Shortening of the Short Refractory Periods in Short QT Syndrome

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Background—Diagnosis of short QT syndrome (SQTS) remains difficult in case of borderline QT values as often found in normal populations. Whether some shortening of refractory periods (RP) may help in differentiating SQTS from normal subjects is unknown.

Methods and Results—Atrial and right ventricular RP at the apex and right ventricular outflow tract as determined during standard electrophysiological study were compared between 16 SQTS patients (QTc 324±24 ms) and 15 controls with similar clinical characteristics (QTc 417±32 ms). Atrial RP were significantly shorter in SQTS compared with controls at 600- and 500-ms basic cycle lengths. Baseline ventricular RP were significantly shorter in SQTS patients than in controls, both at the apex and right ventricular outflow tract and for any cycle length. Differences remained significant for RP of any subsequent extrastimulus at any cycle length and any pacing site. A cut-off value of baseline RP <200 ms at the right ventricular outflow tract either at 600- or 500-ms cycle length had a sensitivity of 86% and a specificity of 100% for the diagnosis of SQTS.

Conclusions—Patients with SQTS have shorter ventricular RP than controls, both at baseline during various cycle lengths and after premature extrastimuli. A cut-off value of 200 ms at the right ventricular outflow tract during 600- and 500-ms basic cycle length may help in detecting true SQTS from normal subjects with borderline QT values.

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Key Words: QT interval electrocardiography • refractory periods • risk stratification • short QT syndrome • sudden death

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tort QT syndrome (SQTS) is an inherited channelopathy initially described in 20001 associating a short QT interval to ventricular and atrial arrhythmias and carrying a risk of sudden cardiac death (SD).2,3 It is a very exceptional syndrome with only some tens of cases reported in the literature so far.4,5

Even if apparently straightforward because simply linked to the value of QT interval, diagnosis of SQTS has in fact remained poorly defined over previous years because of changing cut-off values.6 A diagnostic value of 300 ms,1,7 then of 320 ms8 for the QT interval and of 340 ms for the corrected QT (QTc)9 had been initially proposed, although some symptomatic patients with SQTS may present with longer QTc interval.4,10–12 A diagnostic score was proposed in 2011, including QTc value, and clinical and family history, demonstrating excellent sensitivity,4 although this score has not gained wide acceptance because of some limitations.13,14 SQTS should be currently diagnosed in the presence of a QTc ≤330 to 360 ms according to recent guidelines.2,3

SQTS diagnosis is furthermore complicated by an overlapping range of QT values between healthy subjects and affected cases. Epidemiological studies of control populations showed that a QT interval <320 to 340 ms was not associated with a higher risk of SD over very long-term follow-up.15,16 That is why additional clinical parameters are currently needed for diagnosing SQTS.2,3

However, borderline QTc values may lead to overdiagnosis of SQTS in the general population, especially in case of symptoms or familial SD of undetermined origin, while overestimation of corrected QT at high rates using standard corrective formulas14 may lead to underdiagnosis of true SQTS. Moreover, reliability of QT interval measurement is far from perfect in clinical practice.17 Thus, a more reliable repolarization parameter, with less inter/intraobserver variability and less dependence on the heart rate—or showing different rate dependence—would be very useful for SQTS diagnosis. Earlier works had shown some shortening of ventricular and atrial refractory periods (RP) in patients with
Even if short ventricular RP are common in SQTS, their additional shortening after short cycle lengths has not been evaluated. A greater than normal shortening of repolarization in SQTS may help in detecting borderline forms of SQT.

The aim of the study was to compare RP and their shortening at short cycle lengths between patients with SQTS and controls using standard programmed stimulation during electrophysiological study.

Methods

Study Population

Between 2005 and 2015, 16 successive patients with SQTS (14 men, 24±10 years old) coming from 8 unrelated families (median 1/family) have been investigated, while 15 subjects without SQTS (11 men, 27±14 years old) prospectively included serve as the control group.

Diagnosis of SQTS was made according to the current guidelines: each patient had a history of QTc interval shorter than 340 or <360 ms in association with resuscitated SD, and/or a family history of SD <40 years old and/or of familial SQTS.

Controls were subjects without any heart disease or cardioactive drug, who have been invasively investigated at our center for ablation of supraventricular tachycardia (retrograde accessory pathway n=8, atrioventricular node reentrant tachycardia n=2) or investigation of noncardiac syncope (n=2), palpitations (n=1), and idiopathic premature ventricular beats (n=2).

Electrophysiological Study

The study was approved by our institutional review committee and subjects gave informed consent.

Clinical Perspective

What Is New?

- SQTS patients display clearly shorter ventricular refractory periods compared with controls.

What Are the Clinical Implications?

- Because the diagnosis of SQTS may be difficult in borderline cases, evaluation of ventricular refractory periods during standard electrophysiological study may be useful.
- A cut-off value of 200 ms at the right ventricular outflow tract for 600- or 500-ms basic pacing rate differentiates patients from normal subjects with excellent predictive value.

Patients and controls were studied in the fasting state, under mild sedation and off drugs. QT intervals were measured using calipers on screen (50 mm/s speed) at the beginning of the procedure. Corrected QT were calculated using the Bazett formula. Standard quadripolar electrode catheters (2-mm electrodes, 10-mm interelectrode spacing) were inserted after femoral venous puncture. Programmed ventricular stimulation was performed at the right ventricular apex (RVA) and right ventricular outflow tract (RVOT), at 2-ms duration and twice the pacing threshold.

Baseline RVA and RVOT RP were measured by scanning the diastole using the S2 extrastimulus, with decreasing coupling interval in 10-ms decrements until refractoriness (coupling interval <200 ms allowed), during a drive of 8 S1 beats at 600-, 500-, and 400-ms cycle lengths. RP was defined by the longest S2 coupling interval not achieving ventricular capture. Shortening of RP was evaluated by measuring the RP after S2 and S3 paced events at each pacing site and at each basic drive, using the same method by adding S3 and S4 extrastimuli, respectively. Coupling intervals of the tested S2 or S3 beats were set 20 ms over the RP of S1 and S2, respectively (Figure 1).

Atrial RP were determined using programmed stimulation performed at the right lateral atrium at 2-ms duration and twice the pacing threshold. Only baseline RP were determined during pacing at 600-, 500-, and 400-ms cycle length.

AH, HV intervals were noted, as well as Wenckebach conduction cycle length during fast atrial pacing, and RP of the atrioventricular node was evaluated during atrial programmed stimulation at the 600-ms basic drive.

Statistical Analysis

Continuous data are expressed as mean±standard deviation (or median and range in case of nongaussian distribution of
values). Continuous variables were compared using unpaired \( t \) test or nonparametric Mann–Whitney test, as suitable. Correlations between RP and QT intervals were evaluated using Spearman rank correlation test. Analysis and calculations were performed using StatView™ program 1992–1996, version 5.0 (Abacus Concepts, Inc, Berkeley, CA). A \( P<0.05 \) was considered statistically significant for each analysis.

**Results**

**Population Characteristics**

Clinical characteristics of SQTS patients and controls are shown in Table 1. Nine SQTS patients were symptomatic including cardiac arrest (\( n=2 \)), syncope (\( n=4 \)), or palpitations (\( n=3 \)). Eleven had a family history of SD. One had a history of atrial fibrillation. Genetic screening was performed in all but without finding mutations in anyone. Three patients with SQTS received an implantable cardioverter defibrillator. None of the patients with SQTS or control subjects had any heart disease, cardioactive drug, or relevant comorbidity potentially linked to changes in myocardial electrical parameters.

Patients with SQTS and control subjects had similar cardiac rates before programmed stimulation (70±10 bpm versus 67±11 bpm, \( P=ns \)). QT interval (308±29 ms versus 397±36 ms, \( P=0.0007 \)) and QTc interval (324±24 ms versus 417±32 ms, \( P<0.0001 \)) were significantly shorter in patients with SQTS versus controls.

**Electrophysiological study**

Median pacing thresholds were 0.5 V at the right atrium, 0.5 at RV apex, and 1 V at RVOT without significant difference between patients with SQTS and controls.

None of the following significantly differed between SQTS and controls, respectively: AH interval (88±54 ms versus 88±33 ms), HV interval (44±4 ms versus 42±10 ms), atrioventricular node RP (308±74 ms versus 304±51 ms), or Wenckebach cycle length (390±102 ms versus 350±51 ms).

Atrial RP were shorter in SQTS compared with controls at 600-, 500-, and 400-ms basic cycle lengths with differences being significant for 600- and 500-ms cycle length (Table 2 and Figure 2). Sustained atrial fibrillation was induced by atrial programmed stimulation in 8 patients with SQTS and in only 1 control (\( P<0.008 \)).

Baseline ventricular RP were consistently significantly shorter in patients with SQTS than in controls, both at the RVA and RVOT (Table 2 and Figure 3). For example, at 600-ms cycle length, baseline RP were 181±18 ms versus 236±29 ms at the RVA and 180±19 ms versus 236±25 ms at RVOT (\( P<0.0001 \) for both). The differences remained significant for RP of the S2 and S3 extrastimuli at any cycle length and any pacing site (Table 3 and Figure 4). Interestingly, there was also some paradoxical increase in ventricular RP for the S3 extrastimulus compared with the previous one (Figure 4), which was not seen in controls. An example of very short RP after S2 stimulus in a patient with SQTS is shown in Figure 5.

Shortening of ventricular RP (magnitude of decrease between 600- and 400-ms baseline RP and magnitude of decrease between S1 and S3 beats RP) was constantly lower in patients with SQTS versus controls for each comparison but without reaching statistical significance (Table 4 and Figure 6). Ventricular fibrillation was induced by programmed ventricular stimulation in 6 patients with SQTS and in none of the control subjects (\( P=0.008 \)); ventricular fibrillation was induced with 2 extrastimuli in 2 patients (150- and 190-ms coupling interval for the last stimulus), with 3 extrastimuli in 3 (150, 160, and 160 ms for the last stimulus) (all but 1 at the RVA), and was induced by incidental catheter manipulation in 1.

<table>
<thead>
<tr>
<th>Table 2. Baseline Refractory Periods in SQTS and Controls for Atrium, RV Apex, and RVOT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td>Atrial RP (600 ms)</td>
</tr>
<tr>
<td>Atrial RP (500 ms)</td>
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<tr>
<td>Atrial RP (400 ms)</td>
</tr>
<tr>
<td>RVA RP (600 ms)</td>
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<tr>
<td>RVA RP (500 ms)</td>
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<tr>
<td>RVA RP (400 ms)</td>
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<tr>
<td>RVOT RP (600 ms)</td>
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<tr>
<td>RVOT RP (500 ms)</td>
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<tr>
<td>RVOT RP (400 ms)</td>
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</tbody>
</table>

RP indicates refractory periods; RVA, right ventricular apex; RVOT, right ventricular outflow tract; SQTS, short QT syndrome.

**Table 1. Clinical Characteristics of Patients With SQTS and Control Subjects**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SQTS (( n=16 ))</th>
<th>Controls (( n=15 ))</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>24±10</td>
<td>27±14</td>
<td>ns</td>
</tr>
<tr>
<td>Sex</td>
<td>14 men</td>
<td>11 men</td>
<td>ns</td>
</tr>
<tr>
<td>Height, cm</td>
<td>179±7</td>
<td>176±7</td>
<td>ns</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73±12</td>
<td>75±14</td>
<td>ns</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23±3</td>
<td>24±5</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>0</td>
<td>ns</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; ns, non significant; SQTS, short QT syndrome.
A cut-off value of baseline RP <200 ms at the RVOT (either at 600- or 500-ms cycle length) had a sensitivity of 86% and a specificity of 100% for the diagnosis of SQTS (negative predictive value 88% and positive predictive value 100%) (Figure 7).

Testing this cut-off value in 10 other additional patients with SQTS (6 men, 47±15 years old, QT 281±22 ms, QTc 304±17 ms) and in 20 other additional controls (16 men, 55±22 years old, QT 418±41 ms, QTc 422±37 ms) demonstrated that 9 of 10 patients with SQTS had RVOT RP <200 ms (mean 170±28 ms) and that 20 of 20 controls had RP >200 ms (mean 250±21 ms).

There was no significant correlation between baseline atrial/ventricular RP and clinical parameters or induction of atrial fibrillation or ventricular fibrillation in patients with SQTS, although RP were found to be shorter in inducible cases. Baseline ventricular RP were shorter at each cycle length in patients with familial SD, but this was significant for RVA only (data not shown). Baseline ventricular RPs were positively correlated to QT intervals (P<0.05).

**Discussion**

SQTS should be currently diagnosed in the presence of a QTc ≤330 to 340 ms or of a QTc ≤360 ms together with clinical features according to recent guidelines. However, diagnosis of SQTS may be challenging when QTc are of borderline values, and some patients with true SQTS may have longer QTc duration. Moreover, there is a large overlapping between healthy subjects and SQTS, which is illustrated by long-term follow-up population-based studies showing no adverse prognosis among subjects with a QTc <300 to 360 ms. This suggests that the QT interval value alone is not sufficient to identify patients with SQTS. Based on these findings, recent guidelines proposed that diagnosis of SQTS might be done only when additional clinical parameters are present.

Additional ECG markers have also been proposed to identify true SQTS among patients with borderline QT interval, such as a virtual ST segment, symmetrical and narrow T waves, PQ segment depression, or decrease of QT during exercise. These abnormalities could be helpful to identify SQTS among patients with borderline QT interval. However, the presence of borderline forms still remains an issue, carrying the risk of under- and overdiagnosis. Thus, a more robust repolarization parameter, with better measurement reliability, less inter/intraobserver variability, and less interdependence with the heart rate than QT duration, or showing
different rate dependence, would be very useful for SQTS diagnosis.

In 2004, Gaita et al performed noninvasive programmed ventricular stimulation through the implantable cardioverter defibrillator of 5 implanted SQTS patients. Ventricular RP were short (145±13 ms) and prolonged after quinidine treatment to 220±22 ms.18 Ventricular RP had also been measured during standard electrophysiological study in 2 of these patients with SQTS and did not exceed 150 ms at any pacing site or pacing cycle length.7 More recently, in the European registry, 28 patients had undergone electrophysiological study, and ventricular RP varied between 140 and 200 ms (mean 166±21) and were correlated to HERG mutations (151±14 versus 176±24 ms, P=0.01) but not to clinical events.5 Normal values for baseline ventricular RP in control populations are expected to be higher, previously evaluated to 253±27 ms22 or 245±21 ms.23 Demonstrating a significant difference between SQTS and normal subjects and finding a cut-off value clearly distinguishing patients from controls would be of considerable value for diagnosis of patients with SQTS with borderline QT intervals.

Table 4. Decrease in Refractory Periods in SQTS and Controls for RV Apex and RVOT

<table>
<thead>
<tr>
<th></th>
<th>SQTS</th>
<th>Controls</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 600 to 400 ms RVA*</td>
<td>15±11</td>
<td>23±24</td>
<td>0.2</td>
</tr>
<tr>
<td>Baseline 600 to 400 ms RVOT*</td>
<td>11±11</td>
<td>16±22</td>
<td>0.5</td>
</tr>
<tr>
<td>S3-S1 RVA 600 ms†</td>
<td>39±10</td>
<td>55±32</td>
<td>0.2</td>
</tr>
<tr>
<td>S3-S1 RVOT 600 ms†</td>
<td>38±13</td>
<td>55±23</td>
<td>0.1</td>
</tr>
<tr>
<td>S3-S1 RVA 500 ms†</td>
<td>35±18</td>
<td>49±28</td>
<td>0.2</td>
</tr>
<tr>
<td>S3-S1 RVOT 500 ms†</td>
<td>30±14</td>
<td>44±23</td>
<td>0.2</td>
</tr>
<tr>
<td>S3-S1 RVA 400 ms†</td>
<td>29±13</td>
<td>36±17</td>
<td>0.3</td>
</tr>
<tr>
<td>S3-S1 RVOT 400 ms†</td>
<td>28±12</td>
<td>36±23</td>
<td>0.4</td>
</tr>
</tbody>
</table>

RVA indicates right ventricular apex; RVOT, right ventricular outflow tract; SQTS, short QT syndrome.
*Difference in S1 RP between 600 and 400 ms baseline cycle length.
†Difference between S1 and S3 RP.
In the present study, we compared ventricular and atrial refractory periods between patients with SQTS and controls as retrieved during standard electrophysiological study. Patients with SQTS showed shorter atrial RP than controls for the slowest cycle lengths while demonstrating significantly shorter right ventricular RP than controls, disregarding the pacing site and cycle length, both at baseline and after 1 or 2 extrastimuli, sometimes displaying extremely short values. These excessively shortened RP mean that right ventricular myocardial cells are able to be reactivated sometimes less...
than 130 ms after the preceding activation. This could be the consequence of very fast repolarization because of the mutated ionic currents involved, especially after previous short cycle lengths, which are known to physiologically decrease refractoriness in myocardial tissues.22,24

The magnitude of decrease of RP (either between different pacing rates or between the first and third extrastimuli) even if lower in patients with SQTS, was, however, not significantly different from controls, indicating that the mechanisms controlling the decrease of RP after short cycle lengths are not significantly altered in patients with SQTS, in opposition to the decrease in QT intervals, which seems blunted.21 Thus, such decreased of RP remains possible even with shorter baseline RP (no baseline minimal RP value leading to the lack of further decrease seems to exist for the cycle lengths/coupling intervals investigated here). However, we also observe some paradoxical increase in ventricular RP for the S3 extrastimulus compared with the previous one, which was not seen in controls. Maybe some “fatigue” or blunting in refractoriness may alter the normal physiological repolarizing processes in patients with SQTS. This also may lead to some arrhythmogenicity.

Moreover, we found that a baseline ventricular RP cut-off value of <200 ms at the RVOT during 600- or 500-ms cycle length pacing yielded excellent predictive values for the diagnosis of SQTS: all but 2 patients with SQTS displayed RP ≥200 ms (200 ms in both cases), while no control demonstrated shorter values. Even controls with the shortest QTc—<400 ms—had RP >200 ms. This cut-off value may help in the diagnosis of SQTS in patients with borderline QT values with sufficient confidence. An additional higher decrease in RP may also provide further help in diagnosing SQTS for patients with borderline RP according to our data, even if no cut-off value could be proposed.

Even if RF were found to be grossly correlated to the QT intervals, RP are not a full surrogate for QT duration. Even for the shortest QT durations in controls, RP remain always higher compared with true SQT patients, and a 200 ms cut-off value seems to reliably separate true SQT from normal subjects even with relatively short QT duration. In the normal subjects with the shortest QT (40% of our control population had QTc between 360 and 400 ms), no RP was found to be shorter than 200 ms, and conversely none of the borderline QT (between 340 and 360 ms in one third of true SQT cases) had RP >200 ms.

Thus, based on these findings, we propose here a simple diagnosis technique for differentiating SQTS from the general population. Even if invasive, this would be useful for patients with borderline QT presenting with syncope, for example, or even for asymptomatic cases in order to avoid unnecessary follow-up, although asymptomatic SQTS does not need any special management according to the current guidelines.3 Measurement of RP offers the first objective technique for SQTS diagnosis, since QT measurement has many drawbacks, whereas measurement of RP is straightforward.

Arrhythmogenesis in SQTS has been attributed to heterogeneous abbreviation of the action potential duration among different cell types of the ventricular wall in a canine ventricular-wedge model of SQTS.25 The relationship between the shortening of the QT and ventricular arrhythmias has also been studied in computer models of the human ventricle carrying a HeRG mutation known to be involved in SQTS.26 The authors reported that the mutation accelerated the ventricular repolarization, shortened the AP duration and the effective ventricular RP while increasing electrical heterogeneity at some local areas, leading to increased risk of re-entrant arrhythmia. Shortening of the RP was associated with a reduction of the tissue size required to sustain re-entrant circuits in both 2 and 3 dimensions.26 On the basis of these results, a shortening of ventricular RP may be directly correlated to an increased risk of ventricular arrhythmia in SQTS, although shorter RPs were not linked to the induction of ventricular fibrillation nor to the outcome in our study.

Conclusion
Patients with SQTS have shorter right ventricular RPs than controls, both at baseline during various cycle lengths and after premature extrastimuli. A cut-off value of 200 ms at the RVOT during 600- and 500-ms basic cycle length may help in detecting borderline forms of SQTS.

Disclosures
None.

References


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