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Review

Systematic review of risk stratification of pediatric ventricular arrhythmia in structurally normal and abnormal hearts☆

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ABSTRACT

Pediatric ventricular tachycardia (VT) occurs in both structurally normal and abnormal hearts. Spontaneous, sustained VT has an incidence of 1/100,000 among children. However, short episodes of VT can occur in up to 3% of healthy teenagers and up to 16% in hypertrophic cardiomyopathy. Prevalence of VT after tetralogy of Fallot repair has been estimated to be between 3% and 14% in several large clinical series, with a 2% incidence of cardiac death over 32 years. Because VT-related fatality is more prevalent in adults, it was previously believed that VT in children/adolescents had the same characteristics, etiologies, and outcomes despite not having evidence-based data. So, our systematic literature review was designed to identify evidence-based characteristics, etiologies, and risk stratification of the benign and malignant types of VT.

We performed a systematic review of the literature using *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses (PRISMA) guidelines.

"PubMed," "Science Direct," "Web of Science", "CINAHL" and "Cochrane" databases were searched for relevant studies using the search terms "ventricular tachycardia," "pediatric," "children," "management," "risk," and "treatment". Inclusion criteria included neonatal/pediatric/adolescent subjects; retrospective or prospective case series, case-control studies that described natural history of idiopathic VT in structural normal hearts, and sudden cardiac death risk factors in secondary VT in structurally normal or abnormal hearts. Studies were excluded if they were performed using animal models, exclusively described adult patients, or were review articles. We found 64 studies focused on three types of pediatric VT. These can be subdivided as follows: Idiopathic VT in structurally normal heart (24 studies), secondary VT in structurally normal hearts (22 studies), and VT in structurally normal hearts (18 studies). We propose an algorithm to differentiate benign from malignant VT using EKG morphologies, Holter criteria, and echocardiography. Also we risk stratify SCD in secondary pediatric VT in patients with structurally normal as well as structurally abnormal hearts in evidence-based methodology. Pediatric VT can be benign or malignant according to underlying etiologies. We propose an evidence-based algorithm to make this differentiation, followed by risk stratification of SCD in malignant and secondary VT in structurally normal or abnormal hearts.

1. Introduction

Pediatric ventricular tachycardia (VT) occurs in both structurally normal and abnormal hearts [1]. Spontaneous, sustained VT has an incidence of 1/100,000 among children [2] and more recently non sustained or sustained VT incidence was estimated to be between 0.2 and 0.8 per 10,000 in school aged children [3]. However, VT can occur in up to 16% in hypertrophic cardiomyopathy [4]. Prevalence of VT after tetralogy of Fallot repair has been estimated to be between 3% and 14% in several large clinical series [5], but incidence of cardiac death was only 2% over 32 years [6].

Three settings for pediatric VT were identified: idiopathic, secondary VT in structurally normal hearts, and VT in structurally abnormal hearts. It is estimated that 49% of pediatric VT patients have structurally abnormal hearts [7]. Idiopathic ventricular tachycardia is usually benign and often resolves spontaneously without treatment; however, it is essential to distinguish benign, idiopathic VT from potentially life-threatening conditions (malignant idiopathic variant and secondary VT due to channelopathies, cardiomyopathy, etc.) [8].

Sustained ventricular tachycardia (tachycardia which persists for over 30 s) occurs in the setting of myocarditis, post myocardial infarction, congenital heart disease, and other unknown or idiopathic causes [9–12].

☆ Registration: This systematic review was registered with the International Prospective Register of Systematic Reviews (maintained by University of York Center for Reviews and Dissemination, at http://www.crd.york.ac.uk/PROSPERO/) (Protocol # CRD42015030215).

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Incessant VT (>10% burden over 24 h during Holter testing) often occurs secondary to myocardial tumors or unknown etiology [13,14]. Unfortunately, because VT is more prevalent in adults, often with fatal outcomes, it was falsely believed that VT in children/adolescents had the same characteristics, etiologies, and outcomes without evidence-based data. There is also no standard diagnostic approach, and management is heterogeneous and variable between different centers [15].

Given this, our systemic literature review was designed to identify evidence-based characteristics, etiologies, risk stratification, and initial management plans of pediatric ventricular tachycardia.

2. Methods

We performed a systematic review of the literature using *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses (PRISMA) guidelines [16].

"PubMed," "Science Direct," "Web of Science", "CINAHL" and "Cochrane" databases were searched for relevant studies using the search terms "ventricular tachycardia," "pediatric," "children," "management," "risk", and "treatment" (Fig. 1).

A total of 98 citations were initially selected. 64 studies were included according to the pre set inclusion criteria (Table 1). Inclusion criteria included neonatal/pediatric/adolescent subjects; retrospective or prospective case series, case-control studies that described natural history of idiopathic VT in structural normal heart, and risk factors for sudden cardiac death in secondary VT in structurally normal or abnormal heart. Studies were excluded if they were performed using animal models, exclusively described adult patients, or were review articles.

Risk of bias was assessed using the Cochrane risk of bias tool [17]. This systematic review was registered with International Prospective Register of Systematic Reviews (maintained by University of York Center for Reviews and Dissemination, at http://www.crd.york.ac.uk/PROSPERO/) (Protocol # CRD42015030215).

3. Results

We found 64 studies focused on three types of VT (Fig. 1) (Table 1). These can be subdivided as follows: Idiopathic VT in structurally normal hearts (24 studies), secondary VT in structurally normal hearts (22 studies) and VT in structurally abnormal heart (18 studies).

A) Idiopathic VT in structurally normal hearts:
Wang [18] identified benign and malignant forms of arrhythmias that can occur in normal hearts [19].
The **benign forms** included benign premature ventricular contractions (PVC), accelerated idio-ventricular rhythm (AIVR), and outflow ventricular tachycardia (OVT) of either the right or left ventricle.
AIVR [20–23]: Common in neonates and usually asymptomatic. Its rate is 10–15% faster than the expected sinus rhythm and it is suppressed by activity (feeding/crying). Treatment is reassurance after structural heart disease, and metabolic or toxic causes have been ruled out [8].
OVT [24–29]: The most common cause of pediatric VT (60–80%), and usually asymptomatic. There is a bimodal pattern of peak incidence with peaks in infancy and 8 years of life. Ventricular rates are generally <200 bpm. Treatments of choice are: beta blockade, verapamil (except infants), and ablation. Also, it must be differentiated from arrhythmogenic right ventricular cardiomyopathy

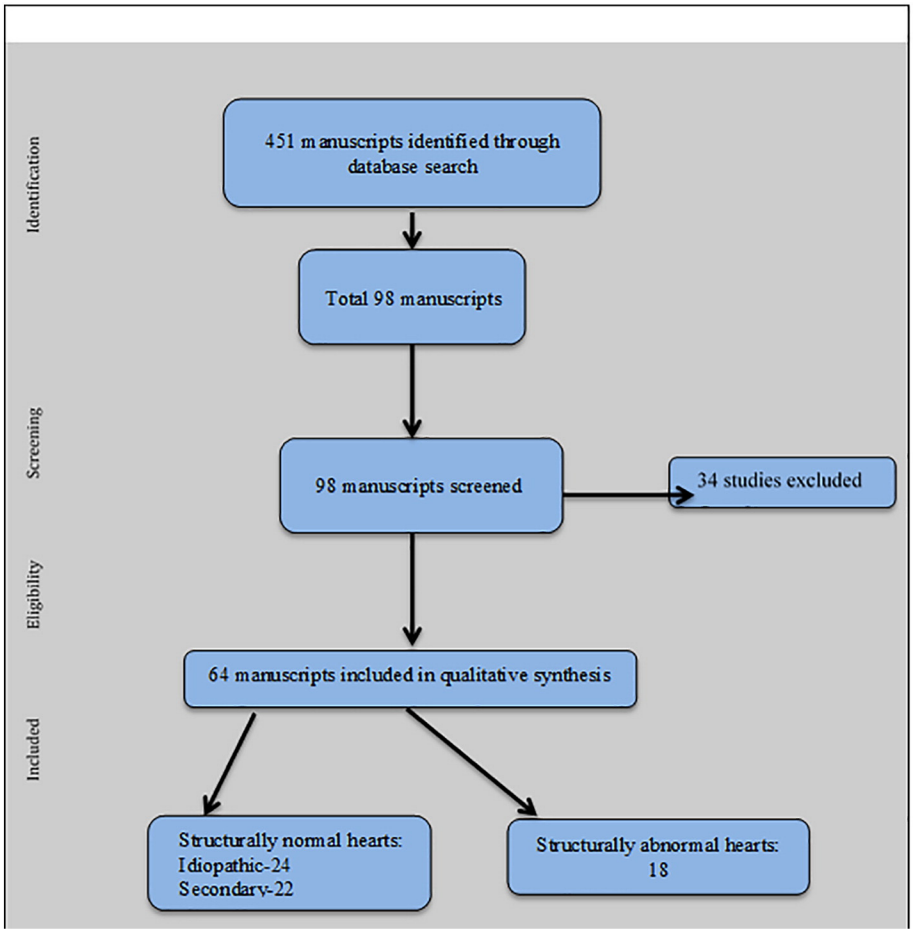

Fig. 1. Systemic literature review PRISMA flow chart.

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Table 1
Risk assessment of studies used for qualitative synthesis.

Studies	Random sequence generation	Allocation concealment	Performance bias	Detection bias	Attrition bias	Reporting bias
Aditya 2013	L	U	L	L	L	L
Altman 1995	L	U	U	L	L	L
Anderson 2014	L	U	U	L	L	L
Baman 2010	L	U	L	L	L	L
Basso 2015	L	L	L	L	L	L
Beaufort 2008	L	U	L	L	L	L
Biffi 2002	L	U	L	L	L	L
Bisset 1984	L	U	L	L	L	L
Brescia 2013	L	U	L	L	L	L
Collins 2013	L	L	U	L	L	L
Czosek 2013	L	U	L	L	L	L
Daliento 1999	U	U	L	L	L	L
Daniels 2006	L	L	L	U	L	L
Davis 1996	U	U	U	L	L	L
De Rosa 2006	L	U	L	L	L	L
Deal 1986	L	H	U	L	L	L
Deniz 2008	L	U	L	L	L	L
Elbardissi 2008	L	U	L	L	L	L
Esra 2012	L	U	L	L	L	L
Freire 2008	H	U	L	L	L	U
Garson 1987	L	U	L	L	L	L
Garson 1991	U	H	U	U	L	L
Gatzoulis 1995	L	L	L	L	L	L
Gehi 2006	L	U	L	L	L	L
Ghai 2001	L	U	L	L	L	L
Goldenberg 2008	L	U	L	L	L	L
Grun 2012	L	U	L	L	U	U
Harris 2006	L	U	L	L	L	L
Harrison 1997	L	H	U	L	L	L
Hasdemir 2011	L	U	L	L	L	L
Hayashi 2009	L	U	L	L	L	L
Huh 2001	L	U	L	L	L	L
Iwamoto 2005	L	U	L	L	L	L
Johnsrude 1995	L	U	L	U	L	U
Kammeraad 2004	L	L	L	L	L	L
Kavey 1984	L	L	L	L	L	L
KEANE 1993	U	U	L	L	L	L
Khairy 2008	L	U	L	L	L	L
Khairy 2008	L	U	L	L	L	L
Kindermann 2008	L	L	L	L	L	L
Leenhardt 1995	L	L	L	L	L	L
Lipshultz 2013	L	U	L	L	L	L
Malhatra 1994	L	U	L	L	L	L
Merino 1998	L	U	L	L	L	L
Pahl 2012	L	U	L	L	L	L
Park 2012	L	L	L	L	L	L
Paul 1990	L	U	L	L	L	L
Pfammatter1999	L	U	L	L	L	L
Priori 2012	L	U	L	L	L	L
Probst 2007	L	U	L	L	L	L
Ram 1995	U	L	L	L	U	L
Roston 2015	L	H	U	L	L	L
Schwerzmann 2009	L	U	L	L	L	L
Song 2010	L	L	L	L	L	L
Suesaowalak 2008	L	U	L	L	L	L
Te Riele 2014	L	U	L	L	L	L
Tsuji 1995	L	U	L	L	L	L
Valente 2014	L	U	L	L	L	L
Van Hare 1991	U	H	U	L	U	L
Vetter 1981	L	U	L	L	L	L
Webber 2012	U	U	U	L	L	L
Wolfe 1993	L	U	L	L	L	L
Yetman 1998	L	U	L	L	L	L
Zuckerman 2011	L	U	L	L	L	L

L: low risk, U; unclear risk, H: high risk.

(ARVC). This differentiation is suggested by high burden (>500 PVCs/24 h), multiple morphologies, family history, echo findings, and T wave inversion in precordial leads [30]. Alternative methods of differentiation/diagnosis were: QRS duration algorithm [31], signal averaged ECG [32], and cardiac MRI [33].

Benign premature ventricular contractions (PVC) [8,34–39]: Frequent in neonates, infants and children. Benign PVCs are characterized by 24-hour burden of <20%, and no complex criteria (bigeminy, multiform, couplets or non-sustained VT). Treatment is reassurance unless it is symptomatic. Right ventricle originated PVCs have better prognosis than left ventricle originated as the natural history of the former is spontaneous resolution [40] and the association with structural disease is low.

Malignant forms include malignant PVCs/VT, infantile incessant

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VT (IIVT), bundle branch reentrant tachycardia (BBRT), and intra-fascicular VT (FVT).

Malignant PVCs and polymorphic VT [36–39]: Burden is more that 20% in 24 h or it shows complex criteria. Secondary causes with structural normal or abnormal heart have to be ruled out. Polymorphic VT is characterized by beat-to-beat variations in QRS morphology and/or axis [8] which is uncommon in the pediatric population and carries a less favorable prognosis than monomorphic VT [41].

IIVT [10,13,14]: Monomorphic VT originating in the LV. Its 24-hour burden is usually > 10%. Its mortality rate is up to 15%. Treatment is procainamide and flecainide, and again, secondary causes must be ruled out.

(BBRT) [42]: It is associated with LV enlargement, heart failure and myotonic dystrophy. It is characterized by intraventricular delay or PR prolongation. Treatment is radiofrequency ablation.

Intra-fascicular VT (FVT) [29,43,44]: Accounts for 10–15% of IVT. It is triggered by stress or exercise. Patient age is usually in the adolescent period. Treatment is calcium channel blocker or ablation. Exercise-induced VT [45] could be either catecholaminergic polymorphic ventricular tachycardia or fascicular VT, but exercise induction cannot be included in differentiation between benign and malignant VT variants [3,46].

B) SCD risk stratification in secondary VT in structurally normal hearts:

While secondary VT typically presents as malignant PVCs or polymorphic VT [47] with positive cardiac symptoms, or positive family history of cardiac disease [48,49] , it may unfortunately have an initial presentation of sudden arrhythmic death syndrome(SADS), sudden infant cardiac death or sudden infant death syndrome (SIDS). SADS constitutes up to 5% of SCD in the general population aged 16–64 years and almost 25–35% of sudden deaths in the <40 years age group [50]. SIDS occurs in approximately 50/100,000 in the Unites States [51–53]. Given the relatively new introduction of molecular autopsy and the difficulty in making post-mortem diagnoses of channelopathies, without genetic testing, and cardiomyopathies that may have variable phenotypic presentations, the true relationship between these abnormalities and SIDS is difficult to confirm.

I. **VT in channelopathies**:

Three main types of channelopathies have been identified as a cause of ventricular arrhythmias in pediatric patients – catecholaminergic polymorphic VT (CPVT), long QT syndrome (LQTS), and Brugada syndrome (BrS). Song, Baek, Kwan et al. [41] did logistic regression analysis that revealed catecholaminergic polymorphic VT(CPVT) , in addition to cardiomyopathy associated VT, polymorphic VT, and sustained VT were significantly correlated with death or cardiac arrest. A summary of risk factors for SCD in **LQTS** [54–56], **Br S** [57–59], and **CPVT** [47,60,61] is shown in Table 2. Again, significant practice variation exists among pediatric electro physiologists with frequent deviation from the accepted diagnostic and therapeutic practices for adult Br S patients [62] in particular.

II. **VT in cardiomyopathies**:

Song et al. [41] observed that the expected life span without cardiac arrest was <4 years in the cardiomyopathy-associated VT group(CMP-VT) which includes : hypertrophic cardiomyopathy (**HCM**) [63,64], arrhythmogenic right ventricular cardiomyopathy (**ARVD**) [65,66], dilated cardiomyopathy (**DCM**) [67], non-compaction of left ventricle (**NCLV**) [68,69] and restrictive cardiomyopathy (**RCM**).

Risk factors for pediatric/adolescent SCD for **HCM** [63,64], (**ARVC**) [65,66], **DCM** [67], **NCLV** [68,69] and **RCM** [70] are shown in Table 2.

III. **VT in myocarditis:**

Eight risk factors were identified for SCD [71–73] in

Table 2
Risk factors for SCD in secondary pediatric VT in structurally normal hearts.

A. Channelopathies	
Long QT Syndrome	LQT2 female >40 years old,
	LQT1 in young asymptomatic male
	LQT8
	QTc > 500 msec
	History of syncope
	Symptoms prior to age 7 years
	Lack of beta blocker therapy
CPVT	Younger age at diagnosis
	Lack of beta blocker therapy
	History of aborted cardiac arrest (ACA)
	Probands
	Male gender
Brugada syndrome	Type 1 ECG
	History of syncope
	QRS fragmentation
	Ventricular effective refractory period <200 msec
	Male gender
B. Cardiomyopathies	
HCM	Presentation in infancy
	Inborn errors of metabolism
	Mixed hypertrophic and dilated or restrictive cardiomyopathy
	Increased corrected QT interval (QTc) dispersion on ECG
	Ventricular tachycardia (VT) on ambulatory ECG
	Myocardial bridging of the LAD coronary artery
	Female >1 year old
	Failure to thrive in <1 year old
	Congestive heart failure in <1 year old
	LV posterior wall diastolic thickness >1 Z score
DCM	Age at diagnosis younger than 14.3 years
	LV dilation
	LV posterior wall thinning
	Fractional shortening <18%
	LV ejection fraction <35%
ARVC	Symptomatic
	Probands
	≥ three precordial inverted T waves
	Any depolarization in right precordial leads
	PVC count of more than 760 on 24 hour Holter
	Male gender
NCLV	Severe left ventricular dysfunction
	Previous history of arrhythmia
	Recurrent syncope
	Presentation in infancy
	ST changes/T wave inversion
	Genetic/metabolic disease
	Family history of sudden cardiac death
RCM	Congestive heart failure
	Lower fractional shortening
	Increased LV posterior wall thickness in RCM/HCM group
	Combined RCM/HCM
C. Myocarditis	
Late gadolinium enhancement (LGA) by MRI	
Class III or IV NYHA	
Histological evidence of inflammation	
Steroid therapy	
Inotropic therapy	
Lack of beta blockers prophylaxis	
CHF	
High BNP	

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Table 3
Risk factors for SCD in congenital heart disease.

TOF s/p repair	RV mass to volume ratio >0.3 g/ml
	LVEF Z score ≤ 2
	Hx of atrial tachyarrhythmia
	RVSP >60 mm Hg
	RVEDP >8 mm Hg
	30 PVC/h, Lown grade 2 or more
	Age >25 years old
	Fragmented QRS complex
	LVEDP > 12 mm Hg
	QRS > 180 msec
	Longer QT dispersion (QTD)
	RV fibrosis
	Prior palliative shunt (Late repair)
	Inducible sustained VT during EPS
	Lower RV ejection fraction
	RV dilatation
	Severe PR
Aortic stenosis	Aortic Gradient >50 mm Hg
	High LVEDP
	High LVSP
	AR
	NYHA 2 or more
	Male gender
Single ventricle palliations	Atrial arrhythmia
	Depressed single ventricle function
	Older Fontan techniques
	Longer time since repair
TGA s/p atrial switch (Mustard or Senning)	NYHA > II
	Complex TGA
	Atrial arrhythmia
	QRS > 140 msec
	Moderate TR
	↓RVEF
MVP	Female gender
	Bi leaflet MVP
	Frequent complex PVCs
	Fibrosis of papillary muscles and infero-basal LV wall

myocarditis.

IV. **VT in cardiac tumors:**
Malignant tumors and infantile oncocytic cardiomyopathy have been identified as being at increased risk for SCD [74,75].

V. **VT post myocardial infarction:** Causes of myocardial infarction in pediatric age were: 58% CHD, 13% cardiomyopathy-induced, and 29% acquired causes. The only identified risk factor for SCD was first 48 h post infarction [12].

C) **SCD risk stratification in VT in structurally abnormal hearts**:
Roggen [7] identified different forms of ventricular tachycardia in structural heart disease as follows: monomorphic VT (75%), ventricular fibrillation (19%), and Torsades de Pointes (3%).
Four adult congenital heart patient populations have been recognized as high risk for SCD secondary to VT: Tetralogy of Fallot status post repair, aortic valve disease, single ventricle palliations, and patients with transposition of the great arteries that are status post atrial switch procedures – Senning or Mustard [76].
Post operatively, QRS duration and corrected JT interval can predict incessant VT [77].
As shown in Table 3, nine studies identified risk factors for SCD in Tetralogy of Fallot [78–86], and two studies were identified in each of the following lesions: aortic valve disease [87,88], single ventricle palliations [89,90], and atrial switches [91,92].
Additionally, four risk factors for SCD in mitral valve prolapse were identified [93,94].

D) **Risk of bias calculation for included studies**
Cochrane risk of bias analysis tool showed low risk of bias for random sequence generation, performance, detection, attrition, and reporting. Allocation concealment bias was unclear (Fig. 2).

4. Discussion

Pediatric PVCs and VT causes, and consequently their risks for SCD, are different from those of adults.

The Pediatric and Congenital Electrophysiology Society (PACES) in conjunction with the Heart Rhythm Society (HRS) has formulated a consensus for the management of pediatric ventricular arrhythmia in structurally normal hearts, but it admittedly lacks evidence and also lacks any suggestion of a diagnostic strategy [8]. PACES/HRS did formulate another consensus focused on management of pediatric arrhythmia in structurally abnormal hearts, but it is focused only on indications of ICD implantation. It cited the ejection fraction of the systemic ventricle <35%, high NYHA class, and prolonged QRS duration as risk factors for VT and SCD regardless congenital heart disease category [95].

Our evidence based systematic literature review is focused on a diagnostic strategy for idiopathic benign, malignant, and secondary causes of VT, in addition to risk stratification for SCD in secondary pediatric VT in both structurally normal and abnormal hearts. Immediate post cardiac surgery VT is beyond the scope of our literature review.

While VT can present as palpitations or syncope, palpitations have a higher diagnostic yield for VT on Holter than syncope (97). Unfortunately, as mentioned previously, asymptomatic secondary VT exists (e.g. channelopathies) and can present the first time as sudden arrhythmic cardiac arrest or sudden infant death syndrome.

Before attributing PVCs/VT on EKG to a primary cardiac problem we have to rule out non-cardiac etiologies/contributors including

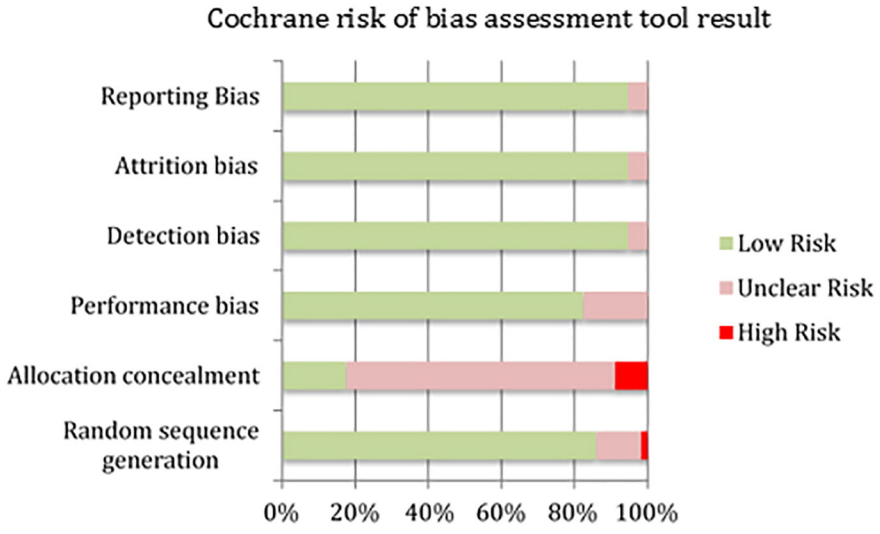

Fig. 2. Cochrane risk of bias assessment tool results.

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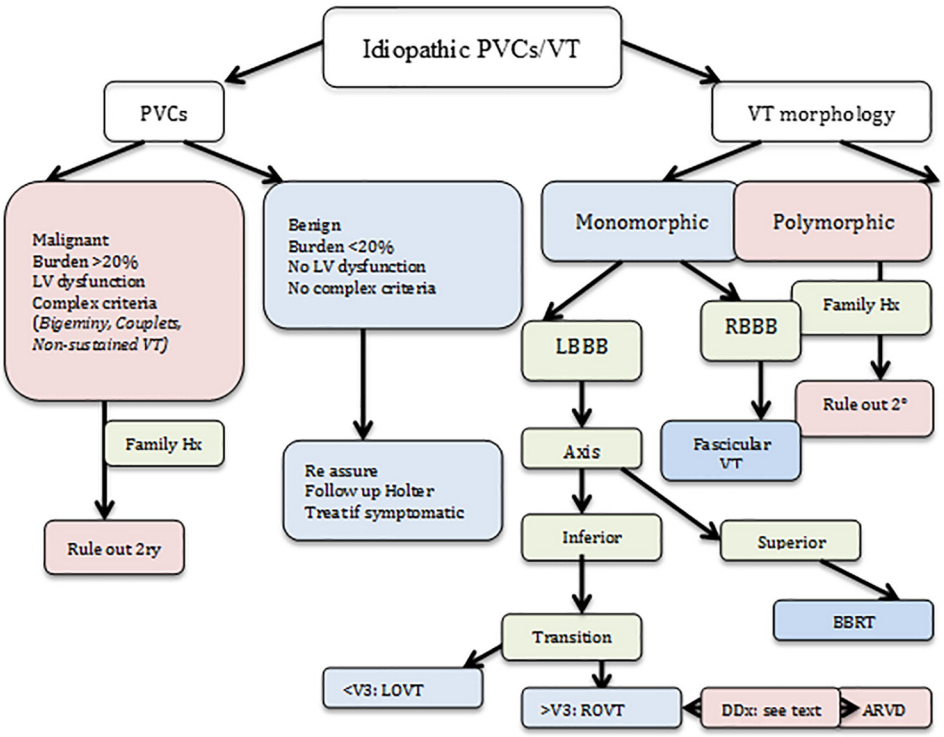

Fig. 3. Evidence based diagnosis and risk assessment of idiopathic benign and malignant variants of VT using EKG, Echo and Holter.

prescribed medication, electrolytes disturbances, recreational/illicit drugs and supplements (e.g., energy drinks and body building products).

Adding Holter monitoring to EKG increases the diagnostic yield for VT [3] and also quantifies arrhythmia burden, PVC/VT complexity/morphology, and can give an idea about the effect of exercise on ventricular arrhythmia provided the child has some periods of increased activity during the monitoring period. Finally echocardiography rules out left ventricular dysfunction secondary to high PVC/VT burden, and rules in/out structurally abnormal hearts and/or secondary causes (DCM, HCM, LVNC etc.).

Using all these criteria for each variant of idiopathic VT, we formulated a diagnostic algorithm to differentiate benign from malignant cases. Also we pointed out criteria that denote possible underlying secondary cause (Fig. 3). Evaluation for secondary etiologies should be performed if any of the following occurs: malignant PVCs, polymorphic VT and/or family history of SCD or family history of inherited cardiac disease. Malignant PVCs are described as any PVCs burden >20% over a 24-hour Holter, any associated LV dysfunction, bigeminy, couplets, or non-sustained VT.

For monomorphic VT; RBBB morphology indicates fascicular VT but LBBB morphology could be BBRT (if superior axis is associated) or it could be an outflow VT (right versus left origin can be differentiated by lead transition in surface EKG as shown in Fig. 3).

Finally, evidence-based risk factors for SCD in channelopathies, cardiomyopathies, myocarditis, cardiac tumors and post myocardial infarction are different in pediatric age population than adult (Table 2). We identified LQT1in young asymptomatic males, symptomatic LQT prior to age 7 years, and CPVT diagnosed at younger age as unique risk factors for SCD in the pediatric channelopathies. Infantile presentation of HCM, female gender after infancy, mixed cardiomyopathy phenotype, associated inborn error of metabolism, infantile failure to thrive, post infancy heart failure, and LV posterior wall diastolic thickness > 1 Z score are risk factors for SCD in pediatric HCM. DCM diagnosis at age < 14.3 year, LV posterior wall thinning in DCM, NCLV infantile presentation, NCLV association with genetic/metabolic disease, RCM with reduced systolic function or mixed RCM/HCM are pediatric specific risk factors for SCD in other cardiomyopathies.

Also we identified risk factors for SCD in congenital heart diseases (Table 3) as follow: SCD risks in TOF S/P repair closely mirror the known indications for pulmonary valve replacement but pure arrhythmia-related indications were also identified: 30 PVCs/h, fragmented QRS complex, QRS > 180 msec, longer QT dispersion, RV fibrosis (nidus for reentry), inducible sustained VT during EPS and Hx of atrial arrhythmias.

The main determinants for SCD risk in patients with aortic stenosis were severity of stenosis, associated regurgitation and male gender while risk factors for SCD in palliated single ventricle physiologies are atrial arrhythmia, depressed systolic function of systemic ventricle and longer time since palliation.

D-TGA s/p repair risk factors for SCD were atrial arrhythmias, moderate TR, complex TGA anatomy, QRS > 140 msec and depressed RV systolic functions. Finally, female gender, bi-leaflet MVP, frequent complex PVCs and fibrosis of papillary muscles or infero-basal LV wall have been identified ad SCD risk factors for mitral valve prolapse.

5. Conclusion

Causes of pediatric VT are different from adults. We propose an evidence-based diagnostic decision making algorithm (Fig. 3) utilizing EKG, echo and Holter, to differentiate idiopathic benign from malignant pediatric VT as well as clues to secondary causes of VT. We also identified evidence-based risks factors for sudden cardiac death in secondary VT in structurally normal and abnormal hearts (Tables 2 and 3).

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