Anemia and the QT interval in hypertensive patients

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Abstract

Introduction: A prolonged ECG QT interval duration and an increased QT dispersion (QTd) are predictors of sudden cardiac death. Anemia is known as a marker of adverse outcome in cardiovascular disease.

Objective: The aim was to assess the relationship between anemia and QT intervals in hypertensive patients.

Method: A total of 72 hypertensive patients underwent standard 12-lead ECG. QT intervals and QT dispersions were manually measured. Complete blood count was also assessed.

Result: Linear regression analysis revealed significant associations between prolonged QTc and increased QTd and anemia and macrocytosis, respectively. Multiple regression analysis revealed a significant association between red cell distribution width (RDW) >15% and prolonged heart rate corrected maximal QT interval duration (QTc) and QT interval in lead DII (QTIIc). The most sensitive and specific predictor of prolonged QTc and QTIIc was anisocytosis. Anemia was the most sensitive predictor of QTd > 60ms and macrocytosis, the most specific.

Conclusion: Anemia, macrocytosis and anisocytosis predict prolonged QT intervals in hypertensive patients.

Key words: QT interval, Electrocardiogram, Anemia, Anisocytosis, Macrocytosis

Introduction

A high risk of sudden cardiac death was previously demonstrated in hypertensive patients, related to left ventricular hypertrophy, myocardial ischemia, interstitial fibrosis and autonomic imbalances.¹

Anemia, a global public health problem, affecting both developing and developed countries, is known as a negative prognosis factor in cardiovascular diseases and a strong predictor of death.

Electrocardiographic changes were previously mentioned in patients with chronic anemia.^{2,3}

Prolonged ECG QT intervals are predictors of sudden cardiac death.^{4,5}

Aim

The aim of the present study was to assess the relationship between anemia and QT intervals in hypertensive patients.

Material and Method

A total of 72 consecutive hypertensive patients were enrolled in the study. They underwent standard 12-lead ECG and complete blood count was performed. The investigations conformed to the principles outlined in the Declaration of Helsinki⁶ and were approved by the Ethics Committee of the university.

Inclusion criteria

Consecutive patients diagnosed with hypertension according to the criteria of the European Society of Hypertension⁷ were included. A written informed consent of the patients was requested.

Exclusion criteria

The most important exclusion criteria were: atrial flutter, atrial fibrillation, electrolytic imbalances, systemic inflammatory processes, active infections and trauma, peripheral edema, chronic obstructive pulmonary disease, history of myocardial infarction, therapy with angiotensin converting enzyme inhibitors and angiotensin receptor blockers.

Sample size and power of the study

A power analysis was conducted to determine the number of participants needed in the present study. The minimum sample size required for regression analysis was 54 (anticipated effect size: 0.15; desired statistical power level: 0.8).

Standard 12-lead ECG

The participants underwent standard 12-lead ECG at a paper speed of 25 mm/seconds. The QT interval duration was manually measured, from the beginning of the Q wave (or R wave) to the

end of the T wave, in all measurable leads. Maximal QT interval duration in all measurable leads (**QTmax**), heart rate corrected QT interval according to Bazett formula (**QTc**), QT interval in lead DII (**QTII**), heart rate corrected QTII interval (**QTIIc**) and QT dispersion (**QTd**) were assessed. QTd was calculated as the difference between the maximal and minimal duration of the QT interval in all measurable leads. Two consecutive QT intervals were measured for each ECG and the arithmetic mean was calculated. A QT interval of 450 ms was considered prolonged.

Complete blood count

Complete blood count was also performed: red blood cell count (**RBC**), hemoglobin (**Hb**), hematocrite (**PCV**), mean corpuscular volume (**MCV**), mean corpuscular hemoglobin (**MCH**), mean corpuscular hemoglobin concentration (**MCHC**), red cell distribution width (**RDW**). Anemia was defined using the World Health Organization criteria: hemoglobin levels < 12 g/dL in women and < 13 g/dL in men, macrocytosis as MCV>97 fl and anisocytosis as RDW>15%.

Statistical methods

Categorical data are given as numbers and percentages, continuous data are given as means±standard deviation (SD). Sensitivity and specificity, linear and multiple regression analysis were used as statistical methods.

Results

The study population comprised 72 hypertensive patients, aged 63 ± 12 years, 39% male. The data obtained for QT intervals and complete blood count results are included in table 1.

Regression analysis

Linear regression analysis revealed significant associations between prolonged QTc and increased QTd and anemia and macrocytosis, respectively (table 2).

Multiple regression analysis revealed a significant association between RDW>15% and prolonged QTc and QTIIc (table 3).

Sensitivity and specificity

The most sensitive and specific predictor of prolonged QTc and QTIIc was anisocytosis. Anemia was the most sensitive predictor of QTd > 60ms and macrocytosis, the most specific (table 4).

Discussion

The most important finding of the present paper is the association between prolonged QT intervals and anemia, macrocytosis and anisocytosis, respectively.

Increased red cell distribution width (RDW) was associated with a worse outcome in several cardiovascular diseases⁷⁻¹⁰ and with mortality in the general population.¹¹ The correlation between RDW, a measurement of the variability in size of circulating erythrocytes, and inflammatory markers, biomarkers of ineffective erythropoiesis, undernutrition and impaired renal function explained the association between RDW and adverse outcomes in heart failure patients^[8] Increased RDW was associated with a worse outcome in myocardial infarction patients too, with or without anemia.⁹

Hemoglobin concentration was previously found as a predictor of prolonged QT intervals in chronic kidney disease patients.¹²

A shortened QT interval was observed in patients with iron deficiency anemia, and a positive correlation was found between serum ferritin and QTc.¹³

Scheller et al.³ reported a gradual prolongation of the QT and QTc interval in normovolemic anemia.

Anemia may increase cardiac output and heart rate, may lead to eccentric left ventricular hypertrophy, activation of the sympathetic nervous system, stimulation of the renin angiotensin aldosterone system, and is closely associated with chronic inflammation and increased oxidative stress.¹⁴ Tissue hypoxia and changes in blood flow patterns due to low hemoglobin may play an atherogenic role.¹⁴ The pathophysiological link between anemia and prolonged QT intervals is, probably, hypoxia and decreased myocardial oxygen supply. Anisocytosis appears as an early sign of anemia, also linked with prolonged QT intervals. The results of the present study indicate that macrocytosis and the degree of heterogenous distribution of red blood cells provide important additive prognostic information. Thus, the present paper reports, for the first time, as far as we know, an association between QT intervals and macrocytosis and anisocytosis, respectively.

The most important limitations of the present study are due to the use of the Bazett formula for heart rate adjustment of QT intervals, methodological differences in delineating the end of the T interval, several sources of variability of the QT interval and lack of standardization of QT dispersion data.

The Bazett formula results in overcorrection of the QT interval at higher heart rates and undercorrection at lower heart rates.¹⁵ Despite the mentioned limitation, it is the most frequently used in clinical practice and it is appropriate for the average physiological heart rate. The heart rates of the patients in the present study ranged between 52 and 113 beats/minute. Only 6 patients had a heart rate below 60 beats/minute and only 2 > 100 beats/minute.

Methodological differences in delineating the end of the T interval may appear if the T wave is flat or bizarre.^{16,17} Leads, in which the Tend could not be assessed, were eliminated in the present study.

Comorbidities, including age, diabetes mellitus (25% of the patients included in the study population), obesity (28%), dyslipidemia (14%), smoking (35%), left ventricular hypertrophy (63%), renal failure (3%), and therapy, including beta-blockers (74%), may change QT interval duration.¹⁵⁻²⁰ However, the number of comorbidities was low in the present study, considering that mainly newly diagnosed hypertensive patients were included. Electrolytic imbalances, systemic inflammatory processes, active infections, chronic obstructive pulmonary disease and history of myocardial infarction were exclusion criteria. Patients taking angiotensin converting enzyme inhibitors and angiotensin receptor blockers, known to suppress erythropoiesis²¹ have been also excluded.

Conclusion

Anemia, macrocytosis and anisocytosis predict prolonged QT intervals in hypertensive patients and may contribute to risk assessment of sudden cardiac death. Longitudinal studies are needed to confirm the association between complete blood count and ventricular arrhythmias and sudden cardiac death. The advantage to treat anemia in hypertensive patients for reducing the risk of sudden cardiac death due to ventricular arrhythmias remains to be demonstrated.

Conflict of Interest: None declared.

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Parameter	
QTmax (ms)	438±54
QTc (ms)	474±53
QTc > 450 ms	50 (69%)
QTII (ms)	406±49
QTIIc (ms)	440±49
QTIIc > 450 ms	26 (36%)
QTd (ms)	74±34
QTd > 60ms	44 (61%)
Heart rate (beats/minute)	72±15
RBC (million/mm ³)	4.15±0.61
Hemoglobin (g%)	13.31±1.83
Packed cell volume (%)	39±5,01
Mean corpuscular volume (MCV) (fl)	94±5.82
Mean corpuscular hemoglobin (MCH) (pg)	32±2.63
Mean corpuscular hemoglobin	34.25±1.69
concentration (MCHC) (g%)	
Red cell distribution width (RDW) (%)	15.13±1.6
Anemia	38 (53%)
MCV>97 fl	20 (28%)
RDW>15%	22 (31%)

Table 1: QT intervals and complete blood count results

QTmax = maximal QT interval duration in all measurable leads, QTc = heart rate corrected QT interval according to Bazett formula, QTII = QT interval duration in lead DII, QTIIc = heart rate corrected QTII according to Bazett formula, QTd = QTdispersion; intervals are expressed as means \pm standard deviation

Parameter	Associated with	Significance F	Multiple R	R square	Adjusted R
Anemia	QTc	< 0.01	0.642	0.412	0.384
MCV>97fl	QTd	< 0.01	0.578	0.334	0.306

Table 2: Linear regression analysis

Anemia was diagnosed according to the World Heatlh Organization criteria: hemoglobin levels < 12 g/dL in women and < 13 g/dL in men, MCV = mean corpuscular volume, multiple R = multiple correlation coefficient, R square = coefficient of determination, adjusted R = the coefficient of determination adjusted for the number of independent variables in the regression model

Associated with	Significance F	Multiple R	R square	Adjusted R
QTc > 450ms p<0.01 QTIIc > 450ms p<0.01	<0.01	0.642	0.412	0.384

Table 3: Multiple regression analysis - Factors significantly associated with anisocytosis

QTc = heart rate corrected QT interval according to Bazett formula, QTIIc = heart rate corrected QT interval in lead DII according to Bazett formula, multiple R = multiple correlation coefficient, R square = coefficient of determination, adjusted R = the coefficient of determination adjusted for the number of independent variables in the regression model

Predictor variable	Predicted variable	Sensitivity (95% CI)	Specificity (95% CI)
Anemia	QTc > 450ms	0.56 (0.35-0.74)	0.54 (0.24-0.81)
Anemia	QTIIc > 450ms	0.66 (0.35-0.88)	0.54 (0.33-0.73)
Anemia	QTd > 60ms	0.5 (0.28-0.71)	0.42(0.18-0.70)
Macrocytosis	QTc > 450ms	0.36 (0.18-0.57)	0.81 (0.47-0.96)
Macrocytosis	QTIIc > 450ms	0.61 (0.32-0.84)	0.73 (0.51-0.88)
Macrocytosis	QTd > 60ms	0.41 (0.21-0.63)	0.85 (0.56-0.97)
Anisocytosis	QTc > 450ms	0.68 (0.46-0.84)	0.91 (0.57-0.99)
Anisocytosis	QTIIc > 450ms	0.85 (0.56-0.97)	0.77 (0.54-0.91)
Anisocytosis	QTd > 60ms	0.5 (0.33-0.66)	0.5 (0.33-0.66)

Table 4: Sensitivity and specificity

QTc = heart rate corrected QT interval according to Bazett formula, QTIIc = heart rate corrected QTII according to Bazett formula, QTd = QT dispersion; anemia was diagnosed according to the World Heatlh Organization criteria: hemoglobin levels < 12 g/dL in women and < 13 g/dL in men, macrocytosis was defined as mean corpuscular volume > 97 fl and anisocytosis as red cell distribution width (RDW) >15%, CI = confidence interval