

# QT Interval Dynamicity Methods of Analysis and Clinical Application

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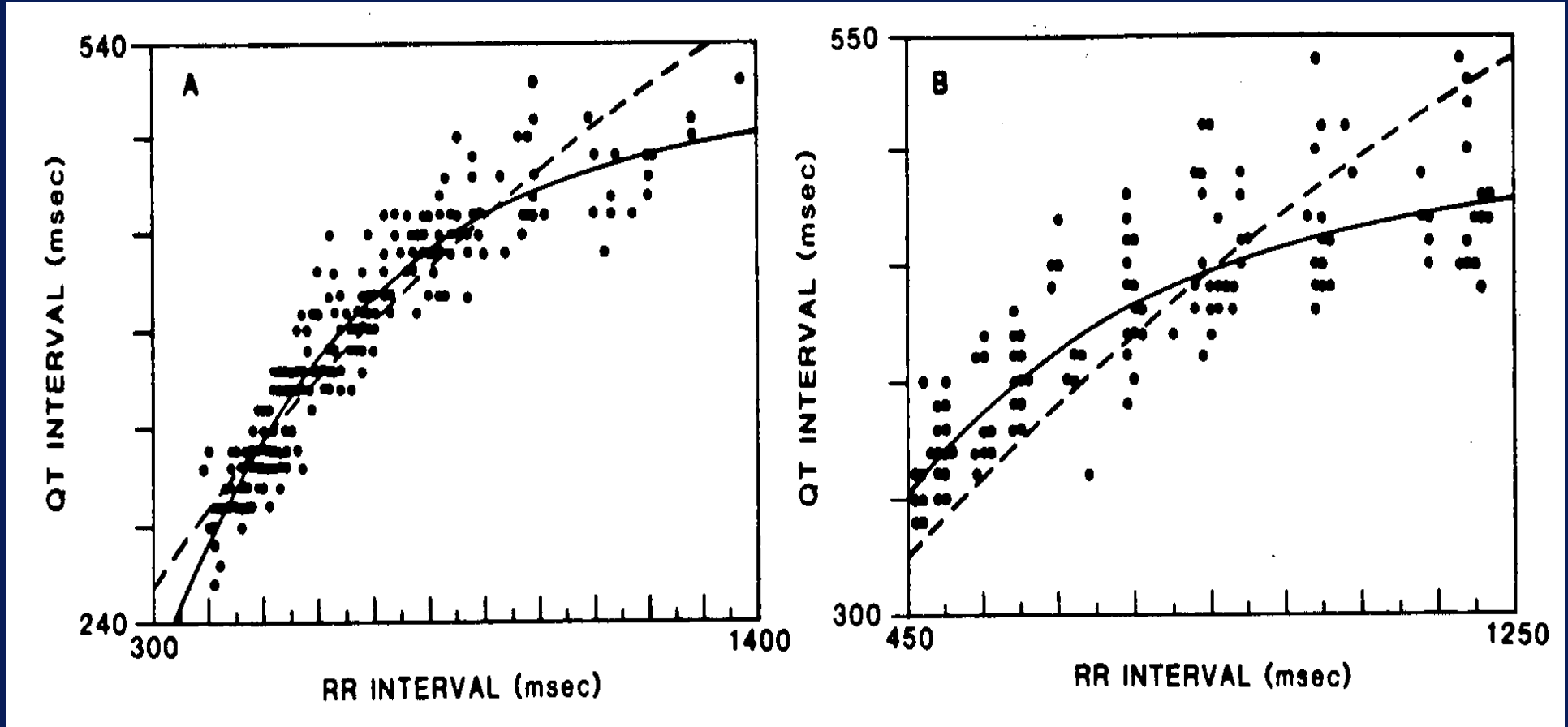
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Istituto di Cardiologia  
Dipartimento di Medicina Clinica e Sperimentale  
Università degli Studi di Perugia*

# Evaluation of QT Interval Dymamicity

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- ✓ Exercise Stress Test
- ✓ Atrial Pacing
- ✓ Ambulatory Holter Monitoring

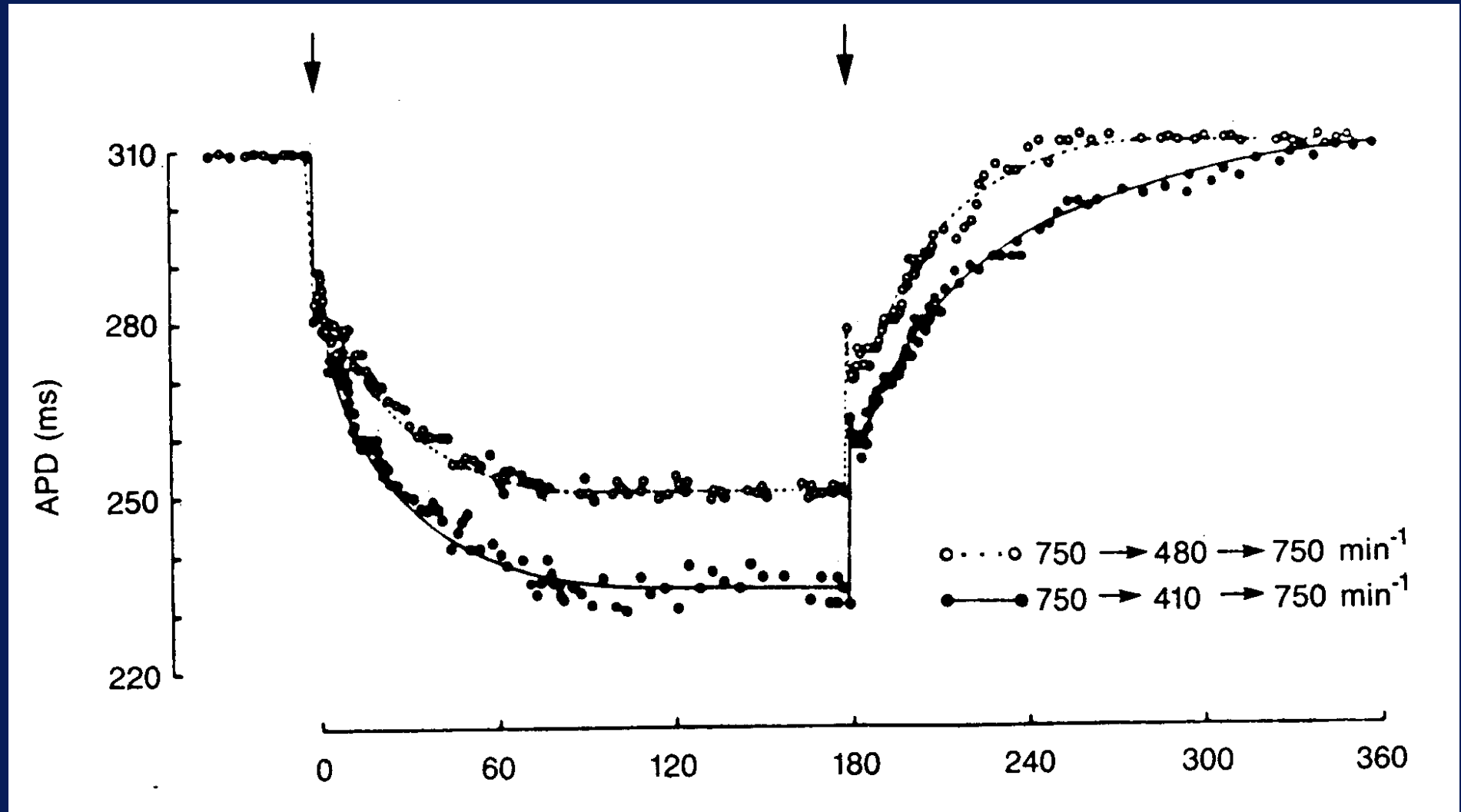
# Heart Rate Dependence of QT Interval During Exercise and Pacing



Sarma J et al, AJC 1994

The adaptation of QT interval to cycle's length changes varies according to the modality of heart rate increase, and the slope of the regression is steeper during exercise than during pacing.

# Human APD Adaptation After Cycle Length Changes



Franz MR, JCI 1988

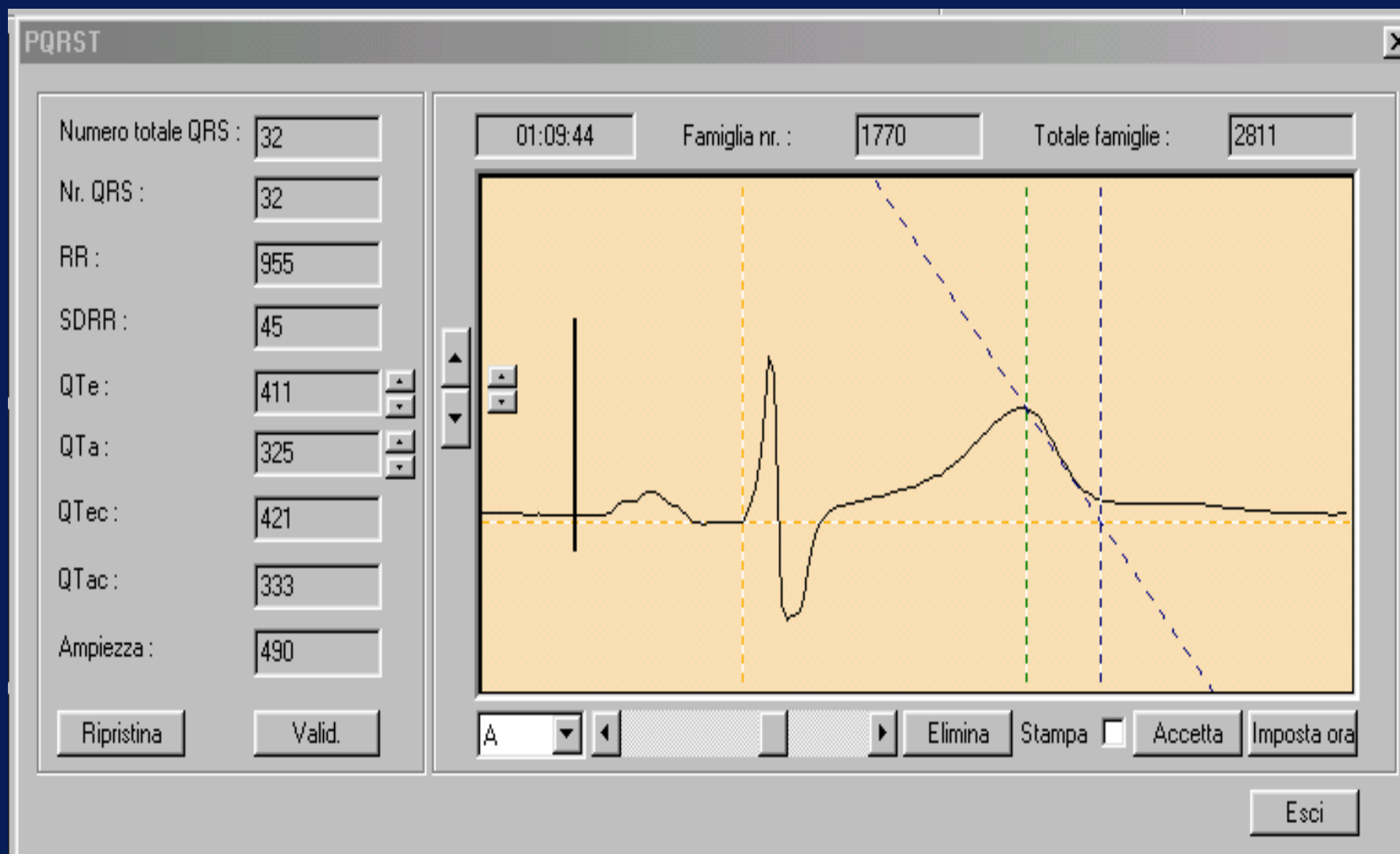
The adaptation of APD after cycle length changes is not instantaneous, but it follows a specific time constant, different for cycle length decrease versus cycle length increase.

# Analysis of QT Dynamicity by Holter Monitoring

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- ✓ Circadian QTc Excursion (QTc Peaks)
- ✓ QT/RR Relation (Beat-to-Beat or Averaging Methods)
- ✓ T Wave Alternans (Correlation Method)
- ✓ Principal Components Analysis
- ✓ Long-term QT Dispersion
- ✓ Beat-to-beat QT Adaptation / Morphology
- ✓ Wavelet Analysis

## Example of Automatic Measurement of QT Interval

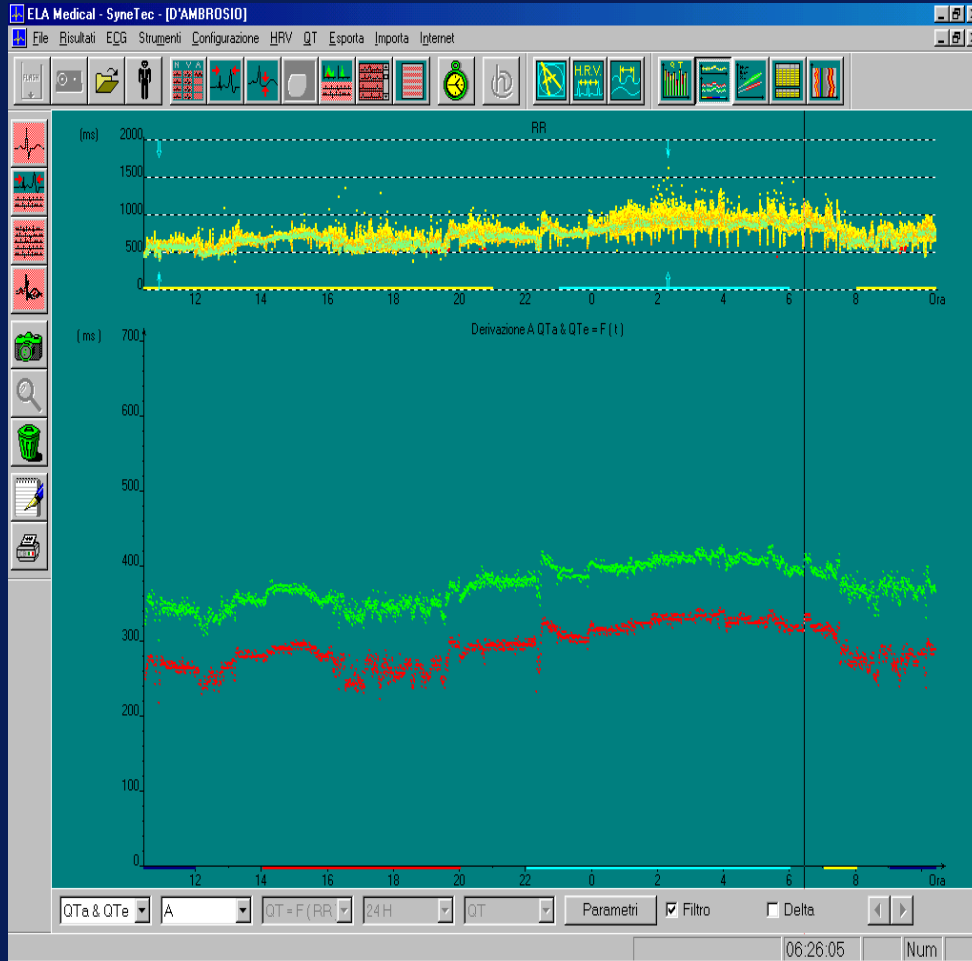


Automatic measurement of RR, QT<sub>apex</sub>, QT<sub>end</sub> on 30 sec median beat

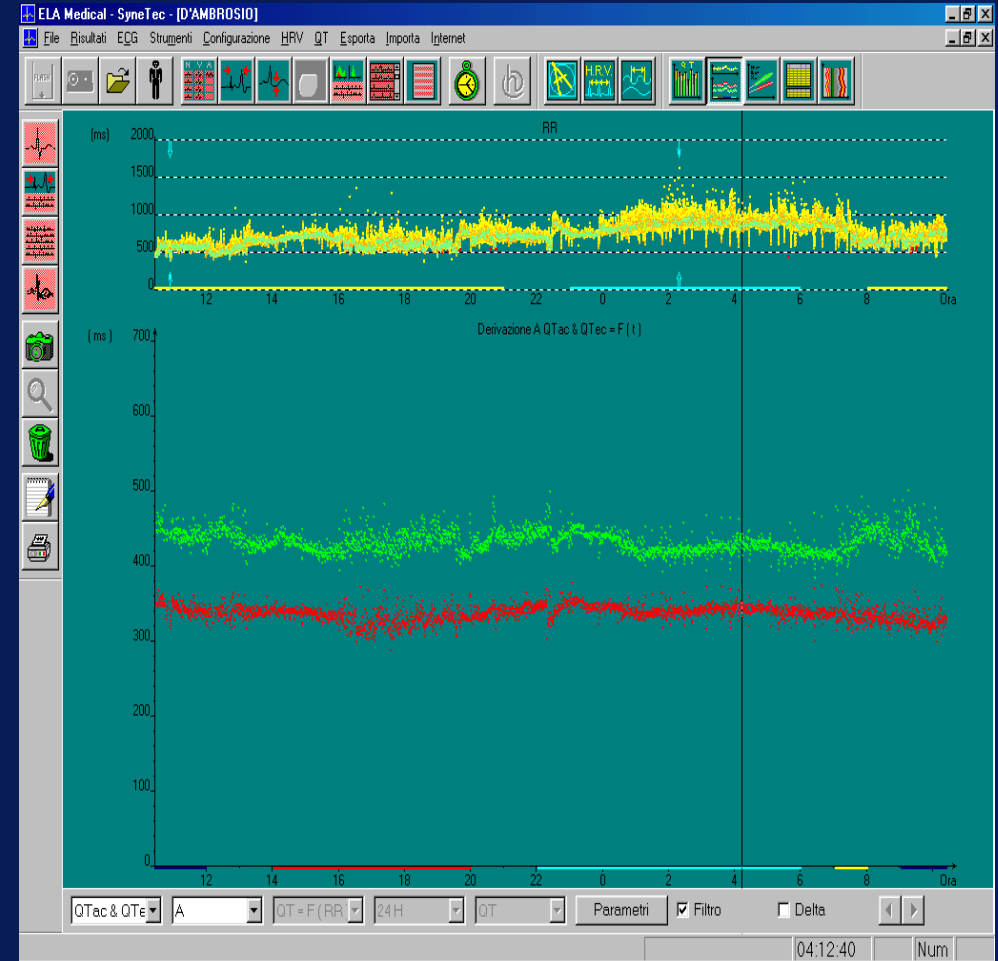


The automatic measurement of QT interval has severe technical problems in Holter monitoring, due to the unfavorable noise-to-signal ratio and to the difficulties in defining the end of the T wave. Therefore more robust methods are utilized, as in this case (commercial system ELA Medical) the measurements are based not on single beats but on a median beat computed on the mean of several beats (in this case on based on 30 seconds). The T wave apex (QTapex) is computed by the interpolation of an inverted parabola with the point of maximal T wave deflection, while the T wave end (QTend) is the intersection of the tangent of the deflection curve with the isoelectric line.

# Automatic Measurement of Circadian Variability QT Interval



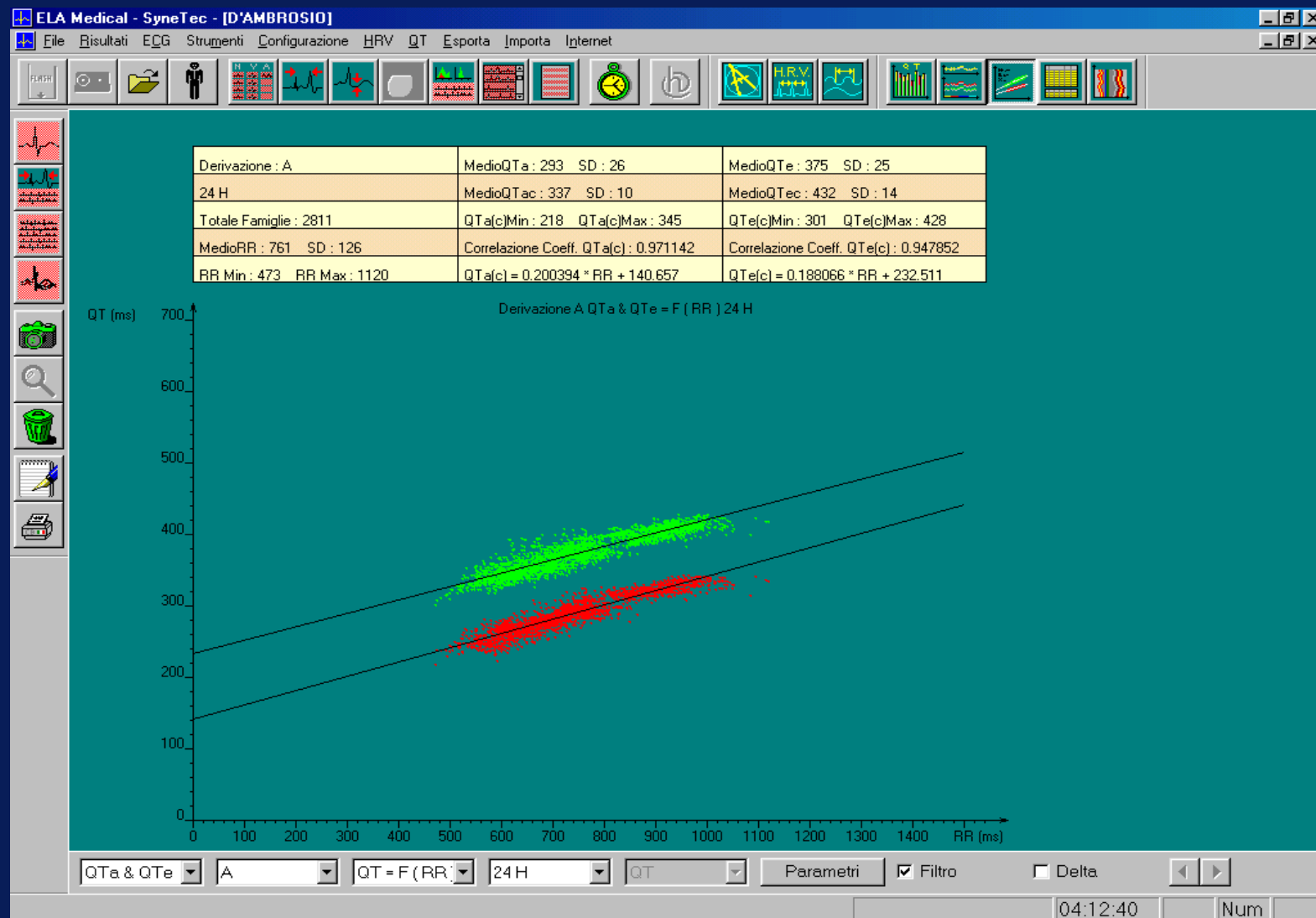
RR, QT apex, QT end



RR, QTac, QTec

The single measurement computed by this method are plotted versus time, obtaining the circadian variation of the different parameters (RR in yellow, QTend in green, QTapex in red). In a normal subjects, the QT measurements corrected for the heart rate (HR) are relatively stable in time during the 24 hours (right panel, while measurements not corrected for HR are evidently largely dependent on HR (left panel).

# Automatic Computation of Linear QT/RR Relation

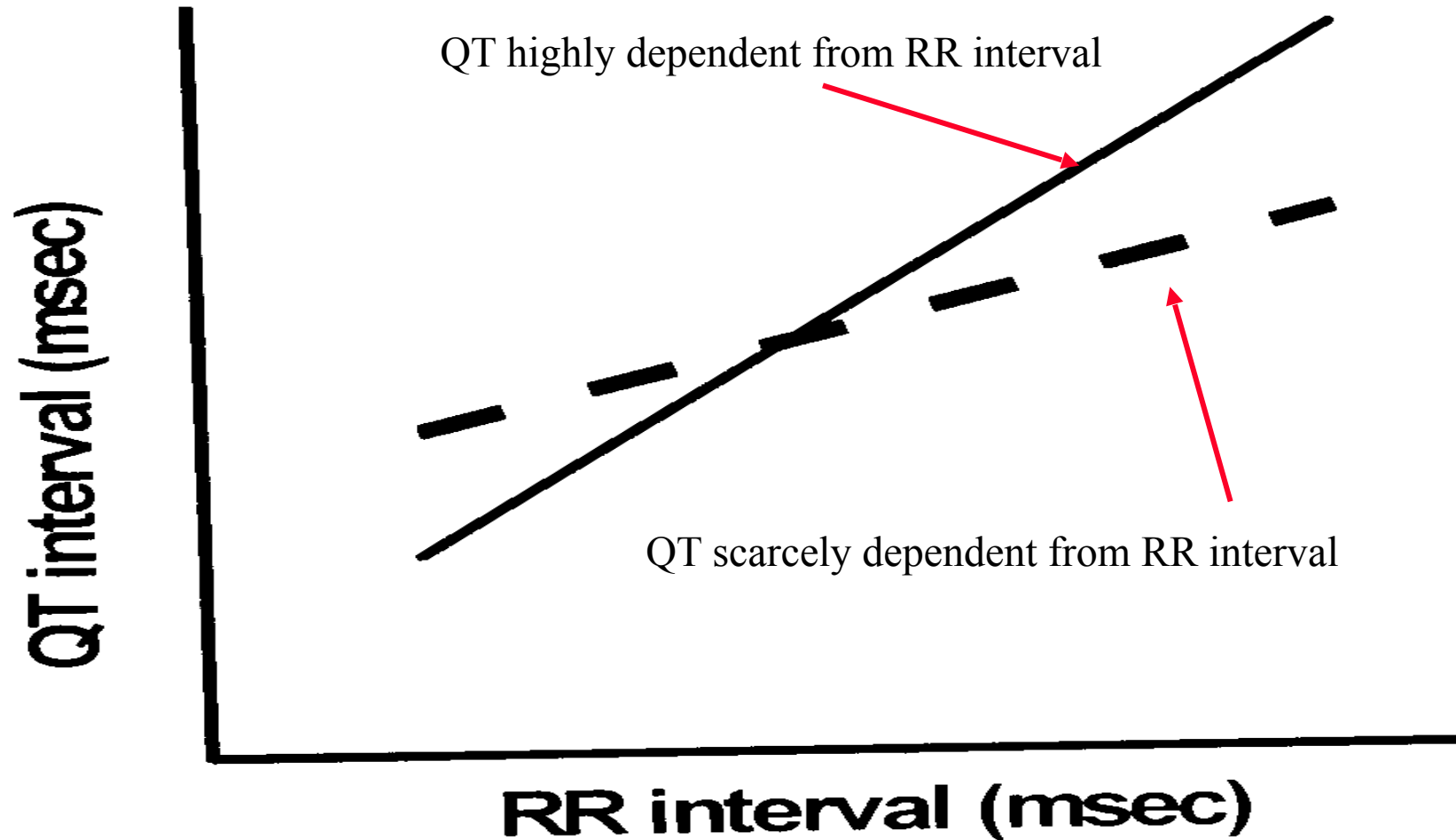


Red: QTapeX/RR

Green: QTend/RR

This method also automatically computes the linear relation between the QT intervals (QT<sub>apex</sub> in red and QT<sub>tend</sub> in green) and RR interval, and the slope of the curve (coefficient of the regression slope) and the dispersion of values (correlation coefficient) are also computed. In a normal subjects QT<sub>apex</sub>/RR and QT<sub>tend</sub>/RR slopes are practically parallel and the dispersion of values is very low in the 24 hours.

# Schematic Representation of QT-RR Relation



Meaning of the slope of the QT/RR relation. A flat slope (low regression coefficient) indicates a QT interval scarcely dependent on the changes of cycle length duration, with modest shortening at high heart rates and modest lengthening at slow heart rates. Opposite, a steep slope (high regression coefficient) indicates that QT interval is highly dependent on heart rate changes, with marked shortening at fast heart rates and marked lengthening at slow heart rates.

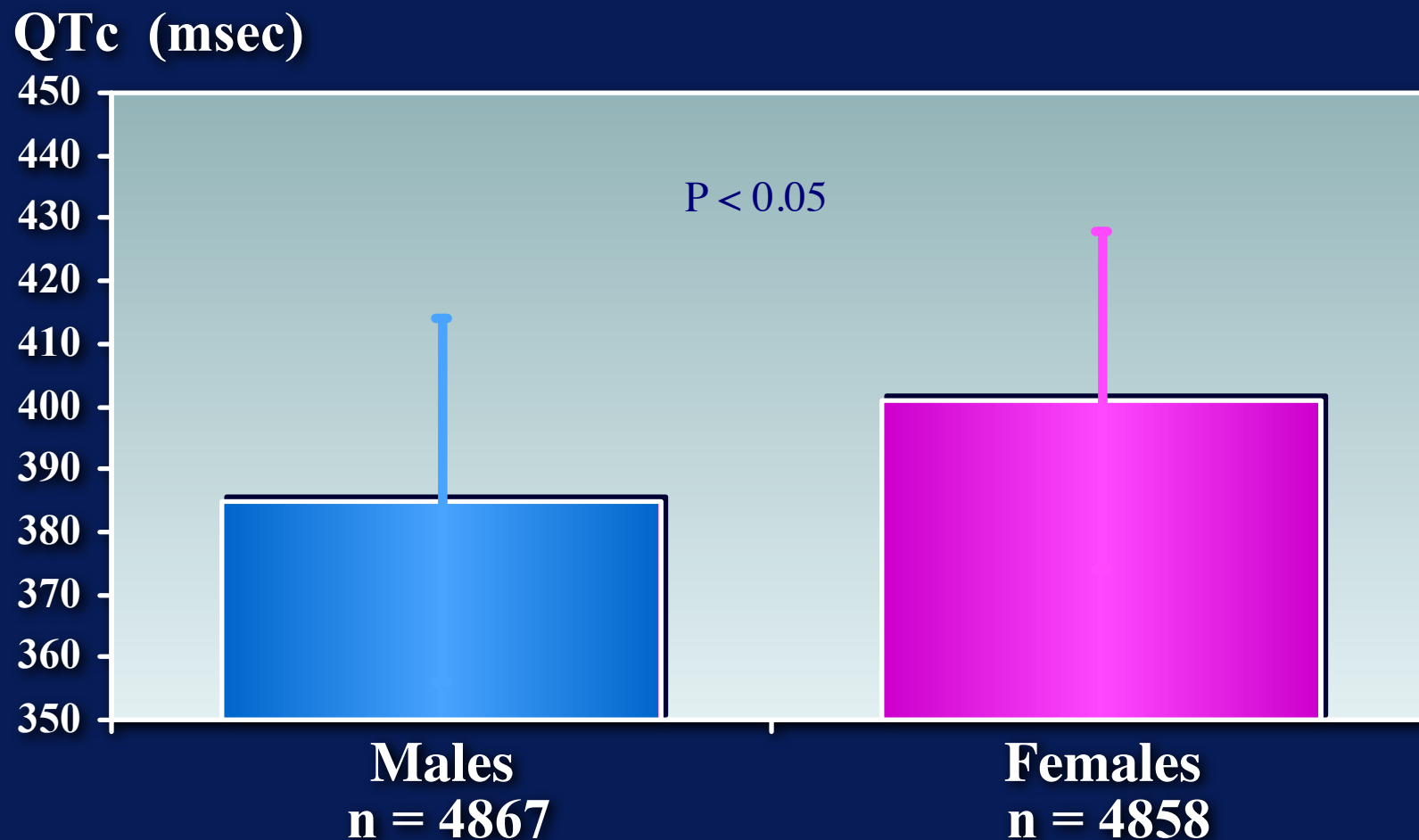
# Modulation of QT Interval Dymamicity

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- ✓ Heart Rate
- ✓ Sex
- ✓ Circadian Trends
- ✓ Autonomic Nervous System
- ✓ Drugs (Antiarrhythmic / Non Antiarrhythmic)
- ✓ Metabolic Disturbances ( $\downarrow K^+$ ,  $\downarrow Ca^{++}$ )
- ✓ Myocardial Ischemia
- ✓ Mutations of Genes Encoding Cardiac Channels

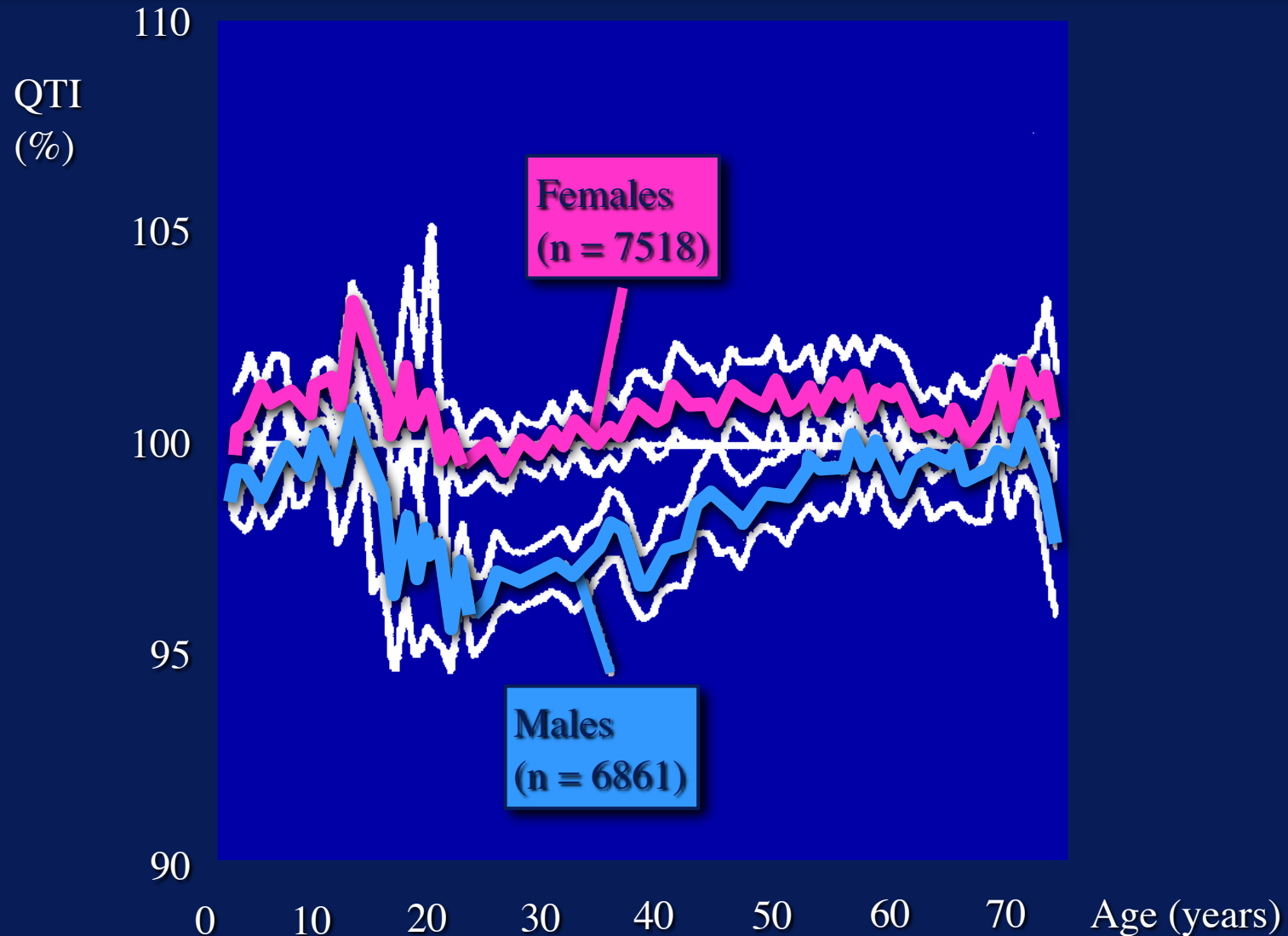


# Correct QT Interval (QTc) by Gender In “Framingham Heart Study”



The basal QT interval corrected for heart rate by Bazett formula (QTc) is known to be longer in adult females than in adult males: wide studies are available, here shown are the Framingham's study results.

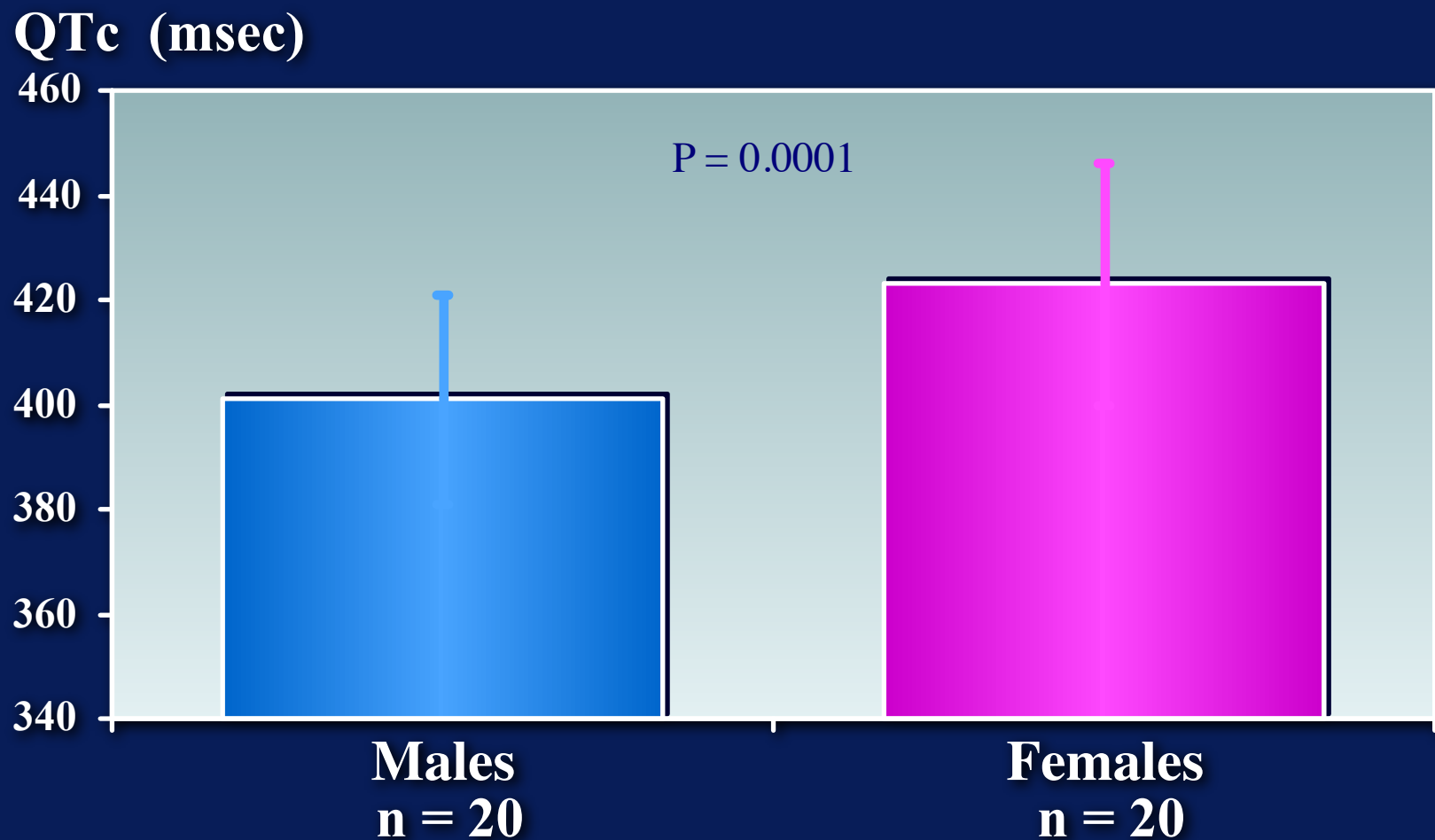
# Differences in QT Interval Duration by Age and Gender



Also age has a major role, particularly in males, who have a shorter QTc during adolescence up to the 5<sup>o</sup> decade of life, while in females a post-puberal shortening is not observed.

The same gender differences are observed in normal subjects during Holter monitoring (see next slide).

# QT Interval Duration During 24-hour Holter by Gender



# QT Interval at Fixed Cycle Length (1000 ms) per Gender

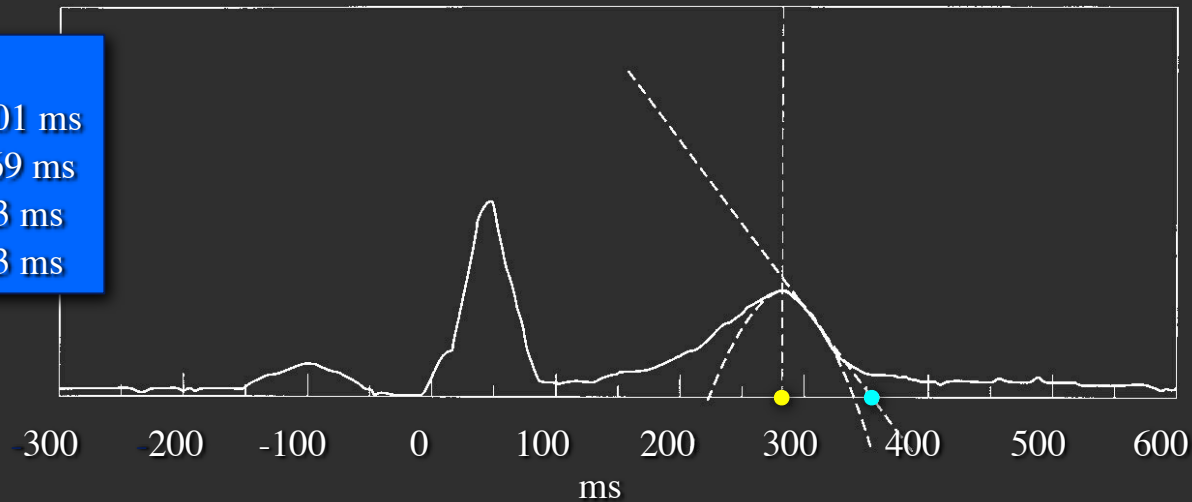
## Male

RR: 1001 ms

PQRST: 69 ms

● QTe: 363 ms

● Qta: 283 ms



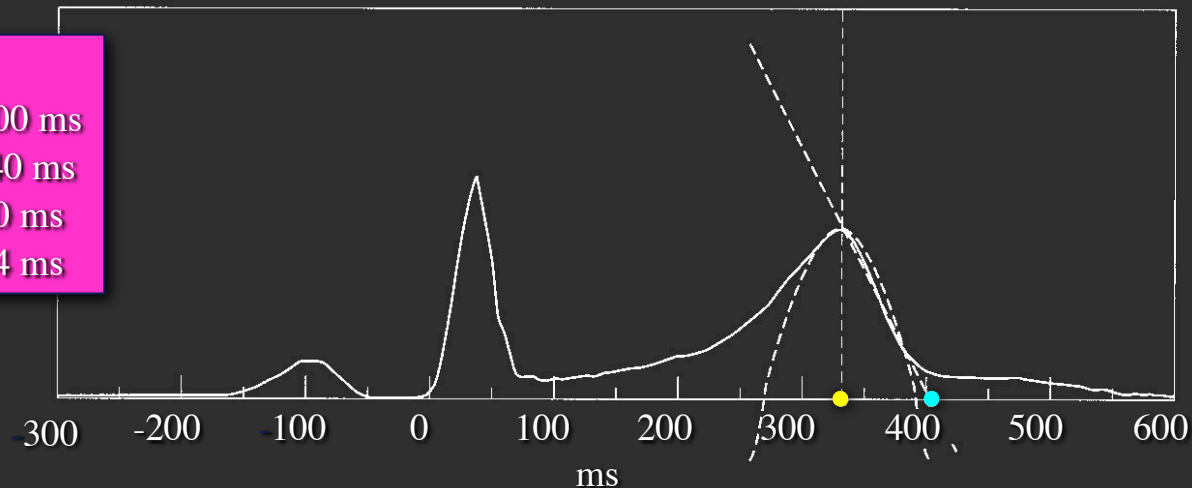
## Female

RR: 1000 ms

PQRST: 40 ms

● QTe: 400 ms

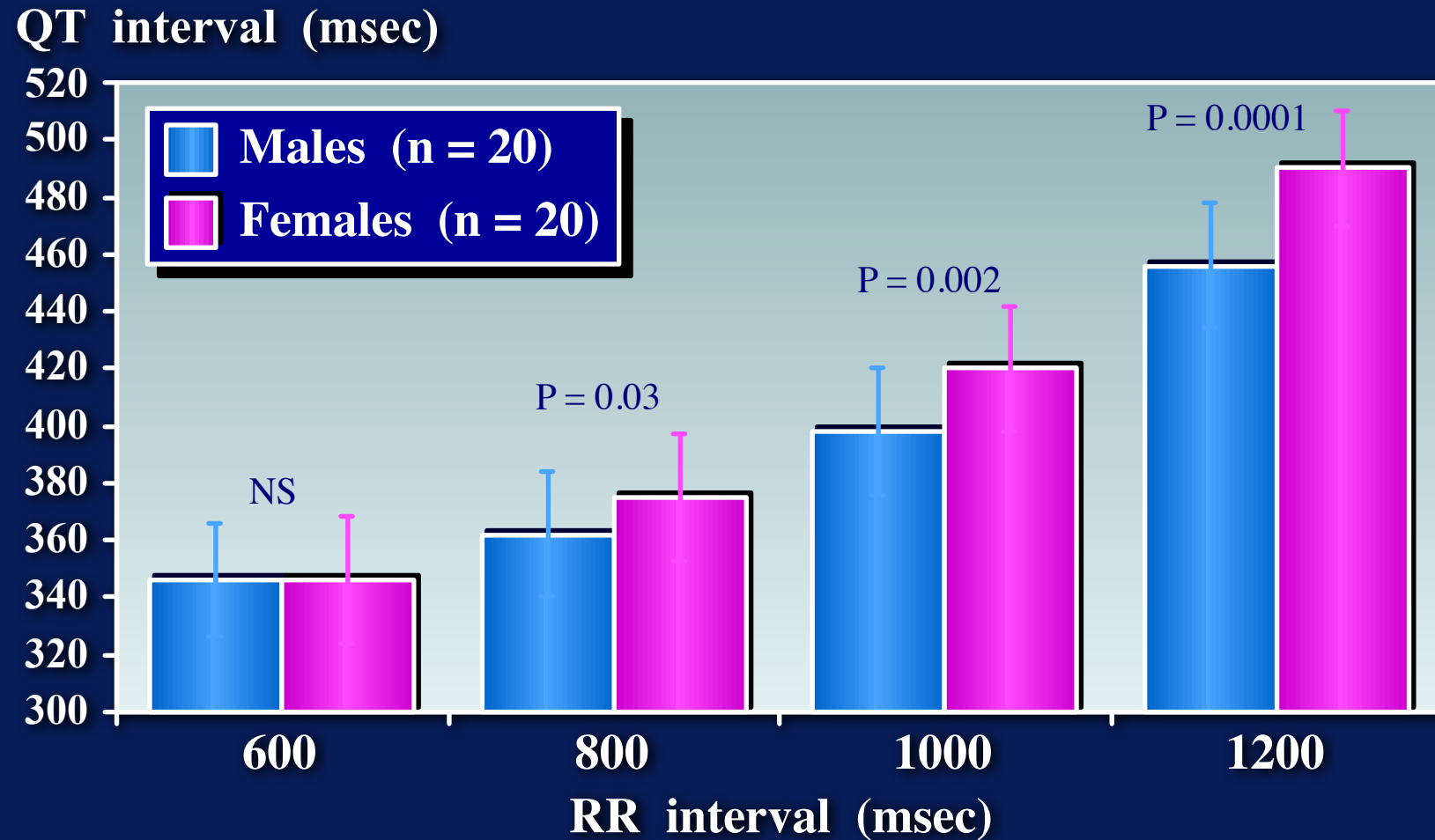
● Qta: 334 ms



Holter monitoring allows to verify that gender QT differences are independent from heart rate differences, known to be present in males and females, as the QT interval is longer in females than in males at the same cycle length (here shown, at RR interval 1000 msec, a difference of 40 msec exists between two normal adult subjects, above normal male, below normal female).

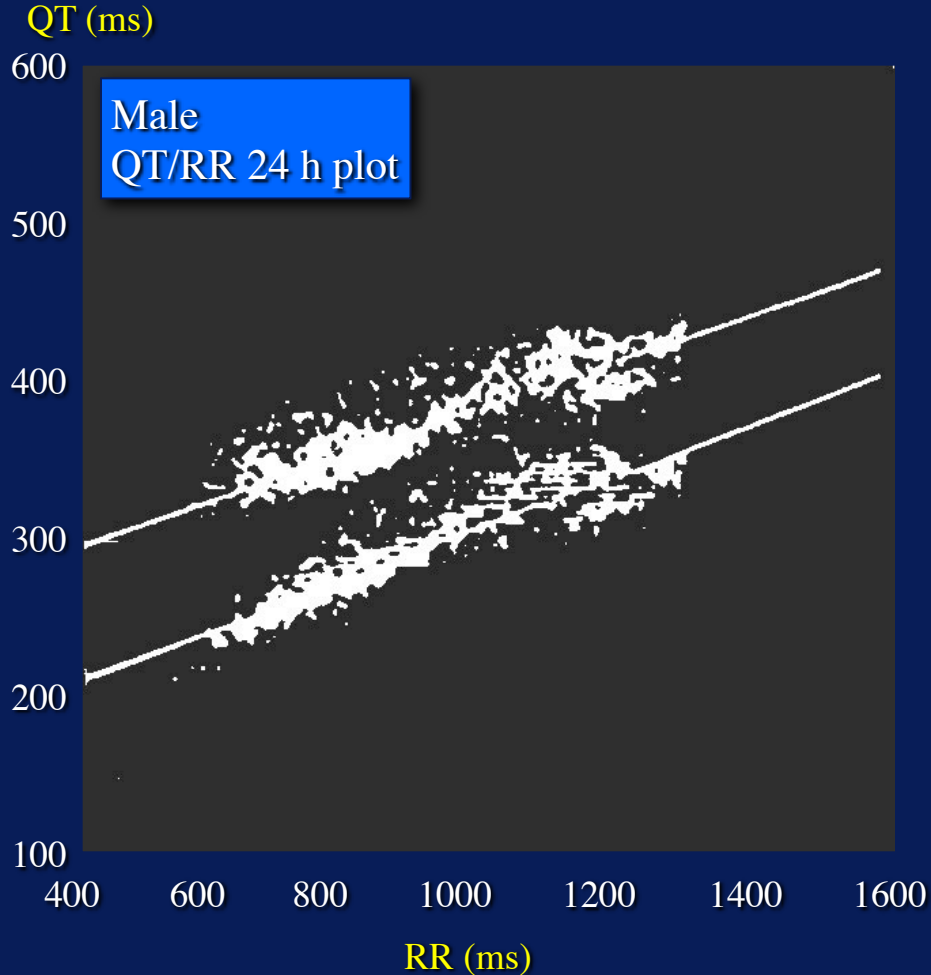
Gender differences are more evident at longer cycle lengths.

# Uncorrected QT Interval at defined CXycle Lenghts per Gender

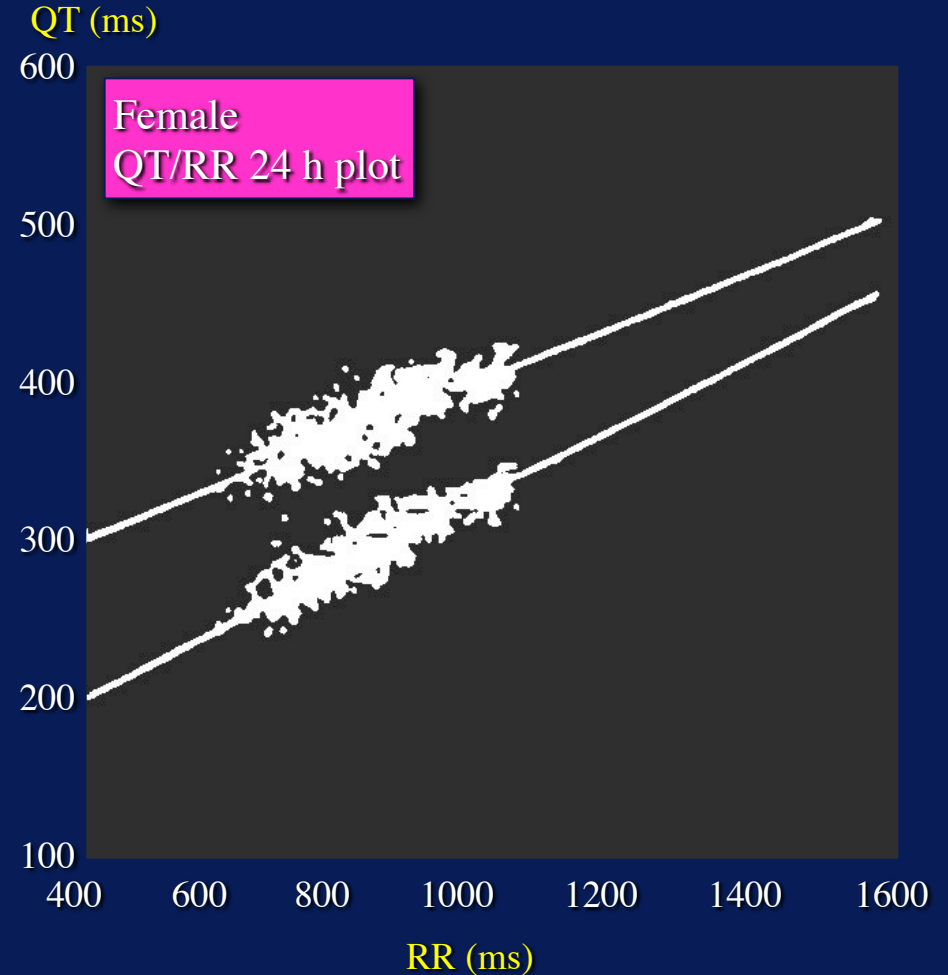




# QT/RR Relation During 24-hour Holter per Gender



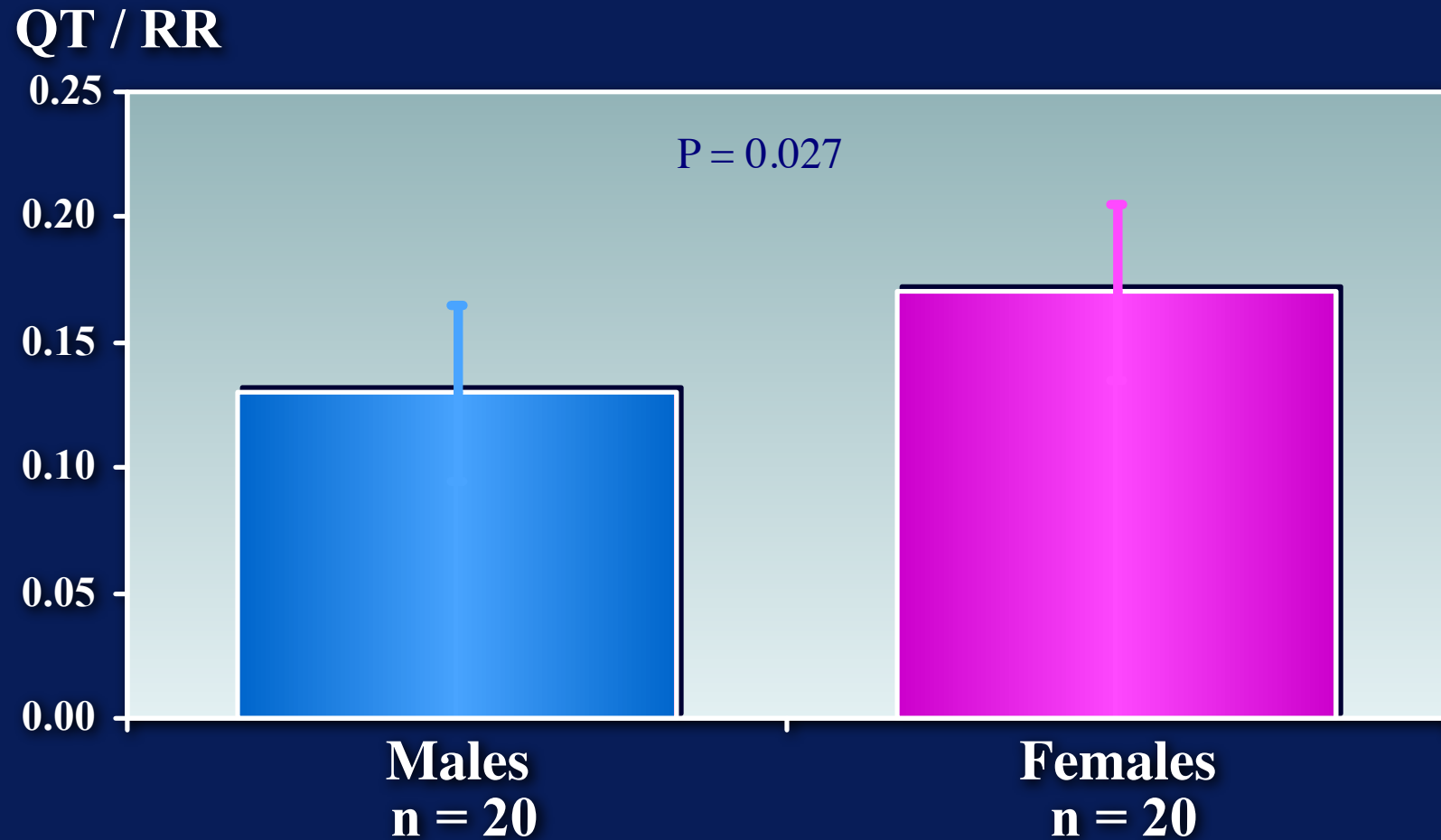
Regression:  $QT_{Tend} = 0.14 * RR + 249 \text{ ms}$



Regression:  $QT_{Tend} = 0.17 * RR + 241 \text{ ms}$

This implies that the linear regressions for QT/RR have different slopes between genders, with steeper slope in females than in males (particularly for QTend/RR).

# QT/RR Relation During 24-hour Holter per Gender



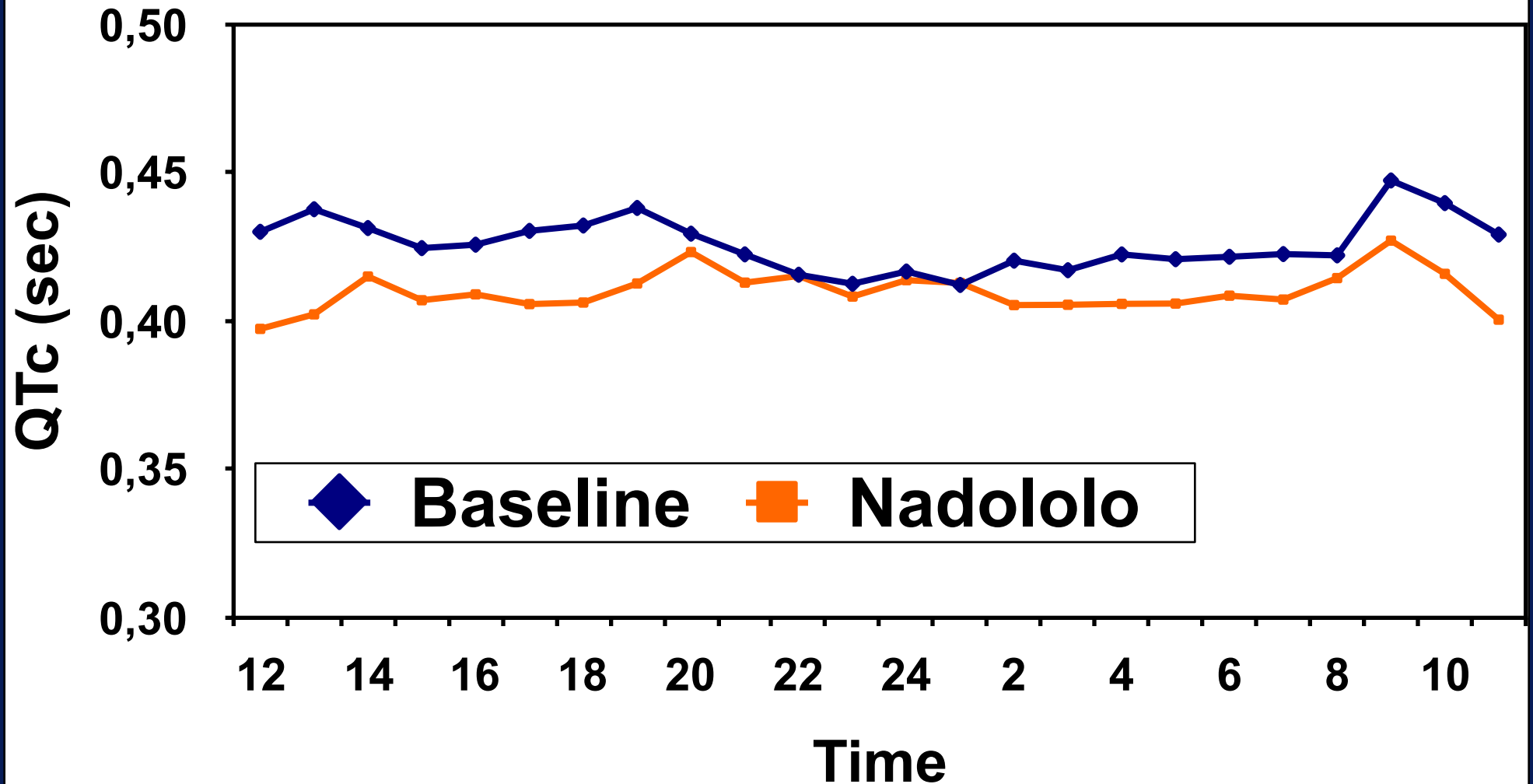
Than the regression coefficient for the relation QT/RR (particularly QTend/RR) is higher in normal females than in males.

# Modulation of QT Interval Dymamicity

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- ✓ Metabolic Disturbances ( $\downarrow K^+$ ,  $\downarrow Ca^{++}$ )
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# CIRCADIAN TREND OF QTc

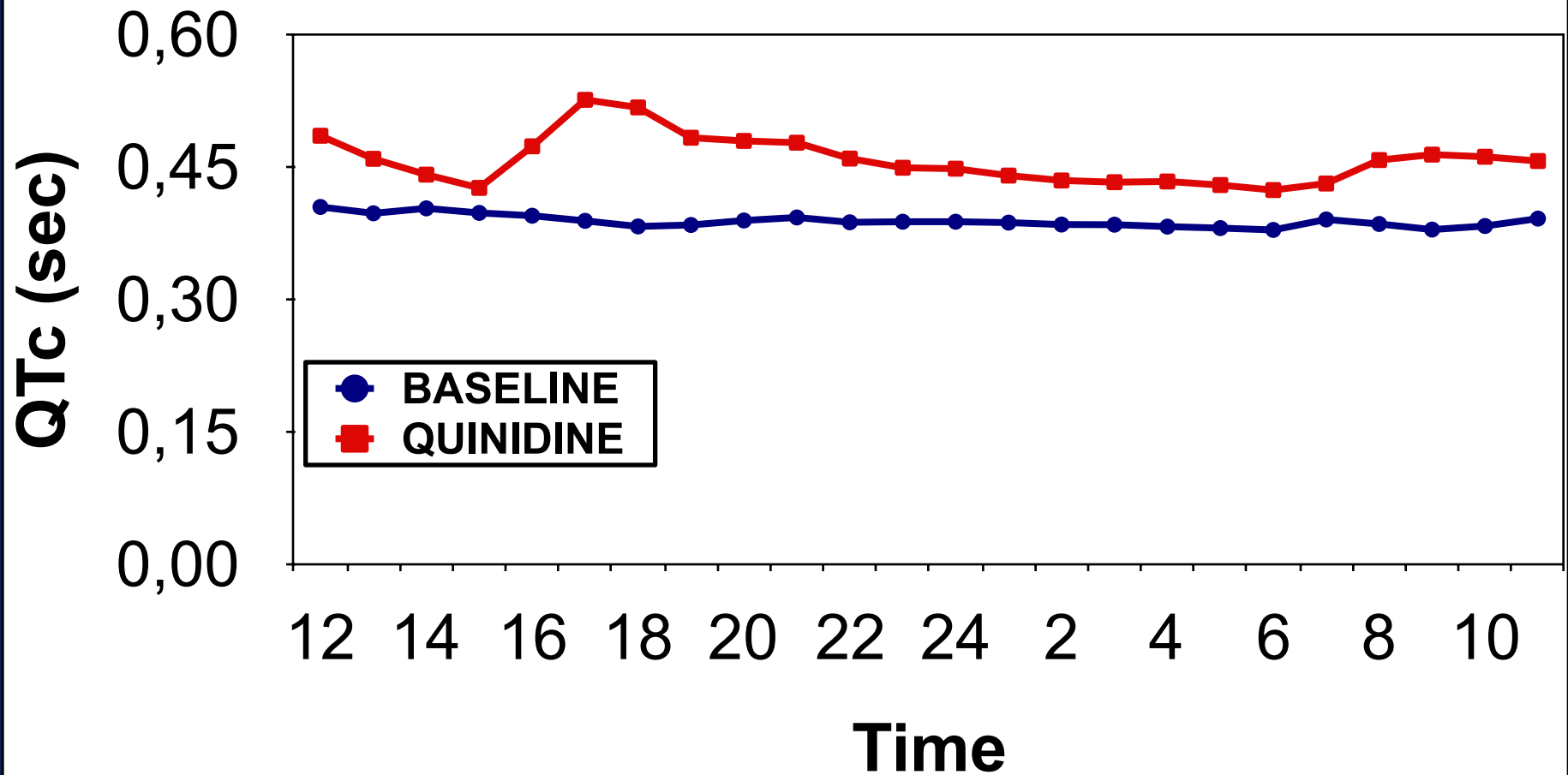


AJ, Female, 70 yrs

Beta-blockers (Nadolol) in a normal subjects reduced QTc duration and QTc circadian variability.

Opposite, Quinidine in a normal subjects increased QTc duration and QTc circadian variability.

## CIRCADIAN TREND OF QTc



BR, Female, 60 yrs

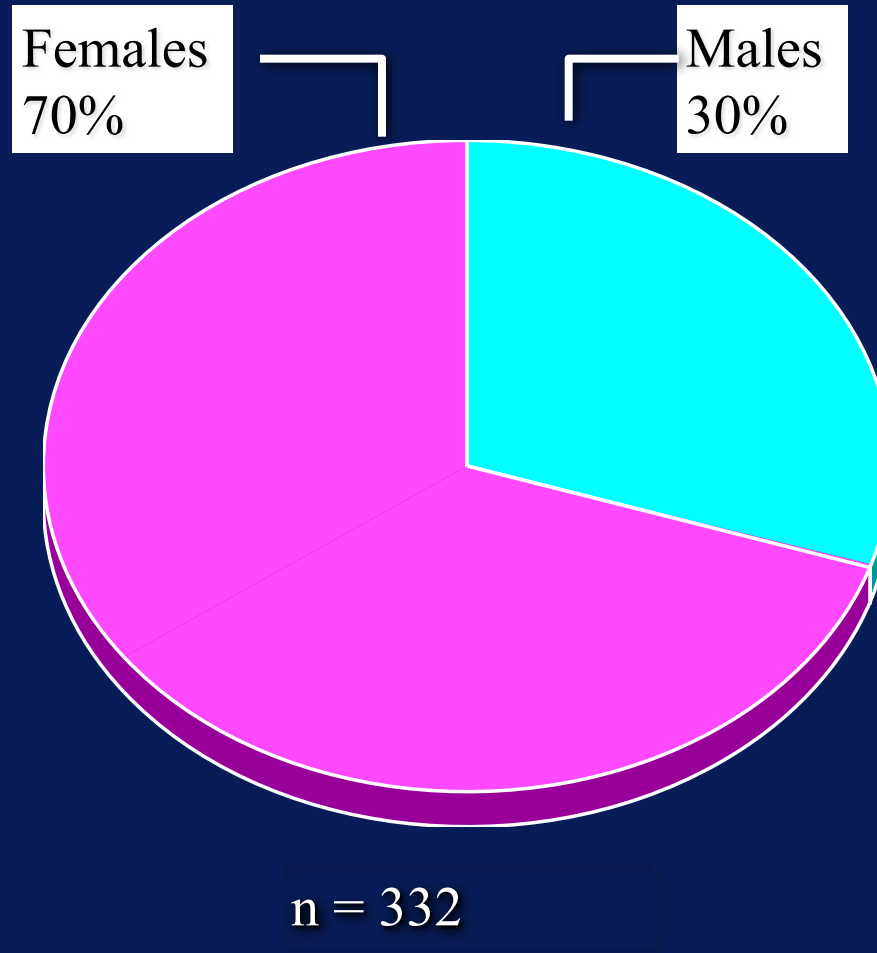


# Modulation of QT Interval Dymamicity

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# Incidence of Drug-Induced Torsades de Pointes



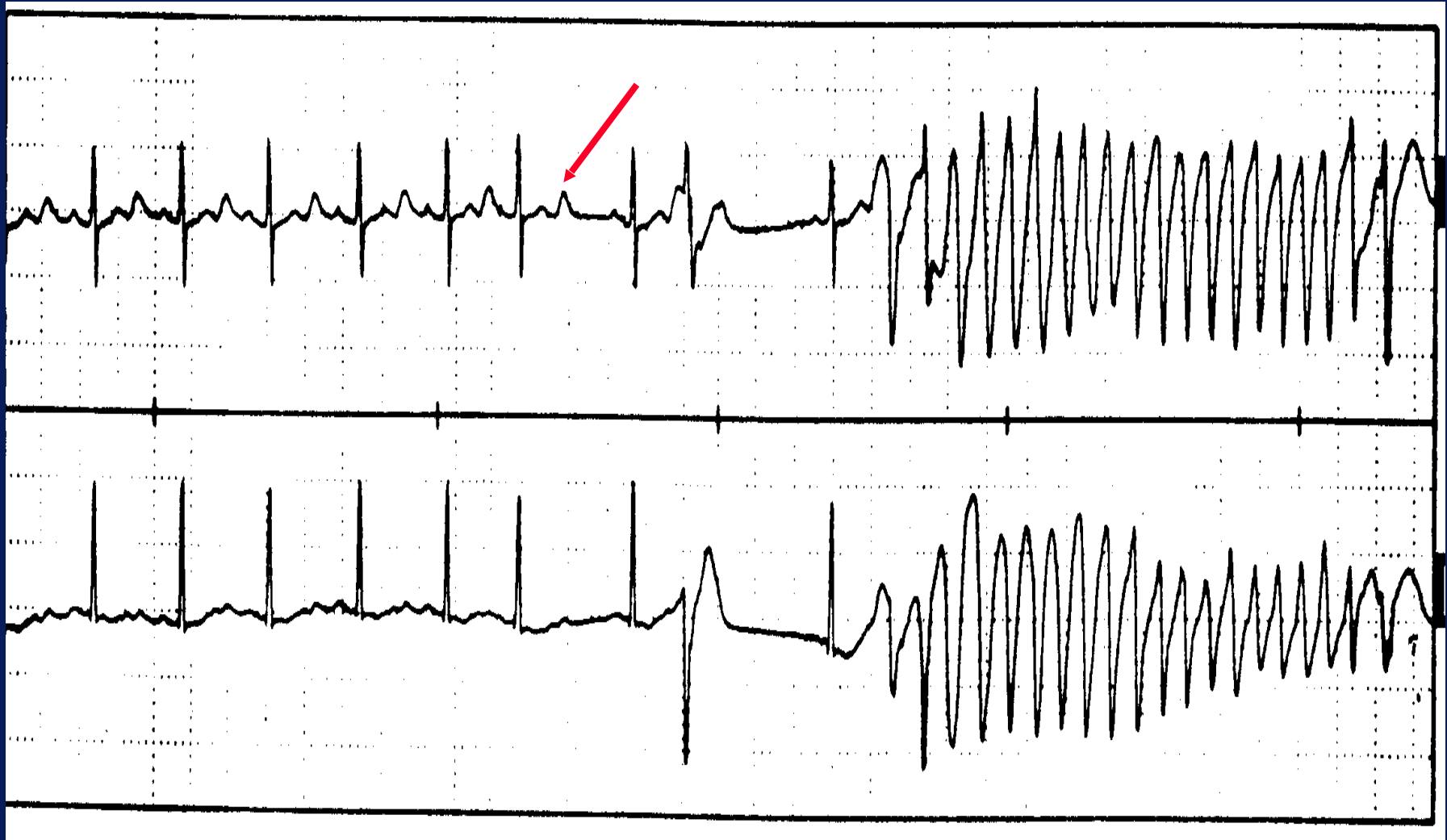
The intrinsic characteristics of longer QT interval duration and higher QT interval dynamicity in females partly explains the greater female vulnerability to the proarrhythmic effect of cardiac and non-cardiac drugs that prolong QT interval and induce ventricular tachyarrhythmias such as torsades-de-pointes.

# Drugs Associated to Risk of Torsades de Pointes

Generic name	Class / Clinical Use	Comments
Amiodarone	Anti-arrhythmic / abnormal heart rhythm	Females > Males, TdP risk regarded as low
Arsenic trioxide	Anti-cancer / leukemia	Females > Males
Bepidil	Anti-anginal / heart pain	
Chloroquine	Anti-malarial / malaria infection	
Chlorpromazine	Anti-psychotic / anti-emetic / schizophrenia / nausea	Restricted availability; Females > Males
Cisapride	GI stimulant / heartburn	
Clarithromycin	Antibiotic / bacterial infection	Females > Males
Disopyramide	Anti-arrhythmic / abnormal heart rhythm	
Dofetilide	Anti-arrhythmic / abnormal heart rhythm	
Domperidone	Anti-nausea / nausea	
Droperidol	Sedative; anti-nausea / anesthesia adjunct, nausea	Females > Males
Erythromycin	Antibiotic; GI stimulant / bacterial infection; ↑ GI motility	Females > Males
Halofantrine	Anti-malarial / malaria infection	Females > Males
Haloperidol	Anti-psychotic / schizophrenia, agitation	
Ibutilide	Anti-arrhythmic / abnormal heart rhythm	Females > Males
Levomethadyl	Opiate agonist / pain control, narcotic dependence	
Mesoridazine	Anti-psychotic / schizophrenia	Females > Males
Methadone	Opiate agonist / pain control, narcotic dependence	Females > Males
Pentamidine	Anti-infective / pneumocystis pneumonia	Females > Males
Pimozide	Anti-psychotic / Tourette's tics	
Procainamide	Anti-arrhythmic / abnormal heart rhythm	Females > Males
Quinidine	Anti-arrhythmic / abnormal heart rhythm	Females > Males
Sotalol	Anti-arrhythmic / abnormal heart rhythm	Females > Males
Sparfloxacin	Antibiotic / bacterial infection	Females > Males
Thioridazine	Anti-psychotic / schizophrenia	

Several cardiac (antiarrhythmic and other cardiac drugs) and non-cardiac drugs prolong QT interval and have proarrhythmic effect. The updated list of such drugs is present on the site [www.qtdrugs.org](http://www.qtdrugs.org).

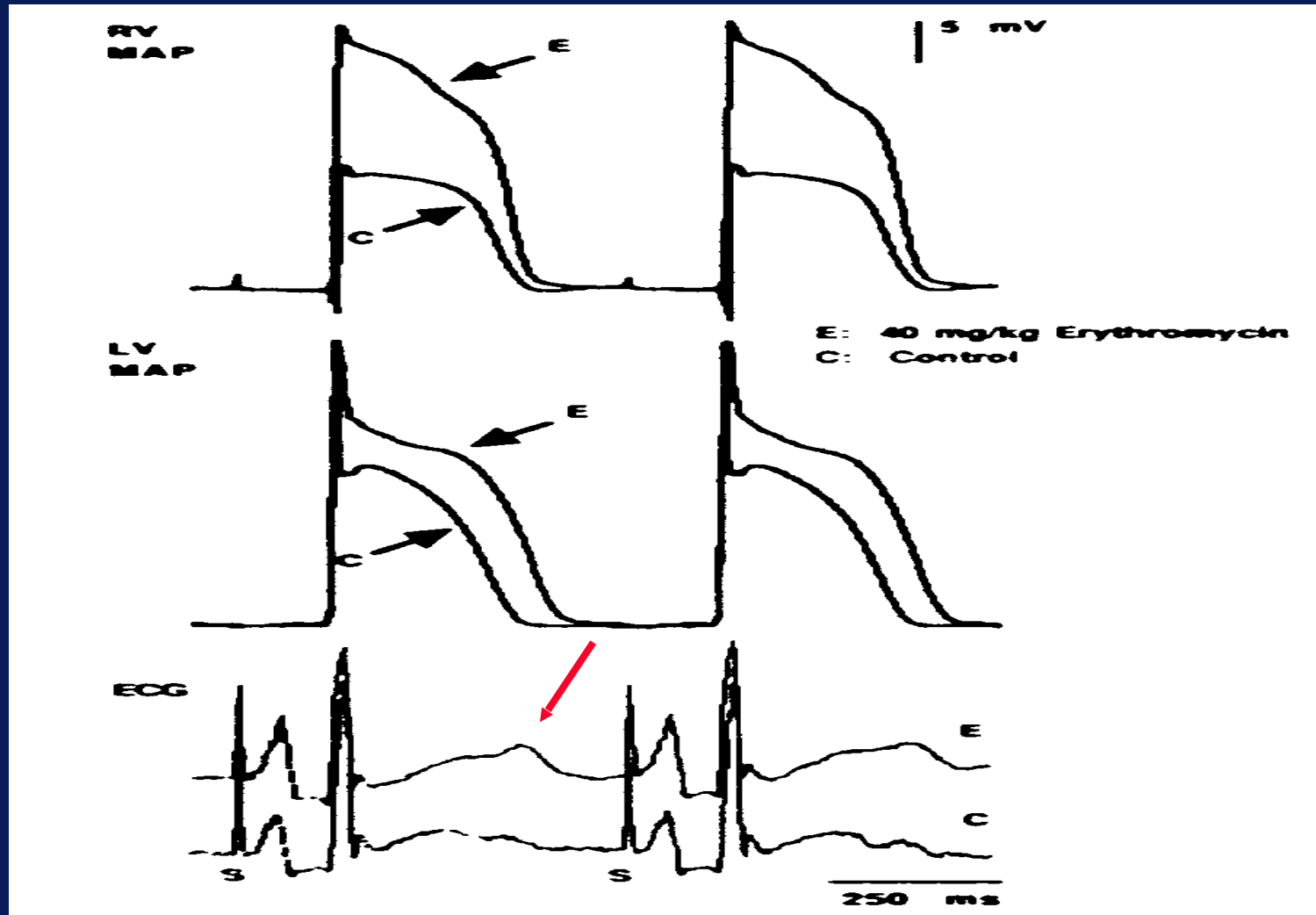
## Pause and Tachycardia-Dependence of TdP



Locati EH et al, JACC 1992

Quinidine increased the late component of the QT interval (QTU wave) and favor the onset of torsades-de-pointes following a short-long sequence.

# Effects of Erythromycin on MAP and ECG

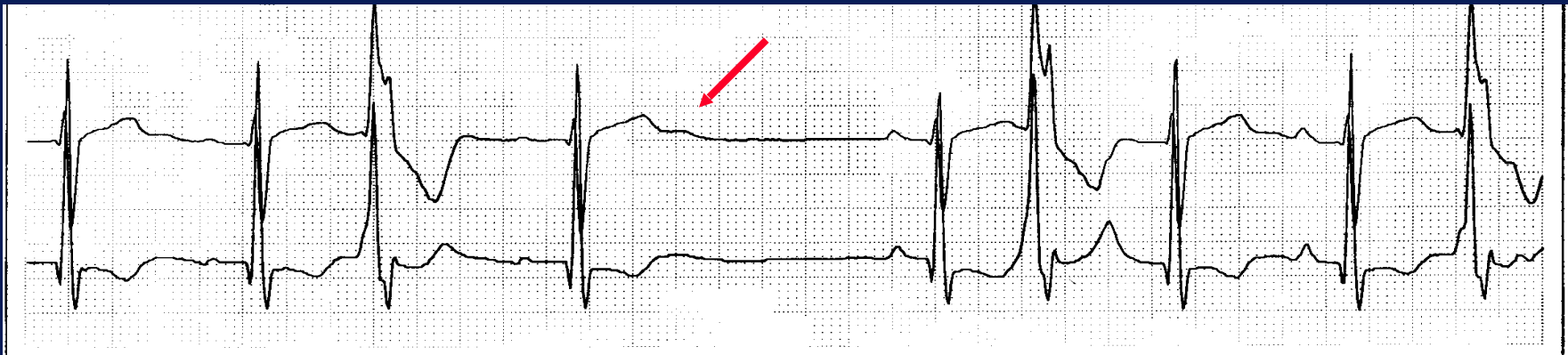




Other non-cardiac drugs, such as Erithromicine, can have major effect on QT interval duration. Several of such drugs can interact and have additive effects potentially very dangerous (e.g., antiarrhythmic + antidepressant + antibiotics + diuretics inducing hypokalemia)

# Bartter's Syndrome

## Potassium Depletion ( $K^+$ 3.7 mEq/l)



M.M, Male, 17 yrs

Locati EH, 2000

QTc interval is prolonged in its late component in a young man with idiopathic potassium depletion due to Bartter's syndrome, and frequent polymorphic unsustained ventricular tachycardias are also observed.

# Left Ventricular Repolarization Abnormalities During Hemodialysis

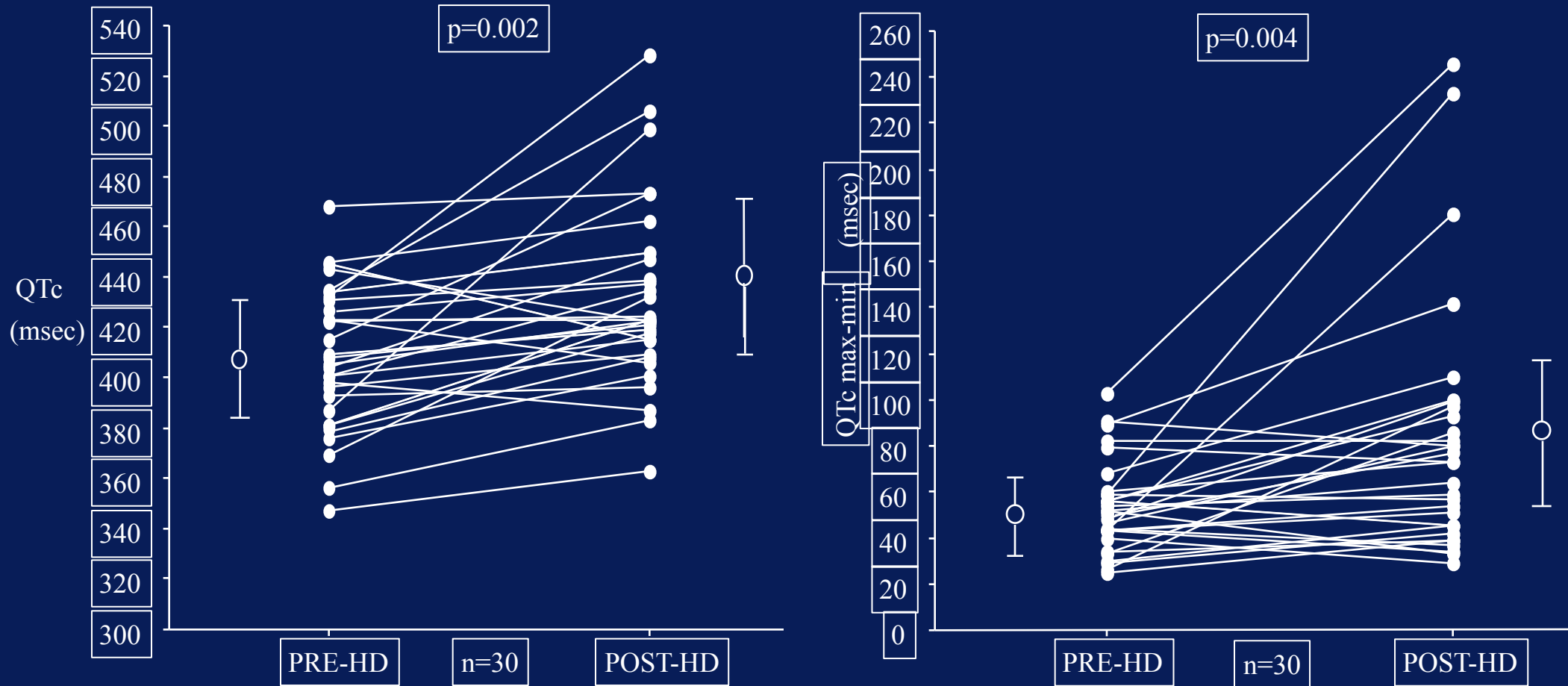
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	Pre-HD	Post-HD	p
QRS (msec)	80±16	80±16	ns
RR (msec)	940±31	930±48	ns
QT (msec)	352±32	374±59	<0.05
QTc (msec)	399±26	428±38	<0.0005
ΔQTc max-min	53±21	89±65	<0.01
QTc_CV	4.6±1.5	7.2±4.9	<0.01
K <sup>+</sup> (mEq/l)	5.2±0.8	3.5±0.6	<0.0001
Mg <sup>+2</sup> (mEq/l)	2.8±0.6	2.1±0.4	<0.0001

During hemodialysis, fast  $K^+$  and  $Mg^{++}$  decrease are observed, with modest but uniform increase of QT and QTc interval duration and QT dispersion.

See in the next slide the individual changes of QTc and QT dispersion in 30 normal subjects during hemodialysis.

# QTc and QT Dispersion Changes During Hemodialysis



# Sodium & Potassium Channel Blockers

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Proarrhythmia may be related to **use-dependent effects**

→ **More extensive block at fast heart rates**

- ✓ Excessive slowing of ventricular conduction at fast rates (↑ QRS)
- ✓ Excessive slowing of ventricular repolarization at fast rates (↑ QT)

→ Effects may be countered by beta-blockers



Baseline

QT 340 msec

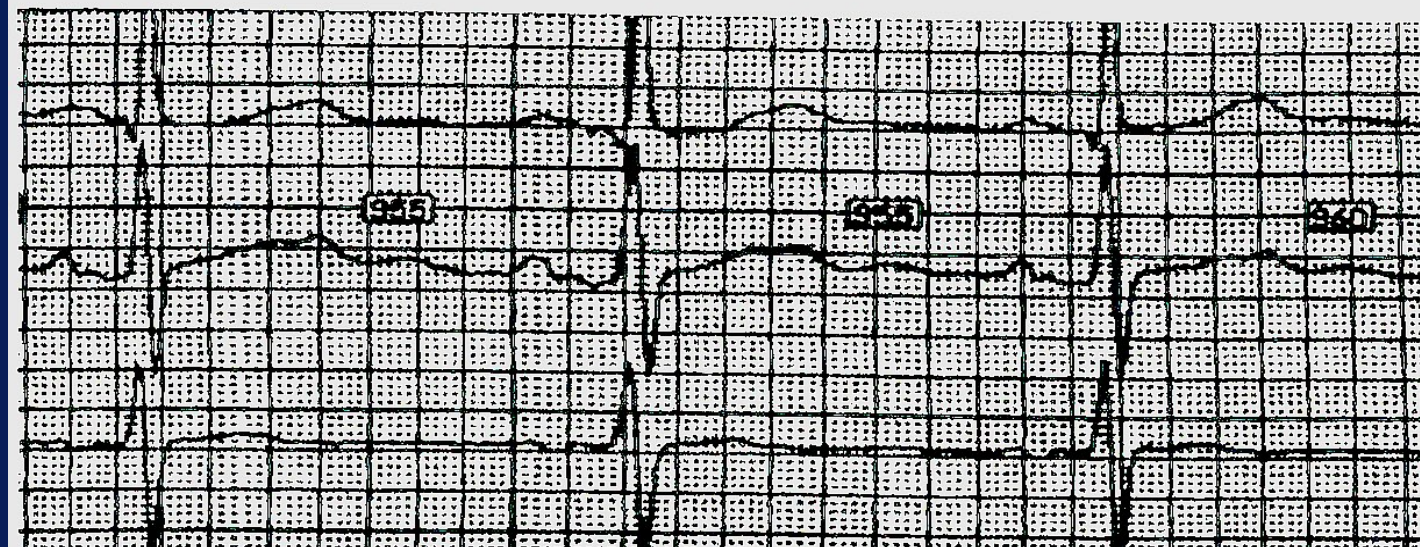
QTc 347 msec



Quinidine

QT 380 msec

QTc 388 msec



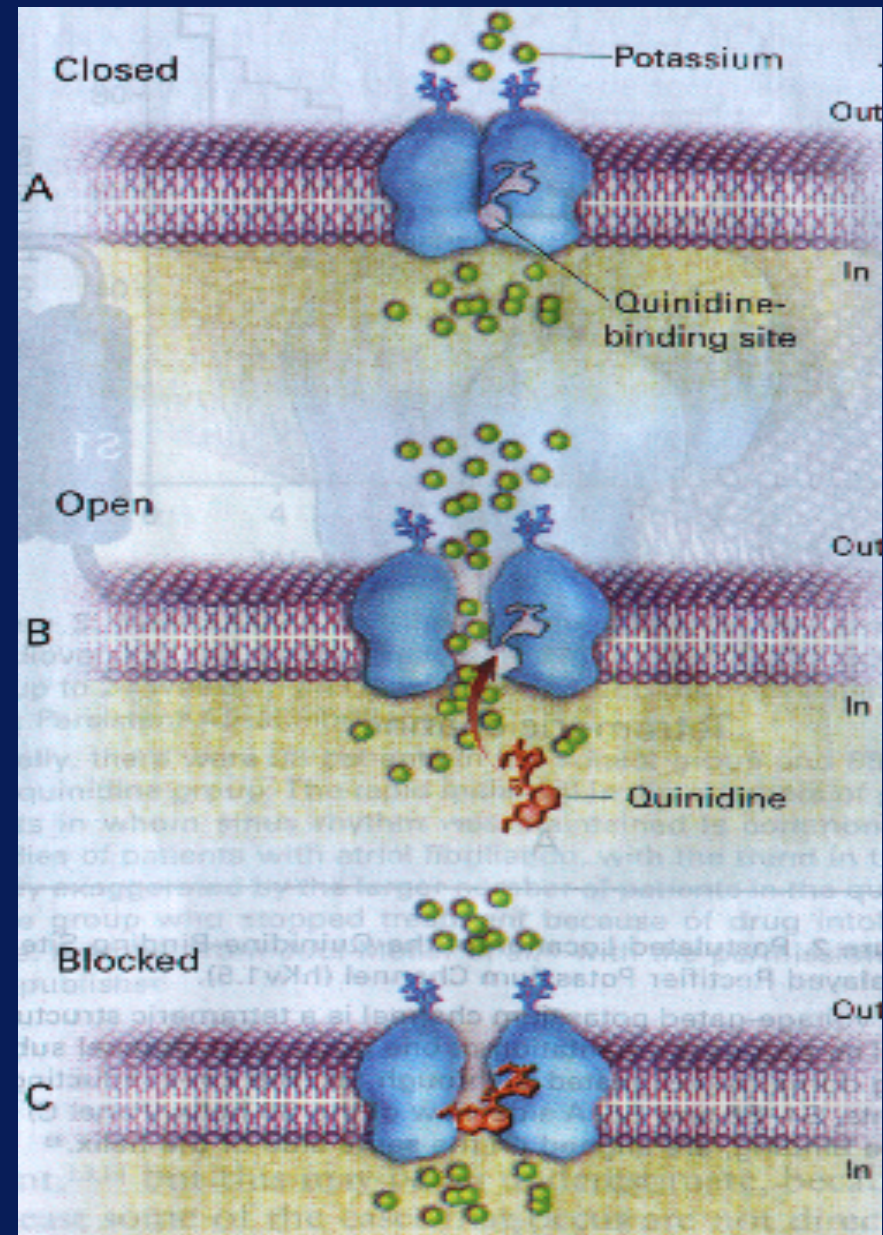


Effect of Quinindine on QT and QTc interval duration and QT morphology at the same cycle length in the same normal subject.

# Quinidine blocks $I_{Kr}$ in the active configuration



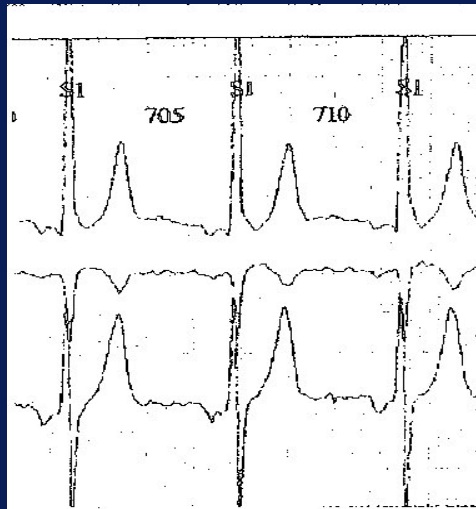
The blockage is more evident during tachycardia, correspondent to a “use-dependent effect”



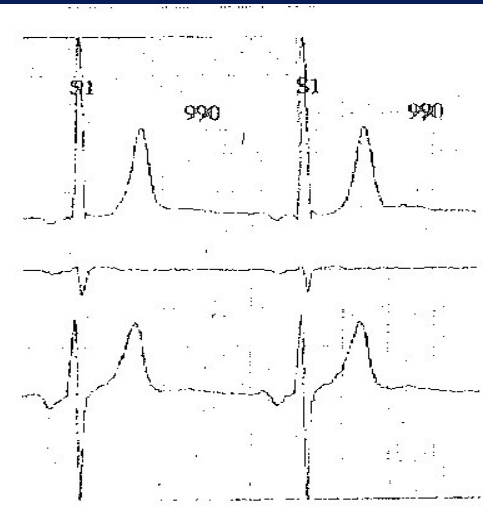
R-R min 710 msec

R-R max 980 msec

Basal

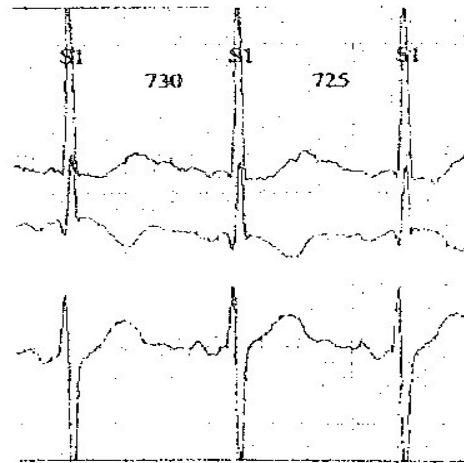


QTc 428 msec

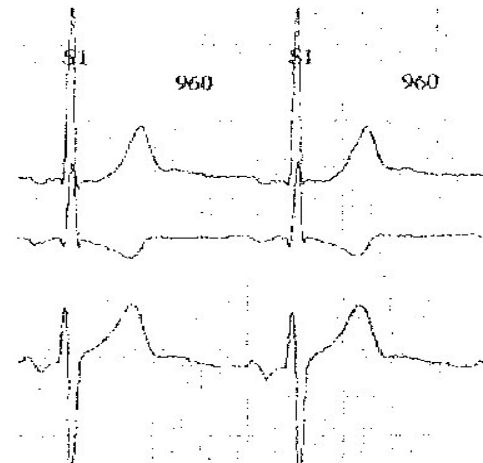


QTc 384 msec

Quindine



QTc 566 msec



QTc 449 msec

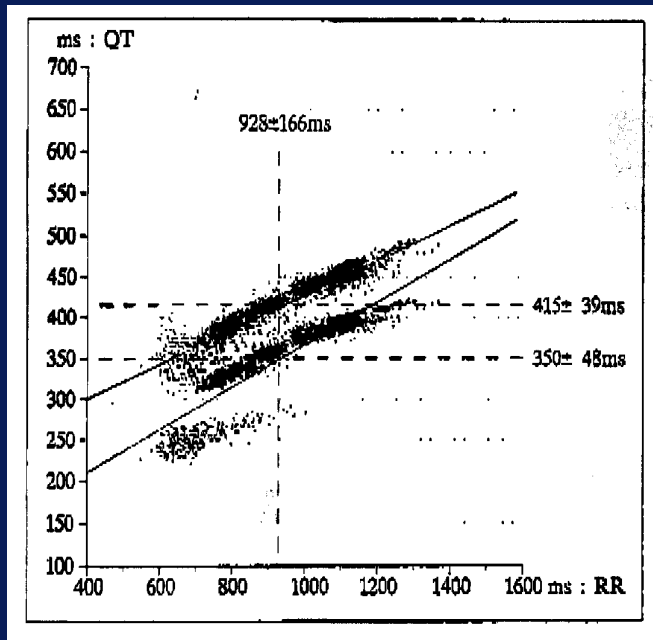
MG, Female, 65 yrs

Locati EH et al, JACC 1998

As expected from the use-dependent effect of Quinindine, in a normal subject the blockage is more evident at faster heart rates, and QT and QTc interval prolongation are more evident at shorter cycle lengths

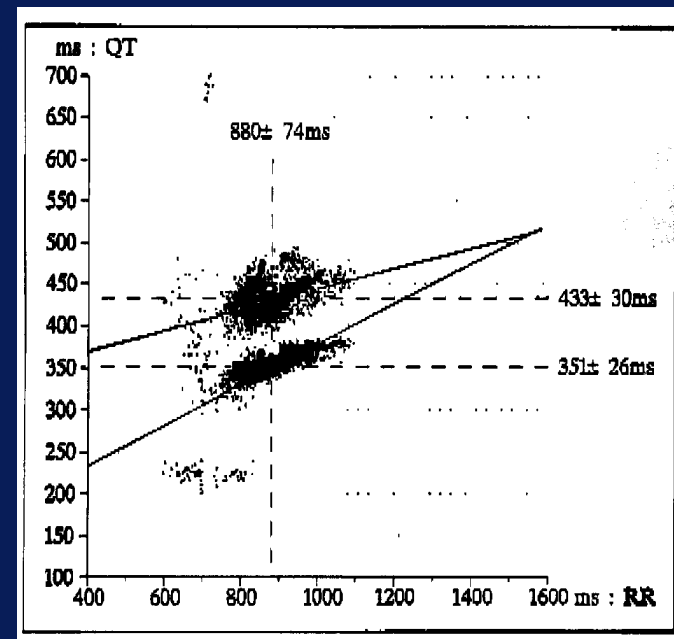
# Heart Rate Dependence of QT Interval

## Baseline



QTc/RR 0.21, QTc 431 ms  
QTa/RR 0.26, QTa 363 ms

## Quinidine



QTc/RR 0.12, QTc 461 ms  
QTa/RR 0.24, QTa 374 ms

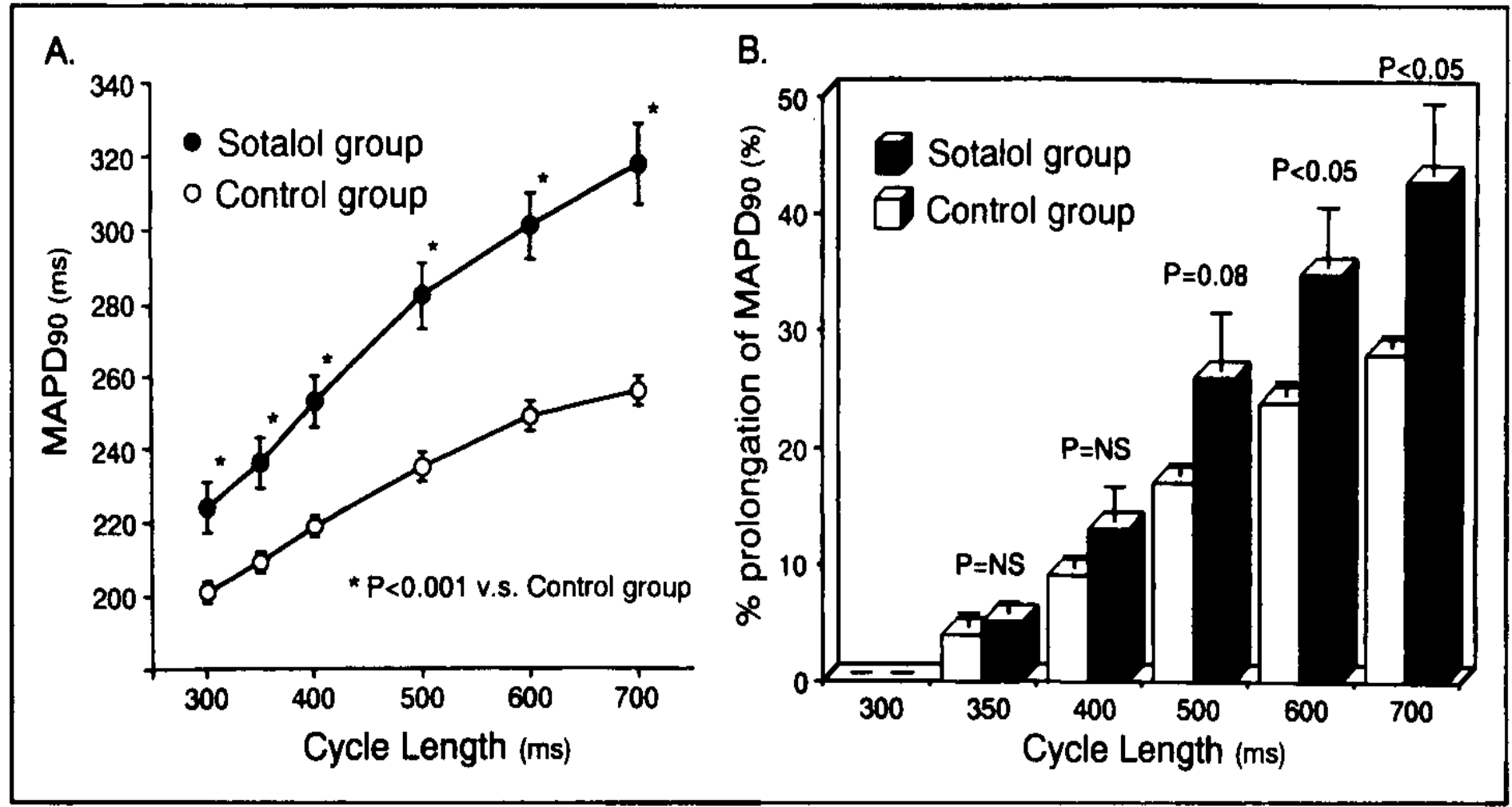
MG, Female, 65 yrs

Locati EH et al, JACC 1998

Therefore the slope of the QT/RR regression, particularly QTend/RR relation, is greatly reduced by Quinidine, and the regression is no longer linear.

Opposite, sotalol (and amiodarone) show a reverse use-dependent effect, with longer QT interval duration at longer cycle lengths (low heart rates)

# Reverse Use-Dependence of Sotalol



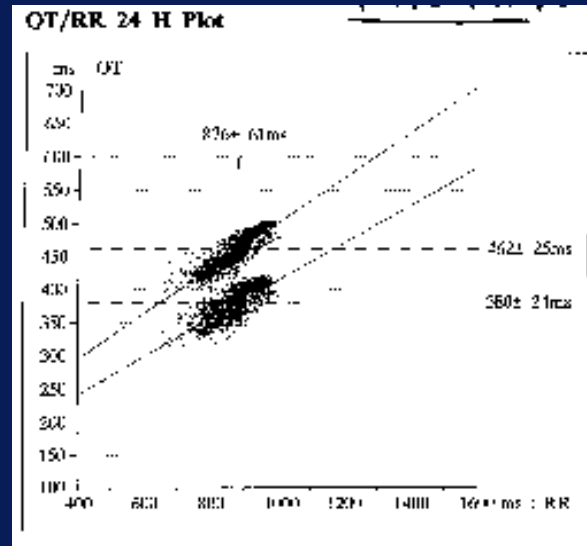
Shimizu W et al, Am J Cardiol 1996

Effect of different antiarrhythmic drugs  
on QTend/RR and QTapex/RR in normal  
subjects (see next slide)

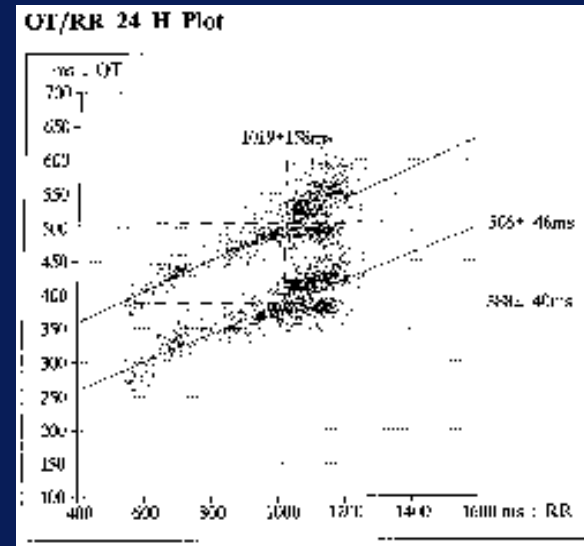


# Rate-Dependence of QT Interval After AA Drugs

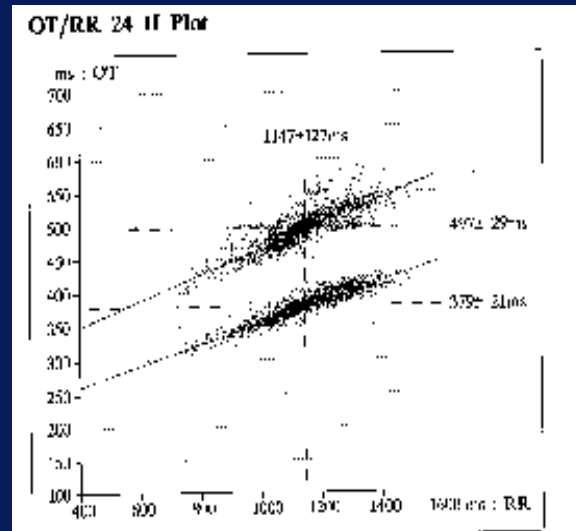
**Propafenone**  
Slope = 0.35  
 $r = 0.85$   
QTc 493 ms



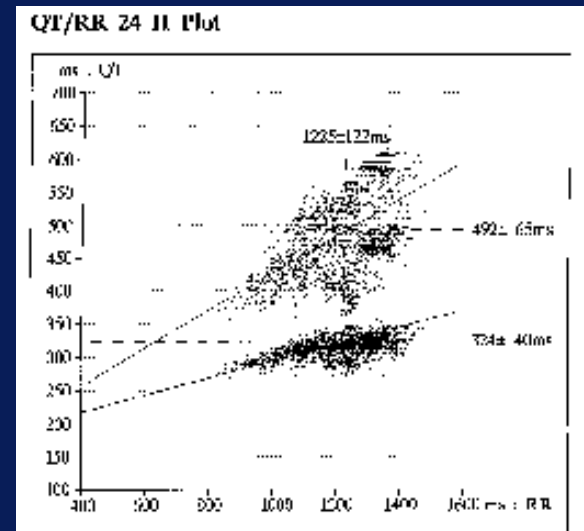
**Disopyramide**  
Slope = 0.23  
 $r = 0.80$   
QTc 501 ms



**Amiodarone**  
Slope = 0.19  
 $r = 0.84$   
QTc 464 ms



**Sotalol**  
Slope = 0.28  
 $r = 0.53$   
QTc 445 ms

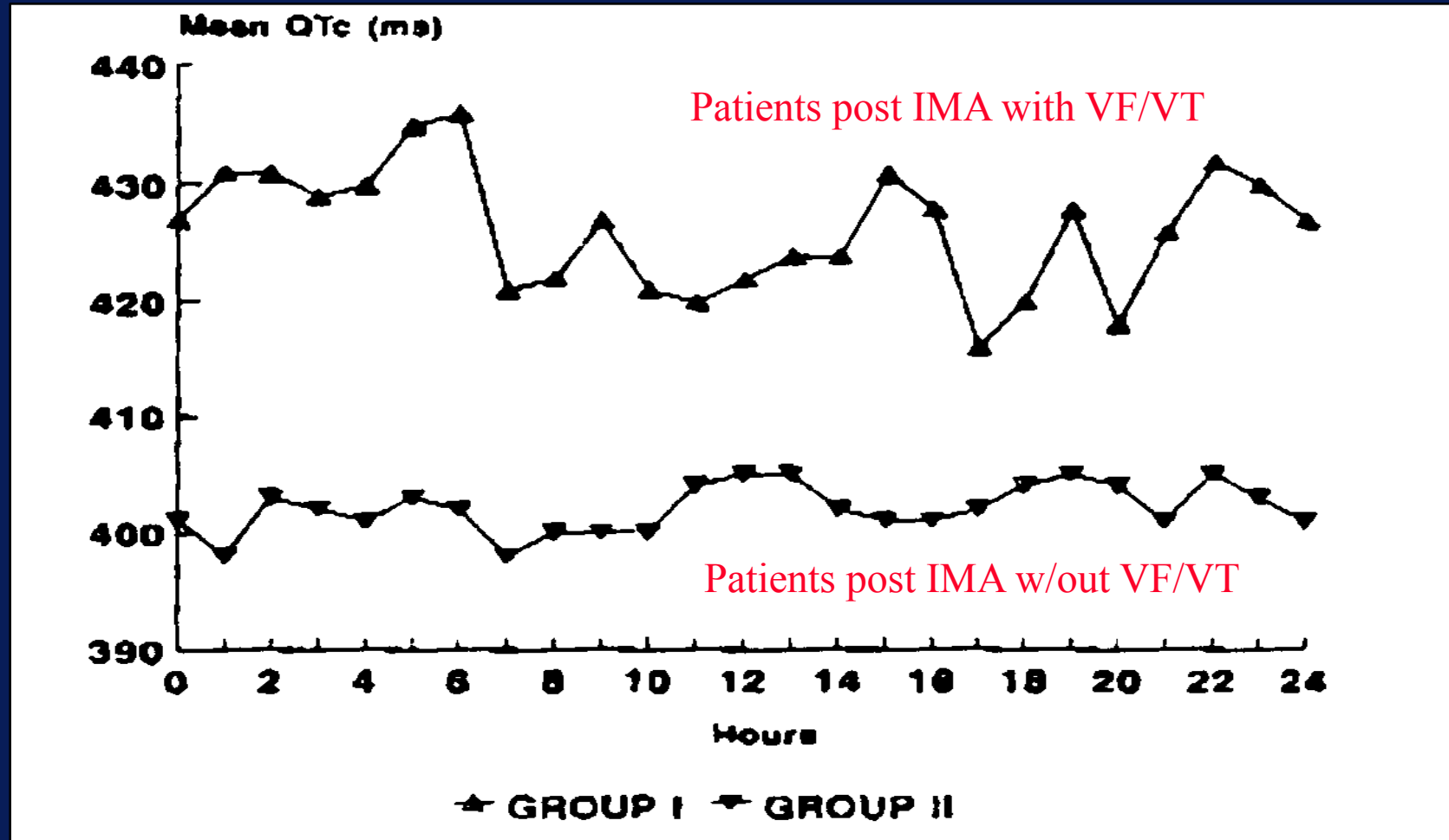


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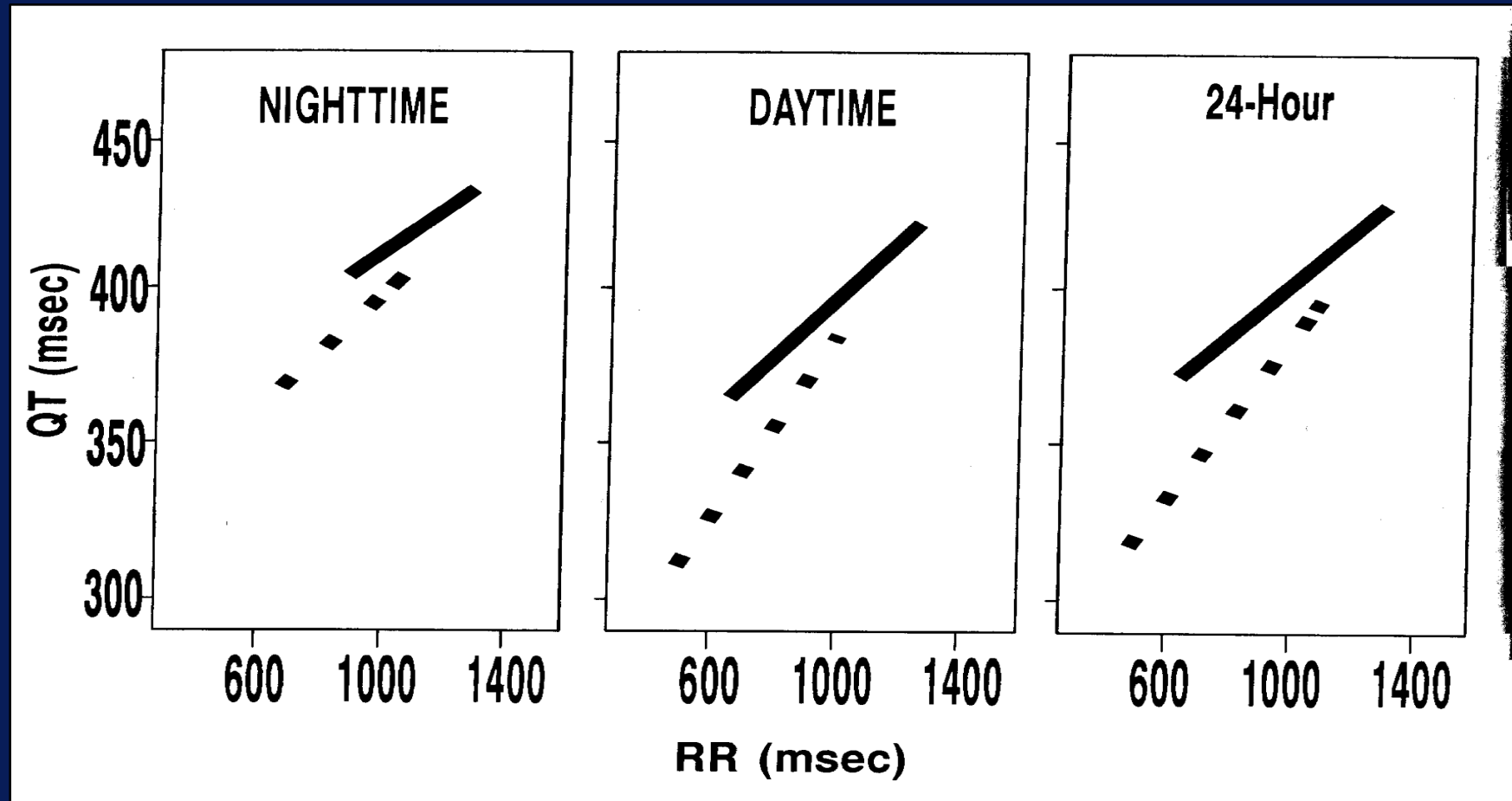
# Circadian QTc Variability Post Myocardial Infarction in Patients With and Without Malignant Ventricular Arrhythmias



Bayes de Luna, Am Heart J 1997

In post-IMA patients, particularly in those with history of malignant ventricular arrhythmias, an increased QTc interval duration and QTc variability (QTc peaks) are observed.

## QT/RR Regression With Placebo (dashed) and Metoprololo (solid) in Patients After Myocardial Infarction



Hintze et al, ANE 1997

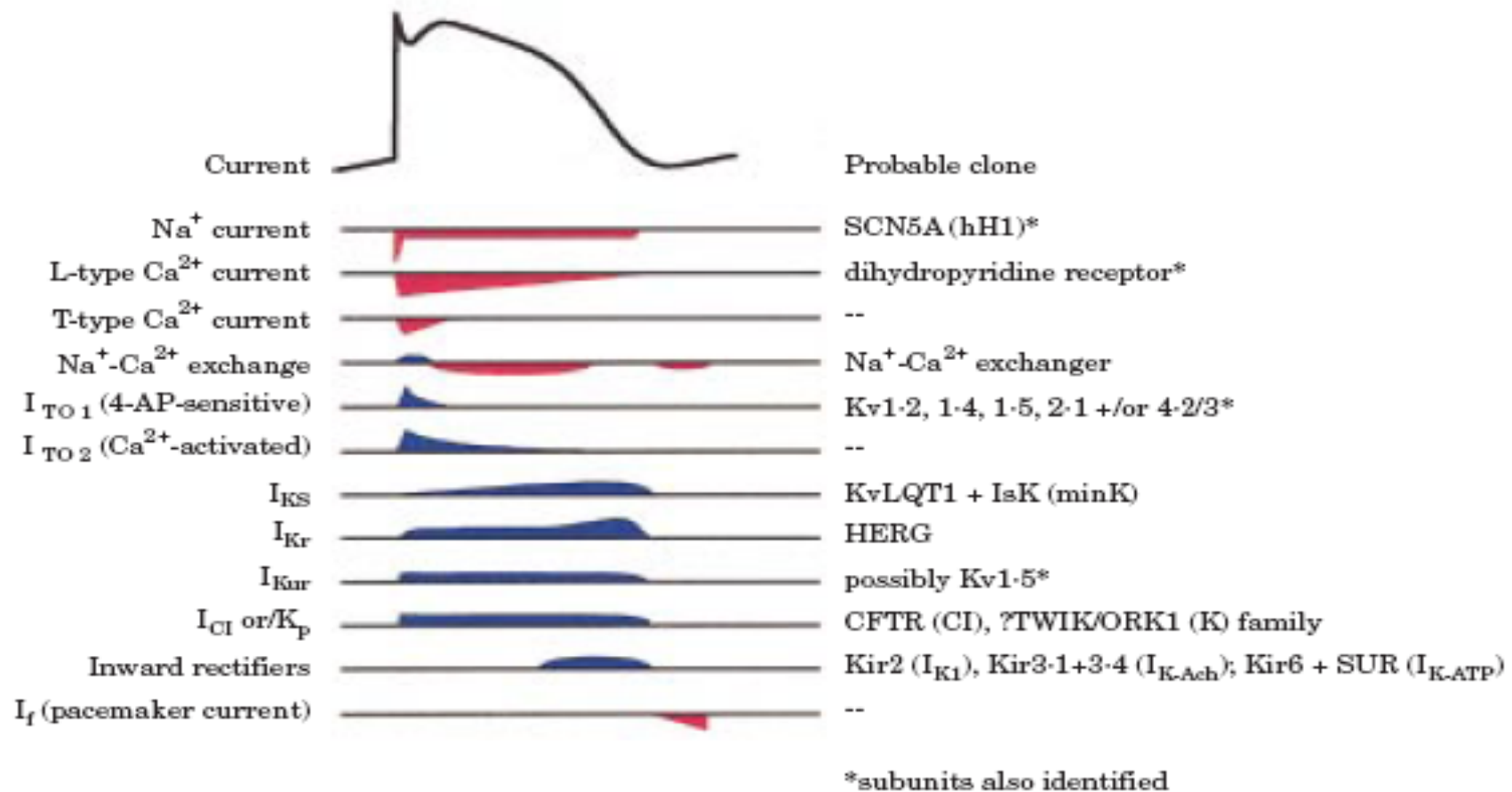
Also QT/RR relation is modified after myocardial infarction, with lower slope (lesser shortening of QT interval during faster heart rates, solid lines), but data in this area are still scanty and controversial.

# Modulation of QT Interval Dymamicity

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# APD, Ionic Currents and Genetic Mutations

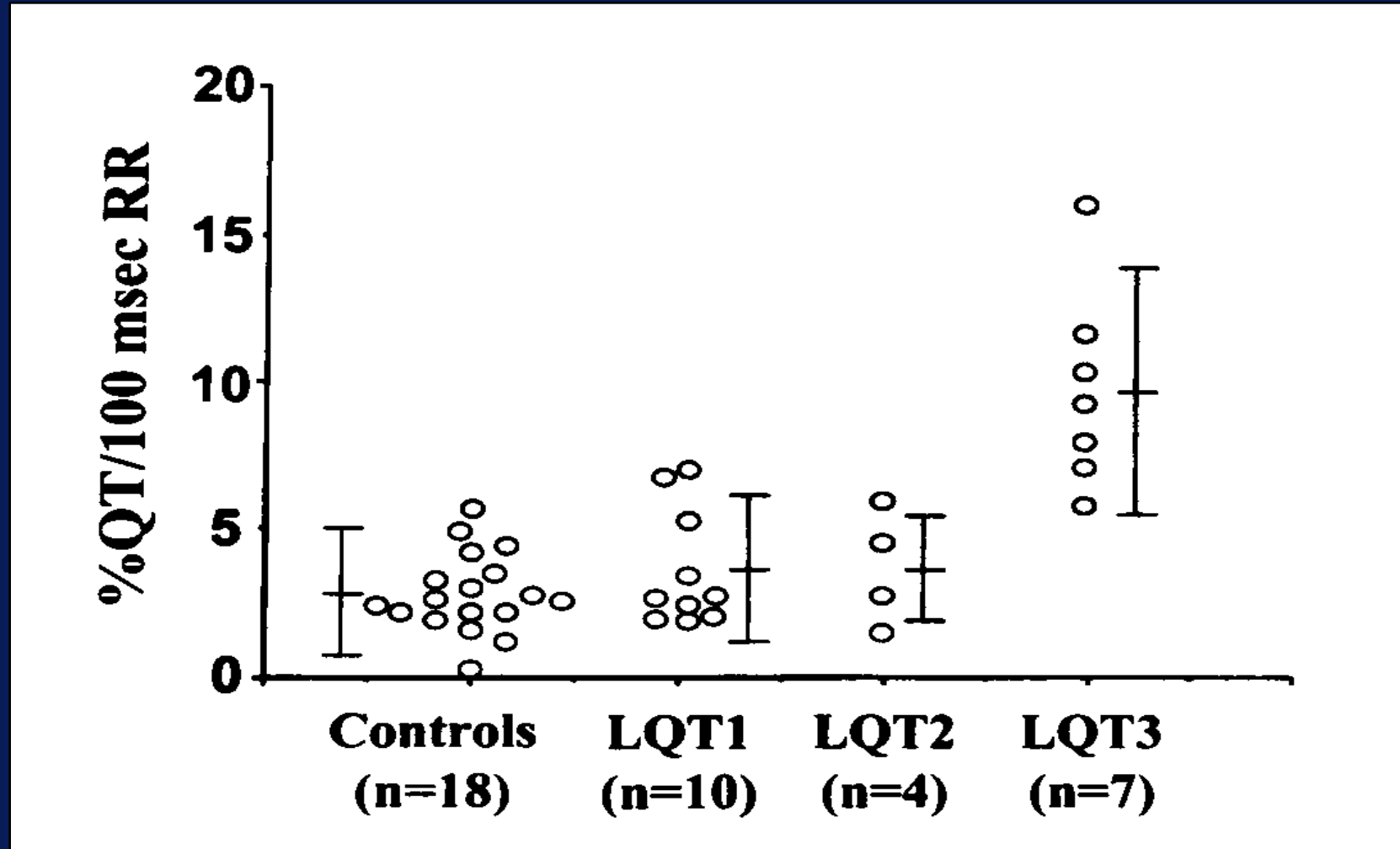


**Figure 4** Cardiac ionic currents and respective ion channel clones responsible for generation of the action potential. Inward currents are drawn in red, outward currents in blue. The amplitudes are not to scale.



Single mutations interfere with the activity of specific ionic currents in different phases of the action potential. As an example, an HERG mutation modifies the activity of the  $I_{Kr}$  current active in the later phase of ventricular repolarization.

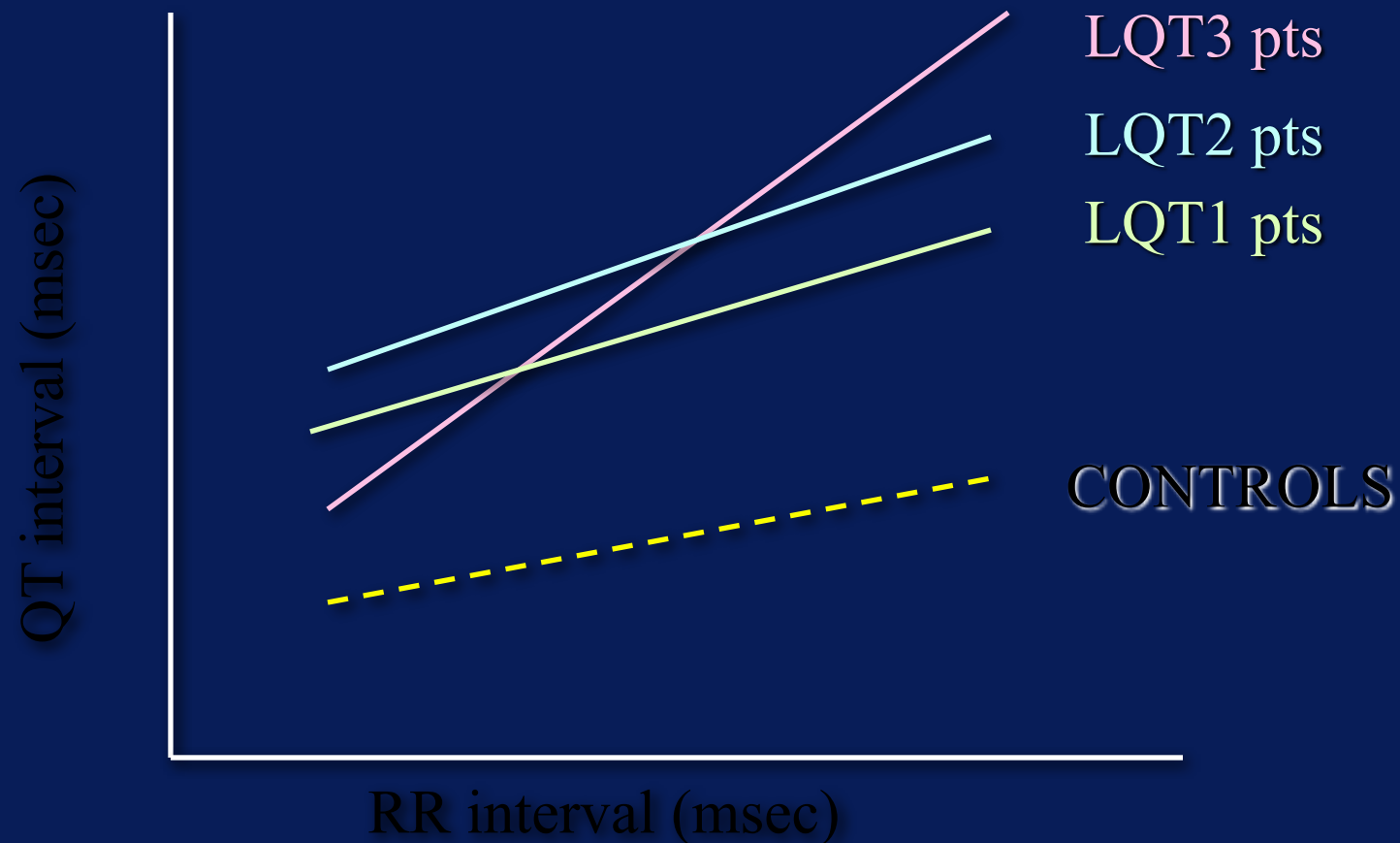
## QT-RR RELATION DURING STRESS TEST IN LQTS PATIENTS BY GENOTYPE



Schwartz et al, Circulation 1995

The capacity of adaptation of QT interval to cycle length changes during stress test which is then different in the distinct genetic variants of long QT syndrome (LQTS). This is particularly evident in LQT3 variant, with SCN5A mutation and altered Na<sup>+</sup> currents, which shows a greater-than-normal shortening of QT interval at increasing heart rates.

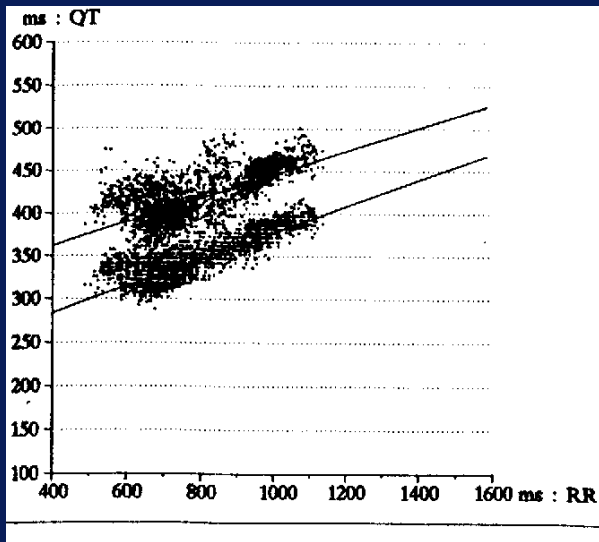
# RELATION BETWEEN QT INTERVAL AND CYCLE LENGTH DURING 24-HOUR HOLTER MONITORING IN LQTS PATIENTS



Then the QT/RR slopes in LQTS are different than in normal subjects, with different slopes among the distinct genetic variants.

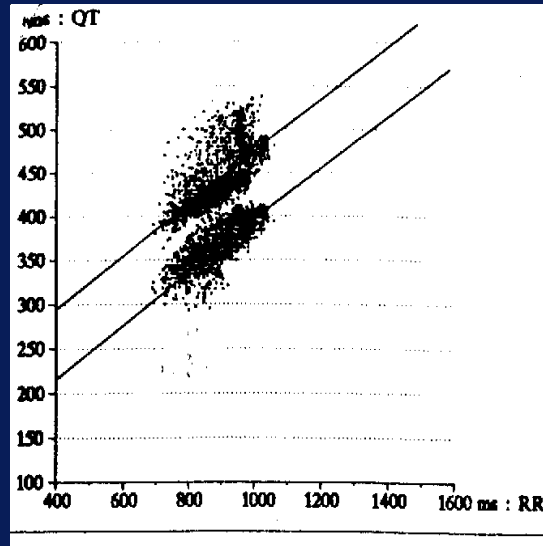
# Rate-Dependence of QT Interval In LQTS

LQT1 Patient



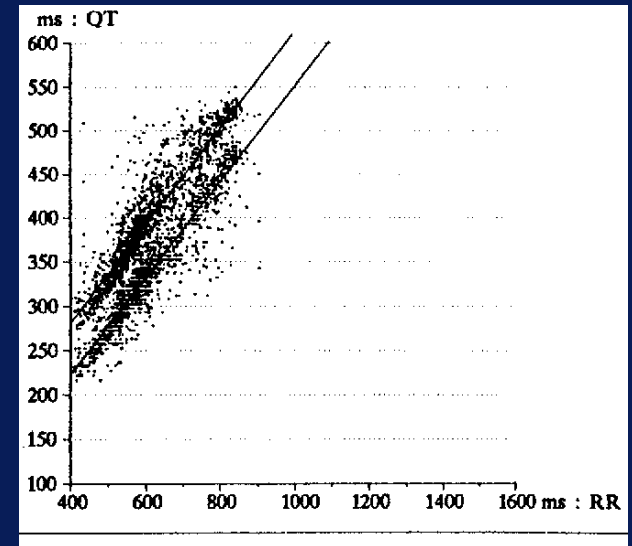
KVLQT1 Mutation

LQT2 Patient



HERG Mutation

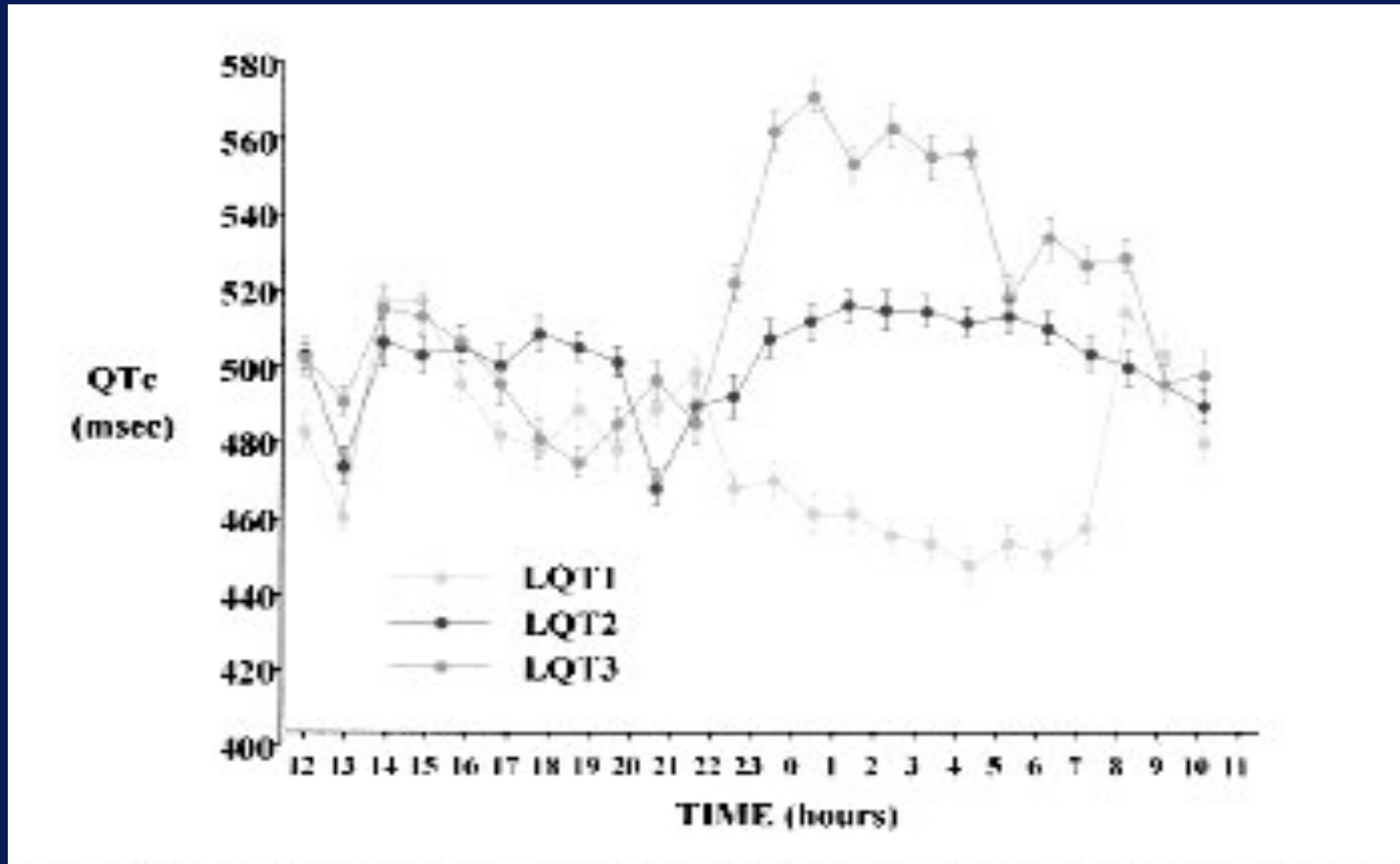
LQT3 Patient



SCN5A Mutation

The QT/RR relation has different slopes in the distinct genetic variants, with flatter slopes in LQT1 (lesser QT shortening at fast heart rates) and steeper slopes in LQT3 (greater QT shortening at fast heart rates, greater QT prolongation at low heart rates).

## Differences by Genotypes in Circadian QT Variability in LQTS



Stramba Badiale et al, It Heart J 2000



As expected, greater QTc prolongation is observed during night (at lower heart rates) in LQT3 subjects, who generally have events during sleep, while greater QT prolongation is observed during day (at high heart rates) in LQT1 subjects, who usually have events during activity or emotions.

# Clinical Applications of QT Dynamicity

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- ✓ Identification of Patients at Risk of Malignant Arrhythmias
- ✓ Detection of Proarrhythmic Effect of Anti-Arrhythmic and Non-Cardiac Drugs
- ✓ Evaluation of Congenital Cardiac Ion Channel Diseases (*LQTS*)