Prevalence and severity of sinus tachycardia and arrhythmias by Holter monitoring in children with Duchenne muscular dystrophy

Magdalena Bazgier[1]*, Jarosław Meyer-Szary[1]*, Renata Tarnowska[1], Katarzyna Lisowska[1], Jolanta Wierzba[2], Joanna Kwiatkowska[1]

[1]Department of Pediatric Cardiology and Congenital Heart Defects, Medical University of Gdansk, Gdańsk, Poland
[2]Department of Pediatrics, Hematology and Oncology, Department of General Nursery, Medical University of Gdansk, Gdańsk, Poland
*Both authors equally contributed to the study.

Correspondence to:
Joanna Kwiatkowska, MD PhD, Department of Pediatric Cardiology and Congenital Heart Defects, Medical University of Gdansk, Dębinki 7, 80–211 Gdańsk, Poland,
phone: +48 58 349 28 70,
e-mail: joannak@gumed.edu.pl

DOI: 10.33963/v.kp.98326

Received:
June 21, 2023

Accepted:
November 27, 2023

Early publication date:
December 31, 2023

INTRODUCTION

Heart failure (HF) currently accounts for 30%–60% of deaths in Duchenne muscular dystrophy (DMD) patients [1, 2]. The development of dilated cardiomyopathy (DCM) is a slow but inevitable process, preceded by ongoing cardiac fibrosis as evidenced by late gadolinium enhancement (LGE) in cardiac magnetic resonance studies (CMR) [3, 4]. Arrhythmias evolve throughout patients' lives, with asymptomatic sinus tachycardia (ST) being one of the most common and early-occurring heart rhythm abnormalities of unknown prognostic value [5–7]. The assessment of the prevalence and severity of ST and arrhythmias in DMD patients of different age groups using Holter monitoring were the aim of our study.

METHODS

The data collected between year 2017–2019 (Supplementary material, *Figure S1*) were analyzed in a cross-sectional, single center prospective observational study. *Table S1* in supplementary material presents inclusion and exclusion criteria. The recordings were performed as a part of a routine, annual cardiological screening using Phillips Holter ECG system (Phillips DigiTrak XT) with the Zymed algorithm analyzer. The analysis included the assessment of heart rate (HR) variables, presence and severity of arrhythmias. The data published by Salameh et al. [8] based on the healthy population was used as reference and for calculations of the standardized values (z-scores) of the analyzed parameters. To characterize ST in detail, we developed sinus tachycardia severity scale (STSS) as shown in Supplementary material, *Table S2*.

Statistical analysis

The statistical analysis was performed using Wizard 2.0 (Evan Miller, Chicago, IL, US). Categorial data are given as counts and percentages and continuous data are presented as mean (standard deviation) or median (interquartile range) dependently on the distribution. The distribution was tested using the Shapiro–Wilk test. Standard statistical tests, including, χ^2, t-test, Pearson correlation test were used. Additionally simple linear and quadratic regressions were used dependently on best fit based on highest R^2 and multivariable models were analyzed. $P < 0.05$ was considered statistically significant.

The study was approved by the Institutional Bioethics Committee for Scientific Research.

RESULTS AND DISCUSSION

Two studies out of 72 collected Holter ECG recordings met the exclusion criteria being conducted in BB-treated patients. Eventually, 70 recordings in 70 caucasian patients including 2 girls, one recording each, were analyzed. Twenty-six (31.9%) recordings were done in patients taking angiotensin-converting-enzyme inhibitor (ACEi) and those patients were on average older (on-ACEi vs. no-ACEi: 11.5 [3.8] vs. 9.0 [3.9] years; $P < 0.001$). Most of the recordings (47, 67.1%) was done in patients taking steroids. There was no age-difference between steroid-treated and steroid-naive patients (10.1 [3.3] vs. 9.5 [4.8], respectively,

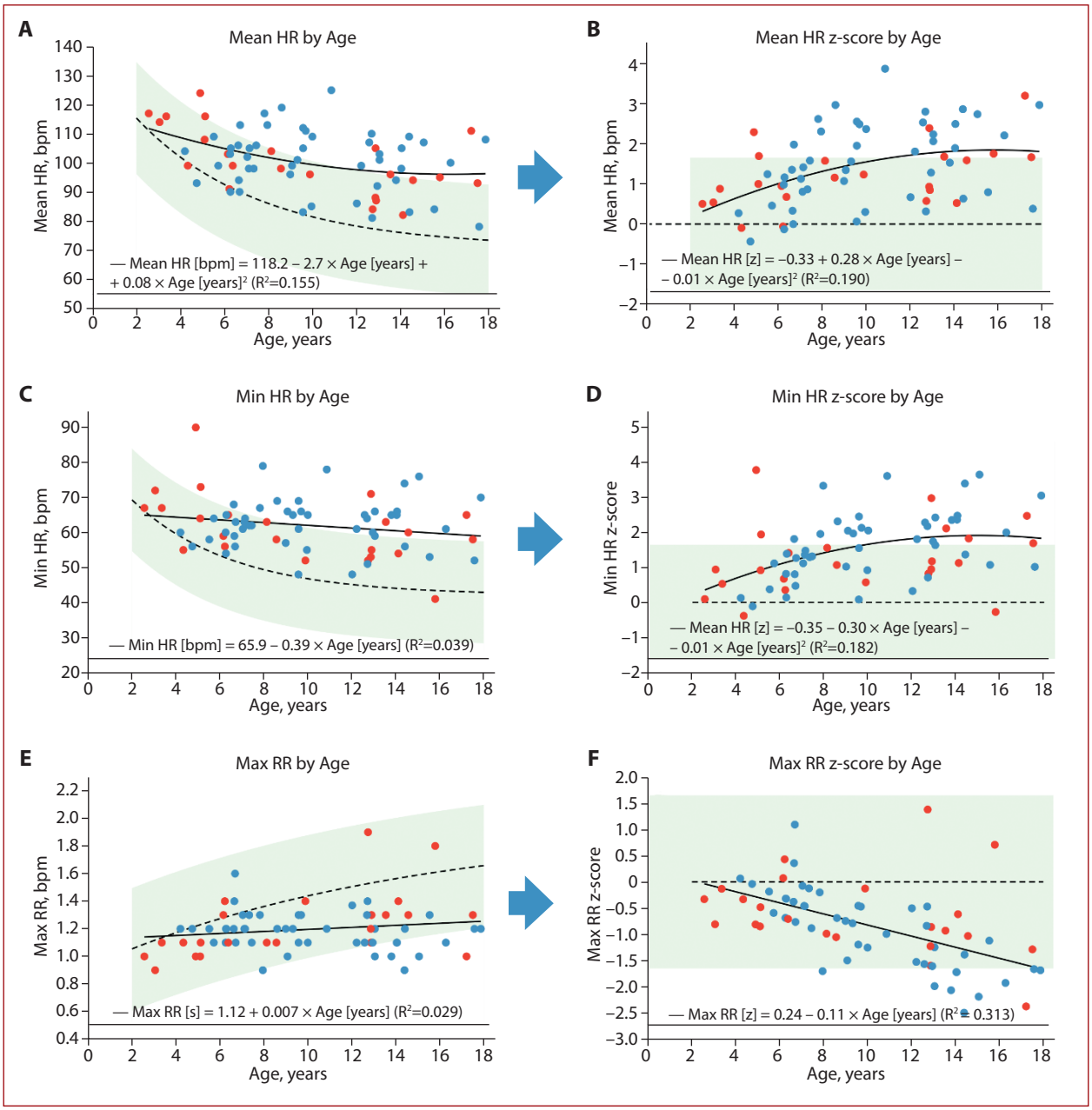

Figure 1. Age dependency of the studied parameters: **A.** Mean HR. **B.** Mean HR z-score. **C.** Minimum HR. **D.** Minimum HR z-score. **E.** Maximum RR. **F.** Maximum RR z-score *P*-value is for t-test for the comparison to the reference population [8]

Abbreviations: HR, heart rate; RR, RR distance

P = 0.51). Baseline and pharmacotherapy characteristics are presented in *Table S3* of the Supplementary material.

None of the analyzed parameters was dependent on total recording time (i.e., shorter recordings were not significantly biased). Mean HR was found to be statistically different from the reference healthy population, *P* <0.001 and inversely correlated with age (R^2 = 0.155; *P* <0.001) dropping at a rate slower than the reference population as shown in Figure 1A. For linear regression the drop was 0.95 bpm/year. The mean HR z-score used for assessment of the severity of ST revealed positive correlation with age (R^2 = 0.190; *P* <0.001), rising 0.09/year. A more detailed analysis of the time trend showed a nonlinear relation of these parameters to age best approximated by a quadratic equation with an inflection point around the age of 11 years as shown in Figure 1B. The age subgroup analysis showed that up to the age of 10 ST is becoming more severe and there is an annual increase of mean HR z-score of 0.20 while after the age of 12 years the mean HR z-score plateaus as 1.69 (0.88) with no significant rise thereafter. Consequently, ST was diagnosed in 27 (38.6%) cases overall in the analyzed sample. The ST prevalence was age-dependent (*P* = 0.02) — more common in older subgroups as shown in *Figure S2* and *S3A* (Supplementary material).

The minimum HR was higher and the maximum RR shorter than in the reference population (*P* <0.001 in both),

presenting no correlation with age ($P = 0.10$ and $P = 0.17$, respectively) as shown in Figure 1C and Figure 1E. Conversely, the minimum HR z-score was positively ($R^2 = 0.182$; $P < 0.001$, Figure 1D) and the maximum RR z-score was inversely correlated with age ($R^2 = 0.313$; $P < 0.001$, annual drop of –0.11, Figure 1F). Significant differences were present in age groups analysis of all the above-mentioned parameters as presented in *Figure S3B–C* in Supplementary material.

There was also no significant difference between ACEi-treated and ACEi-naive patients in Mean HR z-score ($P = 0.16$), minimum HR z-score ($P = 0.31$) and maximum RR z-score ($P = 0.22$) in multivariable model corrected for age.

No complex supraventricular or ventricular arrhythmias or higher degree block were found, thus none of the patients required starting antiarrhythmic treatment based on the analyzed recording. There was no correlation of SVPC and VPC prevalence with age ($P = 0.32$ and 0.140, respectively). The detailed Holter ECG recording results are summarized in *Table S4* of the Supplementary material.

Although the presence of ST is a well-known phenomenon in DMD, its reported prevalence ranges from 0 up to 50% dependently on the method (resting HR measurement vs. Holter monitoring), definition criteria, and cohort characteristics (age) [5, 9, 10]. While in the previous studies it was common to evaluate the prevalence of ST, its severity had not been assessed beforehand. In our study, based on the z-score calculation and analysis, we found that not only the prevalence, but also the severity of ST increases with age up to the age of about 12 years when it reaches its plateau. The exact reasons and pathomechanism behind this finding are uncertain. Previously suggested compensatory reaction to heart failure is improbable as most of the DMD patients in the younger age groups will still have preserved cardiac contractile function while in the older groups, where contractile disfunction onsets, the degree of ST (by Mean HR z-score) is stationary [4, 5, 10]. Alternatively, an autonomous disfunction was a suggested explanation but currently there is not enough scientific evidence to support this hypothesis [10]. Despite Thomas et al. [5] suggested link between elevated heart rate and DMD-CM development, ST's prognostic value remains uncertain.

In the reports available the prevalence and severity of both supraventricular and ventricular arrhythmias varies significantly with prevalence of VPC ranging from 14% to 58% [6, 7, 11]. In the presented study, the prevalence of ventricular arrhythmias was lower than in the study by Villa et al. [7]. Similarly to this study, we found supraventricular arrhythmias more prevalent, which is discrepant from the report by Chiang et al. [6], where ventricular arrhythmias, including nsVT were frequently diagnosed. As the age of 17 or more was found to be associated with the development of SVT/VT, the younger age of the population described in our study might explain this discrepancy. On the other hand, the deterioration of left ventricular systolic function is a predictor of significant Holter ECG findings also in younger patients [6, 7]. Contrary to other muscular dystrophies, e.g. Emery-Dreifuss muscular dystrophy, atrial fibrillation and atrioventricular blocks are rare in DMD [12]. The link between presence of fibrosis based on CMR LGE assessment and life-threatening arrhythmias regardless of contractile function, together with high incidence of fibrosis in DMD patients, poses another potential risk factor in this group of patients [3, 4, 13].

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

Funding: None.

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