QT Interval Dynamicity
Methods of Analysis and Clinical Application

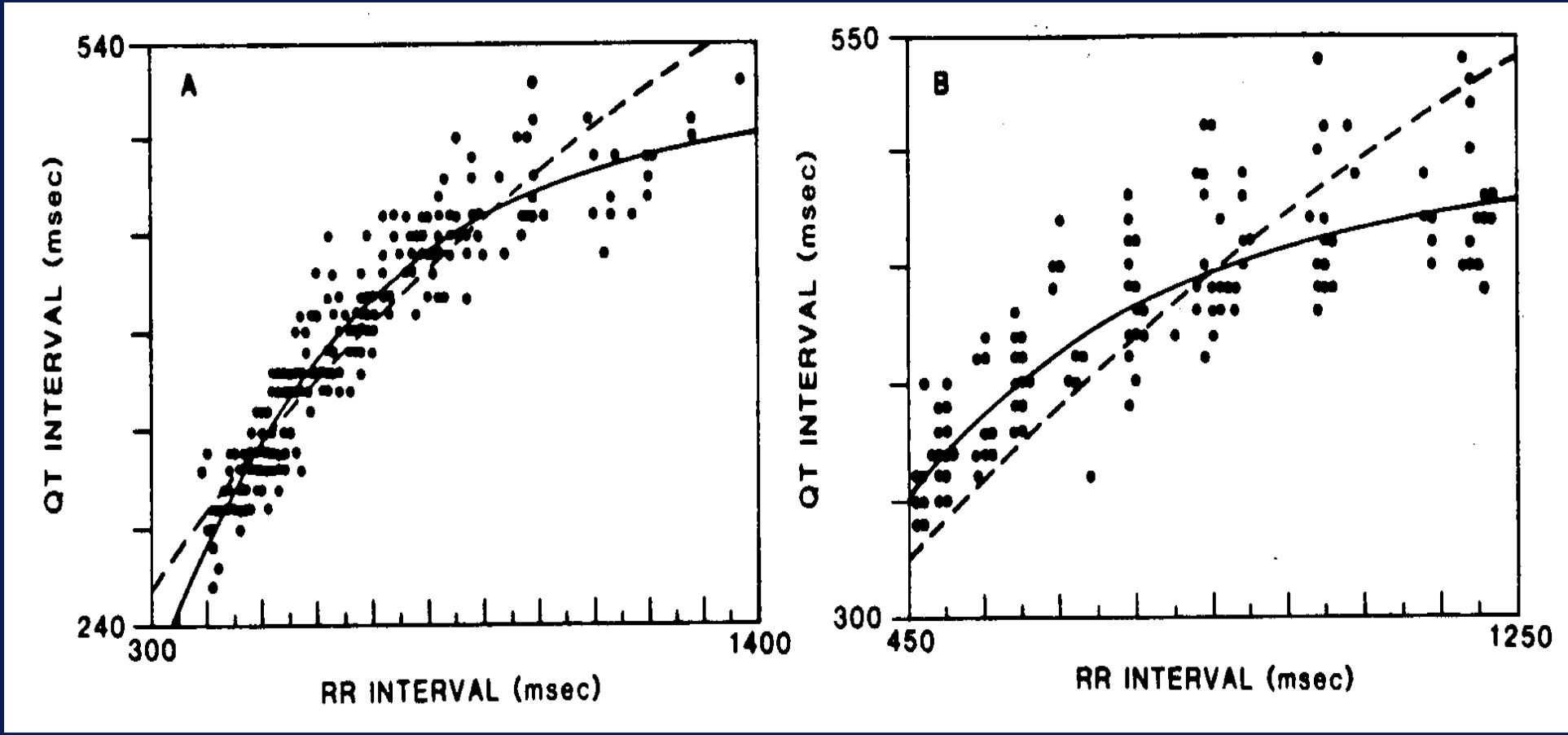
Emanuela T. Locati, MD, PhD

Azienda Ospedaliera Niguarda
Dipartimento Cardio-Toraco-Vascolare Angelo De Gasperis
&
Istituto di Cardiologia
Dipartimento di Medicina Clinica e Sperimentale
Università degli Studi di Perugia

Evaluation of QT Interval Dymamicity

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

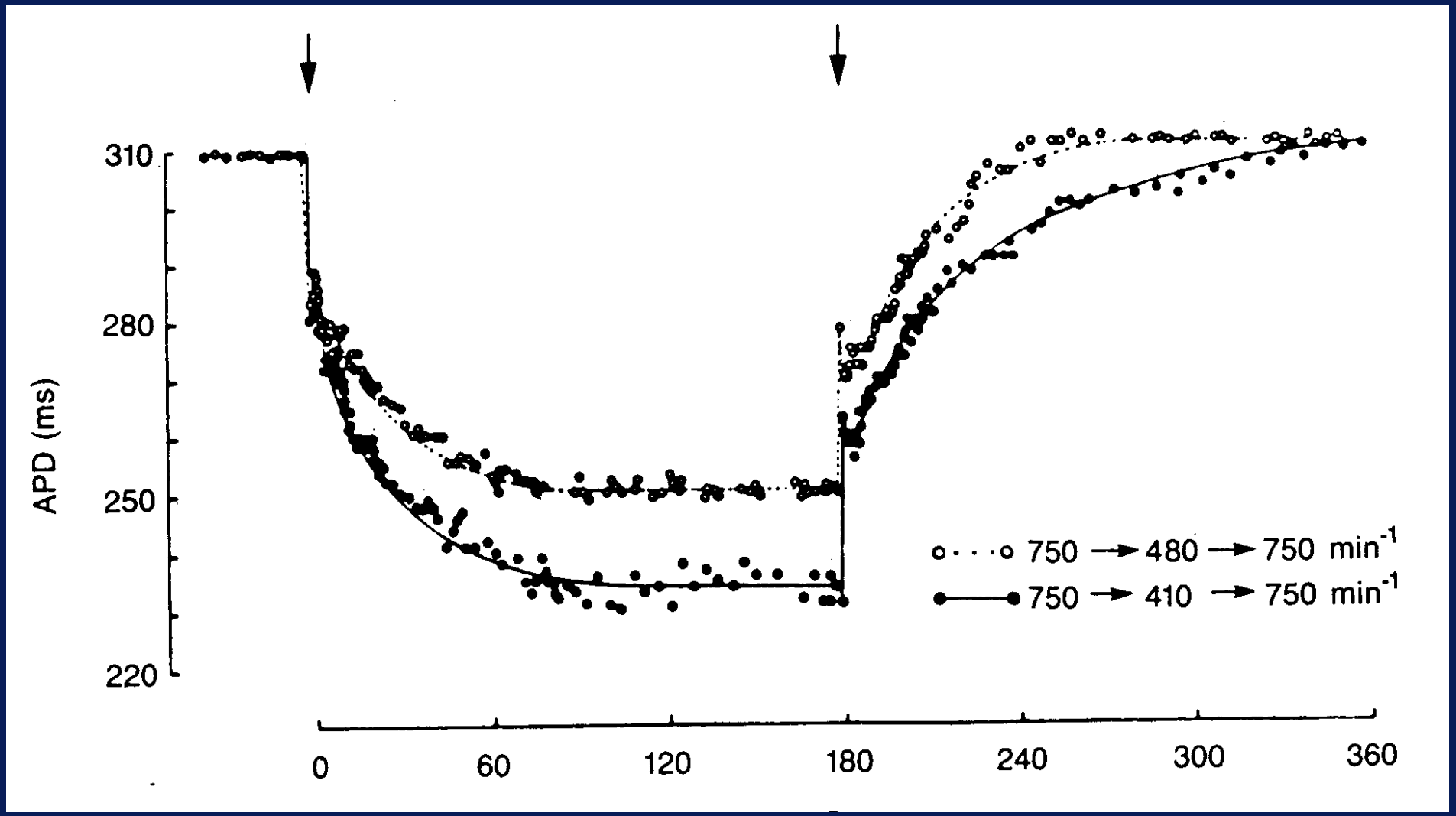
Heart Rate Dependence of QT Interval During Exercise and Pacing



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



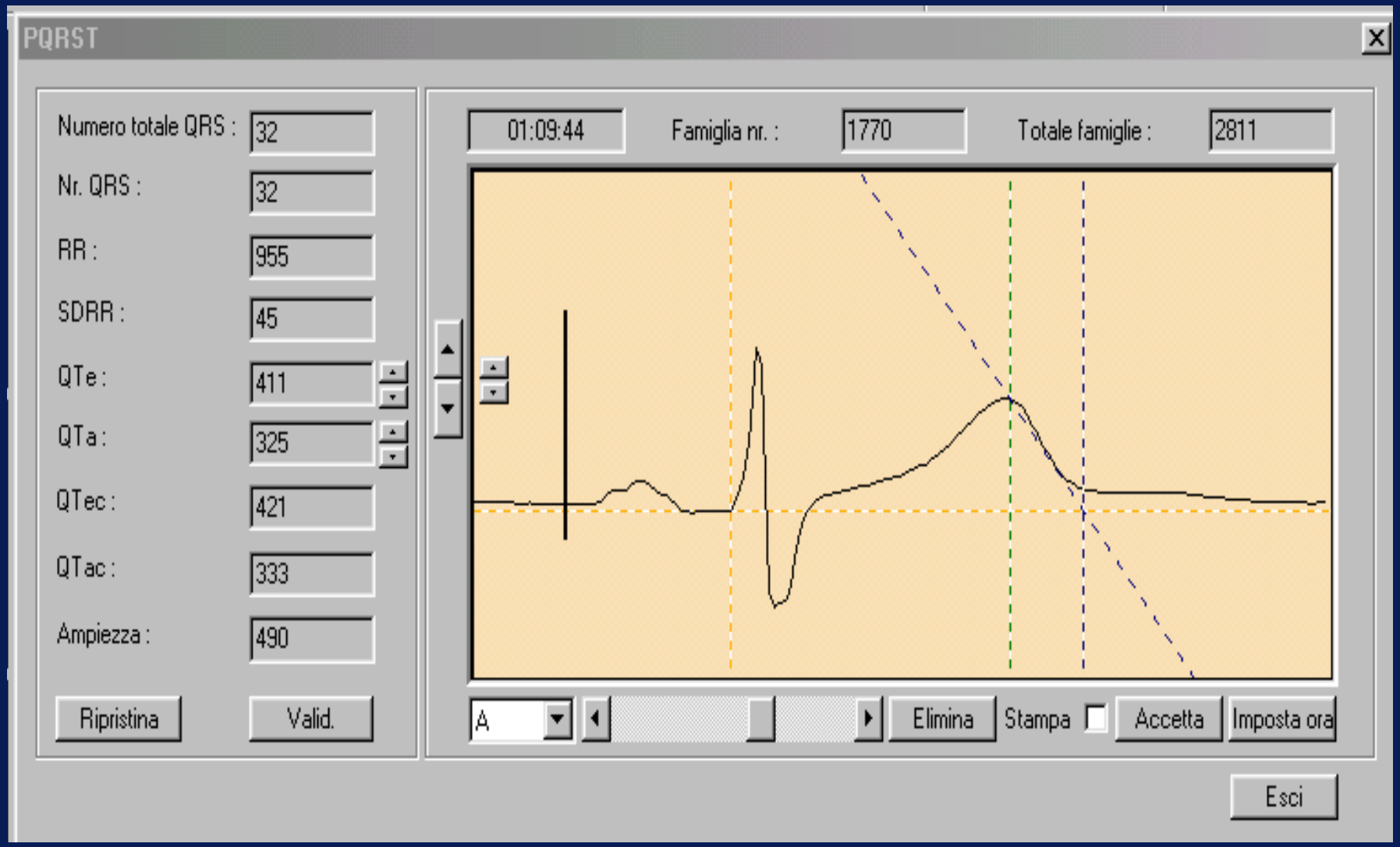
Franz MR, JCI 1988

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

Analysis of QT Dynamicity by Holter Monitoring

- ✓ 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

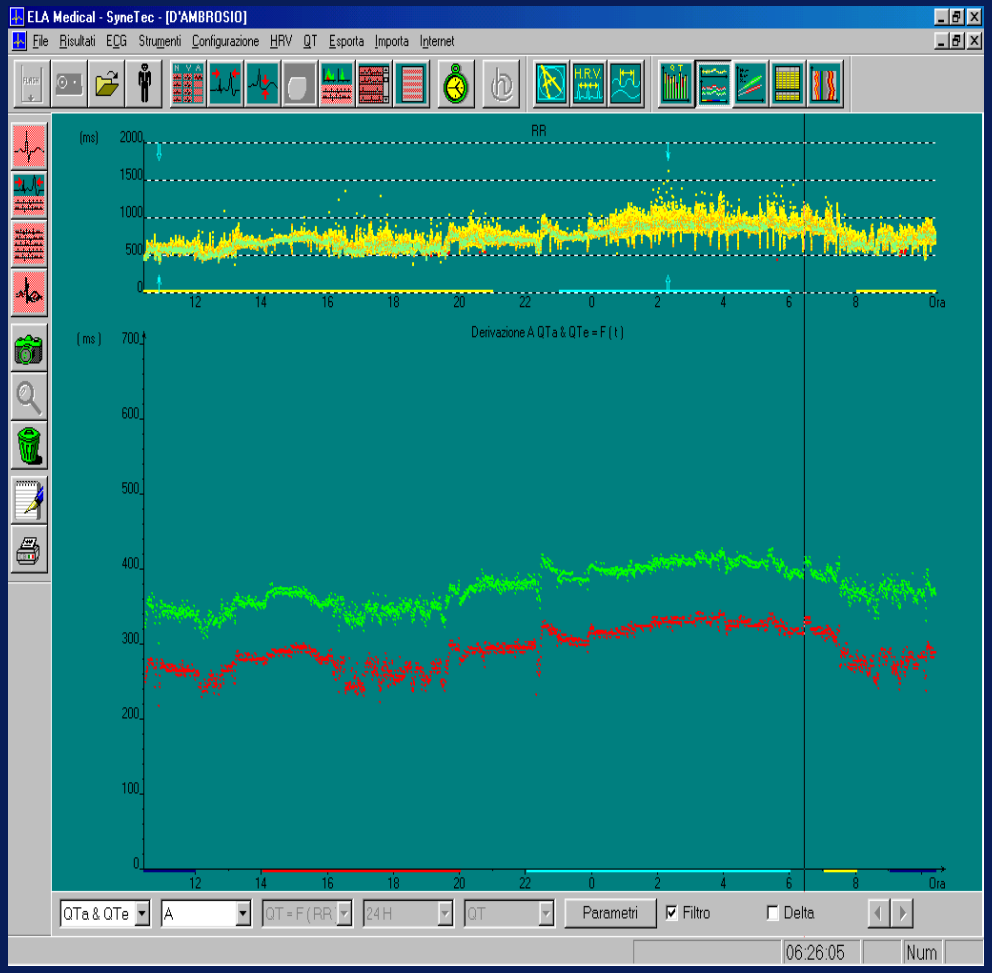
Example of Authomatic Measurement of QT Interval



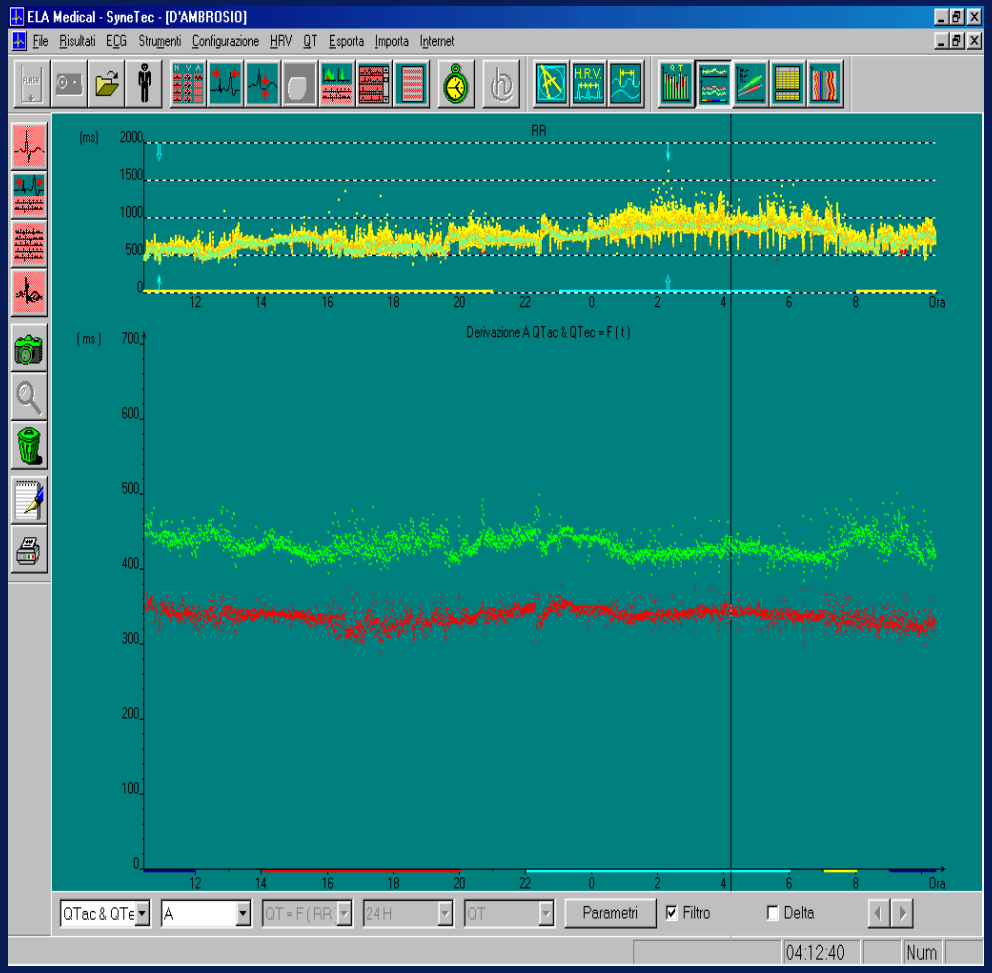
Authomatic measurement of RR, QTapex, QTend on 30 sec median beat

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 withe the point of maximal T wave deflection, while the T wave end (QTend) nyj the intersection of the tanget of the deflection curve with the isoelectric line.

Authomatic Measurement of Circadian Variability QT Interval



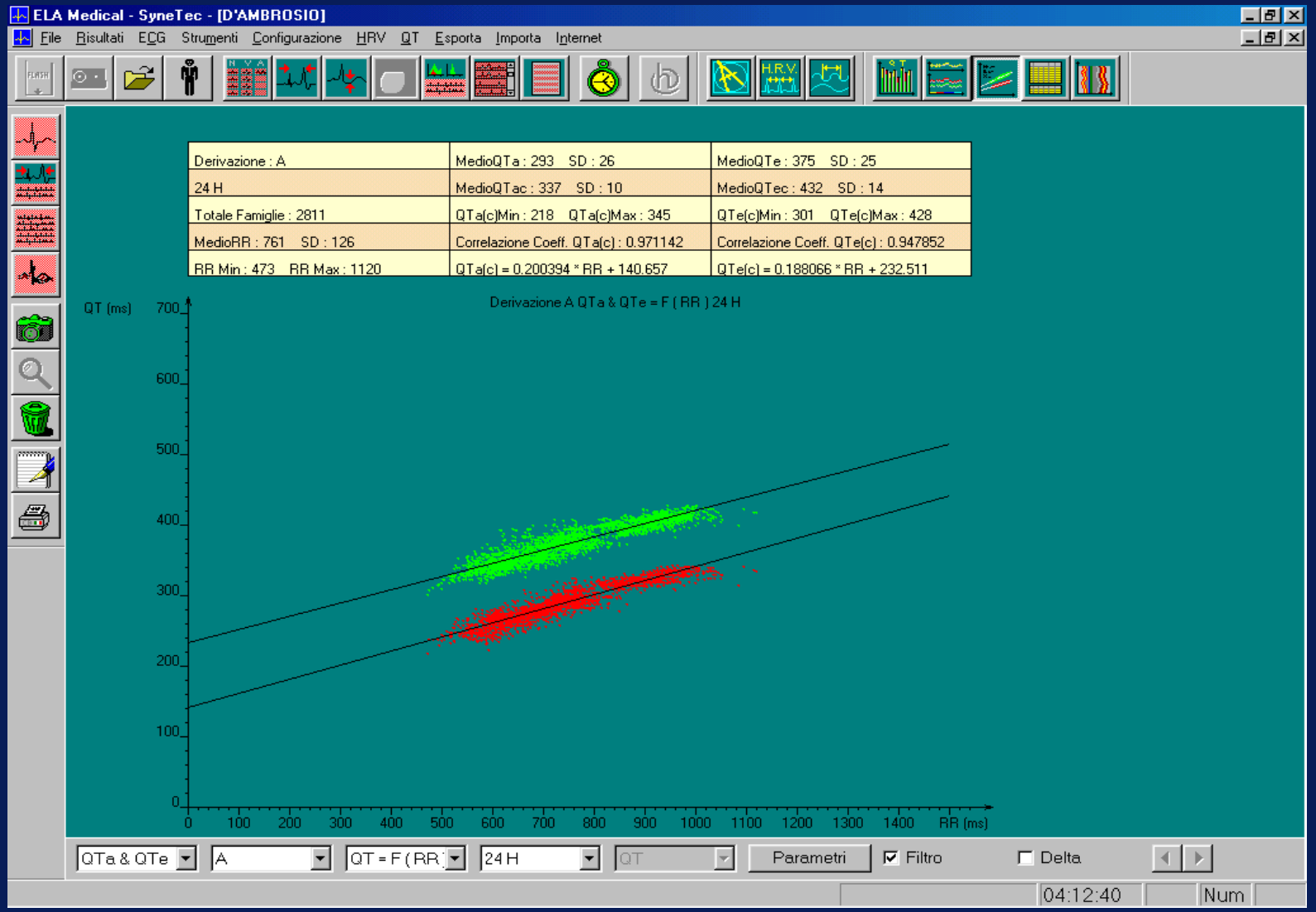
RR, QT apex, QT end



RR, QTac, QTec

The single measurement computed by this method are plotted versus time, obtaining the circadiano variation of the different parameters (RR in yellow, QTend in green, QTapex in red). In a normal sunjects, 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).

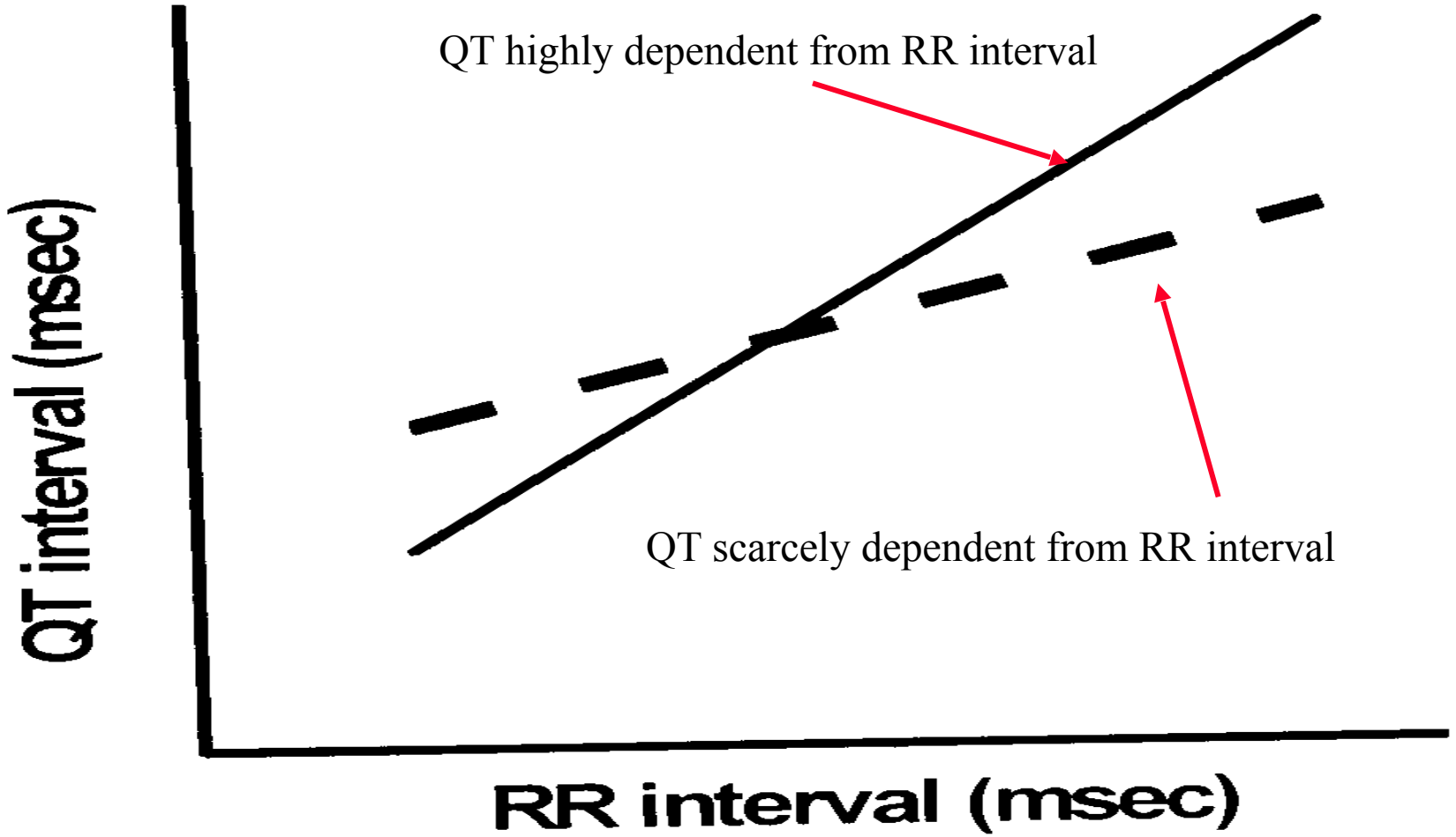
Authomatic Computation of Linear QT/RR Relation



Red: QTapex/RR Green: QTend/RR

This method also automatically computes the linear relation between the QT intervals (QTapex in red and QTend 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 QTapex/RR and QTend/RR slopes are pratictically parallel and the dispersion of valus is very low in the 24 hours.

Schematic Representation of QT-RR Relation



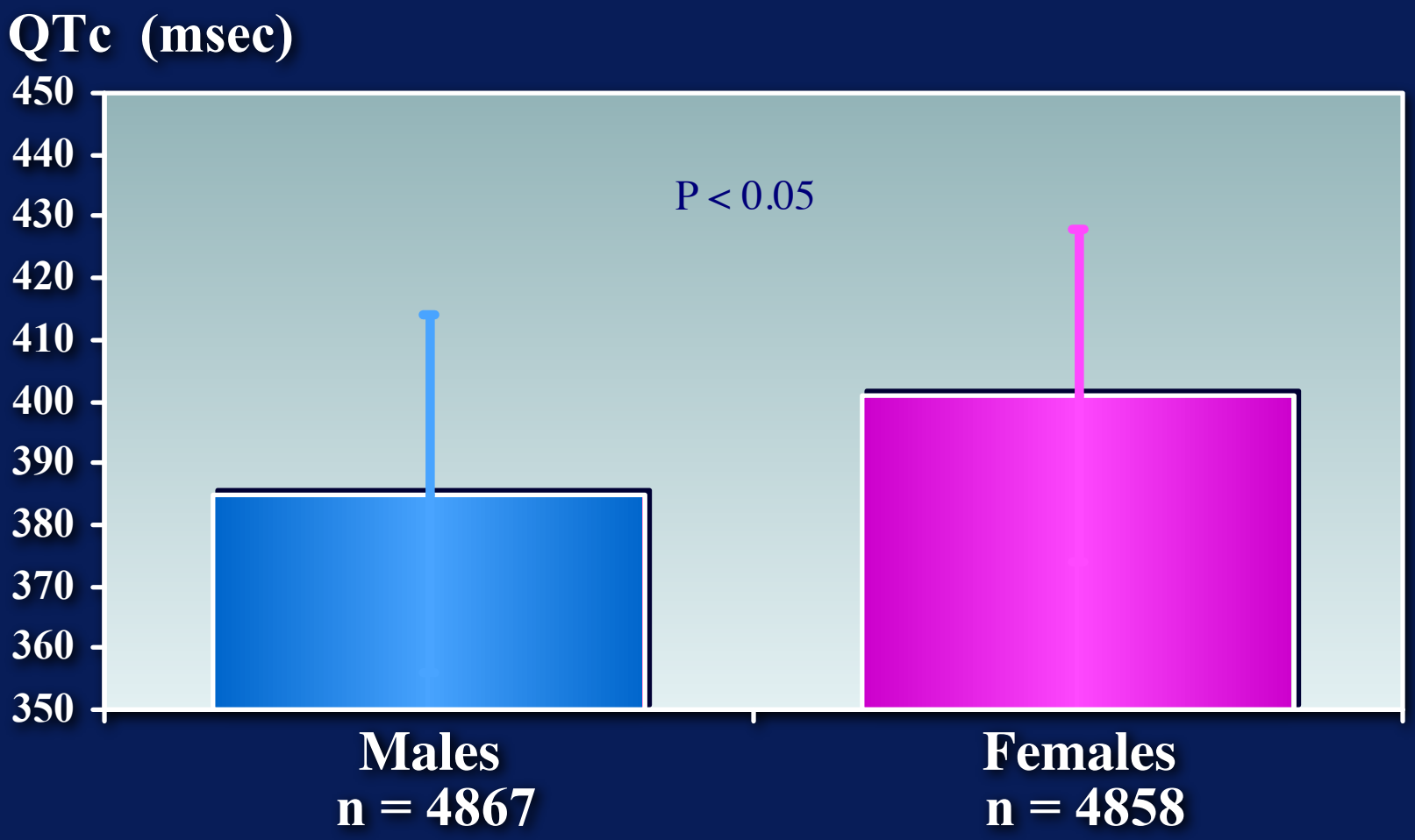
Locati EH, 2005

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 lenght duration, with modest shortening at high heart rates and modest lenghtening at slow heart rates. Opposite, a steep slope (high refression coefficient) indicates that QT interval is highly dependent on heart rate changes, with marked shortening at fast heart rates and marked lenghtening at slow heart rates.

Modulation of QT Interval Dymamicity

- ✓ 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

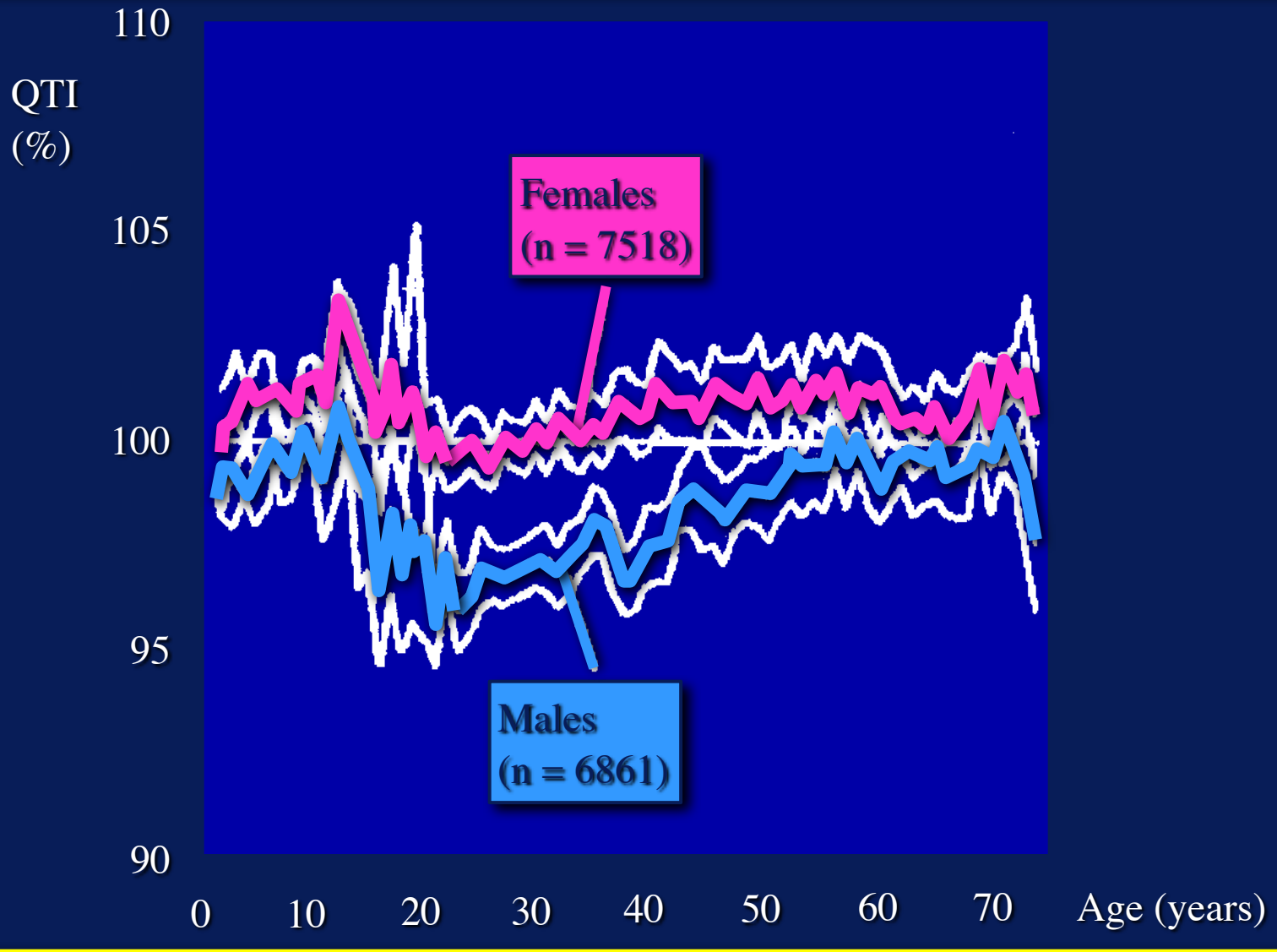
Correct QT Interval (QTc) by Gender In "Framingham Heart Study"



Goldberg et al., Am J Cardiol 1991; 67: 55-8

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

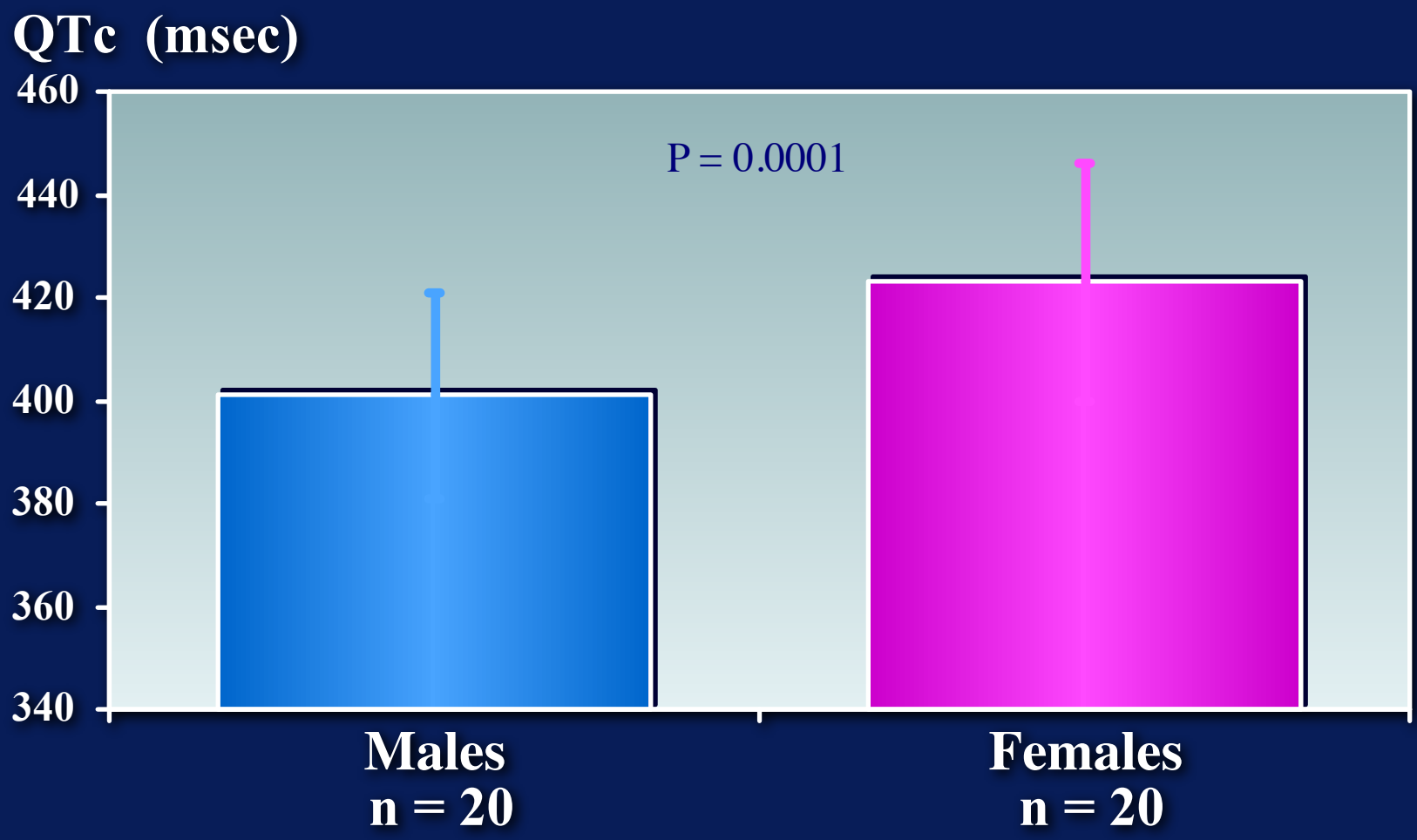


Rautaharju et al., Can J Cardiol 1992; 8: 690-5

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

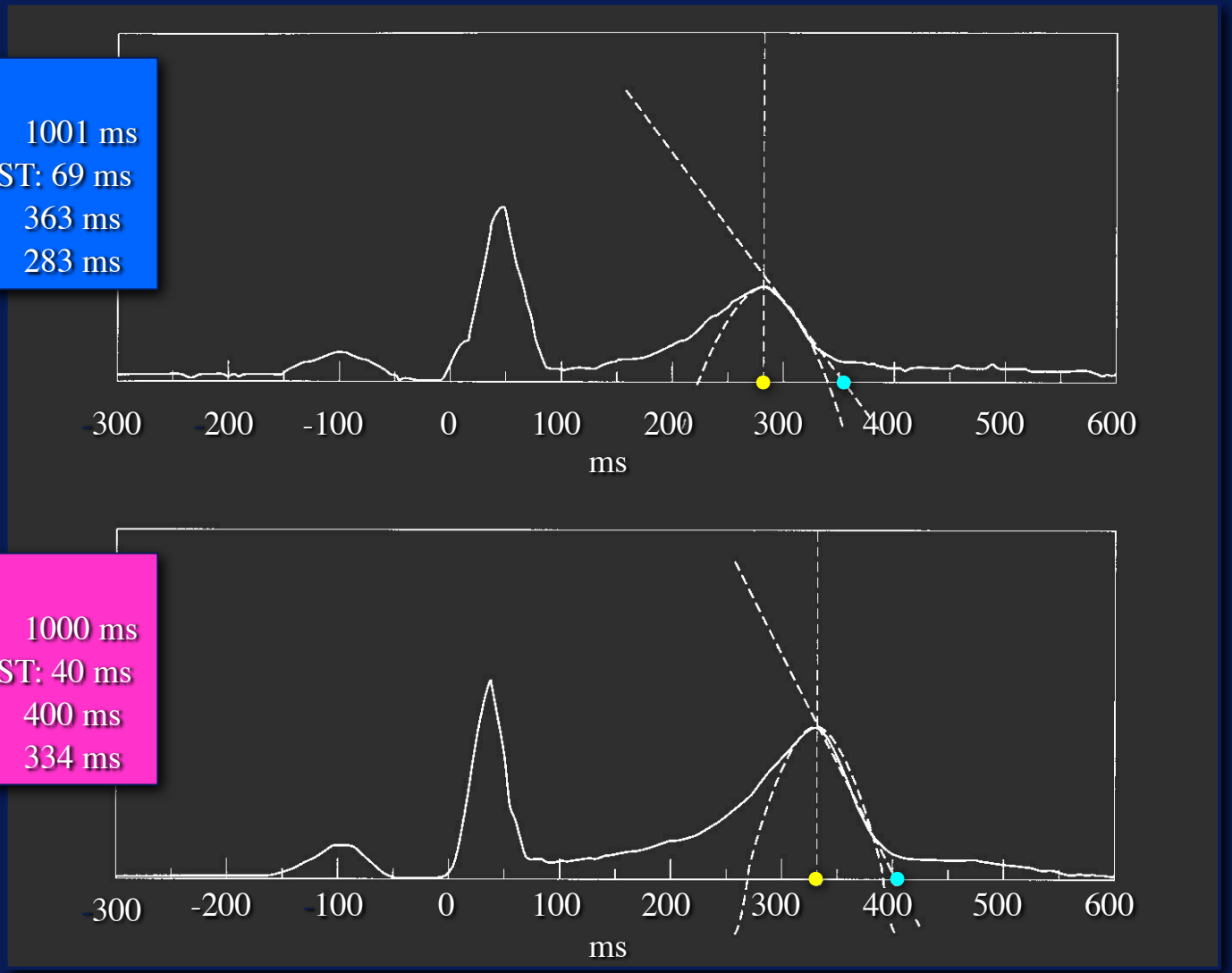
The same gender differences are observed in normal subjects during Holter monitoring (see next slide).

QT Interval Duration During 24-hour Holter by Gender



Stramba-Badiale et al., Eur Heart J 1997; 18: 1000-6

QT Interval at Fixed Cycle Lenght (1000 ms) per Gender

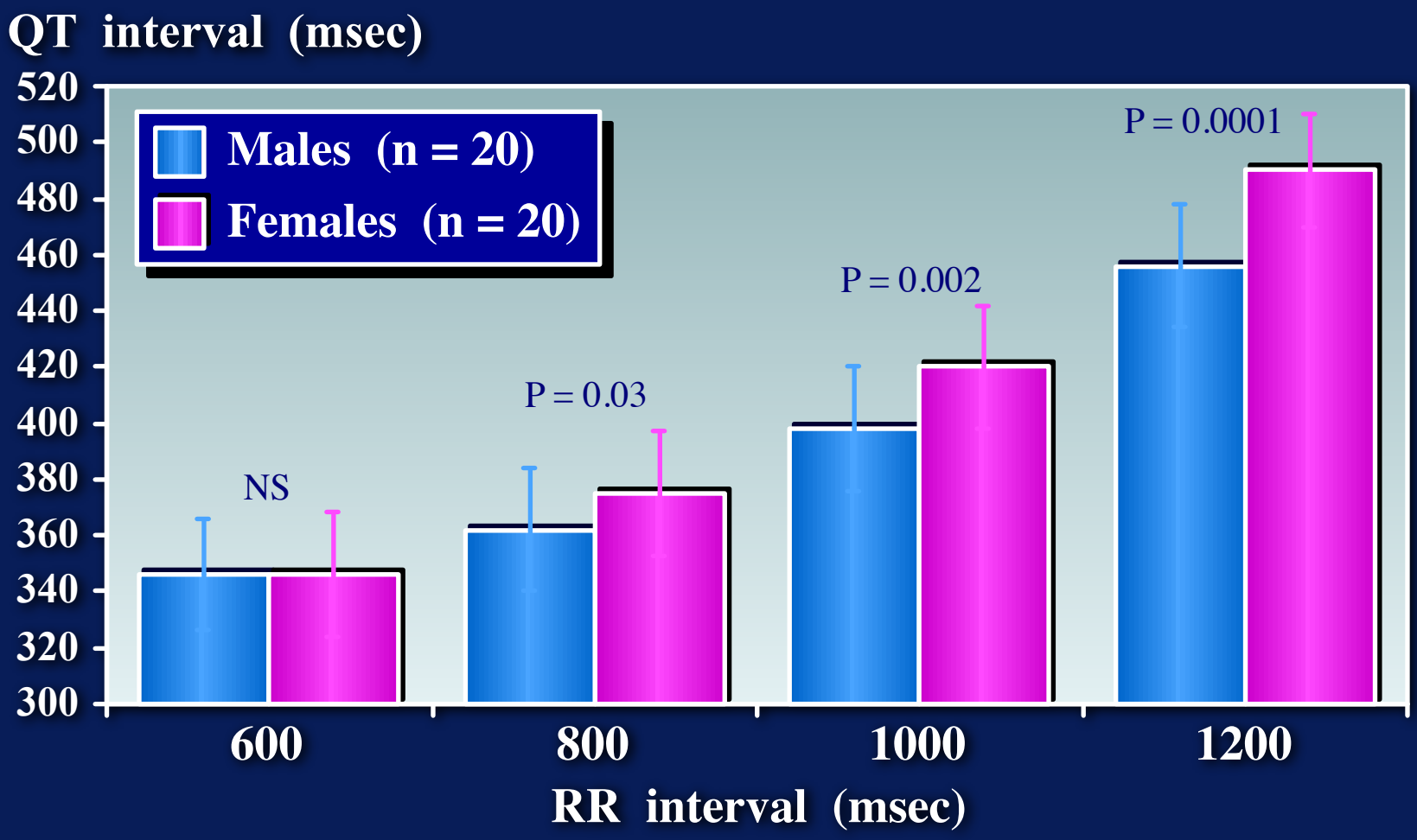


Stramba-Badiale et al., Eur Heart J 1997; 18: 1000-6

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 lenght (here shown, at RR interval 1000 msec, a difference of 40 msec exists between two normal adult subjects, above normal male, below normal female).

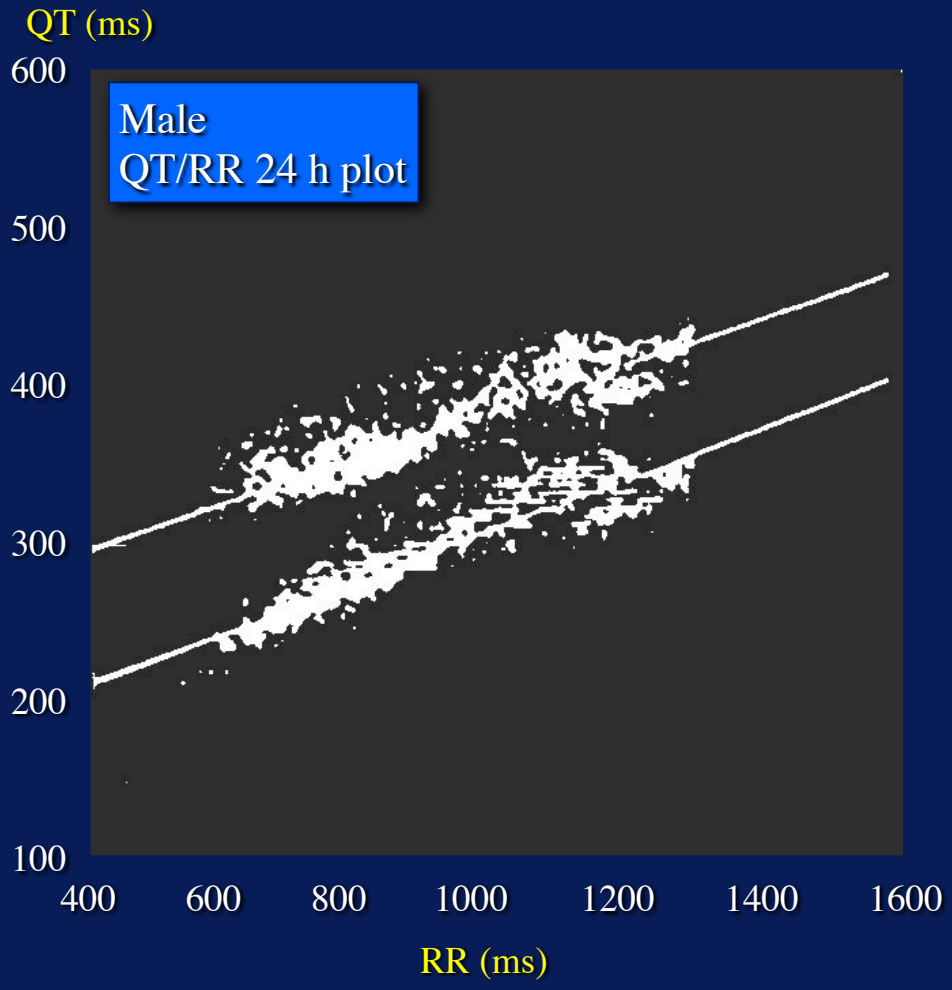
Gender differences are more evident at longer cycle lenghts.

Uncorrected QT Interval at defined CXycle Lenghts per Gender

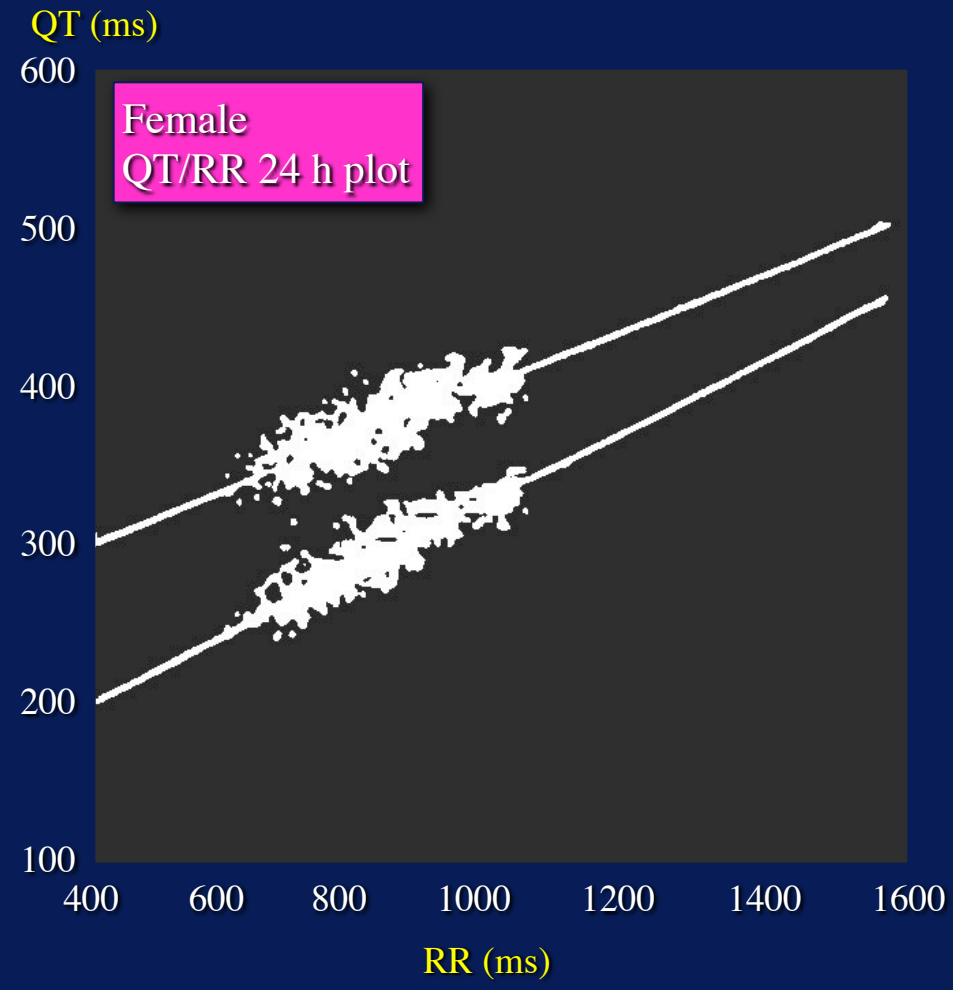


Stramba-Badiale et al., Eur Heart J 1997; 18: 1000-6

QT/RR Relation During 24-hour Holter per Gender



Regression: QTend = 0.14 * RR + 249 ms

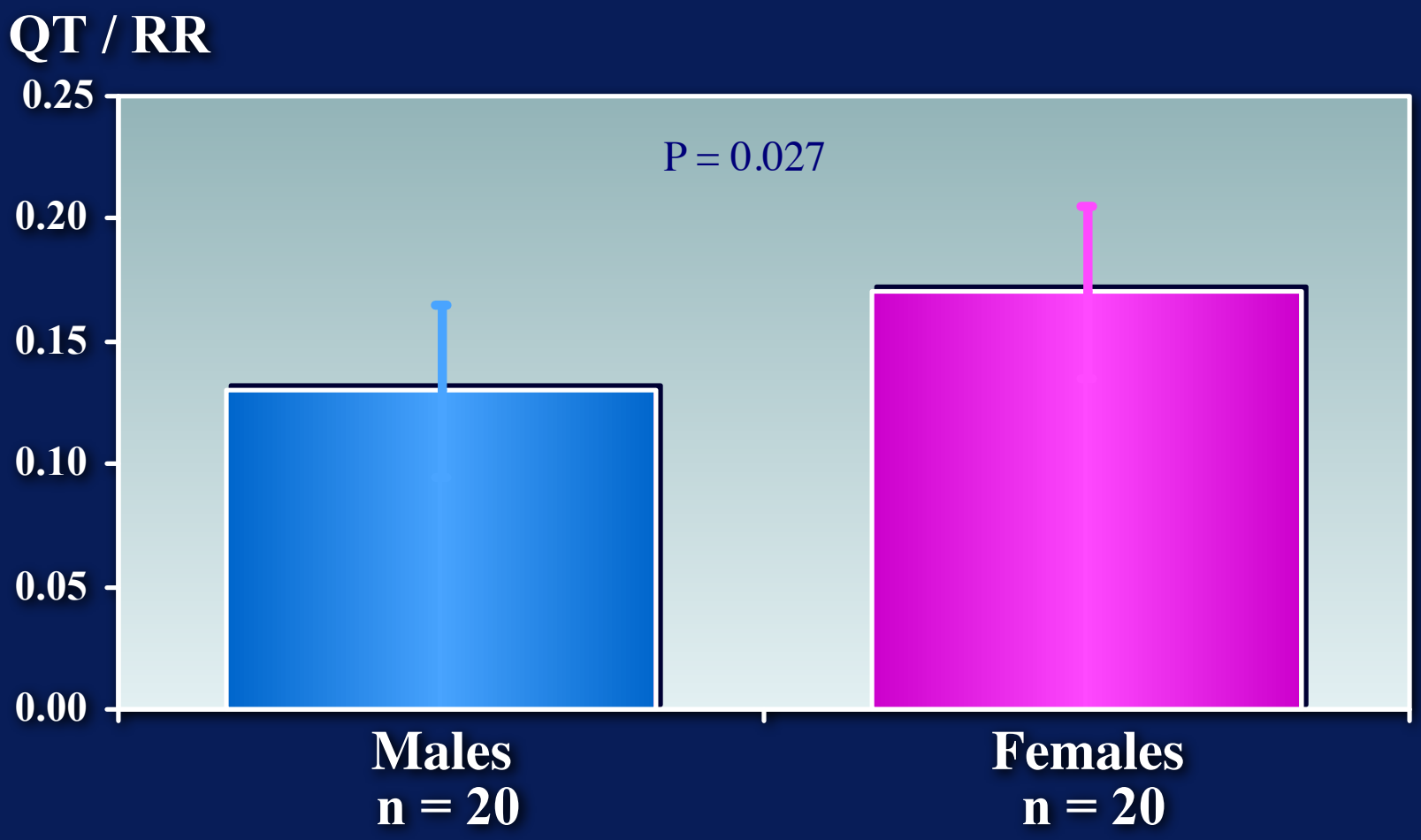


Regression: QTend = 0.17 * RR + 241 ms

Stramba-Badiale et al., Eur Heart J 1997; 18: 1000-6

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

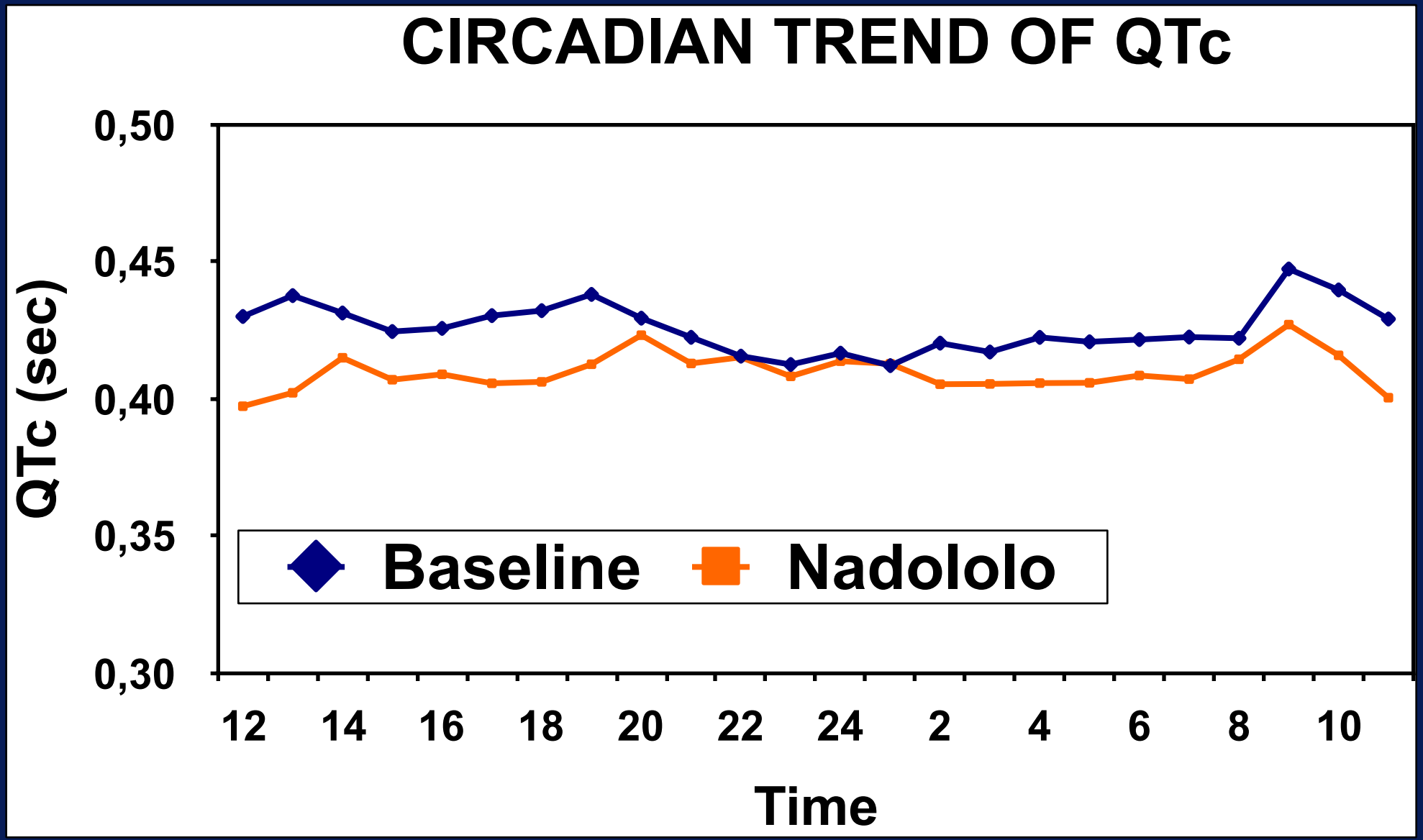


Stramba-Badiale et al., Eur Heart J 1997; 18: 1000-6

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

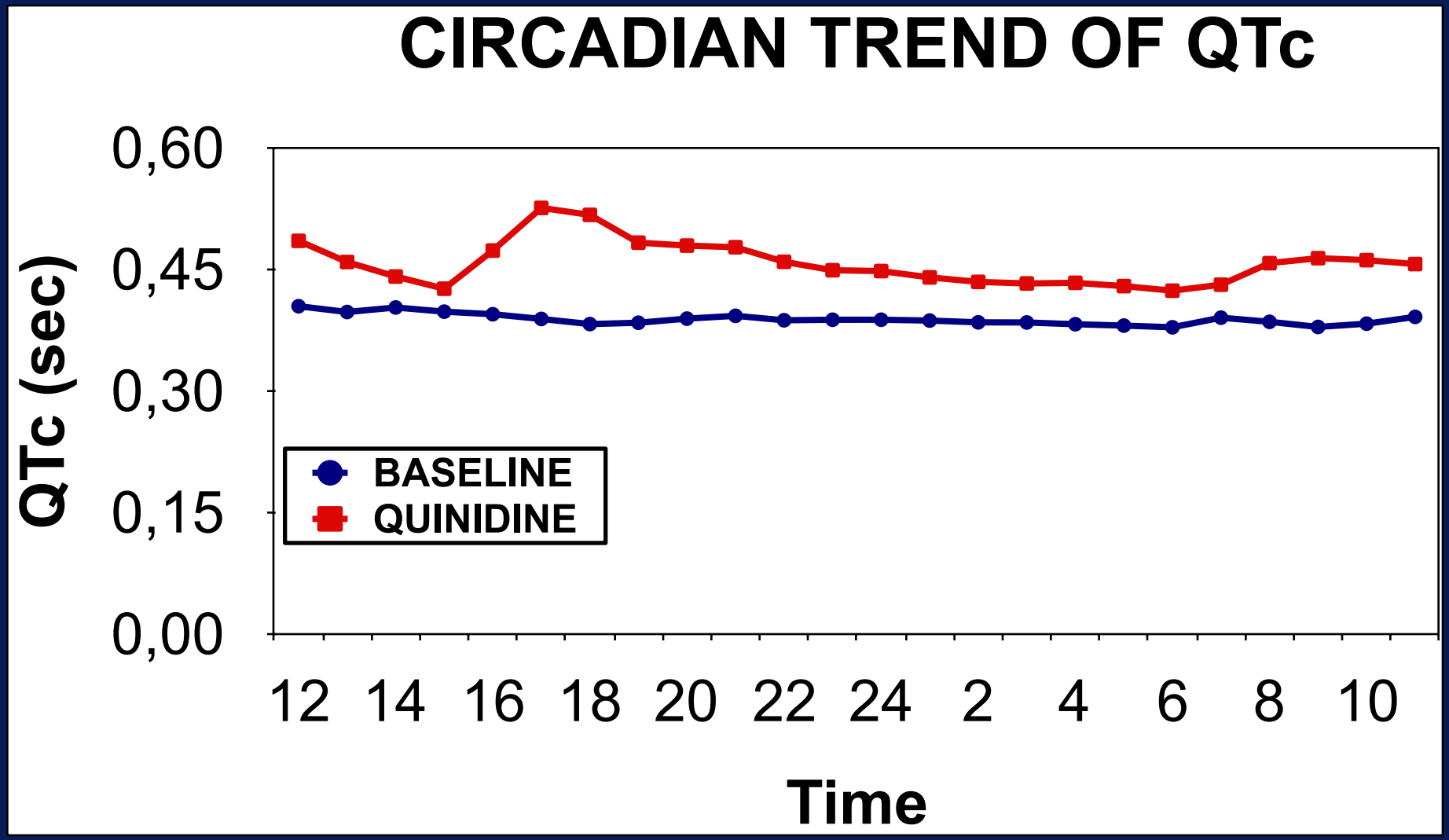
- ✓ Heart Rate
- ✓ Sex
- ✓ Circadian Trends
- ✓ Autonomic Nervous System
- ✓ Drugs (Antiarrhythmic / Non Antiarrhythmic)
- ✓ Metabolic Disturbances ($\Downarrow K^{+}$, $\Downarrow Ca^{++}$)
- ✓ Myocardial Ischemia
- ✓ Mutations of Genes Encoding Cardiac Channels



AJ, Female, 70 yrs

Beta-blckers (Nadolol) in a normal subjects reduced QTc duration and QTc circadian variabilty.

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

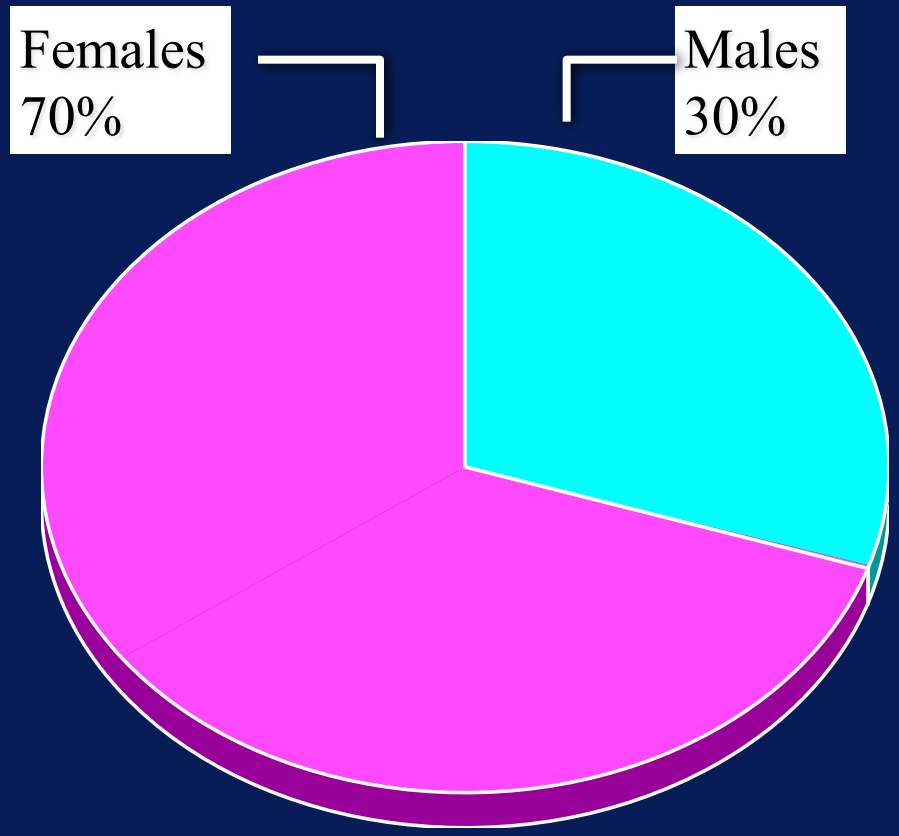


BR, Female, 60 yrs

Modulation of QT Interval Dymamicity

- ✓ 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

Incidence of Drug-Induced Torsades de Pointes



n = 332

Makkar et al., JAMA 1993; 270: 2590-97

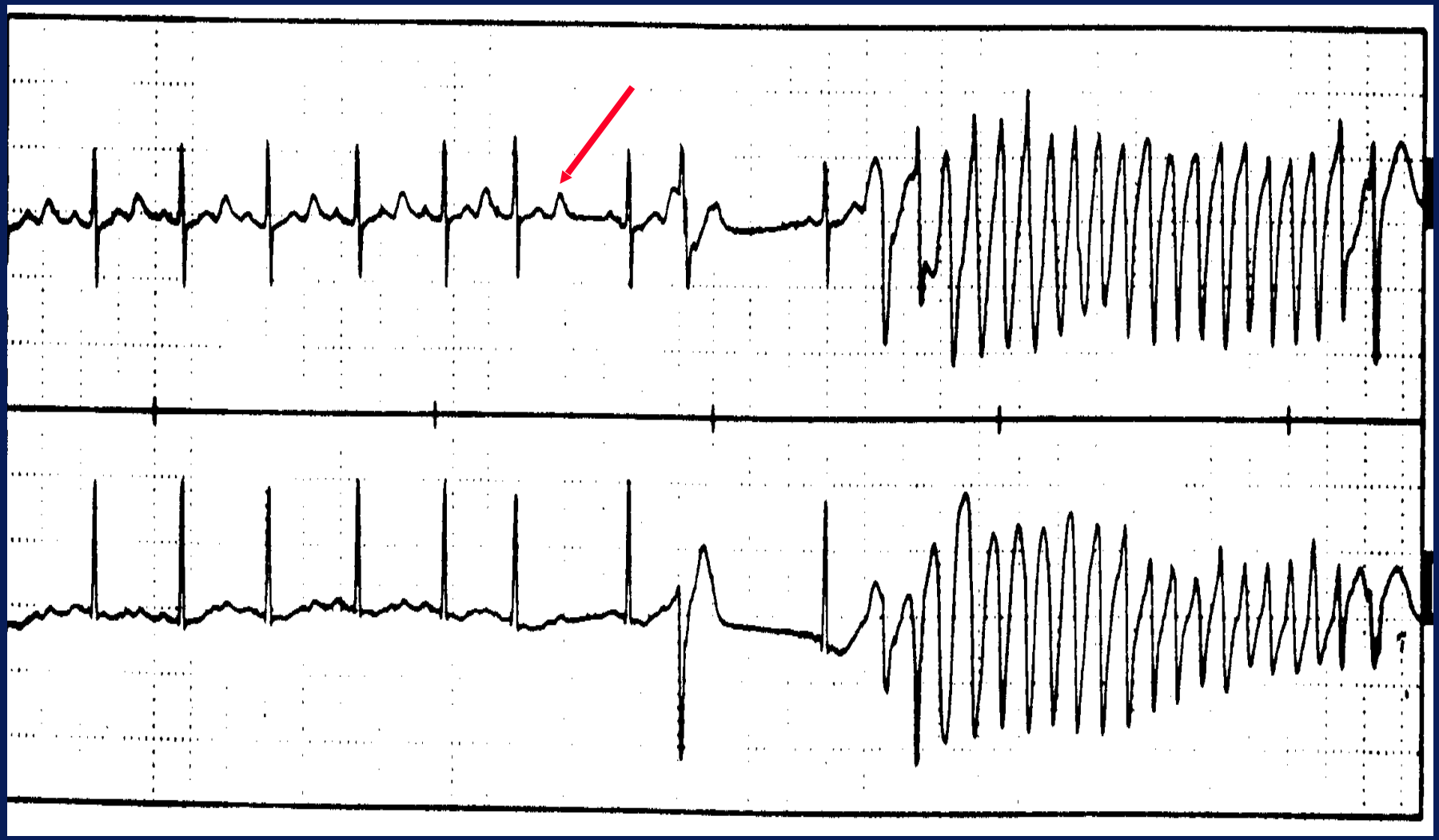
The intrinsic characteristics of longer QT interval duration and higher QT interval dinamicity in females partly explains the greater female vulnerability to the proarrhythmic effect of cardiac and non-cardiac drugs that prolong QT interval and induce ventricular tachyarrhythmias such as torsades-de-pointes.

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	
Bepridil	Anti-anginal / heart pain	Females > Males
Chloroquine	Anti-malarial / malaria infection	
Chlorpromazine	Anti-psychotic / anti-emetic / schizophrenia / nausea	
Cisapride	GI stimulant / heartburn	Restricted availability; Females > Males
Clarithromycin	Antibiotic / bacterial infection	
Disopyramide	Anti-arrhythmic / abnormal heart rhythm	Females > Males
Dofetilide	Anti-arrhythmic / abnormal heart rhythm	
Domperidone	Anti-nausea / nausea	
Droperidol	Sedative; anti-nausea / anesthesia adjunct, nausea	
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	
Methadone	Opiate agonist / pain control, narcotic dependence	Females > Males
Pentamidine	Anti-infective / pneumocystis pneumonia	Females > Males
Pimozide	Anti-psychotic / Tourette's tics	Females > Males
Procainamide	Anti-arrhythmic / abnormal heart rhythm	
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.

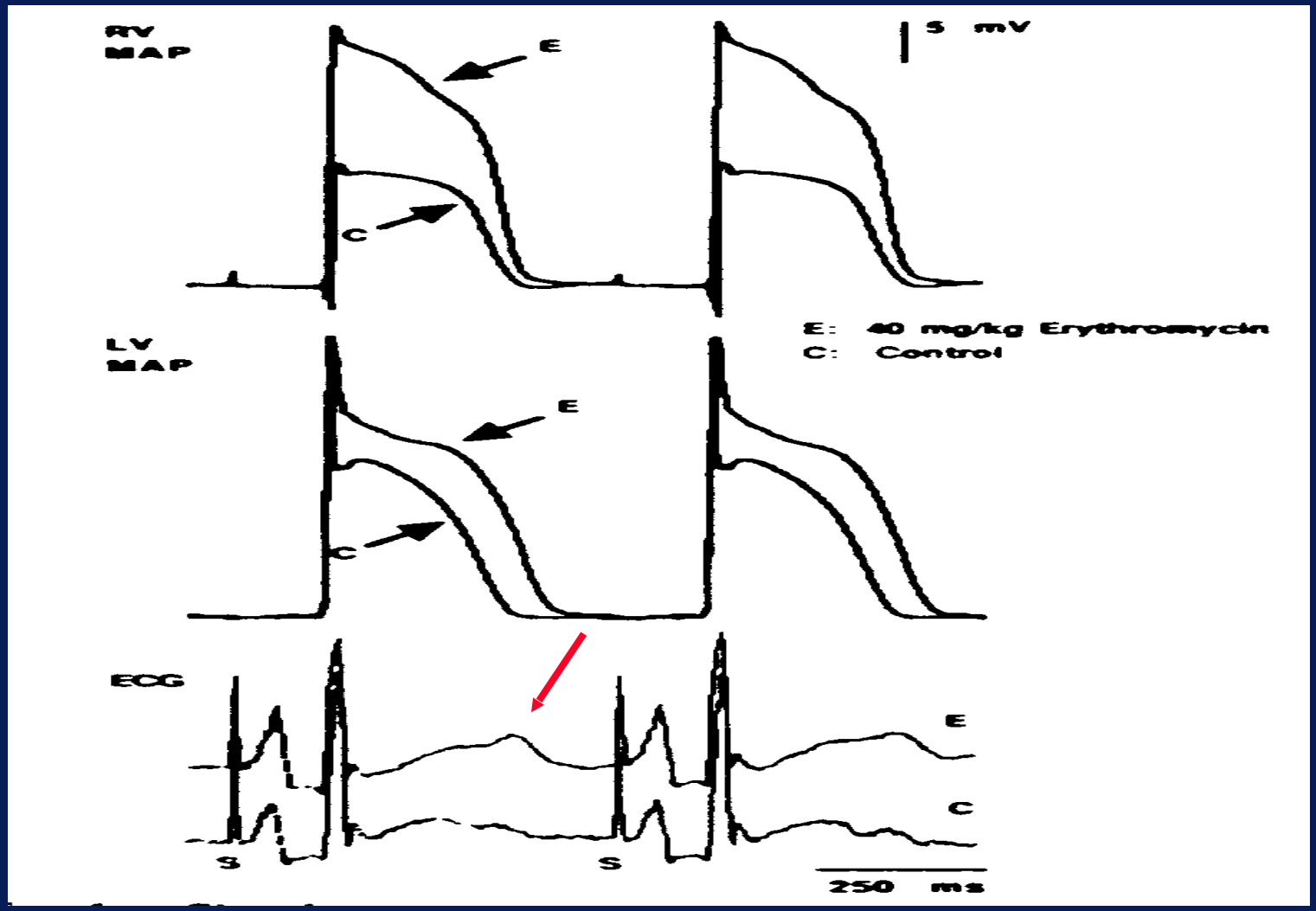
Pause and Tachycardia-Dependence of TdP



Locati EH et al, JACC 1992

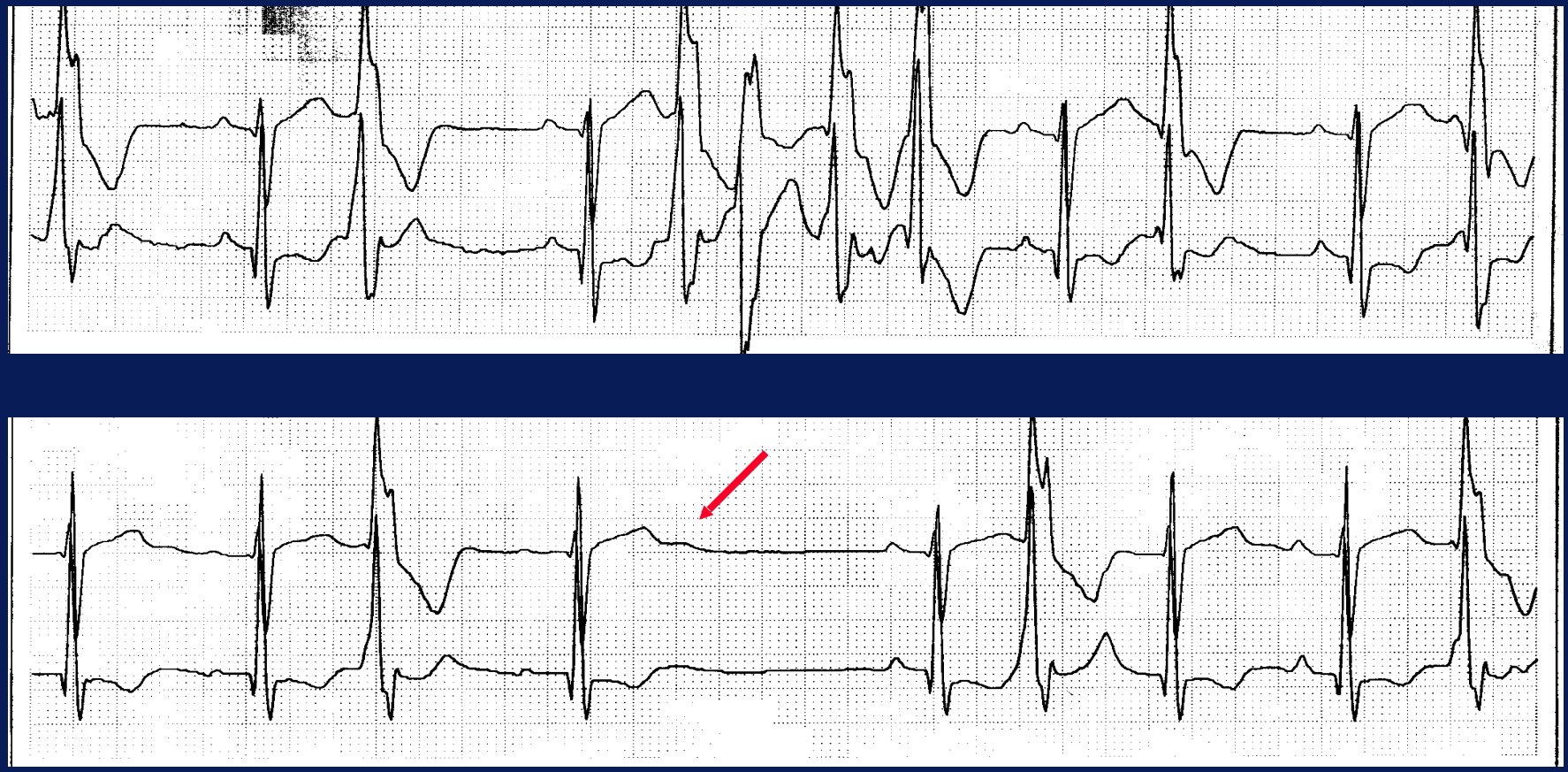
Quinidine increased the late component of the QT interval (QTU wave) and favor the onset of torsades-de-pointes following a short-long sequence.

Effects of Erithromicine 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 addictive effects potentially very dungerous (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 mane with idiopathic potassion depletion due to Bartter’syndrome, and frequent polymorphic unsustained ventricular tachycardias are also observed.

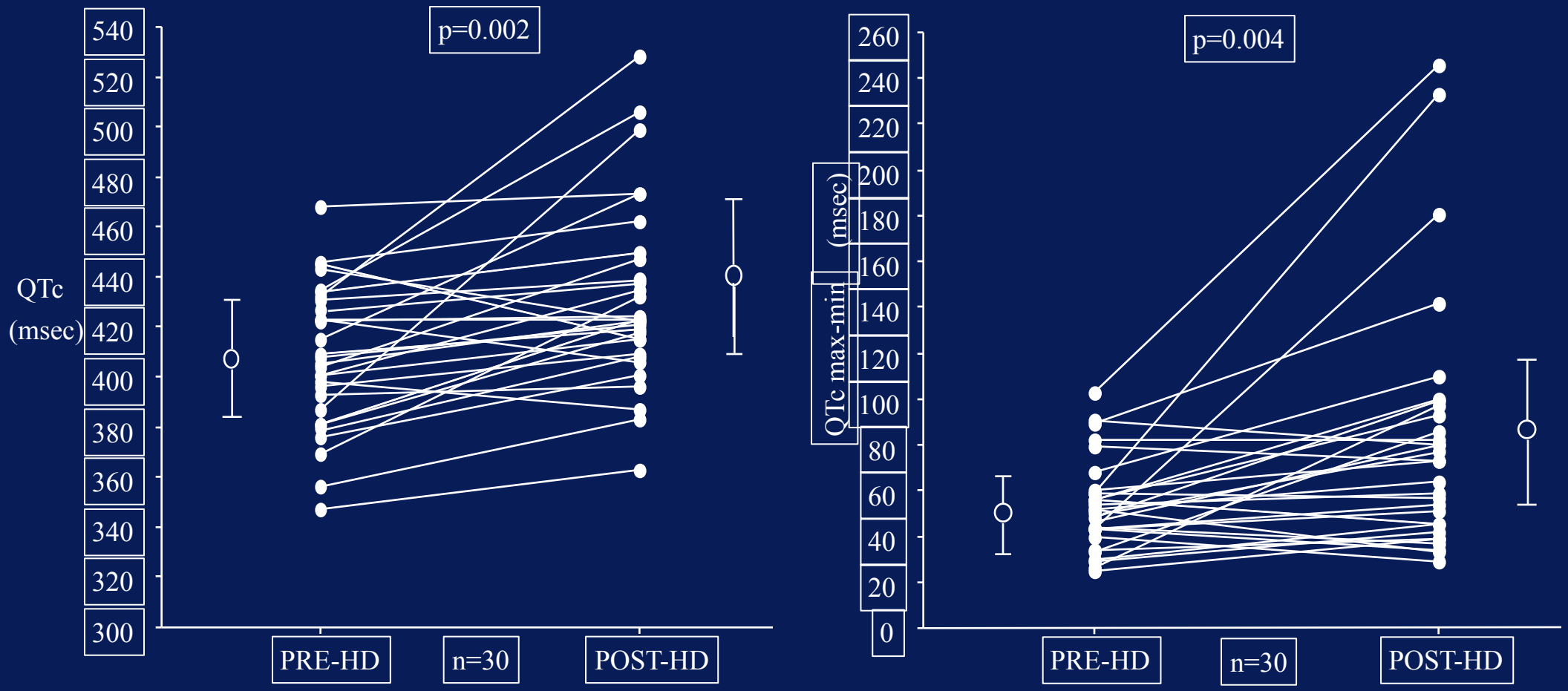
ntricular Repolarization
ents During Hemodyalisis

	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+ (mEq/l)	5.2±0.8	3.5±0.6	<0.0001
Mg+2 (mEq/l)	2.8±0.6	2.1±0.4	<0.0001

During hemodyalisis, 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 hemodyalis.

QTc and QT Dispersion Changes During Hemodyalisis



Sodium & Potassium Channel Blockers

Proarrhythmia may be related to use-dependent effects

→ More extensive block at fast heart rates

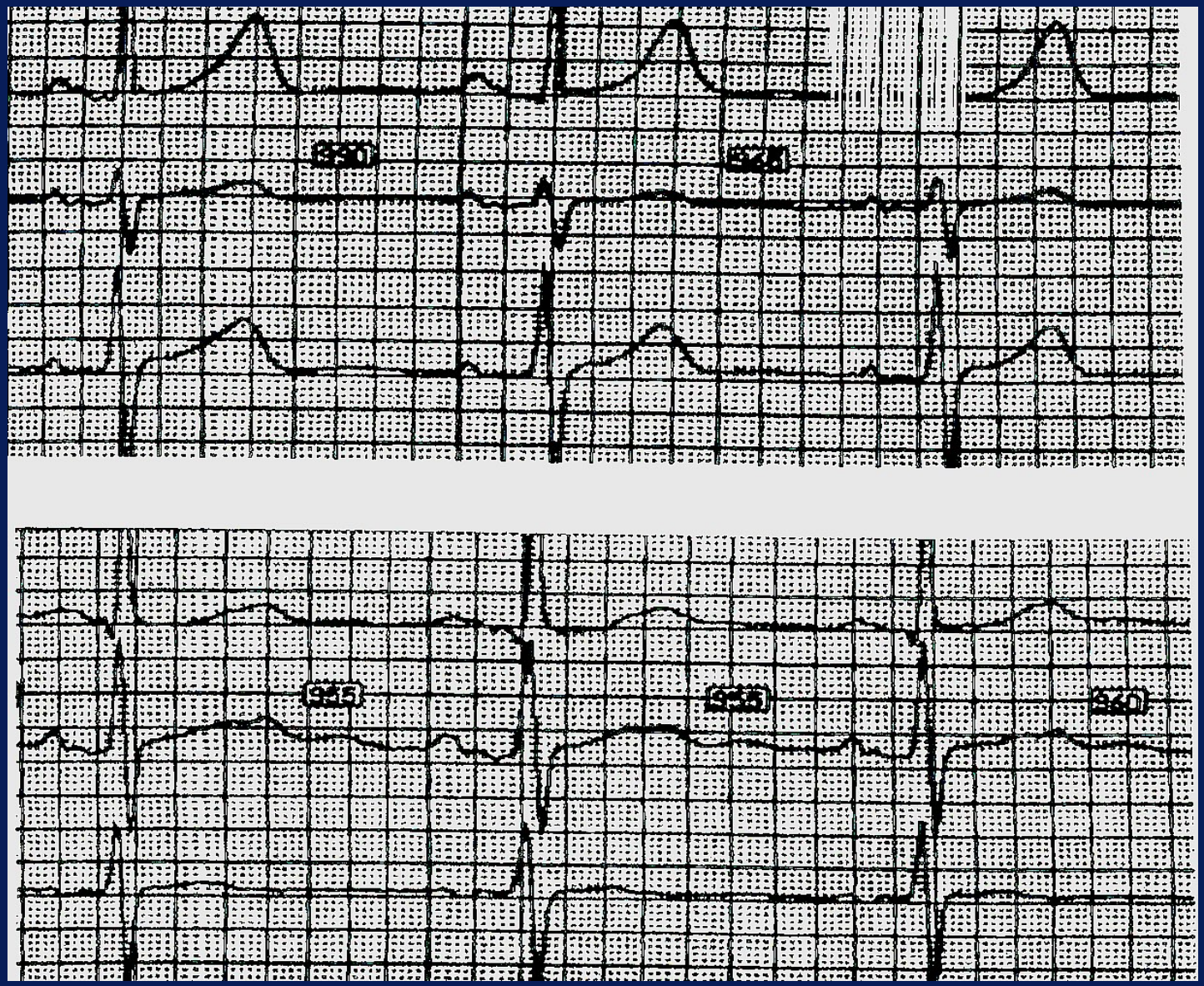
- ✓ Excessive slowing of ventricular conduction at fast rates (⇧ QRS)
- ✓ Excessive slowing of ventricular repolarization at fast rates (⇧ QT)

→ Effects may be countered by beta-blockers

Baseline

QT 340 msec

QTc 347 msec



Quinidine

QT 380 msec

QTc 388 msec

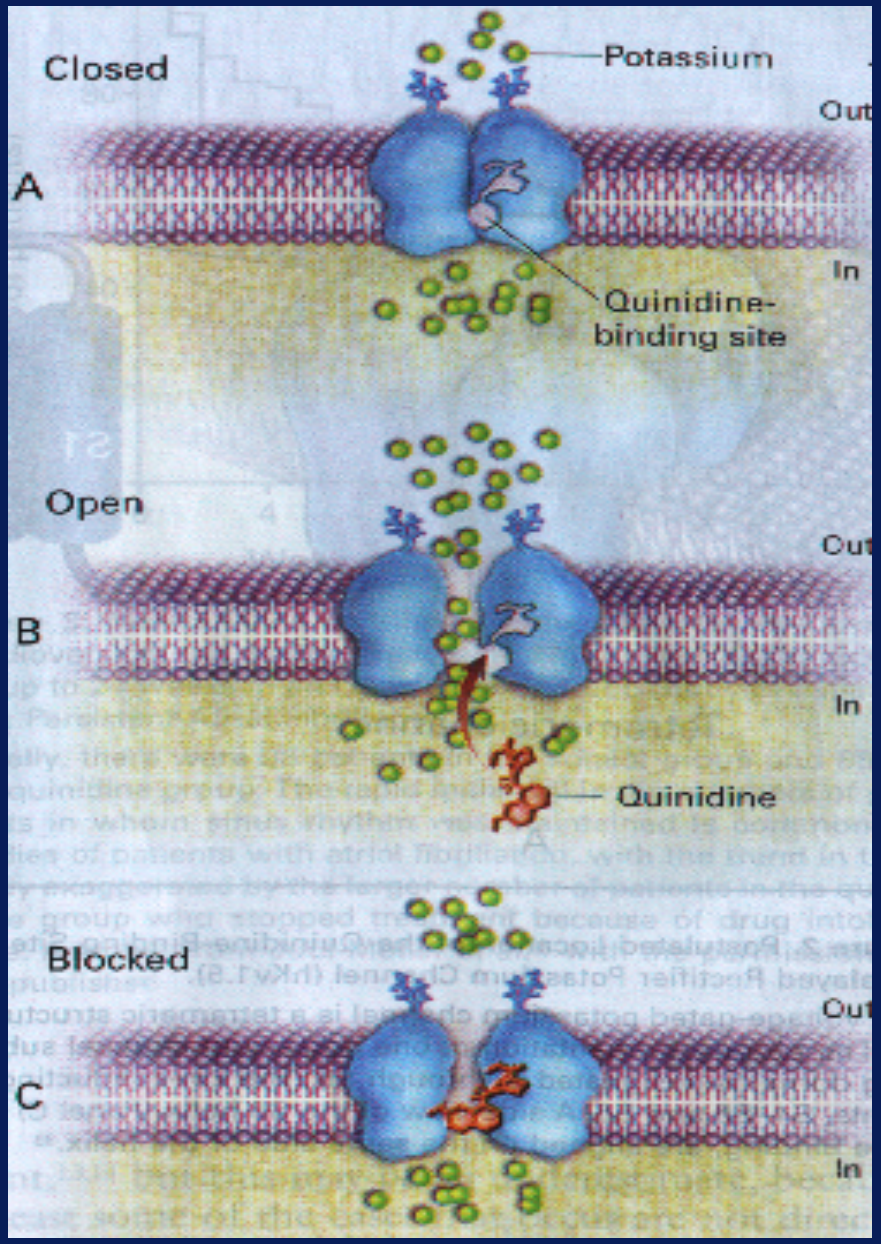
MG, Female, 65 yrs

Locati EH, 2005

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

Quinidine blocks Ikr in the active configuration

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

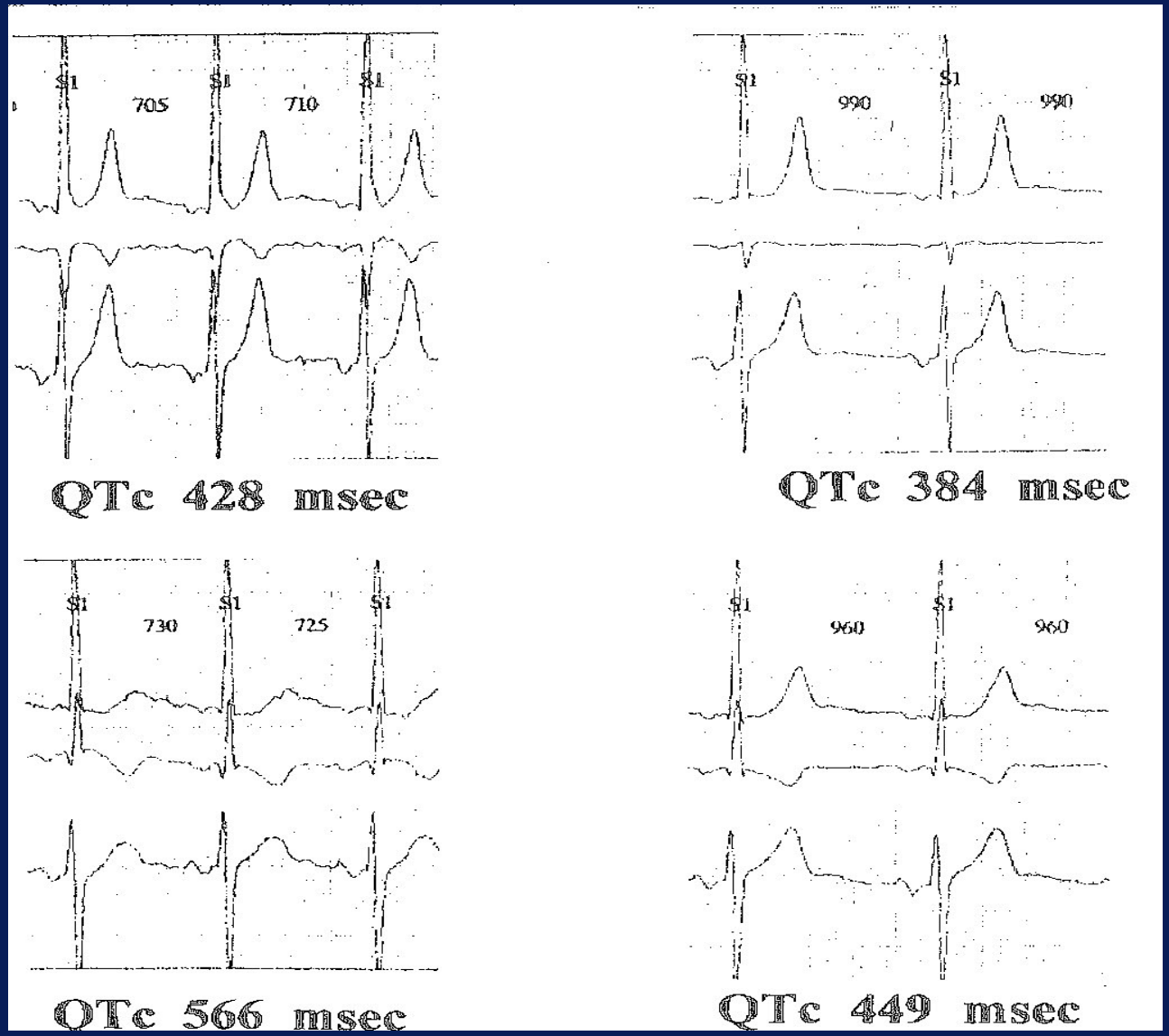


R-R min 710 msec

R-R max 980 msec

Basal

Quindine



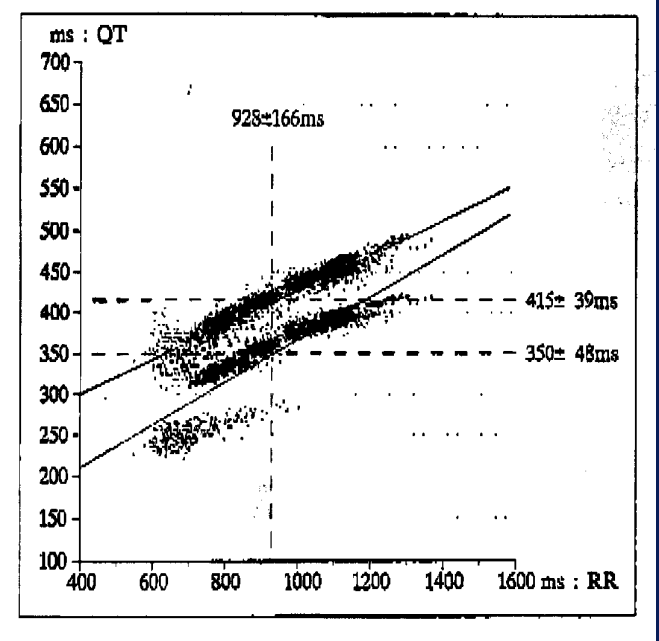
MG, Female, 65 yrs

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 lenghts

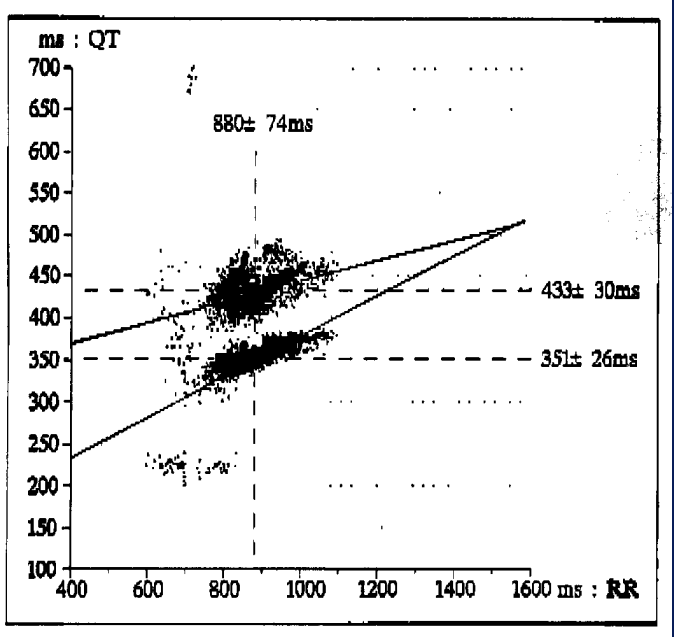
Heart Rate Dependence of QT Interval

Baseline



QTe/RR 0.21, QTec 431 ms
QTa/RR 0.26, QTac 363 ms

Quinidine



QTe/RR 0.12, QTec 461 ms
QTa/RR 0.24, QTac 374 ms

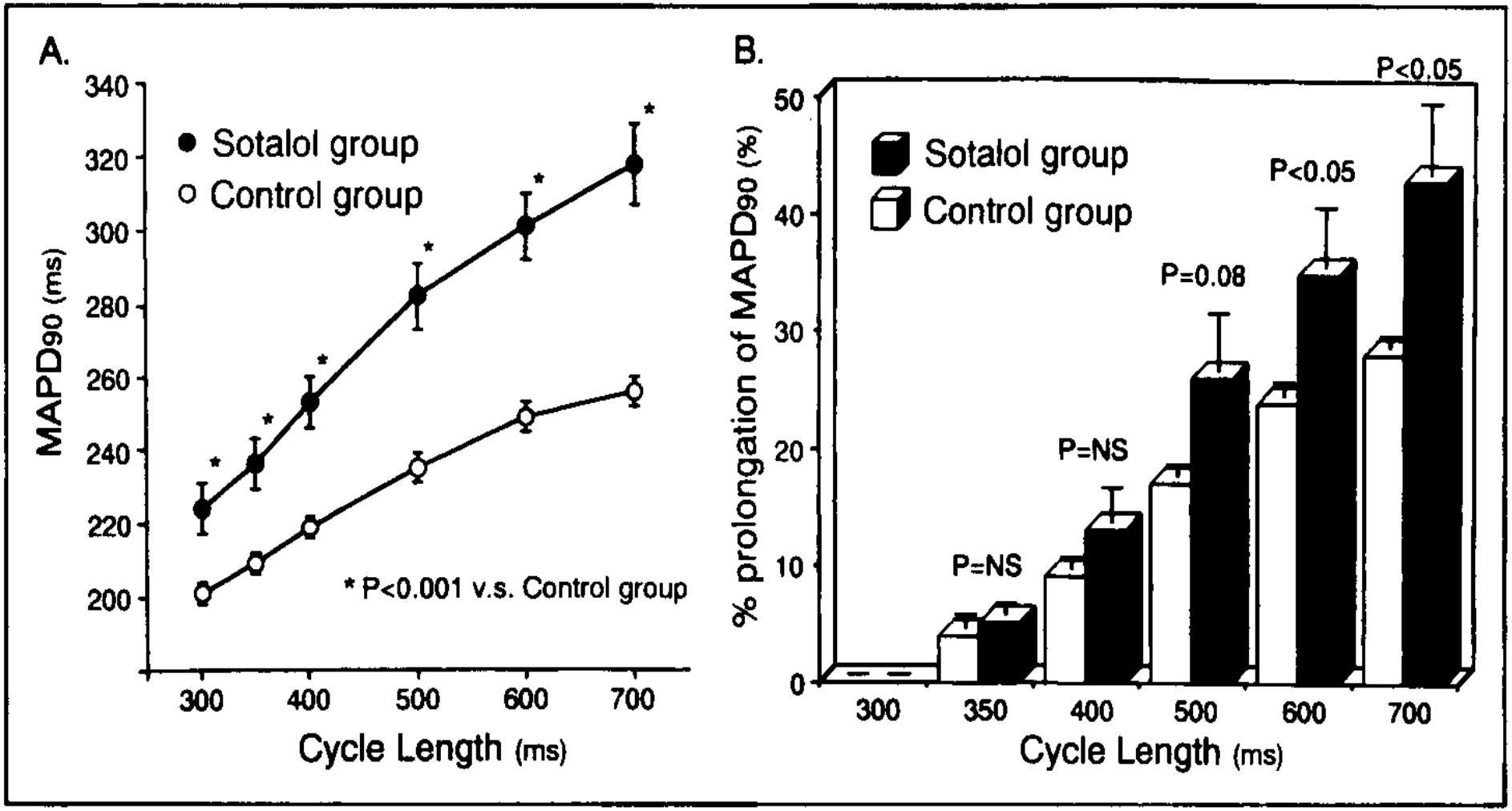
MG, Female, 65 yrs

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 lenghts (low heart rates)

Reverse Use-Dependence of Sotalol

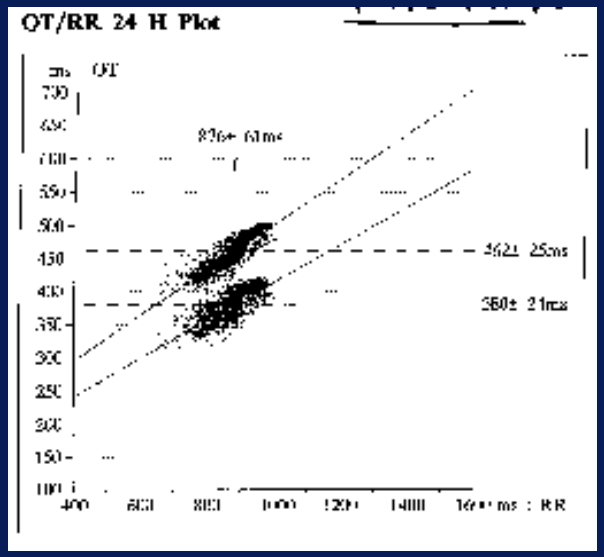


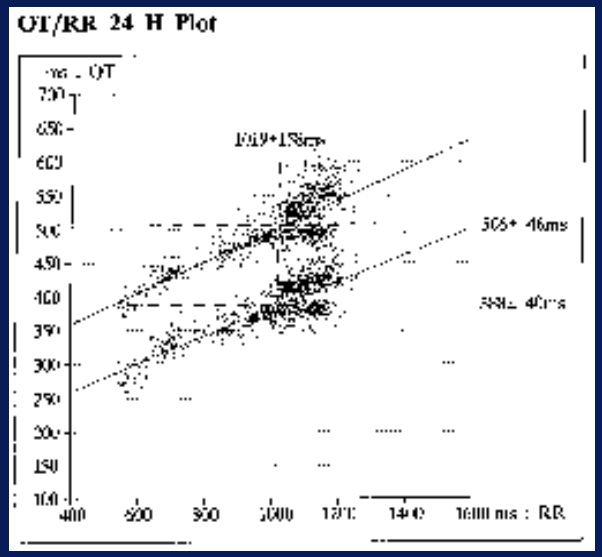
Shimizu W et al, Am J Cardiol 1996

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

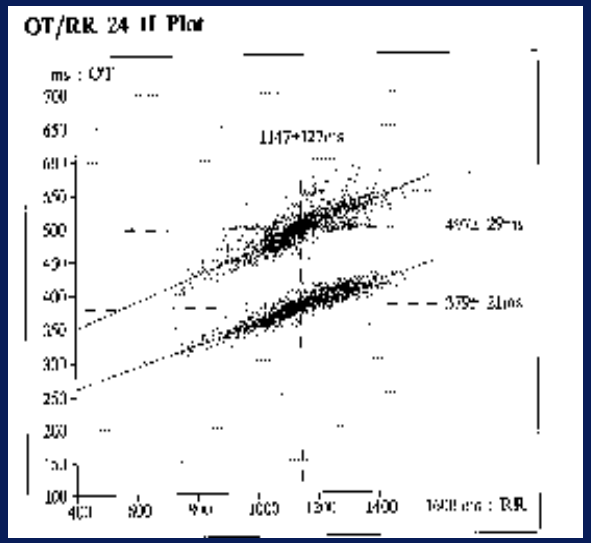
Propafenone
Slope = 0.35
r = 0.85
QTc 493 ms

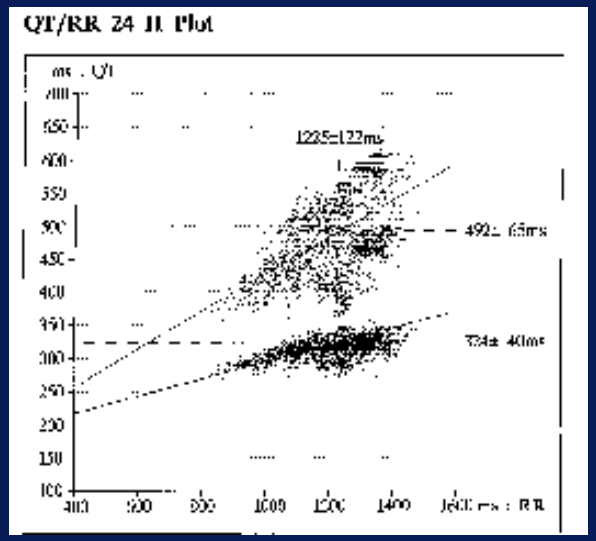




Disopyramide
Slope = 0.23
r = 0.80
QTc 501 ms

Amiodarone
Slope = 0.19
r = 0.84
QTc 464 ms



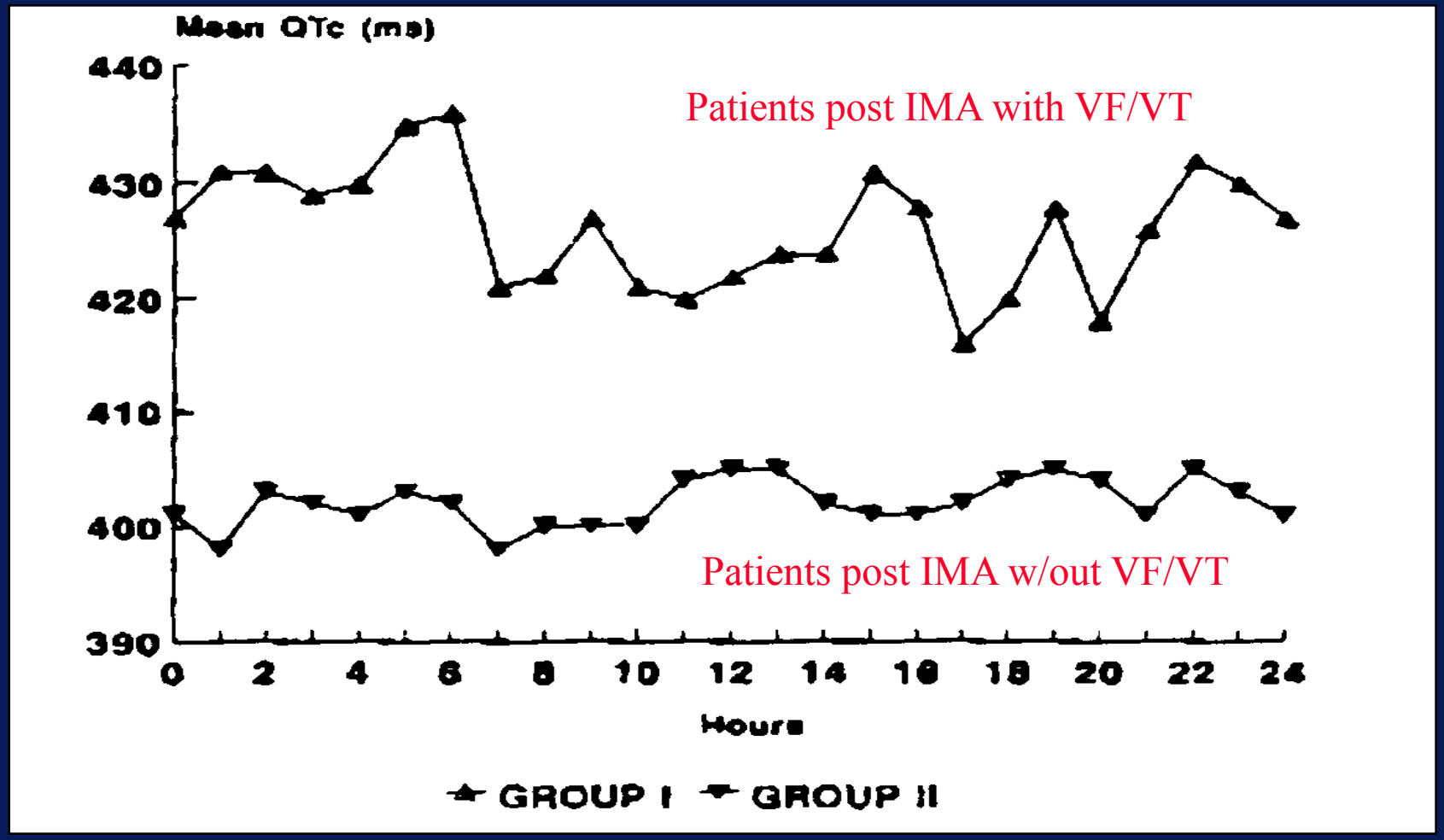


Sotalol
Slope = 0.28
r = 0.53
QTc 445 ms

Modulation of QT Interval Dymamicity

- ✓ 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

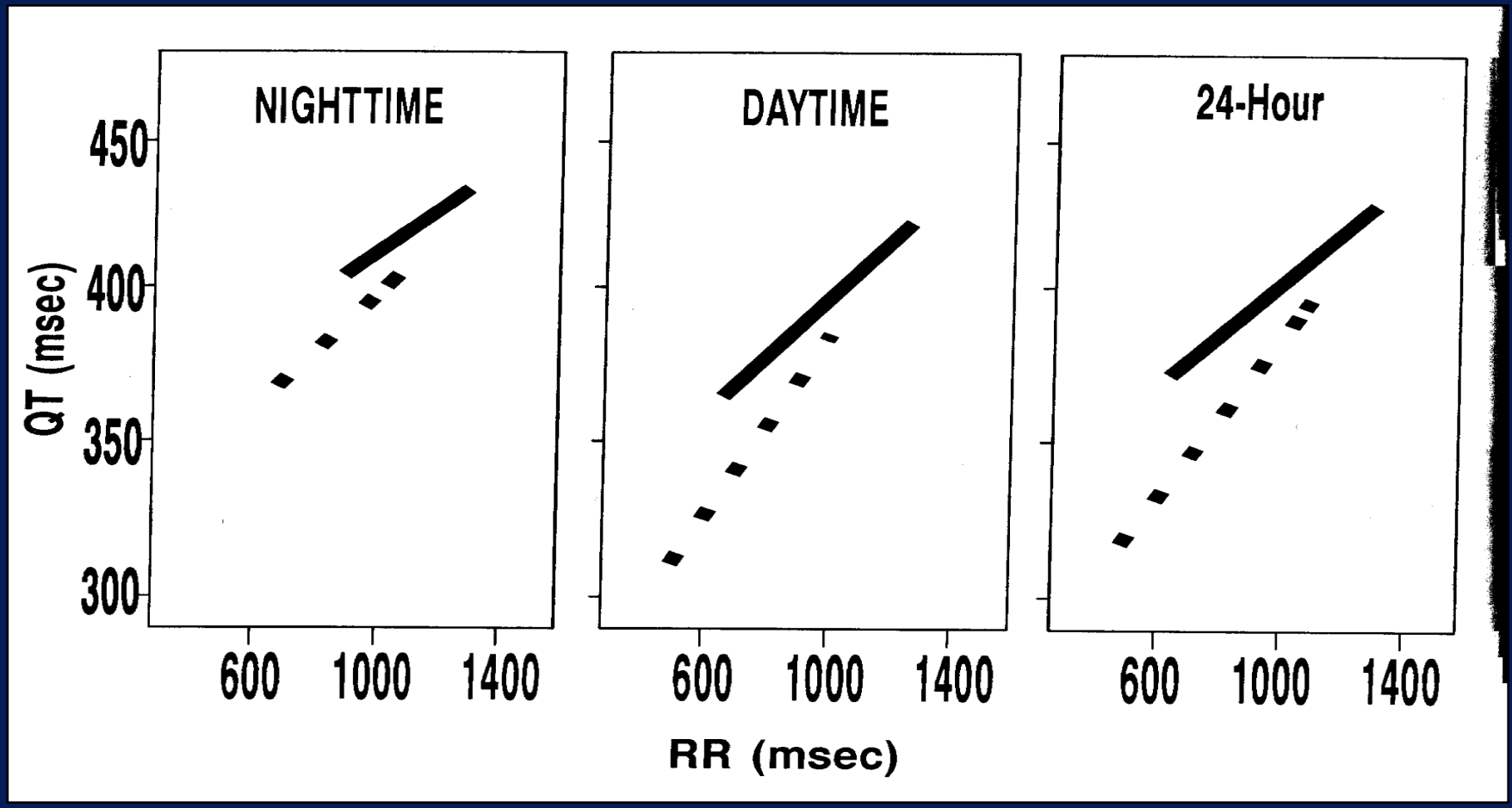
Circadian QTc Variability Post Myocardial Infarction in Patients With and Without Malignant Ventricular Arrhythmias



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

- ✓ 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

APD, Ionic Currents and Genetic Mutations

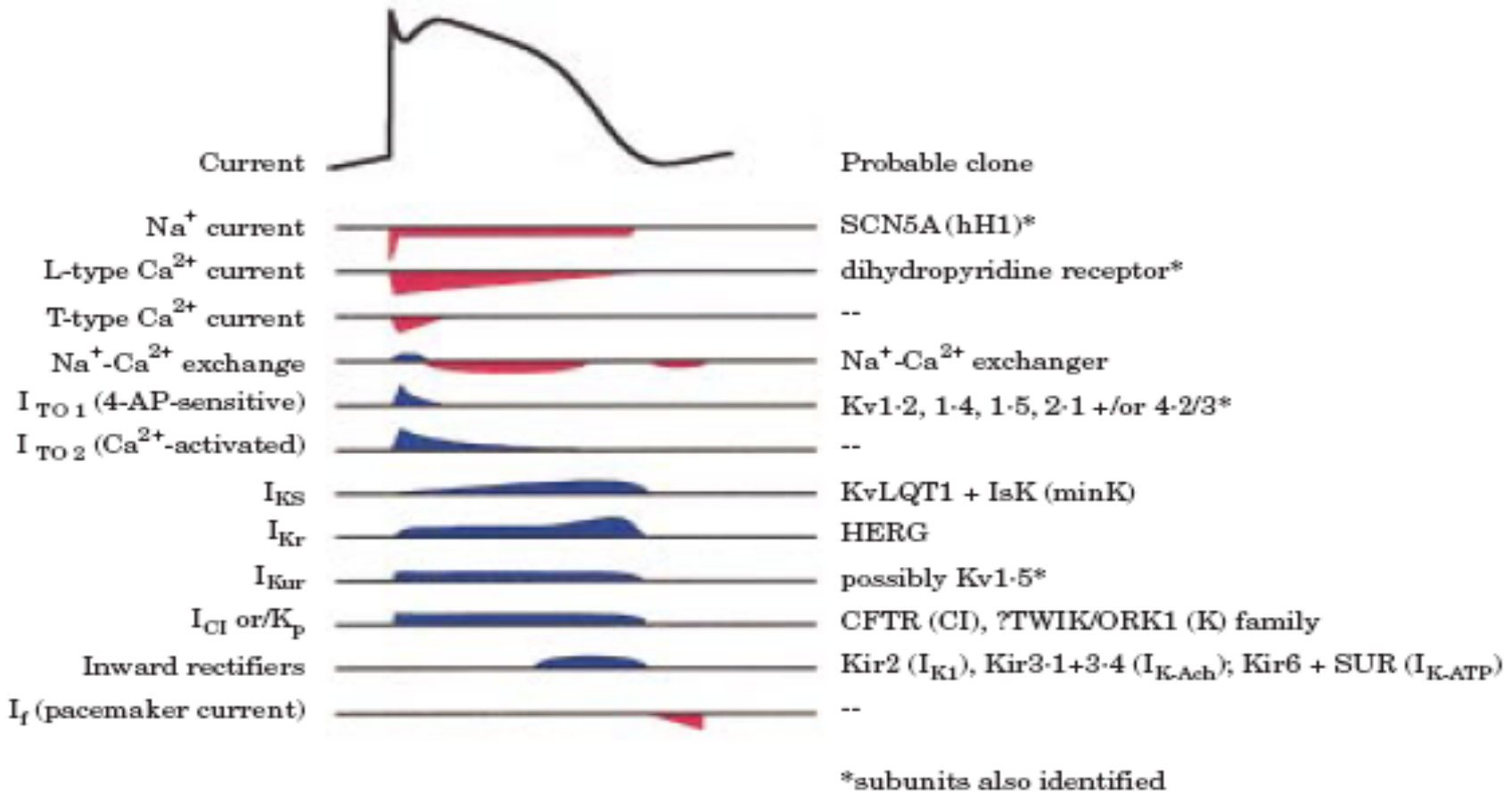
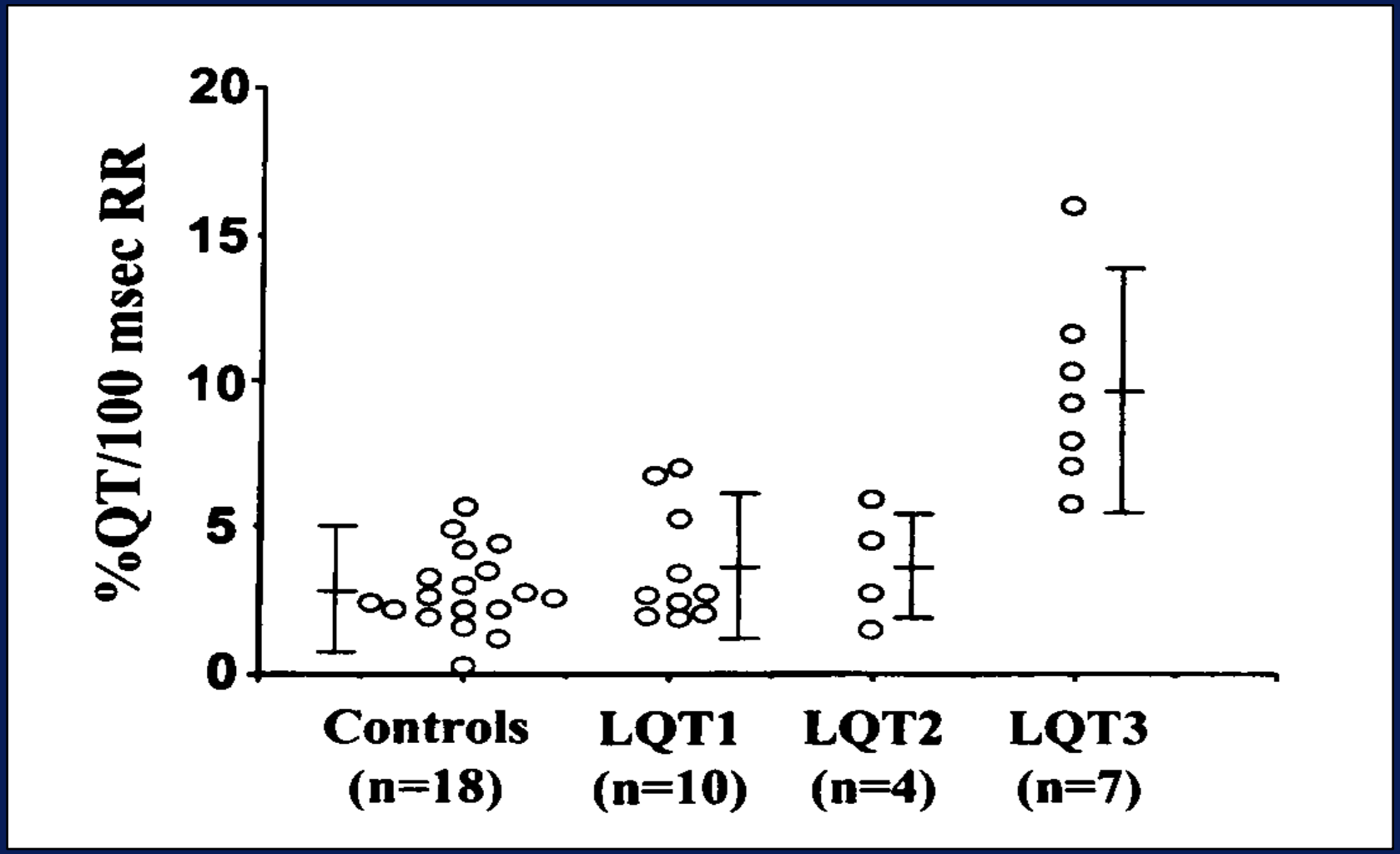


Figure 4 **Cardiac ionic currents and respective ion channel clones responsible for generation of the action potential Inward currents are drawn in red, outward currents in blue. The amplitudes are not to scale.**

Priori SG et al, Eur Heart J 1999

Single mutations interfere with the activity of specific ionic corrents in different phases of the action potential. As an example, an HERG mutation modifies the acftivity of the IKr current active in the later phase of ventricular repolarization.

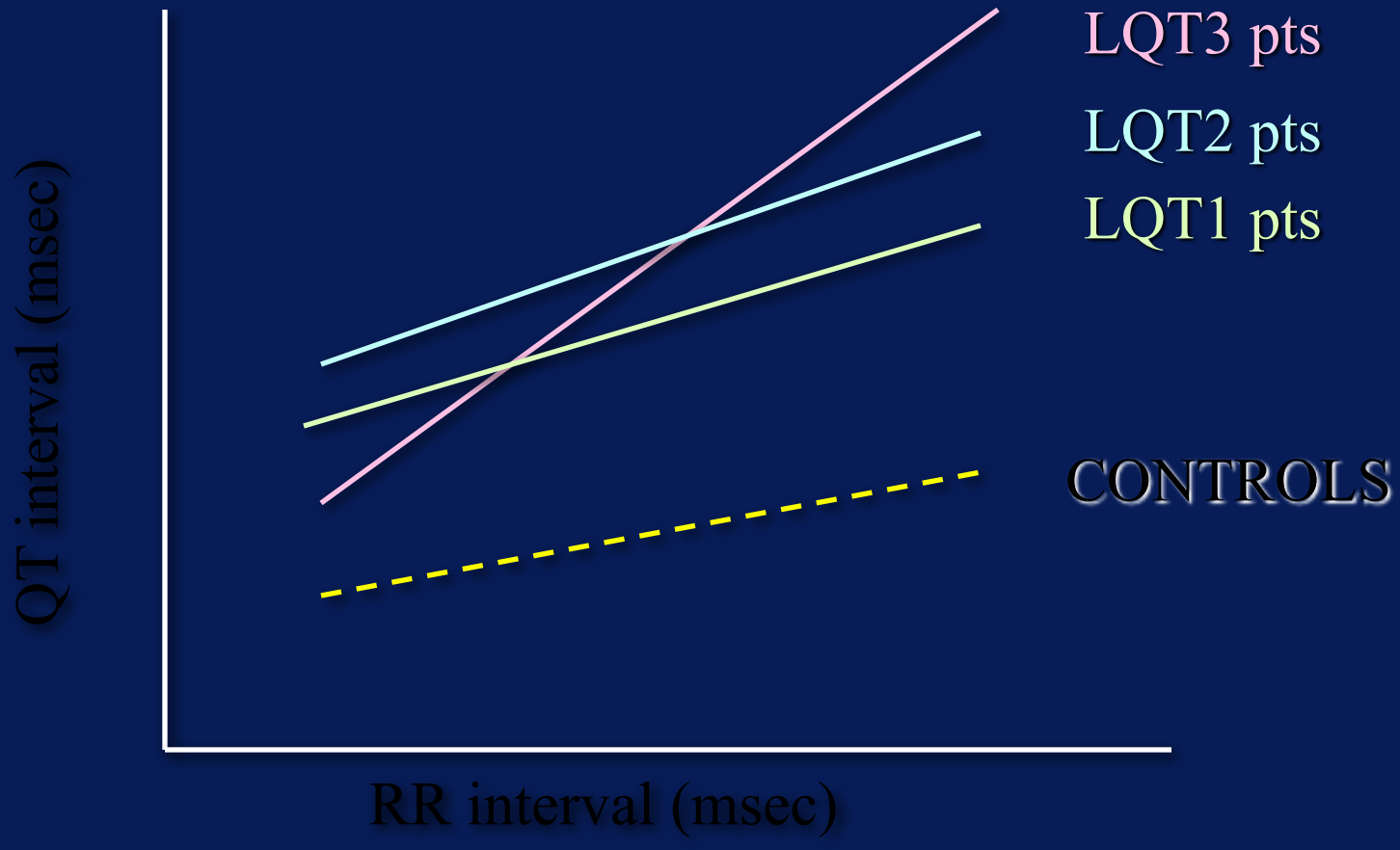
QT-RR RELATION DURING STRESS TEST IN LQTS PATIENTS BY GENOTYPE



Schwartz et al, Circulation 1995

The capacity of adaptation of QT interval to cycle lenght 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+ currents, which shows a greater-than-normal shortening of QT interval at increasing heart rates.

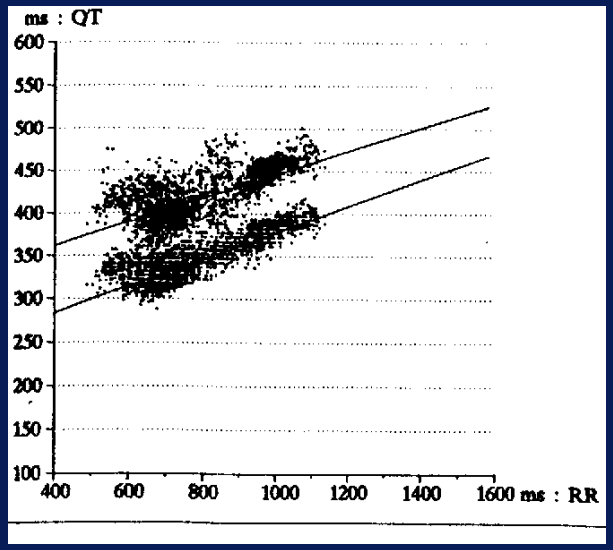
RELATION BETWEEN QT INTERVAL AND CYCLE LENGTH DURING 24-HOUR HOLTER MONITORING IN LQTS PATIENTS



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

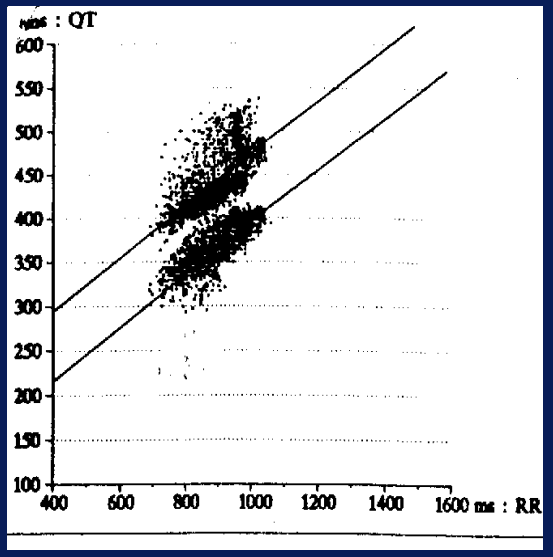
Rate-Dependence of QT Interval In LQTS

LQT1 Patient



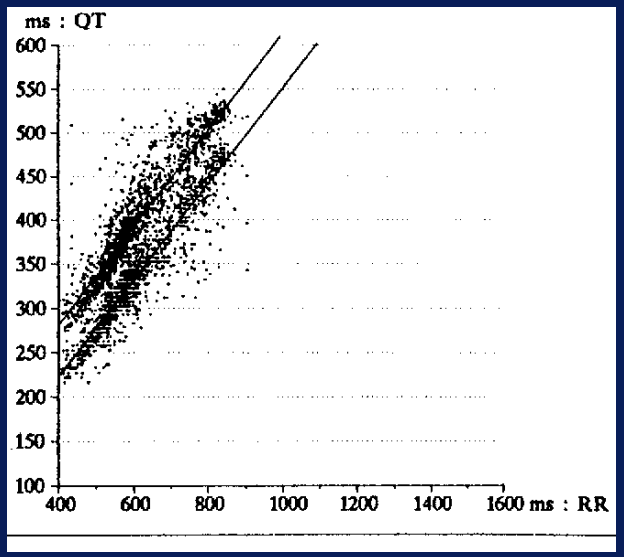
KVLQT1 Mutation

LQT2 Patient



HERG Mutation

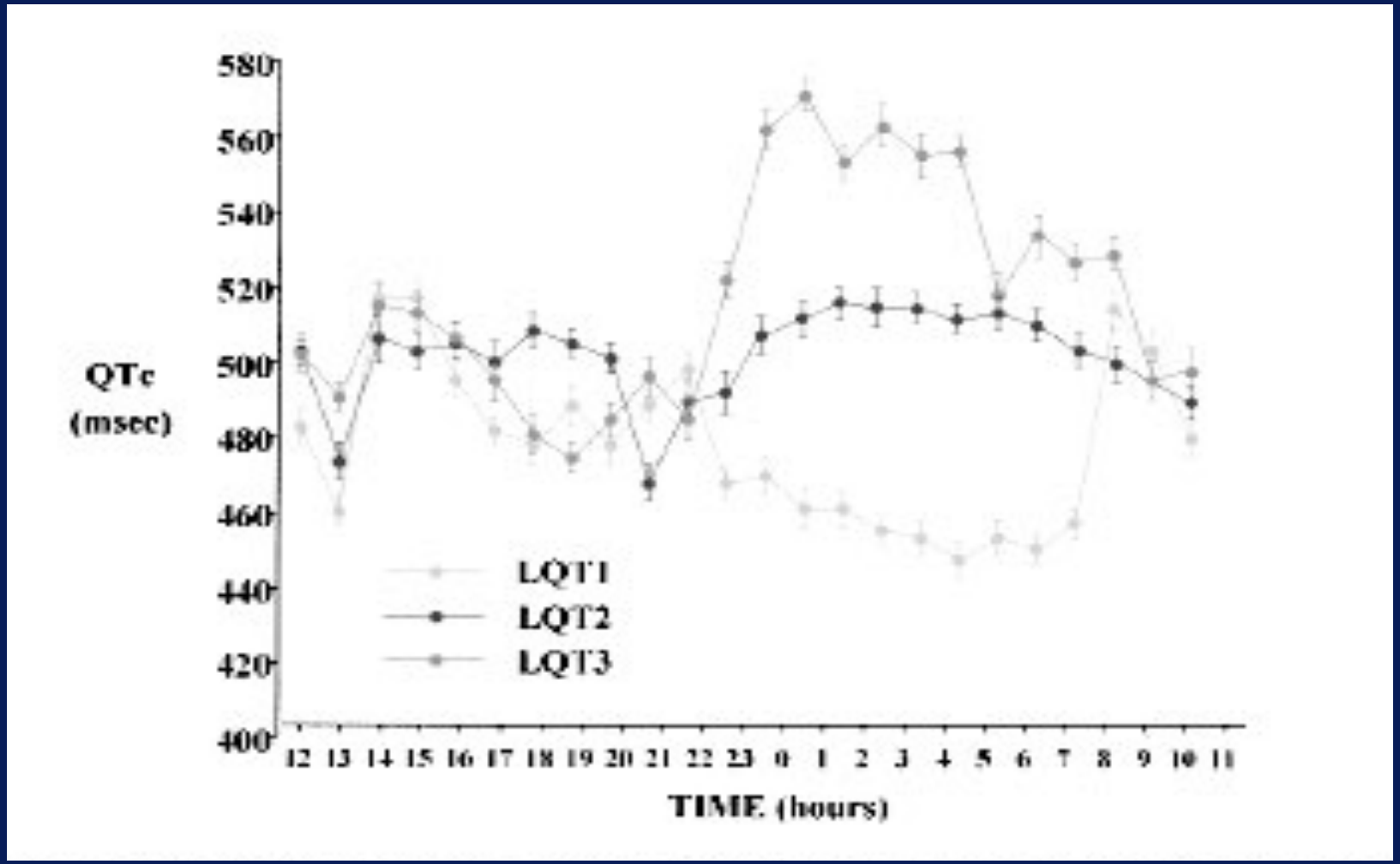
LQT3 Patient



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 steeeper 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 oberved during day (at highr heart rates) in LQT1 subjects, who usually have events during activity or emotions.

Clinical Applications of QT Dynamicity

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