Heart Rate Variability and QT Changes in Children with Hemophilia

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ABSTRACT

Background: Hemophilia-A is a sex-related hereditary bleeding disorder, like the general populations, mortality from cardiovascular diseases is currently responsible for one-third of deaths in hemophilia patients.

Method: A case controlled study was carried out on fifty children; twenty five male with hemophilia-A compared to twenty five healthy male children.12 lead surface ECG, 24 hour holter monitoring and basic echocardiography assessment were done for all participating children.

Results: ECG recording revealed that increased heart rate (b/min), QTc/msec, the maximum and QT dispersion in the hemophilia children vs. the control, increased QT dispersion by 24 hour holter in hemophilia children. Reduced time domain parameters for HRV (ms) in hemophilia children were compared to the healthy controls. A significant difference was observed between the diseased and healthy group in the number and frequency of the subject with increased QTc dispersion more than 70 ms detected by ECG, but not by holter.

Conclusion: There was an increase in QT dispersion in children with hemophilia that put them at risk for developing dysrhythmia, sympathovagal imbalance detected by the presence of depressed HRV, and also exposed them to cardiac morbidities and sudden cardiac death.

KEYWORDS

Children
Hemophilia
Heart rate variability
QT abnormality
Introduction

Hemophilia A (HA) is a sex-related hereditary bleeding condition characterised by decreased or absent factor VIII activity (F-VIII). Hemophilia is the most frequent of the serious bleeding disorders, and it can lead to chronic disease and lifetime disability if not appropriately managed since childhood [1].

With advances in care, children with hemophilia achieve near-normal life, so age-related cardiovascular condition can be the presenting complains. Like the general populations; mortality from cardiovascular diseases are currently responsible for one third of deaths in those population [2].

Prophylaxis, or routine, long-term treatment to avoid hemorrhage, using infusions of plasma-derived or recombinant factor medications, has long been the gold standard for hemophilia treatment. There are many extended half-life (EHL) products in recent years. Nonfactor therapies (NFTs), such as a bispecific antibody mimicking activated factor VIII (FVIIIa) for hemophilia A (HA), small interfering RNA (siRNA) to antithrombin (AT), and antibodies to tissue factor pathway inhibitor (TFPI), are in clinical trials [3].

The time taken by the ventricle to depolarized and repolarized represented on the ECG as the QT interval. QT is commonly affected by heart rate. To overcome this problem, many investigators attempted to use the QT correction (QTc) [4]. QT dispersion which defined as the difference between the maximal and minimal QT interval duration measured in 12 ECG is an easily available marker of ventricular repolarization abnormalities [5, 6].

Heart rate variability (HRV) illustrates the variation extent in R-R intervals noted with continuous ECG monitoring [7]. Reduction in HRV and increase in the ventricular repolarization parameters (QTc and QTd) was attributed to have a strong clinical utility in the risk stratification of diverse types of patients to exclude life threatening arrhythmias and the increased risk of sudden cardiac death (SCD) [8].

Since 1940s when Norman Jefferis Holter did the first mobile ECG, the development of its shape, size, technology, and wires was very rapid, increasing its utility in clinical applications [6]. Regardless of its suboptimal yield and the alternative implementation and more efficient monitoring techniques, the 24-hour Holter monitoring (24H) being an easy reachable noninvasive tool with relatively low cost remains as a first-line indication during the diagnostic work out of several cardiac disorders specially in pediatric patients who cannot reported their complain properly [9, 10].

The aim of this study was to evaluate heart rate variability and QT abnormalities using 24 hours Holter monitoring in hemophilia -A children.
Materials and Methods

Study design
A case-controlled study was conducted on fifty subjects included 25 male children diagnosed as hemophilia A; selected from the hematology outpatient clinic of health insurance of Elgharbia Government, Egypt as patient group compared to 25 male children age matched serve as a control group. Children with hemophilia who had history of congenital or acquired heart disease, significant arrhythmias and chronic diseases were excluded from the study.

A full clinical history with special emphasis on age, factor level, and type of treatment was taken with thorough clinical examination including anthropometric measurements (weight, height, body surface area, and body mass index).

Cardiac investigations
Transthoracic echocardiography
Transthoracic echocardiography studies using Vivid S5 GE ultrasound system Horten Norway were performed, while patients in both supine and left lateral position using multi frequency (1.5-4MHz) probe (6S-Rs). The echo cardiographer obtained the Standard views from all available windows using the various echo cardio graphic modes including transthoracic two-dimensional (2D) and (M Mode).

Electrocardiographic measurements
A routine standard 12-lead body surface ECG recorded at a paper speed of 25 mm/s and a gain of 10 mm/mV in the supine position with freely breath was done. We take the measures of the heart rate in beats per minute (bpm), QT (the shortest and the longest intervals in the whole 12 leads with leads exclusion with artifacts measured from the beginning of the QRS wave to the end of T wave in milliseconds), R-R intervals in seconds and corrected QT interval (QTc calculation using Bazett formula: QTc= QT/(RRA\(^{1/2}\)). QT dispersion was calculated by the difference between the maximum and the minimum QTc interval on the twelve lead ECGs.

24 hours Holter monitoring
Using Meditech Cardiomera Hungary three channel digital Holter (cardioversion 1.23.0 system soft wear), ECG, Holter monitors were typically fitted to the patient in the cardiology department and returned by the patient when recording was complete. We analyzed the data using dedicated software, the following parameters resulted from the analysis of the recording include average, the minimum and the maximum heart rate, QT measurements (QT and QTc maximum and average) and heart rate variability measures which included 1-time domain: SDNN (the standard deviation of NN intervals). The percentage of R-R intervals with more than 50 ms variation (pNN50%), and the square root of mean squared differences of successive R-R intervals (rMSSD), 2-frequency domain measure that includes low frequency/high frequency. The QTc dispersion was calculated by the difference between the minimum average QTc and QTc maximum obtained from the software.

Ethical approval
We obtained an informed written consent from all parents of participants before getting them involved in the study and discussed with them about steps, aim, potential benefits, and hazards of the work. The study protocol was approved by AL-Azhar University Local Ethics Committee, Faculty of Medicine (for Girls); all procedures were in accordance with the Declaration of Helsinki.

Statistical analysis
Data were analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 26). The normality of data was initially tested with Shapiro-Wilk test. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test while Fischer exact test was used when expected cell count less than 5. Continuous variables were presented as mean ± SD (standard deviation) for normally distributed data and median (min-max) for non-normal data. We compare the two groups with
Student t test for normal data and Mann-Whitney test for the non-normally distributed one.

**Results and Discussion**

Children with Hemophilia and the healthy controls were age and sex matched. No significant difference in the body weight, height, body mass index (BMI), and body surface area (BSA) between the two studied groups. There was a significant increase in the heart rate among the children with hemophilia (Table 1). The echocardiography finding of the studied children revealed an increase in the interventricular septum and posterior wall thickness in children with hemophilia compared to the controls. Increased left atrial diameter, left atrium to the aorta ratio and ejection fraction (EF %) in the children with hemophilia compared to the healthy controls (Table 2).

Twelve leads surface ECG recording showed increased heart rate (b/min), QTc/msec; the maximum and QT dispersion in the children with hemophilia compared to the healthy control (Table 2).

### Table 1: Comparison between the two groups regarding the demographic data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hemophilia group N=25</th>
<th>Control group N=25</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>8.1±3.3</td>
<td>9.3±2.0</td>
<td>0.145</td>
</tr>
<tr>
<td>HR beat/min</td>
<td>109.91±14.6</td>
<td>83.57±8.3</td>
<td>0.000</td>
</tr>
<tr>
<td>RR cycle/min</td>
<td>22.26±2.4</td>
<td>22.62±1.9</td>
<td>0.589</td>
</tr>
<tr>
<td>Body weight/kg</td>
<td>30.78±12.2</td>
<td>31.76±8.2</td>
<td>0.76</td>
</tr>
<tr>
<td>Height/ cm</td>
<td>127±15.6</td>
<td>134.2±10.8</td>
<td>0.085</td>
</tr>
<tr>
<td>BSA /m²</td>
<td>1.03±0.26</td>
<td>1.10±0.16</td>
<td>0.26</td>
</tr>
<tr>
<td>BMI /kg/m²</td>
<td>18.2±2.7</td>
<td>17.3±4.2</td>
<td>0.37</td>
</tr>
</tbody>
</table>

*HR: Heart rate, RR: respiratory cycle, BSA: body surface area, and BMI: body mass index.*

### Table 2. Comparison between groups regarding the echocardiographic and ECG findings

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hemophilia group N=25</th>
<th>Control group N=25</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF%</td>
<td>71.3±5.3</td>
<td>66.45±3.1</td>
<td>0.001</td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>3.87±0.46</td>
<td>3.86±0.42</td>
<td>0.93</td>
</tr>
<tr>
<td>LVIDs (cm)</td>
<td>2.38±0.42</td>
<td>2.39±0.36</td>
<td>0.46</td>
</tr>
<tr>
<td>IVSd (cm)</td>
<td>0.75±0.09</td>
<td>0.66±0.06</td>
<td>0.00</td>
</tr>
<tr>
<td>LVPWd (cm)</td>
<td>0.8±0.13</td>
<td>0.65±0.06</td>
<td>0.00</td>
</tr>
<tr>
<td>FS %</td>
<td>40.8±5.6</td>
<td>35.3±3.4</td>
<td>0.000</td>
</tr>
<tr>
<td>LA (cm)</td>
<td>2.76±0.39</td>
<td>2.45±0.43</td>
<td>0.02</td>
</tr>
<tr>
<td>Ao (cm)</td>
<td>2.20±0.33</td>
<td>2.13±0.32</td>
<td>0.44</td>
</tr>
<tr>
<td>LA/AO</td>
<td>1.3±0.17</td>
<td>1.1±0.29</td>
<td>0.008</td>
</tr>
<tr>
<td>HR bpm</td>
<td>100.22±13.097</td>
<td>79.90±9.586</td>
<td>0.000</td>
</tr>
<tr>
<td>P-R (msec)</td>
<td>135.45±21.320</td>
<td>127.62±16.095</td>
<td>0.183</td>
</tr>
<tr>
<td>QRS (msec)</td>
<td>80.00±14.771</td>
<td>72.38±9.952</td>
<td>0.054</td>
</tr>
<tr>
<td>QTc maximum (msec)</td>
<td>460.41±46.942</td>
<td>426.7±14.402</td>
<td>0.003</td>
</tr>
<tr>
<td>QTc minimum (msec)</td>
<td>382.05±40.433</td>
<td>377.29±16.04</td>
<td>0.61</td>
</tr>
<tr>
<td>QT dispersion (msec)</td>
<td>78.36±32.761</td>
<td>49.43±14.975</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*IVSD: Interventricular septum (diastole), LVPWD: Left ventricular posterior wall (diastole), LVIDd: Left ventricular internal dimension (diastole), LVIDs: Left ventricular internal dimension (systole), LVEDV: Left ventricular end diastolic volumes, LVEF%: Left ventricular ejection fraction; FS%: Fraction shortening, LA: Left atrial dimension, and AO: Aortic dimension.*

### Table 3: Comparison between groups regarding 24-hour Holter data
Using 24 hour Holter recording revealed that, the average heart (bpm) was about to be significantly higher in hemophilia group (P = 0.049), no significant difference in the maximum or the minimum heart rate between both groups (Table 3). There was significant increase in the maximum QTc/msec and QTc dispersion measured by the 24hour Holter recording in children with hemophilia compared to the healthy control (Table 3). The time domain parameters for HRV (ms) were significantly reduced in children with hemophilic compared to the healthy group while no significant difference between the two studied groups in frequency domain parameter (LF/HF) (Table 3).

There was significant difference between the hemophilia group and healthy control in the number and frequency of QTc/msec dispersion detected by ECG while no significant difference in number and frequency between both groups in QTc/msec was detected by Holter 24H (Table 4). There is a growing prevalence of chronic diseases in early childhood. Hemophilia is a rare bleeding disorder with difficulty in diagnose and treatment (1). The use of prophylactic factor therapy to prevent bleeding has altered the hemophilia landscape, as a result of advances in treatment and general medical care; patients with hemophilia are living longer [11]. QT dispersion is a useful and non-invasive method to evaluate ventricular myocardium repolarization through superficial ECG. It was proposed as an index of ventricular recovery times to distinguish homogenous myocardium from that display non-homogeneity in the repolarization time [12]. The autonomic nervous system function fluctuation in healthy individuals as well as in those with various diseases can be assessed by a reliable method; the HRV recording [13].

Since 2015 to 2017, the European Heart Rhythm recommended using heart rate variability analysis, as well as their applicability in various physiological situations and clinical research, have gotten a lot of attention [14], HRV reduction was linked to increased risk to sudden death [8]. In the present study, comparing heart rate variability and QT changes in children with hemophilia and healthy controls revealed that significant increased QT maximum and QT dispersion values: (460.41 ± 46.942) and (78.36 ± 32.76) in hemophilia children vs the control (426.71 ± 14.402) and (49.43 ± 14.975) using 12 leads surface ECG and significantly increased range of QT maximum and QT dispersion measured by the 24H recording Holter (497.96 ± 20.7) and (84.65 ± 18.0) versus (473.38 ± 42.2 ) and (68.48 ± 18.5).

Increased QT dispersion in hemophilia children increases the risk of their exposure to dysrhythmia and sudden death, the normal range of QT dispersion value is 10-70 ms with mean 29 ± 26 ms in early age [15].

### Table 4: Comparison between groups regarding QTc dispersion frequency detected by either ECG or Holter

<table>
<thead>
<tr>
<th>Variable (mean± SD)</th>
<th>Hemophilia group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR average (bpm)</td>
<td>94.70 ± 12.47</td>
<td>88.62 ± 6.15</td>
<td>0.049</td>
</tr>
<tr>
<td>HR Maximum (bpm)</td>
<td>158.87 ± 19.13</td>
<td>159.19 ± 17.79</td>
<td>0.95</td>
</tr>
<tr>
<td>HR Minimum (bpm)</td>
<td>66.35 ± 12.80</td>
<td>60.67 ± 6.81</td>
<td>0.077</td>
</tr>
<tr>
<td>QTc maximum (msec)</td>
<td>497.96 ± 20.7</td>
<td>473.38 ± 42.2</td>
<td>0.017</td>
</tr>
<tr>
<td>QTc minimum (msec)</td>
<td>413.30 ± 12.3</td>
<td>404.90 ± 35.6</td>
<td>0.29</td>
</tr>
<tr>
<td>QT dispersion (msec)</td>
<td>84.65 ± 18.0</td>
<td>68.48 ± 18.5</td>
<td>0.005</td>
</tr>
<tr>
<td>SDNN (msec)</td>
<td>97.05 ± 31.42</td>
<td>128.85 ± 19.52</td>
<td>0.00</td>
</tr>
<tr>
<td>pNN50%</td>
<td>11.000 ± 7.55</td>
<td>19.36 ± 7.91</td>
<td>0.001</td>
</tr>
<tr>
<td>rMSSD (msec)</td>
<td>32.85 ± 16.11</td>
<td>49.60 ± 13.47</td>
<td>0.001</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.77 ± 1.6</td>
<td>1.30 ± 0.56</td>
<td>0.215</td>
</tr>
</tbody>
</table>

SDNN: The standard deviation of all normal sinus R-R intervals in the entire 24-hour recording. rMSSD: The root mean square of the mean of the squared differences of two consecutive R-R intervals in the 24-hour recordings. LF: Low frequency power, and HF: High frequency power.
Variable | Hemophilia group N=25 | Control group N=25 | P-value
--|---|---|---
QTc dispersion by ECG<br>Positive >70ms: number (%)<br>Negative ≤70ms: number (%) | 13 (52)<br>12 (48) | 4 (16)<br>21 (84) | 0.01

In the current study regarding corrected (QTc) dispersion frequency detection in children with hemophilia, 52% had QT dispersion >70/msec detected by 12 lead surface ECG while 70.8% detected by 24hour holter, with significant difference in QT dispersion when calculated on 12-lead ECG and on 24 hour Holter monitoring. Agha et al. [16] found that Holter recording using the Bazett formula exhibits high specificity for prolonged QTc prediction in children only with low heart rates, while the Fridericia formula had a high specificity regardless of RR interval. While Maria et al. [17] found no significant difference was found in QT dispersion when calculated on 12-lead ECG and on Holter monitoring in adult with dilated cardiomyopathy.

Based on our knowledge, no previous studies evaluated the QT dispersion in children with hemophilia, though many researchers have reported that [18-21] the cardiovascular autonomic dysregulation can lead to increased QT dispersion. It is a direct measure of the heterogeneity of myocardial repolarization which has been used as a predictor of the adverse outcomes in various cardiac and non-cardiac states [22].

Performing 12 Leads Surface ECG recording, there were increased heart rates (b/min), in the children with hemophilia compared to the healthy control and this could be because of frequent hemorrhage observed in children with hemophilia.

During childhood and adolescence, the heart rate variability (HRV) changes, may indicate developmental changes in the autonomic nervous system function. The autonomic neuronal function of the heart has been found to be extensively related to the HRV fluctuation in terms of time and frequency. The HRV can be significantly related to the cardiovascular morbidity and mortality [23].

When comparing the two studied groups regarding the heart rate variability there were significant reduction in the time domain indexes: SDNN/ms, rMSSD/ms, and pNN50% in children with hemophilia compared to the healthy control, which indicates depressed HRV that reflect sympa-tho-vagal imbalance in hemophilia children while the frequency domain parameter did not show the significant difference between the both groups. Decreased HRV has been observed to be associated with the sudden cardiac death [24].

The study done by Kundu et al. [25] about the investigations of the autonomic function in hemophiliacs using Impedance Plethysmography, revealed that higher time domain parameter rMSSD for blood flow variability in hemophiliacs as compared with healthy controls that may be reflecting peripheral vascular compensation for reduced vagal activity in the studied patients.

In our study, the echocardiographic parameters showed increased interventricular septum thickness in diastole among children with hemophilia compared to the control. Similar reports were observed in adult study done by Amoozgar and their colleagues [26]. The increased interventricular septum thickness may be caused by volume overload that leads to overgrowth of cardiomyocytes Lang et al. [27].

In addition, the left atrial diameter, left atrium to the aorta ratio and ejection fraction %, was higher in the hemophilia children compared to the healthy control, which could be attributed to volume overload secondary to frequent factor transfusion and hyper dynamic circulation associated with anemia in those type of patients.

**Conclusion**
The results of the present study indicate the increased QT dispersion in children with hemophilia that put them at risk for developing dysrhythmia, sympathy-vagal imbalance detected by the presence of depressed HRV, also expose them to cardiac morbidities and sudden cardiac death.

**Disclosure Statement**

No potential conflict of interest was reported by the authors.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Authors’ Contributions**

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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