Takotsubo cardiomyopathy and QT interval prolongation: who are the patients at risk for torsades de pointes?☆

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Abstract

Objectives: QT interval prolongation is prevalent among patients with Takotsubo cardiomyopathy (TC), whereas torsades de pointes (TdP) has rarely been reported in these patients. We studied all peer-reviewed reports on TC-associated QT interval prolongation and all peer-reviewed reports on TC-associated TdP to characterize the clinical circumstances leading to TdP in patients with TC.

Methods: The literature search yielded 14 reports on TC-associated TdP and 26 reports on TC-associated QT interval prolongation. Overall, 15 patients with TC-associated TdP and 86 patients with TC-associated QT interval prolongation were reported. We systematically reviewed each report and recorded the risk factors for TdP as well as the clinical circumstances of TC.

Results: The prevalence of the male sex was higher among patients with TC-associated TdP relative to patients with TC-associated QT interval prolongation (26.7% vs 5.8%; \( P = .01 \)). There was a trend in the mean maximal corrected QT interval being longer among patients with TC-associated TdP relative to patients with TC-associated QT interval prolongation (679.9 ± 230.6 vs 555.9 ± 63.8 milliseconds; \( P = .06 \)). There were no differences between patients with TC-associated TdP and patients with TC-associated QT interval prolongation in mean age, maximal troponin levels, and lowest ejection fraction. Overall, 12 (80.0%) patients with TC-associated TdP had risk factors for TdP other than the female sex and systolic dysfunction, including suspicion of congenital long QT syndrome, bradycardia, hypokalemia, recent conversion from atrial fibrillation to sinus rhythm, and using QT prolonging agents.

Conclusions: Men with TC-associated QT interval prolongation are at risk for TdP. Most patients with TC-associated TdP have risk factors for TdP other than the female sex and systolic dysfunction.

Keywords: QT prolongation; Takotsubo; Torsade de pointes

Introduction

QT interval prolongation might precede torsade de pointes (TdP)—a polymorphic ventricular tachycardia that might lead to ventricular fibrillation and sudden death. This potentially fatal arrhythmia is associated with administration of QT prolonging agents, hypokalemia, hypomagnesaemia, and congenital long QT syndrome.\(^1\)

Takotsubo cardiomyopathy (TC) is a rare acquired disease characterized by acute transient left ventricular dysfunction in the absence of significant obstructive coronary artery disease. Ventriculography or echocardiography might demonstrate apical dyskinesia in patients with TC, also termed apical ballooning (Fig. 1). The precise pathophysiologic mechanism of TC is unknown, though emotional or physical stress is...
believed to be the main triggers by causing adrenergic-based myocardial impairment. 

The prevalence of QT interval prolongation among TC patients is high, ranging from 50% to 100% according to different case series. This is probably because systolic dysfunction is associated with both TC and QT interval prolongation. Although QT interval prolongation is prevalent among TC patients and might precede TdP (Fig. 2), the later has rarely been reported in TC patients; Denney et al. first reported TdP occurring in a patient with TC in 2005. Since then, 13 more reports on 14 patients were published. It is of great importance to study the clinical circumstances leading to TdP in patients with TC-associated QT interval prolongation because TdP can be fatal, whereas the prognosis of TC is usually good. Hence, we studied all reports on TC-associated QT interval prolongation with TdP and all reports on TC-associated QT interval prolongation alone to characterize the clinical circumstances leading to this potentially fatal complication.

Material and methods

Retrieval of reports

We performed a literature search for all peer-reviewed in all languages reports on TC patients diagnosed as having QT interval prolongation and/or TdP, until December 2008, by using the following keywords: “Takotsubo,” “apical ballooning,” “stress cardiomyopathy,” “torsades de pointes,” “QT,” “arrhythmia,” “syncope,” and “sudden death.” The references in each report were further reviewed for additional publications. Only full-length reports were reviewed.

Definitions

Takotsubo cardiomyopathy was defined as a dyskinesia or akinesia of the left ventricular apical segments documented by echocardiography or ventriculography that resolved in a following imaging. QT interval prolongation was defined as corrected QT interval (QTc) more than 430 milliseconds for male patients and QTc more than 450 milliseconds for female patients according to the formula by Bazett. We used the QTc that was mentioned in the text of each case report by the authors. In several cases, we measured the QT interval length in lead II and calculated the QTc according to the electrocardiogram (ECG) strip enclosed in the case. In

![Fig. 1](image1.png)

**Fig. 1.** Left ventriculography in diastole (left panel) and systole (right panel) of a patient with TC. There is an apical ballooning during systole. Taken from Furushima et al. *Europace* 2008;10:1112-5. With permission from the authors and Oxford University Press.

![Fig. 2](image2.png)

**Fig. 2.** A, Corrected QT interval prolongation (740 milliseconds) in a 61-year-old woman with TC. B, The following day, the patient had TdP. Two months later (B) and 6 months later (C), the QTc interval gradually decreased (590 and 470 milliseconds, respectively) (D). Taken from Furushima et al. *Europace* 2008;10:1112-5. With permission from the authors and Oxford University Press.
EF indicates ejection fraction.

* In 36 patients, troponin I was measured, whereas in 7 patients troponin T was measured. In 3 patients, troponin type was not available.

case of a U wave, the QT interval was measured in leads without a U wave.

**Exclusion of reports**

The following reports were excluded: reports on TC with monomorphic ventricular tachycardia,23,24 reports without a detailed description of the patient,25 and reports that did not meet the definitions of TC.26

**Statistical analysis**

Continuous variables were expressed as mean ± SD. The Mann-Whitney test was used to compare the mean para-

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**Table 2**

Clinical characteristics of reported patients with TC-associated TdP

<table>
<thead>
<tr>
<th>First author</th>
<th>Age/sex</th>
<th>Stressor</th>
<th>Admission</th>
<th>Rh</th>
<th>HR (b/m)</th>
<th>Qtc (ms)</th>
<th>T</th>
<th>Ef (%)</th>
<th>TdP day</th>
<th>Rh</th>
<th>HR (b/m)</th>
<th>Qtc (ms)</th>
<th>T</th>
<th>Ef (%)</th>
<th>TdP timing after admission</th>
<th>Peak TnI (g/mL)</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Denney8</td>
<td>32♀</td>
<td>NA</td>
<td>Sinus</td>
<td>91</td>
<td>416</td>
<td>−</td>
<td>NA</td>
<td>NA</td>
<td>Sinus</td>
<td>91</td>
<td>416</td>
<td>−</td>
<td>NA</td>
<td>NA</td>
<td>TdP at admission</td>
<td>0.75</td>
<td>Live</td>
</tr>
<tr>
<td>Ghosh9</td>
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<td>Emotional &amp; alcohol &amp; drug</td>
<td>Sinus 97</td>
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<td>−</td>
<td>25</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>−</td>
<td>2</td>
<td>1</td>
<td>d</td>
<td>NA</td>
</tr>
<tr>
<td>Furushima10</td>
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<td>NA</td>
<td>Sinus 62</td>
<td>740</td>
<td>−</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>−</td>
<td>30</td>
<td>3</td>
<td>d</td>
<td>NA</td>
</tr>
<tr>
<td>Finsterer11</td>
<td>75♂</td>
<td>Tracheal operation</td>
<td>AF</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>NA</td>
<td>1.9 (Tn type NA)</td>
<td>Live</td>
</tr>
<tr>
<td>Okada12</td>
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<td>Pneumonia</td>
<td>Sinus 75</td>
<td>450</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>NA</td>
<td>NA</td>
<td>Live</td>
<td></td>
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<tr>
<td>Boulouffe13</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>NA</td>
<td>Live</td>
<td></td>
</tr>
<tr>
<td>Sasaki14</td>
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<td>NA</td>
<td>Sinus NA</td>
<td>730</td>
<td>−</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>NA</td>
<td>Live</td>
<td></td>
</tr>
<tr>
<td>Patel15</td>
<td>72♂</td>
<td>COPD &amp; alcohol &amp; drug</td>
<td>AF</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
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<td>NA</td>
<td>1.9 (Tn type NA)</td>
<td>Live</td>
</tr>
<tr>
<td>Akashi16</td>
<td>67♂</td>
<td>COPD &amp; alcohol &amp; drug</td>
<td>Sinus 68</td>
<td>394</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
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<td>NA</td>
<td>NA</td>
<td>1.9 (Tn type NA)</td>
<td>Live</td>
</tr>
<tr>
<td>Nault17</td>
<td>76♂</td>
<td>Fall &amp; Immobility</td>
<td>Sinus NA</td>
<td>630</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>NA</td>
<td>1.9 (Tn type NA)</td>
<td>Live</td>
</tr>
<tr>
<td>Kurisu18</td>
<td>87♂</td>
<td>NA</td>
<td>2:1 AVB</td>
<td>46</td>
<td>735</td>
<td>+</td>
<td>NA</td>
<td>2:1</td>
<td>AVB</td>
<td>46</td>
<td>1060</td>
<td>−</td>
<td>62</td>
<td>6</td>
<td>d</td>
<td>NA</td>
<td>Live</td>
</tr>
<tr>
<td>Kurisu18</td>
<td>78♂</td>
<td>NA</td>
<td>Comp AVB</td>
<td>46</td>
<td>735</td>
<td>+</td>
<td>NA</td>
<td>2:1</td>
<td>AVB</td>
<td>46</td>
<td>1135</td>
<td>−</td>
<td>38</td>
<td>2</td>
<td>d</td>
<td>NA</td>
<td>Live</td>
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<tr>
<td>Hirose19</td>
<td>63♂</td>
<td>Respiratory failure</td>
<td>Sinus NA</td>
<td>549</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>NA</td>
<td>1.9 (Tn type NA)</td>
<td>Live</td>
</tr>
<tr>
<td>Inoue20</td>
<td>82♂</td>
<td>Emotional</td>
<td>Comp AVB</td>
<td>38</td>
<td>630</td>
<td>−</td>
<td>45</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>−</td>
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<td>NA</td>
<td>1.9 (Tn type NA)</td>
<td>Live</td>
</tr>
<tr>
<td>Mahida21</td>
<td>55♂</td>
<td>Emotional</td>
<td>Sinus NA</td>
<td>510</td>
<td>−</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>−</td>
<td>NA</td>
<td>NA</td>
<td>1.9 (Tn type NA)</td>
<td>Live</td>
</tr>
</tbody>
</table>

NA indicates not available; EF, ejection fraction; AVB, atrioventricular block; Comp, complete; Rh, rhythm; HR, heart rate; T, T-wave polarity in precordial leads; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; TnI, troponin I; brady, bradycardia.
metric variables between TC patients with QT interval prolongation and TC patients with TdP. The χ² test was used to compare the prevalence of nonparametric variables between TC patients with QT interval prolongation and TC patients with TdP. P ≤ .05 was considered statistically significant throughout. Version 15.0 of the SPSS statistical package (SSPS Inc, Chicago, IL) was used to perform all statistical evaluations.

Results

The literature search yielded 14 reports on 15 patients with TC-associated TdP and 26 reports on 86 patients with TC-associated QT interval prolongation (5,15,17, and 1-23 in the suggested reading list online). Overall, 101 reports were reviewed on 93 (92.1%) female patients and 9 (8.9%) male patients. The prevalence of the male sex was higher among patients with TC-associated TdP relative to patients with TC-associated QT interval prolongation (26.7% vs 5.8%; P = .01).

Mean peak CPK levels were higher among patients with TC-associated QT interval prolongation relative to patients with TC-associated TdP. There were no statistical differences between patients with TC-associated TdP relative to patients with TC-associated QT interval prolongation in mean age, mean baseline QT interval length, mean lowest ejection fraction, and mean peak troponin levels (Table 1). There was a trend in the mean maximal corrected QT interval being longer among patients with TC-associated TdP relative to patients with TC-associated QT interval prolongation (679.9 ± 230.6 vs 555.9 ± 63.8 milliseconds; P = .06), although in most cases it was observed after TdP and not during admission. Torsades de pointes was presented at admission in 3 patients, but in the others, it appeared between few hours and 6 days after admission. All patients survived the arrhythmia, although one patient died 69 days later of other complications (Table 2).

Overall, 12 (80.0%) patients with TC-associated TdP had one or more risk factors for TdP other than female sex and systolic dysfunction, compared with 2 (2.3%) patients with TC-associated QT interval prolongation (P = .002). Among patients with TC-associated TdP, risk factors for TdP included bradycardia with or without atrioventricular block (n = 4), suspicion of congenital long QT syndrome (n = 3), hypokalemia (n = 1), recent conversion from atrial fibrillation to sinus rhythm (n = 1), recent conversion from atrial fibrillation to sinus rhythm and the use of amiodarone (n = 1), suspicion of congenital long QT syndrome and hypokalemia (n = 1), hypokalemia and the use of disopyramide (n = 1).

Discussion

We studied all reports on TC-associated QT interval prolongation and all peer-reviewed reports on TC-associated TdP to characterize the clinical circumstances leading to TdP in patients with TC. Our main finding was that men with TC-associated QT interval prolongation were at higher risk for TdP compared with women, although TC was much more prevalent among women. This finding is consistent with a well-known paradox—women have longer QTc compared with men but lower incidence of sudden death. The mechanism for the longer corrected QT interval in women is unknown but might be related to the effects of hormones or differences in autonomic innervations.

One may assume that markers of severe TC, such as high CPK levels, prolonged QT interval, or low ejection fraction, are associated with increased risk for TdP. However, CPK levels were higher among TC-associated QT interval prolongation, the maximal corrected QT interval was higher among TC-associated TdP only after the arrhythmia most of the times, and the mean lowest ejection fraction was not different between TC-associated QT interval prolongation and TdP patients. For this reason, markers of TC severity were not predictive of TdP. On the other hand, known risk factors for TdP such as congenital long QT syndrome, bradycardia, hypokalemia, using QT prolonging agents, and recent conversion from atrial fibrillation to sinus rhythm were observed among patients with TC-associated TdP. We believe this finding has a great clinical implication (see below).

Limitations

Our study was based on published case reports. We assume that there are more incidents of TdP in patients with TC that have not been published, for example, when a report is rejected from publication because TdP is attributed to early multiple risk factors for TdP rather than to TC or when physicians are reluctant to report on their deceased patients. Indeed, in all the cases we studied, the patients survived the arrhythmia. Patients with sudden death without documentation of an arrhythmia would also go unrecorded. Hence, we believe that our results are more likely an underestimation of the true prevalence of the clinical circumstances that might lead to TdP in TC patients.

Risk factors for TdP were not reported in all cases of TC-associated QT interval prolongation, probably because the authors considered TC itself as a cause for QT interval prolongation or because QT interval prolongation was not the main issue in these reports. Hence, we could not perform a multivariate analysis of the different risk factors for TdP and their weight in predicting TdP. Still, 80% of patients with TC-associated TdP had one or more risk factors for TdP other than the female sex, and systolic dysfunction is of clinical importance.

In several cases, the authors did not mention the QTc interval length. Hence, we measured the QT interval length in lead II and calculated the QTc according to the ECG strip enclosed in the case. Measuring the QT interval in the original ECG strips might have been more accurate, but we believe these differences are minor.

Clinical implications

We believe that previous recommendations regarding taking measures before prescribing any QT prolonging agent are particularly relevant to patients with TC. It is also advisable to monitor the potassium serum levels frequently, especially in TC patients treated with diuretics. QT interval might be prolonged for a while in TC patients; and they
might be discharged before the ECG has returned to normal. Hence, these recommendations are also relevant to the patients’ general practitioner. Finally, in patients with TC and atrioventricular block and bradycardia, it is advisable to implant a temporary pacemaker not only for hemodynamic stability purposes but also to prevent pause-dependent TdP.

All of the above are particularly relevant to men with TC.

Conclusions

Men with TC-associated QT interval prolongation are at risk for TdP. Most patients with TC-associated TdP have risk factors for TdP other than female sex and systolic dysfunction. We wish to raise the awareness levels of risk factors for TdP in patients with TC-associated QT interval prolongation.

References

Suggested reading list


