QRS Prolongation is Associated With High Defibrillation Thresholds During Cardioverter-Defibrillator Implantations in Patients With Hypertrophic Cardiomyopathy

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Background: Although high defibrillation threshold (DFT) is a major and unavoidable clinical problem after implantation of an implantable cardioverter defibrillator (ICD), little is known about the cause and management of a high DFT in patients with hypertrophic cardiomyopathy (HCM). The purpose of this study was to assess the predictors of a high DFT in patients with HCM.

Methods and Results: Twenty-three patients with non-dilated HCM who underwent ICD implantation were included. The DFT at the time of the device implantation was measured in all patients. The patients were divided into 2 groups, a high DFT group (DFT ≥15J, n=13) and a low DFT group (DFT <15J, n=10); and their baseline characteristics were compared. The QRS duration was longer in the high than in the low DFT group (128±31 vs 103±12 ms, respectively; P=0.02). QRS duration, left ventricular (LV) end-systolic diameter, and LV ejection fraction were significant predictors of DFT in univariate analysis. However, in multivariate analysis, the only factor significantly associated with DFT was QRS duration (P=0.002).

Conclusions: QRS duration is the most consistent predictor of a high DFT in HCM patients undergoing ICD implantation. (Circ J 2009; 73: 1028–1032)

Key Words: Defibrillation threshold; Hypertrophic cardiomyopathy; Implantable cardioverter defibrillator; QRS prolongation

A subgroup of patients with hypertrophic cardiomyopathy (HCM) is at a high risk of having ventricular tachycardia and/or ventricular fibrillation. The implantable cardioverter-defibrillator (ICD) is widely recognized as the most effective and essential therapy for this patient population.1–3 It has been demonstrated that both appropriate and inappropriate ICD discharges are frequently observed in HCM patients1–3 and this might impair quality-of-life as well as reduce battery longevity. Class III antiarrhythmic agents such as amiodarone have the potential for reducing ICD shocks4 and might improve patients’ prognosis. Furthermore, class I agents are also used in HCM patients to control atrial fibrillation or reduce the pressure gradient in the left ventricular (LV) outflow tract or mid-ventricle when an obstruction is present.5–7 The combined use of antiarrhythmic agents and an ICD in patients with HCM, and the larger volume of myocardium (caused by hypertrophy of the left ventricle) might result in a high defibrillation threshold (DFT). However, the predictors of a high DFT in patients with HCM have not been fully characterized. Thus, the purpose of this retrospective study was to evaluate the factors causing a high DFT in patients with HCM and ventricular tachycardia/ventricular fibrillation.

Methods

Study Subjects

The study population consisted of 23 consecutive patients with an established diagnosis of HCM who underwent initial implantation of an ICD with a standard transvenous lead system at the National Cardiovascular Center from 1997 through to 2005. ICDs were implanted for secondary prevention in 20 of 23 patients, defined by clinical sustained ventricular tachyarrhythmia or resuscitation from sudden cardiac death. HCM was diagnosed on the basis of echocardiographic criteria defined as the presence of LV hypertrophy in the absence of other causes of hypertrophy. These patients also met the definition and classification proposed by the 1995 World Health Organization/International Society and Federation of Cardiology Task Force8 All defibrillation leads were implanted by a left cephalic vein cutdown and positioned in the right ventricular apex. No patient had an prior pacemaker implantation, and 2 had permanent atrial fibrillation. Patients who were diagnosed with HCM who progressed to a dilated phase of HCM were excluded from the study.

ICD Implantation and DFT Testing

The following ICD models were implanted: 7220C (n=1), 7223Cx (n=6), 7227Cx (n=2), 7229Cx (n=5), 7271Cx (n=1), and 7237Cx (n=5), manufactured by Medtronic, Inc (Minneapolis, MN, USA); and the 1861 (n=3) manufac-
QRS Prolongation and DFTs in HCM

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Defibrillation threshold</th>
<th>&lt;15J (n=10)</th>
<th>≥15J (n=13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>7/3</td>
<td>9/4</td>
<td>NS</td>
</tr>
<tr>
<td>Age, years</td>
<td>52±18</td>
<td>54±16</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163±8</td>
<td>162±8</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>55±49</td>
<td>59±7</td>
<td>NS</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>103±12</td>
<td>128±31</td>
<td>0.02</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>68±16</td>
<td>58±10</td>
<td>0.09</td>
</tr>
<tr>
<td>Defibrillation threshold, J</td>
<td>10±0.4</td>
<td>18±5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Antiarrhythmic agents, n (%)</td>
<td>3 (30)</td>
<td>6 (46)</td>
<td>NS</td>
</tr>
<tr>
<td>Amiodarone, n (%)</td>
<td>2 (20)</td>
<td>4 (31)</td>
<td>NS</td>
</tr>
<tr>
<td>Disopyramide, n (%)</td>
<td>1 (10)</td>
<td>1 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>Mexiletine, n (%)</td>
<td>0 (0)</td>
<td>2 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Single coil lead system, n (%)</td>
<td>9 (90)</td>
<td>8 (62)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are mean±SD. NS, not significant; LV, left ventricular.

Table 2. Echocardiographic Measurements

<table>
<thead>
<tr>
<th>Defibrillation threshold</th>
<th>&lt;15J (n=10)</th>
<th>≥15J (n=13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>39±6</td>
<td>42±6</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-systolic diameter, mm</td>
<td>22±6</td>
<td>26±5</td>
<td>0.048</td>
</tr>
<tr>
<td>Interventricular septal thickness, mm</td>
<td>17±5</td>
<td>18±6</td>
<td>NS</td>
</tr>
<tr>
<td>LV posterior wall thickness, mm</td>
<td>13±3</td>
<td>14±8</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>286±124</td>
<td>369±211</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>178±64</td>
<td>227±26</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are mean±SD. Abbreviations see in Table 1.

Variables Assessed

The following variables were used for analysis: sex, age, height, body weight, QRS duration, LV ejection fraction quantified by radionuclide ventriculography or LV cineangiography, the use of amiodarone or class I antiarrhythmic drugs, utilization of a single-coil transvenous lead system, echocardiographic parameters including the LV end-diastolic and end-systolic diameters, interventricular septal thickness, LV posterior wall thickness, LV mass calculated from echocardiographic data by standard formulas and LV mass index (dividing the LV mass by the body surface area). The QRS duration was defined as the maximal QRS length in any lead measured manually from the first to the last sharp deflection crossing the isoelectric line using standard resting 12-lead ECG (sweep speed, 25 mm/s and 1 mV/cm standardization). The average values of QRS duration that were obtained from 2 independent investigators blinded to each other’s results were used (interobserver correlation for QRS duration was 0.941).

Statistical Analysis

The results are presented as percentages or the mean±SD, as appropriate. Several parameters in the 2 groups were compared with an unpaired Student’s t-test. Categorical variables were compared using a Fisher’s exact test. Linear regression analysis was used to determine the relationship between DFT and QRS duration. The variables with a P value <0.10 were entered into a multiple linear regression analysis to identify the independent predictors of DFT. The level of statistical significance was set at a P value <0.05.

Results

Twenty-three patients (16 men; mean age 53±17 years, range 16–77 years) were included in the analysis. None of the patients had any extreme hypertrophy (≥30 mm), and 4 patients were found to have significant LV outflow obstruction (≥30 mmHg) at rest by continuous Doppler echocardiography. The mean LV ejection fraction was 62±13%. Indications for an ICD implantation were primary prevention in 3 patients, ventricular tachycardia in 4 patients and aborted sudden cardiac death in 16 patients. At the time of device implantation, 6 patients were being treated with amiodarone (200 mg/day), 2 with sotalol and 4 with class I antiarrhythmic agents (disopyramide and mexiletine). No patient showed evidence of abnormalities in serum electrolyte concentrations and/or in acid–base equilibrium at the device implantation stage.
The ICDs were implanted without any complications, and the induction and termination of the ventricular fibrillation were successful in all patients. The DFT (energy delivered) ranged from 10J to 31J (10 patients, 10–14J; 9 patients, 15–19J; 2 patients, 20–24J; 2 patients, 25–31J). The DFTs in patients treated with amiodarone (6 patients), combined amiodarone and a class I antiarrhythmic agent (mexiletine) (1 patient), class I antiarrhythmic agents (3 patients), and sotalol (2 patients) were 16±9J, 15J, 17±7J, and 13±3J, respectively. An unacceptably high DFT (≥25J) was obtained in 2 patients who were receiving amiodarone (1 patient, 200 mg/day) or mexiletine (1 patient, 450 mg/day) at the time of the implantation (these 2 patients were included in the high DFT group). However, the DFT in these 2 patients decreased to a level with a 10J safety margin between the maximum shock energy of the ICD and the DFT after cessation of amiodarone (21J) or mexiletine (20J). Therefore, none of the patients required any additional use of a subcutaneous array or patch.

The baseline characteristics and echocardiographic measurements for the 2 groups are listed in Tables 1 and 2, respectively. The QRS duration was significantly longer in patients with a high than with a low DFT (128±31 vs 103±12 ms, respectively; P=0.02). There was a trend toward a lower LV ejection fraction in the patients with a high DFT (P=0.09). The use of amiodarone and/or class I antiarrhythmic drugs did not differ between the 2 groups. As shown in Table 2, the LV end-systolic diameter was significantly smaller in those patients with a low than with a high DFT (22±6 vs 26±5 mm, respectively; P=0.048). The LV mass and mass index exhibited no statistically significant difference between the 2 groups.

The QRS duration demonstrated a modest positive correlation with the DFT at the time of device implantation (r=0.75, P<0.0001) for the group as a whole (Figure). A multivariate analysis was performed on the 3 variables that had a P value <0.10 in the univariate analysis: QRS duration, LV end-systolic diameter, and LV ejection fraction. This analysis showed that QRS duration was the only independent predictor of DFT (P=0.002).

**Discussion**

In this study, we identified QRS duration as the only variable that was associated with a high DFT at the time of ICD implantation in patients with HCM. To the best of our knowledge, this is the first report to investigate the association between QRS duration and DFT in patients with HCM. Because of the pro-arrhythmic and/or negative inotropic effects of class I antiarrhythmic agents, the use of these drugs in patients with depressed LV function is contraindicated. Furthermore, class Ia antiarrhythmic drugs such as disopyramide or cibenzoline might lead to a rise in DFT by producing a wider zone between the resting membrane potential and threshold potential.

However, class Ia antiarrhythmic agents have been regarded as part of the standardized therapy, not only for reducing LV pressure gradients in patients with obstructive HCM, but also for improving LV diastolic dysfunction even in patients with non-obstructive HCM.

Therefore, it is even more important to predict an increase in DFT before ICD implantation in patients with HCM. Previous studies have described several clinical factors that are associated with a high DFT, such as LV dilatation, body size, decreased LV ejection fraction, administration of antiarrhythmic drugs (class I; flecainide, mexiletine, etc., class III; amiodarone, mexiletine, etc.; class III), myocardial ischemia, the ventricular fibrillation duration, and LV mass. Among these factors possibly associated with high DFTs, only the LV ejection fraction was found to be a univariate predictor of a high DFT in the present study. This might be because HCM exhibits a unique structural and electrophysiologic substrate in the myocardium. Almquist et al reported that extreme LV hypertrophy (wall thickness >45 mm) and the administration of amiodarone were related to a high DFT in patients with HCM. The LV mass index was slightly larger in the high than in the low DFT group in spite of the absence of any extreme LV hypertrophy in our series. Although this result was not statistically significant because of the small sample size, this suggests that a larger LV mass might increase the DFT.

**QRS Duration and DFT**

Although 2 published studies have shown an association between QRS duration and DFT, QRS duration was not an independent predictor of DFT in multivariate analysis. However, those study populations included mainly ischemic heart disease patients. This is the first study to investigate the association between QRS duration and DFT in patients...
with HCM. Dingra et al showed that QRS duration was positively related to LV mass and dimensions in individuals free of heart failure and myocardial infarction. However, there was no significant association between QRS duration and LV mass in our subjects. Asymmetric LV hypertrophy, which is frequently observed in HCM, might make it difficult to precisely evaluate LV mass in the clinical setting. This might be a possible explanation for our observed data.

**Study Limitations**

The results presented here must be viewed as preliminary as they are based on experience in a single center and in a small number of patients. Furthermore, this study was conducted retrospectively. In addition, we did not have any follow-up data on DFT after device implantation. All patients underwent the implantations under general anesthesia using propofol, as described above, which might have elevated the DFT.

Thus, it is possible that the DFT in the operating room differed from that in the clinical setting. A further major limitation is the absence of a uniform strategy for the selection of lead systems and antiarrhythmic agents that could affect the DFT. Finally, 2 patients in this study who had unacceptably high DFTs obtained a 10-J safety margin after cessation of antiarrhythmic agents. Moreover, not all patients taking antiarrhythmic agents at the ICD implantation had their DFTs measured after discontinuation of antiarrhythmic agents. We report here that the QRS prolongation was associated with a high DFT at the time of ICD implantation in patients with HCM, leaving doubt as to how much the antiarrhythmic agents would affect high DFT and QRS prolongation. Additional studies in a larger patient population are needed to determine the impact of QRS prolongation on DFT, as well as the influence of antiarrhythmic agents on DFT, and the long-term consequences of an elevated DFT in HCM patients.

**Clinical Implications**

In patients with HCM, the presence of a QRS prolongation on the 12-lead ECG should raise concern about a high DFT at the time of ICD implantation, and those patients should be started at a higher energy level for DFT measurements using a high-output device to obtain an adequate safety margin for defibrillation. In the patients who have already been implanted with an ICD, antiarrhythmic agents, which might cause a high DFT, should be prescribed very carefully. Moreover, when QRS prolongation is present before drug administration, DFT testing is warranted after the initiation of drug therapy.

**Conclusion**

The present report revealed an association between the QRS duration and DFT at the time of ICD implantation in patients with HCM. This might provide an important insight into the link between simple 12-lead ECG markers and the energy requirements for successful defibrillation in patients with HCM.

**References**


