Risk Factors for Left Ventricle Enlargement in Children With Frequent Ventricular Premature Complexes

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We aimed to assess the risk factors for left ventricle (LV) enlargement in children with idiopathic frequent ventricular premature complexes (VPC) and discuss the clinical features and treatment strategies. Children diagnosed with idiopathic frequent VPC at Xinhua Hospital affiliated to the Shanghai Jiao Tong University during 2013 to 2019 were retrospectively evaluated. Gender, age, body mass index, weight, number and sources of frequent VPC, and changes in the LV structure were analyzed and compared. A total of 29 patient showed changes in LV enlargement at diagnosis [age 7.3 ± 4.0 years, 8 (24.1%) had symptoms such as syncope, palpitations, fatigue, and dizziness], whereas 220 showed a normal LV structure [age 7.2 ± 4.5 years, 77 (32.3%) with symptoms]. Patients with LV enlargement showed a higher percentage of VPC on Holter recordings (30.2 ± 10.7 versus 9.4 ± 6.9, $p < 0.05$), higher prevalence of ventricular tachycardia [22 (75.9%) vs 36 (16.4%), $p < 0.0001$], higher number of couplets [26 (96.7%) vs 132 (60.0%), $p = 0.002$], higher number of trigeminy [27 (97.8%) vs 133 (83.2%), $p < 0.001$], higher QRS wave width [80.0 ± 5.9 vs 77.8 ± 6.8, $p = 0.021$], and higher incidence of right bundle branch block [11 (37.9%) vs 2 (0.9%), $p < 0.001$]. Multivariate analysis suggested that right bundle branch block (Odds Ratio = 143.9 $p < 0.001$) and VPC burden (>20%) (Odds Ratio = 132.6, $p < 0.001$) were the risk factors for LV enlargement in children with idiopathic frequent VPC. In conclusion, frequent VPC can induce prominent enlargement or LV dysfunction in children. LV enlargement are reversible after catheter ablation or medication. © 2020 Published by Elsevier Inc. (Am J Cardiol 2020;131:49−53)

Ventricular premature complexes (VPC), one of the most common arrhythmias, occur in patients with heart abnormalities as well as in healthy patients.[1,2] In recent years, the incidence has increased significantly in children.[3] Idiopathic frequent VPC were always considered benign.[1] However, recent studies in adult have showed that the burden of frequent VPC might be a key factor for left ventricular (LV) dysfunction, LV dilatation and even congestive heart failure.[4−9] The relation between VPC and LV dysfunction or structural changes are still unclear in children . The current guidelines of the European Society of Cardiology recommend anti-arrhythmic drug therapy or catheter ablation as a treatment option for children with symptomatic VPC /VT and rapid nonsustained VT (nsVT).[10−12] Nevertheless, particularly in children, the data regarding treatment of frequent VPC /VTs to prevent LV dysfunction in asymptomatic patients is still lacking. In our study, we aimed to evaluate the risk factors for LV enlargement and dysfunction in asymptomatic children with frequent VPC.

Methods

We retrospectively reviewed the medical records of pediatric patients diagnosed with VTs and VPC admitted to Xinhua Hospital Affiliated to the Shanghai Jiaotong University between January 2003 and November 2019. All patients fulfilled the following inclusion criteria: (1) with frequent monomorphic VPC (defined as 5% VPC burden on a Holter recording) with or without asymptomatic VTs; (2) under the age of 14 years. Patients with structural heart disease, history of cardiac surgery, myocarditis, cardiomyopathy, and prolonged QT syndrome were excluded. The demographic and clinical data were collected, such as gender, age, weight, body mass index, symptoms, triggering factors, laboratory test indicators, treatment, prognosis, and other relevant parameters. A 12-lead surface electrocardiogram (ECG) was used to analyze the characteristics of VPC and evaluate the following VPC parameters: PR interval, QRS interval, block pattern, and QT interval (QTc). The percentage of VPC in a heartbeat was recorded by the Holter, and the absence of couplets, trigeminy, VT (3 or more consecutive VPC and <30 s) in the results of Holter was collected. Frequent VPC was defined as VPC burden >5%.The LV function and structure were evaluated by echocardiograms in all patients. Left ventricular ejection fractions (LVEF), and LV diameter at the end of the diastole (LVEDd) were measured on sinus beats. LV dysfunction was defined as SF <28% or LVEF< 50%. The ventricular structural changes (LV enlargement) were defined as the LVEDd larger than the normal range for this age group.

The patients who weighed >15 kg, had VPC burden >10%, and showed no effect from treatment with oral anti-

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arrhythmic drugs were ablated under general anesthesia. Mapping was facilitated by an electroanatomical mapping system (CARTO, Biosense Webster, USA) using a transvenous or retrograde aortic approach. At the site of the earliest activation based on the onset and reversed polarity in the bipolar electrogram and/or QS-wave configuration in the unipolar electrogram, pace-mapping was performed to confirm the ≥11/12 lead QRS pace match. Radiofrequency energy was delivered with a maximum target temperature of 60˚C and power output of 30 to 60 W depending on age, weight, and focus. After the operation, the same shape of ventricular premature beat was reduced by > 80% and VT disappeared on the Holter, indicating success of the radiofrequency ablation.

After drug treatment, Holter was reviewed every 1 to 3 months. A 12-lead surface electrocardiogram, Holter, and echocardiography were reviewed 24 hours after catheter ablation. Patients with LV enlargement were reviewed for echocardiography every 1 to 3 months until the LV size was almost normal or completely normal.

The software package SPSS 20.0 (IBM Armonk, NY, USA) was used to perform the statistical analyses. Continuous data are presented as mean ± standard deviation, and analyzed using the chi-square test and Fisher's exact test where appropriate. Although categorical data are presented as numbers with percentage and analyzed by independent sample *t* tests . The multivariate logistic regression models to examine the independent predictors. A p value <0.05 was considered statistically significant.

All patients enrolled in this study has signed the broad consent, which permits the researchers to engage in research using identifiable biospecimens and identifiable data during the hospitalization period and future follow-up. And the study was strictly in accordance with the Declaration of Helsinki and International Ethical Guidelines for Health-related Research Involving Humans. Ethical approval was given by the medical ethics committee of Xinhua Hospital.

Results

249 children (142 boys and 107 girls) with frequent VPC with or without asymptomatic VTs were included in this study. The average age of the patients in this study was 7.39 ± 4.31 years(range 0 to 14 years). 29 (11.6%) children showed LV enlargement, of which 3 patients (1.2%) showed LV dysfunction, having an SF < 28% or LVEF < 50% at diagnosis. 220 (88.3%) patients showed a normal LV function and structure at diagnosis. And a total of 79 children (31.7%) had symptoms of heart failure, including syncope, palpitations, chest pain, fatigue, and haze. Compared with the LV structural change group, there were no significant differences in age, gender, weight, height, body mass index blood pressure, symptoms, triggering factor, troponin-I, myocardial enzymes, electrolytes and other aspects in the group with normal LV structure (Table 1).

The VPC parameters of both groups are presented in Table 2. Patients with LV enlargement had higher QRS

Table 1
Patient characteristics in relation to LV enlargement

Variable	Left ventricular enlargement		p-value
	Yes (n = 29)	No (n = 220)	
Age (years)	7.3 ± 4.0	7.2 ± 4.5	0.172
Male	19 (65.5%)	132 (57.6%)	0.657
Weight (kg)	33.3 ± 16.5	32.7 ± 18.5	0.461
Height (cm)	127.9 ± 29.1	125.5 ± 32.9	0.706
Body mass index (kg/m $^{2)}$	20.4 ± 6.9	19.3 ± 6.2	0.380
Systolic blood pressure (mm Hg)	100.2 ± 11.6	104.4 ± 14.9	0.143
Diastolic blood pressure (mm Hg)	63.1 ± 8.9	64.1 ± 12.0	0.662
Symptoms	8 (24.14)	71 (32.3)	0.374
Cardiac arrest	0	0	-
Syncope	1 (12.5%)	16 (22.5%)	
Palpitations	6 (75.0%)	28 (39.4%)	
Fatigue	0	6 (8.45%)	
Chest pain	2 (25.0%)	39 (54.9%)	
Reduced physical activity	0	5 (7.0%)	
Dizziness	0	5 (7.0%)	
Triggering factor	21 (72.4%)	140 (63.6%)	0.353
Infection	21 (72.4%)	125 (89.3%)	
Exercise	0	9 (6.4%)	
Others	0	6 (4.3%)	
Creatine kinase -MB (U/L)	8.9 ± 10.7	17.2 ± 28.6	0.126
Serum troponin I (μg/L)	0.1 ± 0.1	0.1 ± 0.4	0.633
Na^+ (mmol/L)	139.5 ± 2.7	138.9 ± 9.8	0.726
K^+ (mmol/L)	4.3 ± 0.4	4.4 ± 0.5	0.697
Ca^{2+} (mmol/L)	2.3 ± 0.3	2.4 ± 0.2	0.414
N-terminal pro-B-type natriuretic peptide (pg/ml)	139.9 ± 159.4	116.9 ± 193.6	0.897

All values are expressed as mean ± SD or n (%).
LV = left ventricle; SD = standard deviation.

Table 2
Comparison of the determinants of premature ventricular contractions in patients with different left ventricular structure

Variable	Left ventricular enlargement		p- value
	Yes (n = 29)	No (n = 220)	
QRS duration (ms)	80.9 ± 5.9	77.8 ± 6.8	0.021
QT interval (ms)	396.9 ± 8.4	399.7 ± 23.4	0.556
PR interval (ms)	119.5 ± 8.4	119.7 ± 11.9	0.917
Block pattern	11 (37.9%)	8 (3.6%)	<0.001
Atrioventricular block	0	6	-
Right bundle branch block	11 (37.9%)	2 (0.9%)	-
Left bundle branch block	0	0	-
PVC burden	30.2 ± 10.7	9.4 ± 6.9	<0.001
5−20	5 (17.2%)	204 (92.7%)	<0.001
>20	24 (82.8%)	16 (7.3%)	
Couplets	26 (96.7%)	132 (60.0%)	0.002
Trigeminy	27 (97.8%)	133 (83.2%)	0.001
Ventricular tachycardia	22 (75.9%)	36 (16.4%)	<0.001

All values are expressed as mean ± SD or n (%).

Table 3
Logistic regression analysis data

	p-value	OR	95% OR
QRS duration	0.116	1.103	0.976-1.245
Right bundle branch block	<0.001	167.8	10.590-2658.017
PVC burden >20%	<0.001	132.624	13.363-1316.277
Couplets	0.591	2.514	0.088-72.173
Trigeminy	0.845	0.696	0.019-26.203
Ventricular tachycardia	0.298	2.214	0.496-9.885

wave width (p = 0.021) and higher incidence of right bundle branch block (RBBB)(p < 0.001). Other determinants, such as PR duration and QTc showed no statistically significant difference (p > 0.05).

On the Holter, the burden of VPC markedly increased and was significantly higher in the group with LV enlargement than in the group with a normal LV structure (p <0.05). All patients in the LV enlargement group had higher prevalence of VT (p < 0.001), a higher number of couplets(p = 0.002), a higher number of trigeminy (p < 0.001) than those in the normal LV group.

Multiple logistic regression analysis is presented in Table 3. Multiple logistic regression analysis are presented in table 3. The results showed that RBBB (Odds Ratio = 167.7, 95% Confidence Interval: 10.59 to 2658 p <0.001), and the VPC burden (Odds Ratio = 632.1, 95% Confidence Interval: 17.81 to 22428.99 p <0.001) were the Independent risk factors for LV enlargement. The other indicators were not statistically significant.

Discussion

Idiopathic frequent VPC are usually considered benign, and in most patients with frequent VPC, the cardiac function is preserved during follow-up. But the result from an adult study suggested that a causal link between frequent VPC and LV dysfunction and improvement in LV function, after an treatment reducing VPC burden effectively.[13,14] Kakavand et al[15] analyzed 28 children with arrhythmia, and the results showed that the burden of VPC was significantly higher in patients with LV dysfunction (36%) than in patients without barriers (18%). However, Guerrier et al,[16] who included 123 patients with frequent VPC (defined as >5%), suggested no correlation between LV function and VPC burden. Spector et al,[17] who included 36 children with high VPC burden (> 20%), proposed that LV dysfunction was more common in the cohort, but did not further explore the risk factors related to LV dysfunction. Currently, due to the lack of studies on the idiopathic VPC and asymptomatic VTs related to LV function or structure in pediatric patients, the relation between the 2 is not yet clear .

The results of our study showed that 29 children (11.6%) had LV enlargement, 3 of them (1.2%) had LV dysfunction, and 27 of them (93.1%) could return to normal after effective treatment. These results were different from those of previous research. Bertels et al[18] showed that the burden of VPC was a significant risk factor for development of LV dysfunction in children. However, this study did not focus on the relevance of VPC to the heart structure. In our study, patients with LV enlargement had wider QRS waves, significantly increased VPC burden, and higher rates of the doublet, triplet, and VT, consistent with the results in previous studies.[18] Previous studies showed that the existence of the doublet and triplet was associated with LV dysfunction, and 76% nsVT patients with dysfunction and 1% to 40% nsVT patients with normal function,[7,8,19] which is in concurrence with the results of our study. A study reported that reduction in LVEF in patients with VPC was associated with short coupling intervals and extended QT intervals.[20] However, no association was found in our study on pediatric patients.

Meanwhile, our study indicated that the high VPC burden (>20%) and existence of blockages were important factors influencing LV enlargement; 82.8% of children with LV enlargement (including 3 children with dysfunction) had VPC burdens above 20%. Further, children with high VPC burden were more prone to LV enlargement, which appear earlier to dysfunction. This may be related to the stronger compensatory capacity of children's hearts. When VPC occurs, the venous return and preload on the heart increases, which leads to the lengthening of the cardiac muscle fibers and increase in contractility. Sustained VPC will cause changes in the structure of the heart, and decompensation in the later stages of the disease resulting in dysfunction.[21] However, due to majority of patients being asymptomatic, the time from the onset of VPC is unclear, and the influence of the duration of high VPC burden on LV function remains unknown. None of the patients with normal LV structure at diagnosis LV enlargement during the follow-up, including those patients with a high VPC burden.

In addition, the incidence of RBBB in the LV enlargement group was higher than that in the normal LV structure group (37.9% vs 0.9%), which is different from the results of previous studies. Spector et al,[17] who included 123 patients with frequent VPC (defined as> 5%), showed no correlation between LV function and RBBB. This may be attributed to the long and thin right bundle branch, which makes it easier to block. When RBBB occurs, the left and right ventricles contract asynchronously, and the right ventricle influences LV function and structure through

mechanical traction and pressure transmission.[22] A large-scale clinical study has also confirmed the relation between RBBB and LV dysfunction.[23] In our study, 31.9% of patients had clinical symptoms, and 10.1% of them had LV dyfunction or LV enlargement. Symptoms, such as palpitations might have been caused by arrhythmia rather than hemodynamic disorders. Our results showed that LV enlargement was reversible with a decrease in the burden of VPC by catheter ablation or medication. This is in concordance with studies on adult patients, which describe reversibility of VPC - and VT-induced LV dysfunction after treatment, with radiofrequency ablation or pharmacologic therapy.[13–15,24] However, this conclusion was not explored in children. In our study, 93% of patients had normal heart structure after effective treatment, with an overall significant increase of 10% in LVEF and an overall increase of SF in 7%.

It is justifiable to conclude that frequent ventricular ectopy can induce LV enlargement in children and it is reversible by treatment with medication or ablation. A high burden of VPC and the presence of VTs, RBBB, couplets, and trigeminy are associated with LV enlargement and might be used in stratification of patients at risk of developing LV enlargement. However, more data are needed to warrant treatment for prevention of LV enlargement. At the moment, patients with frequent ventricular ectopy must be followed regularly with Holter recordings and echocardiography. If LV enlargement develop, medication or ablation is indicated to reduce the amount of ectopy.

Although this study included a large sample, it was a retrospective, single-center study with a short follow-up time. The relation between VPC duration and LV dysfunction and enlargement cannot be determined accurately owing to these limitations. Future multicenter, prospective studies are warranted to further explore other factors that may cause LV enlargement and provide evidence for preventive treatment. Frequent VPC can induce prominent LV enlargement and LV dysfunction in children. Children with structural changes have wider QRS waves, higher VPC burden, and higher rates of conduction block, couplets, trigeminy, and VT. VPC burden > 20% and presence of RBBB are independent risk factors. Early intervention is recommended for this group of children to prevent LV dysfunction or enlargement. LV enlargement are reversible after catheter ablation or medication.

Disclosures

The authors declare that they have no known competing financial interests or personal relation that could have appeared to influence the work reported in this study.

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