The site of origin of torsade de pointes
Birati, E.Y.; Belhassen, B.; Bardai, A.; Wilde, A.A.M.; Viskin, S.

Published in:
Heart

DOI:
10.1136/hrt.2010.212381

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
The site of origin of torsade de pointes

Edo Y Birati,1 Bernard Belhassen,1 Abdennasser Bardai,2 Arthur A M Wilde,2 Sami Viskin1

ABSTRACT

Objective The electrocardiographic (ECG) characteristics and mode of onset of torsade de pointes (TdP) are well described. Less is known about the site of onset of this arrhythmia. This study was conducted to determine if arrhythmias in the long QT syndrome (LQTS) have a predominant site of origin.

Design A retrospective analysis of all episodes of LQTS-related arrhythmias recorded in two university hospitals.

Patients Patients with LQTS and no structural heart disease, for whom simultaneous 6–12 leads ECG recording of the onset of TdP was available, were included.

Interventions None.

Main outcome measures The site of origin of TdP was defined according to the morphology of the initiating ventricular complex (based on validated criteria). Multiple-lead recordings of 1025 LQTS-related arrhythmias, including 151 episodes of TdP and 874 QT-related extrasystoles (impending TdP) were available for 50 patients.

Results The site of origin of TdP was not homogeneously distributed (p<0.001). Instead, the majority of episodes of TdP (56%) and most QT-related extrasystoles (70%) originated from the outflow tract. There was no correlation between site of origin and the aetiology of LQTS or the QT duration. On a given patient, multiple episodes of TdP tended to originate from the same area and the site of origin of QT-related extrasystoles correlated with the site of origin of TdP.

Conclusion The most frequent site of origin of TdP is the outflow tract. Further studies are needed to understand why this relatively small area of the ventricle is a predominant site of origin of diverse ventricular arrhythmias.

Torsade de pointes (TdP) is a polymorphic ventricular tachycardia (VT) that occurs in the setting of a long QT syndrome (LQTS).1 Prolongation of the QT interval may be due to an inherited disorder (congenital LQTS)2 or may be acquired (secondary to metabolic abnormalities, bradycardia-induced extrasystoles, or drugs that prolong ventricular repolarisation).1 4 The electrocardiographic (ECG) characteristics and mode of onset of TdP have been well described. Specifically, drug-induced5 6 and bradycardia-induced TdP7 are essentially always ‘pause-dependent’ (ie, they are preceded by a heart rate deceleration or short-long sequences).4 6 Whereas TdP in the congenital LQTS may be ‘pause-dependent’ or ‘tachycardia-dependent’ depending on the genotype,7 8 Less is known, however, about the site of origin of TdP.

Determining the site of origin of TdP is of scientific interest. Tissue models of LQTS show that the abnormal prolongation of the action potential (the hallmark of the LQTS) creates the trigger (early after-depolarisations) and the substrate (abnormal dispersion of repolarisation) that start and perpetuate TdP.10 Yet, it is unknown if some areas of the human cardiac ventricle are more sensitive to this process than others. In this regard, it is intriguing to determine if TdP predominantly begins at the ventricular outflow tract. The right ventricular outflow tract (RVOT) is not only the site of origin of the most common form of idiopathic monomorphic VT,11 but has also been described as a predominant site of origin for malignant polymorphic ventricular arrhythmias like catecholaminergic polymorphic VT.12 Brugada syndrome13 14 and some cases of idiopathic ventricular fibrillation.15 16 Furthermore, determining the site of origin of TdP has potentially important clinical implications. Radiofrequency ablation of the site of origin is the first line of therapy for idiopathic monomorphic VT and has also been used successfully to treat polymorphic ventricular arrhythmias.15 16 In fact, radiofrequency ablation of the zone triggering TdP has already been performed in isolated cases of LQTS.14 We therefore performed the present study to determine if TdP has a predominant site of origin and if this region is disease-specific (ie, differs according to the aetiology of LQTS) or patient-specific (if multiple episodes of TdP in the same patient originate from the same region).

METHODS

We reviewed all the traces of TdP collected over the years in the Tel-Aviv Medical Center (Israel) and the Academic Medical Center of Amsterdam (The Netherlands), and selected for this study those traces showing the onset of TdP in 6–12 leads in patients without structural heart disease affecting ventricular function. Absence of ventricular dysfunction was specified as part of the inclusion criteria because the criteria for correlating QRS morphology with the site of origin of a VT differ for patients with and without ventricular scar. TdP was a polymorphic VT lasting three or more beats occurring in a patient with congenital or acquired LQTS. QT-related extrasystoles were ventricular extrasystoles originating from the terminal part of the obviously prolonged QT interval (mostly in sinus complexes following postextrasystolic pauses). Such extrasystoles were saved to our archives because they were recorded shortly before the onset of TdP and were considered signs of ‘impending TdP’.1 Most of the patients in this study have been described in previous studies reporting the mode of onset of TdP.5 7–9

See Editorial, p 1631
1Department of Cardiology, Tel-Aviv Sourasky Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
2Academic Medical Center, Amsterdam, The Netherlands

Correspondence to
Sami Viskin, Department of Cardiology, Tel-Aviv Sourasky Medical Center, 6th Weizman Street, Tel-Aviv 64239, Israel; samiviskin@gmail.com

Accepted 28 March 2011
Published Online First
10 May 2011
The site of origin of all episodes of TdP of each patient was defined according to the morphology of the ventricular complex initiating the tachyarrhythmia in accordance with well-established criteria that have used endocardial mapping for validation, and was then differentiated to three distinct areas: (1) The outflow tract was the area superior to the tricuspid and mitral annulus and inferior to the pulmonary and aortic valve, including a number of essentially contiguous structures, namely, the right and left ventricular outflow tract (RVOT and LVOT), the para-Hisian region, the right ventricular segment above the anterior (superior) aspect of the tricuspid annulus and above the anterolateral (superior) aspect of the mitral annulus. Since accurate distinction of true right-sided from left-sided arrhythmias originating in the outflow tract (a septal structure with complicated three-dimensional anatomy) requires detailed intracardiac mapping, we made no attempt to differentiate RVOT from LVOT origin. (2) The inferior wall of the left ventricle, and 24 (11%) started in the inferior wall of the right ventricle. When comparing the most frequent site in each patient, we found that the most common site of origin of TdP was the outflow tract in 24 patients, followed by the left ventricular free wall and the right ventricular free wall in 21 and five patients, respectively.

Limiting our analysis only to the 57 TdP episodes recorded in 12 leads gave similar results (albeit with smaller numbers). The outflow tract area was the most common site of origin of TdP with 25 (44%) of episodes originating in that area, whereas 22 (39%) TdP episodes started in the inferior wall of the left ventricle, and 10 (18%) started in the inferior wall of the right ventricle (p=0.039).

Only recordings showing the onset of the arrhythmias on multiple leads simultaneously were used for this analysis. Simultaneous recordings of TdP were available in 12 leads, seven leads and six leads in 58%, 59% and 23% of episodes, respectively (all seven-lead recordings include simultaneous recording of leads I to aVF plus V1). Whenever none of the precordial leads was available in six-lead recordings, the ‘right versus left’ allocation was made according to the morphology in aVR.20–22

Statistics
All data were summarised and displayed as mean±SEM or SD for continuous variables with normal distribution and as median and IQR for continuous variables that have non-normal distribution and as number and per cent in group for categorical variables. The comparison of continuous variables between groups was done using independent Student’s t test for two groups and using one-way analysis of variance when comparing more than two groups. The comparison of categorical variables was done using χ². All above analyses were considered significant at p<0.05 (two tailed). The 19.0 SPSS statistical package was used to perform all statistical evaluation.

RESULTS
A total of 1025 episodes of LQTS-related arrhythmias—recorded on multiple leads—were available for analysis. These recordings are from 50 patients (14 men and 36 women, aged 62±22 years). Of these 50 patients, 12 (24%) have congenital LQTS (LQT1, LQT2 and LQT3 in two, nine and one patients, respectively) and 38 (76%) had acquired LQTS related to QT-prolonging medications (22 patients), bradyarrhythmias (14 patients), electrolyte disturbance (four patients); two patients with acquired LQTS had more than one possible aetiology. Their QTc interval was 522±67 msec and their median (IQR) number of events was seven (3–17) arrhythmias per patient.

LQTS-related arrhythmias included 151 episodes of TdP and 874 QT-related extrasystoles (impending TdP) recorded on multiple leads. The number of TdP episodes per patient ranged from one to 27 (median (IQR) three (1–5) episodes per patient). The number of captured QT-related extrasystoles per patient ranged from 0 to 581 (median (IQR) 6 (2–14) PVCs per patient).

Site of origin of torsade de pointes (table 1)
A total of 151 episodes of TdP, for which the onset of arrhythmia was recorded in multiple leads were available for analysis: the distribution of the site of origin of TdP across the heart was not homogeneous (p<0.001). Instead, the outflow tract area was the most common site of origin of TdP (figures 1 and 2): 84 (56%) episodes originated in the outflow tract, 48 (32%) started in the inferior wall of the left ventricle, and 19 (12%) started in the inferior wall of the right ventricle. When comparing the most frequent site in each patient, we found that the most common site of origin of TdP was the outflow tract in 24 patients, followed by the left ventricular free wall and the right ventricular free wall in 21 and five patients, respectively.

Limiting our analysis only to the 57 TdP episodes recorded in 12 leads gave similar results (albeit with smaller numbers). The outflow tract area was the most common site of origin of TdP with 25 (44%) of episodes originating in that area, whereas 22 (39%) TdP episodes started in the inferior wall of the left ventricle, and 10 (18%) started in the inferior wall of the right ventricle (p=0.039).

Site of onset of QT-related extrasystoles (impending TdP)
A total of 874 QT-related extrasystoles (impending TdP) recorded on multiple leads were available for analysis: their site of origin was not homogeneously distributed across the heart (p<0.001). Again, the outflow tract area was the most common site of origin of QT-related extrasystoles: 611 (70%) PVCs originated from the outflow area, 152 (17%) originated from the inferior wall of the left ventricle, and 111 (13%) from the inferior wall of the right ventricle. The outflow tract was the most common site of origin of LQTS-related arrhythmias (including TdP) both for arrhythmias recorded in Tel Aviv and for arrhythmias recorded in Amsterdam.

Limiting our analysis to the QT-related arrhythmias recorded simultaneously in 12 leads led to similar results. A total of 216 episodes of QT-related arrhythmias (57 TdP episodes and 159 impending TdP episodes) recorded in 12 leads were available for analysis: the outflow tract area was the most common site of origin of QT-related arrhythmias: 103 (48%) episodes originated in the outflow tract, whereas 89 (41%) started in the inferior wall of the left ventricle, and 24 (11%) started in the inferior wall of the right ventricle (p<0.001).

Disease-specific site of origin of TdP
There was no statistical correlation between the aetiology of LQTS and the site of arrhythmia origin (p=0.607). Also, there was no statistical significant correlation between the QTc interval or the patient’s gender and the site of arrhythmia origin (p=0.085).

Patient-specific site of origin of TdP
Thirty-four patients had two or more episodes of TdP. In 22 (65%) of these patients all the episodes of TdP originated from

| Table 1 Distribution of the site of origin of long-QT related arrhythmias |
|------------------|------------------|------------------|------------------|
| LQTS-related arrhythmias | 1025 episodes | Impending torsade | 874 episodes |
| Episodes=0 to 381 per patient | Episodes=1 to 27 per patient | Episodes=0 to 381 per patient | Episodes=1 to 27 per patient |
| 611 (70%)* | Outflow tract area | 84 (56%)* | Outflow tract area |
| 152 (17%) | LV-inferior wall area | 48 (32%) | LV-inferior wall area |
| 111 (13%) | RV-inferior wall area | 19 (13%) | RV-inferior wall area |

*p<0.001.

LQTS, long QT syndrome; LV, left ventricle; RV, right ventricle.
the same area (2.4±1.6 episodes of TdP per patient, median (IQR)¼2(1-3.3)). In the remaining 12 (35%) patients, the TdP episodes originated from two sites (8.3±6.9 episodes of TdP per patient, median (IQR)¼6.5 (3.3-11)).

Forty-five patients had two or more QT-related extrasystoles figure 2. In 21 (47%) patients all extrasystoles originated from the same site (6.2±6.8 extrasystoles per patient, median (IQR)=5 (1-8)); in 19 (42%) patients all the extrasystoles originated from two sites (16.0±20.4 extrasystoles per patient, median (IQR)=6 (4-16)). Only five (11%) patients had three different sites of origin (87.8±164 extrasystoles per patient, median (IQR)=17 (11.5-200)).

**Coupling interval and site of origin**

We found no correlation between the site of origin of QT-related arrhythmias and the coupling interval of the initiating beat. The coupling interval of QT related arrhythmias originating from the outflow tract, inferior left ventricle and inferior right ventricle were 657±111, 654±1096 and 651±155 ms, respectively (p=0.297).

**DISCUSSION**

The clinical predictors,23 ECG characteristics4 5 24 and mode of onset of TdP6-8 28 are well described. We report on the site of origin of this intriguing arrhythmia by analysing multiple-lead recordings of 1025 episodes of LQTS-related arrhythmias, including 151 episodes of TdP for which the arrhythmia onset was recorded in at least six leads simultaneously. We show, for the first time, that the sites of onset of QT-related arrhythmias are not homogeneously or randomly distributed along the heart; instead, there is a statistically significant predominance of the outflow tract area as the site of origin of TdP. Only 77% of the QT-related arrhythmic episodes were captured in seven leads or more simultaneously and our grouping of sites of origin into only three areas provides a rather rough classification (albeit similar to the classification used by others).12 Thus, our
conclusions should be viewed with caution. Nevertheless, this is the largest series of TdP captured in multiple-lead recordings. Moreover, limiting our analysis to only those episodes recorded in 12 leads gave similar results.

Why is the outflow tract so arrhythmogenic?
Considering that the ion-channels that malfunction in congenital channelopathies are present across the whole ventricular wall, one would expect the arrhythmias caused by these diseases to have a randomly distributed site of origin. Consequently, our observation that TdP tends to originate preferentially from the outflow tract is somehow unexpected. However, other studies have shown that the outflow tract is particularly arrhythmogenic in other channelopathies. For example, Sumitomo reported that in 20 (74%) out of 27 patients with catecholaminergic polymorphic VT, this triggered arrhythmia originated from the outflow tract. Similarly, limited data showing the onset of polymorphic VT of Brugada syndrome in multiple leads also suggest that the arrhythmias originated from the right ventricular outflow tract. Note the giant T-waves, clearly exceeding the amplitude of the flutter waves, best appreciated in leads V4—V6 (arrows).

Limitations
(1) This is a retrospective analysis of multiple-lead recordings of LQTS-related arrhythmias. The aim of defining the site of onset of TdP was not considered at the time of the original recordings. Therefore, it is possible that not all episodes of LQTS-related arrhythmias were captured or saved. However, no pre-selection of events by site of origin was performed either and the outflow tract was the most common site of origin both in Tel Aviv and in Amsterdam. Therefore, our results are likely to be representative of ‘real-life TdP.’ (2) The ECG provides only an approximation of the site of origin of a ventricular arrhythmia and confirmation by intracardiac mapping was not performed in this study. However, the ECG criteria used in our study have been validated by intracardiac mapping studies. Importantly, our definition of ‘site of origin’ is based on ECG criteria derived from patients without organic heart disease, and thus our findings cannot be extended to patients with organic heart disease. Moreover, such idiopathic arrhythmias rarely develop from the free wall of the left and right ventricle. Therefore, those areas may have remained under-represented in our study. It should be noted, however, that none of the QT-related arrhythmias remained unclassified. (3) Patients with more recordings had more sites of origin. Although this is a retrospective study, the ECGs were prospectively collected by two
authors (SV and AW) and all efforts were made to collect and store all the arrhythmic events. Nevertheless, potential for selection bias exists. However, it should be emphasised that in 76% of patients with TdP, the site of origin of the TdP was identical to the patient’s most frequent PVC site of origin.

Clinical implications

Diagnositc implications

The vast majority of ventricular extrasystoles recorded in patients without organic heart disease originate from the outflow tract. Since idiopathic monomorphic VT originating from this area is a benign arrhythmia, patients with outflow-tract extrasystoles are not necessarily treated. However, our study shows that extrasystoles originating from the outflow area also predominate in the LQTS. This is important because—except for the QT prolongation—the ECG is normal in essentially all patients with congenital LQTS and in many patients with drug-induced LQTS. Moreover, the QT-prolongation is so arrhythmogenic.14 Consequently, LQTS-related extrasystoles may be misdiagnosed as ‘benign arrhythmias’ and such error may have serious consequences because the LQTS is highly lethal when left untreated.

Therapeutic implications

The fact that patients with recurrent TdP have a predominant area of origin suggests that radiofrequency ablation of a patient-specific site may be an alternative therapeutic strategy for patients with arrhythmogenic storms refractory to conventional therapy in whom a single or highly-predominant site of origin is carefully documented. Such therapeutic approach has already been proposed.14

Research implications

The statistically significant predominance of the outflow tract, as site of origin of such diverse forms of benign and malignant ventricular arrhythmias, is an intriguing and so far unexplained finding. Studies are needed to determine why the outflow tract is so arrhythmogenic.

Competing interests None.

Ethics approval This is a retrospective analysis of electrocardiograms recorded over the years.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES
