# Repolarization Morphology and Cardiac Safety

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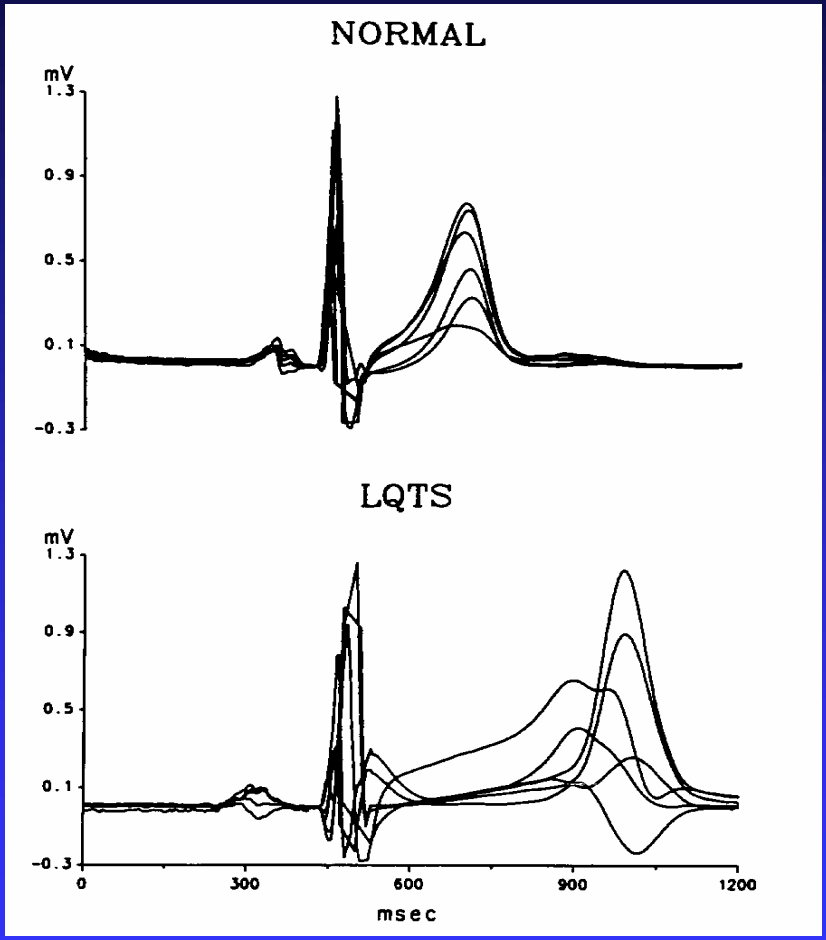
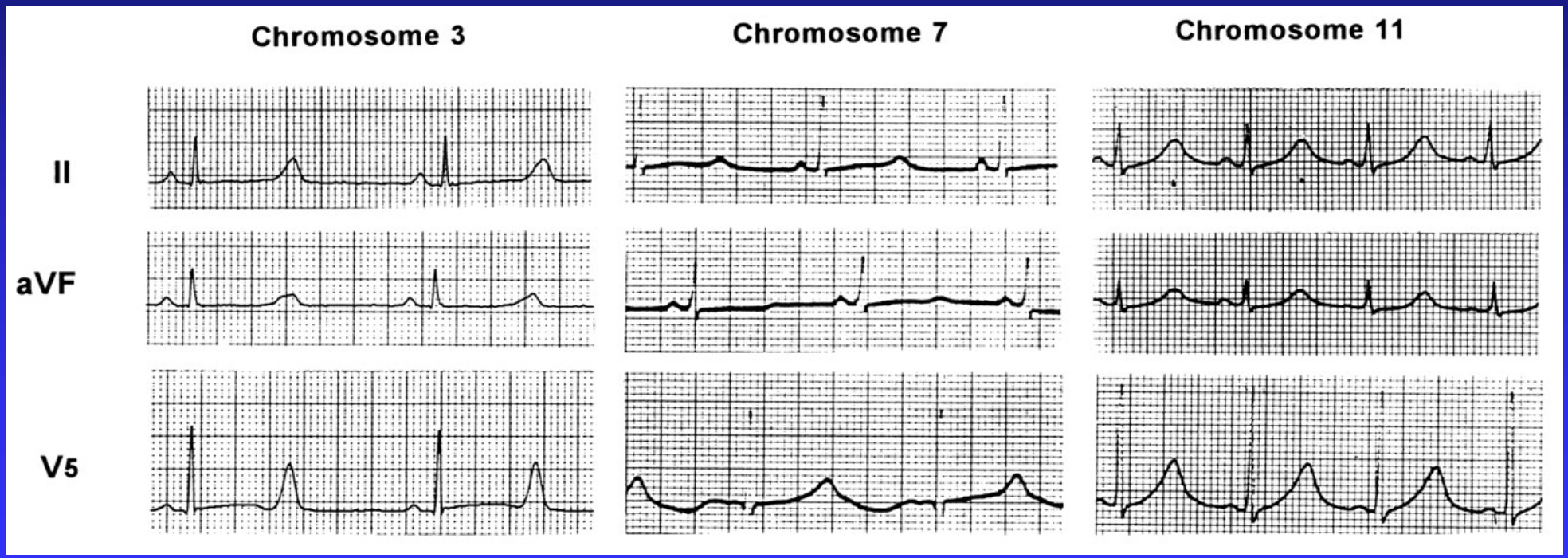
# T Wave Morphology




Benhorin J et al.
Circulation 1990;82:521-7

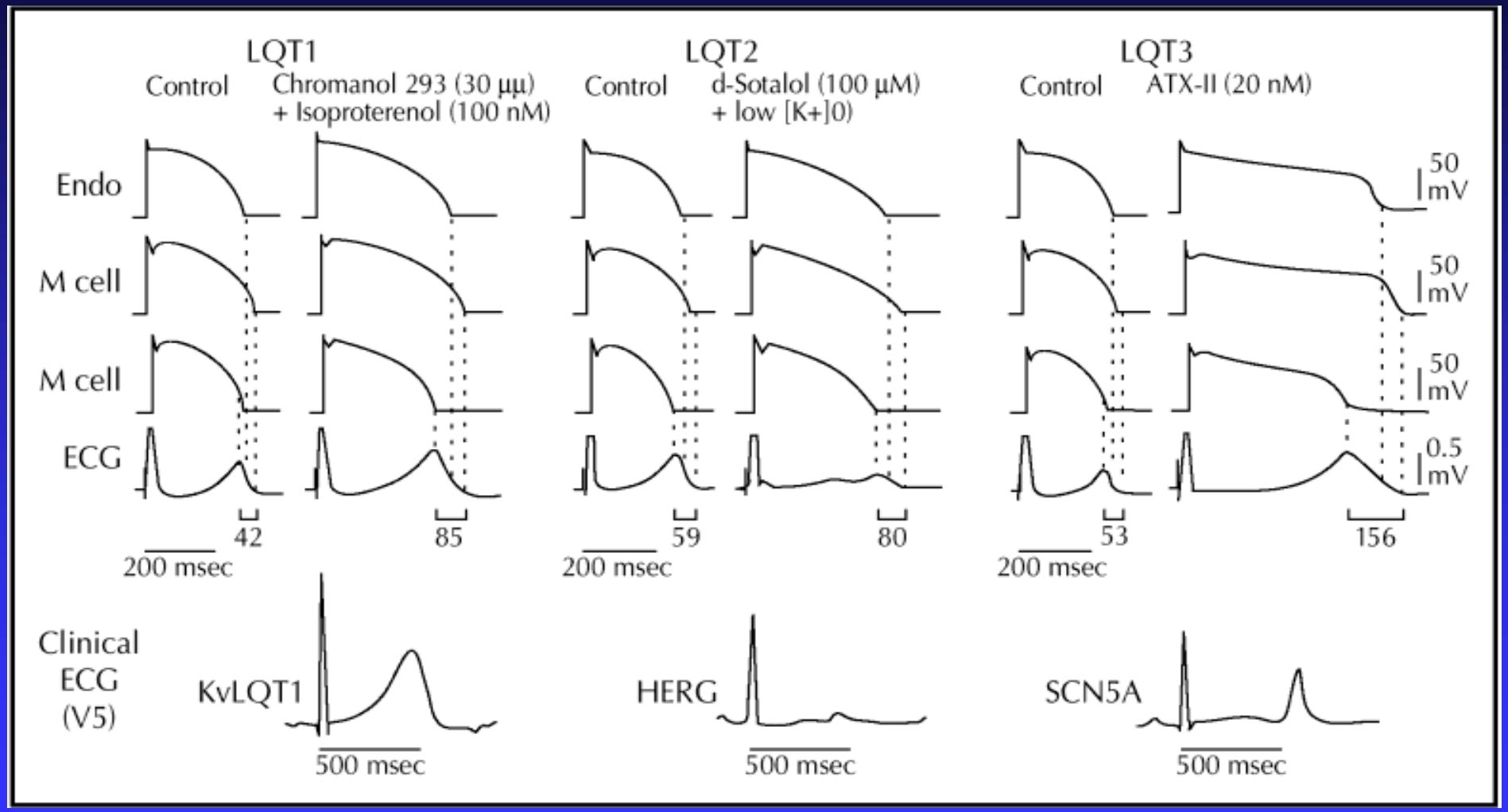
# T-wave morphology and LQTS mutations




LQT3 LQT2 LQT1

Moss AJ, Zareba W, Benhorin J et al. Circulation. 1995;92:2929-2934.

# Transmural Heterogeneity of Repolarization

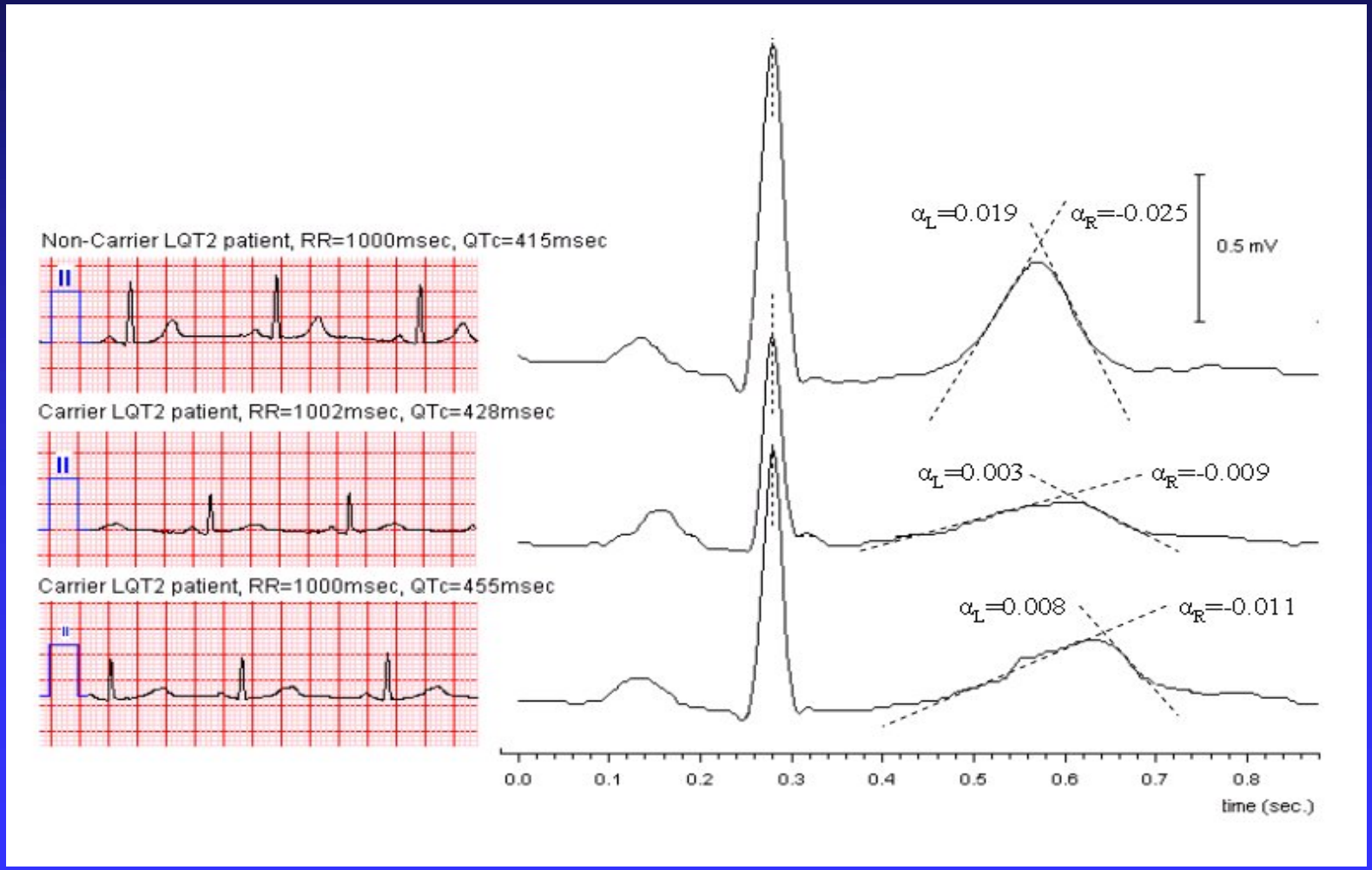



Antzelevitch C and Shimizu W. Curr Opin Cardiol 2002;17:43-51

# Repolarization Duration and T wave Complexity by Genotype

| Variable | LQT1 N=84 | LQT2 N=43 | P value |
|---|---|---|---|
| QTc | 488±26 | 496±26 | 0.098 |
| QTpc | 385±27 | 371±52 | 0.483 |
| TpTo | 95±17 | 117±48 | 0.016 |
| T wave complexity | 0.18±0.08 | 0.27±0.13 | <0.001 |

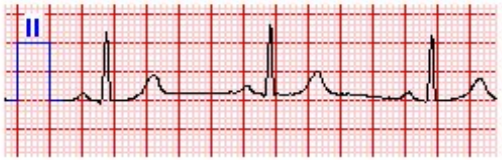
# T Wave Morphology in LQT2 Carriers and Noncarriers



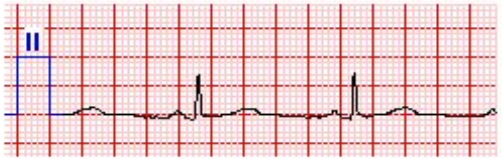
# $I_{kr}$-related Repolarization Abnormalities from Surface ECGs

**HERG mutation, LQT2**

Subject non-carrier of HERG mutation
RR=1000 msec, QTc=415 msec

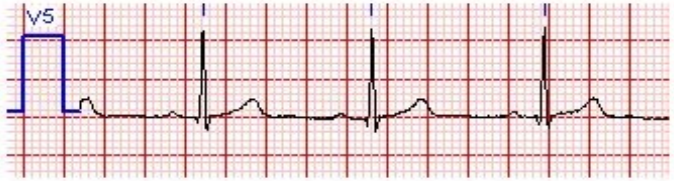



Patient carrier of HERG mutation
RR=1002 msec, QTc=428 msec

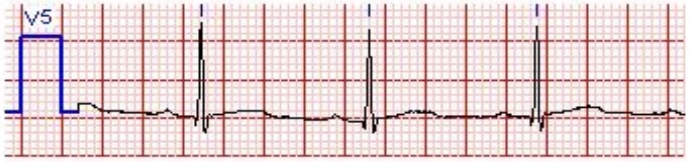



**Sotalol**

Healthy subject
RR=845 msec, QTc=383 msec

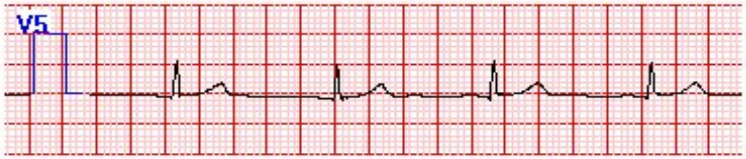



Healthy subject after sotalol dose (1430ng/ml)
RR=845 msec, QTc=417 msec

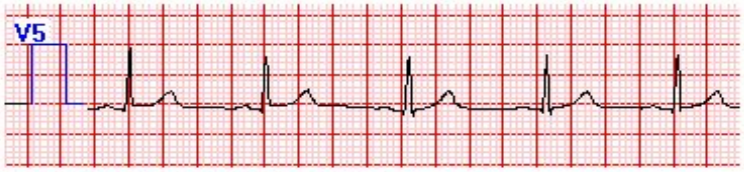



**Moxifloxacin**

Baseline, RR=1072mec, QTc=425 msec

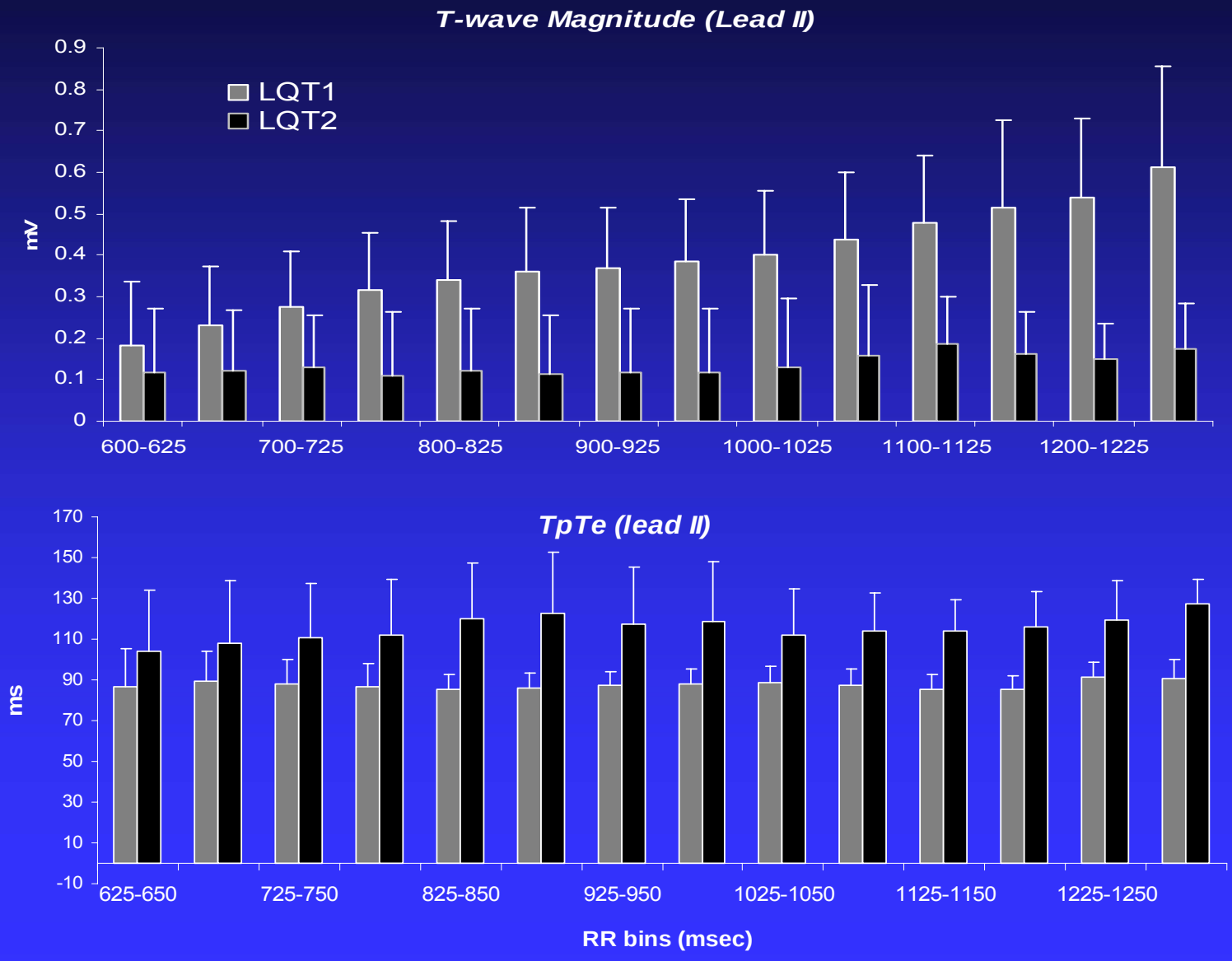



Moxifloxacin, RR=1038mec, QTc=433 msec

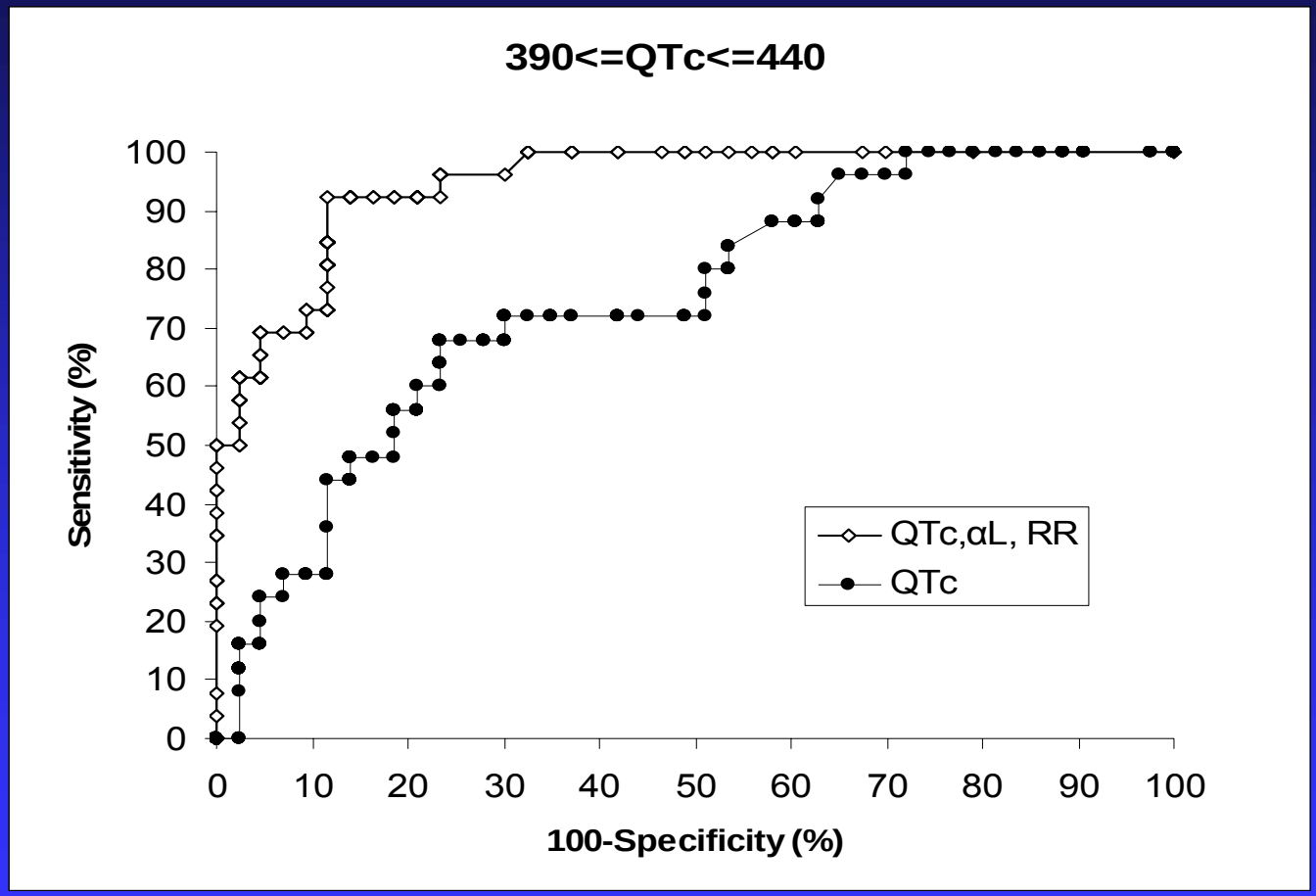



(2 hours after 400 mg dose)

# Scalar T-wave measurements, HR Dependency and LQTS Mutations



# QTc distribution in LQT2 (KCNH2 mutation)




Couderc et al. Heart Rhythm Journal 2006

# T wave Variability Prior to TdP

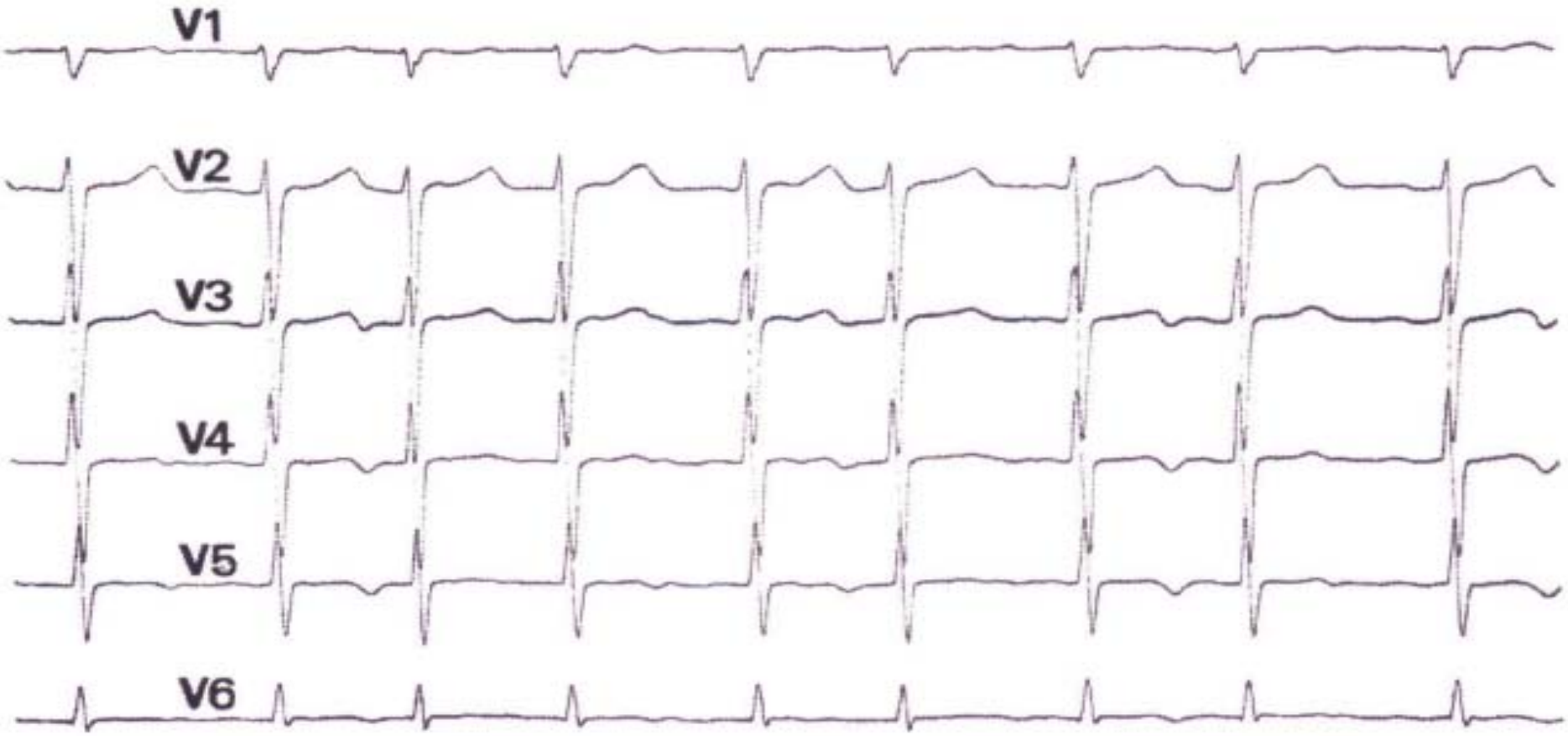


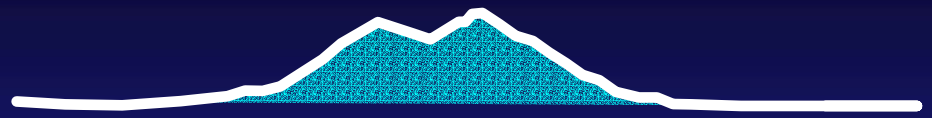

**Figure 2.** *ECG registration of T wave alternans at baseline before the almokalant infusion in TdP patient 3 (see Table II). The registration shows shifting polarity of the T waves, most visible in leads $V_3$-$V_5$.*

**Houltz et al. PACE 1998**

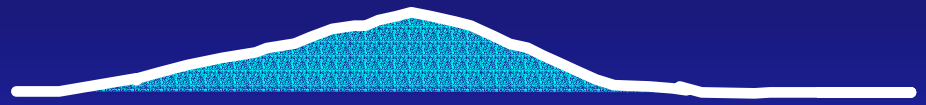
## Distribution of QTc by Categories in 443 LQT2 Gene Carriers (mean age: 26 ± 20 years; 57% females)

| | |
|---|---|
| - normal QTc (<440ms) | n= 62 (14%) |
| - borderline QTc (440-500ms) | n= 264 (60%) |
| - definitely prolonged QTc (>500ms) | n= 117 (26%) |

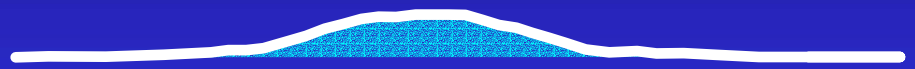
# T Wave Morphology Classification



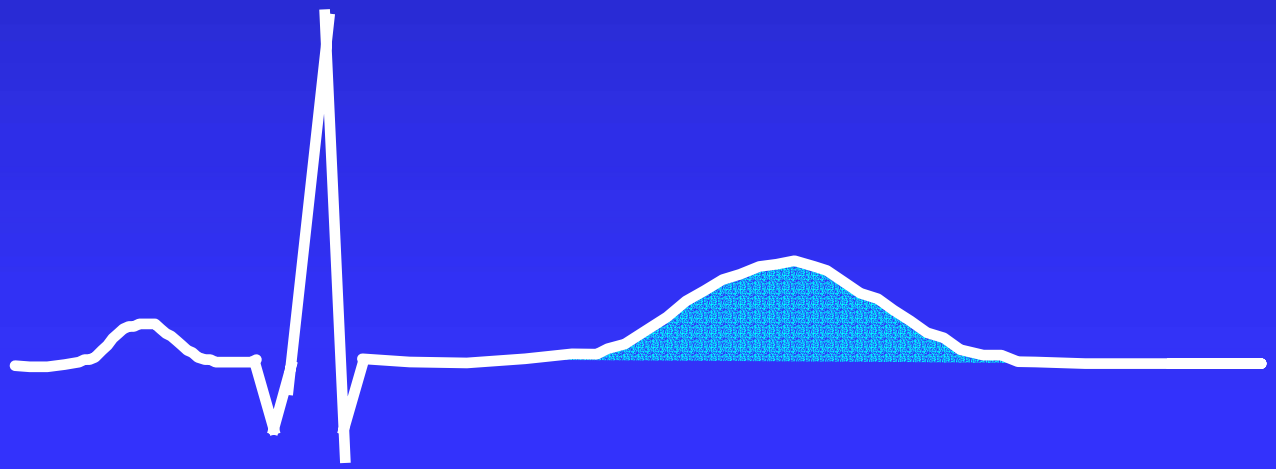
bifid/notched



broad/slow

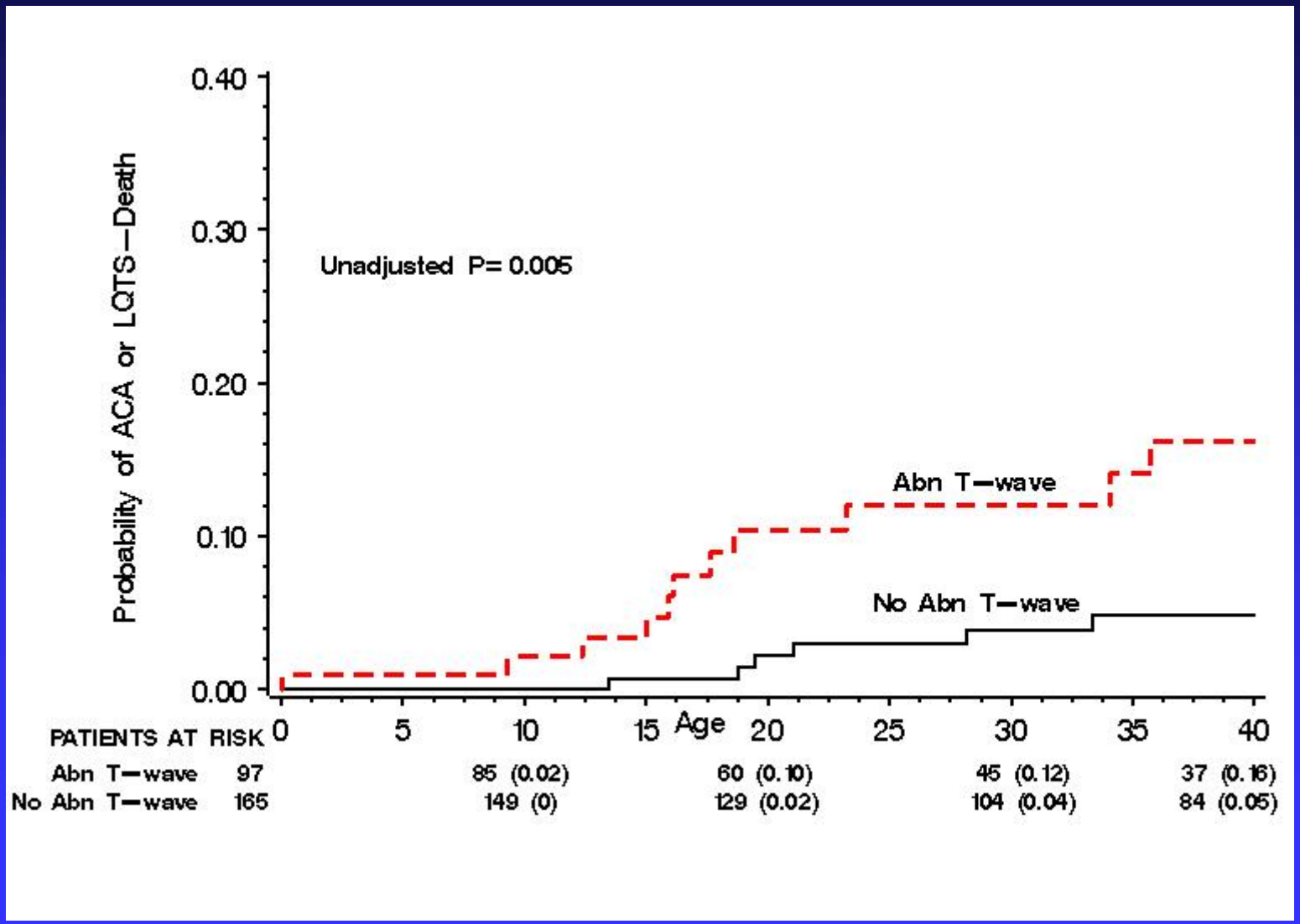


flat

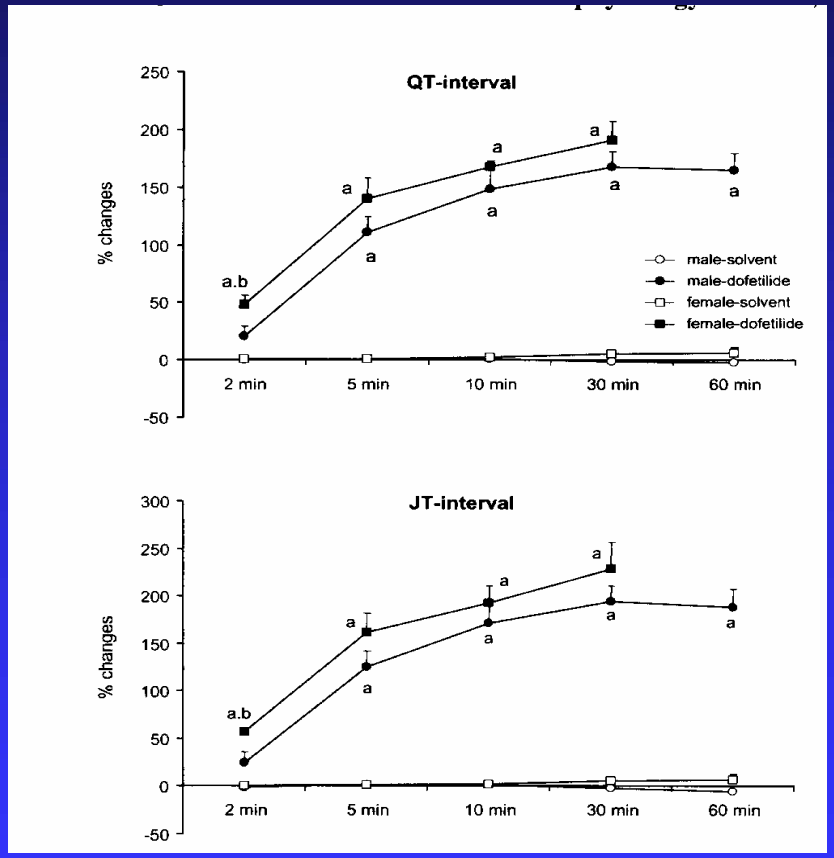


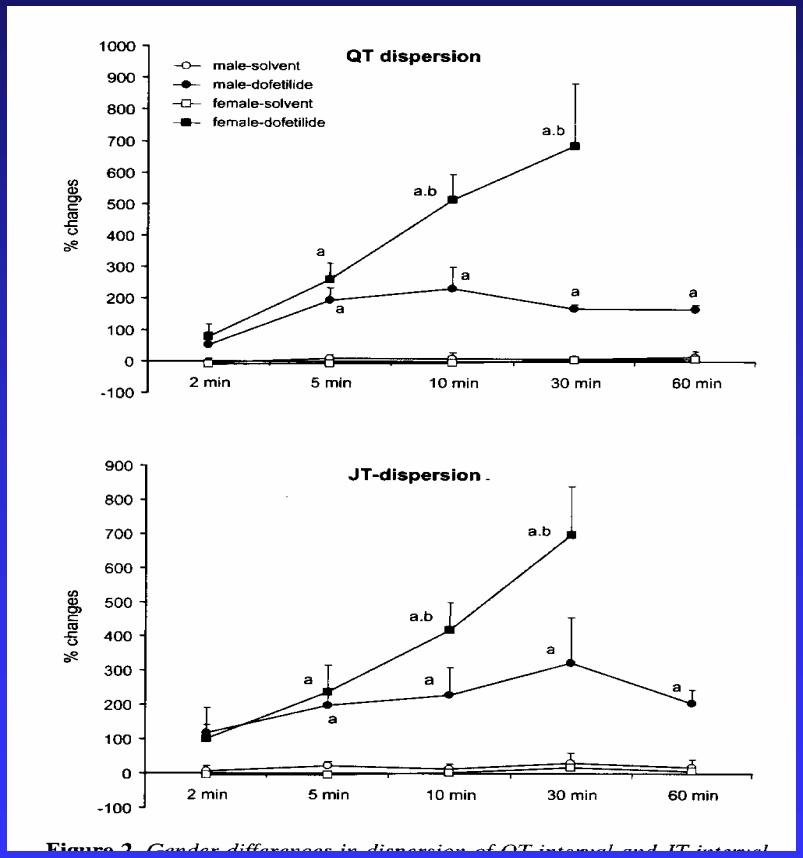
normal

# T wave morphology and ACA or Death in LQT2 Patients with QTc 440-500 ms



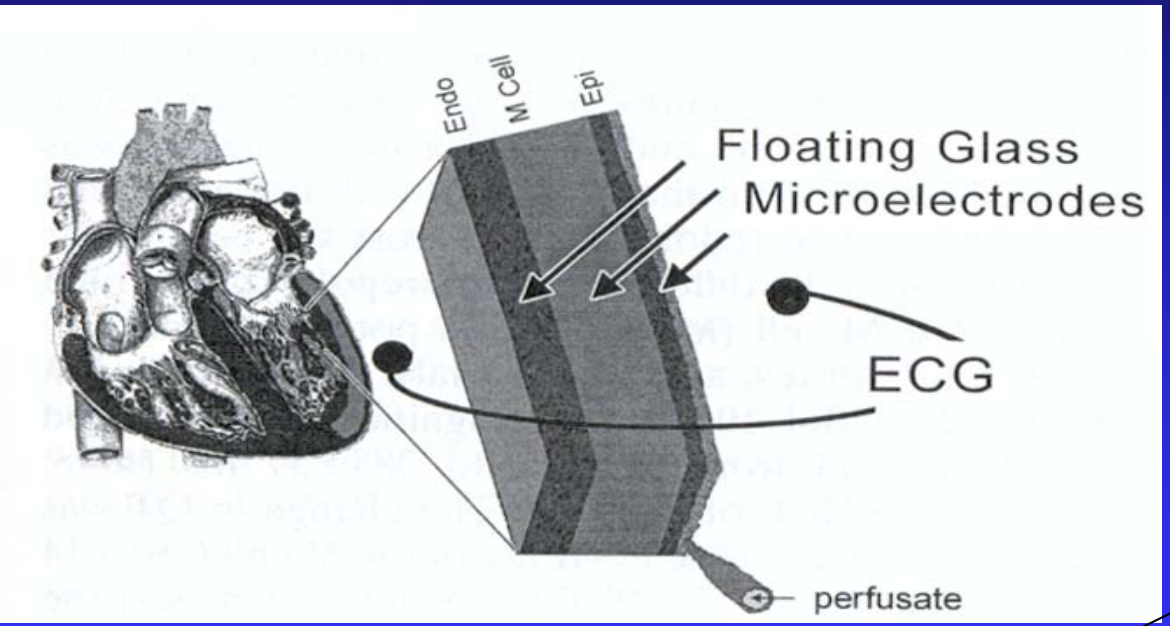
# Percent Change in QT, JT interval and QT, JT Dispersion in Female vs. Male Rabbits after Dofetilide or Placebo

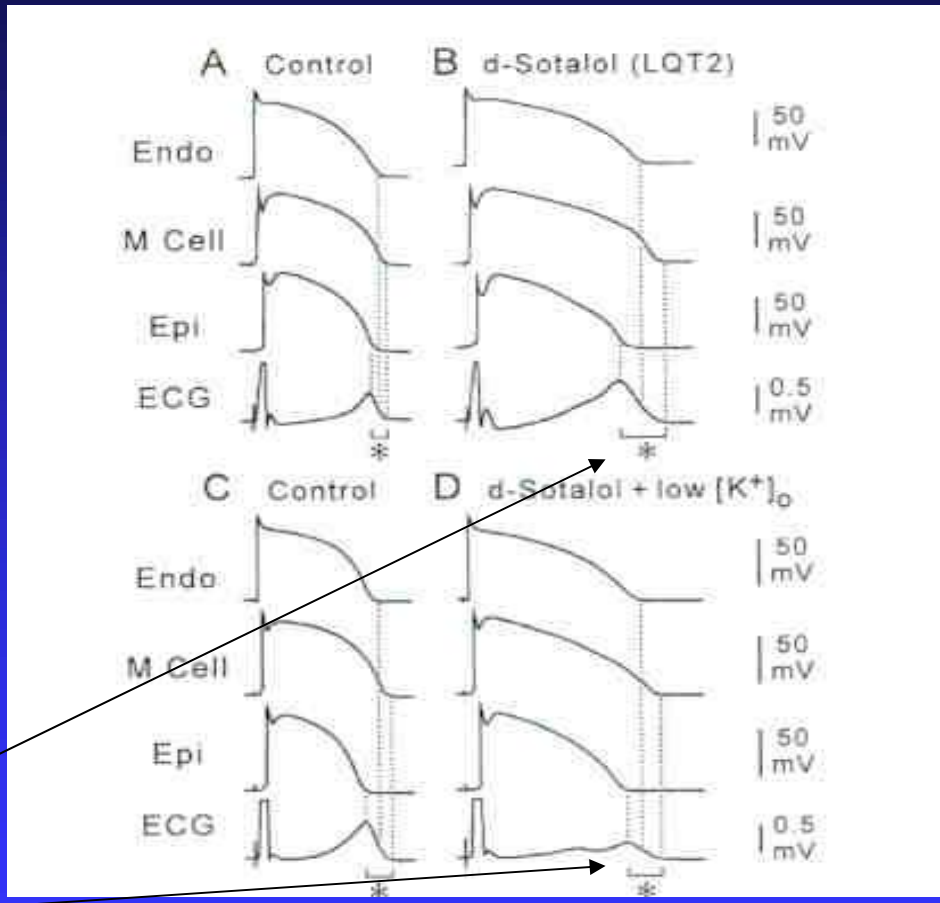



Rong HL et al. J Cardiovasc Electrophysiol 2001;12:538-545

**Different electrophysiology of the myocardial layers accounts for changes in QT-T wave with various lesions**

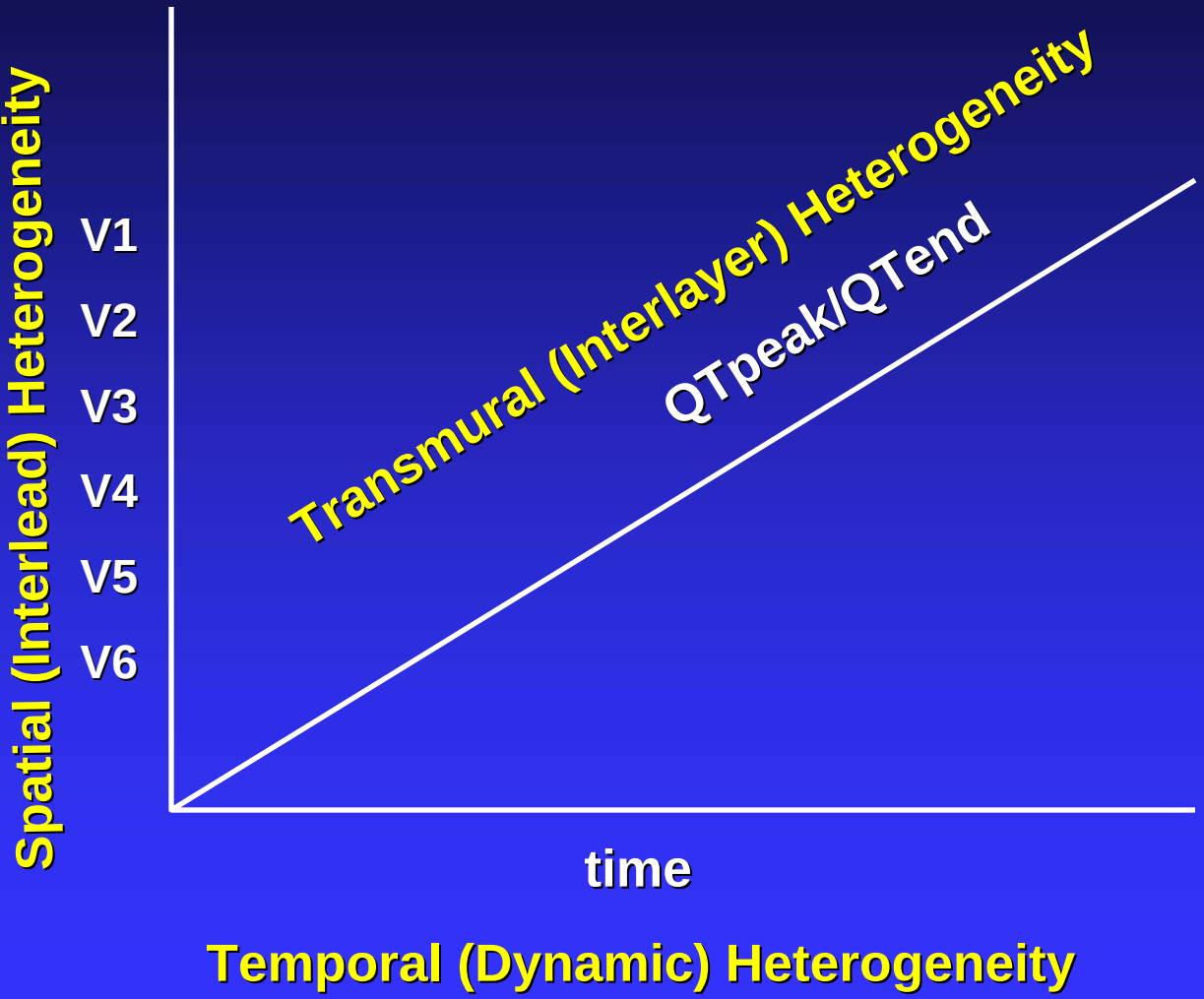


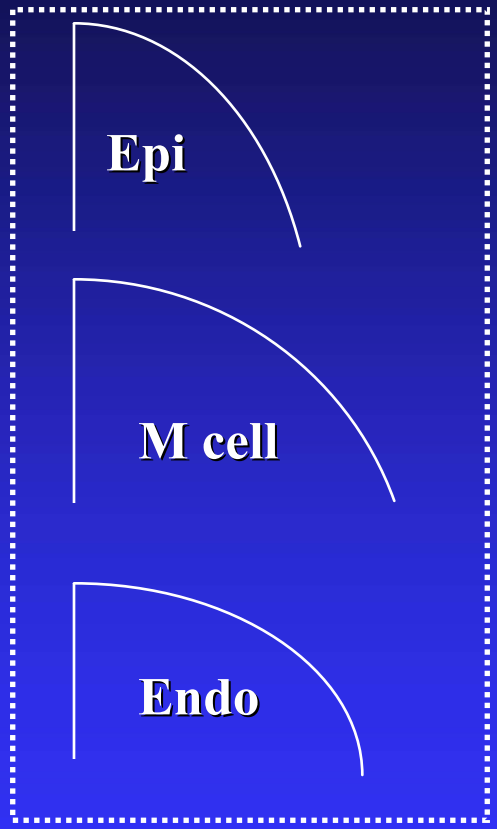




"TDR"= Transmural dispersion of repolarization

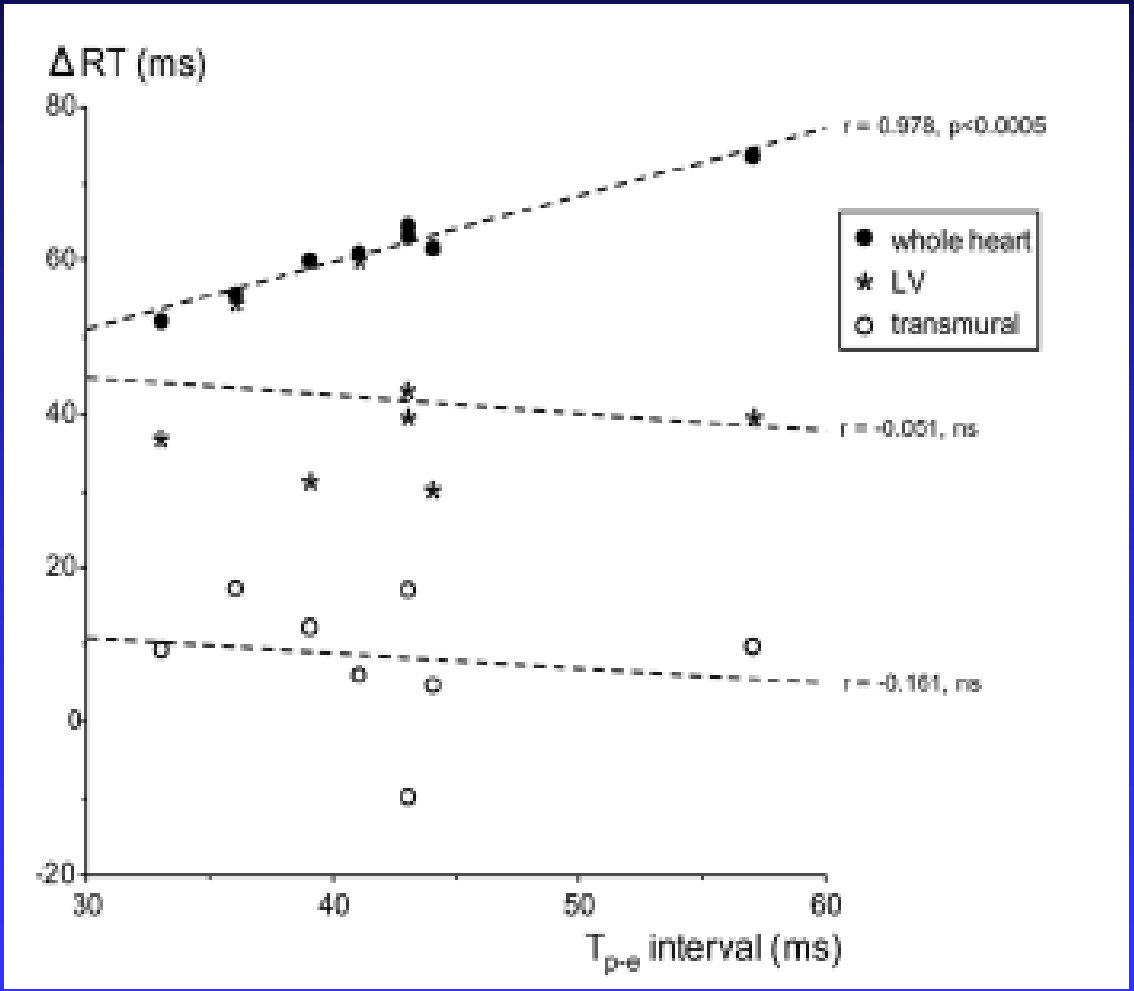
## Global Surface ECG Phenomena

## Local AP Heterogeneity



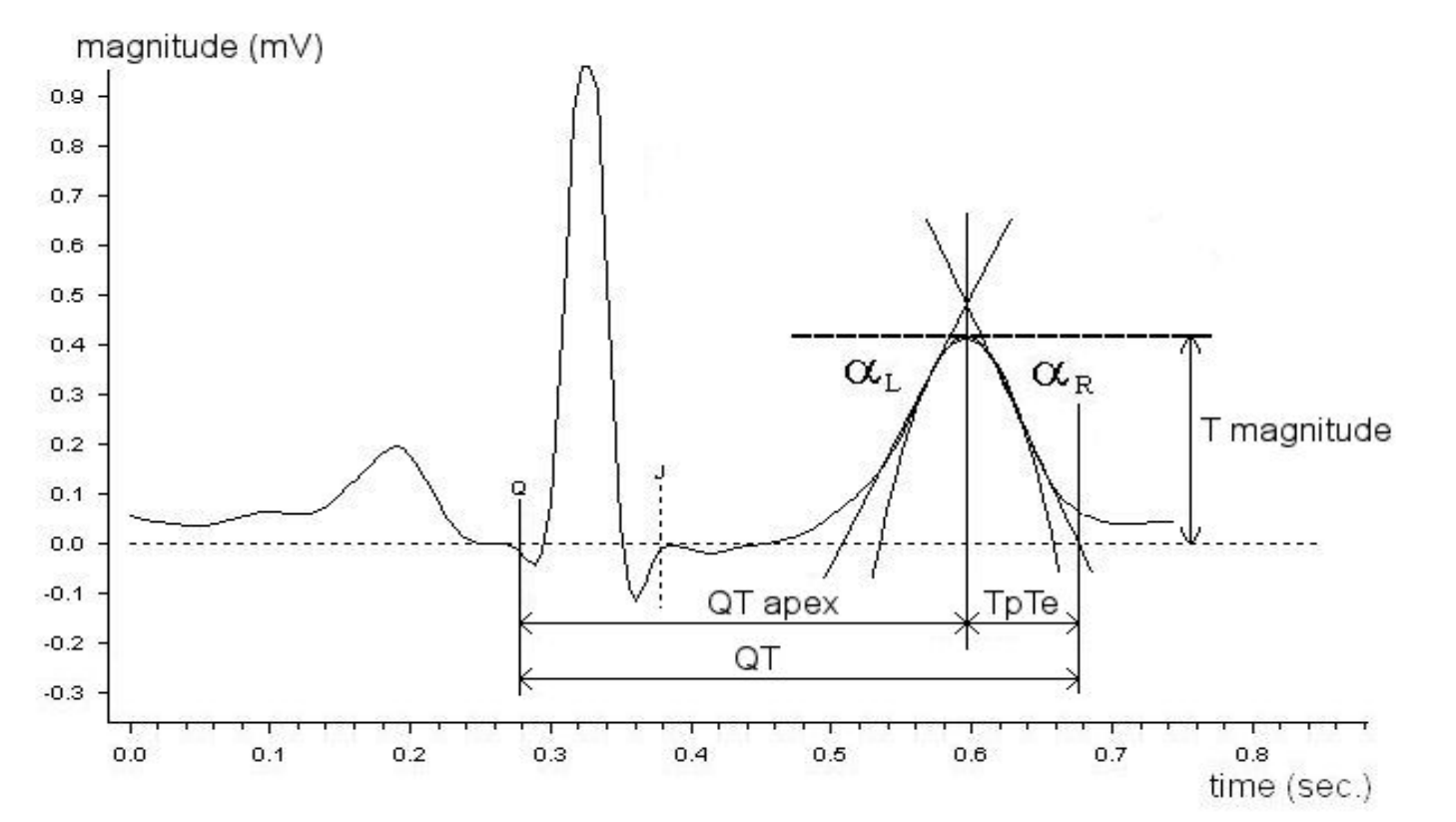



# TpTe Interval and Dispersion of Repolarization



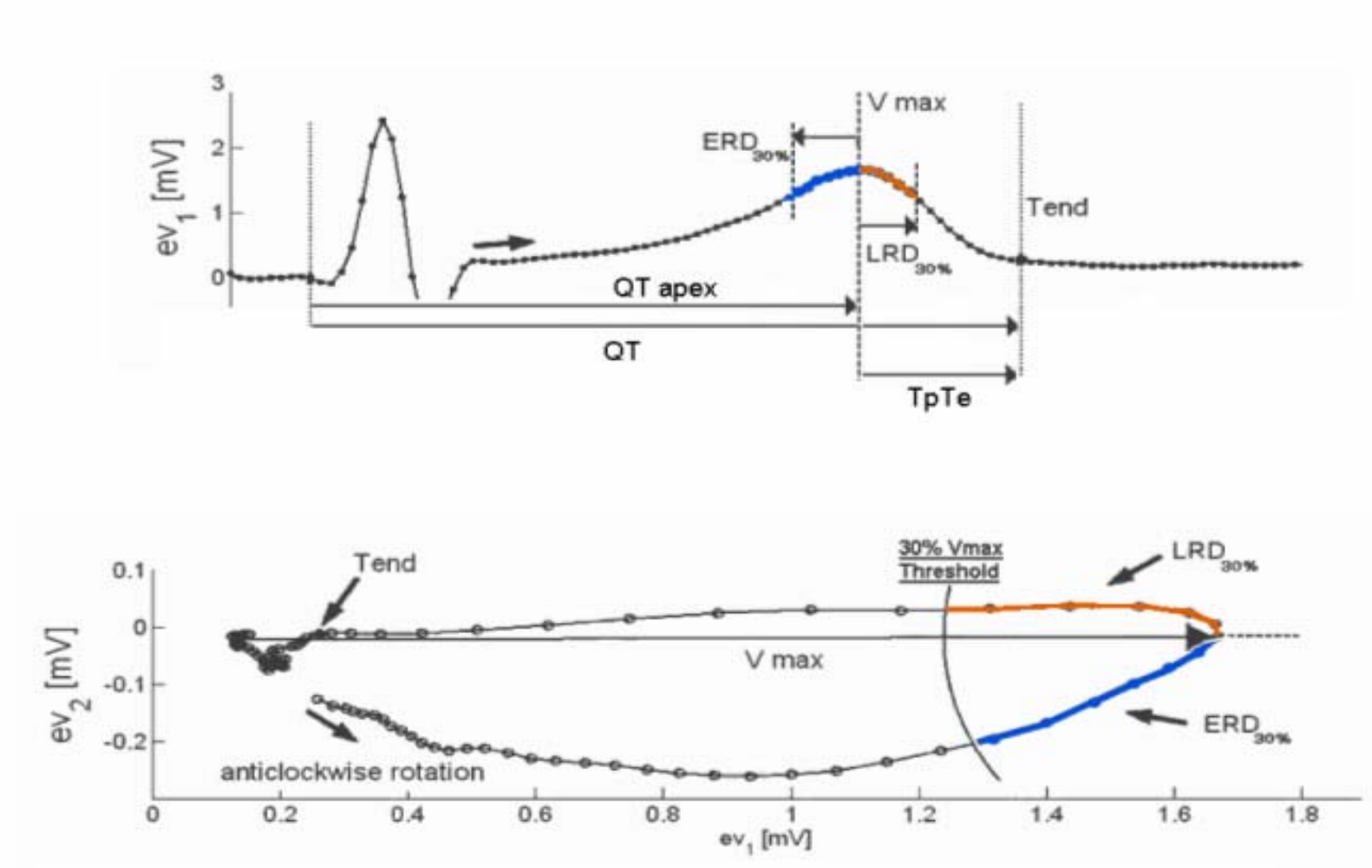

Opthof et al. Heart Rhythm 2007;4:341-8

# Scalar Repolarization Morphology




Couderc JP et al. Computers in Cardiology 2006, 33:pp.705-708

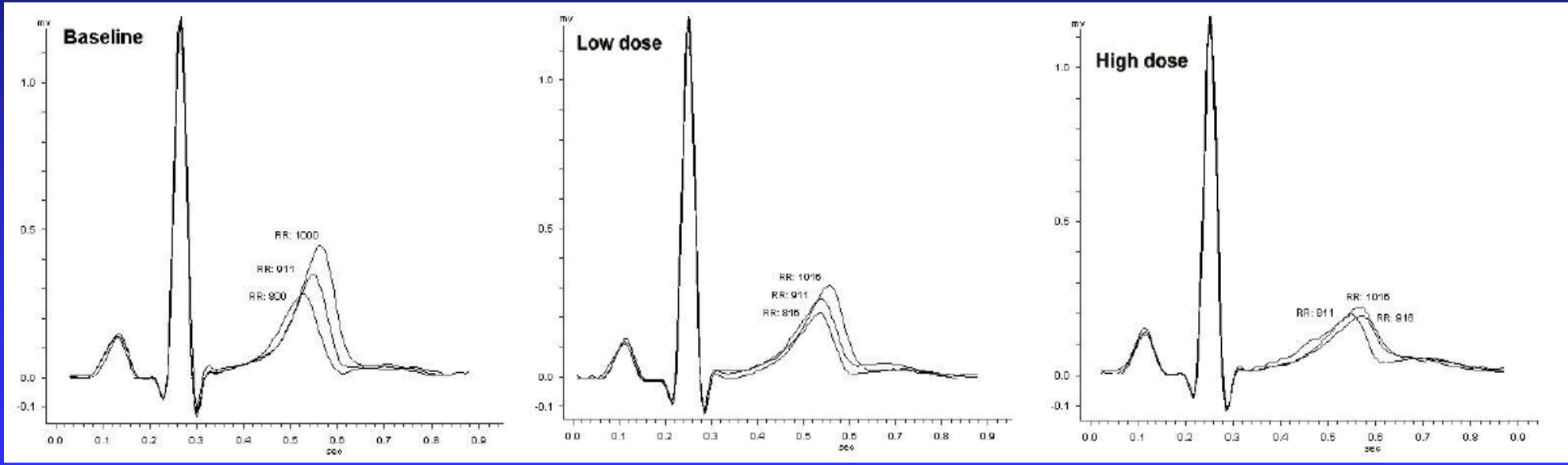
# T-wave Loop Repolarization Parameters




Couderc JP et al. Electrocardiographic Method for Identifying Drug-induced Repolarization Abnormalities Associated with a Reduction of the Rapidly Activating Delayed Rectifier Potassium Current. **IEEE Engineering in Medicine and Biology Society**, New-York 2006 p. 4010-5.

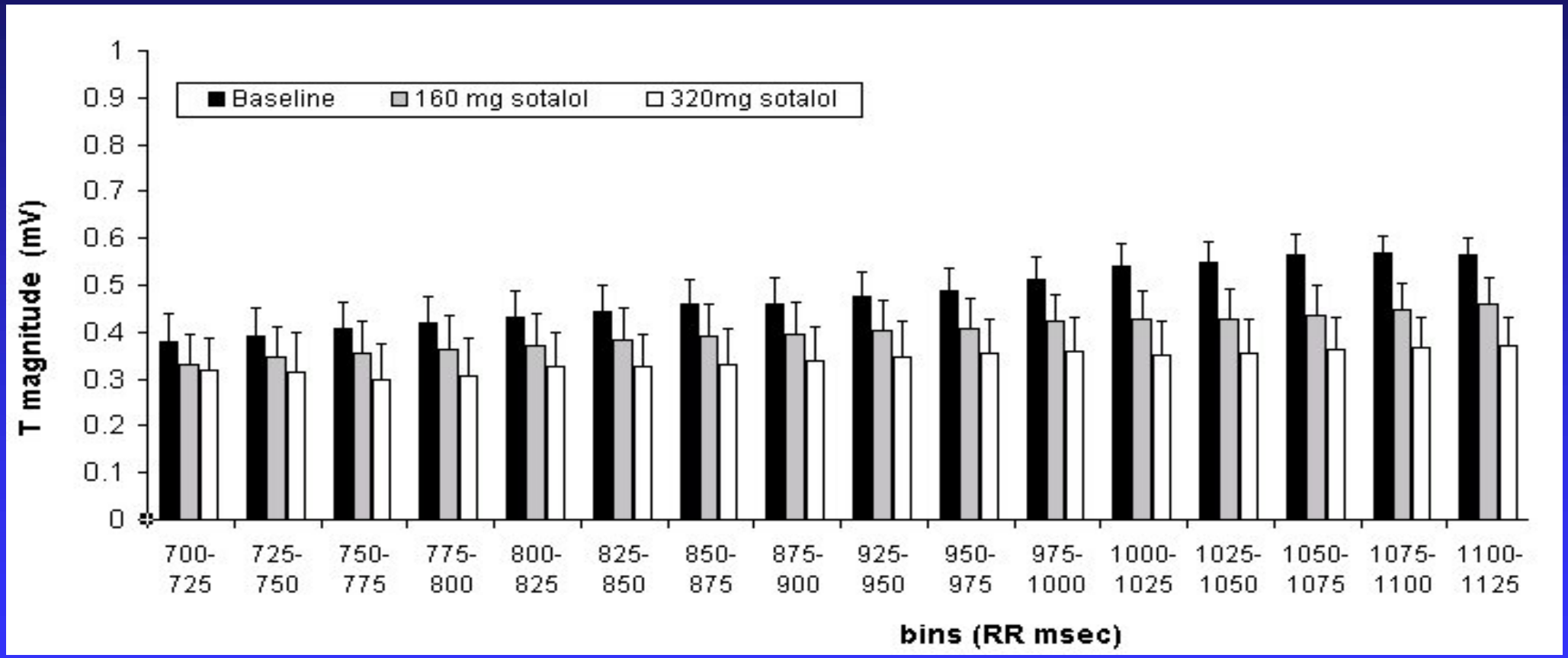
# Sotalol-Induced T-Wave Impairment

Example of ECG tracings illustrating the T-wave amplitude impairment to heart rate induced by sotalol, healthy male subject




**Baseline** **160 mg** **320 mg**

# Sotalol and T-amplitude Dependency to HR

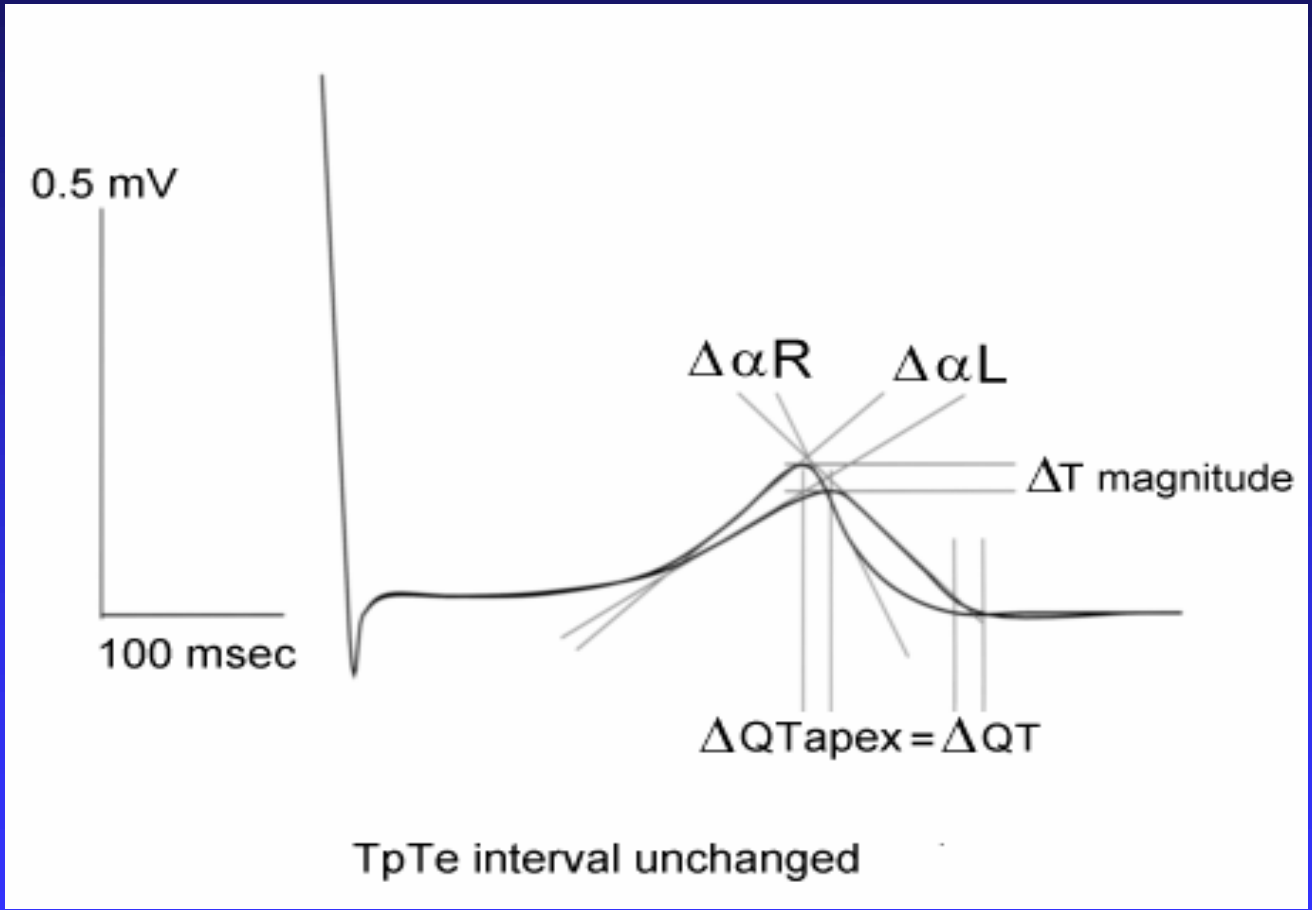


# Moxifloxacin-Induced Repolarization Changes

| | Median difference vs. placebo | p |
|---|---|---|
| QT offset (msec) | 13.6 | 0.020 |
| T magnitude (mV) | -0.03 | 0.023 |
| αL (μV/ms) | -0.36 | 0.007 |
| αR (μV/ms) | 0.58 | 0.011 |
| TpTe (msec) | -0.5 | 0.41 |
| $\lambda_2/\lambda_1$ | 0.01 | 0.41 |
| Planarity (λ3) | -0.05 | 0.14 |
| $ERD_{30\%}$ (msec) | 11.1 | 0.001 |

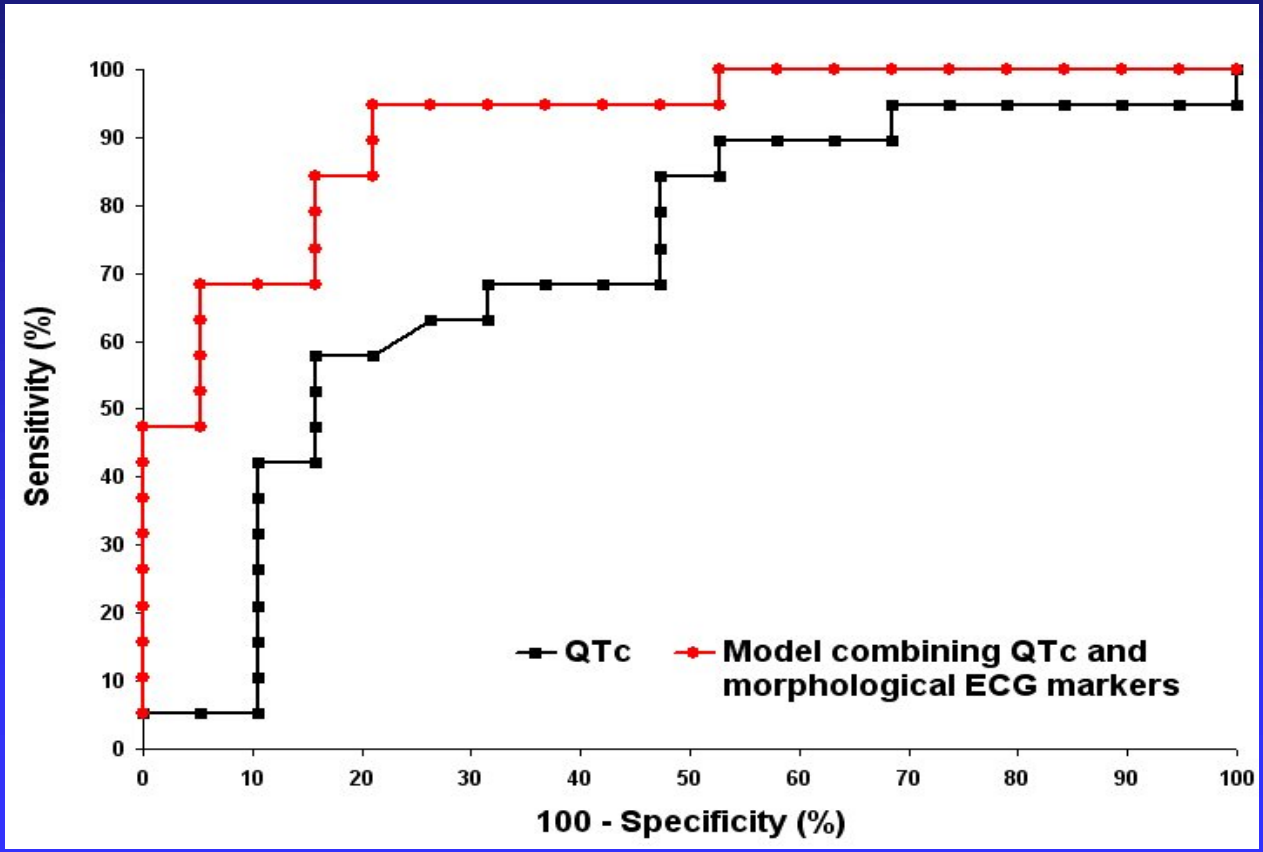
All measurements are corrected for HR using pooled-formula

# Moxifloxacin-induced Repolarization Abnormalities




Simulated ECG tracings

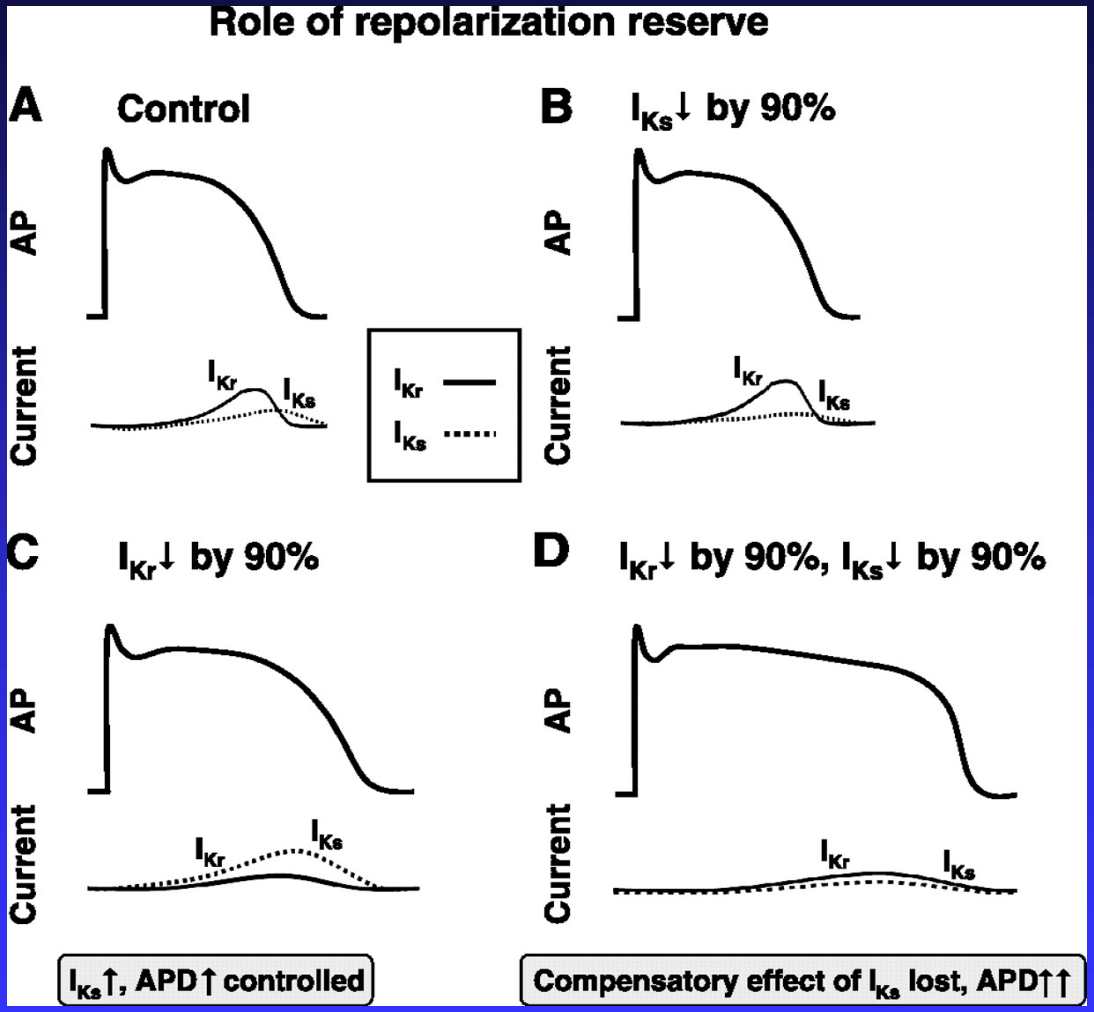
# Moxifloxacin-induced Repolarization Abnormalities



# Ability to Identify TdP Patients at Baseline Before and After Drug Challenge

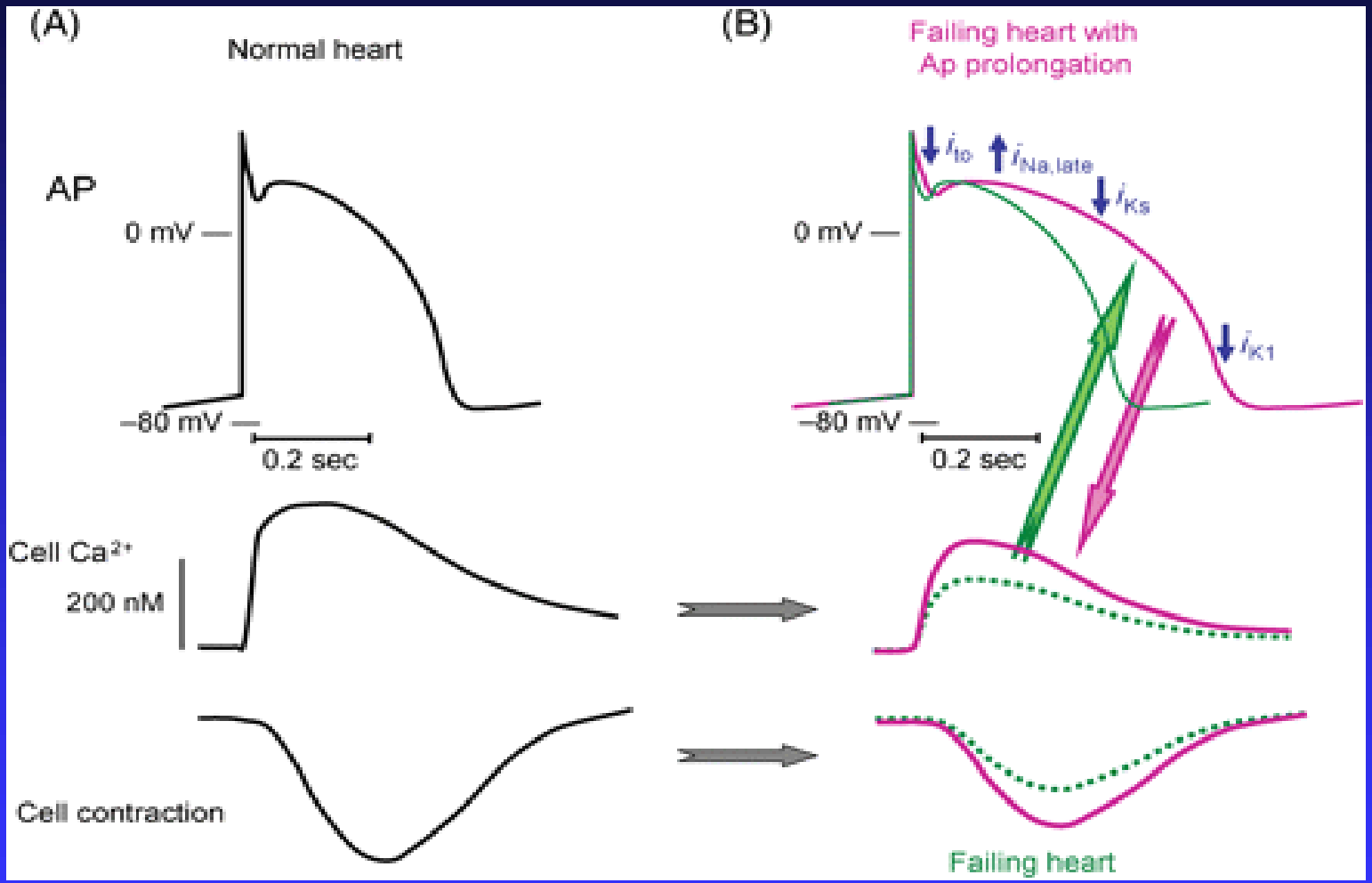
| | Before: Baseline (absolute values) | | P value (baseline) | After: Sotalol challenge (sotalol induced changes) | | P value (challenge) |
|---|---|---|---|---|---|---|
| | (-) TdPs N=17 | (+) TdPs N=16 | | (-) TdPs N=17 | (+) TdPs N=16 | |
| QTc* | *425.7±35.6* | *451.0 ±39.3* | *0.06* | 79.0 ±47.4 | 98.4 ±42.0 | 0.22 |
| TpTe | 104.7 ±30.6 | 108.2 ±30.5 | 0.74 | 8.2 ±23.7 | 38.9 ±40.6 | 0.01 |
| ERD30% | 34.8 ±8.6 | 43.7 ±12.6 | 0.02 | 11.3 ±14.2 | 13.5 ±21.7 | 0.73 |
| ERD50% | 55.9 ±14.6 | 71.4 ±22.1 | 0.02 | 23.3 ±28.7 | 30.9 ±31.9 | 0.47 |
| LRD30% | 27.7 ±4.9 | 35.2 ±17.5 | 0.12 | 3.8 ±3.5 | 6.7 ±15.3 | 0.46 |
| LRD50% | 42.8 ±5.5 | 55.5 ± 31.9 | 0.14 | 5.2 ±5.7 | 20.9 ±27.3 | 0.04 |
| LRD70% | 65.3 ±10.6 | 86.0 ±43.7 | 0.08 | 8.4 ±13.2 | 26.4 ±30.5 | 0.04 |

# Repolarization Reserve



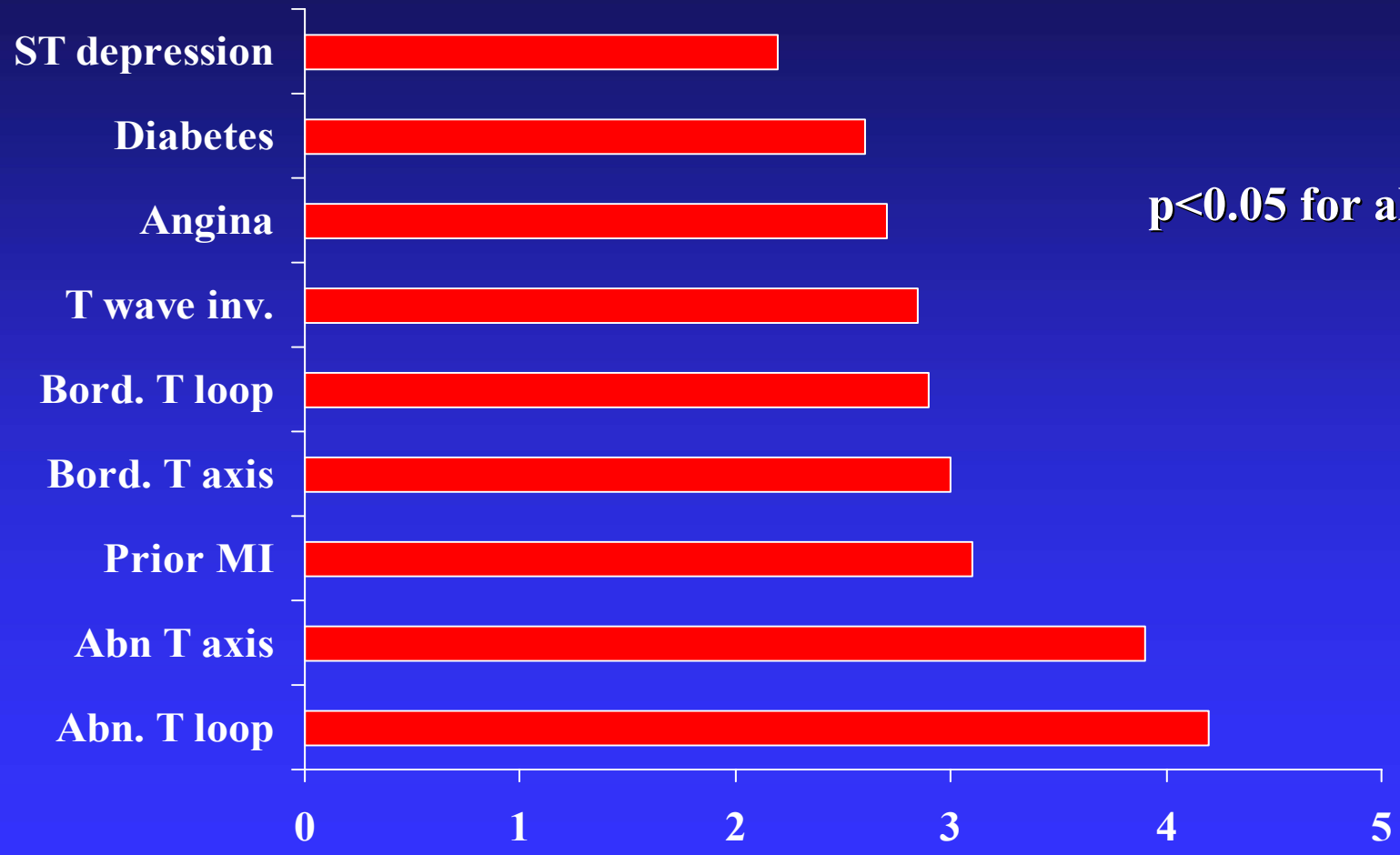

Nattel, S. et al. Physiol. Rev. 2007; 87: 425-456

# A schematic diagram showing the changes in Ca2+ handling and contractility and the potential compensatory function of ion-channel remodelling that causes action potential (AP) duration (APD) prolongation in congestive heart failure




Michael, G. et al. Cardiovasc Res 2008 0:cvn266v2-9;

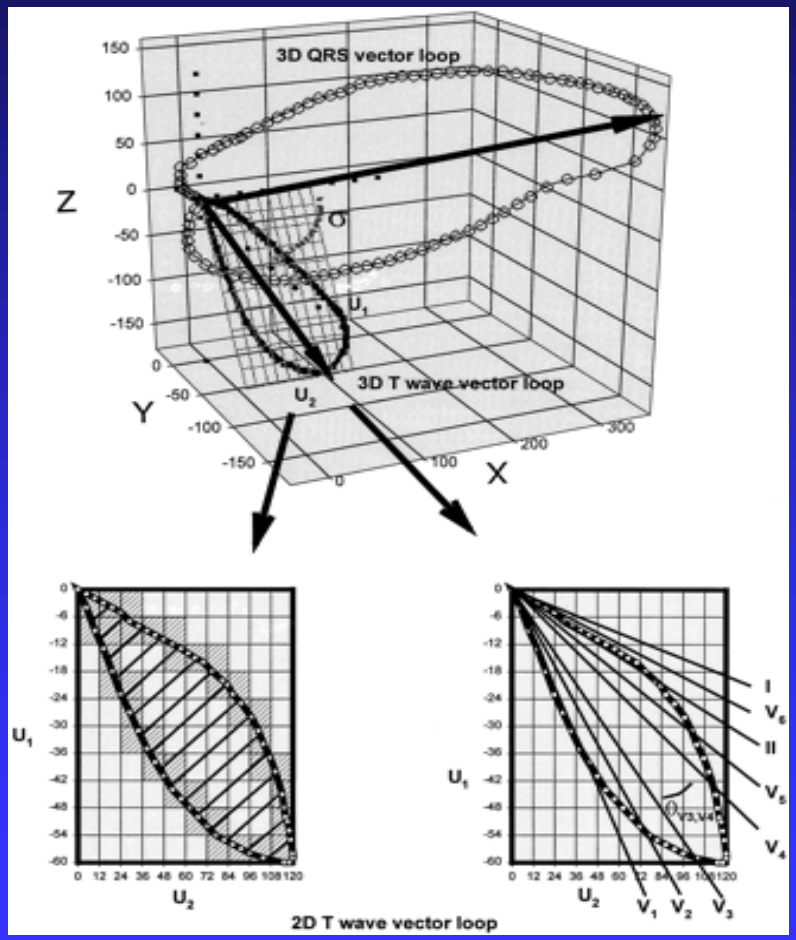
# Age- and Sex-adjusted Hazard Ratios of Cardiac Death in a Population-based Cohort of 5,815 Older (>55 years) Men and Women

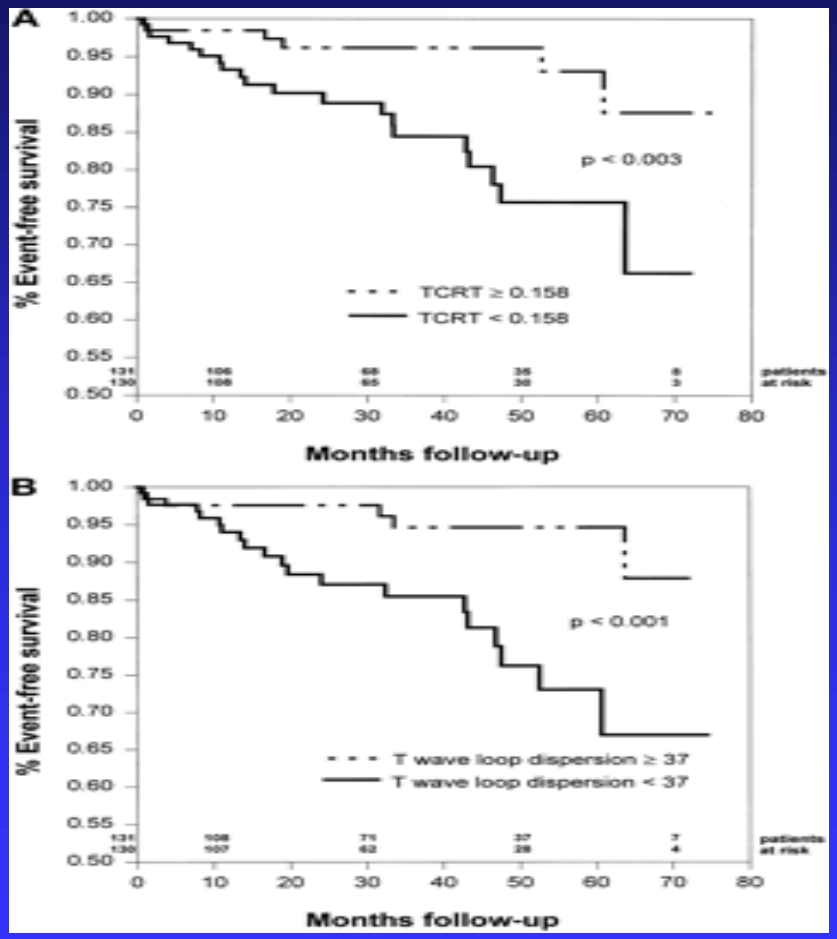



p<0.05 for all HR

Kors et al. J Electrocardiol 1998;31:54-9

# Predictive Value of T Wave Morphology in Postinfarction Patients




Zabel et al. Circulation 2000; 102:1252-1257