



P-wave and QT Interval Dispersion Analysis in Children with End Stage Renal Disease on Regular Hemodialysis

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Authors' contributions

This work was carried out in collaboration among all authors. Author MA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SEN and HAE managed the analyses of the study. Author AZ managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Objectives: The consequences of hemodialysis on P-wave dispersion and QT dispersion have not been unequivocally documented and understood and may be complex. To investigate homogeneity disorders of atrial conduction and ventricular repolarization and tendency to develop various arrhythmias by demonstrating the effects of hemodialysis in children with end stage renal disease through assessment of P-wave dispersion and QT dispersion (By electrocardiography).

Methods: Twenty end stage renal disease patients on conventional hemodialysis for at least 12 months and twenty healthy, age and sex matched volunteers were included. Patients underwent echocardiography to exclude any abnormalities of cardiac valves or muscle. A 12-lead electrocardiogram was undertaken in order to measure minimal and maximal (P wave and QT interval) durations, P wave dispersion and QT dispersion.

Results: In patient group, males were 13, females were 7 with mean age of 11.9 ± 3.4 years, mean P wave dispersion and QT dispersion were significantly longer than control group. P wave dispersion was significantly shorter after dialysis (mean= 34 ± 13.1 ms) than before dialysis

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(mean=42.4 ± 14 ms), whereas QT dispersion was longer after dialysis (59 ± 19 ms) than before dialysis (55.5 ± 17 ms) but the differences in QT dispersion was not significant. Also, there was no correlation between neither P wave dispersion nor QT dispersion and the electrolytes.

Conclusion: P wave dispersion and QT dispersion was found to be higher in end stage renal disease children on regular hemodialysis than healthy control subjects, indicating heterogeneity disorders of atrial conduction and ventricular repolarization in these patients and tendency to develop various arrhythmias.

Keywords: End stage renal disease; hemodialysis; QT dispersion and P-wave dispersion.

ABBREVIATIONS

AF	: Atrial Fibrillation
CKD	: Chronic Kidney Disease
ECG	: Electrocardiography
ESRD	: End Stage Renal Disease
HD	: Hemodialysis
IVSd	: Interventricular Septum Thickness at End-Diastole
IVSs	: Interventricular Septum Thickness at End-Systole
LV	: Left Ventricular
LVIDd	: Left Ventricular Internal Dimension at End-Diastole
LVIDs	: Left Ventricular Internal Dimension at End-Systole
LVM	: Left Ventricular Mass
LVMi	: LV Mass Index
LVPWd	: Left Ventricular Posterior Wall Thickness at end-diastole
Pmin	: (Pmax) and minimum
PWd	: P-wave dispersion
QTd	: QT dispersion
RRT	: Renal Replacement Therapy
RWT	: Relative Wall Thickness
VT	: Ventricular Arrhythmia

1. INTRODUCTION

Many studies have shown an important independent association between chronic kidney disease (CKD) and cardiovascular events, including sudden death, heart failure, and myocardial infarction. Recent clinical trials extend this range of adverse cardiovascular events, also including ventricular arrhythmias and sudden cardiac death [1].

Furthermore, studies have shown structural remodeling of the heart and electrophysiological changes in this population. These processes may explain the greater risk of arrhythmia in kidney disease and help to identify patients who are at increased risk of sudden cardiac death [1].

Many different noninvasive electrocardiography (ECG) based methods have been approved to identify the risk of arrhythmia in chronic kidney disease (CKD) patients and general population. One of these methods, P-wave dispersion (PWd) has been recommended to predict atrial fibrillation (AF) [2].

PWd is defined as the difference between the maximum (Pmax) and minimum (Pmin) durations of P-wave and can be measured easily with ECG. Also, it has been observed that PWd is longer in patients with CKD undergoing renal replacement therapy (RRT), in comparison with the controls [3] and that the increase continued after hemodialysis in comparison to predialysis values [4].

QT dispersion (QTd), defined as maximum QT interval minus minimum QT interval, was considered as an index of ventricular recovery times to differentiate myocardium that is homogenous from myocardium that shows non-homogeneity in the repolarization time. QT dispersion reflects the non-homogeneous recovery of ventricular excitability and might predict ventricular arrhythmias. The causes of the prolongation of QT dispersion in dialysis patients are multifactorial, including fibrosis and hypertrophy of the heart, changes of cellular or interstitial fluid composition during dialysis and iron overload. There are higher percentages of ESRD patients with dialysis therapy that have prolonged QT dispersion and hence are susceptible to ventricular arrhythmias [5].

2. SUBJECTS AND METHODS

This case control study was conducted on 20 pediatric patients with End Stage Renal Disease (ESRD) on regular hemodialysis in Pediatric Nephrology Unit, Pediatric Department, Tanta University Hospital during the period from November 2018 to November 2019.

Twenty (20) healthy children, matched for age and sex, were enrolled as a control group.

Inclusion criteria: Patients aged from 5 to 18 years with End Stage Renal Disease (ESRD) on regular hemodialysis for at least 12 months.

Exclusion criteria: Children with Congenital or acquired arrhythmias, Congenital Heart diseases, Valvular heart diseases, Congestive heart failure, hypertrophic cardiomyopathy or dilated cardiomyopathy, Using cardiac medications or medications that prolong QT interval as macrolides, quinidine, amiodaron, ciprofloxacin, levofloxacin and beta blockers, Severe liver disease, Diabetes mellitus, Patients with metabolic disorders and Thalassemia and other Hemoglobinopathies.

All children enrolled in this study were subjected to the following:

Dialysis was started through AV fistula. Patients were dialyzed for at least one year on Fresenius 4008- B dialysis machine(Germany) at blood flow rate = $2.5 \times \text{weight (kg)} + 100 \text{ ml/min.}$, using polysulphane hollow fiber dialyzers suitable for the surface area of the patients (F3 = 0.4 m^2 , F4 = 0.7 m^2 , F5 = 1.0 m^2 and F6 = 1.2 m^2). Bicarbonate dialysis solutions were used. Patients were receiving supportive therapy in the form of erythropoietin, iron, oral folic acid, calcium, vitamin D and antihypertensive medications for hypertensive patients.

Complete history taking: Including age, sex, cause of ESRD, duration of the hemodialysis, history of usage of antiarrhythmic drugs, antihypertensive drugs, history of nephrectomy, type of iron and calcium therapy and its regularity.

Complete physical examination: Including anthropometric measurements, cardiovascular assessment for pulse rate, blood pressure, presence or absence of murmur and other signs of heart failure.

Investigations: A-Laboratory investigations: Complete blood count, ABG, Predialytic blood urea and serum Creatinine and Pre and post dialytic electrolytes [Ca, K, Na, Mg].

B-12-lead ECG: Pre and post hemodialysis 12-lead ECG to determine P wave and QT interval dispersions, and to evaluate occurrence of various arrhythmias.

- **Measurement of PWD:** Maximum and minimum P-Wave durations were calculated

from the standard ECG during sinus rhythm. PWD is derived by subtracting the minimum P-wave duration from the maximum in any of the 12 ECG leads. PWD was calculated by manual measurement (hand-held caliper measurement). Manual measurement with hand-held calipers is performed by increasing the ECG rate to 50 mm/s and the voltage to 1 mV/cm, accompanied by use of magnification. Each patient and control was in supine position following 15 min of rest and room temperature and lighting kept constant. The beginning of the P-wave is when the point of first detectable upward or downward slope from the isoelectric line appears for positive or negative waveforms, respectively. Return to the isoelectric line is the end of the P-wave) [6].

- **QTd measurement:** QT dispersion is calculated as the difference between the maximum QT duration and minimum QT duration in different leads of 12-lead ECG tracing; QT duration is being the interval from the onset point of QRS complex till the offset of T wave. We used the slope method which determines the T offset as an intercept between the slope of the descending part of the T wave and the isoelectric line, or a threshold line above it. The slope can be the steepest tangent computed by various line fitting algorithms or a straight line through the influx point and the peak of the T wave [7].

QTc interval may be affected by several factors including hemodialysis and electrolyte disturbances. In our study, all electrocardiographic (ECG) measurements were taken just before initiation of dialysis session and all of the patients were undergoing maintenance hemodialysis for at least 12 months, so they were more resistant to antiarrhythmic effects of electrolyte disturbances than new patients to hemodialysis. We did not include patients who had any arrhythmia findings before or during the study and that was in accordance with Temiz [8].

We excluded patients who were using drugs that prolong QT interval like macrolides, quinidine, amiodaron, ciprofloxacin, levofloxacin and beta-blockers according to Bennett, et al. [9].

C-Echocardiographic assessment: Using Vivid 7 ultrasound machine (GE Medical System, Horten, Norway, with 3.5, 4s MHz multi-frequency transducers), Doppler and Echocardiographic assessment of the following parameters was done: Left ventricular (LV)

dimensions, Left ventricular systolic function and Left ventricular mass (LVM) and LV mass index (LVMI).

Statistical analysis: Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation and chi-square test by SPSS V.20.

3. RESULTS

There was no statistically significant difference between the two groups as regards age and sex (P >0.05).The duration of hemodialysis was 19.5 ± 14.859 months Table 1.

As regards Interventricular septum thickness at end-diastole (IVSd), there was no significant difference between the two groups (P >0.05), whereas there was significant increase of the Interventricular septum thickness at end-systole (IVSs) in patient group as compared to control group (P <0.05). As regards Left ventricular internal dimension at end-systole (LVIDs), there was highly significant decrease of LVIDs in patient group as compared to control group (P<0.001), whereas there was no significant difference as regards Left ventricular internal dimension at end-diastole (LVIDd) between the two groups (P >0.05). As regards left ventricular

posterior wall thickness at end-diastole (LVPWd), there was no significant difference between the two groups (P >0.05). As regards relative wall thickness (RWT), there was significant increase of RWT in patient group as compared to control group (P <0.05). As regards left ventricular mass (LV mass), there was no significant difference between the two groups (P >0.05). As regards left ventricular mass index (LV mass index), there was no significant difference between the two groups (P >0.05). As regards ejection fraction (EF %) and fractional shortening (FS %), there was significant decrease of both in patient group as compared to control group (P <0.05) Table 2.

As regards P-wave dispersion (PWd), there was highly significant increase in patient group as compared to control group (P <0.001). As regards QT dispersion (QTd), there was significant increase in patient group as compared to control group (P <0.05) Table 3.

As regards P-wave dispersion before and after dialysis, there was significant decrease in PWd after dialysis as compared to pre dialysis (P <0.05), whereas there was no significant difference between QTd before dialysis as compared to after dialysis (P>0.05) Table 4, Fig. 1.

Table 1. Demographic data of the studied groups

		Groups		T-Test or Chi-Square	
		Patients (n=20)	Controls (n=20)	T or X ²	P-value
Age (Years)	Range	5 -18	5-18	-0.090	0.929
	Mean ±SD	11.900±3.478	12.000±3.554		
Gender	Male	13 (65%)	13 (65%)	0.000	1.000
	Female	7 (35%)	7 (35%)		
Male : Female Ratio		1.86:1	1.86:1		
Duration of hemodialysis (Months)	Range	12-72			
	Mean ±SD	19.500±14.859			

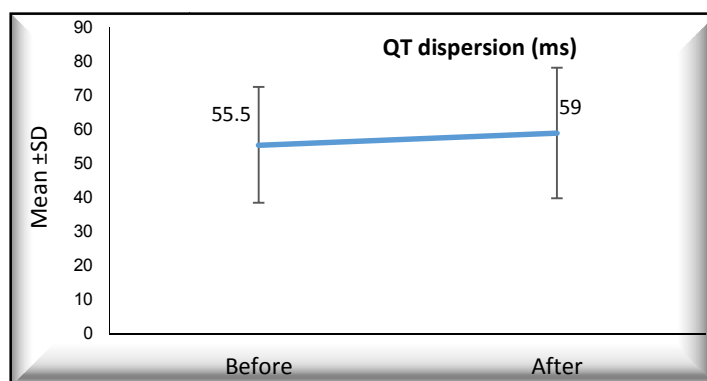


Fig. 1. Comparison between QT dispersion before and after dialysis in HD patients

Table 2. Comparison between the two studied groups regarding echocardiographic measurements

		Groups		T-Test	
		Patients (n=20)	Control (n=20)	T	P-value
IVSd (cm)	Range	0.5-1.4	0.8-1.1	-1.082	0.286
	Mean ±SD	0.860±0.274	0.930±0.092		
IVSs (cm)	Range	0.5-1.5	0.7-0.9	2.835	0.007*
	Mean ±SD	0.985±0.305	0.785±0.081		
LVIDd (cm)	Range	2.8-5.8	3.6-4.8	-1.855	0.071
	Mean ±SD	3.895±0.621	4.200±0.393		
LVIDs (cm)	Range	1.9-3.9	2.8-3.9	-6.051	<0.001*
	Mean ±SD	2.615 ± 0.408	3.395 ± 0.407		
LVPWd (cm)	Range	0.5 - 1.2	0.7 – 1	1.483	0.146
	Mean ±SD	0.930 ± 0.208	0.855 ± 0.089		
LV mass (gm)	Range	19-153	82-105	0.963	0.341
	Mean ±SD	100.28 ± 39.02	91.750 ± 6.703		
LV mass index (gm/ m2)	Range	12 – 139	90 – 111	-0.735	0.467
	Mean ±SD	95.850 ± 30.116	100.900 ± 6.138		
RWT	Range	0.24 - 0.79	0.29 - 0.41	2.794	0.008*
	Mean ±SD	0.460 ± 0.139	0.370 ± 0.038		
EF%	Range	53.2 - 71.37	56.34 - 73.4	-2.300	0.027*
	Mean ±SD	61.747 ± 4.931	65.513 ± 5.414		
FS%	Range	27.1 - 40.48	27.72 - 33.57	2.701	0.010*
	Mean ±SD	30.293 ± 1.875	32.744 ± 3.601		

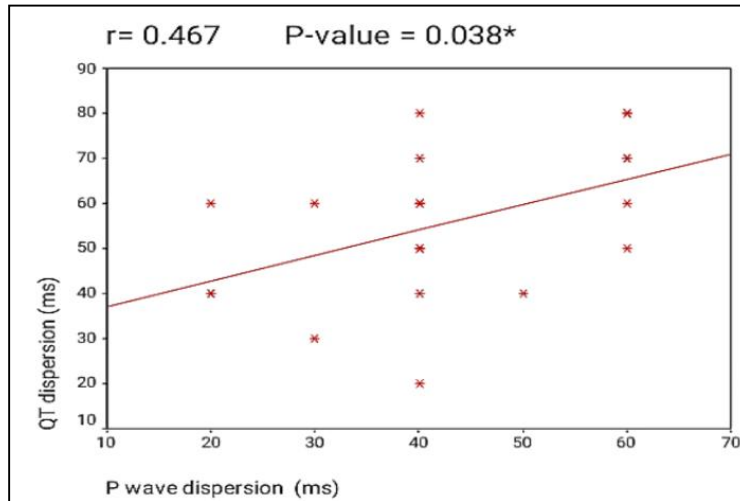


Fig. 2. Correlation between PW dispersion (PWd) and QT dispersion (QTd)

As regards height, there was significant negative correlation between PWd and height (p<0.05).

As regards hemoglobin (Hb), there was significant negative correlation between QTd and Hb (p<0.05) Figs. 2, 3 & 4.

There were no significant correlations, but there was significant negative correlation between QT dispersion and SBP difference (p<0.05) Fig. 5.

4. DISCUSSION

Trials to characterize the abnormalities of ventricular repolarization and inhomogeneity of intra-atrial propagation of sinus impulses from the surface electrocardiogram (ECG) have a long history. It was supposed that the different ECG leads magnify the ECG signal of different myocardial regions and that, consequently, QT dispersion and P wave dispersion are direct measures of the heterogeneity of myocardial

repolarization and intra-atrial conduction abnormalities, respectively [7].

In the present study was conducted on 20 children aged from 5 to 18 years with end stage renal disease (ESRD) on regular hemodialysis compared with 20 healthy control children matching for age and sex.

In the present study, 65% of patients were males while 35% of patients were females with male: female ratio = 1.86:1, This ratio is in agreement with Jamro, et al. [10], who carried out his study in pediatric nephrology unit on seventy eight confirmed cases of chronic renal failure (CRF). Out of them, 51 were males and 27 were females (M: F ratio 1.8:1).

Also, in another study done by Rahman et al. [11], a total of 44 children with CRF having mean age of 8.73 ± 3.56 years were diagnosed during the study period, 30 cases (68.18%) were males and 14 cases (31.81%) were females, with male predominance.

As regards left ventricular posterior wall thickness at end-diastole (LVPWd), there was no significant difference between the two groups, which is in disagreement with Debnath, et al. [12] who showed higher LVPWd in CRF patients.

As regards relative wall thickness (RWT), there was significant increase of RWT in patient group as compared to control group. This is in accordance with Zoccali, et al. [13].

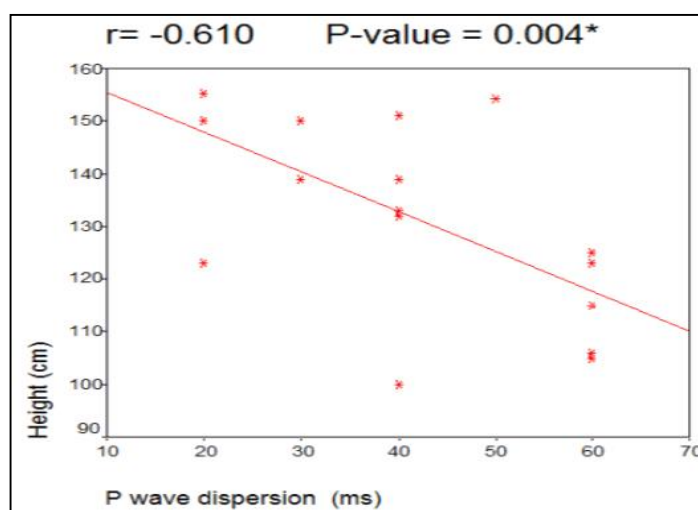


Fig. 3. Correlation between PW dispersion and height

Table 3. Comparison between the studied groups regarding electrocardiographic data P wave dispersion (PWd) and QT dispersion (QTd)

		Groups		T-Test	
		Patients (n=20)	Control (n=20)	T	P-value
P wave dispersion (ms)	Range	20 – 60	20 – 30	5.217	<0.001*
	Mean ±SD	42.500 ± 14.096	25.000 ± 5.130		
QT dispersion (ms)	Range	20 – 80	30 – 60	2.128	0.040*
	Mean ±SD	55.500±17.006	46.000 ± 10.463		

Table 4. Comparison between PWd and QTd before and after dialysis in HD patients

	P Wave dispersion (ms)		Differences		Paired t-test	
	Range	Mean ± SD	Mean	SD	T	P-value
Before	20 - 60	42.50 ± 14.096	8.500	10.894	3.489	0.002*
After	10 - 60	34.00 ± 13.139				
	QT dispersion (ms)		Differences		Paired t-test	
	Range	Mean ± SD	Mean	SD	T	P-value
Before	20 - 80	55.50 ± 17.006	-3.500	15.652	-1.000	0.330
After	20 - 90	59.00 ± 19.167				

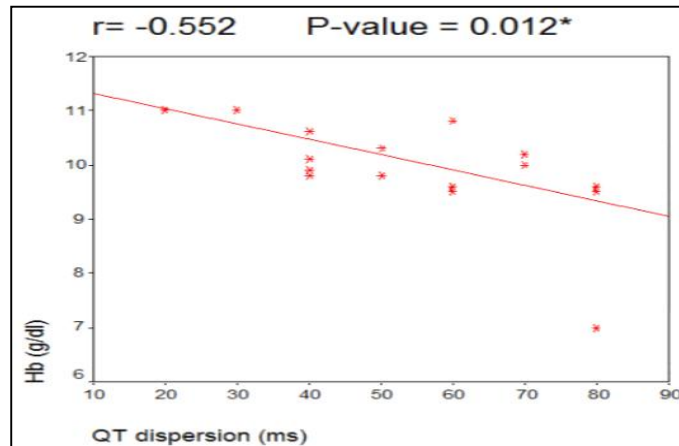


Fig. 4. Correlation between QT dispersion (QTd) and Hb

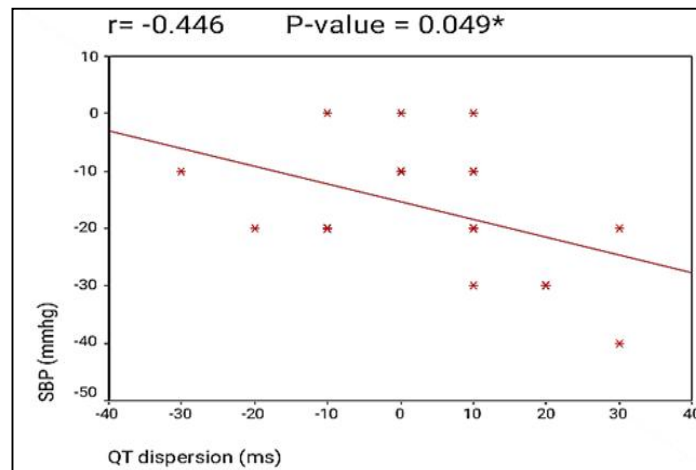


Fig. 5. Correlation between (QTd and SBP) differences before and after dialysis

As regards left ventricular mass (LV mass) and left ventricular mass index (LVMI), there was no significant difference between the two groups. This is in disagreement with Debnath, et al. [12], who stated higher LVMI in CRF patients.

As regards ejection fraction (EF %), there was significant decrease in patient group as compared to control group but no systolic dysfunction. This is in agreement with Debnath, et al. [12], who reported that in mild/moderate CKD only 15% of patients showed low EF (<50%), and 48% of patients with severe CKD had evidence of low EF.

As regards P-wave dispersion (PWd), there was highly significant increase in patient group as compared to control group (P <0.001). Also, as regards QT dispersion (QTd), there was significant increase in patient group as compared

to control group (P <0.05). As regards PWd and QTd before and after dialysis, there was significant decrease in PWd after dialysis as compared to pre dialysis (P <0.05), whereas there was no significant difference between QTd before dialysis as compared to after dialysis (P>0.05). This is in agreement with findings previously published by Galeel, et al. [14].

Kose, et al. [15], reported the PWd to be 27.0 ± 5.4 ms and the maximum P-wave duration to be 102.5 ± 8.7 ms in healthy children. P-Wave dispersion (PWd) was approved to be a sensitive and specific ECG marker for the best separation between patients with history of paroxysmal lone AF and healthy subjects. A cutoff value of 40 ms was reported to have a sensitivity of 83%, a specificity of 85% and a positive predictive accuracy of 89% for the detection of patients with history of paroxysmal lone AF. In addition, during

a 12-month follow-up period, the relative risk of an AF recurrence was 2.4 for a PWd value >40 ms [16].

In Goldener, et al. [17] study, the normal range of QTd was found to be 10-44 ms. The risk of serious ventricular arrhythmia (VT) or sudden cardiac death has been shown in subjects with QTd of more than 65 ms. Also, QTd of more than 40 ms was found to have 88% sensitivity and 57% specificity for prediction of inducibility of sustained VT.

In the current study, we found increased QTd in ESRD patients than the controls and QTd post HD was higher than pre HD, but statistically insignificant. Similar results were published by other authors [18], but in their study the increase in QTd post HD was statistically significant as compared to pre HD.

According to several publications, the normal range for QT dispersion is 40 to 50 ms with a maximum of 65 ms, and if the QT dispersion values are greater than 65 ms the patients are at risk for serious ventricular arrhythmias or sudden death. In this study, the average value of QT dispersion was 59 ± 19.167 ms at the end of HD. The pre and post-HD QT dispersion lengthening were independent of gender and patient age, whereas there was significant proportionate correlation between both PWd and QTd and hypertension. This is in accordance with [18].

This study also analyzed the relation between the changes in serum electrolytes to the increase in the QT and QTc dispersions. Though there was significant decrease in potassium and increase in sodium and calcium values post HD, there was no significant correlation between the electrolyte changes and the increase in the QT and QTc dispersions. None of the studies could show any association between the electrolyte changes post HD to the changes in the PW and QT dispersions, though there were significant individual changes in electrolytes. This is in accordance with the studies of other similar researchers [19].

The relationship of the QTd and absolute changes in electrolyte values during dialysis was inconsistent according to previous studies. Morris, et al. [20] had demonstrated that the absolute changes in electrolyte levels in dialysis patients did not correlate with the changes in QTd, although there were statistically significant differences of electrolytes after the dialysis session. Furthermore, Malhis, et al. [21] found no relationship in multivariate analysis. However,

Cupisti, et al. [22] found that QTd correlates with the change of potassium and magnesium levels in dialysis patients. In the study of Nappi, et al. [23], the QTd increased after dialysis only when a low-calcium dialysate (1.25 mmol/ L) was used. Another study showed correlation of QTd with parathormone [24].

This study found that there was significant negative correlation between PWd and height ($p < 0.05$), this is in accordance with Anari, et al. [25] who related prolonged PWd to disease duration of major thalassemia patients whose heights are affected by age. We also found significant negative correlation between QTd dispersion and Hb ($p < 0.05$), this is in accordance with Mozos, et al. [26].

5. CONCLUSION

P wave dispersion and QT dispersion was found to be higher in ESRD children on regular hemodialysis than healthy control subjects, indicating heterogeneity disorders of atrial conduction and ventricular repolarization in these patients and tendency to develop various arrhythmias.

CONSENT AND ETHICAL APPROVAL

The study was approved by the Ethics Committee of Faculty of Medicine, Tanta University. Written informed consents were obtained from all subjects' parents or guardians.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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