



# Alleviation of arrhythmia burden in children with frequent idiopathic premature ventricular contractions by omega-3-fatty acid supplementation☆

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## ABSTRACT

**Background:** Patients at our pediatric outpatient clinic were offered 24-h Holter electrocardiogram (ECG) before and after 3-month period of dietary supplementation with omega-3 fatty acids to monitor the effect on heart rate variability (HRV) and arrhythmias.

**Methods:** The study included 17 children (mean age:  $11.6 \pm 4.9$  years) with  $>1\%$  premature ventricular contractions (PVC) at baseline. 24-h Holter ECG monitoring was performed before and after omega-3 fatty acid supplementation (mean duration: 143 days).

**Results:** Compared with 86 age-matched healthy control children, baseline HRV was significantly reduced and mean heart rate was significantly increased in children with frequent PVC. After omega-3-fatty acid supplementation, the mean heart rate decreased from  $92.6 \pm 3.4$  bpm to  $83.9 \pm 9.9$  bpm ( $p = 0.001$ ), while global HRV showed a significant increase [standard deviation of all NN intervals (SDNN):  $148.1 \pm 34.4$  ms vs.  $126.5 \pm 39.3$  ms,  $p = 0.022$ ]. Enhanced vagal activity was indicated by significantly higher square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD) ( $42.3 \pm 12.6$  vs.  $33.2 \pm 14.8$ ;  $p = 0.0003$ ). PVC percentage significantly decreased by 45% ( $6.9 \pm 7.0\%$  vs.  $12.1 \pm 8.2\%$ ;  $p = 0.014$ ).

**Conclusions:** Omega-3-fatty acid supplementation caused a 45% reduction in frequent PVC in children with structurally healthy hearts. This antiarrhythmic effect was likely attributable to improved autonomic function, which is consistent with previous findings in children with obesity, attention deficit disorder, and short stature.

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## 1. Introduction

Omega-3 fatty acids are one of the most commonly used food supplements worldwide in children and adults. The annual sales in 2016 were approximately \$3.04 billion (<https://www.grandviewresearch.com/industry-analysis/omega-3-supplement-market>). Omega-3 fatty acid supplements are typically used without medical supervision. Many individuals who take omega-3 fatty acids site their possible benefits for the cardiovascular system. Recently we have examined the effects of omega-3 supplementation on heart rate variability of children with attention deficit disorder [1,2], short stature [3], and obesity [4]. In these studies we have documented that heart rate variability parameters change to increased vagal tone, while taking omega-3 supplements. The current study extends these observations, by examining a

subgroup of 17 patients who had  $>1\%$  premature ventricular contractions (PVC) with structurally normal hearts.

Premature ventricular contractions in children with structurally normal hearts are generally considered benign. Follow-up of these children is documented in studies conducted in Netherland ( $n = 59$ ) [5] and China ( $n = 178$ ) [6]. Both studies found that PVC associated with right bundle branch block resolve during childhood, while PVC with left bundle branch block tend to aggravate with age. Therefore, follow-up of children with PVC associated with left bundle branch block is recommended even during adulthood.

## 2. Methods

### 2.1. Patients

The current study included 17 children with PVC (mean age:  $11.6 \pm 4.9$  years) who were referred to the outpatient clinic of the Department of Paediatrics at the Caritas Hospital (Bad Mergentheim, Germany) during the period 2012–2019 for further management. After a detailed explanation about the benefits and risks of food supplementation with Omega 3 fatty acids, 17 parents have decided for supplementation. We offered 24-h Holter electrocardiogram (ECG) before and after a 3-month supplementation period to monitor the effect on heart rate variability (HRV) and arrhythmias. If the supplementation

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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**Abbreviations**

ADHD	attention deficit (hyperactivity) disorder
BMI	body mass index
ECG	electrocardiogram
PVC	premature ventricular contraction

*Time domain measures*

SDNN (ms)	standard deviation of all NN intervals
pNN50 (%)	number of pairs of adjacent NN intervals differing by >50 ms divided by the total number of all NN intervals
rMSSD (ms)	the square root of the mean of the sum of the squares of differences between adjacent NN intervals

*Frequency domain measures*

Total Power (ms <sup>2</sup> )	heart rate power spectrum between 0.003 and 0.4 Hz
VLF (ms <sup>2</sup> )	very low frequency power spectrum between 0.003 and 0.04 Hz
LF (ms <sup>2</sup> )	low frequency power spectrum between 0.04 and 0.15 Hz
HF (ms <sup>2</sup> )	high frequency power spectrum between 0.15 and 0.4 Hz
LF/HF ratio	ratio of low to high frequency power

was not covered by health insurance, patients usually purchased different products from a retail store based on daily intake of 1–2 g fish oil. Children up to the age of 8 years were recommended at least 1 g omega-3-fatty acids per day in the form of fish oil suspension. Children who were able to swallow capsules were recommended 2 g omega-3-fatty acids per day based on fish oil.

The following patients agreed to participate in the study:

- 1) Children with PVC detected during routine pediatric examination (N = 10).
- 2) Patients with attention deficit (hyperactivity) disorder and PVC detected during Holter ECG monitoring (N = 3).
- 3) Patients with obesity and PVC detected during Holter ECG monitoring (N = 4).

Blood pressure, height and weight were measured for each patient, and the body mass index (BMI) and BMI percentiles were calculated. All patients underwent at least one Doppler echocardiography examination to rule out any heart defect or myocardial dysfunction.

*2.2. Control group*

As a control group, data pertaining to normal healthy children (N = 85) were retrieved from a previous project that investigated normal HRV in children [7].

*2.3. 24-h ECG and analysis of HRV*

A two-channel Holter monitor (Pathfinder™, Spacelabs, Germany) was used for ECG recording while the children followed their normal daily routines. All Holter recordings were reviewed by an experienced cardiologist (R.B.) to validate the system's ECG labeling. Data were included in the analysis only if a minimum of 23 h of analyzable data and at least 95% of analyzable heart beats were available. The average values from the entire 24-h analyzable data were used in the analysis. We performed a second analysis that differentiates between day and night values during sleep. The frequency of PVC in the Holter ECG is presented as the percentage of PVC among all detected heart beats. Measures of

**Table 1**

Clinical data of the patients.

Parameter	Healthy control	Premature ventricular contractions	
	N = 86	Baseline N = 17	Post omega-3-fatty acid supplementation
Age (years)	11.2 ± 2.7	11.6 ± 4.9	11.9 ± 4.8
Male/female	43/43	9/8	
Height (cm)	147.6 ± 17.6	149.8 ± 29.7	150.3 ± 29.3
Body mass index (kg/m <sup>2</sup> )	17.3 ± 2.4	21.2 ± 8.3	21.1 ± 7.4
Systolic pressure (mm Hg)	Unknown	116.5 ± 15.4	118.8 ± 12.6
Diastolic pressure (mm Hg)		68.6 ± 16.8	65.8 ± 13.7
Fractional shortening (%)		36.8 ± 5.0	34.4 ± 2.6
Maximal oxygen uptake (mL/kg/m <sup>2</sup> )		32.0 ± 7.0	

**Table 2**

HRV analysis before and after omega-3-fatty acid supplementation in children with frequent premature ventricular contractions compared to age-matched healthy children.

Parameter	Healthy control	Premature ventricular contractions			
	N = 86	Baseline N = 17	Post omega-3-fatty acid supplementation		
Heart rate (bpm)	83.2 ± 8.8	92.6 ± 13.4***	<0.0001	83.9 ± 9.9**	0.001
Heart rate day (bpm)	92.7 ± 13.5	101.0 ± 16.2*	0.028	92.7 ± 12.4****	0.087
Heart rate night (bpm)	69.8 ± 8.9	82.4 ± 15.2***	<0.0001	73.2 ± 9.6*	0.011
PVC (%)	0.02 ± 0.02	12.1 ± 8.2***	<0.0001	6.9 ± 7.0*	0.014
RMSSD (ms)	46.3 ± 11.6	33.2 ± 14.8***	<0.0001	42.3 ± 12.6**	0.003
pNN50 (%)	26.2 ± 10.2	18.2 ± 12.5**	0.007	25.7 ± 12.7*	0.030
SDNN (ms)	169.2 ± 44.7	126.5 ± 39.3***	<0.0001	148.1 ± 34.4*	0.022
Total power (ms <sup>2</sup> )	6551 ± 2884	5764 ± 3989		7725 ± 3395	0.146
VLF power (ms <sup>2</sup> )	3527 ± 2305	2913 ± 2973		3615 ± 1935	0.368
LF power (ms <sup>2</sup> )	1595 ± 617	1053 ± 620**	0.002	1428 ± 506*	0.035
HF power (ms <sup>2</sup> )	846 ± 317	965 ± 1125		1692 ± 1964	0.144

PVC: premature ventricular contractions; SDNN: standard deviation of all NN intervals; RMSSD: the square root of the mean of the sum of the squares of differences between adjacent NN intervals; pNN50: number of pairs of adjacent NN intervals differing by >50 ms divided by the total number of all NN intervals; VLF: very low frequency power; LF: low frequency power; HF: high frequency power; HF/LF: HF to LF ratio.

Unpaired *t*-test for comparison between healthy control and baseline. Paired *t*-test for comparison between baseline and post-omega 3 fatty acid supplementation.

- \* *P* < 0.05.
- \*\* *P* < 0.01.
- \*\*\* *P* < 0.001.
- \*\*\*\* *P* < 0.0001.

HRV were calculated employing only normal to normal intervals. Autonomic control of cardiovagal function was tested by time domain analysis of 24-h ambulatory digital electrocardiogram (ECG) recordings. Measurement and interpretation of HRV parameters in the current sample were standardized according to the current guidelines. For time domain measures, mean RR interval, resulting heart rate, and the HRV parameters pNN50 (number of pairs of adjacent NN intervals differing by >50 ms divided by the total number of all NN intervals), rMSSD (square root of the mean of the sum of squares of differences between adjacent NN intervals) and the SDNN (standard deviation of NN intervals) are presented as 24-h average values or as day and night values. The rMSSD, pNN50, and heart rate predominantly reflect the response to changes in vagal tone while the SDNN reflects the global HRV. The SDNN is also under the dual influence of cholinergic and adrenergic activity, as well as other physiological inputs.

For frequency domain measures, beat-to-beat fluctuations were transformed to the frequency domain using the fast Fourier transformation algorithm. Spectral power was determined over three frequency regions of interest: very low frequency (VLF, <0.04 Hz), low frequency (LF, 0.04–0.15 Hz), and high frequency (HF, 0.15–0.4 Hz) with derived HF/LF ratio. LF predominantly reflects the sympathetic activity, while HF predominantly reflects the vagal tone.

#### 2.4. Statistical analysis

All data are presented as mean  $\pm$  standard deviation. As most variables exhibited a normal distribution, parametric statistics were used to assess between-group differences. Patients were compared with controls using independent sample *t*-test, while the pre- and post-supplementation values were compared using the paired sample *t*-test.

### 3. Results

Clinical data are shown in Table 1. Mean BMI of patients was higher than that of healthy controls because of the presence of four obese patients. There was no significant between-group difference with respect to blood pressure or fractional shortening of the left ventricle. The second Holter ECG study (post omega-3-fatty acid supplementation) was performed after a mean duration of 143 days. There were no significant changes in BMI or blood pressure during this period.

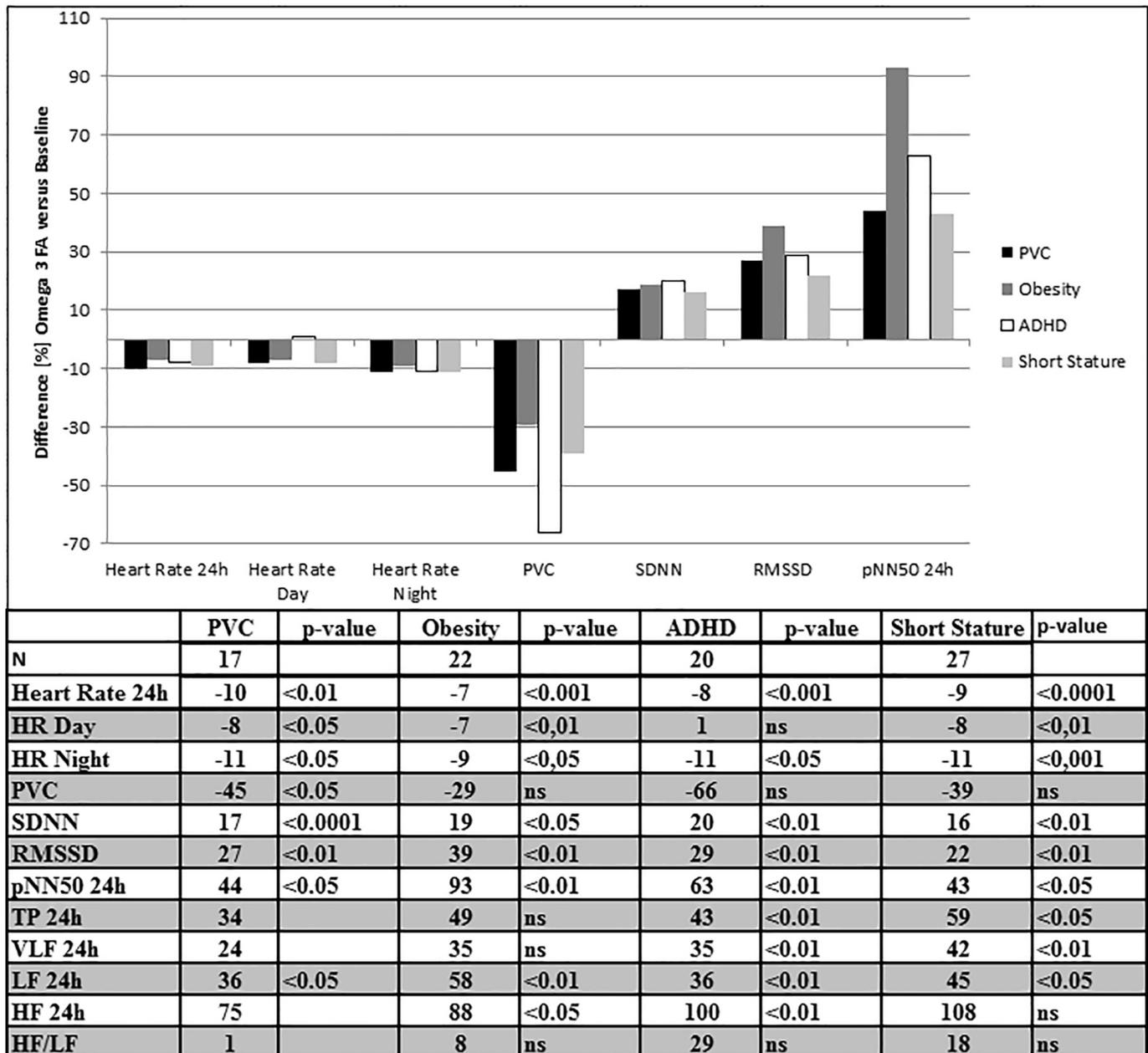


Fig. 1. Summary of the effect of omega-3-fatty acid supplementation in children with PVC, obesity, attention deficit (hyperactivity) disorder, and short stature from recently published studies. Data presented as percentage change between baseline and 3 month omega-3-fatty acid supplementation; *p* values calculated by paired student *t*-test. Some patients are included in more than one group if they fulfill the criteria (e.g., obese children with ADHD may be included in both obesity and ADHD groups).

Our group of children with >1% premature ventricular contraction had autonomic dysfunction at baseline [as indicated by significantly elevated heart rate ( $92.6 \pm 3.4$  bpm versus  $83.2 \pm 8.8$  bpm;  $p < 0.0001$ ) and reduced global HRV [as indicated by SDNN ( $126.5 \pm 39.3$  ms versus  $169.2 \pm 44.7$  ms;  $p < 0.0001$ )]. Vagus activity, as indicated by the rMSSD ( $33.2 \pm 14.8$  ms versus  $46.3 \pm 11.6$  ms;  $p < 0.0001$ ) and pNN50 ( $18.2 \pm 12.5\%$  versus  $26.2 \pm 10.2\%$ ,  $p = 0.007$ ) was significantly reduced in children with frequent PVC. These findings were not confirmed by frequency domain analysis, which only showed significantly reduced low frequency power in these children. (see Table 2)

Autonomic dysfunction improved after three-month supplementation with omega-3-fatty acids, as indicated by significantly lower heart rate ( $83.9 \pm 9.9$  bpm versus  $92.6 \pm 3.4$  bpm;  $p = 0.001$ ) and higher global HRV ( $148.1 \pm 34.4$  ms versus  $126.5 \pm 39.3$  ms,  $p = 0.022$ ). These data are consistent with enhanced vagus activity, as indicated by significantly higher rMSSD ( $42.3 \pm 12.6$  versus  $33.2 \pm 14.8$ ;  $p = 0.0003$ ) and pNN50 ( $25.7 \pm 12.7$  versus  $18.2 \pm 12.5$ ;  $p = 0.030$ ) values.

The percentage of premature ventricular contractions significantly decreased by 45% ( $6.9 \pm 7.0\%$  versus  $12.1 \pm 8.2\%$ ;  $p = 0.014$ ).

4. Discussion

The most important finding of our study is that omega-3-fatty acid supplementation is safe, even in children with a high arrhythmia burden (>1% PVCs). Moreover, we observed a significant reduction of the percentage of premature ventricular contractions by 45%. These confirm a recent publication of Oner et al. pertaining to 25 children with idiopathic PVCs [8]. In contrast, omega-3 fatty acids (1.5 g/day) did not substantially suppress the number of PVCs in a randomized trial in 84 adults [9]. In adults, PVCs seem to be associated with worse cardiovascular outcomes, which may be related to occult structural heart disease [10]. Risk factors for PVC in young and healthy adults include low educational status (RR 3.33; confidence interval [CI] 1.98–5.6), body height > median (RR 1.58; CI 1.11–2.24) and increased waist to hip ratio (RR 2.15; CI 1.77–2.61) [11].

In our previous work published in 2013, we proposed a concept about the relationship between autonomic dysfunction and PVC in children with attention deficit (hyperactivity) disorder [1]. Some of these patients received supplementation with omega-3-fatty acids for the treatment of attention deficit (hyperactivity) disorder and showed a

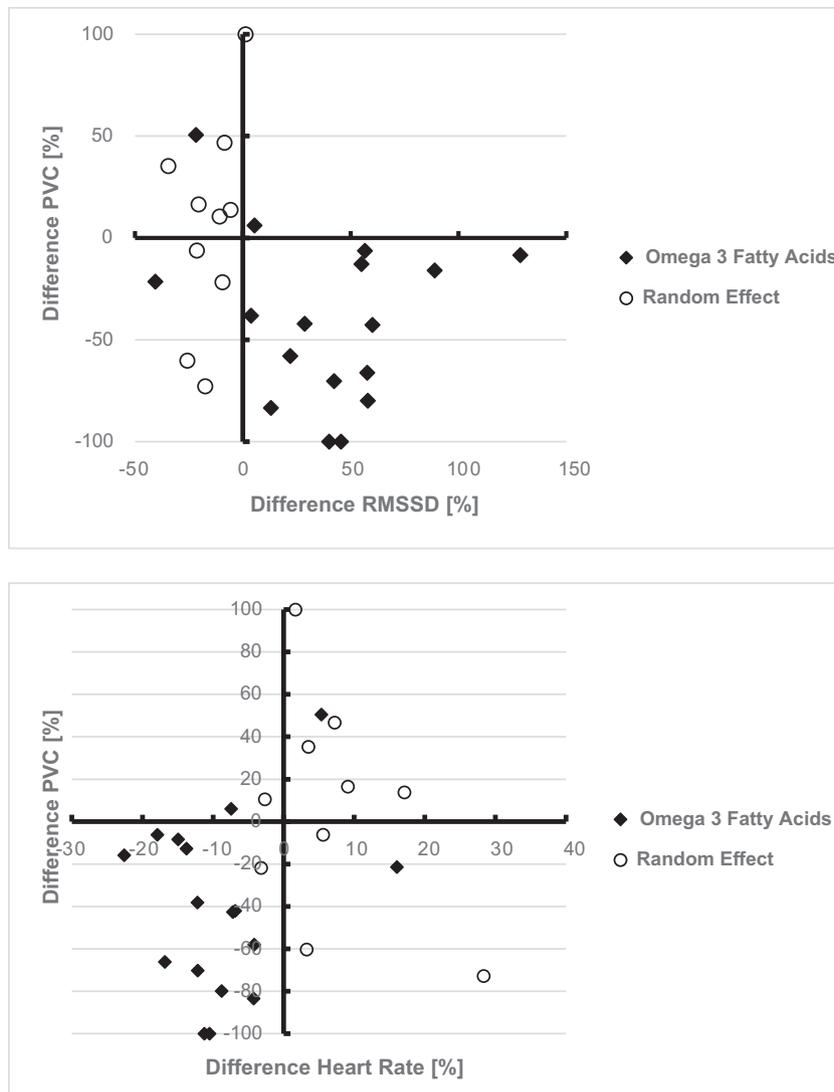


Fig. 2. Individual analysis of the difference of premature ventricular contraction at baseline and after 3 month omega-3-fatty acid supplementation according to the difference of average heart rate and the parameter of vagal activity (rMSSD). The circles represent the random effect of two Holter ECG's in 10 children with frequent premature ventricular contractions within 1 year without change in therapy. The rhombus represent the study group: There was a significant reduction of PVC in 15 of the 17 children who received omega-3-fatty supplementation. At the same time, the vagal activity was increased and the heart rate was decreased in 14 of the 17 children. RMSSD: the square root of the mean of the sum of the squares of differences between adjacent NN intervals; PVC, premature ventricular contraction.

significant reduction in PVC as determined by 24-h Holter ECG. Based upon this observation, we also encourage omega-3-fatty acid supplementation in children with frequent PVC and structurally normal hearts.

In summary, we published a total of 86 children who were substituted with omega-3-fatty acids to treat their autonomic dysfunction measured by Holter ECG monitoring (Fig. 1). There were uniform changes in heart rate and HRV in patients with four indications (PVC/ADHD/obesity/short stature):

- 1) The 24 h mean heart rates decreased significantly in all groups
- 2) The global HRV and vagus activity significantly increased in all groups.
- 3) The percentage of PVC decreased. However, this result was only significant, if all patients with >1% of PVC were included in the current analysis.

The impact of the changes of mean heart rate and the vagus parameter rMSSD on the difference of PVC in each individual patient is illustrated in Fig. 2. The number of PVCs increased in 2 children and decreased in 15 children. This improvement seems to be clinically relevant in 10 children who experienced a 40%–100% reduction in PVC. We illustrate the random effect of yearly Holter ECG examination on the number of PVCs in 10 children without changing the therapy in Fig. 2.

All children except one had premature ventricular contraction with left bundle branch block, which probably indicates a higher cardiovascular risk [5]. Moreover, based upon the current standards of cardiovascular risk stratification, omega-3-fatty acid supplementation seems to be beneficial in children with PVC:

- 1) Omega 3 FA lowers the heart rate by 10% [12]
- 2) Omega 3 FA significantly enhances vagus activity, as indicated by the values of RMSSD and pNN50 [13]
- 3) Omega 3 FA nearly halves the number of PVC on average

However, two children showed no improvement in arrhythmia burden and we are not able to predict the beneficial effect of omega-3-fatty acid supplementation at baseline. We propose Holter ECG monitoring before and 3 months after omega-3-fatty acid supplementation to demonstrate the effect on PVCs and HRV.

## 5. Limitations

While the results from this study provide strong evidence to support omega-3 fatty acid supplementation in children with PVC, it is not without limitations. The sample size is relatively small and is not necessarily representative of all underlying causes of PVC in children. Thus, the positive effects of omega-3 fatty acid supplementation may not be replicated in children with heart disease. The exact dose of omega-3 fatty acids and the ratio of docosahexaenoic acid (DHA) to eicosapentaenoic acid (EPA) given to patients in our study was also variable due to logistical reasons. This may have had an impact on our findings. Further prospective, randomized trials are necessary to proof the impact of omega-3-fatty acids supplementation on cardiovascular end points in children.

## Declaration of Competing Interest

The author has no potential, perceived, or real conflict of interest to declare.

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