Electrocardiographic Markers Associated with Sotalol-induced Torsades de Pointes

Based on Data from the Telemetric and Holter ECG Warehouse (THEW) Initiative

Jean-Philippe Couderc, PhD
Center for Quantitative Electrocardiography and Cardiac Safety
heartjpc@heart.rochester.edu

University of Rochester Medical School Rochester

DIA
www.diahome.org

UNIVERSITY of ROCHESTER
MELIORA
Telemetric and Holter ECG Warehouse

Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. ("DIA"), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.

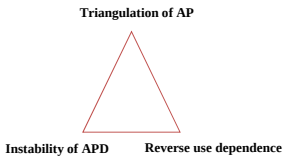
Conflict of Interest Disclosure
Jean-Philippe Couderc, PhD

- Contracted Research: receives **Grants/Research Funding from ELA Medical (Sorin)**
- Ownership Interest (stocks, stock options or other ownership interest excluding diversified mutual funds): **iCardiac Technologies**

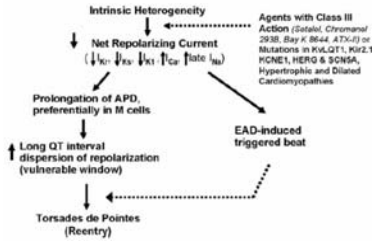
Background

The mechanisms involved in the triggering of drug-induced torsades de pointes (TdPs) remain to be fully elucidated. The current theories involved primarily the role of repolarization delay and heterogeneity, and early after depolarization.

TriAD Concept [1]



Transmural and transeptal Dispersion [2]



[1] Hondeghem LM. TriAD: foundation for proarrhythmia (triangulation, reverse use dependence and instability). Novartis Found Symposium 2005;266:235-44
[2] Antzelevitch C, Sun ZQ, Zhang ZQ, Yan GX. Cellular and ionic mechanisms underlying erythromycin-induced long QT intervals and torsade de pointes. J Am Coll Cardiol 1996 Dec;28(7):1836-48.

Introduction

- **We propose to investigate values of ECG parameters quantifying static and dynamic aspects of the ventricular repolarization prior to the occurrence of drug-induced torsades de pointes (TdPs).**
- **Our work is based on data from the Telemetric and Holter ECG Warehouse in which 12-lead Holter ECGs from patients with sotalol-induced TdPs are available.**
- **We will investigate the values of ECG parameters between a group of healthy individuals exposed to sotalol who did not develop TdPs and a group including cardiac patients who developed TdPs on sotalol.**

Method (I)

Matrix of investigated ECG markers and their association with electrophysiological mechanisms involved in TdPs.

	Repolarization instability	APD triangu-lation	Repolarization delay	Increased heterogeneity (apico-basal and transmural)	EADs
QT/QTc prolongation		X	X		
Increased beat-to-beat QT variability	X	X		X	
Increased ventricular premature beat frequency (couplets, triplets)	X			X	X
Changed in T-wave amplitude (morphology)		X		X	
T-peak to T-end interval prolongation				X	
Increased T-wave complexity				X	
Macro T-wave alternans	X		X	X	

Study populations (I):

Sotalol-induced QT prolongation in individuals with and without TDP triggering

- **Group 1**: three cardiac patients with history of syncope or TdPs had a diagnostic test based on dl-sotalol IV (at 2mg/kg body weight). The test is used to unmask latent repolarization abnormalities.
- **Group2***: three healthy individuals on 320mg of dl-sotalol (oral). Patients were selected based on their maximal QTc prolongation.

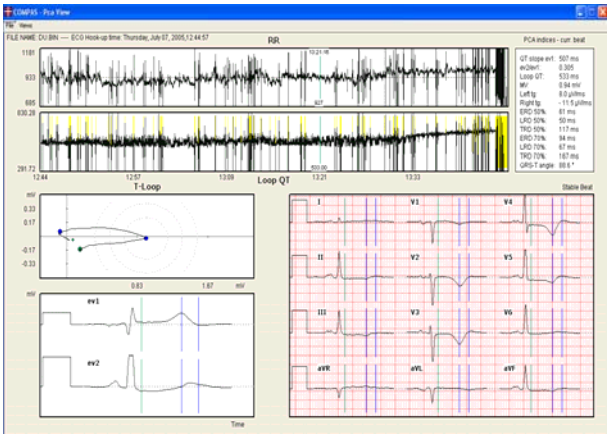
	ID	Age	Gender	CAD	EF (%)	LVH	Normal creatinine	BB
Group 1	T001	65	F	No	63	No	Yes	No
	T003	45	M	No	28	Yes	Yes	No
	T006	77	F	Yes	35	Yes	Yes	No
Group 2	N12*	35	M	No	--	No	Yes	No
	N18*	44	M	No	--	No	Yes	No
	N06*	32	M	No	--	No	Yes	No

*N. Sarapa, J. Morganroth, J. P. Couderc et al. "Electrocardiographic identification of drug-induced QT prolongation: assessment by different recording and measurement methods," *Ann. Noninvasive. Electrocardiol.*, vol. 9, no. 1, pp. 48-57, Jan.2004.

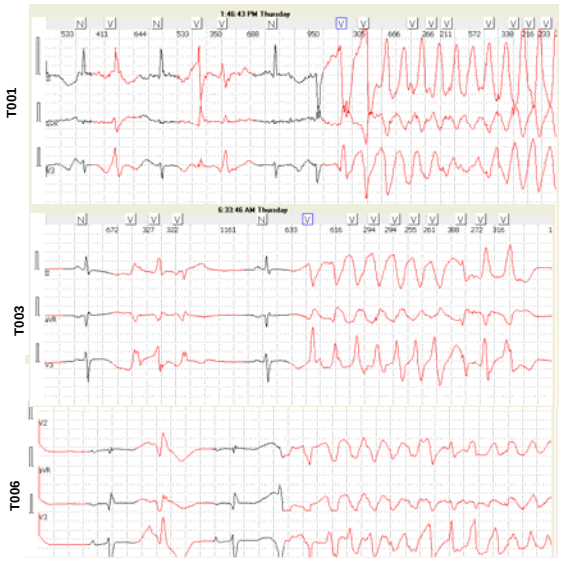
Methods (II)

All measurements were done from lead EV1

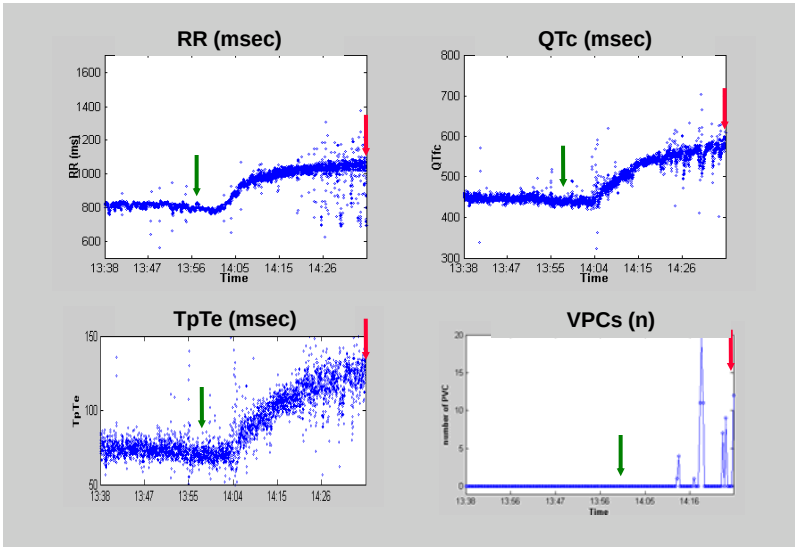
- **QT measurements** (msec): Fridericia correction
- TpTe interval (msec)
- Beat-to-beat QT variability
- T-wave magnitude (mV)
- T-wave alternans (y/n) Visual assessment
- T-wave complexity (n.u.)
- VPCs (n/10 min) Semi-manual annotation



Results (I)



Results (I): monitoring repolarization



Results (II): 10 min average

Average values in repolarization parameters within a 10-minute intervals
In (+) TdP cases: prior to the occurrence of TdPs
In (-) TdP cases: prior to maximum QTc prolongation

Absolute values	(+)TdPs (n=3)	(-)TdPs (n=3)
RR (msec)	1038±119	1038±91
QTcF (msec)	555±34	478±21
TpTe (msec)	118±9	107±28
madQTc* (n.u.)	0.93±0.64	0.23±0.08
T-wave magnitude (mV)	-0.36±0.35	0.22±0.17
Macro T-Wave alternans	No	No
T-wave complexity (n.u.)	0.29±0.18	0.18±0.04
VPCs (n/10 min.)	60±20	0±0

* madQTc is a measurement of QTc variability adjusted for heart rate variability (Couderc et al. Drug. Saf.,2009).

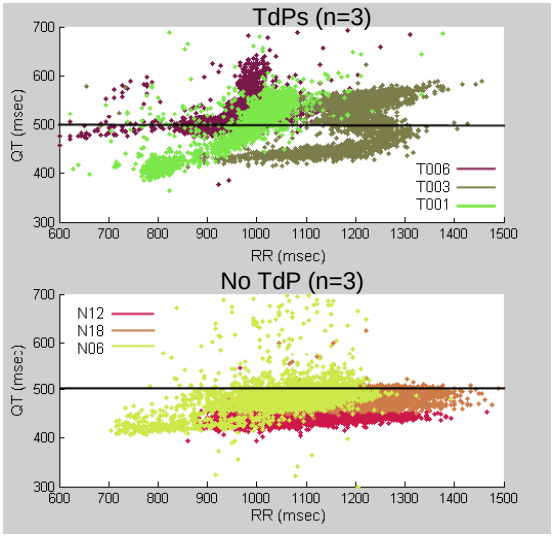
Results (III): delta values

Average changes (delta) between 10-minute intervals
In (+) TdP cases: at 1 hour prior to TdPs and just prior to the occurrence of TdPs
In (-) TdP cases: at baseline and just prior to maximum QTc prolongation

Delta values	(+)TdPs (n=3)	(-)TdPs (n=3)
RR (msec)	128±75	216±134
QTc (msec)	74±12	80±9
TpTe (msec)	35±12	21±15
madQTc (n.u.)	0.7±0.4	0.1±0.1
T-wave magnitude (mV)	-0.06±0.08	-0.01±0.10
Macro T-Wave alternans	No	No
T-wave complexity (n.u.)	-0.07±0.26	0.03±0.03
VPCs (n/10 min.)	56±20	0±0

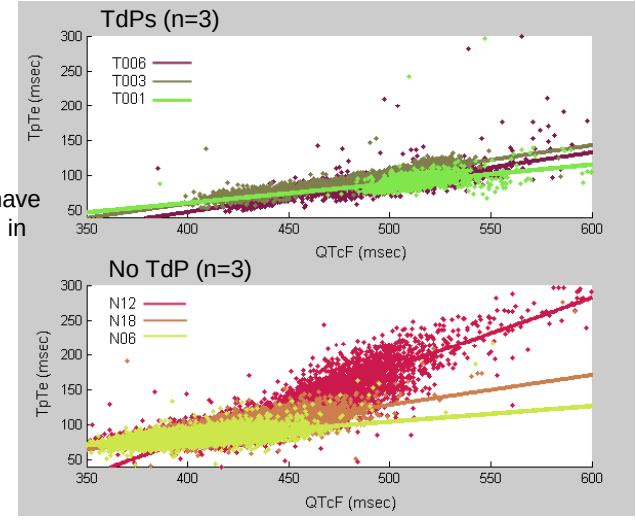
Results (IV): beat-to-beat QT profiles

- One-hour based beat-to-beat analysis of the QT and RR values (each individual plotted in different color)
- In +TdPs : prior to the arrhythmia
- In –TdP: prior to max QT prolongation



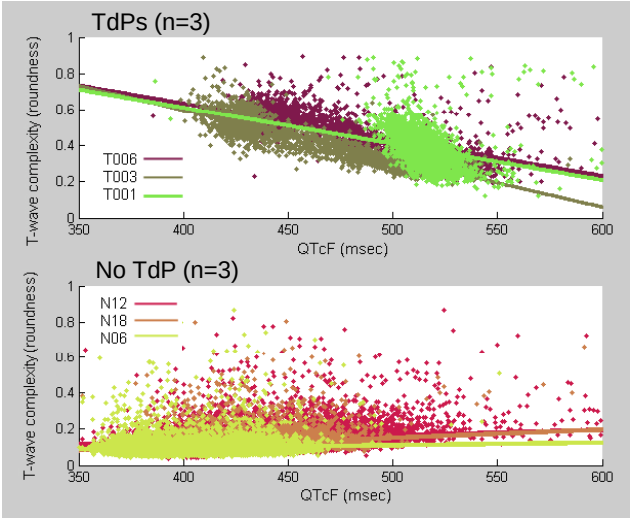
Results (V): TpTe and QTcF

- The groups with and without TdPs do not have significant differences in terms of TpTe relationship to QTcF.



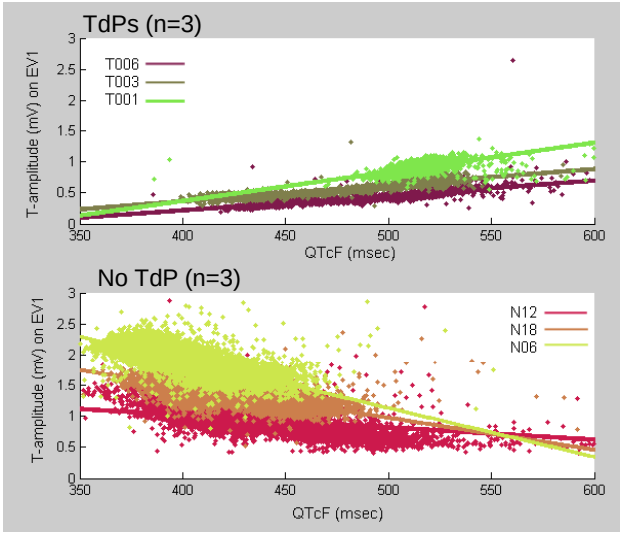
Results (VI): T-wave complexity and QTcF

- In +TdPs : T-loop complexity is QTc dependent
- In –TdP: T-loop complexity is QTc independent



Results (VII): T-amplitude and QTcF

- The relationship between T-amplitude (ev1) and QTcF are opposite between individuals with and without TdPs.



Conclusions (I)

- The individuals who developed sotalol-induced TdPs exhibit longer baseline QTc interval.
- There is no difference in the magnitude of sotalol-induced prolongation of QTc between the groups with and without TdPs.
- Individuals with TdPs reveal larger beat-to-beat variability of the QT intervals, lower T-wave amplitude and presence of VPCs.
- Individual with TdPs have different dynamic profiles of the T-wave morphology (amplitude, T-wave roundness, etc.) across QTcF values which may reveal a very different effects of the drug on repolarization heterogeneity than in individuals exposed to sotalol who did not develop TdPs.

Conclusions (II)

In clinical settings and in drug safety studies, the use of continuous ECG recordings and the analysis of combined dynamic features of QT/QTc prolongation and ECG markers of repolarization heterogeneity may be critical to the assessment of individual predisposition to drug-induced TdPs or to the evaluation of drug cardiotoxicity.

Contributors

Stefan Kaab, University of Munich (Germany)
Martin Hinterseer, University of Munich (Germany)
Xiajuang Xia, University of Rochester Medical Center (NY, USA)
Betty Mykins, University of Rochester Medical Center (NY, USA)
Wojciech Zareba, University of Rochester Medical Center (NY, USA)