QTc Interval Prolongation Predicts Arrhythmia Recurrence After Catheter Ablation of Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy

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**Background:** In hypertrophic cardiomyopathy (HCM) patients complicated with atrial fibrillation (AF), catheter ablation has been recommended as a treatment option. Meanwhile, prolongation of QTc interval has been linked to an increased AF incidence in the general population and to poor outcomes in HCM patients. However, whether QTc prolongation predicts arrhythmia recurrence after AF ablation in the HCM population remains unknown.

**Methods and Results:** Thirty-nine HCM patients undergoing primary AF ablation were enrolled. The ablation strategy included bilateral pulmonary vein isolation (PVI) for paroxysmal AF (n=27) and PVI plus left atrial roof, mitral isthmus and tricuspid isthmus linear ablations for persistent AF (n=12). Pre-procedural QTc was corrected by using the Bazett's formula. At a 14.8-month follow up, 23 patients experienced atrial tachyarrhythmia recurrence. Recurrent patients had longer QTc than non-recurrent patients (461.0±28.8 ms vs. 434.3±18.2 ms, P=0.002). QTc and left atrial diameter (LAD) were independent predictors of recurrence. The cut-off value of QTc 448 ms predicted arrhythmia recurrence with a sensitivity of 73.9% and a specificity of 81.2%. A combination of LAD and QTc (global chi-squared=13.209) was better than LAD alone (global chi-squared=6.888) or QTc alone (global chi-squared=8.977) in predicting arrhythmia recurrence after AF ablation in HCM patients.

**Conclusions:** QTc prolongation is an independent predictor of arrhythmia recurrence in HCM patients undergoing AF ablation, and might be useful for identifying those patients likely to have a better outcome following the procedure.

**Key Words:** Atrial fibrillation; Catheter ablation; Hypertrophic cardiomyopathy; QTc interval; Recurrence

Atrial fibrillation (AF) is the most common arrhythmia and develops in approximately 20% of adult patients with hypertrophic cardiomyopathy (HCM). This arrhythmia can be present in approximately 5% of patients at the time of diagnosis, and is associated with deterioration of clinical status and increased hospitalization, systemic thromboembolism, heart failure and death in HCM patients. While previous studies have shown that converting and maintaining sinus rhythm pharmacologically is sometimes effective in this subset of patients, catheter ablation has emerged as a treatment strategy for symptomatic drug-resistant AF in HCM patients. However, a high recurrence rate has been reported with long-term follow up. Considering that multiple ablations might be required, and that there is potential risk carried with each procedure, it is important to identify which AF patients will most likely benefit from catheter ablation and those who will most likely not benefit, especially in those with structural heart disease like HCM. In addition to the conventional risk factors such as left atrial diameter (LAD), the type of AF and age, new predictors for procedural outcome, are needed to increase the ability to identify patients at high risk of recurrence following AF ablation.

The pathological feature of HCM is eccentric hypertrophy of ventricular myocardium due to sarcomeric gene mutation. As a cardiomyopathy, however, myocardial hypertrophy in HCM is not necessarily limited in ventricle but can also be seen in the atria. Previous studies indicated that HCM is associated with cardiac electrophysiological changes, manifested as...
prolonged QT interval\textsuperscript{10} and ventricular arrhythmias.\textsuperscript{18,19} Because the atrial and ventricular myocytes might have similar cardiac ion channel abnormality due to the shared pathological and genetic mechanism of HCM, the QT/corrected QT (QTc) interval, a measurement of ventricular depolarization/repolarization time,\textsuperscript{20} could indirectly reflect the electrophysiological profile of atrial myocardium. Actually, QT prolongation has been associated with an increased AF incidence in the general population.\textsuperscript{21,22} Under the condition of HCM, one could hypothesize that the high prevalence of AF is not only a result of atrial overload, but an electrophysiological consequence of atrial myocardial disease that could be evaluated by an abnormal QT/QTc interval. In this study, we investigated the relationship of QTc and arrhythmia recurrence after catheter ablation of AF, and whether this measurement can be used to predict procedural outcome in HCM patients.

**Methods**

**Study Population**
From November 2006 to June 2013, 39 HCM patients underwent their primary catheter ablation of symptomatic, drug-resistant AF (paroxysmal AF n=27; persistent AF n=12) at Beijing Anzhen Hospital and were included in this study. The diagnosis of HCM followed the guidelines by American College of Cardiology/European Society of Cardiology (ACC/ESC).\textsuperscript{23,24} Informed consent was obtained from each patient.

**Electrocardiographic Analysis**
A standard 12-lead electrocardiogram (ECG) was registered 1 day prior to the procedure in all patients. Two experienced cardiologists who were blinded to the patients’ medical history manually measured the QT interval in lead II or V5 when possible. The QTc interval was calculated by using Bazett’s formula (QTc=QT/RR\textsuperscript{\textsuperscript{1/2}}). If a patient had AF, the QTc was measured from 3 consecutive cardiac cycles and then a mean value was used for analysis.\textsuperscript{25} Two investigators (S.-N.W. and N.L.) independently assessed the QT interval on all ECGs. There was a very high degree of reproducibility of QTc measurement, as reflected by a correlation coefficient of 0.95.

**Echocardiography Study**
Before the procedure, all patients underwent transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) (Vivid 7; GE). On TTE, standard echocardiographic parameters were obtained by utilizing the techniques recommended by the American Society of Echocardiography (ASE) guidelines.\textsuperscript{26} Specifically, the site and extent of maximum left ventricular wall thickness (MLVWT) were determined on both a M mode and 2D module. On TEE, the left atrial (LA) and LV appendage (LAA) thrombus were excluded.

| Variable                      | Total     | QTc ≤448 ms | QTc >448 ms | P value* |
|-------------------------------|-----------|-------------|-------------|----------|
| No.                           | 39        | 19          | 20          | 0.465    |
| Age (years)                   | 54.0±10.1 | 54.9±9.4    | 53.2±10.9   | 0.608    |
| Sex (M/F)                     | 29/10     | 14/5        | 15/5        | 0.927    |
| Paroxysmal AF (%)             | 27 (69)   | 14 (74)     | 13 (65)     | 0.569    |
| AF duration (months)          | 69.8±67.3 | 81.7±77.0   | 58.5±56.1   | 0.288    |
| Body mass index (kg/m\textsuperscript{2}) | 26.3±3.7 | 26.5±4.0    | 26.2±3.8    | 0.539    |
| BNP (pg/ml)                   | 1,271.0±1,676.8 | 1,413.4±2,356.6 | 1,138.2±653.8 | 0.047 |
| LAD (mm)                      | 45.8±6.7  | 44.7±7.2    | 46.8±6.3    | 0.340    |
| MLVWT (mm)                    | 19.7±3.8  | 18.2±3.3    | 21.2±3.8    | 0.012    |
| LVDD (mm)                     | 45.0±5.4  | 45.8±6.1    | 44.3±4.7    | 0.384    |
| LVMi (g/m\textsuperscript{2}) | 226.5±81.3 | 217.9±95.8 | 233.4±69.4 | 0.664    |
| IVST/LVPWT ratio              | 1.56±0.40 | 1.47±0.34   | 1.63±0.44   | 0.225    |
| LVEF (%)                      | 64.9±8.6  | 62.9±7.0    | 66.8±9.7    | 0.159    |
| Heart rate (bpm)\textsuperscript{a} | 66.6±9.9 | 63.2±7.8    | 70.0±10.6   | 0.034    |
| QT (ms)                       | 433.1±40.1 | 421.3±36.1 | 444.4±41.3 | 0.357    |
| QTc (ms)                      | 450.1±28.1 | 427.3±13.7 | 471.7±19.8 | <0.001   |
| Procedure time (min)          | 177.4±57.9 | 174.7±71.1 | 179.5±46.6 | 0.095    |
| Fluoroscopic time (min)       | 32.9±16.2  | 28.9±14.1   | 17.3±3.9    | 0.583    |

All values are expressed as mean-standard deviation or n (%). AF, atrial fibrillation; BNP, brain natriuretic peptide; IVST, interventricular septum thickness; LAD, left atrial diameter; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; LVPWT, left ventricular posterior wall thickness; MLVWT, maximum left ventricular wall thickness. *P value refers to comparison between subjects with a QTc ≤448 ms and a QTc >448 ms. \textsuperscript{a}Average heart rate on pre-procedural electrocardiogram from where QTc was measured and calculated.
persistent AF included PVI and linear ablation across the LA roofline, mitral isthmus and CTI. If AF sustained or converted to an organized atrial tachyarrhythmia, cardioversion was applied. Achievement of PVI and complete conduction block of the 3 linear lesions were used as the procedural end-point in persistent AF patients. Radiofrequency (RF) energy was delivered with a maximum temperature of 45°C, a power up to 35 W, and a flow rate of 17 ml/min. When ablating inside CS, the maximum power was decreased to 25 W, while the flow rate was increased to 30 ml/min. At each site, the ablation time was restricted to 30–60 s but no more than 30 s when ablating on the LA posterior wall and inside CS.

Follow up
After the procedure, all patients received an AAD if there were no contraindications or intolerance. The drugs were discontinued if no recurrent atrial tachyarrhythmia was detected after 2 or 3 months. All patients had warfarin for at least 3 months after the procedure. All patients were followed up with a 12-lead ECG and 24-h Holter recordings before discharge and at 1, 3, 6 and 12 months after the ablation procedure, and every 6 months subsequently beyond 12 months. A new ECG was obtained when the patients were symptomatic. Additionally, telephone interviews were conducted with all patients by a physician with a 6-month interval. After the blanking period (3 months) following the procedure, any episode of confirmed atrial tachyarrhythmia (documented by an ECG or Holter recordings) lasting for at least 30 s was considered as recurrence in the absence of AAD.

Statistical Analysis
All data were prospectively entered in a central hub database approved by the Institutional Ethical Committee. Continuous data are expressed as mean±SD and compared by using a 2-tailed t-test, while categorical data are reported as counts and percentage (%). A linear regression model was used to correlate QTc with MLVWT. Variables that were statistically significant in univariate regression models (P value <0.1) were included in a multivariate regression model using an “enter” method to determine whether they remained significant after adjustment for potential confounders. The superiority of the combination of LAD and QTc over LAD alone in predicting arrhythmia recurrence was studied by calculating the improvement in the global chi-square. A Kaplan-Meier curve and a Log rank test were utilized to compare arrhythmia-free survival.

Receiver operating characteristic curves were built to establish the values that represented the cut-off point with the greatest sensitivity and specificity to predict arrhythmia recurrence.

Results
Overall Procedural Outcome in HCM Patients
A total of 39 HCM patients with AF (27 paroxysmal AF, 12 persistent AF) were included in the study. All patients had severe asymmetric (eccentric) left ventricular hypertrophy (Table); however, none of them had previous surgical myectomy or percutaneous transluminal septal myocardial ablation (PTSMA), or had history of decompensated heart failure or was previously diagnosed with hypertension. Ten of these HCM patients had mild mitral valve regurgitation with no hemodynamic significance. Clinical characteristics of these patients are summarized in Table.

The procedural end-point was achieved in all patients. After an average of 14.8 months’ follow up, 23 patients (59.0%) experienced atrial tachyarrhythmia recurrence. Patients with recurrences had a pre-procedural longer QTc interval (461.0±28.8 ms vs. 434.3±18.2 ms, P=0.002) and a larger LAD (48.7±5.6 mm vs. 41.6±5.2 mm, P=0.001) compared to those without recurrence (Figures 1A,B).

Predictor of Arrhythmia Recurrence and Subgroup Analysis
All potential confounders were entered into a Cox regression model based on prior knowledge or expected clinical relevance. The variables included in the univariate model were: gender, age, duration of AF, type of AF, LAD, MLVWT, left ventricular diastolic diameter, left ventricular ejection fraction, and QTc interval. Univariate analysis revealed that HCM patients with a longer QTc interval [hazard ratio (HR) 1.063, 95% confidence interval (CI) 1.009–1.120, P=0.021] and larger LAD (HR 1.319, 95% CI 1.064–1.636, P=0.012) were at increased risk of recurrence after AF ablation. The multivariate Cox regression analysis showed that LAD (HR 1.072, 95% CI 1.004–1.145, P=0.038) and QTc (HR 1.02, 95% CI 1.004–1.036, P=0.013) were independent predictors of recurrence. Specifically, every 10 ms prolongation in QTc was significantly associated with a higher AF recurrence rate (HR 1.227, 95% CI 1.053–1.431, P=0.009).

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The QTc interval showed a weak linear relationship with the MLVWT ($r^2=0.086$; Figure 3); however, the P value (P=0.07) was not statistically significant.

Combining QTc With LAD Better Predicted Arrhythmia Recurrence

The 39 HCM patients were further categorized by the combination of cut-off values of LAD and QTc. Of the 13 patients with a QTc >448 ms and a LAD >44.5 mm, 12 (92.3%) had recurrences during follow up after a single procedure of AF ablation, while no recurrence was observed in those with a QTc $\leq$448 ms and a LAD $\leq$44.5 mm (Figure 4).

The cut-off value of the QTc interval was 448 ms, with an area under the curve (AUC) of 0.757 and a standard deviation of 0.079 (95% CI 0.602–0.911, P=0.007); sensitivity of 73.9% and specificity of 81.2%. The cut-off value of LAD was 44.5 mm with an AUC of 0.785 and a standard deviation of 0.078 (95% CI 0.632–0.939, P=0.003); sensitivity of 73.9% and specificity of 62.5%. A Kaplan-Meier curve showed significant difference in recurrence-free survival between patients with a QTc interval >448 ms and $\leq$448 ms or with a LAD >44.5 mm and $\leq$44.5 mm (Log rank P<0.001 and P=0.022, respectively; Figures 2A,B).

Compared with those patients with a QTc $\leq$448 ms (n=19), HCM patients with a QTc >448 ms (n=20) had a thicker LV wall (18.2±3.3 mm vs. 21.2±3.8 mm, P=0.012; Table).
and a LAD >44.5 mm. The multivariate analysis indicated that a combination of LAD and QTc (global chi-square=13.209) was better than LAD alone (global chi-square=6.888, P=0.0119) or QTc alone (global chi-square=8.977, P=0.0397) in predicting arrhythmia recurrence of AF ablation in HCM patients (Figure 5).

**Discussion**

The main findings of this study include that QTc prolongation is an independent risk factor of arrhythmia recurrence in HCM patients undergoing AF ablation. A QTc >448 ms predicts atrial tachyarrhythmia recurrence with a sensitivity of 73.9% and a specificity of 81.2%. A combination of LAD and QTc is better than LAD or QTc alone in predicting recurrence after AF ablation in HCM patients.

Recently, QTc prolongation has been associated with the causative mutation, degree of myocardial hypertrophy and even appropriate implantable cardioverter defibrillator (ICD) therapy in HCM patients. Jouven et al analyzed 206 patients with a mutation in the cardiac myosin binding protein C or β-myosin heavy chain and found that the QT interval was longer in HCM patients than unaffected controls. Johnson et al documented that 13% of HCM patients had a QTc longer than 480 ms, which was associated with a higher New York Heart Association (NYHA) class at diagnosis, higher frequency of left ventricular outflow tract (LVOT) obstruction and increased MLVWT. In a study of 164 HCM patients who received an ICD, Gray et al found that appropriate ICD therapy was 3-fold more frequent in patients with prolonged QTc than those with normal QTc. The mean QTc interval of the HCM subjects in our study was 450 ms, and the QTc interval showed a trend of linear relationship with the MLVWT, which was similar to that reported by others. A longer QTc interval in HCM patient might not only reflect ventricular remodeling (ventricular hypertrophy and dilation), but be a consequence of sarcomeric gene mutation affecting membranous cardiac ion channels, myocytes disarray, and LVOT obstruction.

It is possible that the genetic mutations causing ventricular hypertrophy affects electrophysiological properties of atrial tissue as well. Messenger ribonucleic acid expression studies have shown that the expression of important ion channel complexes involved in cardiac repolarization is very similar in the atrial and ventricular myocytes. One may assume that atrial repolarization duration changes concordantly with that of ventricular myocardium and is prolonged in HCM patients. It is reasonable to use QTc as a marker of atrial myocardial disease (remodeling) in the setting of HCM, while there is no such measurement in ECG that reflects atrial repolarization time. Hence, this provides a theoretical basis of exploring the potential of QTc as a predicting factor of arrhythmia recurrence in HCM patients undergoing AF ablation.

Although catheter ablation has been proven a promising option in the treatment of AF in patients with HCM, the recurrence rate remained high, with more than half of the patients requiring multiple procedures. The 1-year sinus rhythm maintenance rate after a single procedure varied from 28% to 53%. In the present study, 41% of our patients were in sinus rhythm after a mean follow up of >14 months, which was comparable with the results published by other centers. The predictors of the efficacy of AF ablation in HCM patients remain largely unknown. Our study, for the first time, elucidated the relationship of QTc and arrhythmia recurrence in HCM patients undergoing AF ablation.

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Actually, the correlation between QTc and development of AF has been recently investigated. The Copenhagen ECG study revealed a J-shaped association, suggesting that either a prolonged or a shortened QTc interval is a risk factor of development of AF. This might also apply to HCM patients in whom QTc prolongation is quite common. Although a short atrial action potential might predispose an individual to AF, epidemiological studies indicated that a prolonged QTc interval (representing ventricular action potential duration) was also
related to an increased incidence of AF.\textsuperscript{21,22} The possible mechanism of QTc predicting AF recurrence after catheter ablation in HCM patients include: (1) atrial myopathy with similar structural and electrophysiological remodeling as the ventricular myopathy. Prolonged atrial action potential duration could induce trigger activity in the atria and then initiate AF. This was evidenced by a study by Santangeli et al, who observed that non-pulmonary vein foci were present in all HCM AF. This was evidenced by a study by Santangeli et al, who observed that non-pulmonary vein foci were present in all HCM patients undergoing a repeat AF ablation procedure;\textsuperscript{12} (2) “atrial Torsades de pointes” could mediate the susceptibility to AF, similar to the mechanism of the development of Torsades de pointes under the condition of QTc prolongation; and (3) prolonged QTc caused atrio-ventricular dyssynchrony that might worsen LA remodeling.

To the best of our knowledge, this study is the largest single-center study to date that investigated the outcome of AF ablation in HCM patients. Recently, QTc has been associated with the development of AF.\textsuperscript{21,22} It is possible that QTc might also predict the outcome of AF ablation, which has never been reported. The reason we chose a HCM population to test our hypothesis in this pilot study was based on the following understanding: (1) similar pathological changes of atrial and ventricular myocardium in HCM patients; (2) comparing to the general population, QTc prolongation at baseline is much more common in HCM patients regardless of the type of heart rhythm (AF or sinus); and (3) many HCM patients develop AF, but ablation of this arrhythmia in this specific population remains challenging. Because the present study has demonstrated that QTc prolongation is a predictor of arrhythmia recurrence following AF ablation in a HCM population, a study of a larger sample of non-HCM AF patients is warranted to generalize our findings.

Study Limitations
This was a retrospective study and included a relatively small sample of patients; however, all data were prospectively collected and entered into a database. The method of measuring and calculating QTc interval during AF has not been well-established. The Bazett’s formula we used in the present study remains the standard for clinical practice. Genetic data was not available in these patients. Further study with a larger sample size, including a test of mutation, is warranted, of which the results are expected to show the correlation among genetic background, QTc and AF ablation outcome in HCM patients.

Conclusions
Pre-procedural QTc interval is an independent predictor of arrhythmia recurrence in HCM patients undergoing AF ablation. With every 10-ns prolongation in the QTc interval, patients were 1.227-fold more likely to experience recurrence. Future studies are warranted to evaluate the effectiveness of QTc in predicting arrhythmia recurrence following AF ablation in larger HCM or non-HCM population.

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Disclosures
The authors declare that there are no conflicts of interest.

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