

## REVIEW

## Recent Developments in Pediatric and Congenital Electrophysiology

John Papagiannis, MD, Dimosthenis Avramidis, MD

Division of Pediatric Cardiology,  
Mitera Children's Hospital, Athens,  
Greece

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**ABBREVIATIONS**

AP = accessory pathway  
AV = atrioventricular  
AVNRT = atrioventricular node reentry tachycardia  
CPVT = catecholaminergic polymorphic ventricular tachycardia  
EAT = ectopic atrial tachycardia  
ICD = implantable cardioverter defibrillator  
LQTS = long QT syndrome  
RVOT = right ventricular outflow tract  
SVT = supraventricular tachycardia  
TOF = tetralogy of Fallot  
VT = ventricular tachycardia  
WPW = Wolff-Parkinson-White (syndrome)

*Correspondence to:*

John Papagiannis, MD  
Division of Pediatric Cardiology  
Mitera Children's Hospital  
6 Erythrou Stavrou Str  
15123 Maroussi, Athens, Greece  
Tel: +30-210-6869788  
Fax: +30-210-6899405  
E-mail: [papagi@otenet.gr](mailto:papagi@otenet.gr)

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**ABSTRACT**

Pediatric electrophysiology is a relatively young subspecialty of Pediatric Cardiology, but it has experienced rapid progress in the last 2 decades. The revolutionary therapy of tachyarrhythmias with catheter ablation transformed the field of pediatric electrophysiology in a similar or even more dramatic way to that of adult electrophysiology. Improvements in technology have made catheter ablation safe in children. Exposure to radiation can now be markedly decreased with non-fluoroscopic imaging methods. The use of cryothermal energy has made ablation safer in the vicinity of the atrioventricular (AV) node or the coronary arteries. Complex postoperative atrial arrhythmias can be managed with advanced electroanatomic mapping technologies. Postoperative ventricular tachycardia can be treated with a combination of pharmacologic therapy, catheter ablation, surgical methods and implantable defibrillator implantation. Genetically determined arrhythmias can be diagnosed and treated more effectively with molecular genetic testing, pharmacologic methods, surgical techniques such as sympathetic denervation and defibrillators. Pediatric electrophysiologists have also adapted techniques of cardiac resynchronization to children and patients with congenital heart disease. Overall, these developments make the present and future of pediatric electrophysiology very exciting and promising.

**SUPRAVENTRICULAR TACHYCARDIA**

Supraventricular tachycardia (SVT) is the most common sustained arrhythmia in children, with an incidence of approximately 1:250. Accessory pathways (APs) account for approximately 70% of cases, atrioventricular (AV) node reentry tachycardia for 20% and atrial ectopic and other tachycardias (e.g. junctional ectopic, atrial flutter, etc) for approximately 10%.<sup>1</sup>

**1. SVT ASSOCIATED WITH ACCESSORY PATHWAYS**

There are several forms of accessory pathways (Table 1). Most common locations for APs are left lateral and right posteroseptal.<sup>2</sup> Most children with an AP have otherwise anatomically normal hearts. Congenital heart defects that have been most commonly associated with accessory pathways include: Ebstein's anomaly of the tricuspid valve, congenitally corrected transposition of the great arteries, tricuspid atresia and heterotaxy syndromes.

*Presentation and treatment according to age*

Tachycardia due to an AP can present at any age, including fetal life. The special

**TABLE 1.** Types of accessory pathways

Atrioventricular non-decremental	Bidirectional Unidirectional retrograde only Unidirectional antegrade only
Retrograde-only decrementally conducting (causing PJRT)	
Decremental with mostly antegrade conduction (“Mahaim” type)	Atrioventricular Atriofascicular Nodoventricular Nodofascicular
Fasciculoventricular (not causing tachycardia)	

circumstances of fetal life (lack of continuous monitoring, difficulty in delivering effective therapy and relative non-compliance of fetal heart) may result in heart failure due to prolonged periods of SVT, which may present as hydrops fetalis and even fetal death. Treatment of persistent fetal tachycardia is usually performed via oral administration of antiarrhythmic medications to the mother, but other forms of therapy, such as direct umbilical vein delivery can be attempted in resistant cases. The most common drugs used in the fetus are digoxin, flecainide, amiodarone and sotalol. Intramuscular administration of drugs such as digoxin may be effective in the hydropic fetus, usually in combination with maternal intravenous (IV) administration. Delivery of the fetus and direct neonatal treatment should be reserved for fetuses near term, to avoid complications of prematurity.

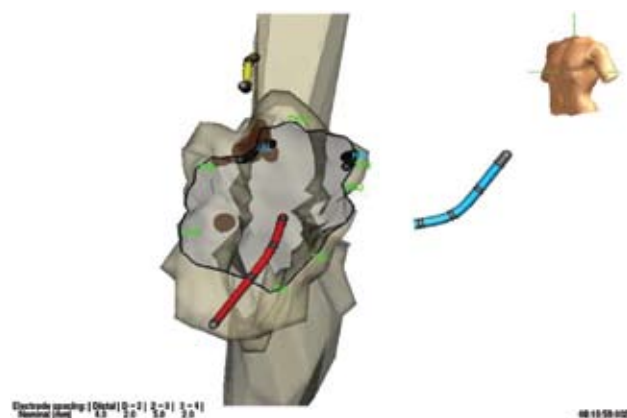
Neonatal and infant management of SVT due to APs can also be problematic, often requiring multiple medications. Fortunately, most APs lose conduction during infancy. The natural history of the Wolff-Parkinson-White (WPW) syndrome in infants is marked by spontaneous loss of preexcitation by age 1 year in 93% of the patients, but with reappearance of it in 31% of children by 8 years of age.<sup>3</sup> Thus, it is quite rare for an infant to require interventional therapy. In addition, data from infant lambs have shown that radiofrequency lesions placed in the infantile myocardium can grow with age and cause potentially significant structural damage, along with the possibility for arrhythmogenesis due to the irregularity of the lesion borders.<sup>4</sup> However, a small number of infants have been submitted to radiofrequency (RF) ablation and there are data from both the Pediatric RF Ablation Registry and individual centers on the outcome of these procedures. The results are comparable to those in older patients, but only when the procedures are performed in experienced centers.<sup>5</sup> In general, the risks of ablation are significantly increased in younger patients. A study of the Pediatric Radiofrequency

Ablation Registry showed that mortality is higher when there is underlying heart disease, lower patient weight, greater number of radiofrequency energy applications, and left-sided procedures.<sup>6</sup>

#### Other safety issues

Prospective studies have evaluated the long term outcomes of ablation in pediatric patients. No intracardiac thrombosis was observed, serious injury to cardiac valves due to RF ablation was very rare, and there was no clear effect of RF ablation on cardiac wall motion or on left ventricular function.<sup>7</sup> Therefore RF ablation has become the standard of care in older children and adolescents with recurrent symptomatic SVT. However, the effects of excessive exposure to radiation are still concerning. Fortunately, new developments in technology have allowed the performance of these procedures with significant reduction, or even complete elimination of radiation. The most important electroanatomical mapping systems that have been used for this purpose are the CARTO system (Biosense Webster, Diamond Bar, CA) and the NavX system (St Jude Medical, St Paul, MN) (Figure 1). Several retrospective studies have shown the efficacy of both systems in this regard without a sacrifice in safety or recurrence rate.<sup>8-10</sup>

Another recent development in the interventional treatment of SVT in children is *cryoablation*. The main areas where this form of therapy has been found to be beneficial are substrates such as the AN nodal reentry tachycardia (AVNRT) (see below) and septal APs. There is also evidence that cryoenergy is less likely to cause coronary arterial damage than radiofrequency energy and therefore it maybe preferable when ablating close to the coronary arteries, such as in posteroseptal areas. Unfortunately, although the acute success rate is similar to RF energy, with no significant complications, the recurrence rate is still relatively high and there is a need for



**FIGURE 1.** Right atrial and tricuspid valve three-dimensional geometry along with electrode-catheters demonstrated using the NavX system. Brown spots represent radiofrequency lesions.

strategies to improve on this aspect.<sup>11,12</sup>

### *Management of asymptomatic WPW syndrome*

Sudden death due to rapid conduction of atrial fibrillation over the AP is uncommon in pediatric patients because of the rare occurrence of this arrhythmia in children. Therefore, until recently, there was little impetus in performing ablation procedures in asymptomatic patients. However, recent prospective studies in adults and children have shown that asymptomatic patients with certain characteristics at electrophysiologic study may be at higher risk of dangerous arrhythmias and even sudden death. These include the presence of multiple accessory pathways, short antegrade refractory period of the pathway (<250 ms) and inducibility of tachycardia.<sup>13,14</sup> Potentially life-threatening events occurred in approximately 10% of the study population.<sup>13</sup> In a prospective randomized study, children with high risk characteristics who did not undergo prophylactic ablation had a significantly higher risk of developing potentially dangerous arrhythmias and even ventricular fibrillation and sudden death. On the other hand, prophylactic ablation did not lead to serious complications and eliminated the incidence of life-threatening events.<sup>15</sup> A survey of Pediatric Electrophysiologists revealed that 83% used invasive electrophysiologic studies for risk stratification in asymptomatic patients with WPW syndrome. Electrophysiologic findings guided selection of patients for RF ablation procedures.<sup>16</sup>

### **2. AV NODE REENTRY TACHYCARDIA (AVNRT)**

This is the second most common form of tachycardia in children. Symptoms are often more prominent in these patients compared to those with AV reentrant tachycardia because the AV valves are closed during atrial contraction, and cannon A waves may be seen. Near syncope is also more common. AVNRT is unusual in infants less than 2 years of age. The natural history of AVNRT in children is largely unknown, but episodes are likely to persist into adulthood.

Catheter ablation is indicated when there are frequent and/or very symptomatic episodes of tachycardia resistant to safe antiarrhythmic therapy or if the patient/family wishes to avoid chronic drug therapy. Participation in sports and professional choices also may be important factors that lead to interventional therapy. For many years RF ablation was used for definitive therapy of AVNRT with excellent results. However, the incidence of AV block although relatively small is not negligible in pediatric series ( $\approx 2\%$ ), and has led many pediatric electrophysiologists to choose cryoablation as a safer method. The main advantages of this approach are: a) the ability to perform cryomapping at a higher temperature ( $-30^{\circ}\text{C}$ ), the effects of which are completely reversible, before deep freezing; b) the stability of the catheter due to ice ball formation (cryoadhesion); c) the more gradual lesion formation, and d) the ability to test AV conduction during freezing. The main disadvantages are the smaller size of the lesions and

the lack of a sign of lesion efficacy such as accelerated junctional rhythm. There have been several series showing similar efficacy to RF ablation, but a higher incidence of recurrence. There has not been any case of permanent AV block in any of the reported cases.<sup>17,18</sup>

### **3. ATRIAL ECTOPIC TACHYCARDIA**

This is the third most common cause of tachycardia in children and accounts for 5-20% in various series.<sup>5</sup> It is not uncommon for these patients to present with congestive heart failure from tachycardia induced cardiomyopathy which may occur in up to 50% of these cases. The mechanism of ectopic atrial tachycardia (EAT) is most likely abnormal automaticity. Although the focus of tachycardia is most commonly right-sided in adults, equally distributed right and left foci are seen in children.

The natural history is one of spontaneous resolution in infants and toddlers. This rarely occurs in older children. A retrospective study compared the natural history and the response to medical therapy in children less than 3 years of age to those older than 3 years. The younger patients had a higher spontaneous resolution rate (78%) compared with the older group (16%) ( $p < 0.001$ ). Control of AET with antiarrhythmic therapy was achieved in 91% of the younger children but only 37% of the older children ( $p < 0.001$ ). Radiofrequency ablation was performed in 35 of the older children, with ultimate success in 74%.<sup>19</sup> In general, the acute success rate has been lower in EAT than in other arrhythmia substrates in children. However, a recent study reported 100% success rate using electroanatomic mapping, compared to 77% with conventional techniques.<sup>20</sup>

### **4. JUNCTIONAL ECTOPIC TACHYCARDIA**

This is the least common form of SVT in children. It occurs mainly in two forms: a) postoperative and b) congenital. The postoperative form is usually transient, lasting 1-7 days and is usually associated with trauma to the AV node or to the His bundle. The rate may be controlled with surface cooling, correction of electrolyte imbalance, reduction in the dose of IV catecholamines and IV medications. Although various drugs have been tried in the past including digoxin, propafenone and procainamide, none has proven very effective, except for procainamide which has shown moderate efficacy. Amiodarone has become the treatment of choice in cases not responding to the usual measures.<sup>21</sup> The loading dose is 5 mg/kg and should be given slowly, over approximately an hour and followed by a continuous infusion of 0.4 mg/kg/day. Rarely a patient may not respond to all measures, including amiodarone and deep hypothermia. In extreme cases, ablation of the AV node and implantation of a permanent pacemaker has been performed.<sup>22</sup>

The congenital form is frequently familial, usually incessant, not associated with congenital heart disease, can often

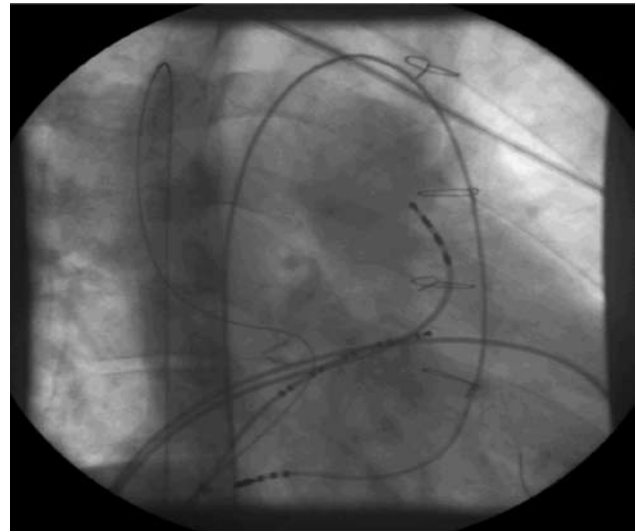
spontaneously resolve but only after many months or years and can lead to a cardiomyopathy.<sup>23</sup> There are reports of sudden deaths in patients with junctional ectopic tachycardia treated with medications, presumably due to AV block. This has prompted a recommendation for back-up pacing in these patients, which remains controversial. A recent multicenter study on 94 patients reported successful medical treatment with amiodarone in 60%. Transcatheter ablation was performed in 44 patients (17 RF ablation, 27 cryo-ablation) with equal success rates (82 vs 85%). Pacemaker implantation was required in 14%. There were 4 deaths, all in patients younger than 6 months of age.<sup>24</sup>

### 5. ATRIAL FLUTTER

This is a rare arrhythmia in children, but it is seen mainly on two occasions: a) in young infants or even fetuses, where it can be either an isolated phenomenon, or associated with Wolff-Parkinson-White syndrome and b) in postoperative patients after surgery for congenital heart disease.<sup>25</sup> When presenting in infancy it is usually transient and all that is needed is cardioversion with rapid atrial pacing, usually by the esophageal route, or direct current shock. Preventive therapy is started if it recurs.

In the postoperative form, the substrate is complex, and is related to the atriotomy and patches, natural conduction barriers and fibrosis from high pressure and hypertrophy. This form is most appropriately called incisional atrial reentry tachycardia (IART). It is most commonly seen after surgery in the atria, such as the Mustard or Senning operations for transposition of the great arteries, the Fontan operation for single ventricle and repair of atrial septal defects. It may also occur after repair of tetralogy of Fallot and related lesions such as truncus arteriosus or double-outlet right ventricle. Catheter ablation can achieve a reasonable success rate (between 80-90%) in most patients except for those with a single ventricle, either before or after a Fontan operation.<sup>26</sup> However, a high recurrence rate (up to 50%) has been reported. In patients after surgery for transposition of the great arteries or single ventricle, the presence of IART is very detrimental and increases the risk of sudden death by 4-fold. Therefore, it is mandatory to achieve the best possible control of this arrhythmia. Unfortunately, medical therapy in these patients is often unsuccessful and may compromise their hemodynamic status. Catheter ablation can be very challenging because of the presence of the intraatrial baffle that precludes access to the cavo-tricuspid isthmus and to the pulmonary venous atrium. Therefore, a retrograde approach (Figure 2), or a trans-baffle approach is usually necessary. Despite the technical difficulties, a reasonable success rate has been achieved either with conventional techniques,<sup>27</sup> or more recently with remote magnetic navigation.<sup>28</sup>

In patients after an old-style Fontan operation (atrio-pulmonary or atrio-ventricular connection) atrial arrhythmias



**FIGURE 2.** Catheter ablation of atrial flutter in a patient with transposition of the great arteries after Senning operation. Access to the pulmonary venous atrium is achieved retrogradely through the aorta and the right ventricle. The tip of the ablation catheter is positioned at the posterolateral part of the cavo-tricuspid isthmus which is bisected by the atrial baffle suture line.

may be very problematic, because of poor response to antiarrhythmic medications and significant technical difficulties with catheter ablation. They often occur in the setting of poor hemodynamics and may lead to heart failure, thrombosis and death. Because of suboptimal results with catheter ablation and the need to improve hemodynamics, these patients are best treated with a revision of the Fontan circuit, which involves conversion to an extra-cardiac total cavo-pulmonary connection, along with a modified Maze procedure of both the right and left atria using cryoablation. Additional arrhythmia substrates such as ectopic atrial tachycardias and accessory pathways can be managed during these procedures, which should be performed in centers with extensive experience.<sup>29</sup>

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## VENTRICULAR ARRHYTHMIAS

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Ventricular tachycardia (VT) in children may occur in the setting of a normal heart or in association with structural abnormalities (Table 2).

### VENTRICULAR TACHYCARDIA WITH NORMAL HEART

#### *Right Ventricular Outflow Tract Tachycardia (RVOT VT)*

This tachycardia has a characteristic left-bundle branch block/inferior axis morphology, may be repetitive or sus-

**TABLE 2.** Etiologies of ventricular tachycardia in children and young adults

1. Idiopathic ventricular tachycardia from the RVOT or the aortic cusps
2. Left ventricular tachycardia sensitive to verapamil (fascicular VT)
3. Postoperative VT (tetralogy of Fallot and other congenital heart defects)
4. Cardiomyopathies (dilated, hypertrophic, arrhythmogenic RV dysplasia)
5. Long QT syndrome
6. Catecholaminergic polymorphic VT
7. Brugada syndrome
8. Short QT syndrome

tained, is not usually inducible by programmed stimulation, and has a cycle length that varies with catecholamine levels. Its mechanism is likely to be triggered activity. Despite the frequent runs of nonsustained VT, most patients are asymptomatic. Treatment is indicated when there is reduced ventricular function due to high burden of ectopy, or when patients are symptomatic. In younger patients who do not fulfill these criteria, expectant management is appropriate, as spontaneous resolution may occur. A recent multicenter study summarized the course and response to therapy in 48 patients. Most (39/48) were asymptomatic and discovered incidentally. Although 26 patients received medical therapy, there was no difference in arrhythmia burden compared to those who were followed without treatment. Catheter ablation was performed in 6 patients and was successful in 4. No patient died during follow-up.<sup>30</sup>

#### *Tachycardias arising from the left ventricle*

There are two common types of tachycardia arising from the left ventricle. The first has right-bundle branch block/superior axis morphology and arises from the left side of the ventricular septum. Its mechanism is most likely reentry within the Purkinje network. It has a remarkable sensitivity to verapamil. The long term prognosis is usually very good, although some patients may develop tachycardia-induced cardiomyopathy because of incessant tachycardia. Catheter ablation is also very effective, guided by identification of a sharp potential preceding ventricular activation, a so-called "Purkinje spike".

A different type of tachycardia may arise from the left ventricular (LV) outflow tract or from the aortic sinuses. This tachycardia is more similar to RVOT VT in terms of mechanism. Successful ablation has been reported in many

adult and few pediatric series.<sup>31</sup>

#### *Arrhythmias related to long QT syndrome (LQTS)*

The long QT (LQT) syndrome (LQTS) is a heterogeneous disorder of various types of cardiac channels. Twelve different types have been described. However, the large majority of cases are caused by the first 3 types: 1) LQT1 caused by a mutation in KCNQ1 gene on chromosome 11, resulting in loss of function of the  $I_{Ks}$  current; 2) LQT2 caused by a mutation in HERG gene on chromosome 7, resulting in loss of function of the  $I_{Kr}$  current; 3) LQT3 caused by a mutation in SCN5A gene on chromosome 3, resulting in a gain of function of the cardiac sodium channel. Patients having these forms are known to be at risk of having episodes of polymorphic ventricular tachycardia (VT) (torsade des pointes), but the triggers are different: Patients with LQT1 and LQT2 develop syncope usually with exertion or loud noise, while LQT3 patients are more at risk during sleep or sedentary periods. The main methods of therapy are beta-blocking agents, anti-bradycardia pacing to prevent pause-induced polymorphic VT, left cardiac sympathetic denervation or defibrillator (ICD) implantation. Genotype-directed therapy, such as mexiletine for LQT3, or potassium supplements for LQT2 may be helpful. Left cardiac sympathetic denervation may be performed in the traditional way, through a thoracotomy, or less invasively using a videoendoscopic approach with excellent results.<sup>32</sup>

A recent study of 128 pediatric patients (ages  $8.0 \pm 5.4$  years) with QTc of  $487 \pm 39$  ms assessed the outcome of LQTS patients in the era of implantable defibrillators. Beta-blockers were used in 126 (98%) and pacemaker/implantable cardioverter-defibrillator implantation was performed in 27 (21%) patients, usually because of symptoms despite use of beta-blockers. Among them, 22% received an appropriate shock, but device-related complications requiring re-intervention occurred in 48%. Device patients had longer QTc intervals ( $p = 0.03$ ) and more symptoms ( $p < 0.001$ ). No one with an isolated KCNQ1 and all patients with an SCN5A mutation had device implantation. During the study period, there were 2 deaths. The authors concluded that in the era of genetic testing and device implantation, overall mortality is low with treatment. Device therapy, although effective, is not without complications and should be reserved for high-risk patients.<sup>33</sup> Recent studies have shown that combination therapy with beta-blockers and mexiletine may be effective in especially malignant forms of LQT3.<sup>34</sup>

#### *Catecholaminergic polymorphic VT (CPVT)*

This is a rare arrhythmia that may be associated with syncope or sudden death during exercise, that may present clinically in a similar way to long QT syndrome type 1. The QT interval is normal and there is no clue to the diagnosis during a baseline 12-lead ECG, other than relative bradycardia. However, the response to exercise is relatively specific



to this entity, with progressive appearance of polymorphic ventricular premature beats, progressing to nonsustained VT and sometimes to bidirectional VT (Figure 3). There are two types of the disease, an autosomal dominant form due to mutations in the RyR2 gene (ryanodine receptors) and an autosomal recessive form due to mutations in the CASQ2 gene (calsequestrin).<sup>35,36</sup> Patients respond to beta-blockers, but not to the same degree as with LQT1 and there are patients who present with lethal or potentially lethal events while on maximal  $\beta$ -blockade. There are also reports of improved control of ventricular arrhythmias when calcium channel blockers are added to beta-blockers.<sup>37</sup>

The response to treatment with implantable defibrillators may also be problematic, since the catecholamine surge caused by DC shocks may re-induce ventricular tachycardia. Inappropriate shocks may also occur due to atrial fibrillation which is sometimes observed in these patients. We have also seen induction of ventricular fibrillation after DC shocks triggered by otherwise hemodynamically stable polymorphic ventricular tachycardia (i.e. a form of device-caused proarrhythmia). Despite these problems, treatment with ICD can be life-saving (Fig 4). There are recent reports that support the role of left cardiac sympathetic denervation in the treatment of CPVT, in a similar way to LQTS.<sup>32,38,39</sup>

#### VENTRICULAR TACHYCARDIA WITH AN ABNORMAL HEART

In children and young adults the best studied situation is the postoperative patient with tetralogy of Fallot (TOF), followed by hypertrophic cardiomyopathy and arrhythmogenic right ventricular dysplasia, which rarely presents in childhood.

#### VT IN POSTOPERATIVE TOF

Initial studies had estimated that sudden death occurs in 1-5% of postoperative TOF patients. A more recent prospec-

tive population based study of sudden death in patients with congenital heart disease has provided a much lower incidence of sudden death.<sup>40</sup> There was 1 death per 1,118 patient-years, with the main diagnoses related to sudden death being aortic stenosis, coarctation, transposition of the great arteries and tetralogy of Fallot. The incidence of sudden death for these diagnoses was 1/454 patients-years. The main risk factors known to be associated with VT in postoperative TOF are greater length of follow-up, older age at repair (mean 7 years) abnormal hemodynamics (elevated systolic or end-diastolic RV pressure). An additional risk factor that has been identified is prolonged QRS duration above 180 ms.<sup>41</sup> Initial reports suggesting that premature ventricular contraction (PVC) suppression decreases the risk of sudden death in patients with TOF, have not been confirmed in later studies. Current therapy is based on improvement of abnormal hemodynamics and treatment of inducible sustained ventricular tachycardia, or sustained tachycardia on 24-hour Holter monitor. Treatment with antiarrhythmic drugs has a rather limited and mostly adjunctive role in the era of implantable defibrillators and radiofrequency ablation. Recent studies have revived the importance of electrophysiological studies in the selection of candidates for treatment with implantable defibrillators. Both monomorphic and polymorphic VT induced during programmed ventricular stimulation had prognostic significance for future development of clinical VT and sudden death.<sup>42</sup>

The role of implantable defibrillators in the management of postoperative VT after TOF repair has been studied in a recent retrospective study of 121 patients (median age 33.3 years). ICDs were implanted for primary prevention in 68 patients (56.2%) and for secondary prevention in 53 (43.8%), defined by clinical sustained ventricular tachyarrhythmia or resuscitated sudden death. Overall, 37 patients (30.6%) received at least 1 appropriate and effective ICD discharge. Annual actuarial rates of appropriate ICD shocks were 7.7% and 9.8% in primary and secondary prevention, respectively

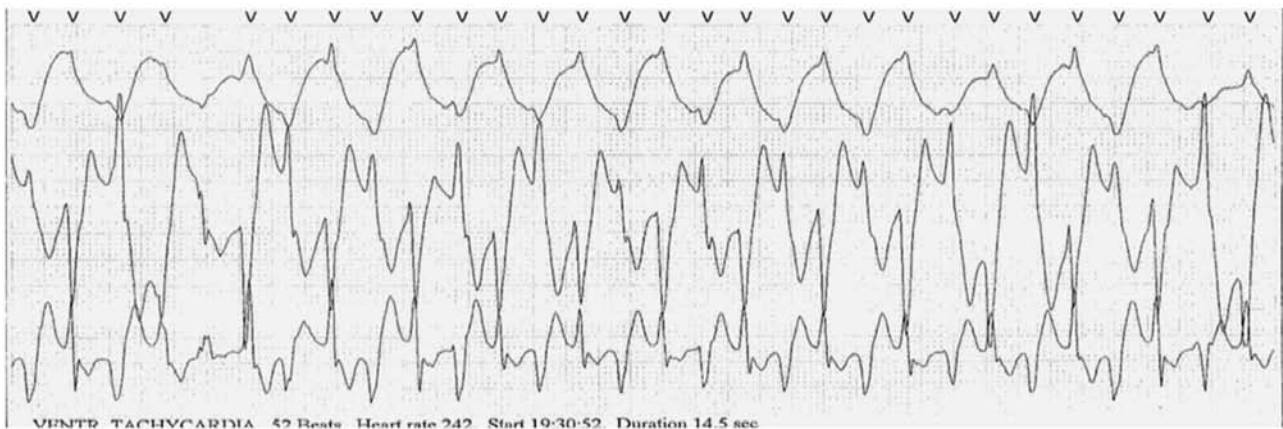


FIGURE 3. Bidirectional ventricular tachycardia in a patient with catecholaminergic polymorphic VT.



FIGURE 4A. Dual chamber defibrillator implanted epicardially in the same patient is in figure 3. The defibrillator lead has been placed behind the left ventricle.

( $P=0.11$ ). A higher left ventricular end-diastolic pressure (hazard ratio 1.3 per mm Hg,  $P=0.004$ ) and nonsustained ventricular tachycardia (hazard ratio 3.7,  $P=0.023$ ) independently predicted appropriate ICD shocks in primary prevention. Inappropriate shocks occurred in 5.8% of patients yearly. The number of complications was significant at 29.8%. Despite the

problems with inappropriate shocks and other complications, the implantable defibrillator seems to have a crucial role in the management of postoperative VT and sudden death in TOF patients.<sup>43</sup> Based on a multivariable analysis of factors related to appropriate ICD discharges, a scoring system has been created (Table 3).<sup>43</sup> A risk score of  $<2$  identifies patients in very low risk (0% annual risk of appropriate shocks), a score of 3-5 places patients in an intermediate category (3.8% annual rate of appropriate shocks), and a score  $>6$  predicts a high risk of appropriate shocks (17.5% per year).

Even though catheter ablation has been used for several years, the reports referred to isolated cases or small series. A recent study of 11 patients presented the results of a systematic approach, with ablation of critical isthmuses to prevent all potential arrhythmia circuits. The results have been impressive in this small series, with 91% of patients remaining free of VT during follow-up for 30 months.<sup>44</sup>

#### VT IN HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) in children has a reported annual mortality rate of 2-6%. A recent population-based study including all Australian children who presented with primary HCM between 0-10 years of age in a 10-year period and followed prospectively for 10 years, revealed a 5- and 10-year survival of 83% and 76% respectively. There was

TABLE 3. Risk score for appropriate ICD shocks in primary prevention for TOF patients

Risk factor	Score
Prior palliative shunt	2
Inducible VT	2
Ventriculotomy	2
LVEDP $\geq 12$ mmHg	3
QRS duration $\geq 180$ msec	1

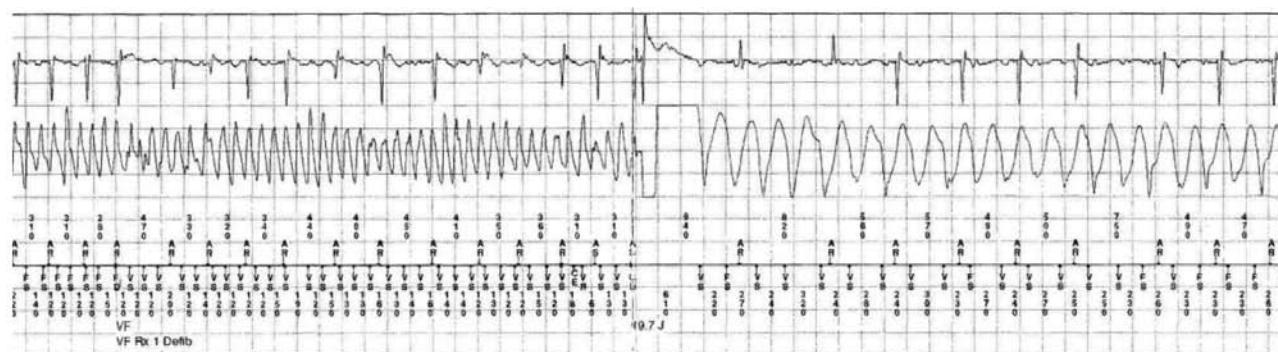


FIGURE 4B. Appropriate ICD therapy in the same patient with CPVT, converting ventricular fibrillation to slower polymorphic VT, which eventually terminated spontaneously.

only one sudden death, and no patient presented with sudden death as the initial manifestation. Two patients presented with arrhythmic symptoms. The annual mortality rate was 3.3%, but it was 1.5% in patients diagnosed after 1 year of age. The main cause of death was heart failure (50%), mostly from diastolic dysfunction. A significant proportion of patients had genetic syndromes, mainly Noonan's syndrome. Four patients underwent ICD implantations. The indications were aborted sudden death, recurrent syncope, easily inducible ventricular fibrillation during an electrophysiologic study for WPW pattern, and a family history of sudden death. None of these patients died.<sup>45</sup> Ischemia may play a more important role than arrhythmias in sudden death of young patients.<sup>46</sup> Treatment includes high dose beta-blockers, amiodarone and in high risk cases ICD implantation. Risk factors for sudden death reported for adult patients with HCM include non-sustained VT, syncope, malignant family history, extreme hypertrophy and abnormal response to exercise. The role of left ventricular outflow obstruction is debatable. In a recent study of pediatric patients ( $10.6 \pm 5.4$  years) with HCM, the compound end-point of death or heart transplantation occurred in 11% of patients over 6.4 years. Only 3 patients died suddenly. Risk factors for

death included extreme hypertrophy (LV thickness z-score >6) and abnormal blood pressure response to exercise.<sup>47</sup> The occurrence of a resuscitated sudden death episode has been considered especially ominous in these patients. A recent study by Maron et al including 39 patients who experienced cardiac arrest or appropriate ICD shock out of a population of 916 patients with HCM, reported that the incidence of recurrent cardiac arrest was 53%. The remaining patients have not experienced life-threatening events. Since the follow-up period was very long (many patients >10-20 years), the annualized incidence of sudden death was 1.4%, similar to that of the general HCM population.<sup>48</sup>

**ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA (ARVD)**

ARVD is a rare genetically determined disease that usually presents in adolescence or young adulthood, sometimes with sudden death as its first manifestation. The diagnosis has evolved from postmortem pathology to a clinical and laboratory diagnosis during life. The task force criteria are very useful in this respect (Table 4).<sup>49</sup> Significant progress has also been achieved in terms of unraveling the genetic

**TABLE 4.** Task force criteria for the diagnosis of ARVD\* <sup>49</sup>

Category	Major Criteria	Minor Criteria
Global or regional dysfunction and structural alterations	(1) Severe dilatation and reduction in the RV ejection fraction with no or only mild LV impairment (2) localized RV aneurysms (akinetic-dyskinetic areas of diastolic bulging) (3) Severe segmental dilatation of the RV	(1) Minor global RV dilatation or ejection fraction reduction with normal LV (2) mild segmental dilation of the RV (3) regional RV hypokinesia
Tissue characterization	Fibrofatty replacement of myocardium on endomyocardial biopsy	
Repolarization abnormalities	None	Inverted T waves in the right precordial leads beyond V1 (patient >12 y, in the absence of a RBBB)
Depolarization or conduction abnormalities	Epsilon waves** or localized prolongation (110 ms) of the QRS complex in precordial leads (V1, V2, or V3)	Late potentials (signal-averaged ECG)
Arrhythmias	Sustained LBBB type of VT (as determined with electrocardiography, Holter monitoring, or exercise testing)	Frequent ventricular extrasystoles with LBBB morphology (>1000 per 24 h, as seen with Holter monitoring)
Family history	Familial disease confirmed at necropsy or surgery	(1) Family history of premature sudden death (<35 y) caused by suspected RVD or (2) family history (clinical diagnosis based on current criteria)

ECG = electrocardiogram; LBBB = left bundle branch block; LV = left ventricle (-ular); RBBB = right bundle branch block; RV = right ventricle (-ular); RVD = right ventricular dysplasia

\*\*Epsilon waves are ventricular postexcitation waves that occur after the QRS complex at the beginning of the ST segment. These waves represent delayed depolarization of some parts of the right ventricle.

\* To fulfill the appropriate criteria for ARVD, the patient's condition must meet 2 major criteria, 1 major and 2 minor criteria, or 4 minor criteria.



background which involves one of several desmosomal proteins. The desmosomes, which are situated in the intercalated disc, ensure mechanical coupling between cells and enable propagation of electrical impulses. The main components of desmosomes consist of the products of three gene super-families: the desmosomal cadherins, the armadillo family of nuclear and junctional proteins, and the plakins.<sup>50</sup>

Mutations in genes encoding major desmosomal proteins (plakoglobin, desmoplakin, plakophilin-2, desmoglein-2, and desmocollin-2) have been implicated in the pathogenesis of ARVD.<sup>51</sup> Mutations in structural components of desmosomes found in skin have also been reported resulting in unusual hair phenotypes. *Naxos disease* is an autosomal recessive condition the clinical features of which comprise arrhythmogenic right ventricular cardiomyopathy, woolly hair and palmo-plantar keratoderma. A homozygous 2 base pair deletion in the plakoglobin gene was identified in the above inherited disorder.<sup>52</sup> Genetic diagnosis is made in approximately 50% of suspected cases. The prevalence is between 1/1,000 and 1/5,000, with 10% of deaths occurring before age 19 and 50% before age 35. Electrocardiography (ECG) and signal-averaged ECG (SAECG) have moderate sensitivity for ARVD. Endomyocardial biopsy in young individuals with ARVD demonstrates fibrosis more frequently than fatty infiltration. Newer technologies of magnetic resonance imaging and voltage mapping hold promise but require further assessment in young individuals suspected to have ARVD.<sup>53</sup> A recent study attempted a clinical and genetic characterization of 200 patients. Correlation of ECG, arrhythmic, and cardiac magnetic resonance imaging (CMR) findings in the study sample revealed 3 patterns of disease expression: (1) classic, defined as isolated RV disease (39%) or LV involvement in the presence of notable RV enlargement and/or dysfunction; (2) left dominant (5%), with prominent LV manifestations in the setting of relatively mild right-sided disease; and (3) biventricular (56%), characterized by equal bilateral involvement with no apparent predilection for either ventricle. Patients with positive genetic testing (n=39) were compared with the 117 individuals who had screened negative for changes in the 5 desmosomal genes. The only significant differences were higher LV lesion scores and an increased prevalence of left-dominant disease and notable ventricular arrhythmia (but not nonsustained VT) in the genotype-positive subset.<sup>54</sup> Some patients respond to medical therapy, but implantation of defibrillator should be considered in patients with definite diagnosis of ARVD according to task force criteria and those with clinical or inducible VT. Patients with arrhythmogenic RV dysplasia represent a group with one of the highest rates of appropriate ICD shocks (78-85%).<sup>55,56</sup>

#### CARDIAC RESYNCHRONIZATION

Following the extensive experience of cardiac resynchronization therapy (CRT) with biventricular pacing in adults,

there has been a rapidly growing utilization of this technology in children and patients with congenital heart disease. The institutional experience from Boston Children's Hospital on 60 patients showed significant benefits from CRT in the majority of patients. Median ejection fraction (EF) increased from 36% to 42% (P <0.001) and improvement was particularly evident in the group with congenital heart disease. Overall, an improvement in functional status was observed in 87% with sufficient follow-up data.<sup>57</sup> Two multicenter studies with data on pediatric and congenital heart disease patients have been published. In the first study which comprised 103 patients mostly from North American centers, the largest group consisted of patients with congenital heart disease (71%). Significant improvements in ejection fraction ( $12.8 \pm 12.7\%$ ) and decrease in QRS ( $37.7 \pm 30.7$  ms) were seen.<sup>58</sup> The second multicenter study reporting on 109 patients from European centers, also consisted largely of congenital heart disease (87), congenital AV block (12) and dilated cardiomyopathy (10). The systemic ventricular function improved by 11-14% and the functional class by at least 1 grade. The presence of a systemic left ventricle was a favorable prognostic factor, whereas dilated cardiomyopathy and poor functional class were predictors of non-response.<sup>59</sup> Patients whose LV dysfunction was related to chronic RV pacing responded particularly well to biventricular pacing.<sup>59</sup> Finally, CRT has been used in the acute treatment of congestive heart failure in the immediate postoperative period, especially in patients with single ventricle.<sup>60</sup>

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