Nigerian Journal of Clinical Practice
December 2008 Vol.11(4) :336-341

PROGNOSTIC SIGNIFICANCE OF QT INTERVAL PROLONGATION IN ADULT NIGERIANS WITH CHRONIC HEART FAILURE

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ABSTRACT

Background and Objectives: Prognostic survival studies for heart-rate corrected QT interval in patients with chronic heart failure are few; although these patients are known to have a high risk of sudden cardiac death. This study was aimed at determining the mortality risk associated with prolonged QTc in Nigerians with heart failure.

Materials and Method: Ninety-six consecutive patients with heart failure were recruited with 90 age and sex-matched controls. All the subjects had a 12-lead electrocardiogram at a paper speed of 25mm/sec and a rhythm strip (lead II) at 50mm/sec. The latter was used to calculate the QTc using the Bazett's formula. Left ventricular systolic and diastolic functions were assessed using 2D guided M-mode and Doppler echocardiogram respectively. They were followed-up for six months.

Results: Ninety-one patients and 90 controls completed the study. Five patients were lost to follow-up. The mean age (51.9±16 years) of the patients was similar to that of the controls (50.3±15) (P = 0.475). Twenty-eight (30.8%) patients died after 6 months of follow-up against none of the controls. The mean QTc was significantly longer in the non-survivors (0.494±0.027) than in the survivors (0.462±0.035) (P = 0.0001). The percentage mortality in patients with prolonged QTc against those with normal QTc was 41% and 14% respectively (P = 0.001). In the stepwise regression analysis, QTc was an independent predictor of mortality (R = 0.412, R^2 = 0.17, P = 0.001).

Conclusion: QTc prolongation is a predictor of mortality in CHF and may be an important adjunct in risk stratification of patients with heart failure.

Key Words: Chronic Heart Failure, QTc Prolongation, Mortality *(Accepted 10 October 2007)*

INTRODUCTION

QT interval, also referred to as the electro-mechanical time is simple to measure from surface electrocardiogram (ECG) and reflects the overall ventricular repolarization status[1]. Prolongation of QT interval in chronic heart failure (CHF) has been implicated as a risk factor for developing potentially life threatening ventricular tachy-arrhythmias such as *torsades de pointes* and sudden cardiac death (SCD)[2]. Initially, QT prolongation was thought to be related purely to ageing process, female gender and persistent systolic pressure overload[3]. However, recent advances have implicated autonomic nervous system hyper-stimulation, non-conducting scar from myocardial infarction, mutations of genes controlling cardiac ionic channels involved in cardiac replolarization, left ventricular hypertrophy (LVH), obesity and elevated insulin level[4-7]. All these mechanisms seem to contribute to QT interval prolongation in patients with CHF depending on the aetiological factor of left ventricular dysfunction (LVD). To date, prognostic survival studies for heart-rate corrected QT interval (QTc) in patients with CHF are few; although these patients are known to have a high risk of SCD[8-10]. With this in mind, the present study was aimed at determining the mortality risk associated with prolonged QTc in Nigerians with CHF.

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PATIENTS AND METHODS

Ninety-six consecutive CHF patients seen at the cardiology units of Departments of Medicine, University of Ilorin Teaching Hospital, Ilorin and Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife, Osun State were recruited between May 2003 and April 2004 with 90 age and sex-matched normal controls without clinical evidence of cardiac diseases. Heart failure was defined as the presence of at least two major criteria or one major criterion in conjunction with two minor criteria using the Framimgham Criteria for detection of congestive cardiac failure[11].

Patients who had recurrent symptoms or persistent symptoms of heart failure greater than three months were eligible to participate. Proper education on the purpose of the study was given to all the subjects and informed consent was obtained from each of them. Approval was obtained from Ethics and Research Committees of the two hospitals. It was a longitudinal case control study of QTc on mortality of patients with CHF.

At presentation, all the subjects had detailed clinical evaluation and were recruited if they were 18 years and above, had normal serum potassium, did not have any central nervous system diseases associated with QTc prolongation (subarachnoid hemorrhage and ischemic stroke) and were not on drugs known to cause QTc lengthening such as amiodarone, halofantrin, risperidol etc[12]. Subjects who did not meet above criteria or those with atrial fibrillation were excluded from the study.

A 12-lead ECG was obtained from each subject using Schiller Cardiovit-10 and Schiller CS 200 machine at a paper speed of 25mm/sec. A rhythm strip was taken in lead II at a speed of 50mm/sec. The latter was used to determine the observed QT (QTo) and the R-R interval. QTo was measured from the beginning of the QRS complex to the visual return of the T-wave to the iso-electric line. QTc was calculated by applying the Bazett's formula[13]: QTc = vQTo/R-R. The same cardiologist who was blinded to the clinical status of the subject read the ECG tracings. Prolonged QTc was defined as QTc = 0.444 and 0.432 in females and males respectively[14]. LVH was determined using the established method in the Negroes[15]. Cardiac arrhythmias were noted and recorded.

The subjects underwent standard 2-Dimensional, M-mode and Doppler echocardiographic examination using Siemen's Sonoline G60S and Siemen's SX machine. The aims were to obtain evidence of left ventricular (LV) systolic and/or diastolic dysfunction and to determine the etiology of CHF in the patients. Anatomic measurements were performed according to the recommendation of the American Society of Echocardiography[16]. LV systolic dysfunction was defined as ejection fraction (EF) of < 50%. However, the ratio of early (E) and late (A) mitral in-flow velocities (E/A), Isovolumic relaxation time (IVRT), deceleration time (DT) and pulmonary venous flow (PVF) were used to assess the LV diastolic function[17]. Normal LV diastolic function was defined as E/A ratio of 1-1.9, IVRT = 80-110ms and DT of 180-240ms while impaired relaxation was E/A < 1, IVRT = 120ms and DT of = 240ms. Pseudo-normalization was defined as E/A = 1-1.9, IVRT = 80-110ms, DT = 180-240ms and ratio of PVF S/D < 1, and restrictive pattern was E/A = 2, IVRT = 70ms and DT = 180ms[17]. The patients were on standard treatment for heart failure including titrated doses of frusemide, potassium supplementation, digoxin if indicated and angiotensin converting enzyme inhibitors (ACEI).

The patients and the controls were followed up for six months. The patients were seen initially after two weeks of presentation or discharge and subsequently at monthly interval until the end of six months or death. Clinical state of the patients, acute exacerbation of symptoms and re-admissions were monitored.

The data was analyzed using the SPSS version 11 and the numerical values were presented as mean ± standard deviation. Student t-test was used to compare means of continuous variables while chi-square test was used for proportions. Test of correlation was done using the Pearson correlation method. Predictors of mortality were determined by the stepwise regression analysis. A statistically significant association was taken at $P < 0.05$.

RESULTS

Ninety-six CHF patients were recruited, but 91 patients (51 males and 40 females) completed the study. Five patients were lost to follow-up. The patients were compared with 90 (51 males and 39 females) age and sex matched controls. Almost all the patients (91.2%) were in New York Heart Association (NHYA) Class IV with the remaining patients (8.2%) being in Class III. Systemic hypertension was the cause of heart failure in 66 patients (72.5%) while peripartal cardiomyopathy was responsible for heart failure in 7 patients (8.8%). Rheumatic heart disease was seen in 5 patients (5.5%), dilated cardiomyopathy in 5 patients (5.5%), alcoholic heart disease in 2 patients (2.2%), atrial septal defect in 1 patient (1.1%) and myocardial infarction in 1 patient (1.1%). HIV/AIDS was seen in 1 patient (1.1%), mitral valve prolapse in 1 patient (1.1%) and hypertrophic cardiomyopathy in 1 patient (1.1%).

Table 1 shows the characteristics of the study population. The mean patient age was 51.9±16 years which is similar to the mean age of the controls (50.3±15) ($P = 0.475$). The mean serum sodium was significantly lower in the patients than in the controls ($P = 0.001$). However, serum potassium level was similar in the two groups ($P = 0.08$). Renal profile (urea and creatinine) were significantly higher in the patients than in the controls ($P = 0.01$ and 0.006 respectively). The mean QTc was significantly prolonged in the patients than in the controls ($P = 0.0001$) and cardiac arrhythmias were more prevalent in the patients than in the controls ($P = 0.0001$). The mean left ventricular ejection fraction (LVEF) was significantly reduced in the patients compared with the controls ($P = 0.0001$). Furthermore, the aortic root dimension, left atrial dimension, and LV mass index

were higher in the patients than in the controls. Twenty eight patients died within 6 months of follow-up against none of the controls.

The characteristics of the CHF survivors and non-survivors are as presented in Table 2. The duration of symptom of heart failure was significantly longer in non-survivors than survivors (P = 0.002). Serum sodium, urea and creatinine were more deranged in the non-survivors than in survivors. The mean QTc was significantly longer in non-survivors (0.494±0.027) than in the survivors (0.462±0.035) (P = 0.0001). With 0.444 and 0.432 used as the cut off value in females and males respectively, the QTc was prolonged in 59 patients (65%) and normal in 32 patients (35%). LV diastolic dimension, LV systolic dimension, aortic root and left atrial dimensions were significantly higher in the non-survivors compared with survivors. However, LVEF was lower in non-survivors than in survivors (P = 0.0001).

Comparing patients with prolonged and normal QTc, the mean age and incidence of LVH were similar between the two groups (P > 0.05). However, cardiac arrhythmias were more prevalent in patients with prolonged QTc than normal QTc (P = 0.001). The percentage mortality in patients with prolonged QTc against those with normal QTc was 41% and 14% respectively (P =0.001) as shown in Table 3.

There was significant correlation of QTc and duration of symptoms of heart failure (r =0.406, p=0.001), LV diastolic dimension (r=0.251, p=0.016), LV systolic dimension (r=0.362, p=0.0001), E/A ratio (r=0.282, p=0.007), deceleration time (r=-0.321, p=0.003), LVEF (r=-0.368, p=0.0001).

In the stepwise regression analysis, QTc was an independent predictor of mortality (r=0.412, R^2=0.17, P = 0.0001) in model 1 which contained all the entered variables. However, LVEF and serum sodium have additive effect to QTc on mortality in model 2 and 3 as presented in Table 4. Therefore, patients who have QTc prolongation, low ejection fraction and hyponatraemia are likely to die than other patients.

Table 1: **Shows Characteristics of The Study Population**

Characteristics	Patients	Control	P-value
Number	91	90	
Mean age ±SD (years)	51.9±16	50.3±15	0.475
Mean Na^+±SD (mmol/L)	134.2±5.4	136.9±3.5	0.001*
Mean K^+ ±SD (mmol/L)	3.9±0.31	4.1±0.4	0.08
Mean Urea ±SD (mmol/L)	6.4±1.4	5.2±1.6	0.01*
Mean Creatinine ±SD (Umol/L)	105±13	66.4±16	0.006*
Mean Heart rate ±SD (beats/min)	94.9±16	80.3±10.5	0.001*
Number with LVH	74 (81.3%)	6 (6.7%)	0.0001*
Mean QTc ±SD	0.472±0.036	0.39±0.032	0.0001*
Number with cardiac arrhythmias	51 (56%)	8 (8.9%)	0.0001*
EF ±SD (%)	38.9±11	72.2±8	0.0001*
AOD ±SD (mm)	32.3±5.4	29.7±3.9	0.0001*
LAD ±SD (mm)	44.1±75	33.2±3.7	0.0001*
LVMI ±SD g/m^2	196.9±65	104.2±23	0.0001*
Number with diastolic dysfunction	58 (63.7%)	8 (8.9%)	0.0001*
Number of Deaths	28 (30.8%)	0 (0%)	

Key: Na^+ - Serum sodium, K^+ - Serum potassium, LVH - Left ventricular hypertrophy, EF -Ejection fraction, AOD - Aortic root dimension, LAD- Left atrial dimension, LVMI - Left ventricular mass index,
* - Statistically significant.

Table 2: **Comparing the Characteristics of CHF Survivors and Non-survivors**

Variable	Survivors	Non-survivors	P value
Number	63	28	
Mean age ±SD (years)	51.5±16.8	52.9±14.7	0.694
Mean DOS ±SD (months)	7.0±3.4	9.2±5.3	0.002*
Mean K^+ ±SD mmol/L	3.96±0.37	3.99±0.49	0.75
Mean Na^+ ±SD mmol/L	139.2±4.1	135.8±3.5	0.001*
Mean Urea ±SD mmol/L	5.5±1.4	7.0±21	0.001*
Mean creatinine ±SD µmol/L	86.3±17.9	106.4±27.2	0.001*
Mean QTc±SD	0.462±0.035	0.494±0.027	0.0001*
Mean LVDd ±SD (mm)	60.4±11.2	66.8±12.8	0.02*
Mean LVDs ±SD (mm)	50.0±11.1	58.4±12.3	0.002*
Mean EF ±SD (%)	41.4±10	31.6±9.9	0.0001*
Mean AOD ±SD	31.4±5.4	34.5±4.8	0.013*
Mean LAD±SD	43.6±7.4	45.4±6.6	0.286

Key: DOS- Duration of symptoms, Na^+ - Serum sodium, K^+ - Serum potassium, LVDd- Left ventricular diastolic dimension, LVDs- Left ventricular systolic dimension, EF- Ejection fraction, AOD Aortic root dimension, LAD- Left atrial dimension, LVMI Left ventricular mass index,
* - Statistically significant.

Table 3: **Comparism of CHF Patients with Prolonged (N1) and normal (N2) Qtc**

Variable	Prolonged QTc (N1)	Normal Qtc (N2)	P-value
Number	59	32	
Mean age ±SD (years)	53.8±13.7	51.2±18	P>0.05
Number with LVH	49 (83%)	26 (81.3)	P> 0.05
Number with cardiac arrhythmias	43 (72%)	8 (25%)	0.0001*
Number of survivors	35 (59%)	28 (87%)	0.001*
Number of Non-Survivors	24 (41%)	4 (13%)	0.001*

Key: LVH Left ventricular hypertrophy
* - Statistically significant.

Table 4: **Regression Analysis: Model Summary**

Model	Variable[d]	R	R^2	P
1	QTc	0.412[a]	0.17	0.0001*
2	QTc, EF	0.487[b]	0.237	0.007*
3	QTc, EF, Na^+	0.548[c]	0.301	0.006*
4	Others[e]	NS	NS	NS

Key: EF Ejection fraction, Na Serum sodium, * - Statistically significant,
NS - Not statistically significant
a Predictors = QTc
b Predictors = QTc, EF
c Predictors = QTc, EF, Na^+
d Dependant variable = outcome
e Age, sex, New York Heart Association (NYHA), Left ventricular mass index (LVMI), Diastolic dysfunction, Duration of symptoms.

DISCUSSION

This study shows derangement of baseline biochemical, electrocardiographic and echocardiographic parameters in patients with heart failure compared with normal controls. Cardiac remodeling and neuro-hormonal alterations as well as emerging cardio-renal syndrome in heart failure may account for these changes.[18,19]

The mean age of the study population was similar to findings in other studies in Nigeria among heart failure patients.[19-20] Majority of patients recruited were in New York Heart Association (NYHA) class IV. This is not surprising because many patients in developing countries often present late to health care facilities in the course of their diseases. Poverty, ignorance and poor access to health facilities may be responsible for this attitude.

The six-month mortality in the present study was 30.8% with survival rate of 69.2%. This rate is high but comparable with previous studies in Nigeria. Isezuo et al[20] reported a 6-month mortality of 22% in adult Nigerians and Gambians with hypertensive heart failure while Ajuluchukwu et al[19] found mortality of 31% in 121 patients admitted in Lagos. These mortality figures are higher compared with those of Caucasians with similar degree of severity of left ventricular dysfunction. Vtovec et al[8] found a 6-month mortality rate of 19% in patients with advanced heart failure. Population-based studies have shown that patients of African origin with CHF have higher mortality rate and risk of progression of LVD than similarly treated Whites.[21-22]

Comparing patients who survived with non-survivors, they differ in serum sodium, renal profile, left ventricular ejection fraction and QTc as shown in Table 2. The mean serum sodium was significantly lower in non-survivors than in survivors. It is an independent predictor of mortality. This is similar to findings by Balogun et al[23] and Ajuluchukwu et al[19] in which hyponatraemia was a predictor of intra-hospital mortality in CHF. Hyponatraemia is probably due to inappropriate anti-diuretic hormone (ADH) secretion, a condition which is common in heart failure and could be dilutional from fluid retention. Extreme hyponatraemia is an index of cell death. The role of impaired renal function in the outcome of patients with heart failure has been recognized.[18,19] This study showed a significantly higher serum urea and creatinine in the non-survivors than in the survivors. Impaired renal function occurs as a result of hypoperfusion of the kidneys and in the hypertensive, there is an additional risk of arteriolosclerosis as well as nephrosclerosis.

Echocardiographic parameters were more deranged in the patients that died than in the survivors. The mean LVEF is an independent predictor of mortality in this study. The role of LVEF as a predictor of mortality in heart failure was clearly shown in the Framingham Heart study[24] and by Balogun et al[23].

The results of our study indicate that QTc prolongation is an adverse prognostic sign in heart failure. Despite the absence of evidence from

Framingham Heart Study, QTc prolongation has been associated with an increased mortality rate in large population based studies in patients with cardiac diseases[25-27]. Until recently, the prognostic significance of increased QTc in patients with heart failure was not clear. Indeed, very few studies have addressed the prognostic significance of increased QTc as a function of LVEF. The United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-HEART)[28], enrolled 554 ambulatory patients with CHF. QTc prolongation was a predictor of mortality on univariate but not on muitivariate analysis. A recent study which enrolled 2265 CHF patients with LVEF of = 40%, found QTc prolongation to be strongly related to mortality in the whole group and in subsets on the basis of age and the level of LV systolic function.[29]

Significant correlation was found between duration of heart failure, LV diastolic dimension, LV systolic dimension, LVEF, DT, ratio of early and late mitral (E/A) filling and QTc. A small scale study had shown correlation between the level of severity of LV diastolic dysfunction and QT interval prolongation and dispersion[30]. In this study, correlation between the indices of diastolic dysfunction (E/A ratio, DT) may suggest the presence of advanced LVD. Progressive left ventricular disease eventually leads to increased myocardial stiffness and a rise in diastolic pressure. The resultant increase in left ventricular filling pressure and consequent subendocardial ischaemia predispose the latter to conduction depolarization delay and QTc prolongation.

In conclusion, QTc prolongation in heart failure is associated with adverse outcome as shown by our study. It is an independent predictor of mortality. Though the underlying mechanism of QTc prolongation is not fully understood, it appears that it may be a good adjunct in risk stratification of patients with heart failure. The relatively small number of patients used in this study is a limitation and we suggest broad base multi-centre studies enrolling larger number of patients in order to establish the prognostic effect of QTc in Nigerians with CHF.

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