Advances in treatment of pediatric arrhythmias

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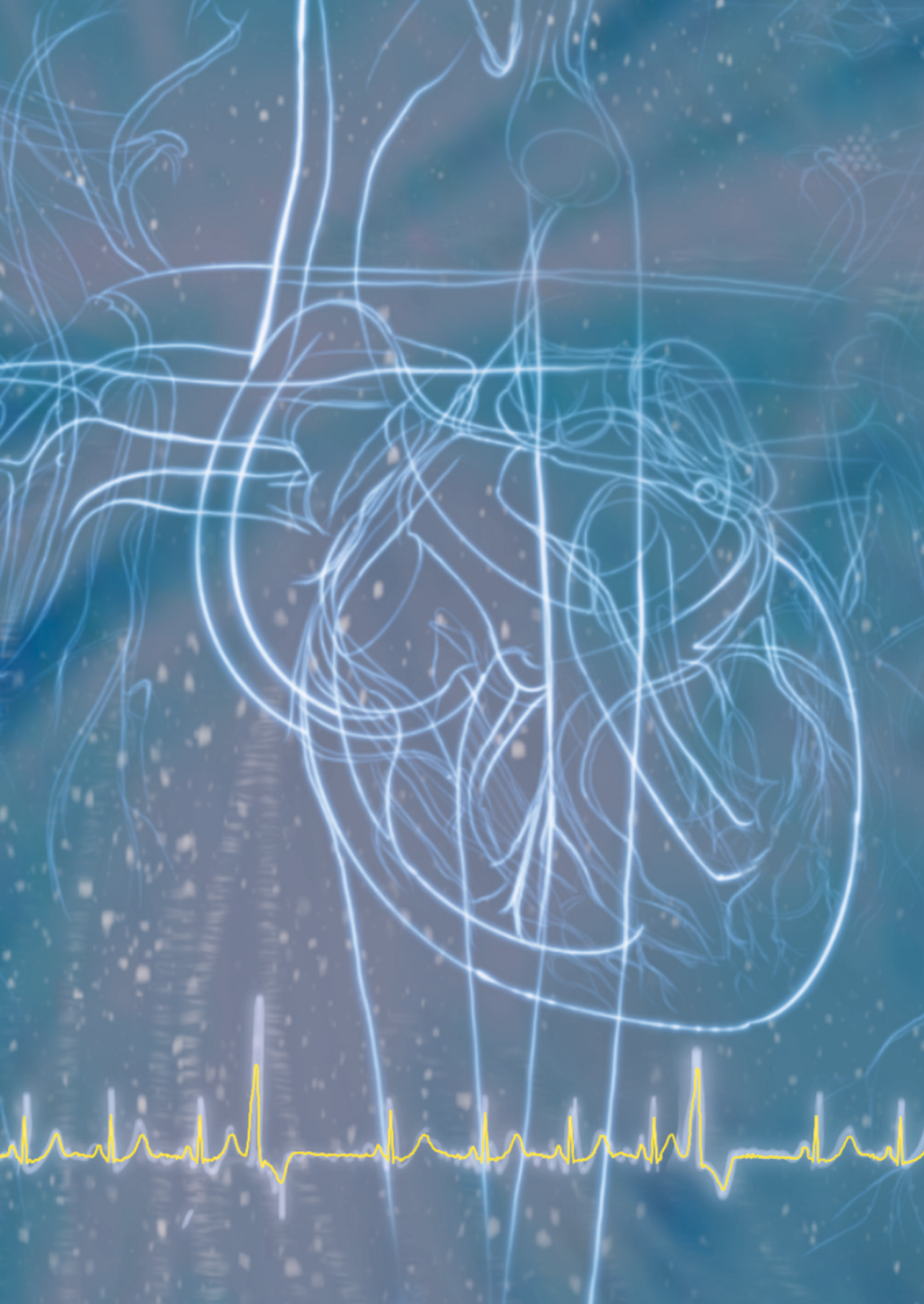
PART II

ANTI-ARRHYTHMIC DRUG TREATMENT OF FREQUENT PREMATURE VENTRICULAR COMPLEXES



5 CHAPTER

Left ventricular dysfunction is associated with frequent premature ventricular complexes and asymptomatic ventricular tachycardia in children

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ABSTRACT

Aims

To assess the risk factors for left ventricular (LV) dysfunction in a paediatric population with idiopathic frequent premature ventricular contractions (PVCs) and asymptomatic ventricular tachycardias (VTs).

Methods

Paediatric patients with the diagnosis of idiopathic frequent PVCs and asymptomatic VTs were retrospectively evaluated. Frequent PVCs were defined as ≥5% on 24 h Holter recording. Left ventricular dysfunction was defined as a shortening fraction of ≤28%.

Results

Seventy-two children were identified. Six patients showed LV dysfunction at diagnosis [age 10+7 years, 2 (33%) had symptoms such as syncope, palpitations, fatigue, and dizziness], and 66 showed normal LV function [age 8+6 years, 22 (33%) with symptoms]. Patients with LV dysfunction had a higher percentage of PVCs on Holter recordings (47+16 vs. 16+11%, P ¼ 0.006), higher prevalence of VT [5 (83%) vs. 27 (41%), P ¼ 0.045] and sustained ventricular tachycardia (sVT) [3 (50%) vs. 4 (6%), P ¼ 0.001], and a higher number of couplets [6 (100%) vs. 34 (52%), P ¼ 0.030]. In patients with LV dysfunction, two responded to medication (Classes Ic and II) and five underwent ablation, of which one was unsuccessful. During follow-up, LV function normalized in five of six patients. In patients with a normal function, none developed LV dysfunction during the follow-up.

Conclusion

In children with idiopathic PVCs and asymptomatic VTs, development of LV dysfunction is associated with a higher burden of PVCs, the presence of sVTs, and couplets. Left ventricular dysfunction appears to be reversible if the burden of PVCs is decreased by medication or ablation.

INTRODUCTION

Frequent idiopathic premature ventricular contractions (PVCs) and asymptomatic ventricular tachycardia (VTs) in children and young adults are rare, especially in in the first decade.(1) In older children and young adults the incidence increases,(2) although exact numbers are unknown, since most patients are asymptomatic. Idiopathic frequent PVCs were always considered benign in all age groups.(1) However, over the past decade frequent PVCs have emerged as cause of LV dysfunction, LV dilatation, congestive heart failure and even sudden cardiac death in the adult population.(3;4) Pediatric data on PVCs in relation to left ventricular dysfunction is limited. In children with frequent PVCs decreased shortening fraction (SF) or decreased left ventricular ejection fraction (LVEF) has been reported.(5-7) Also small series in children with asymptomatic idiopathic VTs have described development of LV failure and cardiomyopathy.(8-10) In adults risk factors for PVC/asymptomatic VT induced LV dysfunction have been identified. Different studies have shown the burden of PVCs to be a significant determinant of developing LV dysfunction.(11-14) Other risk factors reported in adult series are a short coupling interval, prolonged QT interval, retrograde P-wave, duration of PVCs and presence of (non-sustained) VTs.(5;12-14)

Current guidelines recommend anti-arrhythmic drug therapy or catheter ablation as treatment options for children and adults with symptomatic PVCs/VTs and fast non-sustained VT (nsVT).(15;16) However, especially in the pediatric population data are lacking to justify treatment of frequent PVCs/VTs in asymptomatic patients to prevent LV dysfunction. This study aims to assess which determinants of asymptomatic PVCs/VTs are associated with development of LV dysfunction in children.

METHODS

For this retrospective study, the paediatric cardiology databases of three collaborating university hospitals in the Netherlands were searched for patients with the diagnosis of VTs and PVCs under the age of eighteen. All children with frequent monomorphic PVCs (defined as more than 5% PVC burden on a holter-recording) with or without asymptomatic VTs were included. Patients with a structural heart disease, a history of cardiac surgery, myocarditis, cardiomyopathies, prolonged QT syndrome or verapamil sensitive PVCs/VTs were excluded. Data of eligible subjects were collected using all available medical records, electrocardiograms (ECG's), holter-recordings and echocardiographic parameters. Demographic and clinical data, including sex, age, weight, length, symptoms, operations and use of anti-arrhythmic medication or radiofrequency ablation were recorded.

PVC characteristic were reviewed on 12 lead surface ECGs. The following PVC parameters were evaluated: QRS axis, block pattern, QRS duration QTc interval , and coupling/R-R ratio (the coupling interval divided by R-R interval during sinus rhythm). The frequency of PVCs was defined as percentage of the total QRS complexes on holter-recordings. Holters were

reviewed for the presence of couplets, bigemy, trigemy, and quadrigemy, non-sustained ventricular tachycardia (nsVT) (three or more consecutive PVCs and less than 30 seconds) and sustained ventricular tachycardia (sVT), holter. In all patients echocardiograms were reviewed to evaluate LV function. LV shortening fraction (SF) and left ventricular diameter at end of the diastole (LVEDd) were measured on sinus beats. The latter value was normalized by z-Score. LV dysfunction was defined as a SF less than 28%.

Statistical analysis

Statistical analyses were performed using SPSS 20.0 software. A ***p*** value of 0.05 or less was considered statistically significant. Continuous data were analyzed using the binary logistic regression and categorical data were analyzed using the chi-square test and Fisher's exact test where appropriate. Continuous data are presented as mean ± standard deviation and categorical data as numbers with percentages.

Dutch law does not require informed consent for retrospective observational studies, provided the results are reported anonymously; therefore, the need for informed consent was waived by the local medical ethical committee.

Table 1: Patient Characteristics in relation to LV function

	SF < 28% (n= 6)	**SF > = 28% (n= 66)**	**p-value**
Age (y)	10.3 (± 6.8)	8.2 (± 5.8)	0.409
Male sex (%)	3 (50)	38 (58)	0.737
Weight (kg)	47 (± 36)	32 (± 22)	0.204
Length (cm)	134 (± 65)	133 (± 37)	0.973
Body mass index (kg/m2)	20 (± 5)	18 (± 3)	0.192
Syst. BP	92 (± 36)	107 (± 19)	0.298
Diast. BP	58 (± 39)	65 (± 13)	0.498
Symptoms (%) *Cardiac arrest (%)* *Syncope (%)* *Palpitations (%)* *Dizziness (%)* *Fatigue (%)* *Reduced physical activity (%)* *Chest pain (%)*	2 (33) *0 (0)* *1 (17)* *1 (17)* *1 (17)* *0 (0)* *0 (0)* *1 (17)*	22 (33) *0 (0)* *5 (8)* *13 (20)* *5 (8)* *4 (6)* *1 (2)* *5 (8)*	1.000
Follow up (years)	*3.8 (± 4.1)*	*3.8 (± 4.0)*	0.993

All values are expressed as mean (± SD) or n (%). LV = Left Ventrical; SF = Shortening Fraction; Syst. BP = Systolic Blood Pressure; Diast. BP = Diastolic Blood Pressure.

RESULTS

Eighty children (45 male, 35 female) with frequent PVCs with or without asymptomatic VTs were included into this study. Eight children did not have ECG or holter recording at follow-up and were defined as lost to follow-up. The median age of the remaining 72 patients in this study was 8 years, range 0-17. A total of six children (8%) showed LV dysfunction, having a SF of less than 28% at diagnosis, of which two (33%) had symptoms of heart failure. Sixty-six children showed a normal LV function at diagnosis. The baseline characteristics are presented in Table 1. Symptoms including vasovagal syncope, palpitations, dizziness, fatigue, reduced physical activity and chest pain were reported in 24 patients.

Table 2: Comparison of determinants of PVCs in patients with different Left Ventricular (LV) function

	SF < 28% (n=6)	SF >= 28% (n=66)	p value
QRS axis			0.939
Inferior	5 (83)	53 (80)	
Superior	1 (17)	13 (20)	
Block pattern			0.611
LBBB	3 (50)	43 (65)	
RBBB	3 (50)	23 (35)	
QRS duration	173 (± 22)	162 (± 28)	0.356
QTc	493 (± 23)	486 (± 65)	0.811
Coupl/R-R ratio	0.63 (± 0.14)	0.65 (± 0.13)	0.760
Couplets	6 (100)	34 (52)	0.030
Bigeminy	6 (100)	50 (76)	0.327
Trigeminy	4 (67)	45 (68)	0.939
Quadrigeminy	2 (33)	9 (14)	0.219
VT	5 (83)	27 (41)	0.045
nsVT	2 (33)	23 (35)	0.941
sVT	3 (50)	4 (6)	0.001
PVC burden	47 (± 16)	16 (± 11)	0.006
LV Z-score	2.2 (± 1.8)	1.3 (± 1.0)	0.112

All values are expressed as mean (± SD) or n (%). QRS axis = axis of PVC in frontal plane; SF = Shortening fraction; Block pattern = pattern of PVC; LBBB = Left bundel branch block; RBBB = Right bundel branch block; QRS duration = length of QRS of PVC (ms); QTc = QTc of PVC (ms); Coupl/R-R ratio = Coupling interval divided by R-R interval during sinus rythm; VT = Ventricular Tachycardia; nsVT = nonsustained VT; sVT = sustained VT; PVC burden = Total precentage PVCs on holter; LV z-score = an adjusted value of left ventricular end diastolic diameter by size; Couplets, bigeminy, trigeminy and quadrigeminy are present when seen on Holter recording.

There were no statistically significant differences in baseline age, sex, weight, length, blood pressure, presence of symptoms and follow up duration between the group with LV dysfunction and the group with a normal LV function.

Determinants of PVCs

The PVC parameters of both groups are presented in Table 2. All PVCs and VTs were classified as inferior or superior axis and as LBBB or RBBB pattern. There was no difference in QRS axis (p=0.939), block pattern (p=0.611) between children with LV dysfunction versus normal LV function. There were no differences in QRS duration (p=0.356), QTc (p=0.811) and coupling-interval/RR-interval (p=0.760) between the groups .

The burden of PVCs was markedly increased and significantly higher in the group with LV dysfunction than in the group with a normal LV function (47 ± 16% vs 16 ± 11%, p=0.006). On holter-recording all patients with LV dysfunction had couplets, as compared to 52% of patients with normal LV function (p=0.030). Also, in the group with LV dysfunction five patients (83%) had VTs which is significantly higher compared to 27 (41%) patients in the group without LV dysfunction (p=0.045). In patients with LV dysfunction sustained VT was more frequently present than in the group with normal LV function (3 pts (50%) vs 4 pts (6%), p=0.001). Other determinants such as trigeminy, quadrigeminy and bigeminy showed no statistical difference. Furthermore, the LVEDd measured during sinus beats on echocardiograms tended to be higher in patients with LV dysfunction, but were not significantly different (p=0.112).

Individual patients

The individual patients with LV dysfunction are presented in Table 3. PVC/VT has an inferior axis in 5 out of 6 patients. All patients had a high PVC burden of 30 % or more. Only one child with LV dysfunction did not have VTs, this patient also had the lowest PVC burden in this group. The shortening fraction at diagnosis was 23-26% in 5 patients and less than 18% in one patient. LV function recovered in 5 of 6 patients after medication (N=2, class Ic and II) or ablation (N=3). Ablations were performed under general anaesthesia in children under the age of 16 and local anaesthesia over the age of 16 years. Mapping was facilitated by an electroanatomical mapping system (CARTO, Biosense Webster, USA) using a transvenous or retrograde aortic approach. At the site of earliest activation based on the onset of bipolar electrogram, reversed polarity in the bipolar electrogram and/or a QS configuration in the unipolar electrogram, pace-mapping was performed to confirm a ≥ 11/12 lead QRS pace-match. Radiofrequency energy was delivered using a Navistar Thermocool uni-directional catheter (Biosense Webster, USA) with a target temperature of maximum 60°C and power output of 30 to 60 Watt depending on age, weight and focus.

PVCs remained and LV dysfunction persisted in one of 6 patients after an initially successful ablation procedure with recurrence of the PVCs. Based on scattered subendocardial patchy delayed enhancement (and no mesocardial or epicardial delayed enhancement) with a

dilated LV and a moderate systolic function on MRI made before the ablation procedure in our center, we think that the LV dysfunction was possibly related to extensive scarring due to multiple ablation lesions during prior procedures in another center. In the group of patients with a normal function, none developed LV dysfunction during a follow up of 3.8 years (+/- 4.1).

Table 3: Characteristics of patients with Left Ventricular (LV) dysfunction

	1	2	3	4	5	6
Sex	M	M	F	M	F	F
Age at diagnosis	1 month	15 y	15 y	16 y	11 y	3 y
QRS axis	Inferior	Inferior	Inferior	Inferior	Inferior	Superior
Block pattern	RBBB	RBBB	LBBB	LBBB	LBBB	RBBB
PVC burden (%)	40	47	74	30	34	57
VT	Yes	Yes	Yes	No	Yes	Yes
SF (%)	25	26	25	23	< 18	26
LVED Z-score	3.7	4.5	0.5	3.0	0.8	1.3
Medication	2	1C	NR	NR	NR	NR
Ablation	No	US	Yes	Yes	Yes	Yes
Focus PVC during EP study	N/A	Antero Lateral PM	Antero Septal RVOT	Anterior RVOT	Left Coronary Cusp	Postero Medial PM
PVC burden at FU	26	7	1	1	0	14
SF at FU (%)	43	31	29	32	40	12

QRS axis = QRS axis of PVC or VT on frontal plane; Block pattern = Block pattern of PVC; LBBB = Left bundel branch block; RBBB = Right bundel branch block; PVC burden (%) = Total percentage PVCs on Holter; VT = Ventricular tachycardy; SF = Shortening fraction; FU = Follow up; M = Male; F = Female; NR = Not responding on medication; US = Unsuccessful ablation; PM = papillary muscle; RVOT = right ventricular outflow tract. Numbers at medication correspond with anti-arrhythmic drugs according to Singh Vaughan Williams classification.

DISCUSSION

Idiopathic frequent PVCs are generally regarded as a benign condition and in the majority of patients with frequent PVCs cardiac function remains preserved during follow-up. However, studies in adults have shown a causal relationship between frequent PVCs and LV dysfunction and improvement of LV function after effective treatment of the PVC burden. (17-19) In children, studies on idiopathic PVCs and asymptomatic VTs related to LV function are limited and data about risk factors for LV dysfunction is lacking.(5-7;15)

In the present study we reviewed 72 patients with idiopathic frequent PVCs with or without asymptomatic VTs, which is one of the largest series of paediatric patients published. Major findings of our study are that LV dysfunction was present in 8 % of all children, which normalized after successful therapy and secondly, that the presence of LV dysfunction was significantly associated with a higher burden of PVCs, the presence of couplets and VTs. Furthermore, all children with LV dysfunction had a PVC burden of 30% or more.

None of the patients with normal LV function at diagnosis developed LV dysfunction during the follow-up, including those patients with a high PVC burden. Comparable to other studies, the impact of duration of a high PVC burden on LV function remains unknown since the time from onset of PVCs is unknown, as the majority of patients are asymptomatic. Furthermore, the follow-up period of this study is relatively short, longer follow-up might be needed for LV dysfunction to develop.

Studies performed in adults show that the burden of PVCs is a significant risk factor for the development of LV dysfunction. The patients that developed LV dysfunction had a burden of 29-33%, compared to patients without LV dysfunction having a burden of 9-22%.(11-14) Another significant risk factor confirmed in adult studies is the presence of nsVTs, with 24-76% of nsVTs in patients with LV dysfunction and 1-40% nsVTs in patients without LV dysfunction.(12-14) In our study we found that the presence of VT was significant related to LV dysfunction. Other possible risk factors like the focus of the PVCs and the couplings interval have not been identified as such in adult studies, which is in accordance to the results in our study.(11-14)

Pediatric data on risk factors for the development of LV dysfunction is scarce. Sun et al. report a decrease in ejection fraction of PVC beats and found an association with a short coupling interval and a prolonged QT-interval.(5) A study by Kakavand et al. describes a series of 28 patients in which those with LV dysfunction are compared to those without dysfunction.(6) The burden of PVC was significantly related to LV dysfunction, 36% compared to 18%, which is in concurrence with our study. The morphology of the PVCs was not significantly associated to LV dysfunction. Spector et al recently published a study of 36 patients with frequent PVCs (defined as more than 20%), in which no significant risk factors for LV dysfunction were found, although LV function tended to occur more of often in children with a high burden of PVCs, male gender and LBBB PVC morphology.(7) Another recent study by Guerrier et al included 123 patients with frequent PVCs (defined as more than 0.5%) in which there was no correlation between the LV function and the burden of PVCs.(20)

In our study we showed that LV dysfunction was reversible when the burden of PVCs is decreased by catheter ablation or medication. Although the number of successful ablations in this study is small, and success needs to be confirmed in larger series in this age group, it is in concordance with studies in adult patients, which describe reversibility of PVC- and

VT-induced LV dysfunction after treatment, with radiofrequency ablation or pharmacologic therapy.(6;17;18) Zang et al performed a meta-analysis of 15 studies including 712 adult patients who underwent catheter ablation of frequent PVCs.(19) The LV ejection fraction (LVEF) significantly increased after ablation by 7.7% overall and 12.4% in the subgroup of patients with LV dysfunction at baseline.

It is justifiable to conclude that frequent ventricular ectopy can induce LV dysfunction in the pediatric age group and that it is reversible by treatment with medication or ablation. A high burden of PVCs and the presence of VTs are both associated to LV dysfunction and might be used in stratification of those patients at risk for developing LV-dysfunction. However, more data are needed to warrant treatment to prevent LV dysfunction. At the moment patients with frequent ventricular ectopy should therefore be followed regularly with holter-recordings and echocardiography. If LV dysfunction develops medication or ablation is indicated to reduce the amount of ectopy. Ablation should only be performed in centers with experience in the younger age group, since the risk of side effects is higher in a younger age.

Study Limitations

This study is retrospective in design and although it is one of the largest series of patients published in the pediatric age group, the group is too small to perform a multi-variate analysis of risk factors. Therefore, we could not identify independent risk factors for development of LV dysfunction.

Conclusion

This is one of the largest studies published in children, that describes the risk factors of LV dysfunction in the presence of PVCs with or without asymptomatic VTs. The burden of PVCs, presence of VT and couplets are significantly related to LV dysfunction. LV dysfunction is reversible after treatment by catheter ablation or medication. Prospective studies are needed to identify otherwise asymptomatic patients at risk for LV dysfunction and to justify preventive treatment.

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