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Presentation and prognosis of excessive asymptomatic atrial ectopy in children and adolescents with structurally and functionally normal hearts

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Presentation and Prognosis of Excessive Asymptomatic Atrial Ectopy in Children and Adolescents With Structurally and Functionally Normal Hearts

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Excessive premature atrial complexes (PACs) in pediatric patients with a structurally normal heart are presumed to be benign and self-resolving, but no studies have confirmed this. Adults with excessive PACs, however, are at increased risk for future sustained atrial arrhythmias and cardiovascular morbidity and mortality. Therefore, we sought to evaluate the clinical course of frequent PACs in asymptomatic children. Patients < 21 years old with numerous asymptomatic PACs (>50/24 hours) were retrospectively selected over a 10-year period. Demographics, clinical characteristics, and results of cardiovascular testing were tabulated. Two groups were defined: those with a significant (>20%) reduction in burden of atrial ectopy versus those with an insignificant (<20%) reduction or increase. Of 6,902 patients, 343 patients (5%) met criteria. Initial median age was 8.3 (interquartile range [IQR] 4.1 to 14) years with comparable male: female ratio. Follow-up Holters were performed on 188 patients (54.8%) at a median interval of 2.2 (IQR 1.3 to 3.6) years. Overall, there was a significant decrease in atrial ectopy burden from 4.2% (IQR 1.9 to 6.5) down to 0.5% (IQR 0.01 to 2.3), with 166 patients (88.3%), demonstrating a decrease of over 20%. Five percent had a small increase, and 6% had an insignificant decrease. None developed cardiac symptoms or sustained supraventricular tachydysrhythmia. Male gender, athletic participation, and discontinuation of stimulant medications were the chief predictors for a reduction of PAC burden on follow-up. Atrial triplets at presentation were associated with a 5.4% increase. In conclusion, this study confirms that excessive asymptomatic childhood PACs with structurally normal hearts are rare and short-term to medium-term prognosis is benign. **(Am J Cardiol 2023;192:160−165)**

Excessive premature atrial complexes (PACs) are early atrial depolarizations that originate in the atrial myocardium at a site distinct from the sinus node.[1] Ambulatory electrocardiographic monitoring studies of healthy pediatric subjects, from neonates to adolescents, have reported the maximum normal number of PACs from 24 to 50/24 hours.[2−5] In pediatric patients, excessive PACs are more common in the fetus, during the second and third trimester, and next in the newborn period.[6] Most PACs noted in the fetus resolve by the time of birth and those in newborns by a few weeks to months of age.[5,6] These are only occasionally associated with a functional or structural cardiac abnormality and usually do not predispose to symptomatic arrhythmias. The presentation of numerous isolated PACs is infrequent in children and adolescents and, in the absence of symptoms or evident heart disease, is presumed to be benign with likely gradual resolution and a good prognosis.[1] Unlike younger pediatric patients, adults with excessive PACs, variably defined as >76 to >100 PACs/24 hours, have been shown to be at increased risk of developing cardiovascular morbidity and mortality.[7−9] There are no published studies that have evaluated asymptomatic children and adolescents with excessive PACs and no other evidence of heart disease. Therefore, the purpose of this study was to outline the clinical presentation, risk factors, and prognosis of excessive PACs in these patients.

Methods

The study was a retrospective review of pediatric patients at both the University of Florida-Jacksonville Pediatric Cardiology at Wolfson Children's Hospital and Jacksonville Pediatric and Adult Congenital Cardiology. The 2 programs together serviced Northeast Florida and Southeast Georgia with a population of nearly 4.5 million. Twenty-four hours Holter monitor reports for pediatric patients from 1 to 20 years of age over a 10-year period were reviewed for the frequency of premature atrial contractions. Holters tabulated had at least 22 of 24 hours

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worth of data. The following definitions were used: excessive premature atrial contractions were defined as >50/24 hours; nonsustained atrial tachycardia was defined as ≥ 4 beats of consecutive ectopic atrial complexes, 2 and 3 consecutive PACs were defined as an atrial couplet and triplet respectively, blocked PAC was defined as a PAC not followed by a QRS complex and multifocal PACs were defined as PACs with 2 or more P wave morphologies. Patients that had an indication for Holter with a corresponding diagnosis in the Electronic Medical Record that listed any category of congenital or noncongenital cardiac disease, preexisting arrhythmia disorder and/or cardiac symptoms were excluded from the analysis. Data for Holters was extracted from MUSE Cardiology Information System (GE Healthcare, Inc., Little Chalfont, United Kingdom) and the Electronic Medical Record. Of the 11,216 Holters performed on 6,902 patients, 356 patients met inclusion criterion. Complete records were obtained for 343 patients that consisted of the study group and were analyzed retrospectively. Patient characteristics, including demographics, pertinent medical history, examination findings, medication use, laboratory data, and athletic inclination (defined as participation in a sport that involved physical strength, speed, or endurance) were collected. Previous medical diagnosis included (1) attention deficit hyperactivity disorder (ADHD) defined as an inattentive, hyperactive, or combination type disorder that interferes with functioning or development, (2) asthma, defined as a respiratory condition marked by spasms in the bronchi of the lungs, causing difficulty in, and (3) prematurity defined as birth before 37 completed weeks of gestation. All cardiac testing, including 12-lead electrocardiogram, echocardiogram, Holter monitor, or treadmill stress test (when obtained) were also collected and reviewed. All cardiac testing results were read by a pediatric cardiologist/electrophysiologist.

The number of follow-up Holter monitors was noted; however, for the purpose of analysis, results of the most recent Holter assessments were tabulated for comparison. Patients with a repeat Holter were classified into 2 groups on follow-up: those with a significant (≥20%) reduction in burden of atrial ectopy versus those with an insignificant (<20%) reduction or increase in burden of atrial ectopy. The number of patients with an increase was few, and the percentage increase was minimal, so a separate group was not created for patients with an increased burden. The study was approved by the Institutional Review Boards at the University of Florida and Baptist Medical Center (Wolfson Children's Hospital, Jacksonville, Florida). Results are presented as median with interquartile range (IQR) for non-normal quantitative data and mean ± SD for parameters that were normally distributed. The presence of a normal distribution was determined using the Shapiro−Wilk test. The Student's *t* test and/or 95% confidence intervals (CI) were used for normally distributed continuous data, and the chi-square test for categorical data. A p value < 0.05 was considered statistically significant.

The primary outcome was the change in the burden of atrial ectopy (mean percentage of PACs) from baseline to follow-up on repeat Holter monitoring. Repeated measures mixed models were built for each predictor. To capture if the changes in the burden of atrial ectopy from baseline to follow-up were significantly associated with the predictor, an interaction term between the predictor and time was included in the model. Then, the predictors found to be significant at 5% level of significance in the 1-predictor models were included in multivariable analyses. The multivariable model fit was tested using the log:likelihood ratio test. The magnitude of a change from baseline to follow-up was described using the coefficient for the interaction term between the predictor and time, along with its unadjusted 95% CI and the bootstrapped adjusted 95% CI, respectively. Both unadjusted and adjusted analyses were computed, and as they were similar, the authors reported the adjusted estimates. The secondary outcome was a determination of patients that had a significant reduction (>20%) in burden of atrial ectopy. The optimal cutoff point for the baseline burden of atrial ectopy to classify the patients into having or not having a significant reduction in the burden of atrial ectopy was estimated using the area under curve and Youden index J: Maximum (Sensitivity + Specificity−1). Additional outcome measures evaluated were progression to supraventricular tachycardia and other cardiovascular morbidity. Analyses were performed using SAS Version 9.4 for Windows (SAS Institute Inc., Cary, North Carolina) and SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, New York).

Results

A total of 343 patients were identified from 6,902 patients (5%) who underwent Holter monitoring between January 1, 2010, to December 31, 2019. The median age at the initial Holter was 8.3 (IQR 4.1 to 14) years. The male: female ratio was comparable. The demographics and clinical parameters for the initial study group and sub-group with follow-up Holters are listed in Table 1. In the indications for obtaining a Holter, the most common was an irregular heart rhythm. The most common preexisting medical condition was a history of ADHD, followed by asthma. The most common medications were those for ADHD and asthma. No patients were on cardiac medications. An athletic inclination was noted in 99 patients. On cardiac examination, an innocent murmur was noted in 80 patients. Echocardiograms were performed in all except 5 patients, and no structural or congenital heart disease was identified. Treadmill testing was performed in 63 patients, with persistence of ectopy noted in only 4 patients during peak exercise. The results of the treadmill stress tests were otherwise normal. The number of patients that had a follow-up Holter was 188.

In the 188 patients (54.8% of the initial group) who accomplished a follow-up Holter, the median age at last Holter was 11.7 (IQR 6.8 to 17) years and was performed at a median of 2.2 (IQR 1.3 to 3.6) years after the first Holter. Recheck Holters were completed a median of 2 (range 1 to 5) times in those that had a follow-up Holter monitor. At the time of the last repeat Holter, stimulant medications for ADHD had been discontinued in 25 of 26 patients. Atrial ectopic burden characterization is listed in Table 2.

Overall, there was a significant decrease in atrial ectopy burden on repeat Holter examinations in terms of percentage PACs, atrial couplets, triplets, number of multifocal,

Table 1
Baseline characteristics of study population and sub-group with follow-up Holters

Parameters	All patients(n = 343)	Patients with follow-Up Holters (n = 188)
Sex Male	184 (53%)	96 (51%)
Age at initial Holter (years)	8.3 (IQR 4.1-14)	7.6 (IQR 4-13.9)
Age at last Holter (years)	-	11.7 (IQR 6.8-17)
Height(cm) for age z-score*	+0.62 (95%CI +0.41,+0.83)	+0.49 (95%CI +0.37,+0.61)
Weight (kg)	34 (IQR 17.9-62)	27.9 (IQR 16-61.4)
Body Surface Area	1.15 (IQR 0.72-1.69)	0.97 (IQR 0.67-1.68)
Body Mass Index	17.98 (IQR 15.94-23.19)	17.45 (IQR 15.6-23.01)
Clinic heart rate	82 (IQR 74-98)	87 (IQR 76-100)
Systolic blood pressure	107 (IQR 98-120)	104 (IQR 97-120)
Diastolic blood pressure	65 (IQR 60-70)	64 (IQR 60-70)
Oxygen Saturation	99 (IQR 98-100)	99 (IQR 99-100)
Preexisting medical condition:		
None	254 (74%)	141(75%)
ADHD	39 (11.3%)	26 (13.8%)
Asthma	33 (9.6%)	16 (8.5%)
Prematurity	5 (1.4%)	2 (1.1%)
Other	2 (0.5%)	0
Reason for Clinical Presentation:		
Irregular Heart Rhythm	193 (56.2%)	105 (55.8%)
Sports screen	30 (8.7%)	22 (11.7%)
Murmur	72 (20.9%)	38 (20.2%)
ADHD screen	19 (5.5%)	11 (5.8%)
Drug screen	13 (3.8%)	5 (2.6%)
Elevated blood pressure	8 (2.3%)	3 (1.6%)
Abnormal Electrocardiogram	5 (1.5%)	4 (2.1%)
Other	2 (0.6%)	0
Medications:		
ADHD	39 (11.4%)	26 (13.8%)
Asthma	20 (5.8%)	10 (5.3%)
Other	1 (0.3%)	0
None	283 (82.5%)	152 (80.8%)

Data are median and IQR for continuous data and percentage in parentheses for categorical variables.
* z scores that are presented as mean and 95% CI.
ADHD = attention deficit hyperactivity disorder; IQR = interquartile range.

blocked, and aberrantly conducted PACs. A total of 166 patients (88.3%) demonstrated a decrease in atrial ectopy by over 20% from baseline. A total of 10 patients (5.3%) had an increase in the ectopy burden over time, and 12 patients (6.3%) had an insignificant decrease. Nonsustained AT, up to a maximum duration of 6 beats, was noted in 3 patients on the initial Holter but none on subsequent final evaluations. Additionally, no patients had cardiovascular morbidity documented during follow-up.

Table 3 lists the results from univariate and multivariate logistic regression with associated 95% CI and odds ratio. The change in percentage of PACs on follow-up was not associated with age, height *z*-score or body mass index when adjusting for all the other variables. When compared

Table 2
Holter data

Parameters	All patients (n = 343)	Patients with follow-Up data (n = 188) Initial Holter	Follow-up Holter	p Value (Initial vs. Follow-up)
Interval between Holters (years)		-	2.22 (1.3-3.6)	
Average HR	88 (IQR 80-98)	89 (IQR 82-98)	82 (IQR 71-91)	
HR Range- Low	52 (IQR 49-57)	53 (IQR 49-59)	51 (IQR 45-56)	
High	176 (IQR 161-187)	176 (IQR 164-188)	172 (IQR 156-189)	
% PACs	3.6 (IQR 0.7-5.4)	4.2 (IQR 1.9-6.5)	0.5 (0.01-2.3)	<0.001
Atrial couplets(n)	137 (39.9%)	73 (39%)	48 (25.5%)	<0.001
Atrial triplets(n)	24 (6.9%)	20 (10.6%)	8 (4.3%)	0.001
AT(n)	3 (0.87%)	3 (1.6%)	0	
Multifocal PAC(n)	101 (29.4%)	67 (35.6%)	16 (8.5%)	<0.001
Blocked PACs(n)	112 (32.6%)	97 (51.6%)	20 (10.6%)	<0.001

AT = atrial tachycardia; HR, = Heart rate; IQR = interquartile range; PACs = premature atrial complexes.
Data are median and IQR for continuous and percentage for categorical variables.

Table 3
Multivariable models analysis with significant predictors and magnitude of difference in change

Predictor	Unadjusted Analyses (univariate)		Adjusted Analyses* (multivariate)	
	Estimate† (95%CI)	p Value	Estimate‡ (95%CI)	p Value
Sex, Male vs. Female	−1.55 (95%CI −2.43, −0.66)	**0.0007**	−1.59 (95%CI −2.48, −0.69)	**0.0006**
PMH: ADHD vs. none	−2.02 (95%CI −3.33, −0.71)	**0.003**	−2.02 (95%CI −3.33, −0.71)	**0.003**
Asthma vs none	−0.57 (95%CI −2.19, 1.05)	0.491	−0.81 (95%CI −2.48, 0.85)	0.339
Medication: ADHD vs none	−2.83 (95%CI −4.12, −1.53)	**<0.0001**	−2.85 (95%CI −4.15, −1.55)	**<0.0001**
Asthma vs none	−0.90 (95%CI −2.52, 0.71)	0.275	−0.92 (95%CI −2.55, 0.70)	0.339
Athletic participation: yes vs. no	−1.29 (95%CI −0.19, −2.39)	**0.023**	−1.22 (95%CI −0.10, −2.34)	**0.034**
Couplets none vs. present	−0.15 (95%CI −1.08, 0.01)	0.756	−0.43 (95%CI −0.92, 0.06)	0.086
Triplets none vs. present	−5.4 (95%CI −6.66, −4.14)	**<0.0001**	−5.40 (95%CI −6.66, −4.14)	**<0.0001**
Triplets and non-sustained runs none vs. present	−4.6 (95%CI −6.8,-3.14)	**<0.001**	−4.6 (95%CI −6.2, −3.31)	**0.001**
Treadmill test: PACs persist vs. PACs suppressed	−1.25 (95%CI −4.33, 1.83)	0.430	−1.17 (95%CI −4.35, 2.00)	0.474
Presenting age, per unit increase	−0.02 (95%CI −0.11, 0.07)	0.642	−0.03 (95%CI −0.11, 0.06)	0.567
Height z-score, per unit increase	−0.01 (95%CI −0.40, 0.38)	0.954	−0.01 (95%CI −0.40, 0.38)	0.948
BMI, per unit increase	−0.01 (95%CI −0.13, 0.10)	0.799	−0.01 (95%CI −0.14, 0.10)	0.948

ADHD = attention deficit hyperactivity disorder; BMI = body mass index; PACs = premature atrial complexes.
* Multivariable models included gender, past medical history, medications, athletic predisposition, triplets on Holter.
† Estimates (95% CI) corresponding to the interaction terms.
‡ Estimate for the interaction term between predictor and time (a negative estimate indicates larger reduction by the value of the coefficient at follow-up, whereas a positive estimate indicates a smaller reduction).

with female patients, male patients had an additional 1.6% (95% CI 0.7% to 2.5%, p value: 0.0006) decrease in mean percentage of PACs from baseline to follow-up. The change from baseline was different between patients on ADHD stimulant medications that were subsequently discontinued and those not on medications (p value <0.0001). Patients who were on ADHD stimulant medications at the initial Holter had an additional 2.9% (95% CI 1.6% to 4.2%) decrease in mean percentage of PACs from baseline to follow-up when those medications were discontinued. Patients that were noted to be athletic at baseline had an additional 1.2% (95% CI 0.1% to 2.3%) decrease in mean percentage of PACs from baseline to follow-up. On the contrary, patients that had triplets at presentation had an additional 5.4% (95% CI 4.1% to 6.6%) increase in mean percentage of PACs from baseline to follow-up.

Receiver operating characteristic curves were constructed to assess the discriminative value of initial ectopy burden to predict a reduction on follow-up. The Youden index (J) obtained corresponded to a sensitivity of 0.57 and a specificity of 0.67. The optimal cutoff value corresponding to Youden index was 0.27, suggesting that subjects with a mean percentage of PACs at baseline $< 0.27\%$ were likely to have a significant reduction in atrial ectopy as compared with subjects that had an initial burden of $\geq 0.27\%$.

Discussion

In this study, we examined the clinical presentation and prognosis of excessive PACs in asymptomatic pediatric patients beyond infancy without other evidence of heart disease. Risk factors for persistence of excessive atrial ectopy over time were also explored. At presentation, we did not find any difference in prevalence between genders. Most adult studies have likewise not found a difference in prevalence between men and women.[7,9–11] There was a wide range of ages at presentation in our study with no association with older pediatric age. Analyses of adult patients with excessive PACs have demonstrated associations with older age, over a wider spectrum of decades, and taller height.[10,11] Our pediatric group had a mean height *z*-score of +0.62, indicating that these patients were at the seventy-third percentile for height and generally taller than the average child. Asthma as a preexisting condition was noted in 9.6% of our study population, whereas the current prevalence of asthma in children in the United States is 5.8%.[12] Inadequate asthma control in adults has been associated with increased risk of developing atrial fibrillation, but beta-agonist therapy has not been associated with such.[13] A significant proportion of our patients (11.4%) were on stimulant medications for ADHD. This is also increased compared with the general prevalence of ADHD medication use in children, most recently reported at approximately 5.2%.[14] Safety concerns with regard to prescription medications have guided governmental regulatory policy and prescriber behavior, and, as in this study, a large number of children on ADHD medication are referred for screening electrocardiograms.[15] No pediatric investigation has revealed evidence of an association between ADHD stimulant medication use and atrial arrhythmia other than sinus tachycardia.[16] However, adult active amphetamine users have been shown to have an increased risk of developing atrial arrhythmias.[17] Additionally, a randomized trial of the acute effects of caffeinated energy drinks in children and adolescents demonstrated a significant increase in supraventricular extrasystoles compared with placebo.[18]

Regarding prognosis, none of our patients developed supraventricular tachycardia or cardiovascular symptoms or disease over time. Furthermore, even in those patients with runs of nonsustained AT on baseline monitoring, no recurrence of such was noted on follow-up. Studies in adults with excessive PACs have demonstrated that even mildly increased PACs are an independent predictor of new-onset atrial fibrillation, stroke, congestive heart failure, and increased all-cause and cardiovascular mortality, including sudden cardiac death.[7–9,11] The 1 study of excessive PACs

in adult patients with congenital heart disease also confirmed a significant association with new-onset atrial fibrillation.[19] Only very frequent PACs ≥ 1% on Holter monitoring in adults have been associated with an increased incidence of developing supraventricular tachycardia, in addition to atrial fibrillation.[20] Cardiac function was normal in all our patients, suggesting that a high PAC burden is not likely to contribute to a decrease in function. A recent study in adults found that, unlike with premature ventricular complexes, a high PAC burden is not associated with myocardial dysfunction.[20]

When evaluating the change in burden of PACs over time in this study, there were a few factors that predicted the magnitude and direction of change. In patients with triplets at presentation, there was an increase in the burden of PACs over time. Also, the combined group of patients that demonstrated either triplets or nonsustained runs of AT had an additional increase in the mean percentage of PACs from baseline to follow-up. An adult series reported by Acharya et al[21] linked frequent atrial couplets, triplets, and runs with a greater risk of new-onset atrial fibrillation.

Multivariate model analysis showed that our patients with a percentage PAC burden of under 0.27% were more likely to demonstrate a reduction in burden with time. Additionally, being a female child was a risk factor for nonresolution of PACs with time. We found that a history of physical activity with athletic involvement was a strong predictor for a decrease in PAC burden with time. As the patients in this study were asymptomatic with normal cardiac anatomy and function, exercise limitation was not recommended. This effect of physical activity is in agreement with data from adult studies, which showed that moderate-intensity exercise was associated with a reduced burden of PACs over time.[10,11] Increased physical activity has been shown to reduce general inflammation and sympathetic nervous activity, both of which may be related to atrial arrhythmias.[22]

The change in percentage of PACs over time in our study was not associated with age, height z scores, body mass index, asthma, presence of couplets, or suppression of PACs on treadmill testing. There are no similar adult studies looking for associations between such parameters and the change in burden of PACs with time. Stimulant ADHD medications were discontinued or replaced with nonstimulant medications in 25 of 26 patients at the time of the repeat Holter, and it is likely that discontinuation of stimulant medications could have played a role in the significant decrease in atrial ectopy in this group of patients versus those not on medications. This study was not, however, designed or powered to evaluate the effects of stimulant medications on the burden of PACs. The main limitation of this study was that data were obtained retrospectively, which may have increased the risk of information bias. Patient compliance with follow-up Holter monitoring was incomplete, likely due to the asymptomatic nature of the condition. This was a midterm study, and therefore, we are unable to draw conclusions on the long-term effects of persistent PACs on the health of a pediatric patient. In conclusion, PACs in the setting of asymptomatic children and adolescents with structurally normal hearts are rare and although not all patients had follow-up studies, medium-term prognosis is benign with the great majority demonstrating a significant decrease over time with growth and maturation. Male gender, athletic physical activity participation, discontinuation of ADHD stimulant medications, and initial PAC burden < 0.27% were the chief predictive factors associated with a reduction in PAC burden over time.

Disclosures

The authors have no conflicts of interest to declare.

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1. Walsh EP, Berul CI, Triedman JK. Cardiac arrhythmias. Kean JF, Lock JE, editors. Cardiac arrhythmias. *Nadas' Pediatric Cardiology; Philadelphia* 2006:477–524.
2. Southall DP, Richards J, Mitchell P, Brown DJ, Johnston PG, Shinebourne EA. Study of cardiac rhythm in healthy newborn infants. *Br Heart J* 1980;43:14–20.
3. Scott O, Williams GJ, Fiddler GI. Results of 24 hour ambulatory monitoring of electrocardiogram in 131 healthy boys aged 10 to 13 years. *Br Heart J* 1980;44:304–308.
4. Southall DP, Johnston F, Shinebourne EA, Johnston PG. 24-hour electrocardiographic study of heart rate and rhythm patterns in population of healthy children. *Br Heart J* 1981;45:281–291.
5. Nagashima M, Matsushima M, Ogawa A, Ohsuga A, Kaneko T, Yazaki T, Okajima M. Cardiac arrhythmias in healthy children revealed by 24-hour ambulatory ECG monitoring. *Pediatr Cardiol* 1987;8:103–108.
6. Southall DP, Richards J, Hardwick RA, Shinebourne EA, Gibbens GL, Thelwall-Jones H, De Swiet M, Johnston PG. Prospective study of fetal heart rate and rhythm patterns. *Arch Dis Child* 1980;55:506–511.
7. Chong BH, Pong V, Lam KF, Liu S, Zuo ML, Lau YF, Lau CP, Tse HF, Siu CW. Frequent premature atrial complexes predict new occurrence of atrial fibrillation and adverse cardiovascular events. *Europace* 2012;14:942–947.
8. Lin CY, Lin YJ, Chen YY, Chang SL, Lo LW, Chao TF, Chung FP, Hu YF, Chong E, Cheng HM, Tuan TC, Liao JN, Chiou CW, Huang JL, Chen SA. Prognostic significance of premature atrial complexes burden in prediction of long-term outcome. *J Am Heart Assoc* 2015;4:e002192.
9. Huang TC, Lee PT, Huang MS, Su PF, Liu PY. Higher premature atrial complex burden from the Holter examination predicts poor cardiovascular outcome. *Sci Rep* 2021;11:12198.
10. Conen D, Adam M, Roche F, Barthelemy JC, Felber Dietrich D, Imboden M, Künzli N, von Eckardstein A, Regenass S, Hornemann T, Rochat T, Gaspoz JM, Probst-Hensch N, Carballo D. Premature atrial contractions in the general population: frequency and risk factors. *Circulation* 2012;126:2302–2308.
11. Kerola T, Dewland TA, Vittinghoff E, Heckbert SR, Stein PK, Marcus GM. Predictors of atrial ectopy and their relationship to atrial fibrillation risk. *Europace* 2019;21:864–870.
12. Centers for Disease Control and Prevention. Most recent national asthma data. Available at: http://cdc.gov/asthma/most_recent_national_asthma_data.htm. Accessed on February 10, 2023.
13. Cepelis A, Brumpton BM, Malmo V, Laugsand LE, Loennechen JP, Ellekjær H, Langhammer A, Janszky I, Strand LB. Associations of asthma and asthma control with atrial fibrillation risk: results from the Nord-Trøndelag Health Study (HUNT). *JAMA Cardiol* 2018;3:721–728.
14. Danielson ML, Bitsko RH, Ghandour RM, Holbrook JR, Kogan MD, Blumberg SJ. Prevalence of parent-reported ADHD diagnosis and associated treatment among U.S. Children and adolescents, 2016. *J Clin Child Adolesc Psychol* 2018;47:199–212.
15. Vetter VL, Elia J, Erickson C, Berger S, Blum N, Uzark K, Webb CL. American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee. American Heart

Association Council on Cardiovascular Nursing. Cardiovascular monitoring of children and adolescents with heart disease receiving medications for attention deficit/hyperactivity disorder [corrected]: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing [published correction appears in *Circulation* 2009 Aug 18;120:e55−e59] *Circulation* 2008;117:2407–2423.

16. Hennissen L, Bakker MJ, Banaschewski T, Carucci S, Coghill D, Danckaerts M, Dittmann RW, Hollis C, Kovshoff H, McCarthy S, Nagy P, Sonuga-Barke E, Wong IC, Zuddas A, Rosenthal E, Buitelaar JK, ADDUCE consortium. Cardiovascular effects of stimulant and non-stimulant medication for children and adolescents with ADHD: a systematic review and meta-analysis of trials of methylphenidate, amphetamines and atomoxetine. *CNS Drugs* 2017;31:199–215.
17. Dominic P, Ahmad J, Awwab H, Bhuiyan MS, Kevil CG, Goeders NE, Murnane KS, Patterson JC, Sandau KE, Gopinathannair R, Olshansky B. Stimulant drugs of abuse and cardiac arrhythmias. *Circ Arrhythm Electrophysiol* 2022;15:e010273.
18. Mandilaras G, Li P, Dalla-Pozza R, Haas NA, Oberhoffer FS. Energy drinks and their acute effects on heart rhythm and electrocardiographic time intervals in healthy children and teenagers: a randomized trial. *Cells* 2022;11:498.
19. Teuwen CP, Korevaar TIM, Coolen RL, van der Wel T, Houck CA, Evertz R, Yaksh A, Roos-Hesselink JW, Bogers AJJC, de Groot NMS. Frequent atrial extrasystolic beats predict atrial fibrillation in patients with congenital heart defects. *Europace* 2018;20:25–32.
20. Gunda S, Akyeampong D, Gomez-Arroyo J, Jovin DG, Kowlgi NG, Kaszala K, Tan AY, Koneru JN, Kron J, Ellenbogen KA, Huizar JF. Consequences of chronic frequent premature atrial contractions: association with cardiac arrhythmias and cardiac structural changes. *J Cardiovasc Electrophysiol* 2019;30:1952–1959.
21. Acharya T, Tringali S, Bhullar M, Nalbandyan M, Ilineni VK, Carbajal E, Deedwania P. Frequent atrial premature complexes and their association with risk of atrial fibrillation. *Am J Cardiol* 2015;116:1852–1857.
22. Elliott AD, Linz D, Mishima R, Kadhim K, Gallagher C, Middeldorp ME, Verdicchio CV, Hendriks JML, Lau DH, La Gerche A, Sanders P. Association between physical activity and risk of incident arrhythmias in 402 406 individuals: evidence from the UK Biobank cohort. *Eur Heart J* 2020;41:1479–1486.