidity or to prevent disease progression in patients with NYHA function Class II, LVEF $\leq$35%, QRS $\geq$150 ms and sinus rhythm being on optimal medical therapy (Class I, level of evidence A).[321,322,328] These guidelines do not completely match the current paediatric/CHD practice of CRT indication. CRT-D systems within a primary preventive ICD indication have by far not been used as frequently as in the adult population. Data from the paediatric transplant registry showed a very low incidence of SCD in children awaiting heart transplantation indirectly arguing against the automatic use of LV ejection fraction $\leq$35% as a criterion for primary preventive ICD

implantation in young patients with DCM.[329] Presence of mechanical dyssynchrony is not required for CRT indication in adult idiopathic and ischaemic DCM population. The only prospective trial available so far could not show sufficient reproducibility and predictive power of echocardiography to efficiently contribute to CRT indication.[330] However, in CHD patients with a diversity of structural and functional CRT substrates (e.g. presence of systemic RV, single ventricle, and RBBB) QRS duration may be an even worse predictor of systemic ventricular dyssynchrony than in patients with a structurally normal heart. Thus, individual evaluation of mechanical dyssynchrony in context with other findings may have value in this specific population.

The consensus statement panel suggests the following amendments of the current adult CRT indication guidelines for patients with paediatric and CHD:

- The need for primary preventive defibrillation capability of a planned CRT device should be assessed individually and should not be based just on the value of systemic ventricular ejection fraction.
- The indication cut-off value of QRS duration may be adapted for age using the 98th percentile of normal.
- Evaluation of mechanical dyssynchrony of the systemic ventricle should be performed in patients with non-standard structural or functional CRT substrate (systemic right or single ventricle, RBBB, presence of conventional ventricular pacing from an atypical pacing site, and QRS duration $<$120 ms).
- Cardiac resynchronization therapy device implantation may be considered within other planned cardiac surgery in the presence of significant systemic ventricular dyssynchrony (e.g. surgery aimed at relieve of structural systemic AV valve regurgitation) even if the patient does not fulfil all indication criteria with respect to the systemic ventricular function.[324,327]
- Cardiac resynchronization therapy indication should be considered carefully and individually in patients with specific progressive forms of DCM (ventricular non-compaction, neuromuscular, and mitochondrial disease), where CRT effect has not yet been clearly proven.

Pre- and post-procedural follow-up

Given the paucity of data on CRT effects in paediatric and CHD and low number of patients treated at each institution, functional, electrocardiographic as well as echocardiographic assessment should be an integral part of the pre- and long-term post-procedural work-up.

Functional assessment should include NYHA class grading or the Ross Heart Failure Score in infants, evaluation of functional capacity (6 min walking distance or spiroergometry, if applicable), and biochemical congestive heart failure markers.

Analysis of the 12-lead ECG should focus on QRS complex duration as well as the type of electrical conduction delay with regard to the morphology of systemic ventricle. Left bundle branch block along with a systemic LV and RBBB along with systemic RV, respectively, are indicative of a significant intra-ventricular conduction delay and potential mechanical dyssynchrony.

Although none of the echocardiographic indices has been shown to have sufficient reproducibility and predictive power in terms of CRT response in the multicentre PROSPECT trial,[330] several single-centre studies reported on the utility of septal to posterior wall motion delay, tissue velocity imaging, speckle tracking, or 3D techniques in the analysis of global and segmental LV dyssynchrony and prediction of CRT efficacy.[331–333] Despite the lack of data in children and patients with CHD it is the perception of this panel that besides the measurement of systemic ventricular size and function the assessment of global cardiac timing and global and segmental systemic ventricular dyssynchrony should be an integral part of the pre-procedural evaluation and decision process. Segmental systemic ventricular contraction occurring after the end of ejection or even continuing through the beginning of systemic ventricular filling is very often indicative of severe ventricular desynchronization. Evaluation of mechanical dyssynchrony should be at least performed in patients with non-standard CRT substrates (systemic right or single ventricle, RBBB, presence of conventional ventricular pacing from an atypical pacing site, and QRS complex $<$120 ms). The purpose of such assessment should be identification of early and late contracting systemic ventricular segments and their geographic (spatial) clustering into larger wall areas with early and late contraction as well as confirmation of myocardial viability in terms of contraction potential. These are the two major pre-requisites of CRT efficacy.[334] Further, echocardiography may be used for post-procedural AV and VV delay optimization (see further). Evaluation of systemic ventricular size and function should be repeated using the same measurement method during regular device follow-up to assess long-term reverse ventricular remodelling.

Technical implantation issues

In young patients CRT device implantation may be technically challenging because of inaccessibility of the systemic ventricular free wall through a transvenous route due to either small vessel size or abnormal cardiac anatomy. No data exist on the long-term behaviour of coronary sinus leads in growing or young individuals, on the incidence of coronary sinus thrombosis and complications of lead removal. As a consequence, 56–72% of patients reported in the three larger paediatric and CHD CRT studies had either thoracotomy or mixed lead systems.[323–325] Given the paucity of data, it is the perception of this panel that coronary sinus leads should be reserved for older children and adults with a normally sized cardiac venous system, where complication rates should be acceptable and comparable to those reported in the adults CRT series. The remaining patients or individuals with inaccessible pacing sites through the transvenous route should have a liberal access to a thoracotomy implantation.

Cooperation between the implanting surgeon and the cardiologist during the procedure is desired to ensure the placement of the systemic ventricular lead in the area of latest electrical and mechanical activation as mapped by pre-operative echocardiography and peri-operative measurements of local activation times during the baseline rhythm. The transvenous RV lead is usually placed in the RV apex or septum. Optimal position of an epicardial lead on the subpulmonary ventricle has not yet been specified. In parallel to the transvenous procedure, lead placement should be attempted close to the interventricular septum. The subpulmonary and the systemic ventricular leads should be spatially as well as

electrically separated as much as possible across the systemic ventricle. In patients with a single ventricle, importance has been placed on obtaining maximal distance between the two leads and aiming for the midventricular regions rather than the base.[325] Use of single-site resynchronization pacing has been anecdotically reported in the paediatric literature.[335,336] Sufficient fusion between the spontaneous (mostly septal) and paced (mostly free wall) activation wave fronts is perceived to be the prerequisite of success and may be achieved in patients with normal baseline AV conduction times. Still, accurate adaptation of the AV interval to changes in heart rate may pose a challenge. Thus, this technique should be limited to patients with normal and relatively fix PR intervals during rest and exercise.

Post-procedural optimization of the AV and VV intervals may be performed using echocardiography[337] or intrinsic device algorithms[338] as described in adults. Simultaneous optimization of both intervals by echocardiography is difficult given the number of combinations and poor sensitivity for detection of minor changes in systemic ventricular function or output. Generally, aiming maximum systemic ventricular filling time and maximum $+dP/dt$ as estimated from systemic AV valve regurgitation (if present) may be the simplest way to achieve this goal. In the paediatric and CHD population as opposed to patients with ischaemic cardiomyopathy scars in the systemic ventricle are rare and trans-myocardial conduction mostly homogenous limiting thus the need for non-simultaneous biventricular stimulation and V–V delay optimization.

Conflict of interest: see appendix.

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Appendix

Table A1 EHRA-AEPC Pediatric Cardiac Arrhythmias Consensus Document

Expert	Type of Relationship with Industry
Abrams Dominic James	None
Blom Nico	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - None B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Abbott Laboratories : Synagis (2011)
Blomstrom-Lundqvist Carina	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Sanofi Aventis : AF (2011) B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Biotronik : Arrhythmia (2011) - Medtronic : ICD, AF (2011) D - Research funding (departmental or institutional). - Medtronic : AF (2011) - Atricure : AF (2011) - Biotronik : Arrhythmias (2011)
Brugada Terradellas Josep	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Boston Scientific : devices (2011) - Medtronic : devices (2011) - Sorin Group : devices (2011) - St Jude Medical : devices (2011) - Biotronik : devices (2011)
Brugada Terradellas Ramon	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Gendiag.exe : genetic tools (2011)
de Groot Natasja	None
Deanfield John Eric	None
Drago Fabrizio	None
Happonen Juha-Matti	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Medtronic : Pacing (2011) - St Jude Medical : Pacing and electrophysiology (2011)
Hebe Joachim	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Biosense Webster : 3-D-navigation, Catheter Ablation (2011) - Medtronic : Catheter Ablation (2011)
Ho Siew Yen	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - St Jude Medical : anatomy (2011)

Continued

Table A1 ***Continued***

Expert	Type of Relationship with Industry
Janousek Jan	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - None D - Research funding (departmental or institutional). - Ministry of Health, Czech Republic: conceptual development of research organization 00064203 (University Hospital Motol, Prague,Czech Republic) : None (2011) E - Research funding (personal). - Ministry of Health, Czech Republic, Internal Grant Agency : None (2011)
Marijon Eloi	None
Paul Thomas	None
Pfammatter Jean-Pierre	None
Rosenthal Eric	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Shire HGT : ADHD (2011) - W.L. Gore & associates : Helix (2011)
Sarquella Brugada Georgia	None

Table A2 EHRA-AEPC Pediatric Cardiac Arrhythmias Consensus - Document Reviewers 2012

Expert	Type of Relationship with Industry
Farre Jeronimo	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - saint Jude medical : implantable devices, catheters (2011)
Hocini Meleze	None
Kriebel Thomas	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Medtronic : electrophysiology (2011)
Mavrakis Iraklis	None
Napolitano Carlo	None
Sanatani Shubhayan	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - None E - Research funding (personal). - CIHR : CIHR grant on Long QT syndrome (2011)
Viskin Sami	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Boston Scientific : European Scientific Advisory Board (2011)