Title

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ORIGINAL ARTICLE

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High burden of premature ventricular contractions in structurally normal hearts: To worry or not in pediatric patients?

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Abstract

Background: There is paucity of data regarding the significance of high percentage of premature ventricular contractions (PVCs) in healthy children and their impact on left ventricular (LV) function and the risk of ventricular arrhythmias. The purpose of this study was to assess the prevalence of LV systolic dysfunction in children with frequent PVCs and determine whether PVC characteristics were predictive of LV dysfunction.

Methods: We performed a single-center retrospective review to examine the prevalence of PVC-induced cardiomyopathy and natural history of PVC burden in children with frequent PVCs. Children aged 6 months–21 years with PVCs noted on 24-hr Holter monitoring studies were enrolled. The four categories included those with a PVC burden of >10%, 10%–20%, and those with more than 20% PVC burden.

Results: A total of 134 children were included, 65 with more than 10% PVCs and 31 with more than 20% PVCs. Median age of the patients was 10.5 years (IQR 6.1–14.8 years), with 79 males (54.5%). Median PVC burden was 8.7% (IQR 4.2%–16.9%) with median follow-up of 2.8 years (IQR 1.2–4.6 years). During 2.8 years (1.3–4.3 years) of follow-up, the PVC burden decreased by 67% of baseline PVC burden in those who did not undergo any intervention. There were no deaths.

Conclusion: PVCs in children with structurally normal hearts are associated with a relatively benign course, with trend toward spontaneous resolution.

KEYWORDS
pediatric, premature ventricular contractions, structurally normal heart, ventricular tachycardia

1 | INTRODUCTION

Premature ventricular contractions (PVCs) are common in clinical practice. They are an independent predictive factor of total mortality and sudden death in adults with heart disease. (Bikkina, Larson, & Levy, 1993; Ruberman, Weinblatt, Goldberg, Frank, & Shapiro, 1977) In adults, a burden of at least 10% ectopy, and generally 20%–30%, increases the risk of ventricular dysfunction. (Baman et al., 2010; Ban & Kim, 2013; Kanei et al., 2008) Frequent PVCs also increase the risk for arrhythmias like nonsustained ventricular tachycardia (NSVT) or sustained ventricular tachycardia which are important predictor of adverse cardiac events, and in adults without apparent structural heart disease, frequent PVCs are associated with a worse cardiovascular outcome (Bethge, Bethge, Meiners, & Lichtlen, 1983; Desai, Hershberg, & Alexander, 1973; Engstrom, Hedblad, Janzon, & Juul-Moller, 1999; Fleg & Kennedy, 1992; Fujimoto et al., 1994; Gaita

et al., 2001; Hoffmann, Buhler, & Burckhardt, 1983; Kennedy et al., 1985; Lee, Hemingway, Harb, Crake, & Lambiase, 2012; Morshedi-Meibodi, Evans, Levy, Larson, & Vasan, 2004; Niwano et al., 2009; Rabkin, Mathewson, & Tate, 1981; Rodstein, Wolloch, & Gubner, 1971) although some studies have shown variable results. (Abdalla, Prineas, Neaton, Jacobs, & Crow, 1987; Bjerregaard, Sorensen, & Molgaard, 1991; Cheriyath et al., 2011; Hirose et al., 2010; Pedersen et al., 2014; Sajadieh et al., 2006) These conflicts are reflected in the 2014 EHRA/HRS/APHRS Expert Consensus on Ventricular Arrhythmias (Alexander & Berul, 2000).

The relation between decreased cardiac function and PVC burden in children remains unknown with a limited number of studies with small cohorts and variable results. Premature ventricular contractions with a structurally normal heart in children are thought to be benign (Aliot & Stevenson, 2009; Crosson et al., 2014; Guerrier et al., 2015; Jacobsen, Garson, Gillette, & McNamara, 1978; Tsuji et al., 1995; Yabek, 1991) although some studies have suggested adverse outcomes. (Abadir et al., 2016; Spector & Seslar, 2016; Sun et al., 2003) Abadir et al reported incidence of mild LV dysfunction as 15% in a cohort of 47 children with had a mean PVC burden of 20.9 ± 11.9% at baseline.(Abadir et al., 2016) Spector et al reported incidence of cardiomyopathy as high as 19.4% (7 out of 36 patients with more than 20% PVCs; Spector & Seslar, 2016) Currently, there is no consensus for routine evaluation and management of frequency PVCs. PACES/HRS expert consensus statement on the evaluation and management of ventricular arrhythmias in the child with a structurally normal heart recommended monitoring those with more than 10% PVCs while acknowledging that no large study had addressed the risk of developing this dysfunction in the pediatric population and the burden of PVCs required to produce this effect was unclear (Crosson et al., 2014).

The purpose of the study was to validate the association of cardiac dysfunction and ventricular tachycardia with high PVC burden. We assessed the presence of PVC burden at the time of presentation and the progression or resolution of the same at the last follow-up. We also sought the association or progression of PVC burden and any predictive risk factors for the same (extent of PVC burden, presence with exercise, morphology, and association with stimulant or anti-arrhythmic medications).

2 | PATIENTS AND METHODS

This study was approved by the Institutional Review Board of Penn State Children's Hospital.

2.1 | Study population

A retrospective review of Holter studies from December 2015 to December 2017 using electronic medical records was used to identify children and young adults aged 6 months–21 years of age with structurally normal hearts on the echocardiogram and presence of PVCs. Holters were obtained on patients by pediatric cardiologist recommendation after evaluation of electrocardiogram. They were divided into three categories: category 1 constituting patients with >10% PVC burden on their 24-hr Holter monitor; category 2 included those with 10%–20% PVC burden; category 3 included those with more than 20% PVC burden. PVC couplets and nonsustained VT did not affect categorization. The study adhered to rigorous exclusion criteria to ensure a sample population without any predisposing factors for PVCs such as children with congenital heart disease, vascular rings/slings, history of cardio-pulmonary bypass (CBP) or extra-corporeal membrane oxygenation (ECMO), cardiomyopathies diagnosed either clinically or genetically (e.g. muscular dystrophies, aortopathies) with the exception of those with premature ventricular contraction-induced cardiomyopathy. Exclusion criteria also included patients with a family history of cardiomyopathy and channelopathies, or if the patient had ion channelopathy, ventricular tachycardia, intracardiac or coronary abnormalities, history of chemotherapy, or anti-inflammatory disease. Patients with supraventricular tachycardia, heart block, or sinus node dysfunction were also excluded, as well as patients with cardiac genetic tests positive for variants of unspecified significance to remove any element of ambiguity in the cohort.

2.2 | Data collection

We collected demographic data, echocardiogram, and earliest Holter monitor results at first presentation as well as last Holter available. The echocardiogram within 1 month of Holter was reviewed for evidence of significant structurally heart disease, left ventricular shortening fraction, left ventricular ejection fraction, left ventricular end-diastolic diameter with respective *Z*-scores, and any mitral regurgitation. Whenever appropriate, stress test, cardiac MRI, and electrophysiology procedures were reviewed. A diagnosis of attention-deficit/hyperactivity disorder (ADHD) and the need for medical therapy was noted. Decision to continue or discontinue stimulant medication was determined on an individual patient basis. Premature ventricular contraction-induced cardiomyopathy was defined by echocardiographic findings of left ventricular shortening fraction <28%, left ventricular ejection fraction <54%, left ventricular end-diastolic *Z*-scores >2, or diminished function on qualitative interpretation. Resolution of high premature ventricular contraction burden was defined as decrease to <10% of total daily rhythm on the most recent Holter monitor. Review of echocardiogram images was done to ensure that the measurements were taken on a sinus beat which was not preceded by a PVC. Holters were also reviewed for the presence of ventricular tachycardia, maximum run of ventricular tachycardia, and morphology of PVC.

2.3 | Statistical analysis

The data collected were analyzed for parametric or nonparametric distribution and was found to be nonparametric. Continuous variables were expressed by median and interquartile range (IQR; 25th, 75th percentiles). Kruskal–Wallis was used to compare categorical

variables. Bonferroni post hoc analyses set the significant *p*-value to 0.0016 (31 analyses). Analyses were performed using SPSS version 24 (2016) software.

3 | RESULTS

In total, 134 patients met inclusion criteria with 65 patients having more than 10% PVC burden and 31 having more than 20% PVC burden. The median age of the patients was 10.5 years (IQR 6.1–14.8 years), with 79 males (54.5%). PVCs were monomorphic in all 65 patients with more than 10% PVCs. Syncope was seen in 4 (2.8%) patients. Median PVC burden of the entire group was 8.7% (IQR 4.2%–16.9%) with median follow-up of 2.8 years (IQR 1.2–4.6 years). Seventy-two patients had exercise stress testing; out of which, only 4 patients were noted to persist during peak exercise. The median baseline shortening fraction was 36% (IQR 33%–39%) with median *Z*-score of 0.23 (IQR −0.81 to 1.06) with median baseline EF of 64.5% (IQR 60%–70%), median baseline LVEDd of 4.2 cm (IQR 3.4–4.8 cm), and median baseline LVEDd *Z*-score of −0.4 (IQR −1.03 to 0.255). Only 2 patients had mitral regurgitation presence (both mild, 1.4%).

One patient had baseline shortening fraction *Z*-score of −2.41 with PVC burden of 2.7%.

The last echo median shortening fraction was 36% (IQR 33%–40%) with median *Z*-score of 0.54 (IQR −0.55 to 1.34), with median baseline EF of 67% (IQR 61%–71%), median baseline LVEDd of

TABLE 1 Demographics for PVC burden <10%, 10% to <20%, and >20%

	PVC <10% (*N* = 70)	PVC 10 <20% (*N* = 34)	PVC ≥20% (*N* = 31)	*p*-value
Age	10.3 (5.3 to 15.4)	11.3 (6.5 to 14.1)	10.6 (7.0 to 14.6)	NS
Male sex	39 (56.5)	18 (52.9)	14 (45.2)	NS
ADHD presence	3 (4.3)	0 (0)	3 (9.7)	NS
Stimulant medication	0 (0)	0 (0)	3 (9.7)	NS
Syncope (%)	1 (1.5)	3 (8.8)	0 (0)	NS
Initial holter PVC burden (IQR)	4.5 (1.0 to 6.2)	14.0 (11.7 to 15.9)	26.7 (21.9 to 34.4)	<0.001[a]
Longest run (IQR)	1 (1 to 2)	1 (1 to 1.5)	2 (1 to 3)	NS
Nonsustained VT presence	9 (12.8%)	0 (0.0%)	4 (12.9%)	NS
Monomorphic (%)	67 (95.7)	34 (100)	31 (100)	NS
PVC coupling interval (ms)	401 ± 71	428 ± 69	430 ± 64	NS
Average follow-up (years)	3.1 (1.2 to 4.9)	2.2 (1.3 to 3.9)	3.0 (1.8 to 3.8)	NS
Anti-arrhythmic	0 (0)	0 (0)	0 (0)	NS
Beta or calcium channel blocker	2 (2.9)	2 (5.9)	2 (6.4)	NS
Ablation	1 (1.4)	1 (2.9)	2 (6.5)	NS
F/-up Holter PVC (IQR)	1.8 (0.1 to 6.7)	9.6 (2.1 to 14.2)	14.6 (2.3 to 31.5)	<0.001[a]
Exercise testing (%)	29 (41.4)	22 (64.7)	18 (5.8)	NS
PVC, peak exercise (%)	3 (4.3)	0 (0.0)	0 (0.0)	NS
Initial echo parameters				
Shortening fraction (%)	36 (33 to 40)	37 (36 to 39)	35 (32 to 38)	NS
SF *Z*-score	0.2 (−0.5 to 1.4)	0.4 (−0.2 to 1.0)	−0.3 (−1.0 to 0.7)	NS
Ejection fraction	64 (60 to 69)	66 (61 to 70)	64 (60 to 69)	NS
LVEDd (IQR)	4.2 (3.2 to 4.7)	4.3 (3.7 to 5.0)	4.2 (3.6 to 4.5)	NS
LVEDd *Z*-score (IQR)	−0.6 (−1.1 to 0.1)	−0.2 (−7 to 0.5)	−0.3 (−0.8 to 0.2)	NS
Mitral regurgitation (%)	1 (1.4)	0 (0)	0 (0)	NS
Last echo parameters				
Shortening fraction (%)	38 (36 to 38)	33 (31 to 36)	35 (33 to 37)	NS
SF *Z*-score	0.6 (0.5 to 0.9)	0.9 (0.8 to 1.0)	0.0 (−0.9 to 0.9)	NS
Ejection fraction	68 (66 to 70)	61 (57 to 65)	65 (60 to 67)	NS
LVEDd (IQR)	3.8 (3.2 to 5.1)	5.4 (4.9 to 5.9)	4.3 (3.6 to 4.9)	NS
LVEDd *Z*-score (IQR)	0.1 (−7 to 0.8)	0.1 (−0.5 to 0.4)	−0.3 (−1.0 to 0.5)	NS
Mitral regurgitation (%)	0 (0)	0 (0)	0 (0)	NS

Abbreviations: ADHD, attention-deficit disorder; LVEDd, left ventricular end-diastolic diameter; NS, not significant; PVC, premature ventricular contraction.

[a]PVC burden grouped based on differences.

4.3 cm (IQR 3.5–4.9 cm), and median baseline LVEDd *Z*-score of −0.5 (IQR −0.94 to 0.42). No patients had mitral regurgitation present at last echo. Median change in *Z*-score for SF was −0.29 (IQR −1.71 to 0.55, *p*-value 0.175), and median change in EF was −3.2% (IQR −10.8% to 3.1%, *p*-value 0.151). No significant differences noted change in LVEDd or LVEDd *Z*-score either.

Please see Table 1 for demographics based on 3 separate groups of PVC burden. Table 2 demonstrates odds ratios for development of left ventricular dysfunction. No parameters predicted low shortening fraction (*Z*-score ≤−2 or EF < 50%).

The treatment included medical therapy (8) and ablation (4) with improvement. During 2.8 years (1.3–4.3 years) of follow-up, the PVC burden fell from 12.9% (4.7%–20.9%) to 4.4% (1.9%–14.6%) in those who did not undergo any intervention.

Figure 1 demonstrates changes in PVC burden in all patients which demonstrates median decrease in PVC burden of −2.3% (IQR −9.4% to 1.9%), while those with >20% PVC burden have a median PVC burden decrease of −10.7% (IQR −0.3% to −20.6%) with a *p*-value of <0.001.

The sample size was adequate to exclude a 15% incidence of cardiomyopathy in the groups with a PVC burden of greater than 10% with a statistical power of at least 0.8.

4 | DISCUSSION

PVCs in structurally normal heart are a common occurrence. Studies have shown increased LV dysfunction and mortality in adults with frequent PVCs with or without any heart disease. The LV function is reversible with ablation. Extrapolating this to pediatric population has its limitations as pediatric hearts do not typically have the comorbidities and coronary artery disease seen later on in life. In pediatric patients with structurally normal heart, PVCs are considered to have benign course but is recognized that higher PVC burden can cause LV dysfunction and cardiomyopathy. In our study, 31 patients had more than 20% PVC burden and none of them had any LV dysfunction. There was overall trend toward resolution of the PVC burden with the median PVC burden decreasing from 27% at the time of initial presentation to 15% at the last follow-up with the median duration of follow-up being 2.8 yearrs (1.3–4.3 years). The trend toward resolution of PVCs was observed in the study where PVC burden fell from 12.9% (4.7%–20.9%) to 4.4% (1.9%–14.6%) in those who did not undergo any intervention. This is important to note as ablations or interventions can have potential complications like injury to conduction system, adjacent coronary arteries, and fluoroscopy exposure (Crosson et al., 2014).

Interestingly, higher PVC burden (more than 20%) did not correlate with nonsustained ventricular tachycardia, persistence of PVCs at exercise, PVC coupling interval, or LV dysfunction, similar to previously reported results (Aliot & Stevenson, 2009; Crosson et al., 2014; Guerrier et al., 2015; Jacobsen et al., 1978; Tsuji et al., 1995; Yabek, 1991). There was only one patient with shortening fraction *Z*-scores >2, and this patient had >10% PVCs all of which were monomorphic.

Only 3 patients were on stimulant medications, all of them with PVCs more than 20%. The number was too small to deem any significant conclusion.

For patients with significant PVCs, the treatment included medical therapy in eight and ablation procedures in four patients. The ablation procedure indication was four for PVCs or NSVT. Four of the four ablations were successful with resolution of PVC burden to >10%. Our study had only no sudden cardiac deaths.

TABLE 2 Odds ratios for parameters and prediction of left ventricular dysfunction (shortening fraction *Z*-score ≤−2 or EF <55%). Parameters not available for statistical testing marked as not available (N/A)

Parameter	Odds ratio	95% confidence interval
Age	0.951	0.661–1.368
Male sex	1.31	0.079–21.844
ADHD presence	N/A	N/A
Stimulant medication	N/A	N/A
Syncope	N/A	N/A
Initial Holter PVC Burden	1.394	0.770–2.524
Longest run (IQR)	1.007	0.981–1.033
Nonsustained VT presence	N/A	N/A
Monomorphic	0.888	0.016–50.719
PVC coupling interval (ms)	0.621	0.310–1.269
PVC, peak exercise (%)	N/A	N/A
QRSd (ms)	1.099	0.517–2.337

5 | LIMITATIONS

The retrospective nature of study is a limitation in itself. Although we had a total of 134 patients, it was not a large study. Since we had no significant LV dysfunction, we could not assess the correlation of origin of PVC as risk factor for cardiomyopathy. The evaluation, testing, frequency of follow-up, and decision to treat

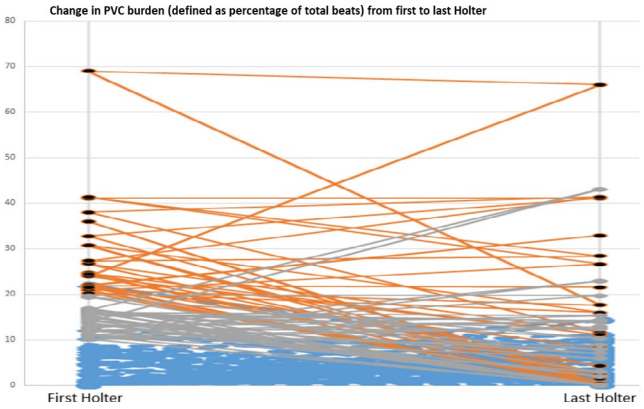

FIGURE 1 Percentage PVC burden, first and last Holter (Blue-PVC burden <10%, Gray-PVC burden 10% to <20%, Orange-PVC burden 20% or higher)

were heterogeneous and at the discretion of the caring physician, including who received a Holter or follow-up Holter monitor; thus, there is likely some selection bias in the data. Even though our study had 31 patients with a high burden of PVC's, more than 20%, these were all monormophic and not persistent with exercise, hence at a likely lower risk of developing cardiac dysfunction. Although most PVCs were initially noted incidentally, not all patients had well-documented symptoms either due to lack of detailed charting or patient age and ability to report symptoms consistently, as ability to report symptoms is not always straight forward in a pediatric population. A larger, multicenter study, preferably prospective is needed with standardized protocol for assessment, risk stratification, and follow-up.

6 | CONCLUSIONS

PVCs in children with structurally normal hearts are associated with a relatively benign course, with spontaneous resolution in many children. Our study had no prevalence of cardiomyopathy or association of ventricular tachycardia in children with high premature ventricular contraction burden. Although it is recommended to have regular follow-up in patients with a PVC burden of more than 10%, who otherwise do not have suspicion for cardiomyopathy or ion channelopathy, perhaps these structurally normal patients have more of a benign course than previously thought.

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