Association between C-reactive protein, corrected QT interval and presence of QT prolongation in hypertensive patients


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Abstract C-reactive protein (CRP) and corrected QT (QTc) interval are predictors of cardiovascular disease. Whether CRP is associated with QTc interval and QT prolongation is unknown in hypertensive patients. We recruited hypertensive patients from a cardiovascular clinic in a tertiary medical center in Taiwan. All received standard 12-lead electrocardiogram examination. QT prolongation was defined as QTc interval ≥440 ms in men or ≥450 ms in women. High-sensitive CRP kits were used for the measurement of the CRP levels. A total of 466 consecutive patients were finally enrolled. Mean age was 60.6 ± 12.0 years. CRP level was correlated with QTc interval (p < 0.001) and presence of QT prolongation (p = 0.014). Multivariate regression analysis showed that CRP level (p = 0.001), age (p = 0.004), sex (p < 0.001), height (p = 0.001), low-density lipoprotein (p = 0.041), and QRS interval (p < 0.001) were associated with QTc interval. Furthermore, CRP level [odds ratio (OR) = 1.203, 95% confidence interval (CI) = 1.027–1.410, p = 0.022], age (OR = 1.040, 95% CI = 1.010–1.071, p = 0.009), waist (OR = 1.033, 95% CI = 1.000–1.066, p = 0.047), triglyceride (OR = 0.993, 95% CI = 0.987–0.999, p = 0.021) and QRS interval (OR = 1.046, 95% CI = 1.028–1.065, p < 0.001) independently predicted the...
Introduction

Framingham risk score, using age, sex, cholesterol, hypertension, and smoking, as a tool to assess the risk of coronary heart disease (CHD) has been used for decades. However, Framingham risk score tends to falsely reassure persons deemed to be at low risk [1,2]. The addition of laboratory testing to the traditional risk factors has been suggested to improve the 10-year risk assessment [3]. C-reactive protein (CRP) is the most extensively studied of numerous inflammatory biomarkers potentially linked to underlying atherosclerosis and subsequent cardiovascular disease (CVD). Several meta-analyses have found a significant relationship between baseline serum CRP and subsequent CHD or CVD [4–11]. Evaluation of CRP values in predicting the likelihood of CHD has been recommended [12]. CRP had ever been considered as a probable risk assessment biomarker for those with metabolic syndrome and hypertension [13].

QT interval is the time from the start of the Q wave to the end of the T wave in the electrocardiogram and represents the beginning of ventricular depolarization to the end of ventricular repolarization. Prolongation of corrected QT (QTc) interval is associated with an increased risk of life-threatening cardiac arrhythmia and sudden death [14]. Furthermore, hypertension is known to be associated with an increased prevalence of prolonged QTc interval [15].

Although CRP and QTc interval are independent risk factors for hypertensive patients, few studies have reported the association between CRP and QTc interval in these patients [16]. In this study, our aim was to investigate the correlation of CRP, QTc interval and presence of QTc prolongation in hypertensive patients who are known as the high-risk population for future cardiovascular disease [17].

Materials and methods

Patient characteristics

This population-based cross-sectional study was conducted from January 2007 to December 2009. In total, 466 patients with hypertension followed at a cardiovascular clinic in a tertiary medical center in Taiwan were enrolled in the study. The inclusion criteria were: (1) diagnosed as essential hypertension; and (2) with regular cardiovascular outpatient clinic follow-up for at least 6 months. Exclusion criteria were: (1) patients with CRP > 10 mg/dL; and (2) patients who suffered from acute illness at the time of enrollment.

Definition and calculation

Hypertensive patients were diagnosed based on hypertension guidelines when systolic blood pressure is ≥ 140 mmHg, diastolic blood pressure is ≥ 90 mmHg, or patients who received hypertension drugs.

QT interval is the time from the start of the Q wave to the end of the T wave in the electrocardiogram. The QT interval and R–R interval were automatically measured on a computer screen using a digital caliper at a screen rate of 100 mm/second. The means of the QT intervals and R–R intervals were obtained by measuring the QT intervals and R–R intervals of three consecutive beats in each lead. The QT interval is dependent on the heart rate: the faster the heart rate the shorter of the QT interval. We used Bazett’s formula to calculate heart rate-corrected QT interval: maximal mean QT interval/(mean R–R interval)^0.5. QTc prolongation was defined as QTc interval ≥ 440 ms in men and ≥ 450 ms in women [16].

Measurement

Study participants underwent a detailed review of their medical history consisting of patients’ age, sex, height, weight, body mass index, and waist. Biochemistry laboratory measurements were done including fasting glucose, 2 hours postprandial glucose, glycated hemoglobin, blood urea nitrogen, blood creatinine, albumin, urine albumin and complete lipid profiles including total cholesterol, triglyceride, low- (LDL) and high-density lipoprotein, and antihypertension drugs including diuretic and beta blocker and statin. All measurements were analyzed at the central laboratory of Kaohsiung Medical University Hospital, Kaohsiung, Taiwan. High-sensitivity CRP kits were used to measure CRP levels.

Statistical analysis

All continuous data were expressed as mean ± standard deviation. Chi-square test and Wilcoxon rank-sum test were used to compare categorical data and nonparametric data respectively. The t test was used for analysis between continuous variables. Multiple and binary regression analysis were used to adjust the covariates. Age, sex, height, QRS, CRP, and LDL were added into multiple regression analysis. Age, waist, QRS, CRP, and triglyceride were added into binary regression analysis for adjustment. All tests were two-sided, and the level of significance was established as \( p < 0.05 \).
Results

The study group consisted of 466 consecutive hypertensives and 250 (53.6%) participants were men. Ages ranged from 26 years to 91 years (mean, 60.55 ± 12.04 years). QTc interval ranged from 277 ms to 563 ms. Overall, 43 patients (9.23%) were found to have QTc prolongation.

Baseline characteristics between those with and without QT elongation

Table 1 demonstrates the characteristics between patients with normal and prolonged QTc interval. Comparing to those with normal QTc interval, patients with QTc prolongation were significantly older (age 66.66 ± 12.71 years vs. 59.93 ± 11.81 years, p < 0.001), had increased waist (94.27 ± 12.25 cm vs. 90.62 ± 10.78 cm, p = 0.038), higher CRP (2.43 ± 1.96 mg/L vs. 1.72 ± 1.78 mg/L, p = 0.014), blood urea nitrogen (18.67 ± 7.72 mg/dL vs. 15.68 ± 8.81 mg/dL, p = 0.032), and blood creatinine (1.09 ± 0.50 mg/dL vs. 0.92 ± 0.27 mg/dL, p = 0.033). The percentages of use of statin, diuretic, and β-blocker were similar between the two groups.

Correlation between baseline characteristics and QTc interval

Table 2 demonstrates that the QTc interval was positively correlated with QRS interval (r = 0.232, p < 0.001), CRP (r = 0.170, p < 0.001), and age (r = 0.242, p < 0.001). The

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 466)</th>
<th>Normal (n = 423)</th>
<th>Prolongation (n = 43)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.55 ± 12.04</td>
<td>59.93 ± 11.81</td>
<td>66.66 ± 12.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>250 (53.6)</td>
<td>227 (53.57)</td>
<td>23 (53.5)</td>
<td>0.982</td>
</tr>
<tr>
<td>Height, cm</td>
<td>160.96 ± 8.22</td>
<td>161.08 ± 8.24</td>
<td>159.83 ± 8.01</td>
<td>0.345</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69.60 ± 12.15</td>
<td>69.57 ± 12.01</td>
<td>69.88 ± 13.59</td>
<td>0.872</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.79 ± 3.83</td>
<td>26.73 ± 3.67</td>
<td>27.41 ± 5.22</td>
<td>0.410</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>90.96 ± 10.96</td>
<td>90.62 ± 10.78</td>
<td>94.27 ± 12.25</td>
<td>0.038</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>87.61 ± 14.72</td>
<td>86.30 ± 12.72</td>
<td>100.56 ± 24.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>1.79 ± 1.80</td>
<td>1.72 ± 1.78</td>
<td>2.43 ± 1.96</td>
<td>0.014</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>113.90 ± 24.67</td>
<td>114.19 ± 24.81</td>
<td>111.16 ± 23.38</td>
<td>0.444</td>
</tr>
<tr>
<td>Postprandial glucose, mg/dL</td>
<td>141.95 ± 51.94</td>
<td>141.22 ± 52.39</td>
<td>147.07 ± 47.42</td>
<td>0.346</td>
</tr>
<tr>
<td>HbA1C, %</td>
<td>6.10 ± 0.90</td>
<td>6.10 ± 0.89</td>
<td>6.15 ± 0.98</td>
<td>0.737</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>187.76 ± 41.87</td>
<td>188.97 ± 41.94</td>
<td>175.86 ± 39.72</td>
<td>0.050</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>138.21 ± 82.87</td>
<td>140.59 ± 84.72</td>
<td>114.81 ± 57.48</td>
<td>0.052</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dL</td>
<td>111.67 ± 34.20</td>
<td>112.62 ± 34.06</td>
<td>102.32 ± 34.52</td>
<td>0.060</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dL</td>
<td>42.80 ± 20.46</td>
<td>42.55 ± 20.96</td>
<td>45.30 ± 14.50</td>
<td>0.401</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>4.28 ± 0.26</td>
<td>4.29 ± 0.26</td>
<td>4.22 ± 0.28</td>
<td>0.107</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>15.96 ± 8.75</td>
<td>15.68 ± 8.81</td>
<td>18.67 ± 7.72</td>
<td>0.032</td>
</tr>
<tr>
<td>Blood creatinine, mg/dL</td>
<td>0.93 ± 0.30</td>
<td>0.92 ± 0.27</td>
<td>1.09 ± 0.50</td>
<td>0.033</td>
</tr>
<tr>
<td>Urine albuminuria, mg/g</td>
<td>42.12 ± 148.90</td>
<td>42.01 ± 151.38</td>
<td>53.97 ± 122.84</td>
<td>0.616</td>
</tr>
<tr>
<td>Statin</td>
<td>171 (36.7)</td>
<td>155 (36.6)</td>
<td>16 (37.2)</td>
<td>0.941</td>
</tr>
<tr>
<td>Diuretics</td>
<td>232 (49.8)</td>
<td>207 (48.9)</td>
<td>25 (58.1)</td>
<td>0.250</td>
</tr>
<tr>
<td>β-blocker</td>
<td>310 (66.5)</td>
<td>284 (67.1)</td>
<td>26 (60.5)</td>
<td>0.377</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± SD, unless otherwise indicated.

BMI = body mass index; BUN = blood urea nitrogen; CRP = C-reactive protein; HbA1C = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
QTc interval was negatively correlated with height ($r = -0.194$, $p < 0.001$), weight ($r = -0.115$, $p = 0.013$), LDL ($r = -0.124$, $p = 0.008$), and albumin ($r = -0.129$, $p = 0.005$).

Independent predictors in regression analysis

Multivariable model showed that CRP ($p = 0.001$), QRS interval ($p < 0.001$), LDL ($p < 0.041$), age ($p < 0.004$), sex ($p < 0.001$), and height ($p = 0.001$) were independent predictors for QTc interval (Table 3). Binary logistic regression analysis demonstrated that age [odds ratio (OR) = 1.040; 95% confidence interval (CI) = 1.010–1.071, $p = 0.009$], waist (OR = 1.033; 95% CI = 1.000–1.066, $p = 0.047$), CRP (OR = 1.203; 95% CI = 1.027–1.410, $p = 0.022$), QRS (OR = 1.046; 95% CI = 1.028–1.065, $p < 0.001$), and triglyceride (OR = 0.993; 95% CI = 0.987–0.999, $p = 0.021$) were significantly independent predictors of QTc prolongation in the hypertensive patients (Table 4).

Discussion

There were three major findings in this cross-sectional study in hypertensive patients. First, CRP is a significant predictor for the QTc interval and presence of QT prolongation. Second, age is also an independent factor associated with QT parameters in the hypertensive patients. Third, waist is independently associated with the presence of QT prolongation.

Hypertension is one of the well-known risk factors of coronary heart disease in the Framingham risk score [1,2]. Patients with hypertension and especially those with left ventricular hypertrophy are at an increased risk of sudden cardiac death [18–20]. QT interval is a measure of the duration of ventricular depolarization and repolarization. Some studies demonstrate the correlation with QTc interval and hypertension. Akintunde et al. [15] showed that maximum QTc interval were significantly higher among patients with hypertension than that without hypertension. Mozos and Serban [21] concludes that hypertension is associated with an increased prevalence of prolonged QT interval and left ventricular hypertrophy is associated with prolonged QT interval. Because prolonged QTc interval is associated with an increased risk of life-threatening cardiac arrhythmia and sudden death, it is mandatory to find factors associated with QTc interval and QT prolongation in hypertensive patients [14].

Inflammation is central to the initiation and progression of atherosclerosis and to triggering CVD events [22]. CRP is the most extensively studied inflammatory biomarker potentially linked to underlying atherosclerosis and subsequent CVD. The Multiple Risk Factor Intervention Trial was the first of many primary prevention, prospective epidemiological studies to show a strong relationship between levels of CRP and mortality from CHD in high-risk middle-aged men [23]. In the Women’s Health Study, CRP was a stronger predictor of cardiovascular events than LDL-C, which is an established causative biological marker of atherosclerosis [24]. The correlation between CRP and QTc has been demonstrated in two studies. Kazumi et al. [25] showed that CRP is independently related to QTc interval in young apparently healthy men. Kim et al. showed that prolonged QTc interval in middle aged men and women is associated with the elevated CRP, independent of confounding factors [16]. CRP had been suggested as a risk assessment biomarker for hypertensive patients [26]. However, there is no study to investigate the correlation between CRP and QTc interval in the hypertensive patients. Our research first found that CRP is an independent predictor of QTc interval and presence of QT prolongation in hypertensive patients.

Some cross-sectional population studies have investigated the impact of age on QTc interval and showed that QTc interval prolonged with increasing age [27,28]. Our previous longitudinal study also showed that maximal QTc interval significantly increased during a 4-year follow up in healthy elders [29]. Compatible with previous study, our research also demonstrates a positive correlation between age and QTc interval in the hypertensive patients.

Obesity causes significant abnormalities in cardiac morphology including left atrial enlargement, left ventricular geometric changes and diastolic dysfunction [30–33]. In addition to morphological changes, obesity may lead to atrial and ventricular repolarization anomalies and QT interval prolongation [34,35]. Although both QT prolongation and obesity are associated with ventricular arrhythmia and sudden cardiac death, the relationship between obesity and QTc interval prolongation is not clear. Arslan et al. [35] observed that QTc interval in young men with uncomplicated obesity is longer than in healthy individuals. Park and Swan [36] showed that QTc interval positively associated with upper body obesity in premenopausal women. In our study, there is a positive correlation between waist and the

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Standard error</th>
<th>T</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>2.494</td>
<td>0.724</td>
<td>3.446</td>
</tr>
<tr>
<td>QRS</td>
<td>0.474</td>
<td>0.091</td>
<td>5.231</td>
</tr>
<tr>
<td>Age</td>
<td>0.344</td>
<td>0.120</td>
<td>2.880</td>
</tr>
<tr>
<td>Sex</td>
<td>13.398</td>
<td>2.739</td>
<td>4.892</td>
</tr>
<tr>
<td>Height</td>
<td>-0.593</td>
<td>0.176</td>
<td>-3.379</td>
</tr>
<tr>
<td>LDL</td>
<td>-0.080</td>
<td>0.039</td>
<td>-2.054</td>
</tr>
</tbody>
</table>

CRP = C-reactive protein; LDL = low-density lipoprotein.
presence of prolonged QTc interval. These results may imply that central obesity correlates with abnormal electrical activity in hypertensive patients. Because studies have demonstrated that weight loss may shorten QTc interval, body weight control may provide additional benefit for the hypertensive patients [37–40].

Several limitations of our study should be considered. First, in this cross-sectional study, the results are primarily hypothesis-generating findings, rather than conclusive results. Therefore, enrollment of more patients for propensity score matching and a longitudinal study are needed to confirm the hypothesis. Second, 466 hypertension patients were recruited from a tertiary medical center, selection bias could exist and our patients may not represent the general population. Third, hypertensive patients in this study were not medication naïve. It is well known that several medications such as statin, β-blocker, and diuretics can influence CRP levels. However, we found that use of above-mentioned drugs was not related with QT parameters.

In conclusion, because CRP is an independent predictor of QTc interval and presence of QT prolongation in the hypertensives, it could be considered in the risk assessment for the hypertensives.

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References


