account for the increase in both VF and acute HF risk in patients presenting with STE in lead V4R. The interventricular septum is known to play an important role in arrhythmias after myocardial infarction (1). Morita et al. (2) demonstrated that acute ischemia of the interventricular septum in canine cardiac wedge preparations produced asymmetric suppression of conduction velocity in the septum, and they suggested that such changes could contribute to the initiation of arrhythmia in patients with septal infarction. More recently, Sicouri et al. (3) demonstrated that dispersion of repolarization across the interventricular septum in canine wedge preparations is twice that of the left ventricular free wall, predisposing to development of Torsades de Pointes arrhythmias. The relatively low incidence of the combined end point (primary VF, acute HF, or both) calls for caution in the interpretation of the results, especially with regard to the multivariate analysis. Should our findings be confirmed in a larger cohort, we would recommend that right precordial leads be a routine part of the initial electrocardiographic study in all patients with anterior STEMI.

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References

Table 1  Risk Associated With ST-Segment Elevation in the Right Precordial Leads by Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude Event Rate (Right vs. Nonright STEMI)</th>
<th>Odds Ratio*</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary VF, acute HF, or death</td>
<td>54% vs. 18%</td>
<td>8.8</td>
<td>2.7–28.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute HF</td>
<td>39% vs. 17%</td>
<td>3.6</td>
<td>1.1–12.4</td>
<td>0.038</td>
</tr>
<tr>
<td>Primary VF</td>
<td>21% vs. 3%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, left ventricular ejection fraction, the sum of ST-segment elevation by electrocardiography, and jeopardy score. The multivariate analysis for VF cannot be reported because of the small number of VF events.

HF = heart failure; STEMI = ST-segment elevation myocardial infarction; VF = ventricular fibrillation.

Proposed Diagnostic Criteria for Short QT Syndrome Are Badly Founded

I would like to commend Gollob et al. (1) for their attempt to generate criteria on how to diagnose short-QT syndrome (SQTS), but I would also like to point out some of the shortfalls and errors in their report.

In Table 1 of their report, at least 1 patient appears to have been included twice (Patients #23 and #49) with different ages and different QT intervals. Patient #46, published in 2008, was a 22-year-old man who “experienced unheralded syncope for the first time while driving, resulting in a motor vehicle accident” which in the current report is categorized as aborted cardiac arrest. This patient had no documented arrhythmias and no short QT interval on electrocardiography (QT interval 366 ms at 66 beats/min). The electrocardiogram appears to display early repolarization, and genetic testing discovered a novel KCNH2 mutation of undetermined significance, which was also present in the patient’s mother, who also had a normal QT interval. This patient does not fit the general concept of a patient with SQTS. Patients #59 to #61, from a letter to the editor, are also outliers and should not have been included. These patients had a C-terminal KCNH2 mutation (R1135H) shown (2) to cause both a short QT interval and a Brugada-type electrocardiographic pattern, as seen in Patient #59.

The exclusion of Patients #59 to #61 would have changed Table 2 in their report. Instead of an upper value for the range of QT intervals in patients with SQTS of 401 ms, the actual value would have been 334 ms.

Using the QT interval corrected by Bazett’s formula in the proposed diagnostic criteria has important limitations. As already observed in the very first patient diagnosed with SQTS (3), the QT interval in SQTS changes very little with changes in heart rate, and correction of the QT interval is therefore barely necessary at normal
heart rates. Bazett’s formula will greatly overcorrect the QT interval at any heart rate >60 beats/min, and attempts should always be made to record an electrocardiogram as close to 60 beats/min as possible by obtaining data from Holter monitoring or using a beta-blocker.

There is no doubt about the potential arrhythmic risk of a short QT interval, but corrected QT intervals as low as 340 to 350 ms (considered normal by some) have been observed for years without reports of any increased risk for sudden cardiac death. So far, SQTS has been an extremely rare diagnosis, with no documentation of sudden cardiac death or aborted sudden cardiac death due to SQTS when the QT interval is >315 ms.

Therefore, it is my opinion that the proposed diagnostic criteria for SQTS are poorly founded and should be used with great caution.

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doi:10.1016/j.jacc.2011.03.037

REFERENCES


Reply

Dr. Bjerregaard challenges the inclusion of 5 of 61 patients used in our analysis of reported cases of short-QT syndrome (SQTS) (1). We commend him on the considerable amount of time spent reviewing these cases and focusing on the relevance of their inclusion. Dr. Bjerregaard suggests that cases 23 and 49 are the same patient and that we have reported the patient twice but with “different ages and QT intervals.” His rationale for arriving at this conclusion is unclear. These patients are reported from different published reports, without any indication of having been previously described, and their differing QT intervals reflect the values quoted directly from these reports. With regard to patient #46, Dr. Bjerregaard is concerned about the terminology used in describing this patient’s clinical event and the fact that his mother carries the same KCNH2 gene mutation (E50D) despite having a normal corrected (QTc) interval. This patient’s QTc intervals ranging from 349 to 381 ms had a sudden loss of consciousness in the absence of a prodrome, resulting in a motor vehicle accident. After cardiac evaluation, clinically his event was attributed to a sudden arrhythmia with spontaneous reversion, consistent with the concept of an aborted cardiac arrest. Dr. Bjerregaard’s concern regarding a gene carrier demonstrating a normal phenotype is quite surprising, as this is a common observation in virtually all inherited arrhythmia conditions. The E50D mutation has never previously been observed and was absent from the screening of more than 2,600 chromosomes analyzed in a healthy control cohort (2). In collaboration with Dr. Charles Antzelevitch, biophysical analysis of this mutation confirmed a significant gain of function consistent with previous mutations reported in patients with SQTS.

The remaining 3 patients (patients #59 to #61) of concern to Dr. Bjerregaard were reported to have a novel KCNH2 gene mutation (R1135H). Biophysical studies demonstrated a significant gain of function of the mutant protein consistent with the SQTS phenotype in these 3 patients (3). One of these patients was also reported to have a “Brugada-type” electrocardiographic (ECG) pattern, although the 12-lead electrocardiogram was not published. Our view is that it is extremely unlikely that this patient had a type 1 Brugada ECG pattern, required to conclude a Brugada phenotype, and that the observed Brugada-type ECG pattern more likely reflected the non-specific type 2 or 3 pattern. The KCNH2 gene, which has been the subject of analysis in inherited arrhythmias for more than 15 years, has never been associated with a type 1 Brugada ECG pattern.

More relevant to the challenge of diagnosing the SQTS is the issue of QTc ranges that may be associated with the condition. Dr. Bjerregaard suggests that QT interval correction should be avoided and that instead, analysis of the absolute QT interval should be restricted to periods when the heart rate approximates 60 beats/min, and he suggests that Holter monitoring would be useful. We do not believe that this approach is feasible in clinical practice and do not advocate using Holter monitors for the evaluation of QT intervals. All currently reported SQTS cases have reported the QTc interval, and although the use of the Bazett correction formula has certain limitations, these limitations are minimized when appropriate reference ranges of “normal” are considered. As described in our report, numerous large epidemiologic studies have reported the QTc interval range in thousands of subjects, providing a useful resource of the normal distribution of QTc intervals on resting 12-lead electrocardiography in the general population.

Last, Dr. Bjerregaard emphasizes that QTc intervals “as low as 340 to 350 ms...have been observed for years without reports of any increased risk for sudden cardiac death.” This comment is rather naive, as the majority of patients with long-QT syndrome and QTc intervals in excess of 480 ms diagnosed later in life have led asymptomatic and prosperous lives. This does not reflect the fact that a significant proportion of patients with long-QT syndrome with similar QTc intervals have succumbed to the tragedy of a premature sudden death. In addition, we would reiterate that a diagnosis of SQTS using the diagnostic criteria cannot be made based on a QTc interval in isolation and requires the inclusion of relevant clinical and genetic information.

Despite the negative perspective offered by Dr. Bjerregaard, we believe that our diagnostic criteria will allow a thoughtful and systematic evaluation of patients potentially harboring the SQTS. The use of a diagnostic scorecard will assist in bringing uniformity to the diagnosis of this rare condition, as it has for other conditions, such as arrhythmogenic right ventricular cardiomyopathy, for which a single clinical test or observation cannot define the disease. Certainly, this approach should be favored over personal opinion.

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