Original Article

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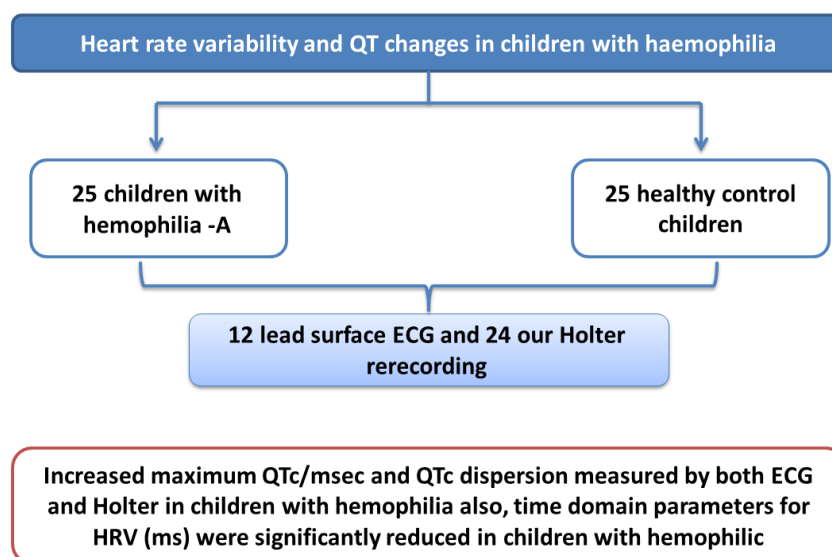**Conclusion:** There was an increase in QT dispersion in children with hemophilia that put them at risk for developing dysrhythmia, sympathy-vagal imbalance detected by the presence of depressed HRV, and also exposed them to cardiac morbidities and sudden cardiac death.

G R A P H I C A L A B S T R A C T

Heart rate variability and QT changes in children with haemophilia

25 children with hemophilia -A

25 healthy control children

12 lead surface ECG and 24 our Holter rerecording

Increased maximum QTc/msec and QTc dispersion measured by both ECG and Holter in children with hemophilia also, time domain parameters for HRV (ms) were significantly reduced in children with hemophilic

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 24hour 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 compline 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/(RR^½). 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

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

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

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

Variable	Hemophilia group N=25	Control group N=25	P-value
LVEF%	71.35±5.3	66.45 3.1	0.001
LVIDd (cm)	3.87 ± 0.46	3.86 ±0.42	0.93
LVIDs (cm)	2.38 ± 0.42	2.39 ± 0.36	0.46
IVSd (cm)	0.75 ± 0.09	0.66 ± 0.06	0.00
LVPWd (cm)	0.8 ±0.13	0.65±0.06	0.00
FS %	40.8 ± 5.6	35.3 ± 3.4	0.000
LA (cm)	2.76±0.39	2.45 ± 0.43	0.02
Ao (cm)	2.20±0.33	2.13±0.32	0.44
LA/AO	1.3±0.17	1.1± 0.29	0.008
HR bpm	100.22 ± 13.097	79.90 ± 9.586	0.000
P-R (msec)	135.45 ±21.320	127.62 ±16.095	0.183
QRS (msec)	80.00±14.771	72.38± 9.952	0.054
QTc maximum (msec)	460.41± 46.942	426.71± 14.402	0.003
QTc minimum (msec)	382.05 ± 40.433	377.29 ±16.04	0.61
QT dispersion (msec)	78.36 ± 32.761	49.43 ± 14.975	0.001

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

Variable (mean± SD)	Hemophilia group N=25	Control group N=25	P-value
HR average (bpm)	94.70 ± 12.47	88.62 ±6.15	0.049
HR Maximum (bpm)	158.87± 19.13	159.19 ± 17.79	0.95
HR Minimum (bpm)	66.35 ± 12.80	60.67± 6.81	0.077
QTc maximum (msec)	497.96 ± 20.7	473.38± 42.2	0.017
QTc minimum (msec)	413.30 ± 12.3	404.90 ±35.6	0.29
QT dispersion (msec)	84.65 ± 18.0	68.48 ± 18.5	0.005
SDNN (msec)	97.05 ±31.42	128.85 ±19.52	0.00
pNN50%	11.000 ±7.55	19.36 ± 7.91	0.001
rMSSD (msec)	32.85 ± 16.11	49.60 ± 13.47	0.001
LF/HF	1.77 ± 1.6	1.30 ± 0.56	0.215

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.

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-homogenicity 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

Variable	Hemophilia group N=25	Control group N=25	P-value
QTc dispersion by ECG Positive >70ms: number (%) Negative ≤70ms: number (%)	13 (52) 12 (48)	4 (16) 21 (84)	0.01
QTc dispersion by Holter Positive >70ms: number (%) Negative ≤70ms: number (%)	18 (72) 7 (28)	11 (44) 14 (56)	0.075

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 sympatho-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.

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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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References

[1]. Srivastava A., Santagostino E., Dougall A., Kitchen S., Sutherland M., Pipe S.W., Carcao M., Mahlangu J., Ragni M.V., Windyga J., Llinás A., WFH guidelines for the management of hemophilia, 3rd edition, *Haemophilia*, 2020, **26**:1 [Crossref], [Google Scholar], [Publisher]

[2]. Ferraris V.A., Boral L.I., Cohen A.J., Smyth S.S., White G.C., Consensus Review of the Treatment of Cardiovascular Disease in People with Hemophilia A and B, *Cardiology in Review*, 2015, **23**:53 [Crossref], [Google Scholar], [Publisher]

[3]. Anandani G., Patel T., Parmar R., The Implication of New Developments in Hemophilia Treatment on Its Laboratory Evaluation, *Cureus*, 2012, **14**:e30212 [Crossref], [Google Scholar], [Publisher]

[4]. Tamr Agha M.K., Fakhri G., Ahmed M., El Sedawy O., Abi Saleh B., Bitar F., Arabi M., QTc interval on 24-hour holter monitor: To trust or not to trust?, *Annals of Noninvasive Electrocardiology*, 2022, **27**:e12899 [Crossref], [Google Scholar], [Publisher]

[5]. Barcelos A.M., Baldo M.P., Rodrigues S.L., Mil J.G., QT Interval dispersion behavior in patients with and without obstructive coronary artery disease undergoing exercise test, *International Journal of Cardiovascular Sciences*, 2020, **33**:263 [Crossref], [Google Scholar], [Publisher]

[6]. Kosmopoulos M., Roukoz H., Sebastian P., Kalra R., Goslar T., Bartos J.A., Yannopoulos D., Benditt D.G., Increased QT Dispersion Is Linked to Worse Outcomes in Patients Hospitalized for Out-of-Hospital Cardiac Arrest, *Journal of the American Heart Association*, 2020, **9**:e016485 [Crossref], [Google Scholar], [Publisher]

[7]. Sharma A.N., Baranchuk A., Ambulatory external electrocardiography monitoring: Holter, extended Holter, Mobile cardiac telemetry Monitoring, *Cardiac Electrophysiology Clinics*, 2021, **13**:427 [Crossref], [Google Scholar], [Publisher]

[8]. Yeragani V.K., Rao K.R., Pohl R., Jampala V.C., Balon R., Heart rate and QT variability in children with anxiety disorders: A preliminary report, *Depression and anxiety*, 2001, **13**:72 [Crossref], [Google Scholar], [Publisher]

[9]. Hegazy R.A., Lotfy W.N., The Value Of Holter Monitoring In The Assessment Of Pediatric Patients, *Indian Pacing and Electrophysiology Journal*, 2007, **7**:204 [Google Scholar], [Publisher]

[10]. Aldalati A., House M., Butterfield B., Homme J., The utility of Holter monitors in pediatric patients, *Annals of Emergency Medicine*, 2021, **78**:S112 [Crossref], [Google Scholar], [Publisher]

[11]. Sood S.L., Cheng D., Ragni M., Kessler C.M., Quon D., Shapiro A.D., Key N.S., Manco-Johnson M.J., Cuker A., Kempton C., Wang T.F., A cross-sectional analysis of cardiovascular disease in the

hemophilia population, *blood advances*, 2018, **2**:1325 [Crossref], [Google Scholar], [Publisher]

[12]. Kautzner J., Malik M., QT dispersion and its clinical utility, *Pacing and Clinical Electrophysiology*, 1997, **20**:2625 [Crossref], [Google Scholar], [Publisher]

[13]. Gąsior J.S., Sacha J., Jeleń P.J., Pawłowski M., Werner B., Dąbrowsk M.J. Interaction Between Heart Rate Variability and Heart Rate in Pediatric Population. *Front Physiol.*, 2015, **6**:385 [Crossref], [Google Scholar], [Publisher]

[14]. Catai A.M., Pastre C.M., de Godoy M.F., da Silva E., de Medeiros Takahashi A.C., Vanderlei L.C.M., Heart rate variability: are you using it properly? *Standardisation checklist of procedures: Brazilian Journal of Physical Therapy*, 2020, **24**:91 [Crossref], [Google Scholar], [Publisher]

[15]. Malik M., Batchvarov V.N., Measurment, interpretation and clinical potential of QT dispersion, *Journal of the American College of Cardiology*, 2000, **36**:1749 [Google Scholar], [Publisher]

[16]. Tamr Agha M.K., Fakhri G., Ahmed M., El Sedawy O., Abi Saleh B., Bitar F., Arabi M., QTc interval on 24-hour holter monitor: To trust or not to trust? *Annals of Noninvasive Electrocardiology*, 2022, **27**:e12899 [Crossref], [Google Scholar], [Publisher]

[17]. De Maria E., Curnis A., Garyfallidis P., Mascioli G., Santangelo L., Calabrò R., Dei Cas L., QT dispersion on ECG Holter monitoring and risk of ventricular arrhythmias in patients with dilated cardiomyopathy, *Heart International*, 2006, **2**:33 [Crossref], [Google Scholar], [Publisher]

[18]. Day C.P., McComb J.M., Campbell R.W., QT dispersion: an indication of arrhythmia risk in patients with long QT intervals, *Heart*, 1990, **63**:342 [Crossref], [Google Scholar], [Publisher]

[19]. Barr C.S., Naas A., Freeman M., Lang C.C., Struthers A.D., QT dispersion and sudden unexpected death in chronic heart failure, *The Lancet,* 1994, **343**:327 [Crossref], [Google Scholar], [Publisher]

[20]. De Bruyne M.C., Hoes A.W., Kors J.A., Hofman A., van Bemmel J.H., Grobbee D.E., QTc dispersion predicts cardiac mortality in the elderly: The Rotterdam Study, *Circulation*, 1998, **97**:467 [Crossref], [Google Scholar], [Publisher]

[21]. Sander D., Klingelhöfer J., Stroke associated pathological sympathetic activation related to size of infarction and extent of insular damage, *Cerebrovascular Diseases*, 1995, **5**:3815 [Crossref], [Google Scholar], [Publisher]

[22]. Rahar K.K., Pahadiya H.R., Barupal K.G., Mathur C.P., Lakhotia M., The QT dispersion and QTc dispersion in patients presenting with acute neurological events and its impact on early prognosis, *Journal of Neurosciences in Rural Practice*, 2016, **7**:61 [Crossref], [Google Scholar], [Publisher]

[23]. Cetin M., Moumin N., Karaboga B., Coskun S., Gulen H., Evaluation of cardiac autonomic functions in Children with Thalassemia Trait, Iron Deficiency Anemia and Iron Deficiency, *Eastern Journal of Medicine*, 2018, **23**:23 [Google Scholar], [Publisher]

[24]. Sessa F., Anna V., Messina G., G Cibelli G., V Monda V., Marsala G., Ruberto M., Biondi A., Cascio O., Bertozzi G., Pisanelli D., Heart rate variability as predictive factor for sudden cardiac death, *Aging (Albany NY)*, 2018, **10**:166 [Crossref], [Google Scholar], [Publisher]

[25]. Kundu T.K., Barde P.B., Jindal G.D., Motiwala F.F., An exploratory study of autonomic function investigations in hemophiliacs on homoeopathy medications using impedance plethysmography, *Journal of Evidence-Based Complementary & Alternative Medicine*, 2017, **22**:760 [Crossref], [Google Scholar], [Publisher]

[26]. Amoozgar H., Fath M., Parisa Jooya P., Karimi M. *Evaluation of Heart Function in Patients with Hemophilia. Clinical and Applied Thrombosis/Hemostasis.* 2017, **23**:374 [Crossref], [Google Scholar], [Publisher]

[27]. Lang R.M., Bierig M., Devereux R.B., Flachskampf F.A., Foster E., Pellikka P.A., Picard M.H., Roman M.J., Seward J., Shanewise J.S., Solomon S.D., Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology, *Journal of the American society of echocardiography*, 2005, **18**:1440 [Crossref], [Google Scholar], [Publisher]