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Journal of Clinical and Experimental Cardiology

Research Article

Frequency and Associated Factors with QT Interval Prolongation in Adults with Chronic Heart Failure in Yaoundé

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ABSTRACT

Background: Heart failure is a chronic cardiovascular disease that has an increasing incidence and a poor prognosis in adults in Sub-Saharan Africa due to the rhythm disorders frequently associated to it. Although QT interval prolongation increases cardiovascular mortality in chronic heart failure, there is poor knowledge and it remains undiagnosed... in Sub-Saharan Africa. We therefore deemed it appropriate to determine the frequency and identify the factors associated with QT interval prolongation in adult patients with chronic heart failure in Yaoundé. Our main objective was to study the frequency and factors associated with QT interval prolongation in adult patients with chronic heart failure in Yaoundé-Cameroon.

Objective: The objective of our study was to study the frequency and factors associated with QT interval prolongation in adults with chronic heart failure in Yaounde.

Methods: We conducted a descriptive cross-sectional study from January to May 2020 (05 months) at the Central Hospital and General Hospital of Yaoundé. Adults with chronic heart failure presenting in these two hospitals without signs of decompensation were recruited on an outpatient basis. A 12-lead electrocardiogram was performed to all these patients to determine the type of heart rhythm, measure the QT interval, look for rhythm disturbances and hypertrophy indices (ventricular and atrial). For heart rates between 60 and 100 beats per minute, Bazett's formula was used for the calculation of the corrected QT; for heart rates outside this range, Framingham's formula was used. Patients' left ventricular systolic and diastolic functions were assessed by Trans Thoracic Echocardiography (TTE). Blood measurements of creatinine, urea, potassium, sodium and total calcium were performed. The significance level was set at 5%.

Results: Out Of 104 patients, 19 (18.27%) had a prolonged QT interval and 01 (0.09%) had an abnormally high QTc interval (>500 ms). Secondary repolarization disorders (p=0.035), hypocalcaemia (p=0.015), hypokalemia (p=0.0016), left ventricular hypertrophy (p=0.005), and plasma creatinine level>13mg/l (p=0.010) were associated with QT interval prolongation. QT prolongation was not significantly associated with advanced age or sex. No association was found between QT prolongation and heart failure drugs.

Conclusion: QT interval prolongation was present in 1/5 of our patients. The associated factors found were: Hypokalemia, hypocalcaemia, a plasma creatinine concentration higher than 13mg/l, left ventricular hypertrophy and secondary repolarization disorders.

Keywords: Cardiovascular disease; Heart rhythm; Hypokalemia; Hypocalcaemia; Electrocardiogram

INTRODUCTION

Cardiovascular disease is a group of disorders affecting the heart and vessels [1]. According to the WHO, by 2015, they will be responsible for 17.5 million deaths worldwide, with a prevalence of 75% in low- and middle-income countries[1]. Among cardiovascular diseases, the incidence of Heart Failure (HF) is increasing and its prognosis remains poor despite various treatment modalities that

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Received: May 25, 2021; **Accepted:** June11, 2021; **Published:** June 18, 2021

Citation: Boombhi J, Tonye BNT, Nganou-Gnindjo CN, AmaMoor V, Nzounji FU, Temgoua MN, et al.(2021) Frequency and Associated Factors with QT Interval Prolongation in Adults with Chronic Heart Failure in Yaoundé. J Clin Exp Cardiolog.12: 684.

are expected to improve its prognosis [2-4]. This mortality can be explained by the non-negligible place of rhythm disorders (29.33%) on the standard Electrocardiogram (ECG) in a series conducted in Yaoundé in 2005. Although many markers of poor prognosis are known to date, it remains difficult to accurately predict high-risk groups in ambulatory patients with signs of ventricular dysfunction [5]. The two most common mechanisms of death in patients with chronic heart failure are progressive heart pump failure and sudden unexpected deterioration [6]. In patients with moderate to mild chronic heart failure, sudden death is the most common mechanism [7]. In sudden cardiac death, the underlying mechanism is the result of malignant ventricular arrhythmias [8]. However, it is difficult to predict this event clinically with precision [7]. The common denominator of ventricular arrhythmias is variations in the duration of ventricular repolarization and/or depolarization, which can be assessed on a standard 12-lead ECG by measuring the duration of the QT interval [9]. QT interval duration on a standard ECG has been shown to predict arrhythmic events in patients with various myocardial diseases [10]. In patients with chronic heart failure, QT interval prolongation is associated with 41% mortality compared to those with a normal QT interval (14%) [11]. QTc interval prolongation is no longer solely related to age, diuretic prescription and persistent systolic overload as shown in some studies [12].Therefore, health care providers should be adequately educated about the importance of QT interval duration in the cardiovascular stability of patients with chronic heart failure, which could not yet be the case. Indeed, according to a survey of healthcare professionals in the United States, 57% of healthcare professionals do not know how to measure the QT interval or how to correctly identify factors that can prolong the QT interval [13,14]. QT interval prolongation is therefore under-diagnosed and unknown to healthcare professionals in our context. Furthermore, this abnormality is associated with increased mortality in adults with chronic heart failure. Thus, it seemed appropriate to us to study this electrical anomaly in adults with chronic heart failure in the Cameroonian context, more specifically in the city of Yaounde.

MATERIALS AND METHODS

Study design, setting and population

We conducted a descriptive cross-sectional study during the period from January 1 to May 31, 2020. One hundred and four (104) heart failure patients were consecutively enrolled at the Central Hospital (54) and the General Hospital (50) of Yaoundé. Heart failure was defined by the presence of clinical or paraclinical signs of heart failure in accordance with the recommendations of the European Society of Cardiology. Patients with symptoms of heart failure more than three months old were eligible for our study. They were then given an educational session on the various key concepts of the study in order to obtain their informed consent. Those who gave their informed consent were selected for the study. Patients who were at least 18 years of age, showed clinical or paraclinical signs of chronic heart failure without signs of decompensation, and who gave free and informed consent were included in our study. Excluded from our study were chronic heart failure patients with atrial fibrillation or flutter, bundle branch block (right or left), and those with a cardiac pacemaker.The medical records of outpatients were used to collect information about ventricular function.

Procedure

Systolic function was assessed using the most recent value of the left ventricular ejection fraction present on the Trans Thoracic Echocardiogram (TEE) and the heartfailure was divided into three classes:

- HF with reduced ejection fraction: LVEF<40%.

- HF with intermediate ejection fraction: 40%<LVEF<49%.

- HF with preserved ejection fraction: FEVG ≥ 50%50%.

Diastolic function was assessed according to the recommendations of the European Society of Cardiology [15]. Normal diastolic function was defined as: An E/A ratio of 0.8-1.9, an E/E' ratio<14, a TD of 150ms-220ms, a left atrial surface area of less than 34 cm2. Left ventricular diastolic dysfunction was defined by the following criteria:

➢ Grade I: E/A ≤ 0.8 and E ≤ 50cm/s

➢ Grade II: E/A ≤ 0.8 and E ≥ 50cm/s and at least two of the following three (03) criteria:

- E/e' average>14

- Vmax IT>2.8 m/s

- Indexed OG volume>34 ml/m2

➢ Grade III: E/A ≥ 2

For any patient with heart failure, a standard resting Electrocardiogram (ECG) was performed using ECG devices (brand MAC 1200 ST and NIHON KOHDEN Cardiofax) at a paper speed of 25 mm/sec to: Determine the type of heart rhythm, measure the QT interval and look for disorders of rhythm, conduction and excitation. Automatic QT interval values were recorded. If these were not available, the DII and V5 leads were used for QT interval measurement. The QT interval was measured from the beginning of the QRS complex to the visible return of the T-wave to the isoelectric line on three successive QRS complexes. The average was taken as the value of the measured QT. If the end of the T-wave could not be clearly identified, the branch with the more visible end of the T-wave was chosen between the left lateral (V5/V6), and antero-septal (V2V3) branches. When the T wave was interrupted by the U wave, the end of the T wave was defined as the nadir between the T wave and the U wave. The QT interval was measured by the principal investigator under the supervision of a cardiologist "blinded" to the patient's clinical data. The QT interval was prolonged for values greater than 450 ms and 460 ms in men and women [14].

Several factors can affect the repolarization of the myocardium and thus modify the duration of the QT interval, including the serum concentrations of certain ions. Blood tests were performed to investigate a possible association between electrolyte changes and QT interval duration. For this purpose, a sample was taken from each patient in order to measure Natraemia (Na+), Calcaemia (Ca2+) and Kalaemia (K+). Hypokalemia was defined by a serum level of <3.5 mmol/L, hypocalcemia by a value of <81 mg/L and hyponatremia by a value of <135 mmol/L [15]. Renal function data, i.e. urea and plasma creatinine, were also recorded. The normal values for blood urea and creatinine were 0.15 g/l-0.45 g/l and 6mg/l-13 mg/l, respectively [15]. The biological analyses were performed in the biochemistry laboratory of the Centre Yaoundé Teaching Hospital (YTH). Total calcium was determined by the 0-Cresolphthalein Complexon method. Creatinine and plasma urea were determined by the kinetic method, while the values of Kalemia and Natremia were obtained by the Genrui GE 300

ionometer.

Statistical analyses

Data analysis was done with Epi-info software version 7.2.2.6. The Chi-square test and the Fischer's exact test were used for the association of the qualitative variables with a significance threshold lower than 0.05. The Chi-square test and the Fischer's exact test were used for the association of the qualitative variables with a significance threshold lower than 0.05. The degree of association was measured by calculating the odds ratio with their confidence interval, and a multivariate analysis was performed to eliminate confounding factors. The Mann Whitney test was used to measure the association between the quantitative variables.

Ethics

Our study was submitted to and received a clearance from the Regional Committee for Ethics and Research in Human Health of the Centre for Ethical Clearances (CRERSH) No. 3340/AP/MINSANTE/SG/DRSPC/CRERSH. Also, a clearance was obtained from the Faculty of Medicine and Biomedical Sciences of Yaoundé I. We also obtained research authorizations from the directors of the hospitals serving as study sites.

RESULTS

We included 155 chronic heart failure patients in both hospitals for our study. In accordance with our criteria, 49 patients were excluded (24 Left Bundle Branch Blocks; 06 Right Bundle Branch Blocks; 17 Atrial Fibrillation; 02 Atrial Flutter). A total of 104 patients were retained (Figure 1).

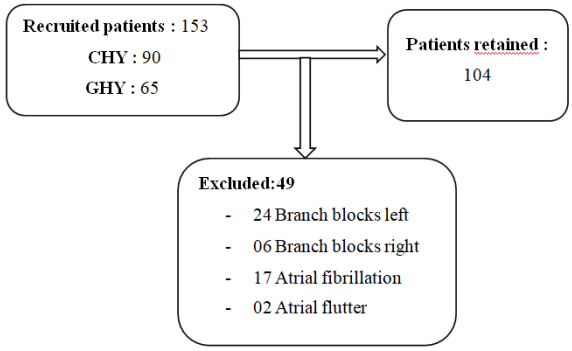

Figure 1: Data analyzed from recruited patients (out of 153, 104 patients were retained).

Socio-demographic characteristics of participants

The average age of our population was 62 ± 12 years, with a minimum age of 18 and a maximum age of 84. The most represented age group was: [60-70] years old, followed by over 70 years old.

Clinical characteristics of heart failure patients

The majority of our patients presented with stage II NYHA (68.27%), followed by stage I (21.15%) and stage III (10.57%). The most common type of heart failure by chamber was congestive heart failure (54.81%). By ejection fraction, the most represented type of heart failure by chamber was fraction-preserved heart failure (44.23%). The predominant etiology was hypertensive heart disease (60.58%), followed by dilated cardiomyopathy and valvular heart disease which shared second place (13.46%).The most commonly used drugs for heart failure were: Diuretics (32%), Converting Enzyme Inhibitors (26%) and beta-blockers (19%) as shown in the figure below. The clinical and paraclinical characteristics of chronic heart failure patients are presented (Table 1).

Table 1: Qualitative clinical features of heart failure. 1: Heart Failure; 2: New York Heart Association; 3: Heart failure with reduced ejection fraction; 4: Heart failure with intermediate ejection fraction; 5: Heart failure with preserved ejection fraction.

Characteristics	Staff (N=104)	Percentage (%)
Clinical Stage of HF[1] (NYHA[2])		
Class I	22	21,15
Class II	71	68,27
Class III	8	07,69
Class IV	3	02,88
Type of heart failure by chamber		
Right HF	5	04,81
Left HF	42	40,38
Global HF	57	54,81
Types of heart failure by ejection fraction		
HFiEF3	40	38,46
HFrEF4	18	17,31
HFpEF5	46	44,23
Heart failure aetiology		
Ischemic heart disease	5	04,81
Hypertensive heart disease	63	60,58
Valvularcardiopathy	14	13,46
Dilated cardiomyopathy	14	13,46
Other heart disease	8	07,69

Frequency of QT interval prolongation in IC patients

Out of 104 patients, 19 patients had an elongated QT giving us a prevalence of 18.27%.

Factors Associated with QT Interval Prolongation

The associated factors found in bi-variate analysis were: conduction disorders, excitation disorders, secondary repolarization disorders, and left ventricular hypertrophy. Furthermore, the associated biological data were hypokalemia ($p<0.001$), hypocalcemia ($p<0.001$), a creatinine level>13 mg/L ($p=0.010$) were significantly associated with QT interval prolongation. The table below shows the results of the bivariate analysis. The independently associated factors obtained after logistic regression were: Hypocalcemia (0.01), hypokalemia(0.001), plasma creatinine>13 mg/L (0.010), secondary repolarization disorder (0.035) and left ventricular hypertrophy (0.005) (Table 2-4).

Table 2: Population distribution according to paraclinical data.

Variables	Min-Max	Mean +/- standard deviation	Median [Interquartile range]
Natremia (mmol/L)	126-171	138,93 ± 6,14	137,95[135-142,1]
Kalemia (mmol/L)	2,5-5,64	3,72 ± 0,56	3,7[3,43-4,1]
Calcaemia (mmol/L)	66-99,99	85,30 ± 7,40	84[80,5-89]
Nitrogen (g/l)	0,09-2,22	0,39 ± 0,32	0,28[0,19-0,4]
Creatinine (mg/l)	5,5-71,9	16,47 ± 10,55	13,15[11,6-16,2]
GFR1 (ml/min)	12-133	53,66 ± 23,30	55[39-65]
LVEF1 (in %)	15-93	48,48 ± 18,88	45,53 [31,5-62,41]

Table 3: Bi-various analyses.

Variables (Oui/non)	QT allongé (n_1=19) Effectif (%)	QT normal (n_2=85) Effectif (%)	OR (IC à 95%)	Valeur-P
TdC[1]	6 (37,5)	75(85,2)	3,4 (1,07-11,1)	0,030
TdE[2]	9 (31,03)	65 (86,6)	2,9 (1,04-8,1)	0,069
TdR[3]	14 (42,4)	66 (92,9)	9,7 (3,1-30,4)	<0,001
HVG[4]	17 (38,6)	58 (96,6)	18,2 (3,9-84,7)	<0,001
Hyponatrémie	10 (41,6)	71 (88,7)	5,6 (1,9-16,3)	0,002
Hypokaliémie	9 (69,2)	81 (89,0)	18,2 (4,7-70,2)	<0,001
Hypocalcémie	12 (46,1)	71 (91,03)	8,6 (2,9-25,9)	<0,001
Créatinine>13 mg/l	15 (28,3)	47 (92,1)	4,6 (1,4-15,1)	0,010

Table 4: Multivariate analysis in logistic regression.

Variables	CRO (IC à 95%)	AOR (IC à 95%)	Valeur-p ajustée
TDR1	9,7 (3,1-30,4)	5,09 (1,1-23,3)	0,035
Hyponatrémie	5,6 (1,9- 16,3)	3,7 (0,7-19,6)	0,116
Hypokaliémie	18,2 (4,7- 70,2)	6,7 (1,4-31,7)	0,015
Hypocalcémie	8,6 (2,9- 25,9)	15,2 (2,8-82,04)	0,001
Diurétiques	2,9 (0,7- 10,7)	1,4 (0,2-8,02)	0,702
HVG2	18,2 (3,9- 84,7)	16,2 (2,2-118,2)	0,005
Créatinine>13 mg/l	4,6 (1,4- 15,1)	12,8 (1,8-89,8)	0,010

DISCUSSION

Our study revealed that QT interval prolongation is common in chronic stable adult CI in Yaoundé. In addition, the associated factors were found to be biological (hypokalemia, hypocalcaemia), and echocardiographic (HVG, and secondary repolarization disorders).

Socio-demographic characteristics of patients

Our study population had an average age of 62 ± 12 years, a peak incidence in the 6th decade, and a sex ratio of 0.79. The study population had a mean age of 62 ± 12 years, a peak incidence in the 6th decade, and a sex ratio of 0.79. Our average age of one decade higher than that of kolo, et al. [11] in Nigeria could be explained by the importance of peripartum cardiomyopathy in the peripartum series which predominates in younger and female subjects; in addition, our higher life expectancy compared to Nigeria could explain this finding. Nevertheless, this result is close to that of who presents heart failure as pathology of the elderly with an average age of diagnosis above 60 years [16]. This could be explained by the fact that essential hypertension is among the major providers of heart failure in the Caucasian population as well as in sub-Saharan Africa [17,18]. As essential hypertension is pathology of the elderly, heart failure would therefore be more present at this age.

Clinical characteristics of heart failure patients

In our study, a small proportion (21.15%) of our patients were asymptomatic, while more than half (68.27%) were Class II. This result is different from that of kolo, et al. [11] for whom NYHA classes III and IV occupied almost all cases. We can explain this by the fact that the recruitment of patients in this series took place in an inpatient department with severe forms while our patients were recruited on an outpatient basis. Thus, they presented few or no symptoms, as shown in the study by Brooksby, et al. [19].

Etiology of heart failure

In our study hypertensive heart disease was the most represented (60.58%) followed by valvular heart disease and dilated cardiomyopathy which shared second place (13.46%). This result is similar to that of kolo, et al. [11]in Nigeria where hypertensive heart disease was the predominant etiology with 77.5%. These results are explained by the fact that hypertension remains a major contributor to heart failure in Africa. The prevalence of valvulopathies can be explained firstly by the insufficient prevention of rheumatic heart disease in sub-Saharan Africa, which remains frequent and serious, but also by the ageing of the population [18,20]. The place of cardiomyopathies in our population is comparable to that reported by in Nigeria. The increase in the frequency of cardiomyopathies is explained by a preponderance of sub-clinical Trypanosome infections that remain under-diagnosed in our context [21].

Frequency of QT interval lengthening

Out of 104 patients, 19 patients had an elongated QT, a prevalence of 18.27%. This frequency is lower than that found by kolo, et al. [11] in Nigeria which was 65%. This can be explained by the difference in the method of QT interval correction. Indeed, Bazett's formula overestimates the QT value in case of tachycardia which could falsely prolong the QT interval. Moreover, the values used by Bazett for the cut-off were lower than ours, i.e. 444 and 432 for men and women respectively, compared to 450 and 460 for men and women.

Factors associated with QT interval prolongation

The independently associated electrocardiographic factors found were: secondary repolarization disorders, and left ventricular hypertrophy. These results corroborate those found by Seftchick, et al. [22] in Switzerland who also highlighted the association between left ventricular hypertrophy and QT interval prolongation. Indeed, left ventricular hypertrophy is at the origin of a mechanical re-modelling that reverses the transmural pressure gradient. This inversion of the transmural gradient causes a reduction in the outgoing potassium current, which lengthens the repolarization phase of the cardiac cycle. Secondary repolarization disorders are directly related to left ventricular hypertrophy. In terms of biology, hypokalemia, hypocalcemia, creatinine>13 mg/L (p=0.010) were significantly associated with QT interval prolongation. These findings converge with those of Tisdale, et al. [23] in the United States. This is explained by the fact that hypokalemia as well as hypocalcemia lengthen the phases 2 and 3 of depolarization of these myocardial cells.The increase in plasma creatinine concentration in heart failure is due on the one hand to ACE inhibitors and on the other hand to prolonged renal hypo perfusion in the case of congestive heart failure. A large majority of our patients with congestive CI were treated with loop diuretics, which provide hypokalemia that prolongs the QT interval.

CONCLUSION

QT interval prolongation was present in 1/5 of our patients. The independently associated factors found were: hypokalemia, hypocalcemia, plasma creatinine concentration above 13 mg/l, left ventricular hypertrophy and secondary repolarization disorders. The major limitation of our study was the premature discontinuation of our collection due to the health crisis related to COVID-19. We determined the proportion of our stable chronic heart failure patients at risk of sudden death using 12-lead resting ECG.Knowledge of the associated factors will thus make it possible

to prevent this electrical abnormality with a view to reducing mortality from chronic heart failure. This study raises other questions, including the prognosis of QT interval prolongation in stable chronic heart failure adults in Yaoundé. On the other hand, the search for other arrhythmias that would increase the risk of mortality in stable chronic heart failure patients.

ACKNOWLEDGEMENTS

The authors express their deep gratitude to all the medical and paramedical staff of the Outpatient Consultation Service of the Yaoundé General Hospital, the Central Hospital and the Biochemistry Laboratory of the Yaoundé Hospital and University Centre. Our thanks also go to the persons in charge of the different hospitals who allowed us to carry out our study in their establishments.

FINANCIAL SUPPORT AND SPONSORSHIP

None.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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