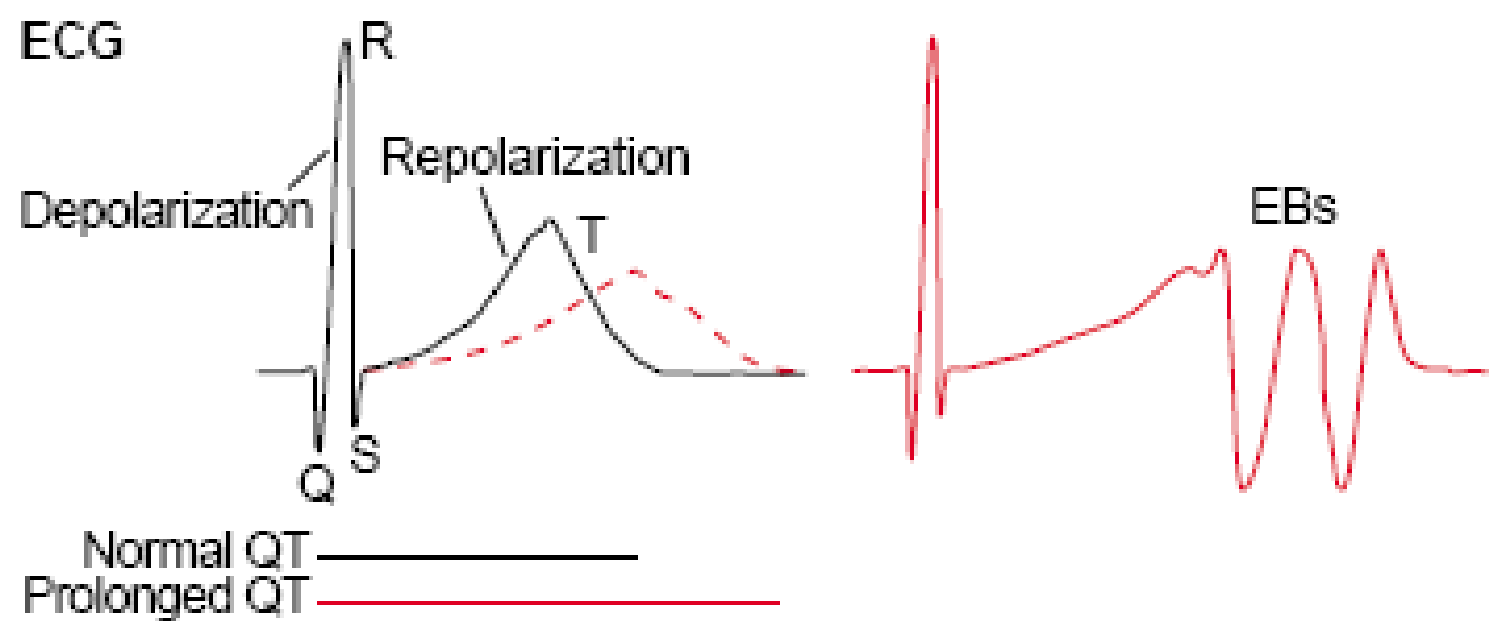
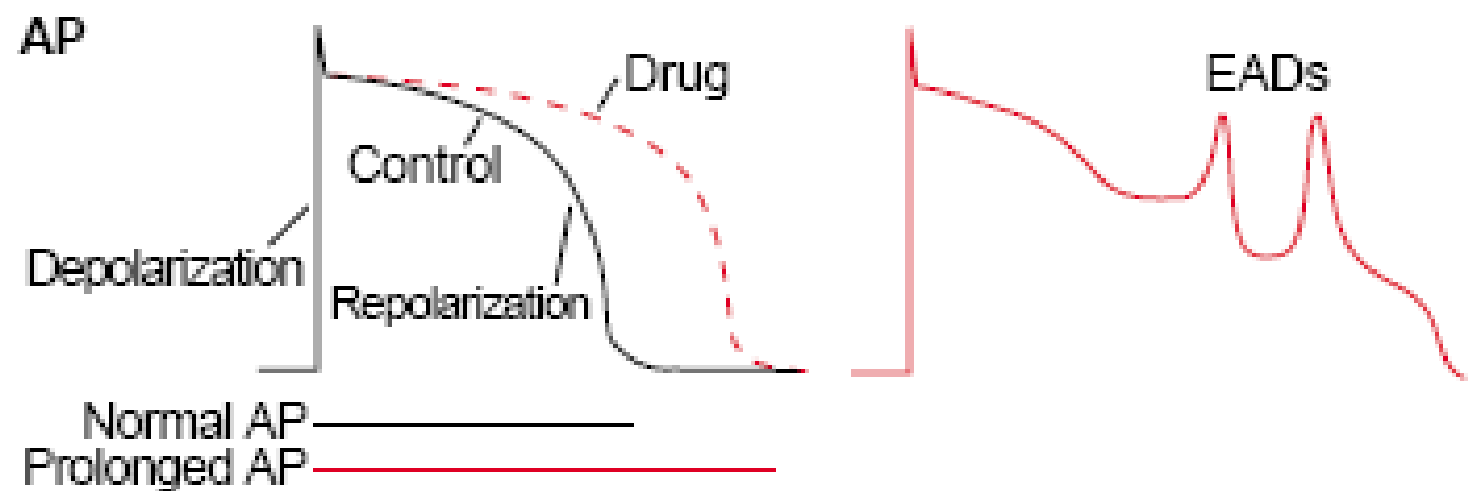


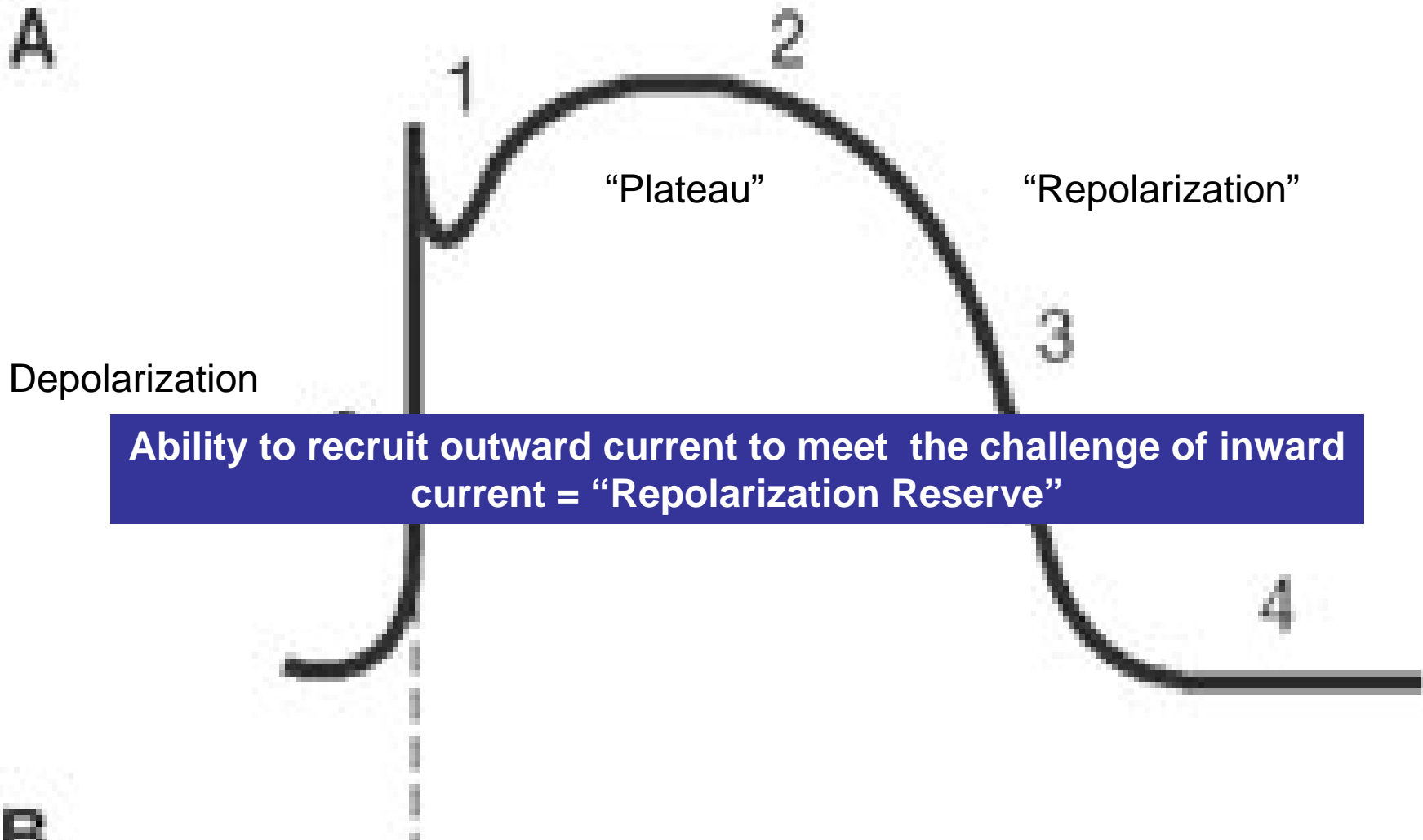
# QT Variability: Application to Drug Studies

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*No relationships to disclose*



**Figure 1** The ventricular action potential

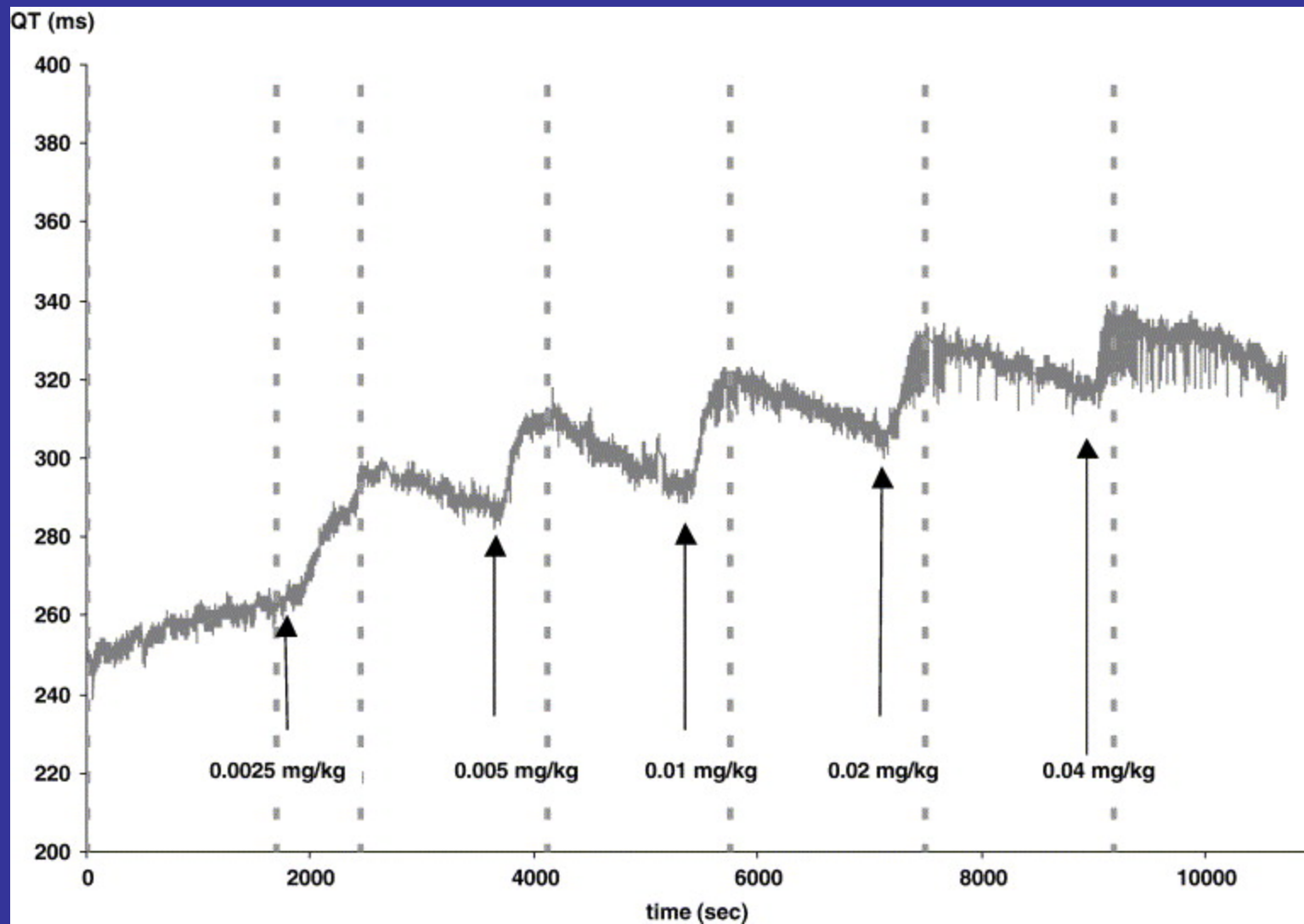


**B**

Nass RD *et al.* (2008) *Nat Clin Pract Cardiovasc Med*

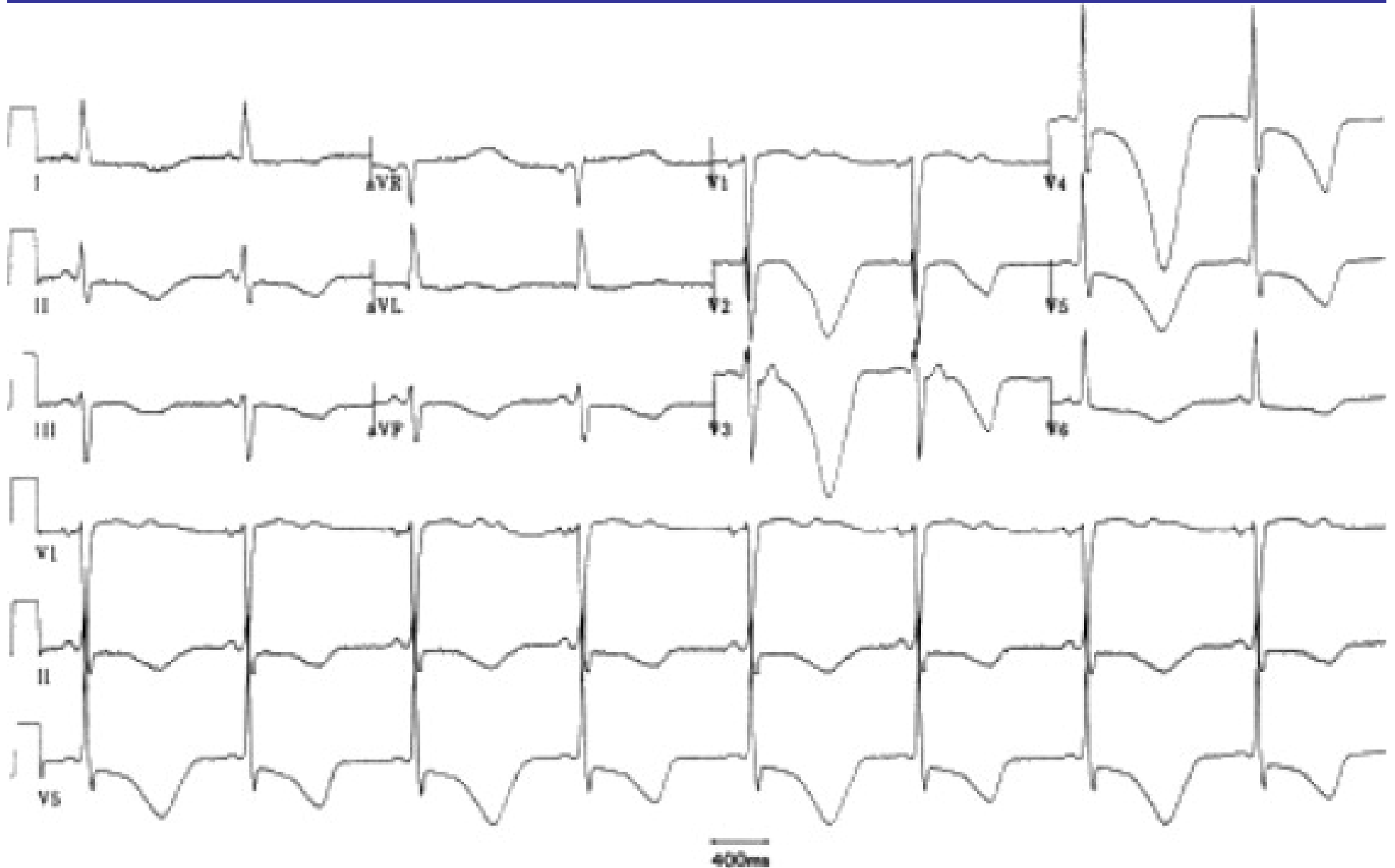
nature CLINICAL PRACTICE  
**CARDIOVASCULAR  
MEDICINE**

# hERG blockade destabilizes QT in dog

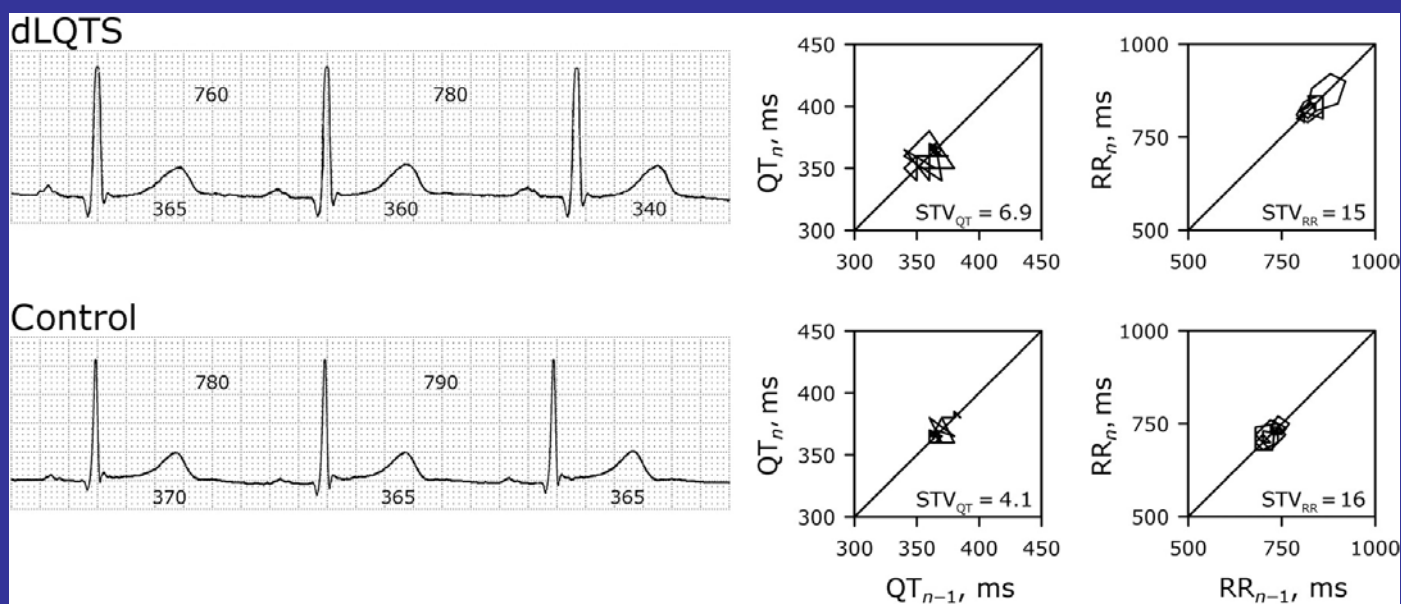


Van der Linde *J Pharmacol Toxicol Methods*. 2005

# QT Variability is significantly increased in LQTS



## Representative ECG tracings and associated Poincare plots of the QT and RR intervals: QT variability is significantly increased in survivors of drug induced TdP



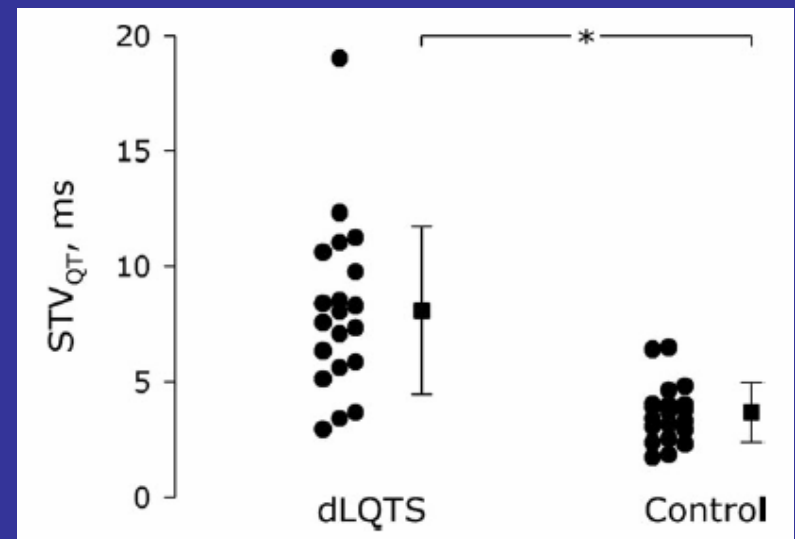
Hinterseer, M. et al. Eur Heart J 2008 29:185-190; doi:10.1093/eurheartj/ehm586

# QT variability increased in subjects at risk for drug-induced TdP

Beat-to-beat variability of the QT interval

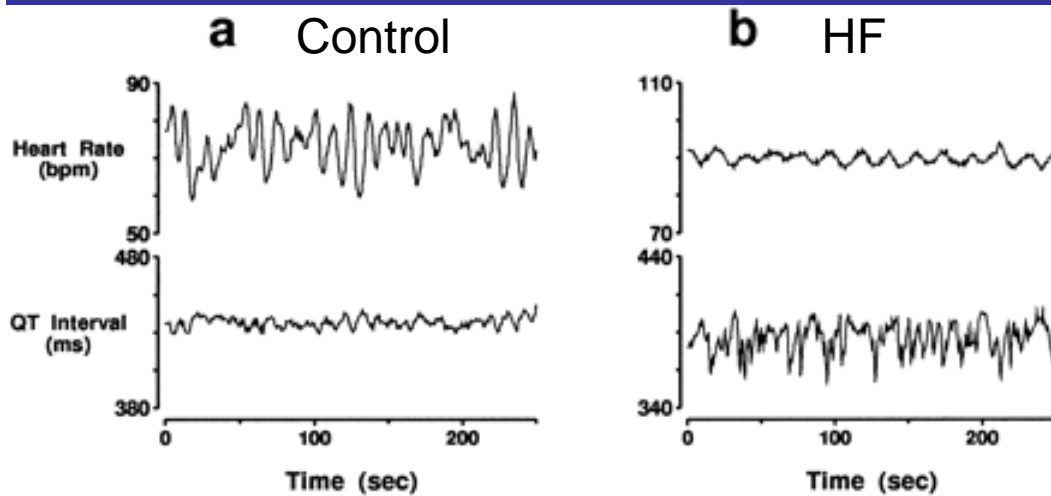
**Table 2** Electrocardiographical characteristics of dLQTS patients and age- and sex-matched controls

	dLQTS	Controls	P-value
Group size	20	20	
Age, years	59 ± 17	63 ± 18	0.57
RR, ms	909 ± 166	873 ± 131	0.45
QRS, ms	96 ± 13	92 ± 9	0.62
QT, ms	408 ± 47	391 ± 30	0.25
QTc, ms	428 ± 25	421 ± 34	0.26
STV <sub>QT</sub> , ms	8.1 ± 3.7	3.6 ± 1.3	0.001
STV <sub>RR</sub> , ms	15 ± 11	19 ± 16	0.36



# QTVI

## QT Variability Index

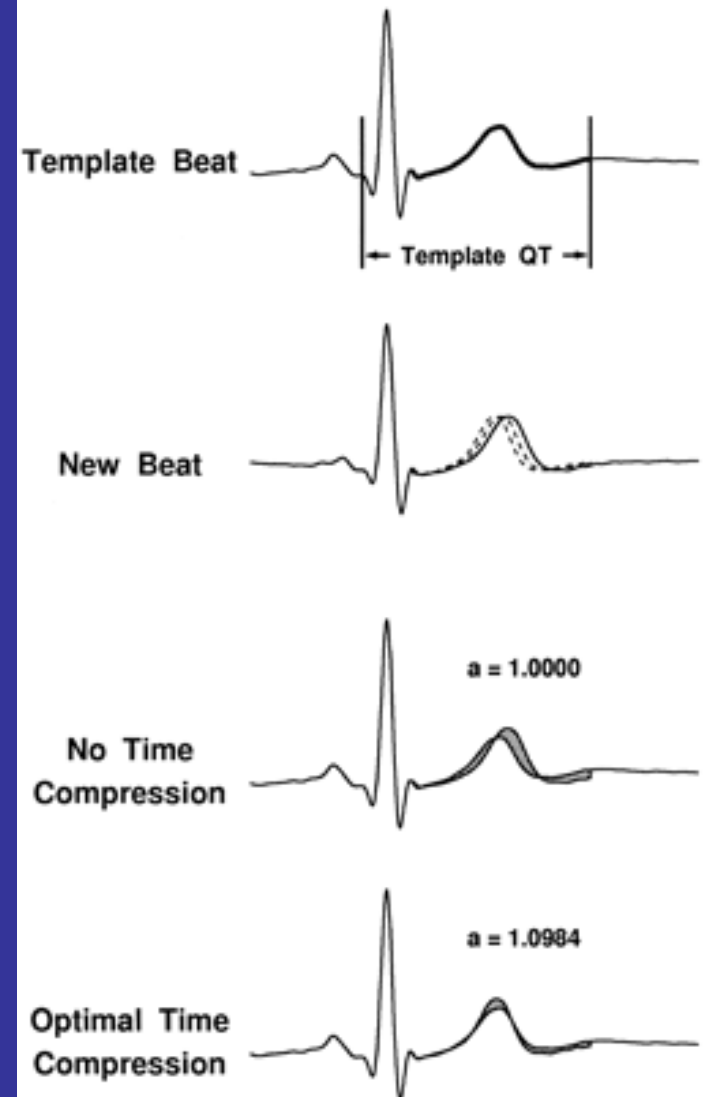


HR

QT

Time series of QT and HR generated

### QT Variability Algorithm



*Berger, et al.*

*Circulation. 1997;96:1557-1565*

## QT Variability Index

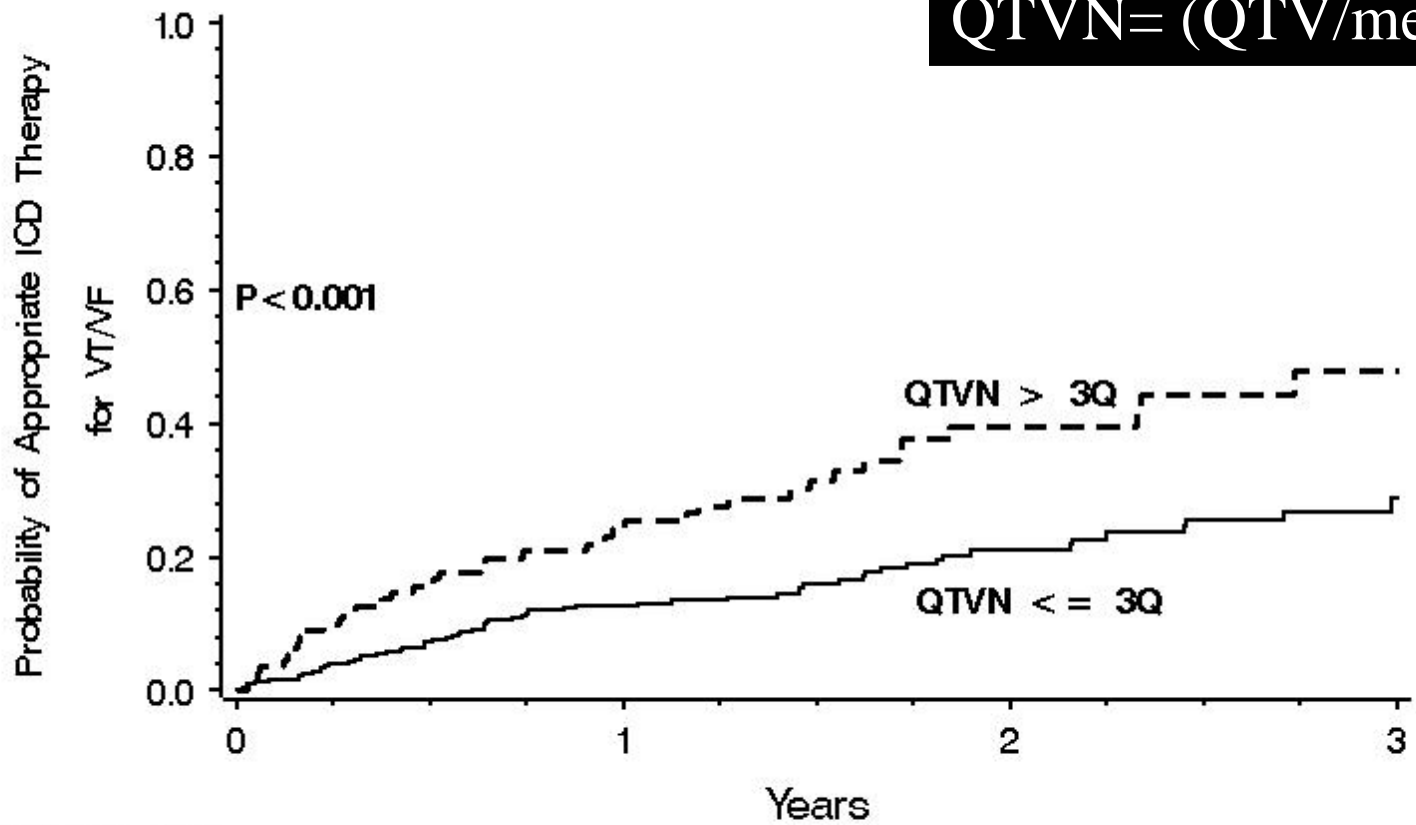
$$\text{QTVI} = \frac{\text{Log}(\text{QTV}/\text{mean QT}^2)}{(\text{HRV}/\text{mean HR}^2)}$$

## QT Variability Normalized

$$\text{QTVN} = (\text{QTV}/\text{mean QT}^2)$$

# QTVN and Appropriate ICD Therapy in 476 subjects

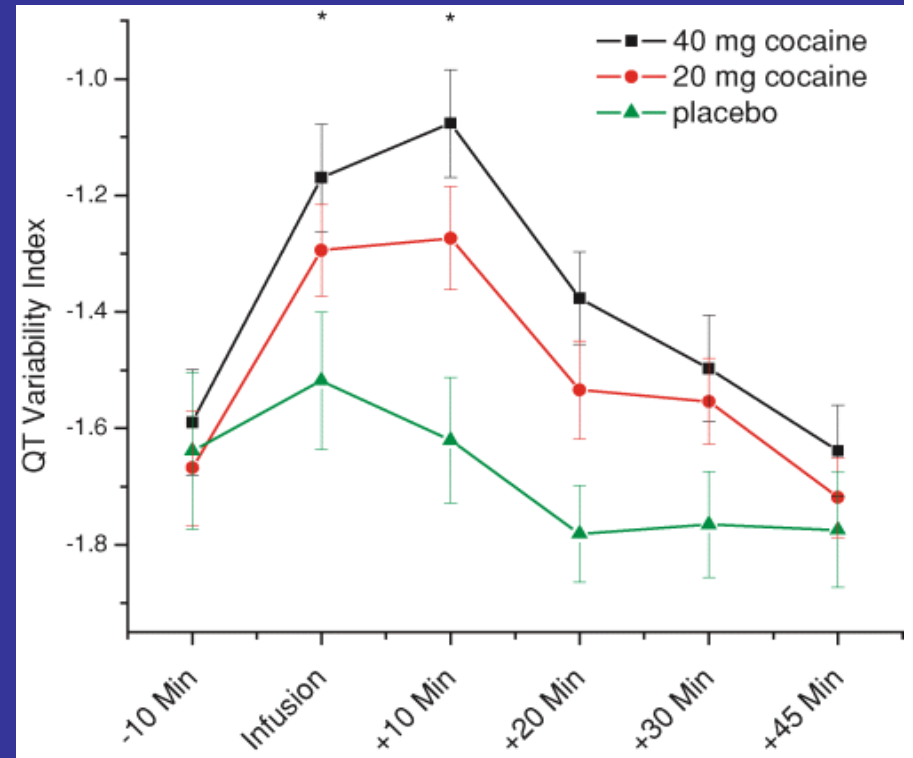
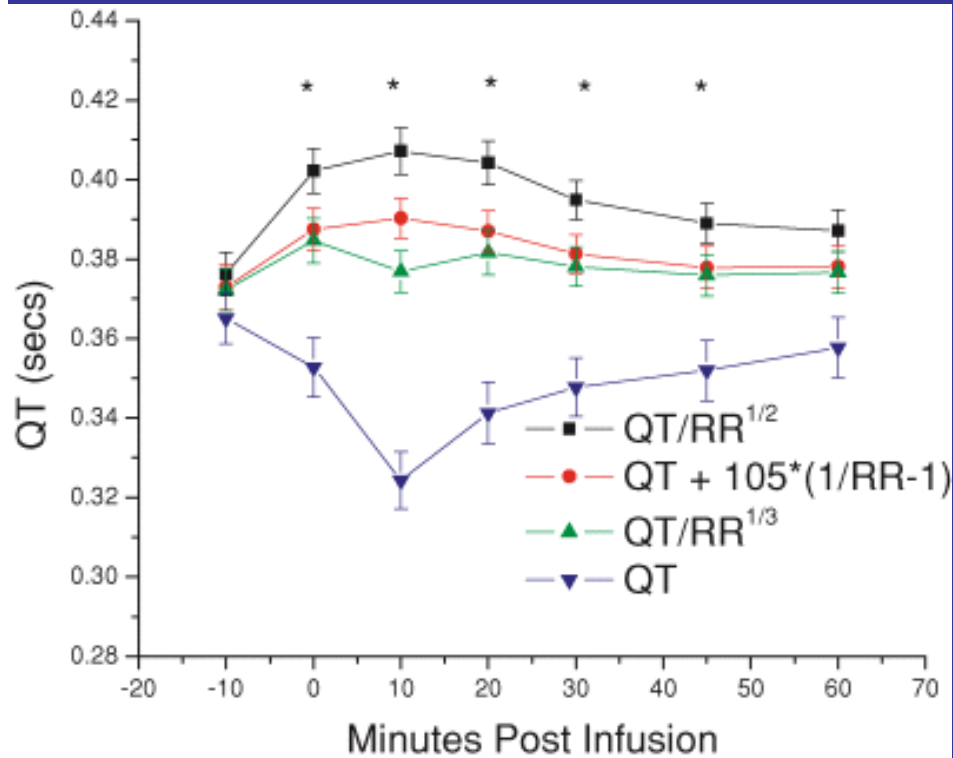
$$QTVN = (QTV / \text{mean } QT^2)$$



PATIENTS AT RISK							
QTVN > 3Q	112	68 (0.24)	30 (0.40)	11 (0.48)			
QTVN <= 3Q	351	215 (0.13)	106 (0.21)	33 (0.29)			

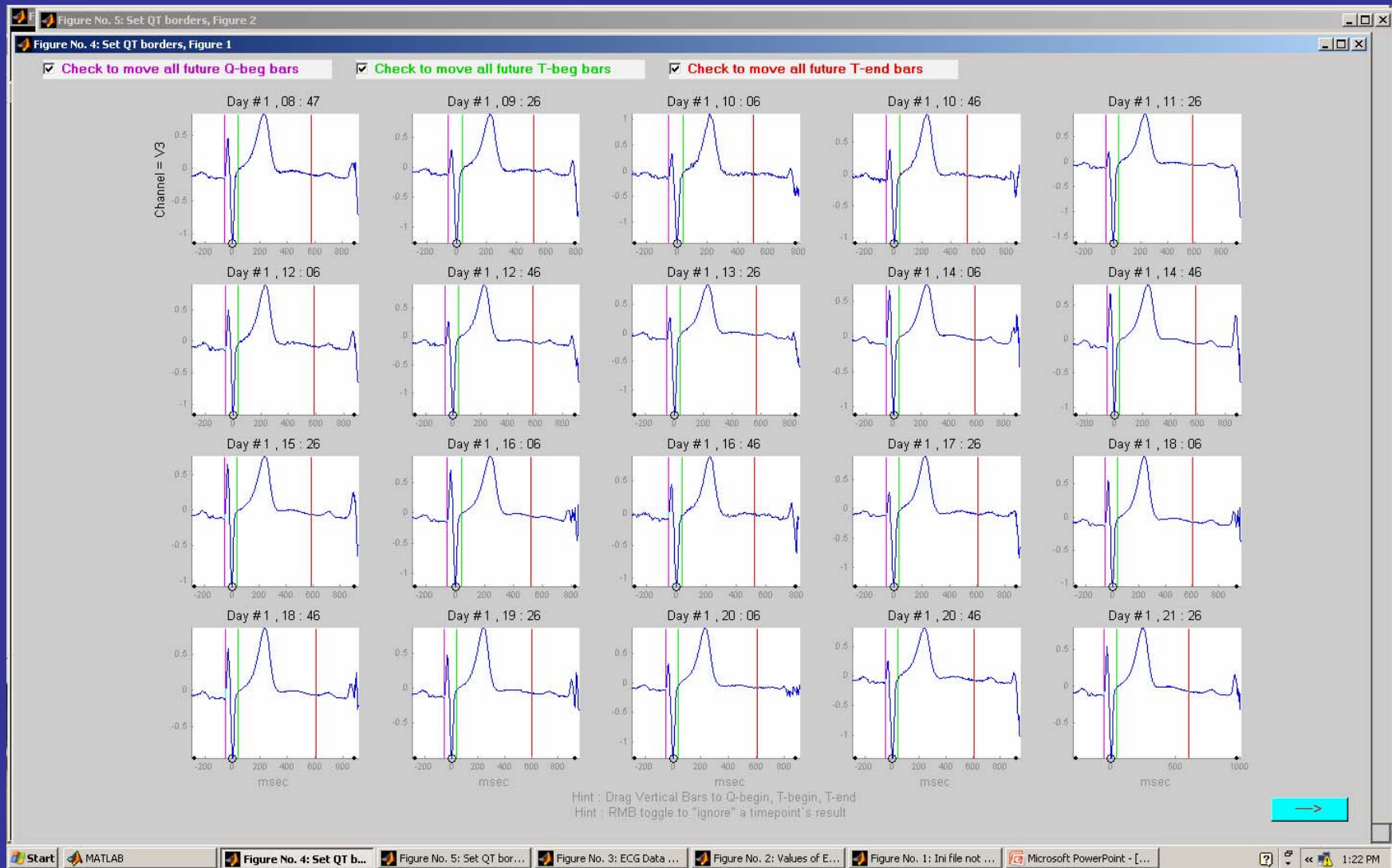
Haigney, Zareba, Gentlesk et al. *JACC* 2004; 44(7): 1481-1487.

## QTVI and Cocaine



Haigney et al., JCE 2006

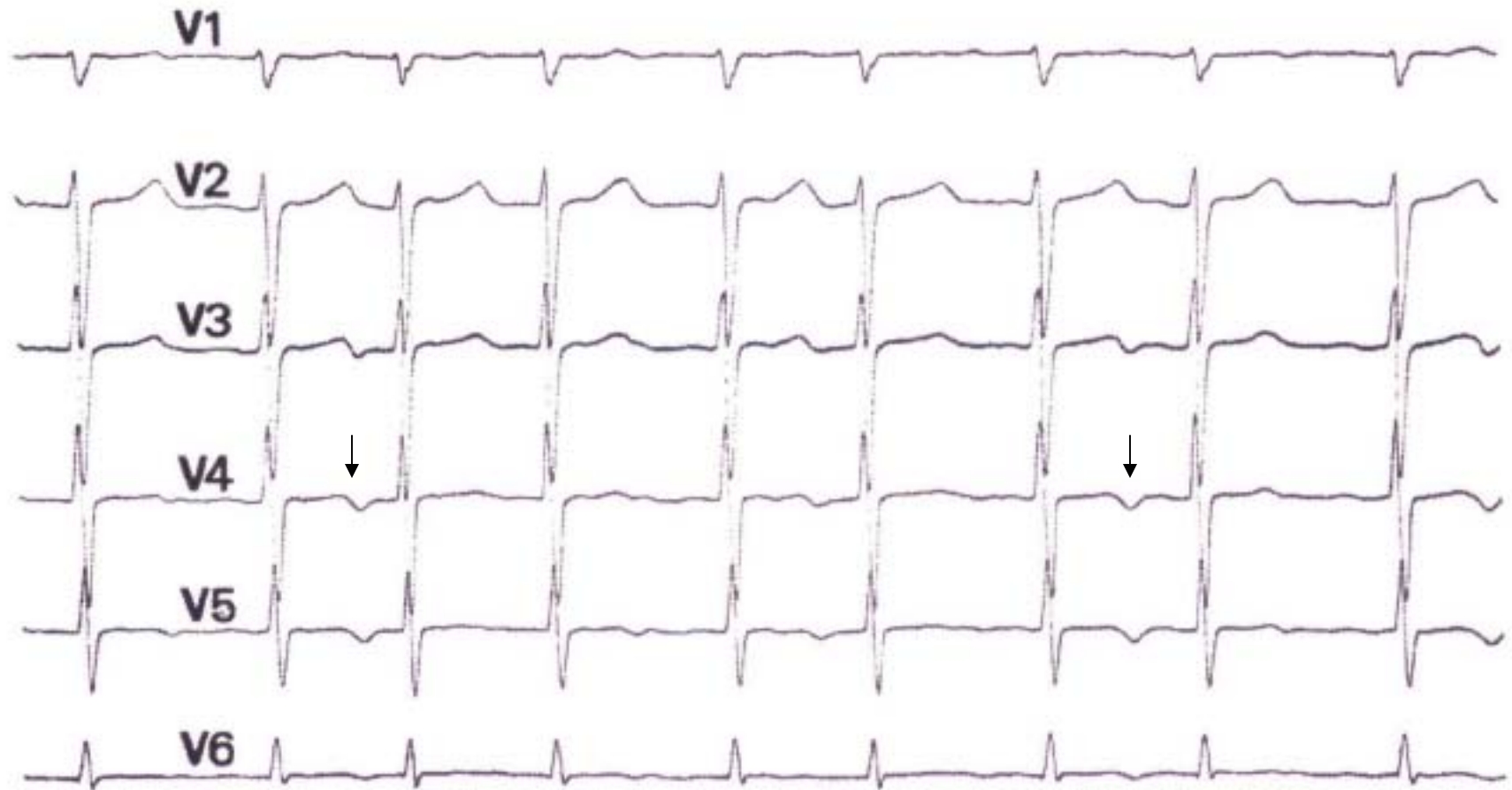
# Program interface



## Conclusions

- Hypothesis: Increased QT variability may be a more accurate indicator of depressed repolarization reserve
  - Prior to drug
  - On drug
- The utility of QT (or T wave) variability to assess the risk of drug-induced proarrhythmia has not been adequately tested
- The ideal method for measuring *in vivo* repolarization instability unclear
  - ?Include the U wave?
  - Normalize for heart rate/HRV?

## 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  $V_3$ - $V_5$ .

## Induction of Short-term Variability in MAP Predicts TdP

