Hemodialysis Impact on QTc Interval: An Arrhythmia Precursor

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Abstract

Background: **Cardiovascular disease, particularly sudden cardiac death (SCD) from arrhythmias, is a leading cause of mortality in hemodialysis (HD) patients. The fluctuations in electrolytes and volume during and between HD sessions are suspected to be a key trigger for these fatal events.** ***Aim:*** **This study aimed to identify modifiable factors that contribute to arrhythmias, specifically QTc prolongation, in this high-risk population.** ***Subjects and Methods:*** **This was a cross-sectional observational study of 60 patients with end-stage renal disease (ESRD) on maintenance HD. Researchers assessed the prevalence of QTc prolongation using electrocardiograms and a 48-hour Holter monitor. They also collected data on patient demographics, dialysis parameters, and pre- and post-dialysis laboratory values to identify associations with QTc prolongation.** ***Results:*** **A high prevalence of QTc prolongation was observed in 73.3% of the population studied. Glomerulonephritis (GN) was the commonest as a primary cause of End-Stage Renal Disease (ESRD) among patients with prolonged QTc (43.2%, p=0.006). Furthermore, QTc prolongation was significantly associated with a longer HD duration (p=0.020), HD session lengths of four hours or more (p=0.004), intradialytic hypotension (IDH) (p=0.029), and the use of non-high flux dialyzers (p=0.016). Additionally, patients with QTc prolongation had significantly higher pre-dialysis potassium (K^+) and sodium (Na^+) levels (p<0.001 and p=0.002, respectively).** ***Conclusion:*** **QTc prolongation is common in HD patients. Various factors, including prolonged HD duration, GN as the primary cause of ESRD, IDH, and elevated pre-dialytic K^+ and Na^+ levels, are linked to the onset of arrhythmias in HD patients.**

Keywords: QTc, HD**,** sudden cardiac death.

Introduction

Cardiovascular disease poses a significant burden on hemodialysis patients, accounting for up to 41% of deaths, with half of these attributed to sudden cardiac death (SCD). [(1)] SCD is the largest cause of death in end stage renal disease (ESRD) patients, accounting for 25% - 29% of all-cause mortality. [(2)]

A substantial proportion of these deaths are likely linked to fatal cardiac arrhythmias [(3)]

Both tachyarrhythmias and bradyarrhythmias contribute to SCD in ESRD patients [(4)] As reported by the United States database of Renal Data System (USRDS), arrhythmic factors

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causes about 62% of cardiac deaths equal to 27% of all-cause mortality.

Arrhythmogenic stimuli differ between HD patients and the general population, with some being unique to the HD procedure. Combined, these elements may make changes to the types of terminal arrhythmias that lead to SCD.[5]

SCD is believed to occur when a vulnerable cardiac muscle is exposed to a sudden event that promotes arrhythmia. [5]

The types of fatal arrhythmias causing SCD vary between pre- and post-HD periods. This may imply that the causes of SCD could be lethal ventricular arrhythmia due to QT interval prolongation in post dialysis setting.[6]

Current evidence suggests that electrolyte shifts, such as K+ and Ca2+, during hemodialysis can cause rapid QT interval prolongation post-HD, potentially leading to ventricular arrhythmia and SCD.[7]

Furthermore, Intradialytic hypotension (IDH) is a known complication of HD and is accompanied by declined myocardial perfusion, a prospective risk factor for arrhythmia. [3]

Subjects and Methods

Study Design and Participants

This cross-sectional, observational study was conducted on a cohort of 60 patients with ESRD receiving HD. Participants were recruited from the dialysis units and outpatient clinics at Suez Canal University Hospitals in Ismailia, Egypt.

Inclusion and Exclusion Criteria

Eligible participants were of both genders aged 18 years or older on regular HD with well-controlled blood pressure on antihypertensive medications. Patients were excluded from the study if they had a history of atrial fibrillation, were on beta-blockers, or had an implanted cardiac defibrillator (ICD) or pacemaker. Further exclusion criteria included a newly inserted hemodialysis catheter (within 24 hours of the study), use of antihypertensive medications known to prolong the QT interval, or an ejection fraction (EF) of less than 40%.

Data Collection

A comprehensive dataset was collected for each patient. Clinical and demographic information included age, gender, occupation, residence, and smoking status. Medical history was also documented, including the primary cause of ESRD, duration of maintenance HD, type of dialysis access, and history of chronic illnesses, cardiac problems, hospital admissions for arrhythmias, blood transfusions, and surgeries.

Physical examinations were conducted to measure body mass index, intradialytic weight gain, and vital signs before, during, and after the HD session. Detailed dialysis parameters were recorded, such as session length, ultrafiltration rate (ml/hour), rate of blood flow, and surface area of the dialyzer. The properties of the bicarbonate dialyzing concentrate was the same for all patients.

Pre- and post-dialysis laboratory investigations were performed, testing for a complete blood count, as well as serum levels of potassium, sodium, creatinine, phosphorus, calcium, magnesium, uric acid, and bicarbonate. The panel of investigations also included cardiac enzymes, liver enzymes, a lipid

profile, and albumin. A 12-lead electrocardiogram (ECG) was obtained before the HD session. In addition, a 48-hour Holter monitor was used to assess QT and QTc intervals, starting one day before the HD session and concluding the day after. Transthoracic echocardiography was done.

Statistical Analysis

All collected data were entered and analyzed using SPSS version 24. Statistical comparisons between groups were performed using the Chi-square test and the independent t-test. Multiple logistic regression analysis was also utilized to identify independent risk factors. A p-value of < 0.05 is statistically significant.

Results

Our study revealed a high prevalence of QTc prolongation, observed in 44 (73.3%) of the 60 studied patients (figure 1).

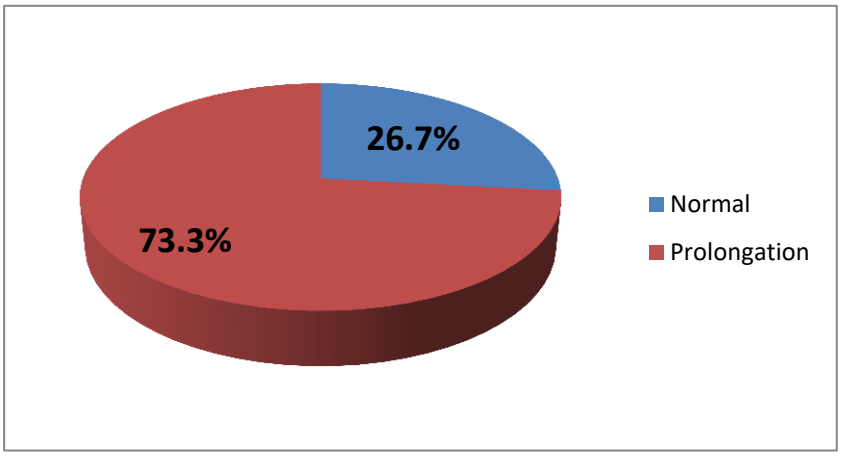

Figure 1: Prevalence of QTc prolongation among the studied population was 73.3%.

Regarding primary renal disease (Table 1), glomerulonephritis (GN) was the most common etiology among patients with prolonged QTc, accounting for 19 (43.2%) cases, a statistically significant finding (p=0.006). While 19 (31.7%) of the total patient cohort had glomerulonephritis, no patients with normal QTc had GN as a primary disease. Hypertension and obstruction were not reported as primary diseases in our cohort, while diabetes was present in 12 (20%) patients (6 [37.5%] with normal QTc, 6 [13.6%] with prolonged QTc). Genetic causes were found in 9 (15%) patients (3 [18.8%] normal QTc, 6 [13.6%] prolonged QTc). The primary cause of ESRD was unknown in 16 (26.7%) patients (7 [43.8%] normal QTc, 9 [20.5%] prolonged QTc).

Table 1. Dialysis related data and patients' characteristics				
	Total (n= 60)	QTc		p-value
		Normal (n= 16)	Prolonged (n=44)	
Primary disease, n (%)				
Glomerulonephritis	19 (31.7)	0 (0)	19 (43.2)	0.006* [c]
Hypertension	0 (0)	0 (0)	0 (0)	
Diabetes	12 (20)	6 (37.5)	6 (13.6)	
Genetic causes	9 (15)	3 (18.8)	6 (13.6)	
Obstructive uropathy	4 (15)	0 (0)	4 (9.1)	
Unknown	16 (26.7)	7 (43.8)	9 (20.5)	
Dialysis duration, n (%)				
< 1 years	9 (15)	6 (37.5)	3 (7)	
1 – 5 yrs	18 (30)	3 (18.8)	15 (34)	
> 5 years	33 (55)	7 (43.8)	26 (59)	0.020* [c]
Access of hemodialysis, n (%)				
Fistula	54 (90)	16 (100)	38 (86.4)	
Graft	3 (5)	0 (0)	3 (6.8)	0.458 [c]
Permicatheter	3 (5)	0 (0)	3 (6.8)	
Dialysis lenght, n (%)				
< 4hours	19 (31.7)	10 (62.5)	9 (20.5)	
≥ 4hours	41 (68.3)	6 (37.5)	35 (79.5)	0.004*
Frequency of dialysis, n (%)				
< 3 / week	0 (0)	0 (0)	(0)	
≥ 3 /week	60 (100)	16 (100)	44 (100)	1.000 [c]

[a] Chi-Square test. [c] Fisher Exact test. - P < 0.05 Statistically significant

Further analysis of dialysis-related parameters (Table 1 and Table 2) indicated significant associations with QTc prolongation. Patients with prolonged QTc were significantly associated with a longer overall HD duration (p=0.020), specifically with 26 (59%) patients having prolonged QTc being on HD for more than 5 years, compared to 7 (43.8%) patients with normal QTc in this category. Additionally, a longer HD session length of ≥ 4 hours was significantly associated with QTc prolongation (p=0.004), with 35 (79.5%) of patients with prolonged QTc having sessions of this duration compared to 6 (37.5%) with normal QTc.

Regarding other dialysis characteristics (Table 2), intradialytic hypotension (IDH) was significantly more prevalent in patients with QTc prolongation (38 [86.4%] vs. 9 [56.3%] in normal QTc group; p=0.029). The use of non-high flux dialyzers was also significantly associated with QTc prolongation (44 [100%] vs. 13 [81.3%] in normal QTc group; p=0.016). Other parameters like intradialytic weight gain (IDWG), ultrafiltration rate (UFR), blood flow (BLF), and heparin use during HD did not show a statistically significant association with QTc prolongation.

Table 2. Dialysis related data and patients' characteristics (continued)				
	Total (n= 60)	QTc		p-value
		Normal (n= 16)	Prolonged (n=44)	
	60 (100)	16 (100)	44 (100)	
IDWG, n (%)				
< average	11 (18.3)	4 (25)	7 (15.9)	0.746[c]
Average	25 (41.7)	6 (37.5)	19 (43.2)	
> average	24 (40)	6 (37.5)	18 (40.9)	
ID hypotension, n (%)				
Yes	47 (78.3)	9 (56.3)	38 (86.4)	0.029*[b]
No	13 (21.7)	7 (43.8)	6 (13.6)	
Ultrafilteration rate, n (%)				
Appropriate	54 (90)	16 (100)	38 (86.4)	0.179 [c]
More than appropriate	6 (10)	0 (0)	6 (13.6)	
Blood flow, n (%)				
<300 ml/min	6 (10)	3 (18.8)	3 (6.8)	0.328 [c]
≥ 300 ml/min	54 (90)	13 (81.3)	41 (93.2)	
Dialyser type				
high flow	3 (5)	3 (18.8)	0 (0)	0.016*
not high flow	57 (95)	13 (81.3)	44 (100)	
Heparin on HD				
Yes	54 (90)	16 (100)	38 (86.4)	0.179 [c]
No	6 (10)	0 (0)	6 (13.6)	
[a] Chi-Square test. [c] Fisher Exact test. - P < 0.05 Statistically significant IDWG: intradialytic weight gain, ID: intradialytic, HD: hemodialysis				

A comparison of pre-dialysis laboratory characteristics between both the study groups(Table 3) revealed significant differences in electrolytes. Patients with QTc prolongation exhibited statistically significantly higher pre-dialysis serum potassium (K+) levels (6.03 ± 0.29 mmol/L) compared to patients with normal QTc interval (4.67 ± 0.43 mmol/L) (p<0.001). Additionally, pre-dialysis serum sodium (Na+) levels were significantly higher in patients with QTc prolongation (140.3 ± 4.23 mmol/L) compared to those with normal QTc interval (137.43 ± 2.65 mmol/L) (p=0.002). No statistically significant differences were observed for other pre-dialysis parameters including hemoglobin, total leukocyte count, platelet count, creatinine, total calcium, phosphorus, uric acid, magnesium, bicarbonate, or cardiac enzymes.

Table 3. pre- dialysis laboratory results in QTc prolonged and non prolonged cases					
		Total (n= 60)	QTc prolongation		p-value
			normal (n= 16)	prolonged (n=44)	
Hemoglobin		9.74 ± 1.67	9.93 ±2.08	9.67 ± 1.52	0.405
Total leucocyte count		7.85 ± 1.83	7.75 ± 1.71	7.88 ± 1.89	0.744
Platelet		166.6 ± 57.28	157.3 ± 38.4	169.9 ± 62.7	1.000
Sodium		139.5 ± 4.07	137.43 ± 2.65	140.3 ± 4.23	0.002*
Potassium		5.67 ± 0.69	4.67 ± 0.43	6.03 ± 0.29	<0.001*
Creatinine		10.37 ± 1.93	9.96 ± 1.21	10.52 ± 2.12	0.210
Calcium		8.97 ± 0.91	9.18 ± 0.79	8.89 ± 0.95	0.241
Phosphorus		4.50 ± 1.39	3.96 ± 1.45	4.69 ± 1.33	0.189
Uric acid		5.74 ± 0.98	5.69 ± 0.73	5.75 ± 1.06	0.891
Magnesium		1.81 ± 0.23	1.78 ± 0.199	1.18 ± 0.244	0.577
Bicarbonate		14.3 ± 2.33	13.81 ± 2.50	14.47 ± 2.27	0.349
Cardiac enzymes					
	Normal	60 (100)	16 (100)	44 (100)	1.000
	High	0 (0)	0 (0)	0 (0)	
[b] *Mann Whiney U* test. [c] Fisher Exact test. - P < 0.05 Statistically significant IDWG: intradialytic weight gain, ID: intradialytic, HD: hemodialysis					

Regarding post-dialysis laboratory characteristics (Table 4), no statistically significant differences were observed between patients with and without QTc prolongation for any of the measured parameters, including hemoglobin, total leucocyte count, platelet count, sodium, potassium, creatinine, total calcium, phosphorus, uric acid, magnesium, bicarbonate, or cardiac enzymes.

Table 4. post- dialysis laboratory results in QTc prolonged and non prolonged cases					
		Total (n=60)	QTc prolongation		p-value
			normal (n= 16)	prolonged (n=44)	
Hemoglobin		9.47 ±1.60	9.69± 1.96	9.40 ± 1.47	0.356
Total leucocyte count		7.96 ± 1.74	7.94 ± 1.65	7.97 ± 1.79	0.867
Platelet		167.8 ± 57.4	159.2 ± 36.7	170.1 ± 63.4	0.867
Sodium		131.5 ± 4.9	129.4 ± 5.3	132.3 ± 4.6	0.060
Potassium		4.09 ± 0.61	4.18 ± 0.42	4.06 ± 0.66	0.302
Creatinine		7.14 ± 1.69	6.56 ± 1.50	7.35 ± 1.72	0.124
Total calcium		8.86 ± 0.96	9.01 ± 0.70	8.81 ± 1.05	0.383
Phosphorus		4.01 ± 1.17	3.60 ± 1.13	4.16 ± 1.16	0.119
Uric acid		5.21 ±0.79	5.24± 0.74	5.20 ± 0.82	0.847
Magnsium		1.53 ± 0.26	1.49 ± 0.20	1.54 ±0.28	0.560
Bicarbonate		17.10 ± 2.01	16.50 ±2.31	17.31 ± 1.87	0.213
Cardiac enzymes					
	Normal	60 (100)	16 (100)	44 (100)	1.000
	High	0 (0)	0 (0)	0 (0)	
[b] *Mann Whiney U* test. [c] Fisher Exact test. - P < 0.05 Statistically significant					

Further parameters from the 48-hour Holter assessment (Table 5) showed that among patients with QTc prolongation, 15 (34.1%) exhibited abnormal premature ventricular contractions (PVCs), while 3 (18.8%) of those with normal QTc had abnormal PVCs. Additionally, 6 (13.6%) of patients with QTc prolongation had a high-risk RR/SDNN ratio, compared to 6 (37.5%) of those with normal QTc. The RR/SDNN ratio showed a significant difference between groups (p=0.005). Furthermore, 19 (43.2%) of the patients with QTc prolongation demonstrated sympathetic overactivity, as indicated by an elevated LF/HF ratio, compared to 4 (25%) of those with normal QTc (p=0.242).

Table 5. 48 hours halter assessment results in the study groups

		Total (n=60)	QTc prolongation		p-value
			Normal (n= 16)	Prolonged (n=44)	
PVCs					
	Normal	16 (26.7)	13 (81.3)	29 (65.9)	0.346[c]
	Abnormal	44 (93.6)	3 (18.8)	15 (34.1)	
QT					
	Normal	57 (93.6)	16 (100)	41 (93.2)	0.558[c]
	Prolonged	3 (5)	0 (0)	3 (6.8)	
RR/SDNN risk					
	low	16 (26.7)	7 (43.8)	9 (20.5)	0.005*[c]
	moderate	32 (53.3)	3 (18.8)	29 (65.6)	
	High	12 (20)	6 (37.5)	6 (13.6)	
LF/HF ratio (Sympathetic over activity)					
	Normal	37 (61.7)	12 (75)	25 (56.8)	0.242[b]
	Overactivity	23 (38.3)	4 (25)	19 (43.2)	

[b] *Mann Whiney U* test. [c] Fisher Exact test. - P < 0.05 Statistically significant
PVCs: Premature ventricular contractions

A multivariate logistic regression analysis revealed two statistically significant and independent predictors of ECG changes (Table 6). Patients who had been on hemodialysis for over five years were **six times more likely** to experience these ECG changes on contrast to those on HD less than one year (OR= 6.000; 95% CI: 1.003–35.908; p=0.045). Additionally, for every 1 mmol/L increase in the pre-dialysis serum K+ levels, the odds of developing these ECG changes increased by **9.185 times** (OR = 9.185; 95% CI: 2.087–40.428; p=0.003). Other variables included in the model, such as current smoking status, intradialytic hypotension, pre-dialysis sodium, and pre-dialysis phosphorus, did not show a statistically significant association with the observed changes.

Table 6. Multivariate logistic regression analysis						
	B	S.E.	OR	95% C.I.		p-value
				Lower	Upper	
Constant	-3.495	1.532	0.030	-		0.023*
Smoking (present)	0.731	0.485	2.076	0.802	5.377	0.132
Dialysis duration (< 1 year)	Reference					
Dialysis duration (1 - 5 year)	1.386	1.000	4.000	0.563	28.396	0.166
Dialysis duration (> 5 year)	1.792	0.913	6.000	1.003	35.908	0.045*
IDH (present)	2.133	1.274	8.437	0.695	102.424	0.094
Predialysis sodium	0.385	0.298	1.469	0.820	2.633	0.196
Predialysis potassium	2.218	0.756	9.185	2.087	40.428	0.003*
Predialysis Phosphorus	1.398	0.796	4.046	0.850	19.254	0.079
* - P < 0.05 Statistically significant			IDH: intradialytic hypotension			

Discussion

Our study revealed a **high prevalence of QTc prolongation (73.3%)** in maintenance hemodialysis (HD) patients, aligning with increasing concerns about this cardiac abnormality in this vulnerable population. A prolonged QT interval on ECG increases the risk of ventricular repolarization abnormalities and life-threatening arrhythmias [8]. This is particularly critical as cardiac disease, including SCD, accounts for a significant proportion of mortality in hemodialysis patients [1, 2]. The altered ventricular repolarization in uremia is attributed to factors like hypertrophied myocytes, increased interstitial matrix, and autonomic neuropathy [4].

A notable and potentially novel finding was the significant association of QTc prolongation with GN as an ESRD primary cause (p=0.006). This finding is relevant given GN's prevalence in our cohort and warrants further research into its specific mechanisms in cardiac electrophysiological abnormalities.

We observed a significant association between QTc prolongation and a longer duration of HD (greater than 5 years, p=0.020). This suggests that the cumulative effects of chronic dialysis on cardiac electrical stability become more pronounced over extended periods [10]. Furthermore, HD session lengths of ≥ 4 hours were significantly associated with QTc prolongation (p=0.004), likely due to more pronounced ion imbalances during these longer sessions. The complex and dynamic interplay of $Ca2^{+}$, K^{+}, and Mg^{2+} during HD contributes to QTc variability, making straightforward explanations challenging [9].

While we observed no association between QTc prolongation and HD frequency per week (p=1.000), likely due to all patients receiving standard ≥3 sessions, it's crucial to acknowledge that less frequent dialysis is known to increase fluid overload and electrolyte imbalance, both established arrhythmia risk factors [12]. Indeed, studies report higher adverse events during prolonged interdialytic periods [11].

A significant association was observed between intradialytic hypotension (IDH) and QTc prolongation (p=0.029). IDH is a known risk factor for arrhythmia, as it can induce myocardial ischemia that acutely affects repolarization [2, 12]. The use of non-high flux dialyzers was

also significantly associated with QTc prolongation (p=0.016). Less efficient clearance with these dialyzers may contribute to a higher uremic toxin burden, exacerbating cardiac electrical instability [13].

Crucially, patients with QTc prolongation had statistically significantly higher pre-dialysis serum potassium (K+) (p<0.001) and sodium (Na+) (p=0.002) levels. Hyperkalemia directly impacts myocardial excitability and repolarization, increasing arrhythmia risk, and dysnatremia can alter cellular membrane potentials [14, 15]. No significant post-dialysis electrolyte differences were found, highlighting the dynamic nature of electrolyte shifts and the importance of pre-dialysis assessment to mitigate arrhythmia risk [16].

Our 48-hour Holter assessment provided further insights, revealing that patients with QTc prolongation exhibited abnormal premature ventricular contractions (PVCs) and a high-risk RR/SDNN ratio (p=0.005). These findings indicate increased ventricular arrhythmias and impaired heart rate variability, established markers of cardiovascular risk and predictors of SCD in ESRD [17, 18]. A trend towards sympathetic overactivity was also noted. This autonomic dysfunction, combined with electrolyte derangements and myocardial vulnerability, fosters a pro-arrhythmic environment in HD patients [19].

Finally, our multivariate logistic regression analysis identified two key independent risk factors for HD-induced electrocardiographic changes: more than five years on HD (p=0.045) and pre-dialysis potassium levels (p=0.003). These results emphasize the long-term impact of chronic HD on cardiac electrophysiology and the acute role of hyperkalemia. These findings are vital for identifying high-risk patients who could benefit from closer monitoring and aggressive management, potentially through optimized dialysis prescriptions or interventions targeting autonomic dysfunction.

Conclusion

Our study highlights the significant prevalence of QTc prolongation in HD patients and identifies several potentially modifiable risk factors. Early recognition and targeted management of these factors—including optimizing dialysis duration and session length, selecting appropriate dialyzer type, and meticulous pre-dialysis electrolyte correction—are paramount in preventing potentially fatal arrhythmias and reducing the incidence of SCD in this vulnerable population.

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