Acta Paediatrica

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NURTURING THE CHILD

ORIGINAL ARTICLE OPEN ACCESS

Extrasystoles on 24-h Holter Monitoring During the First Year of Life

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Received: 2 April 2025 | **Revised:** 16 September 2025 | **Accepted:** 30 September 2025

Funding: The authors received no specific funding for this work.

Keywords: extrasystoles | Holter | infants

ABSTRACT

Aim: To assess the natural course of extrasystoles and their association with tachyarrhythmias on 24-h Holter monitoring during the first year of life.

Methods: A retrospective chart review was performed among newborns referred for 24-h Holter monitoring at Tampere University Hospital from 2011 to 2017. Children with more than 1% extrasystoles on the initial Holter recording were included.

Results: In total, 75 children and 290 Holter recordings were included. Forty-seven (63%) children were followed up due to atrial premature contractions (APCs) and 28 (37%) children were followed up due to ventricular premature contractions (VPCs). The amount of extrasystoles peaked during the first 14 days and decreased significantly during the first 2 months. However, in one-third of the children, extrasystoles increased between recordings. Extrasystoles disappeared during the first year among 92% of children with APCs and 78% of children with VPCs. Short supraventricular or ventricular tachycardias were found in 17 (23%) children's recordings. A higher percentage of extrasystoles was associated with tachyarrhythmias.

Conclusion: The results support the prevailing understanding regarding the favourable prognosis of extrasystoles in newborns. Serial Holter monitoring may be advisable during the newborn period for infants with frequent extrasystoles, as some may be susceptible to tachyarrhythmias.

1 | Introduction

While extrasystoles are common in newborns, their prevalence is not well described. A commonly used reference for incidences of atrial premature contractions (APCs) and ventricular premature contractions (VPCs) in newborns is the study by Nagashima et al. from 1987 [1]. In this Holter study of 63 healthy newborns, 51% and 18% of infants presented APCs and VPCs, respectively. In other studies, the incidence of extrasystoles has been lower [2–4]. In our recent study, the incidences of APCs and VPCs among healthy newborns were much higher (77% and 40%, respectively) [5]. Extrasystoles tend to disappear during the first year in most infants as the conduction system matures [6]. However, follow-up studies on extrasystoles in infants are sparse.

Abbreviations: APC, atrial premature contraction; bpm, beats per minute; ECG, electrocardiogram; HR, heart rate; IQR, interquartile range; LBBB, left bundle branch block; RBBB, right bundle branch block; SD, standard deviation; SVT, supraventricular tachycardia; VPC, ventricular premature contraction; VT, ventricular tachycardia.

Summary

- While extrasystoles are common in newborns and are generally considered benign, research on extrasystoles in infants is sparse.
- While extrasystoles significantly decreased during the first year, they increased between recordings in one-third of the infants, and a higher percentage of extrasystoles was associated with short tachyarrhythmias.
- Follow-up may be necessary for newborns and infants who have frequent extrasystoles.

Foetal APCs have been associated with a small risk of perinatal supraventricular tachycardia (SVT) [6–9]. Thus, frequent APCs in newborns, especially when arising from multiple foci, should be evaluated [6]. There is a small risk that some patients with frequent VPCs may develop sustained ventricular arrhythmias or arrhythmogenic cardiomyopathy [10–12]. The Paediatric and Congenital Electrophysiology Society's (PACES) and the Heart Rhythm Society's (HRS) expert consensus statement defines the threshold for the term 'frequent' for VPCs as more than 10% of beats in a 24-h period [10]. No such cut-off value for frequent APCs has been defined.

The aim of this study was to retrospectively assess the natural course of extrasystoles in newborns and infants during the first year of life and to discover whether extrasystoles in newborns are associated with tachyarrhythmias.

2 | Methods

A retrospective chart review was performed among all newborns referred for 24-h Holter monitoring at Tampere University Hospital from 2011 to 2017. During this period, the clinical practice at this centre involved conducting 24-h Holter monitoring on newborns aged 5–7 days if a tendency for multiple extrasystoles appeared to be non-transient. Additionally, Holter monitoring was performed on infants with clinically suspected tachyarrhythmia or bradyarrhythmia, or on those with heart disease predisposing to arrhythmia.

This study included infants with either APCs or VPCs exceeding 1% on the first recording and with at least one follow-up recording. Additional inclusion criteria were an age of less than 14 days at the time of the first recording and a gestational age of $\geq 37+0/7$ weeks at birth. Infants with heart disease were not excluded.

Demographic data, diagnoses, medications and echocardiography results were obtained from medical records. VPC morphology (right bundle branch block [RBBB] or left bundle branch block [LBBB]) was determined from standard 12-lead electrocardiograms (ECGs).

A SEER Light or SEER Light Extend Holter recorder (GE Medical Systems Information Technologies, Milwaukee, WI, USA) with two- or three-channel recording was used for 24-h ECG monitoring. Holter monitoring was either performed at the hospital (during initial hospitalisation) or ambulatory (most of the control recordings). A diary of the symptoms and activities was maintained during the recording.

The analysis of the recorded Holter data was performed with MARS V8 software (GE Medical Systems Information Technologies, Milwaukee, WI, USA). The software automatically analysed the heart rate (HR), maximum R–R interval, number of QRS complexes, number of APCs and VPCs, and number and length of tachyarrhythmias. The software calculated HR in beats per minute (bpm) from 10 R–R intervals. After the automated analysis, the Holter data were reviewed for software misinterpretations and edited manually. Wide-complex extrasystoles were manually corrected to aberrant APCs if appropriate.

For this study, SVT was defined as three or more consecutive APCs at a rate of more than 160 bpm (HR above two standard deviations [SDs] of the mean HR of healthy newborns [5]). Ventricular tachycardia (VT) was defined as three or more consecutive VPCs at a rate of more than 160 bpm. If the second Holter visit occurred before the age of 14 days, the first visit between 14 and 60 days of age was defined as the second Holter visit. The Holter recording of each child with the most APCs or VPCs was included in the analyses of extrasystoles and associated factors, except for the assessment of antiarrhythmic medication, which was based on the second Holter visit. The resolution of extrasystoles was defined as a total count of fewer than 100 extrasystoles on the Holter monitoring, based on the typical number observed in most healthy newborns [1, 5].

Means and SDs were calculated for normally distributed variables and medians, ranges and interquartile ranges (IQRs) for skew-distributed variables. Frequencies and percentages were used for categorical variables. For two-group comparisons, the independent sample *t*-test (two-sided) for normally distributed continuous variables and the Mann–Whitney *U*-test for nonparametric variables were used. Fisher's exact test was used for categorical variables. The persistent occurrence of extrasystoles of more than 100 beats per recording was displayed with Kaplan–Meier analysis. In cases of missing data, a complete case analysis was used. The statistical significance level was defined as a p-value (two-sided) <0.05. Statistical analyses were performed using IBM SPSS Statistics for Macintosh version 28.0 (IBM, Armonk, NY, USA).

This is an observational study. The research project was approved by the Regional Ethics Committee of Tampere University Hospital (ETL R18083).

3 | Results

The study population consisted of 75 children (Figure 1, Table 1). Forty-seven (63%) children were followed up due to APCs, and 28 (37%) children were followed up due to VPCs (Table 2, Figure 2). Echocardiography was performed on 65 (87%) children, and significant heart diseases were found in 5 (7%) children (Table 1). None of the study subjects developed arrhythmogenic cardiomyopathy. Antiarrhythmic medication was initiated in 14 (19%) children during follow-up, either due to SVT or VT detected on Holter monitoring (Tables 1 and 3).

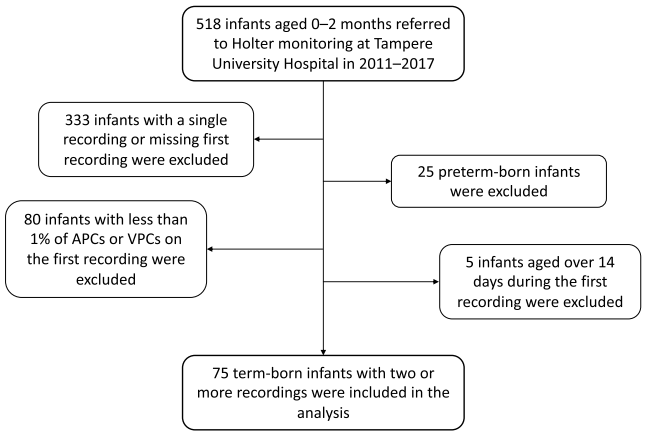

FIGURE 1 | Flowchart of patient selection. APC, atrial premature contraction; VPC, ventricular premature contraction.

The first and second Holter visits occurred at a median (IQR) age of 6 (5–7) days and 37 (26–44) days, respectively. Between the first and second visits, the median (IQR) APC percentage decreased from 3.7% (2.0–5.2) to 0.6% (0.0–3.9) ($p < 0.001$) and the median (IQR) VPC percentage decreased from 3.8% (1.7–9.8) to 0.05% (0.0–4.9) ($p = 0.001$). In 18 (38%) infants with APCs and 9 (32%) infants with VPCs, extrasystoles increased between recordings (Figure 2). The median (IQR) ages for the highest APC and VPC percentages were 7 (6–10) and 7 (6–15) days, respectively.

LBBB-VPCs were associated with a higher VPC percentage (median) compared to RBBB-VPCs (12.2 vs. 5.7; $p = 0.003$). VPC bigeminy was associated with a higher VPC percentage (median) (17.8 vs. 5.7; $p = 0.001$). Sex, minimum HR, mean HR, or maximum HR, foetal extrasystoles, multifocal VPCs, antiarrhythmic medication, or significant heart disease were not associated with APC percentage or VPC percentage.

The follow-up was terminated for 69 (92%) children during the first year once the extrasystoles either decreased below 1%–2% ($n = 12$) or vanished ($n = 57$). Extrasystoles decreased in all children with either APCs or VPCs > 10% in the first recording (Figure 2). The cumulative percentage of extrasystoles resolution during the first year was 92% among children with APCs and 78% among children with VPCs (Figure 3).

Five (18%) children continued to have VPCs beyond the first year (Figure 3). None of them had antiarrhythmic medication or significant heart disease. Three of them still had VPCs at 4 years of age. Persistent VPCs were not associated with sex, foetal extrasystoles, VPC morphology, bigeminy or VPC percentage. The children with persistent VPCs had multifocal VPCs more often than children whose VPCs resolved during the first year, but the association was not statistically significant (60% vs. 17%; $p = 0.082$).

In total, 14 (19%) children had SVT on 25 Holter recordings, and three children (4%) had VTs on four Holter recordings (Table 3). Except for one child with an SVT of up to 170 beats, all SVTs and VTs were 6 beats or shorter. The median (range) age for the first SVT and VT on Holter was 8 (6–74) and 9 (7–17) days, respectively.

SVT or VT was not associated with sex or heart disease. Ten out of forty (25%) children with foetal extrasystoles had SVT on Holter (not significant, $p = 0.151$). Two out of three (67%) children with VT had multifocal VPCs (not significant, $p = 0.145$).

TABLE 1 | Data characteristics.

Characteristic	
Patients, *N*	75
Male sex, *n* (%)	40 (53)
Age during the first recording (days), mean (SD)	6.3 (1.7)
Gestational age at birth (weeks), median (range)	40 (37–42)
Birth weight (g), mean (SD)	3640 (450)
Foetal extrasystoles, *n* (%)	40 (53)
Significant heart disease, *n* (%)	5 (7)
Tetralogy of Fallot, *n* (%)	1 (1)
Large atrial septal defect with multiple ventricular septal defects	1 (1)
Pulmonary valve stenosis	1 (1)
Cardiomyopathy with left ventricular dysfunction	1 (1)
Left ventricular dysfunction due to birth asphyxia	1 (1)
Antiarrhythmic medication, *n* (%)	14 (19)
Propranolol, *n* (%)	11 (15)
Propranolol combined with Flecainide, *n* (%)	3 (4)
Length of treatment[a] (months), median (range)	7 (6–13)
Holter recordings during the first year, *N*	290
Recordings per person, median (range)	3 (2–10)
Antiarrhythmic medication-free recordings, *n* (%)	223 (77)

[a]$n = 12$, one patient's antiarrhythmic treatment was long-term, and one patient's length of treatment was missing.

A higher APC percentage (median) was associated with SVT (5.4 vs. 3.7; $p = 0.013$). A higher VPC percentage (median) was associated with VT (32.1 vs. 6.1; $p = 0.001$). APCs > 5% and VPCs > 10% were associated with SVTs (39% vs. 7%; $p = 0.018$) and VTs (43% vs. 0%; $p = 0.011$), respectively.

SVTs disappeared by the age of 24 days in 10/14 (71%) children, and 13/14 (93%) children were SVT-free by the age of 87 days. One child continued to have SVT beyond the first year of life. VTs resolved by the age of 34 days.

4 | Discussion

This retrospective dataset included newborns exhibiting more than 1% extrasystoles during initial Holter monitoring, derived

TABLE 2 | Holter results by reason for follow-up.

Measure	APC group ($n = 47$)	VPC group ($n = 28$)
APC percentage, first Holter, median (range)	3.7 (1.0–14.6)	0.0 (0.0–2.7)
APC percentage, highest, median (range)	4.5 (1.2–14.6)	0.0 (0.0–2.7)
APCs > 10%, *n* (%)	5 (11)	0 (0)
APCs > 20%, *n* (%)	0 (0)	0 (0)
VPC percentage first Holter, median (range)	0.0 (0.0–0.1)	3.8 (1.1–32.9)
VPC percentage, highest, median (range)	0.0 (0.0–0.2)	6.4 (1.3–32.9)
VPCs > 10%, *n* (%)	0 (0)	7 (25)
VPCs > 20%, *n* (%)	0 (0)	5 (18)
VPCs > 30%, *n* (%)	0 (0)	3 (11)
VPC bigeminy, *n* (%)	—	12 (43)
Multifocal VPCs, *n* (%)	0 (0)	7 (25)
RBBB-VPCs, *n* (%)	—	9 (32)[a]
LBBB-VPCs, *n* (%)	—	12 (43)[a]
Any SVT, *n* (%)	12 (26)	2 (7)
Any VT, *n* (%)	0 (0)	3 (11)

Abbreviations: APC, atrial premature contraction; ECG, electrocardiogram; LBBB, left bundle branch block; RBBB, right bundle branch block; SVT, supraventricular tachycardia; VPC, ventricular premature contraction; VT, ventricular tachycardia.
[a]Documentation of VPCs on the 12-lead ECG was missing for seven (25%) children.

from a large dataset of Holter recordings performed for various reasons at a tertiary centre. The amount of extrasystoles varied during the follow-up period, but they disappeared in most children by 1 year of age. Only a small proportion of children had a significant number of extrasystoles (> 10%) on Holter. A higher percentage of extrasystoles was associated with tachyarrhythmias.

While many reviews state that extrasystoles in the neonatal period are a self-limiting phenomenon [6, 7, 13], no large follow-up study on the natural course of extrasystoles in newborns has been published. Schwartz et al. conducted a prospective study of screening ECGs on newborns starting from 1976 [14]. Albeit they stated that both APCs and VPCs disappeared in 95% of the children by 1 year of age [14], it seems that they have not published the final results.

We found three original studies where the same children were followed up due to neonatal extrasystoles [15–17]. In these studies involving 26–35 children each, extrasystoles disappeared in 40%–50% of infants during the neonatal period, in 80%–85% of infants by the fourth month of life, and in 77%–90% of infants by the age of 1 year. Our results were similar at the age of 1 year. However, according to our definition, the threshold of 40%–50% resolution was reached later, at 2 months of age. Since most of our control recordings were performed after 1 month of age, our results may underestimate the disappearance of extrasystoles during the first month. In addition to the timing of the control recording, the discrepancies between the present study and prior research could be explained by the small sample sizes and differences in methodology: none of the previous studies provided a definition for the disappearance of extrasystoles, and Holter monitoring was not conducted on all subjects during follow-up in these studies.

In the present study, the occurrence of APCs and VPCs peaked in the neonatal period, most often during the first 14 days. While extrasystoles decreased significantly during the first 2 months, the decrease was not linear in all cases. In one-third of the infants, the APC or VPC percentage increased between the recordings. The largest increase was from almost 0% to over 30%. In a previous study, 2/35 (6%) newborns with extrasystoles had an unusual course showing an increase in extrasystoles and tachycardia during the neonatal period [17].

Frequent VPCs have been associated with congenital heart disease [18], and according to the PACES/HRS Expert Consensus Statement, VPCs that exceed the threshold of 10% warrant monitoring and evaluation to exclude structural or functional heart disease [10]. However, the threshold of 10% considers children in general. Whether this threshold for frequent extrasystoles is valid for newborns is not clear. In the present study, only 12 children had APCs or VPCs over 10% on Holter. Only five children with marked heart disease were included, and no association between heart disease and frequent extrasystoles was found. Thus, our results principally depict the population of infants with healthy hearts.

In most children, extrasystoles disappeared during the first year. Interestingly, those few who continued to have extrasystoles did not differ from the others in the initial frequency of extrasystoles. None of the children with extrasystoles over 10% (including children with extrasystoles > 30%) needed follow-up due to extrasystoles beyond the first year. Half of the study subjects had extrasystoles during foetal life, but this did not affect the postnatal prognosis of extrasystoles. Retrospectively, it was not possible to predict which of the children would have required follow-up due to neonatal extrasystoles.

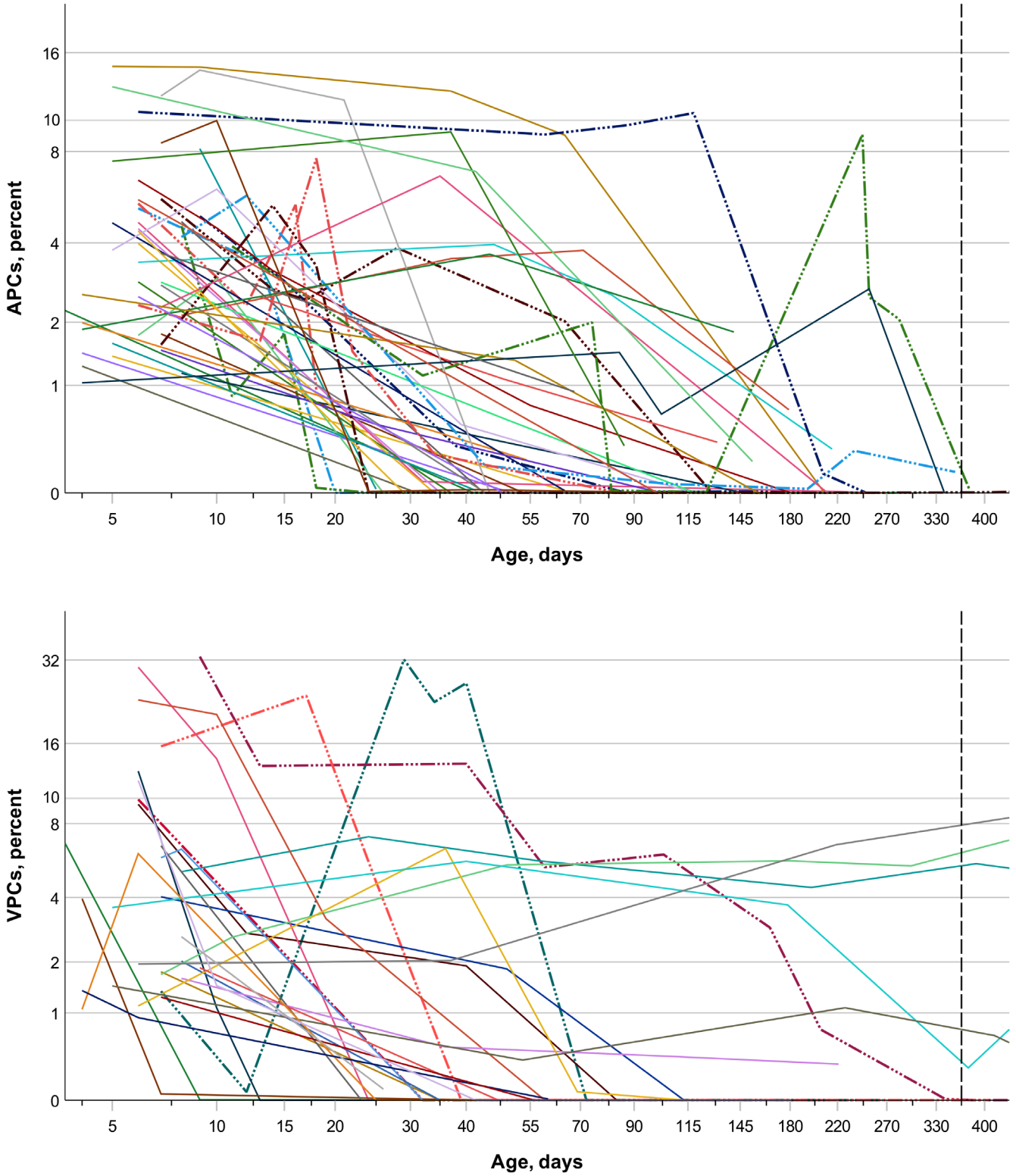

FIGURE 2 | APC percentage ($n = 47$) and VPC percentage ($n = 28$) by age. Each line displays one infant. Infants with antiarrhythmic medication are indicated with dash-dotted lines. The vertical dashed line marks the age of 365 days. APC, atrial premature contraction; VPC, ventricular premature contraction.

Previous data suggest that VPCs with RBBB morphology are likely to disappear during childhood [10, 19], but data on VPC morphology and prognosis during infancy are lacking. We found no association between VPC morphology and the disappearance of extrasystoles during the first year of life, but LBBB-VPCs were associated with a higher VPC percentage on Holter. Multifocal VPCs were uncommon and were not associated with a higher VPC percentage or persistent extrasystoles.

TABLE 3 | Holter results among the children with SVT or VT.

		1st Holter				2nd Holter				3rd Holter				
Child	SVT/VT	Number of SVTs/VTs	Longest SVT/VT, beats	Fastest SVT/VT, bpm	APC/VPC percentage	Number of SVTs/VTs	Longest SVT/VT, beats	Fastest SVT/VT, bpm	APC/VPC percentage	Number of SVTs/VTs	Longest SVT/VT, beats	Fastest SVT/VT, bpm	APC/VPC percentage	Anti-arrhythmic treatment
1	SVT	4	3	263	6	1	3	217	3	0	—	—	2	P
2	SVT	0	—	—	11	1	3	192	9	0	—	—	9	P
3	SVT	0	—	—	<0[a]	1	5	319	<0	0	—	—	<0	P
4	SVT	119	17	254	5	100	170	171	1	175	78	182	2	P, F
5	SVT	1	3	217	<0[b]	0	—	—	<0	0	—	—	<0	—
6	SVT	2	3	223	5	0	—	—	3	0	—	—	<0	P
7	SVT	3	5	214	5	1	5	256	2	0	—	—	5	P
8	SVT	72	5	277	2	4	4	241	2	1	4	247	8	P, F
9	SVT	1	3	187	12	1	3	180	14	0	—	—	12	—
10	SVT	80	6	245	5	0	—	—	3	0	—	—	<0	P
11	SVT	1	3	258	4	0	—	—	6	0	—	—	<0	P
12	SVT	0	—	—	4	0	—	—	1	5	3	217	2	P
13	SVT	1	5	240	2	1	4	225	5	1	3	220	3	P, F
14	SVT	0	—	—	9	0	—	—	10	1	3	178	<0	—
15	VT	1	5	217	1	0	—	—	<0	2	3	189	32	P
16	VT	1	3	230	33	0	—	—	13	0	—	—	13	P
17	VT	0	—	—	16	1	3	205	24	0	—	—	5	P

Abbreviations: APC, atrial premature contraction; bpm, beats per minute; F, Flecainide; P, Propranolol; SVT, supraventricular tachycardia; VPC, ventricular premature contraction; VT, ventricular tachycardia.
[a]APCs; VPCs 10%.
[b]APCs; VPCs 2%.

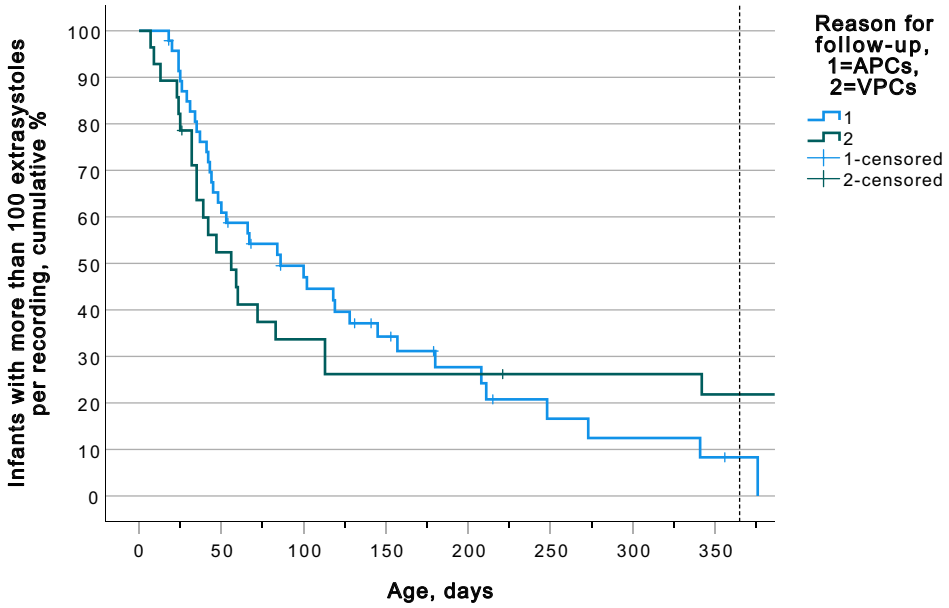

FIGURE 3 | Kaplan–Meier analysis of the reduction in extrasystole burden (more than 100 beats per recording) during the first year of life. The vertical dashed line marks the age of 365 days. APC, atrial premature contraction; VPC, ventricular premature contraction.

Southall et al. studied newborns with standard ECG, and if extrasystoles were frequent enough to be found on short ECG strips, they were associated with SVT or VT in about 30% of cases on subsequent Holter monitoring [2, 16, 20]. We also found an association between a higher percentage of extrasystoles and tachyarrhythmias.

The SVTs and VTs in this study population were incidental findings when evaluating extrasystoles. Nearly all the tachyarrhythmias were only 3–6 beats long—making them impossible to be spotted without continuous ECG monitoring. Although incidental, short runs of APCs were considered SVTs if they occurred at a rapid rate and were, in most cases, deemed treatable with antiarrhythmic medication. The decision to initiate antiarrhythmic therapy was made by a paediatric cardiologist, and factors such as the overall burden of extrasystoles and the presence of functional or structural heart disease may have influenced the treatment decision. The infants received antiarrhythmic medication for at least 6 months according to the national treatment recommendation [21], which was based on the consensus of prophylactic antiarrhythmic treatment of infantile SVT until the tendency for SVT ceases spontaneously [22]. Previously, we have observed similar short SVTs as in this present study among healthy newborns [5]. Those infants were not treated with antiarrhythmic medication, and the arrhythmia did not recur.

Prophylactic antiarrhythmic treatment for infantile SVT is commonly used up to 6–12 months of age, but recurrences of SVT after 4 months of therapy are uncommon [23]. In the present study, SVT resolution occurred most frequently during the first 4 weeks, suggesting that short SVTs could be treated with shorter therapy or close monitoring without antiarrhythmic therapy.

The prognosis of VT in children with a healthy heart is good, and an even better prognosis has been reported when VT occurs in infancy [24]. After a comprehensive diagnostic investigation, most children with VT will not require antiarrhythmic therapy [10]. The infants with isolated VTs in the present study were treated; therefore, we cannot report the natural course of infantile VT without medication.

The strengths of this study are the use of modern technology in 24-h ECG monitoring and the careful analysis of Holter data. Additionally, nearly all the subjects were evaluated for heart disease with echocardiography. The study's limitation is its retrospective design. The impact of various clinical conditions, such as infections, on the frequency of extrasystoles in each Holter could not be assessed. The timing of the follow-up recordings was variable. Furthermore, while the data originated from a large sample at a tertiary centre (more than 500 infants), the final sample encompassed a limited number of subjects with a significant amount of extrasystoles. However, the sample size was larger than in previous follow-up studies on neonatal extrasystoles.

5 | Conclusion

Our study supports the prevailing understanding and the limited previous data on the favourable prognosis of extrasystoles in newborns without heart disease. Serial Holter monitoring may be advisable during the neonatal period for infants with frequent extrasystoles, as some may be at risk of developing tachyarrhythmias. Further research is warranted to establish cut-off values for frequent extrasystoles that require follow-up in newborns.

Acknowledgement

Open access publishing facilitated by Tampereen yliopisto ja Tampereen ammattikorkeakoulu, as part of the Wiley - FinELib agreement.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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