Prolonged QTc Interval and High B-Type Natriuretic Peptide Levels Together Predict Mortality in Patients With Advanced Heart Failure

Bojan Vrtovec, MD, PhD; Reynolds Delgado, MD; Aly Zewail, MD; Cynthia D. Thomas, RN; Barbara M. Richartz, MD; Branislav Radovancevic, MD

**Background**—The role of QTc interval prolongation in heart failure remains poorly defined. To better understand it, we analyzed the QTc interval duration in patients with heart failure with high B-type natriuretic peptide (BNP) levels and analyzed the combined prognostic impact of prolonged QTc and elevated BNP.

**Methods and Results**—QTc intervals were measured in 241 patients with heart failure who had BNP levels >400 pg/mL. QT interval duration was determined by averaging 3 consecutive beats through leads II and V 4 on a standard 12-lead ECG and corrected by using the Bazett formula. QTc intervals were prolonged (>440 ms) in 122 (51%) patients and normal in 119 (49%). The BNP levels in these 2 groups were not significantly different (786±321 pg/mL in the prolonged QTc group versus 733±274 pg/mL in the normal QTc group, P=0.13). During 6 months of follow-up, 46 patients died, 9 underwent transplantation, and 17 underwent left ventricular assist device implantation. The deaths were attributed to pump failure (n=24, 52%), sudden cardiac death (n=18, 39%), or noncardiac causes (n=4, 9%). Kaplan-Meier survival rates were 3 times higher in the normal QTc group than in the prolonged QTc group (P<0.0001). On multivariate analysis, prolonged QTc interval was an independent predictor of all-cause death (P=0.0001), cardiac death (P=0.0001), sudden cardiac death (P=0.0004), and pump failure death (P=0.0006).

**Conclusions**—Prolonged QTc interval is a strong, independent predictor of adverse outcome in patients with heart failure with BNP levels >400 pg/mL. (*Circulation. 2003;107:1764-1769.*)

**Key Words:** heart failure ■ prognosis ■ mortality ■ natriuretic peptides

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Q Tc interval prolongation has been proposed as a risk factor for ventricular arrhythmia and death in an apparently healthy population,1 in patients after myocardial infarction,2 and in diabetic patients.3 However, the data on the predictive power of QTc interval duration in patients with heart failure are relatively scarce and variably negative and positive. For example, in dofetilide-treated patients with moderate to severe heart failure and reduced left ventricular systolic function, a short baseline QTc interval was associated with reduced mortality rates.4 QTc interval prolongation has also been shown to correlate with an increased 6-year mortality rate in patients after myocardial infarction with clinical signs of heart failure.5

However, the United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-HEART) indicated that QTc interval has no multivariate prognostic value in predicting all-cause death in patients with mild to moderate heart failure.6 Furthermore, QTc interval duration was not a significant predictor of cardiac death or sudden cardiac death in a group of patients with heart failure with New York Heart Association (NYHA) class II-IV function and left ventricular ejection fraction <35%.7

Recently, the measurement of plasma B-type natriuretic peptide (BNP) has been suggested as a cost-effective method for predicting the outcome of patients with heart failure.8 Indeed, BNP levels correlate with functional deterioration and increased mortality rates.9 Up to 50% of deaths of patients with heart failure may be due to an arrhythmia rather than deterioration of pump function,10 and increased BNP levels have been shown to predict sudden death in these patients.11 Thus, it is possible that high BNP levels may be related to both mechanical dysfunction and arrhythmic instability in patients with heart failure.

The aim of our study was to investigate QTc interval duration in the presence of high BNP levels and to analyze the
combined impact of prolonged QTc and elevated BNP on mortality rates in patients with advanced heart failure.

Methods

Patients
We reviewed the data on all patients with heart failure referred to the Heart Failure Center at the Texas Heart Institute at St Luke’s Episcopal Hospital from May 1, 2001, to December 1, 2001. From this cohort, we selected patients with BNP levels >400 pg/mL, who had been in NYHA class III or IV for at least 2 months before referral and evaluation here. Patients with pacemakers or implantable cardioverter-defibrillators and patients taking type III antiarrhythmic drugs were excluded.

BNP Measurement
All plasma BNP levels were measured at the time of evaluation. Blood was collected into an EDTA-coated tube containing apyrase, immediately placed on ice for up to 4 hours, and then centrifuged at 4500 rpm for 15 minutes at 0°C. The serum was extracted and stored at −80°C until BNP assay. All BNP assays were performed with a commercially available kit (Triage BNP Test; Biosite Diagnostics, Inc).

QTc Interval Measurement
At the time of evaluation, resting, 12-lead ECGs were recorded at a paper speed of 25 mm/s on a Marquette Resting ECG recorder (Marquette Electronics Inc). Two independent observers who were blinded to the clinical and survival data determined QT interval duration. In accordance with the latest recommendations for clinical QT interval measurement, QT interval duration was recorded for 3 consecutive beats through leads II and V6. With calipers used on printed ECGs, each QT interval was measured from the beginning of the QRS complex to the visual return of the T wave to the isoelectric line. When the T wave was interrupted by the U wave, the end of the T wave was defined as the nadir between the T and the U wave. When the nadir was not clearly visible or the maximal T-wave amplitude in leads II or V4 did not exceed 0.25 mV, the patient was excluded from the study. Also excluded were patients with evidence of arrhythmias or pacemaker rhythms. Heart rate correction was done by use of the Bazett formula, and QTc interval duration was defined as the mean duration of all QTc intervals measured. Prolonged QTc was defined as a QTc interval >440 ms.

Follow-Up and End Points
Patients were followed over a period of 6 months. The primary end point was all-cause death. The secondary end points were cardiac death, sudden cardiac death, pump failure death, and left ventricular assist device (LVAD) implantation. Cardiac causes of death included sudden cardiac death and pump failure. Sudden cardiac death was defined as either a witnessed cardiac arrest or death within 1 hour after the onset of acute symptoms, or an unexpected death in a patient known to have been well within the previous 24 hours. Pump failure death was defined as a death resulting from multiorgan failure caused by heart failure progression.

Statistical Analysis
Continuous variables were expressed as mean±SD. Differences between survivors, patients who died of pump failure, and patients who died of sudden death were analyzed by means of 1-factor ANOVA followed by Tukey’s test for continuous variables. Comparisons of categoric variables were made by use of a χ² test. Univariate and multivariate stepwise Cox proportional hazard regression analyses were performed to identify independent predictors of all-cause death, cardiac death, sudden cardiac death, pump failure death, and LVAD implantation. The probability value for entering and staying in the model was set at 0.05. The Kaplan-Meier method was used to analyze and compare survival in the prolonged and normal QTc groups. A value of P<0.05 was considered significant.

Results

Patient Characteristics
Of 371 patients eligible for the study, 63 were excluded because they had BNP levels >400 pg/mL, and 7 were excluded because they did not have NYHA class III or IV function. Of the remaining 301 patients, we excluded 13 (4%) who were taking type III antiarrhythmic drugs. Furthermore, 47 patients (16%) were excluded because of ECG abnormalities including atrial fibrillation (n=34), pacemaker rhythm (n=9), and low T-wave amplitude or inadequate definition of T-wave offset (n=4).

Of the remaining 241 patients, 46 died (19%), 9 (4%) underwent heart transplantation, and 17 (7%) underwent LVAD implantation during the follow-up period. Of the 46 deaths, 24 were attributed to pump failure, 18 to sudden cardiac death, and 4 to noncardiac causes. Baseline patient characteristics are displayed in Table 1, according to clinical outcome.

QTc Interval Duration and BNP Levels
In our study, the intraobserver relative error of QTc measurements was 3.2%. Mean QTc interval duration was significantly longer in patients who died of pump failure (491±31 ms; P<0.001) and in patients who died of sudden cardiac death (480±42 ms; P<0.001) than it was in survivors (438±43 ms). With 440 ms used as the cutoff value, the QTc interval was prolonged in 122 patients (51%) and normal in 119 (49%). A prolonged QRS complex (>120 ms) was present in 31 patients with QTc interval prolongation (25%) and in 18 patients with a normal QTc interval (15%) (P=0.08). There was no significant difference in BNP levels between patients with a prolonged QTc (786±321 pg/mL) and patients with a normal QTc (733±274 pg/mL) (P=0.13).

QTc Interval and Outcome
At 6 months, the all-cause mortality rate was significantly higher in the prolonged QTc group (39/122, 32%) than in the normal QTc group (7/119, 6%) (P<0.0001). The same was true of the pump failure mortality rate (22/122 [18%] versus 2/119 [2%], P<0.0001) and the sudden death mortality rate (15/122 [12%] versus 3/119 [2%], P<0.001) (Figure 1). The QTc interval was prolonged in 14 patients (82%) and normal in 3 patients (8%) who subsequently underwent LVAD implantation (P=0.004).

Univariate and Multivariate Predictors of Outcome
The results of the univariate and multivariate Cox proportional hazards regression analysis of all-cause death, cardiac death, sudden cardiac death, pump failure death, and LVAD implantation at 6 months are presented in Tables 2 and 3. Both prolonged QTc and elevated BNP predicted all-cause, cardiac, and pump failure death. Only prolonged QTc predicted sudden cardiac death and LVAD implantation.

Kaplan-Meier Survival Estimation
Despite the similar BNP levels in both study groups, survival as evaluated by Kaplan-Meier analysis was 3 times higher in the normal QTc group than in the prolonged QTc group (P<0.0001) (Figure 2).
The results of our study indicate that QTc interval prolongation is an adverse prognostic sign in patients with heart failure with BNP levels $\geq 400$ pg/mL and that prolonged QTc interval correlates with increased sudden cardiac death and pump failure death in this patient population. They also indicate that the degree of plasma BNP elevation is an independent predictor of all-cause, cardiac, and pump-failure death but not of sudden cardiac death within this patient cohort.

**Discussion**

The results of our study indicate that QTc interval prolongation is an adverse prognostic sign in patients with heart failure with BNP levels $\geq 400$ pg/mL and that prolonged QTc interval correlates with increased sudden cardiac death and pump failure death in this patient population. They also indicate that the degree of plasma BNP elevation is an independent predictor of all-cause, cardiac, and pump-failure death but not of sudden cardiac death within this patient cohort.

**QTc Interval Duration and High Plasma BNP Levels**

Elevated BNP levels are not only associated with left ventricular systolic and diastolic dysfunction, but they are also present in patients with left ventricular hypertrophy, atrial fibrillation, and valve disease. This suggests that BNP is more than an indicator of elevated intracardiac pressure than of specific cardiac pathology.14 BNP levels $\geq 400$ pg/mL have been shown to be relatively specific for cardiac pressure elevation due to left ventricular failure.10 Myocardial stretch caused by increased intracardiac pressure has been shown to slow conduction, enhance refactoriness, and trigger afterdepolarizations and ventricular ectopic beats.15–17 These changes may lead to ventricular action potential prolongation and

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**Figure 1.** Clinical outcomes at 6 months in patients classified according to baseline QTc interval duration (prolonged vs normal).
ventricular repolarization instability in patients with heart failure. 

In our study, a significant degree of myocardial stretch, as indicated by BNP levels  400 pg/mL, was accompanied by QTc prolongation in only half of the patients. This suggests that factors other than electromechanical interaction may be important in determining the QTc interval length in patients with advanced heart failure. Furthermore, patients with comparable BNP levels had a significantly different outcome when stratified according to QTc interval duration. This may reflect a different pathophysiological background for these two parameters.

**Plasma BNP Levels and Death**

Elevated plasma BNP is a powerful marker for prognosis and risk stratification in the setting of heart failure. Patients with BNP levels >480 pg/mL have been shown to have a 42% 6-month cumulative probability of heart failure admission or death, and higher BNP levels are associated with progressively worse prognosis. In our study, a significant elevation of BNP levels was associated with increased all-cause, cardiac, and pump-failure mortality rates; however, no correlation between sudden cardiac death and high BNP was found. In a recent study of patients with heart failure with left ventricular ejection fraction <35%, plasma BNP levels >130 pg/mL were associated with a significantly higher risk of sudden cardiac death than were lower BNP levels. Since we included only patients with BNP levels  400 pg/mL in the present study, the mean BNP value of our patient cohort was considerably greater than the cutoff point used in the study by Berger et al, which may account for the observed differences. Therefore, the degree of BNP elevation still remains a powerful predictor of all-cause, cardiac, and pump-failure

**TABLE 2. Univariate Analysis of Potential Predictors of All-Cause Death, Cardiac Death, Sudden Cardiac Death, Pump Failure Death, and LVAD Implantation**

<table>
<thead>
<tr>
<th></th>
<th>All-Cause Death</th>
<th>Cardiac Death</th>
<th>Sudden Cardiac Death</th>
<th>Pump Failure Death</th>
<th>LVAD Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc &gt;440 ms</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.004</td>
<td>0.0004</td>
<td>0.004</td>
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<tr>
<td>BNP &lt;700 pg/mL</td>
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<tr>
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<td>0.0004</td>
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<tr>
<td>BNP &gt;1000 pg/mL</td>
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<td>0.0002</td>
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<td>NS</td>
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<td>NS</td>
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</tbody>
</table>

All values given indicate P value. BP, Blood pressure; LVAD implant, left ventricular assist device implantation; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; and NS, not significant.

**TABLE 3. Multivariate Analysis of Potential Predictors of All-Cause Death, Cardiac Death, Sudden Cardiac Death, Pump Failure Death, and LVAD Implantation**

<table>
<thead>
<tr>
<th></th>
<th>All-Cause Death</th>
<th>Cardiac Death</th>
<th>Sudden Cardiac Death</th>
<th>Pump Failure Death</th>
<th>LVAD Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc &gt;440 ms</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.004</td>
<td>0.0006</td>
<td>11.34</td>
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<td></td>
<td>(3.71–16.53)</td>
<td>(3.94–19.31)</td>
<td></td>
<td>(2.64–48.68)</td>
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</tr>
<tr>
<td>BNP &gt;1000 pg/mL</td>
<td>0.0005</td>
<td>0.0007</td>
<td>1.76</td>
<td>0.0007</td>
<td>3.78</td>
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<tr>
<td></td>
<td>(1.18–3.36)</td>
<td>(1.01–3.07)</td>
<td></td>
<td>(1.63–8.78)</td>
<td></td>
</tr>
</tbody>
</table>

LVAD implant indicates left ventricular assist device implantation; CI, confidence interval.
death in patients with BNP levels >400 pg/mL. However, it does not appear to correlate with the risk of sudden cardiac death within this patient cohort.

QTc Interval Duration and Death
In our study population, prolonged QTc interval was a strong predictor of both pump failure death and sudden death, and the predictive value of prolonged QTc was independent from that of concomitant QRS changes. Previously, in a cohort of patients with heart failure awaiting heart transplantation, the QTc interval prolongation was inversely correlated with peak exercise oxygen consumption and was associated with increased mortality rates. Ventricular repolarization dynamics, as measured by beat-to-beat QT interval variability, has been shown not to correlate with QTc interval duration in patients with heart failure. Furthermore, QTc interval duration is significantly affected by changes in sympathetic nervous tone. Advanced heart failure is associated with extensive neuroendocrine activation, which may affect the duration of the QTc interval. Therefore, QTc prolongation in patients with heart failure appears to be more a marker of advanced disease than merely a reflection of ventricular repolarization instability. The duration of QTc interval was not shown to predict all-cause death, sudden cardiac death, or pump failure in patients on the heart transplantation waiting list. This suggests that in patients with advanced heart failure, the predictive power of QTc interval prolongation is significantly dependent on concomitant elevation of intracardiac pressure, as indicated by high plasma BNP.

QTc Interval Duration, Plasma BNP Levels, and LVAD Implantation
In the present study, a subset of patients with concomitant BNP elevation and QTc interval prolongation had a 6-month mortality rate of 32%. This outcome is comparable to the outcome of patients from the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure (REMATCH) trial who were not treated by implantation of an LVAD. QTc duration has been shown to decrease significantly after LVAD implantation, suggesting a beneficial effect of left ventricular mechanical support. Since QTc interval prolongation was the only independent predictor of the need for LVAD implantation in our patient cohort, the presence of prolonged QTc, in patients with advanced heart failure and BNP levels >400 pg/mL, may serve as a tool in selecting candidates for implantation of an LVAD.

Study Limitations
Our study and its results have several limitations. First, the study excluded a subgroup of patients with heart failure in whom heart failure progression was associated with atrial arrhythmias or with the need for permanent pacing. It also excluded patients taking type III antiarrhythmic drugs, patients with implantable cardioverter-defibrillators, and patients with BNP levels <400 pg/mL. Therefore, our results cannot be directly applied to all patients with advanced heart failure. Second, even though QT dispersion measurements have been proposed as a risk marker in advanced heart failure, they have been associated with poor reproducibility. Therefore, we did not attempt to analyze QT interval dispersion in our study. By using only leads II and V6 to determine QT interval length, we minimized the intraobserver variability.

Conclusions
QTc intervals >440 ms are associated with adverse outcomes in patients with heart failure with BNP levels >400 pg/mL. 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 advanced heart failure. It may be of particular significance in identifying those at risk who are already known to have pressure or volume overload of the left ventricle. Further studies are needed to determine its pathophysiological significance and whether it can be used with other markers to develop a multivariate risk stratification protocol that could aid in determining the need for advanced therapies.

References
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