ISHNE –
International Society for Holter and Noninvasive Electrocardiology

1st Worldwide Internet Symposium on Drug-Induced QT Prolongation
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Pacing in Drug Testing

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Disclosures: former investigator in the NESI study sponsored by Servier

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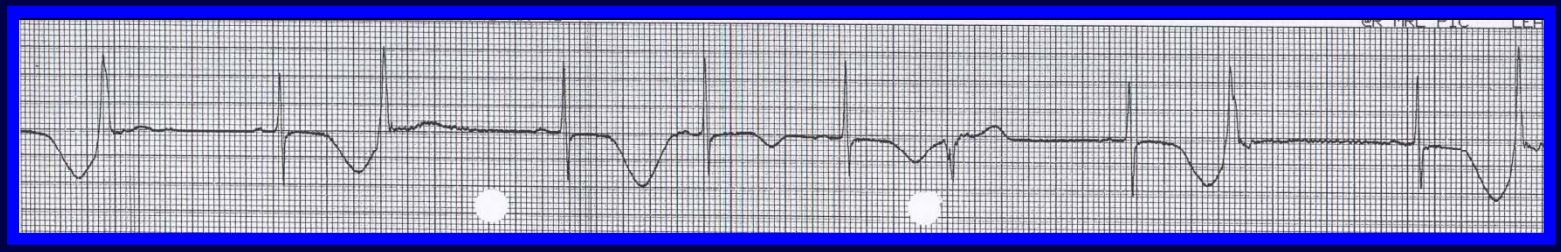
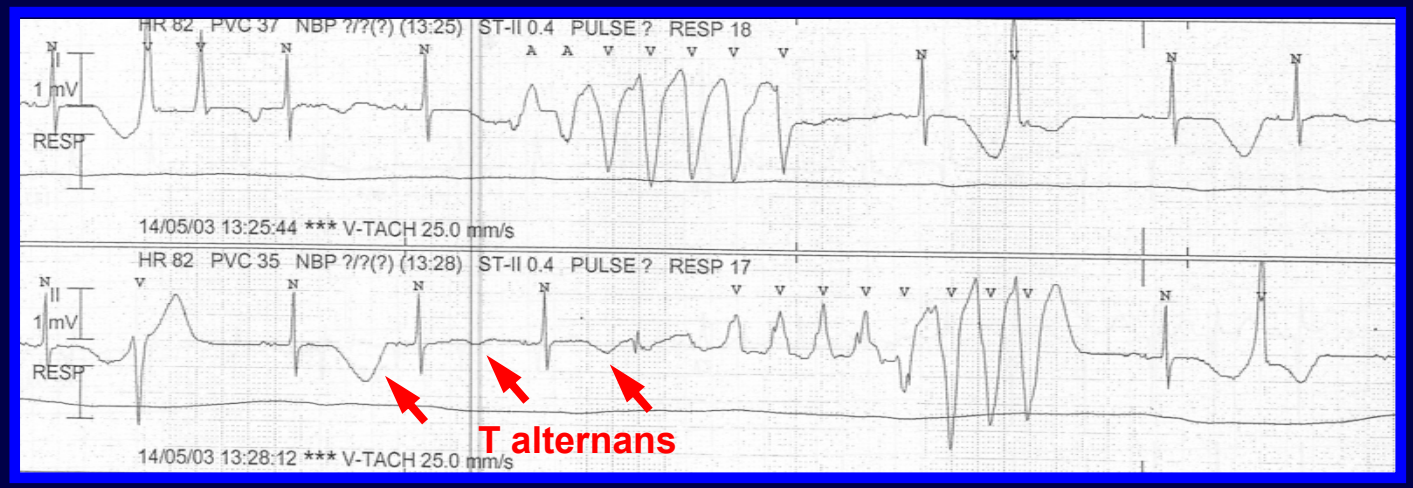
Scope of the Problem – Amiodarone-Induced QT Prolongation Resulting in TdP

- 72-year old man with controlled hypertension, no left ventricular hypertrophy, no evidence of coronary artery disease, no family or personal history of prolonged QT
- Electrically cardioverted for new onset (~ 6 months) persistent atrial fibrillation and started on Amiodarone for prevention of AF recurrence
- Admitted with pronounced bradycardia, prolonged QT, T wave alternans, bigeminy, and ventricular tachycardia





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Scope of the Problem

- The potential of both cardiovascular and non-cardiovascular drugs to prolong the QT interval has important implications for drug development and may lead to a withdrawal or restricted use of approved agents[1]
- The U.S. survey of outpatient prescription claims database has shown that drugs with an official warning on QT prolongation or with published data on QT effects may represent up to 20% of total prescriptions[2]
- Therefore, testing for a potential to influence cardiac repolarization in the so called 'thorough QT/QTc study' in man is a necessary component of the clinical portfolio of every new compound submitted for regulatory approval[3]

1. Haverkamp W, Breithardt G, Camm AJ, et al. The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications: Report on a Policy Conference of the European Society of Cardiology. Eur Heart J 2000;21:1216-1231

2. Curtis LH, Ostbye T, Sendersky V, et al. Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. Am J Med. 2003;114:135-141

3. U.S. Food and Drug Administration. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Preliminary concept paper. Available at: http://www.fda.gov/cder/calendar/meeting/qt4jam.pdf

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Limitations of Existing Models - Need for Correction for Heart Rate

- One of the significant problems of the QT studies is the appropriate correction of the QT interval for heart rate. A number of mathematical formulae for rate correction of the QT interval have been proposed to describe the physiological QT/RR interaction but none has been accepted as universally applicable

Proposed Forms of QT/RR Regressions

Model	Expression
Bazett	$QTc = QT/RR^{1/2}$
Fridericia	$QTc = QT/RR^{1/3}$
Linear	$QTc = QT + \alpha \times (1 - RR)$
Hyperbolic	$QTc = QT + \alpha \times (1/RR - 1)$
Parabolic log/log	$QTc = QT/RR^{\alpha}$
Logarithmic	$QTc = QT - \alpha \times \ln(RR)$
Shifted logarithmic	$QTc = \ln(e^{QT} + \alpha \times (1 - RR))$
Exponential	$QTc = QT + \alpha \times (e^{-RR} - 1/e)$,
Arcus tangent	$QTc = QT + \alpha \times (\text{arctg}(1.0) - \text{arctg}(RR))$,
Hyperbolic tangent	$QTc = QT + \alpha \times ((e^2-1)/(e^2+1) - \text{tgh}(RR))$
Arcus hyperbolic sine	$QTc = QT + \alpha \times (\ln(1+\sqrt{2}) - \text{arcsinh}(RR))$
Arcus hyperbolic cosine	$QTc = QT + \alpha \times (\ln(2+\sqrt{3}) - \text{arccosh}(RR+1))$
Square root linear	$QTc = QT + \alpha \times (1 - RR^{1/2})$
Cube root linear	$QTc = QT + \alpha \times (1 - RR^{1/3})$

Summarised by Malik M. PACE 2004; 27:1659-69

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Limitations of Existing Models
Problems With Traditional Formulae

The most commonly used Bazett and Fridericia formulae for rate correction are tempered by the non-linear, complex relationship between QT and RR intervals and often lead to overcorrecting (QTc shortening) or undercorrecting (QTc lengthening) of the QT interval, respectively, which in some cases may exceed the accepted safety threshold of 5-10 ms

Drug-unrelated variations in QTc corrected using different formulae are 4.7 ± 8.9 ms
Malik M. PACE 2004; 27:1659-69

In animal pacing models, Bazett's formula was associated with a mean overcorrection of 67.9 ms, and Fridericia's formula with a mean error of 28.7 ms
King A, et al. ANE 2006;11:289-8

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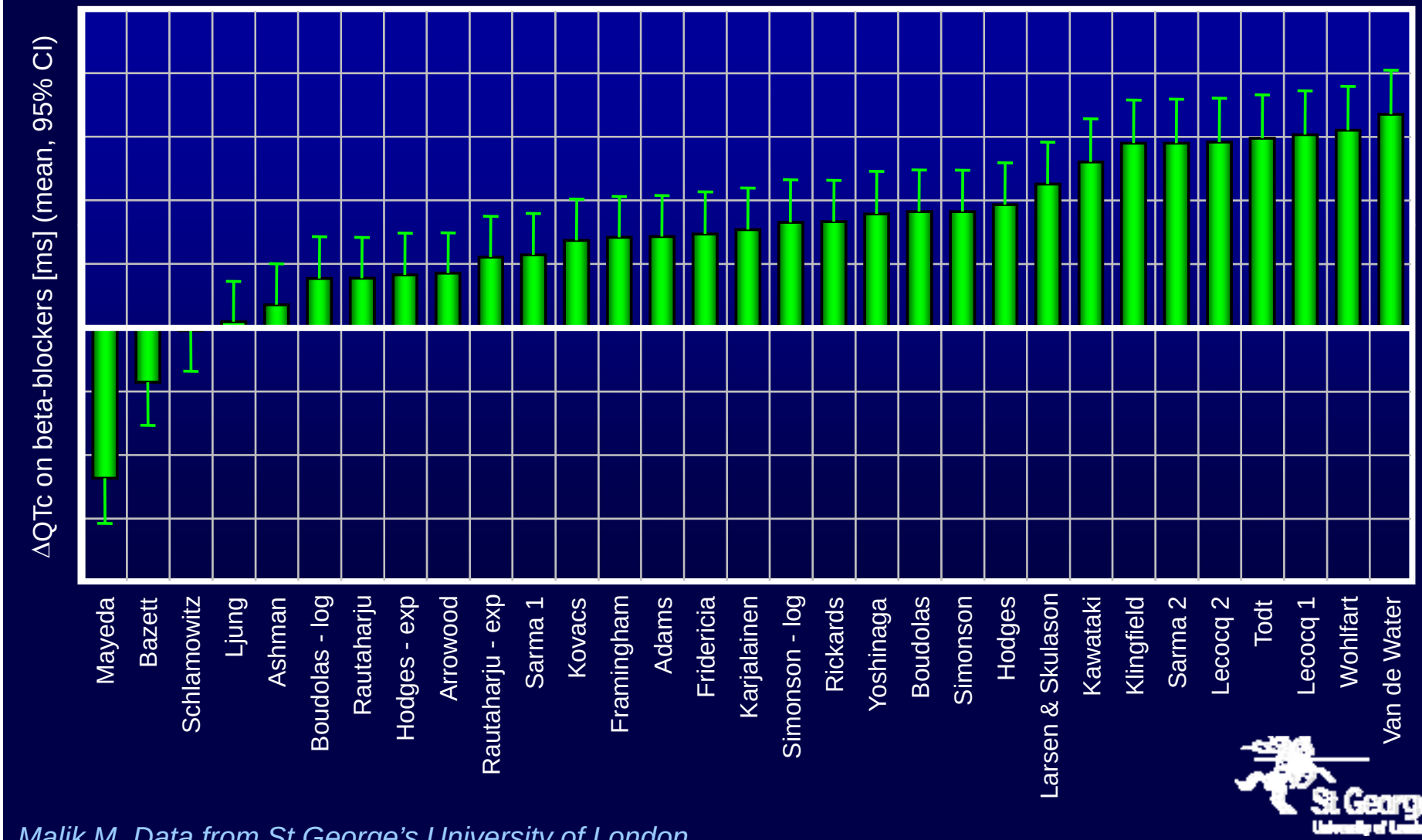
Assessment of the Effects on QT of Beta-Blockers Using Different Rate Correction Formulae: EMIAT Data



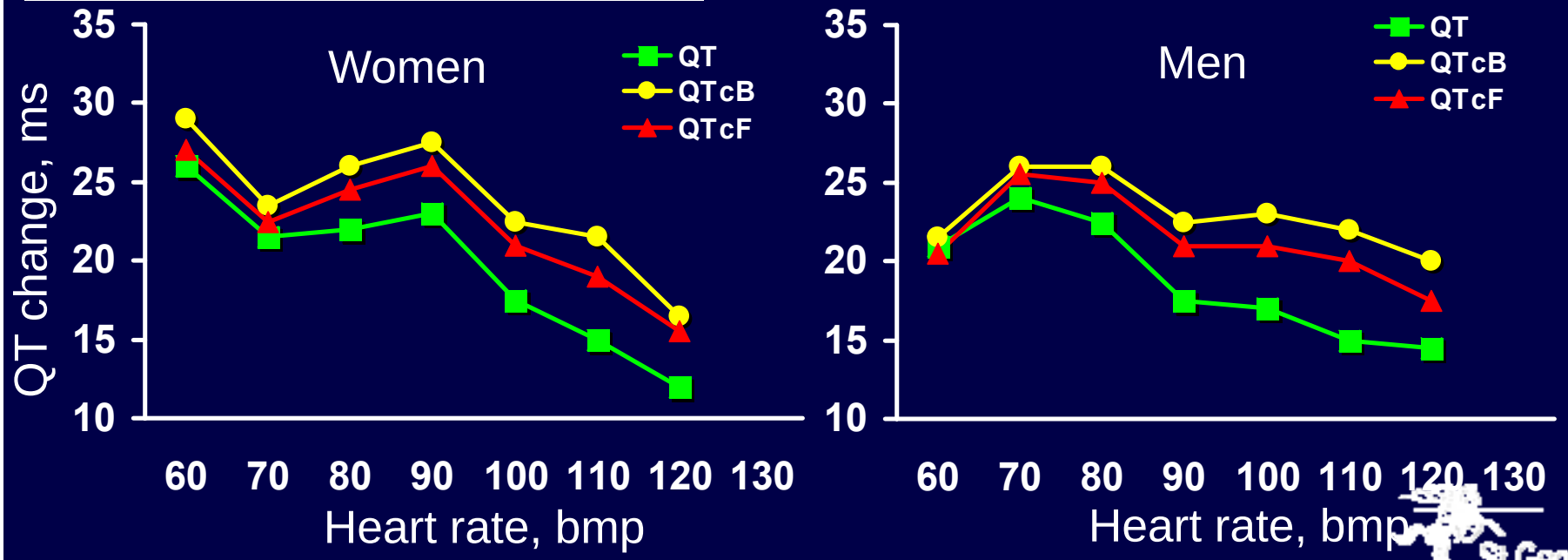
Malik M. Data from St George's University of London

Limitations of Existing Models -
Bazett and Fridericia Formulae Interfere With QT Assessment

Healthy subjects	Women n = 9	Men n = 9
Age, years	27.9	25.6
Height, cm	162.8	175
Weight, kg	63.2	72.2
BMI, kg/m^2	23.9	23.8
Ibutilide PK, pg/mL	557.9	558.7

Rate correction of QT intervals using the standard Bazett and Fridericia formulas can introduce significant errors in the assessment of drug effects on the QT interval. This has implications for the clinical assessment of drug effects and for the safety assessment of new drugs under development

QT change assessed during ibutilide

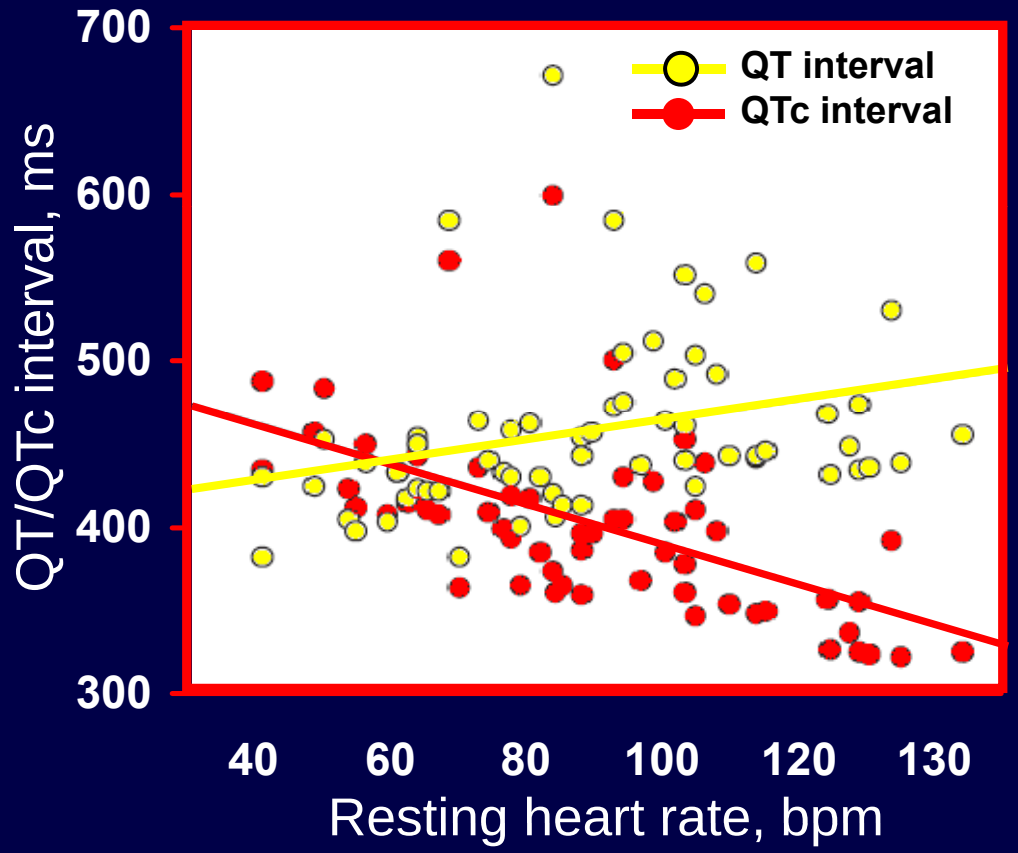


Indik JH, et al. Heart Rhythm 2006;2006;3:1003-7

Limitations of Existing Models -

Overcorrection of the QT interval by Bazett Formula

Data obtained at rest from a population of controls and patients with heart failure, left ventricular hypertrophy. There is a significant negative correlation between heart rate and QT interval, and a positive correlation between heart rate and QTc interval



Davey PP, et al. Clin Cardiol 1999;22:793-9

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Limitations of Existing Models - QT Hysteresis

- In addition, the QT interval adapts to changes in heart rate with a delay, a phenomenon termed QT interval hysteresis, which makes it difficult to compare the QT interval recorded at non-constant heart rates

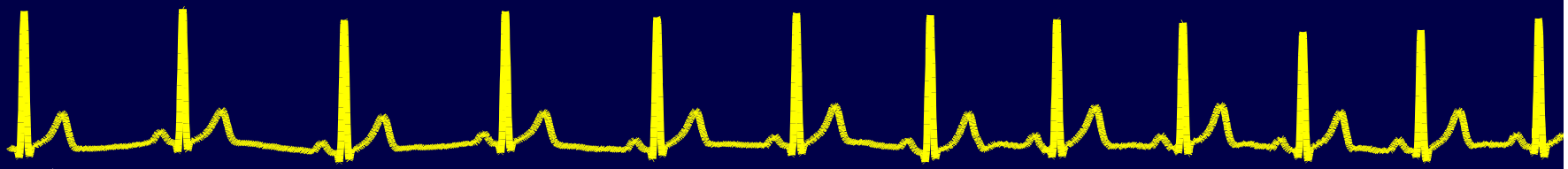
Hysteresis of the ventricular paced QT interval in response to abrupt changes in pacing rate

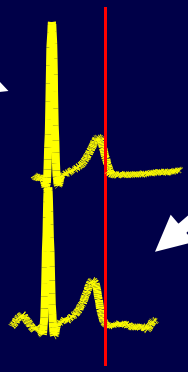
CHU PAK LAU, ANDREW R FREEDMAN,* SIMON FLEMING,† MAREK MALIK, A JOHN CAMM, DAVID E WARD

From the Department of Cardiological Sciences, St George's Hospital Medical School, London

SUMMARY The rate of QT adaptation to abrupt changes in pacing rate was studied in seven patients v newly diagnosed complete heart block with a ventricular escape rate of less than 40 beats·min^{-1}. T median age was 70 (range 36-84) years, and none was taking any cardioactive medication known to af the QT interval. From a baseline pacing rate of 50 or 110 beats·min^{-1} the ventricular rate was increase decreased to a new level. The time taken for the ventricular paced QT interval to complete 90% of change secondary to the change in rate was found to be 136(16) s (mean(SEM)) when the rate increasing and 189(25) s when the rate was decreasing ($p<0.01$). This time interval was independent of magnitude of the rate change and the baseline heart rate from which the change occurred. Furthermore time course of QT adaptation was found to be exponential and was characterised by a time constar 49.1(2.2) s when the rate was increasing and 60.4(2.0) s when the rate was decreasing ($p<0.01$). concluded that QT measurements in response to a change in pacing rate should take into account the t dependent nature of QT changes.

Example of QT/RR Hysteresis





RR = 1000 ms
HR = 60 bpm
QT = 373 ms
QTc (Bazett) = 371 ms

RR = 742 ms
HR = 81 bpm
QT = 373 ms
QTc (Bazett) = 433 ms

During the 10 sec ECG, the QT interval has not changed (i.e. has not yet adapted to the dynamic changes in the heart rate). The “measurement” results depends on where the RR interval is measured. ECGs of this kind MUST be excluded

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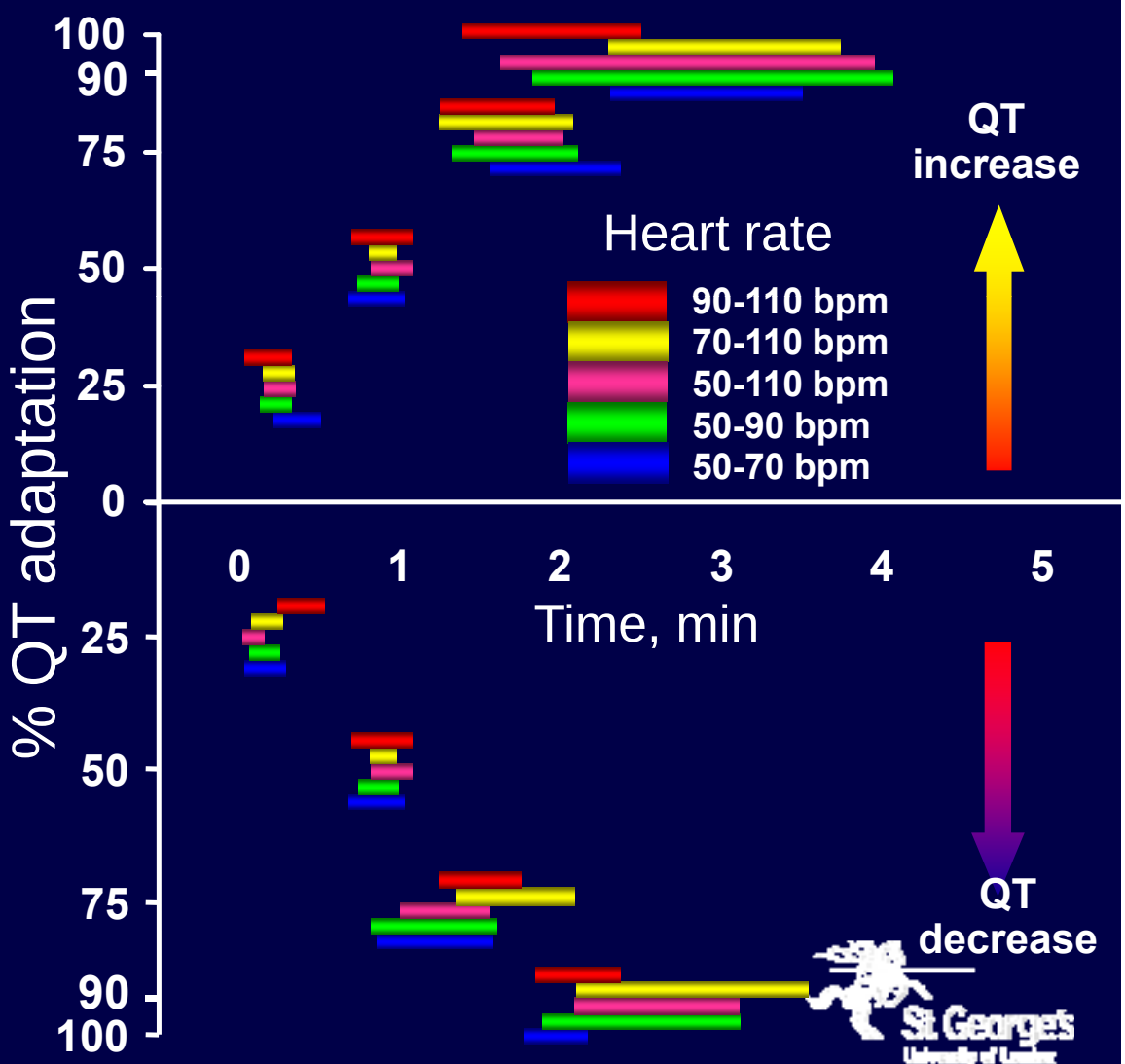
Studies of QT Adaptation to Changing Heart Rates During Pacing

- 7 patients with recent onset complete heart block
- Ventricular pacing at changing rates from a baseline of 50 bpm to max 110 bpm or from baseline 110 bpm to min 50 bpm
- During pacing, there is a significant time delay in the QT change after an abrupt change in the pacing rate (QT hysteresis)
- When the controlled rate is restored, the QT interval resumes its initial value over a different time course
- The steady state QT interval may only be reached after several minutes
- The time course of QT adaptation to changes in pacing rates was found to fit an expo-nential model, with r = 0.994



Lau CP, et al. Cardiovasc Res 1988;22:67-72

Time Taken to Achieve 25% to 100% QT Change for Rate Change During Pacing

Time for completing 25, 50, 75, and 90% of QT changes induced by an increase or decrease in pacing rate (pooled data, mean ± SEM)

Time, seconds	25%	50%	75%	100%
Increase in pacing rate	20 ± 2	36 ± 3	79 ± 6	136 ± 16
Decrease in pacing rate	23 ± 2	44 ± 3	92 ± 6	189 ± 25

In this model, the time taken for completion 25, 50, 75, and 90% of QT changes was significantly faster when pacing rates were increased (QT became shorter) than when pacing rates were decreased (QT became longer)

As the time course of QT adaptation to changes in pacing rates appeared to fit an exponential model, he time constant was 49.1(2.2) s when the rate was increasing and 60.4(2.0) s when the rate was decreasing

Lau CP, et al. Cardiovasc Res 1988;22:67-72

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Limitations of Existing Models - Rate Correction

- Other models, such as the subject-based QT correction formula and a Holter-based "bin" method have been criticized. The Holter Bin method, in which QT intervals associated with specific preceding RR intervals are compared before and after drug/placebo administration, is compromised by:

- Comparisons inevitably being made in different autonomic environments, particularly when the drug in question has a powerful effect on heart rate
- Variations in QT/RR relationship over 24 hours should be accounted for
- The Holter Bin method takes no account of QT/RR hysteresis
- Potential positional changes in T wave morphology that may affect reliable QT measurements
- Persistent sinus arrhythmia or ectopy may interfere with the results

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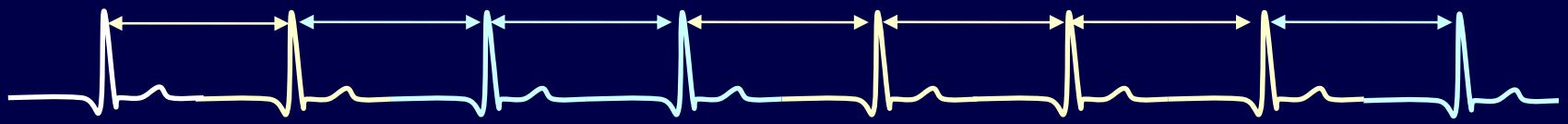
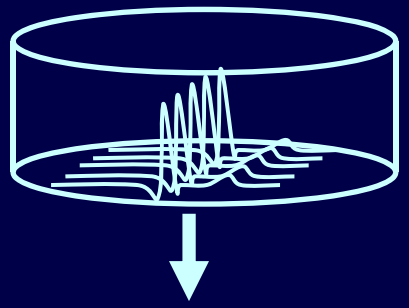
RR Control Rather Than QT Correction – "Bin" Method

1. RR interval measurement

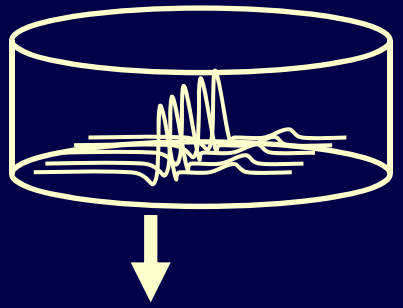
1006 msec 995 msec 995 msec 1007 msec 1005 msec 1005 msec 1000 msec



2. Classification of ECG complexes into 10 ms groups « Bins »

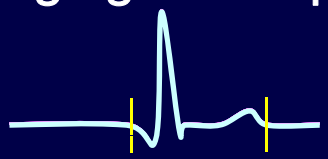


1000 msec
RR Bin

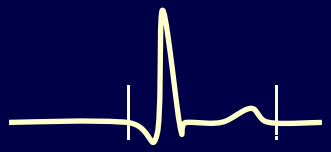


1010 msec
RR Bin

3. Averaging of complexes and measurement of QT intervals



QT_{1000}



QT_{1010}

After Maison-Blanche P and Badilini F
http://www.amps-llc.com/publications/chapter9.pdf
http://www.fda.gov/ohrms/dockets/ac/03/slides/3956s1.htm

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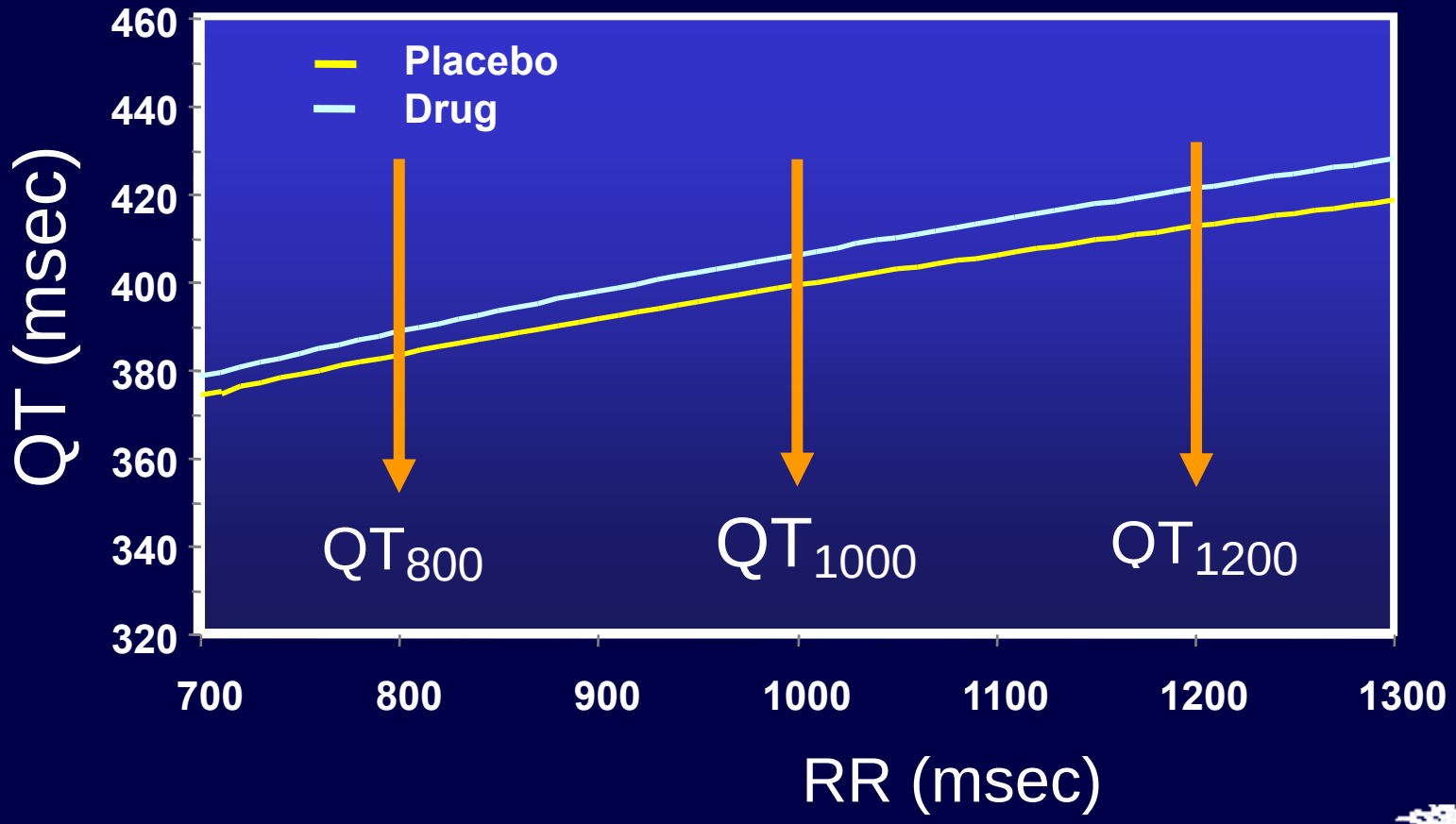
Individual QT/RR Relationship
Holter "Bin" Method

Aflusozin

$QT = Ai*RR^{Bi}$



After Maison-Blanche P and Badilini F
http://www.fda.gov/ohrms/dockets/ac/03/slides/3956s1.htm

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Autonomic Nervous System Influences on Rate-Dependent QT Changes

Mean ± SD	RR, ms	QT, ms	QTc, ms	QT/RR slope
Baseline	770 ± 91	366 ± 34	417 ± 26	0.22 ± 0.12
Beta-blockade	909 ± 97*	380 ± 31*	399 ± 22*	0.23 ± 0.08
Autonomic blockade	671 ± 72	346 ± 19*	422 ± 12	0.10 ± 0.04*

** $p < 0.05$ vs baseline*

Atrial pacing has been used to achieve changes in heart rate independent of autonomic tone; atrial pacing abolishes the natural relation of heart rate and ventricular repolarization induced by autonomic tone, thus allowing evaluation of the direct effects on the QT interval exerted by pharmacological autonomic manipulations

28 subjects referred for EP testing because of PSVT underwent atrial pacing at 600, 540, 500, 460, 430, 400 ms at baseline, after beta-blockade with i.v. propranolol 0.2 mg/kg, and after autonomic blockade with propranolol plus i.v. atropine 0.04 mg/kg

Increased vagal activity increased intrinsic dependence of the QT interval on heart rate at increasing pacing cycle length, whereas sympathetic stimulation did not seem to interfere significantly

Cappato R, et al. Am J Cardiol 1991;68:1188-93

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Assessment of Drug-Induced QT Changes During Controlled Heart Rates: A Canine Model

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Journal of Pharmacological and Toxicological Methods 53 (2006) 1–10

Journal of Pharmacological and Toxicological Methods

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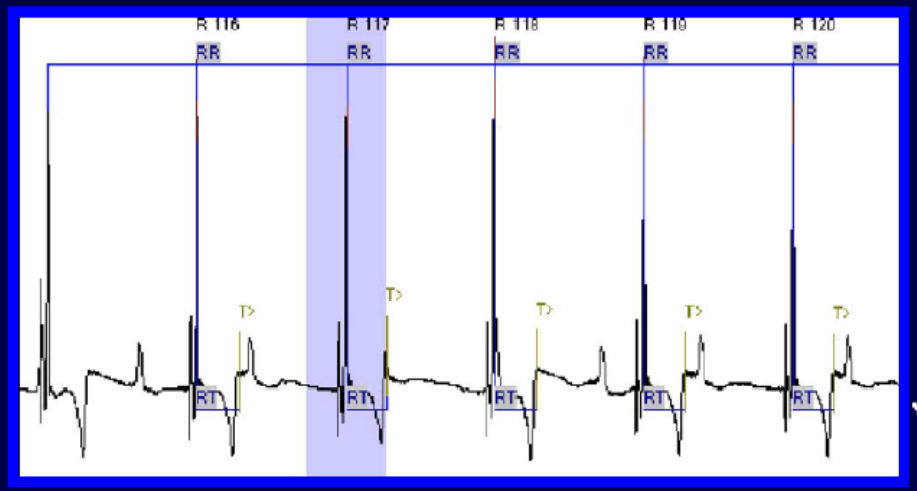
Original article

A novel predictive pharmacokinetic/pharmacodynamic model of repolarization prolongation derived from the effects of terfenadine, cisapride and E-4031 in the conscious chronic av node—ablated, His bundle-paced dog

Emily R. Nolan[a,*], Meihua Rose Feng[a], Jeffrey R. Koup[a], Jing Liu[a], Daniel Turluck[a], Yiqun Zhang[a], Jerome B. Paulissen[a], N. Bari Olivier[b], Teresa Miller[a], Marc B. Bailie[a]

[a]*Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, MI 48105, United States*
[b]*Michigan State University College of Veterinary Medicine, East Lansing, MI, United States*

An example of typical His bundle-paced ECG tracings and fiduciary points identified by the EMKA system (EMKA Technologies, Paris, France). A "library" beat was used as a template for EMKA's shape-based algorithm to identify R-peak and T-end for beats of interest. Complexes with no distinguishable end of T or with dissociated P-T superimposition (highlighted waveform) were excluded from analysis



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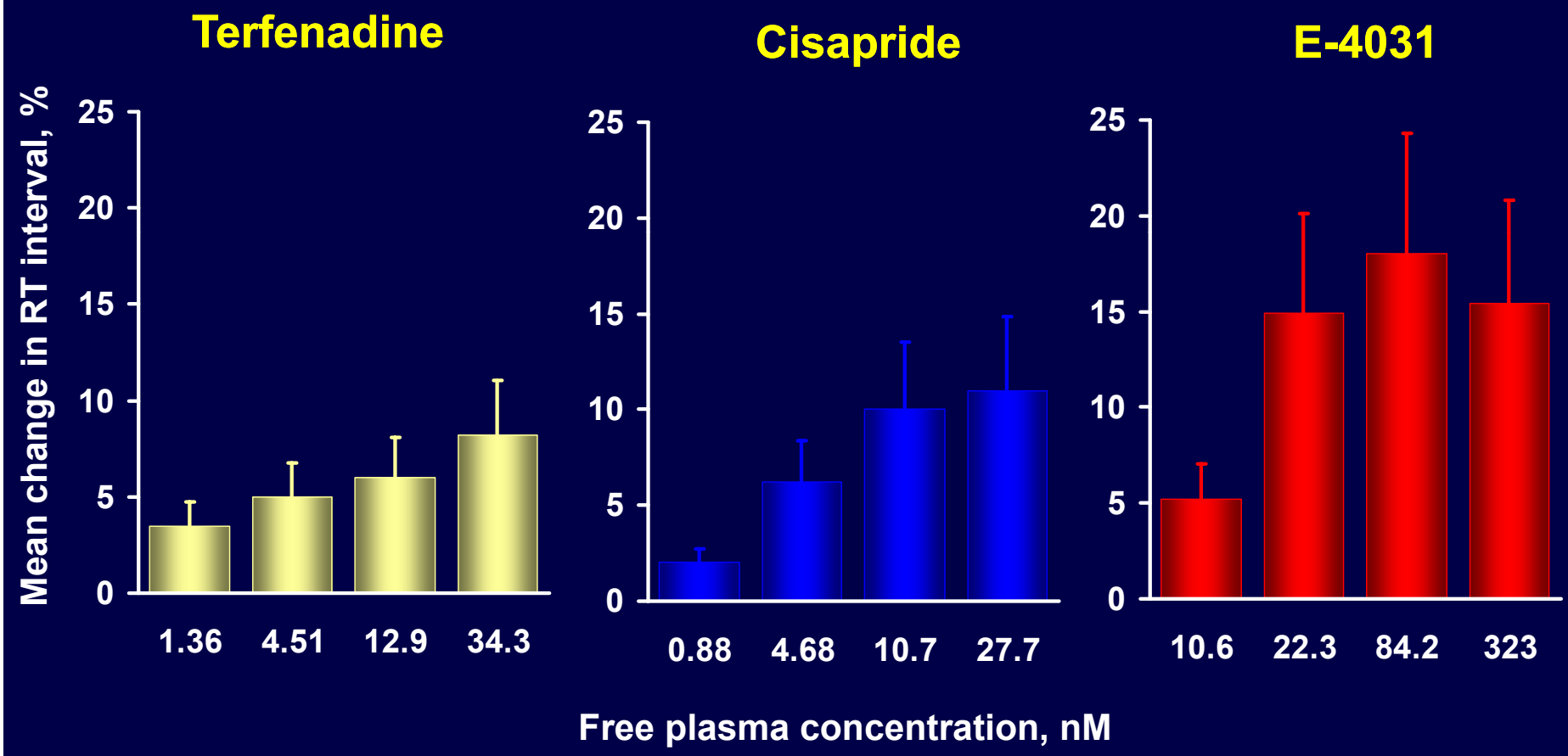
Effects of i.v. Rising Dose of Terfenadine, Cisapride, and E-4031 on RT interval During Controlled Heart Rates in His Bundle Paced Dogs



Nolan ER, et al. J Pharmacol Toxicol Method 2005;53:1-10

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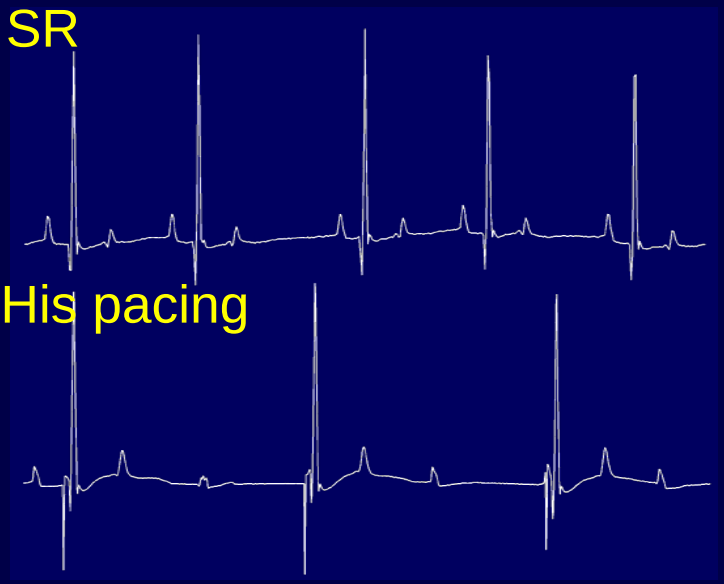
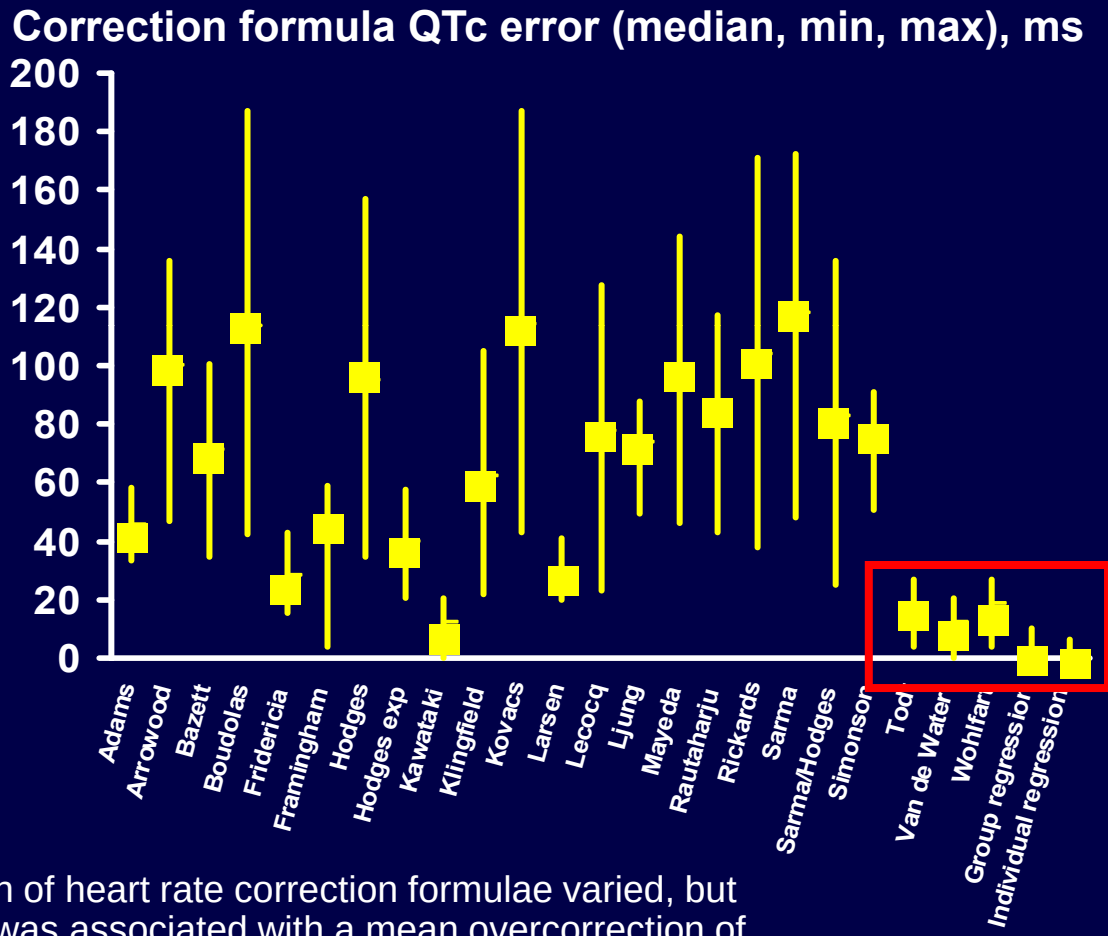
Magnitude of Error Introduced By Rate Correction Formulae: Assessment in a Canine Model

Chronic atrioventricular dissociated His-paced canine model



Lead II electrocardiogram of a representative dog in sinus rhythm and after AV dissociation and His bundle pacing. The morphology of the QRS complex is almost identical



The magnitude of error discovered by application of heart rate correction formulae varied, but in many cases was very large. Bazett's formula was associated with a mean overcorrection of 67.9 ms; Fridericia's 28.7 ms. As expected, group and individual corrections derived from linear regression of the HR-QT data offered improvement over the traditional formulas. Both were able to predict QTc values independent of the heart rate. However, errors of the magnitude of 10 and 6 ms, respectively, were still introduced

King A, et al. A.N.E. 2006;11:289-98

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Previous Experience –
Summary of Selected Studies

Author	Journal	Year	Patients	Model	Drug
Milne JR	Br Heart J	1980	16	Atrial pacing at 100, 130, 150 bpm during routine cath	Propranolol
Camm AJ	Eur Heart J	1984	9	Atrial and ventricular pacing at 110 bpm during routine cath or EPS (x1)	Disopyramide, lignocaine, flecainide
Kawataki M	J Electrocardiol	1984	9	Atrial pacing in healthy subjects	N/A
Sarma JSM	Am J Cardiol	1984	6	Ventricular pacing at 50-180 bpm using fitted VVI pacemakers	N/A
Dickhuth HH	PACE	1991	10	Atrial pacing at 70-160 bpm in healthy subjects	Sotalol
Cappato R	Am J Cardiol	1991	28	Atrial pacing at 6 cycle length bpm during EP testing	Propranolol, atropine
Shimizu W	PACE	1991	11 LQTs,12 controls	Atrial pacing at 500 ms	N/A
Debbas NMG	JACC	1999	51	Atrial pacing using fitted DDD pacemakers	Propranolol, disopyramide, flecainide
Zabel M	JACC	2000	35	Atrial pacing during EP testing	N/A

Effect of i.v. Propranolol on QT Assessment During Atrial Pacing

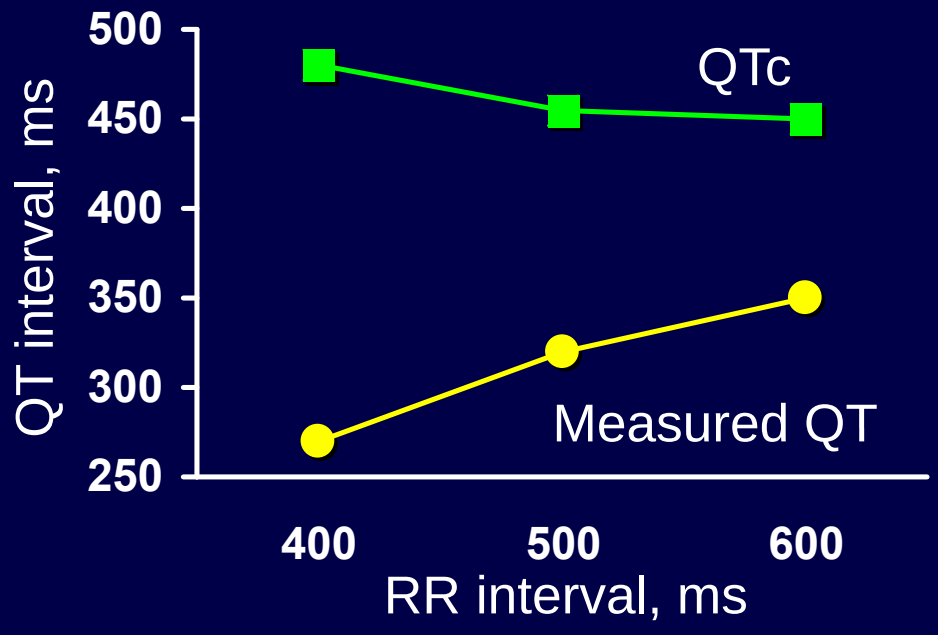
Br Heart J 1980; **43**: 1–6

Effect of intravenous propranolol on QT interval

A new method of assessment

J R MILNE, A J CAMM, D E WARD, R A J SPURRELL

From the Department of Cardiology, St. Bartholomew's Hospital, London



This study was designed to circumvent the use of a correction factor by directly comparing the measured QT before and after the administration of propranolol at identical atrial paced rates

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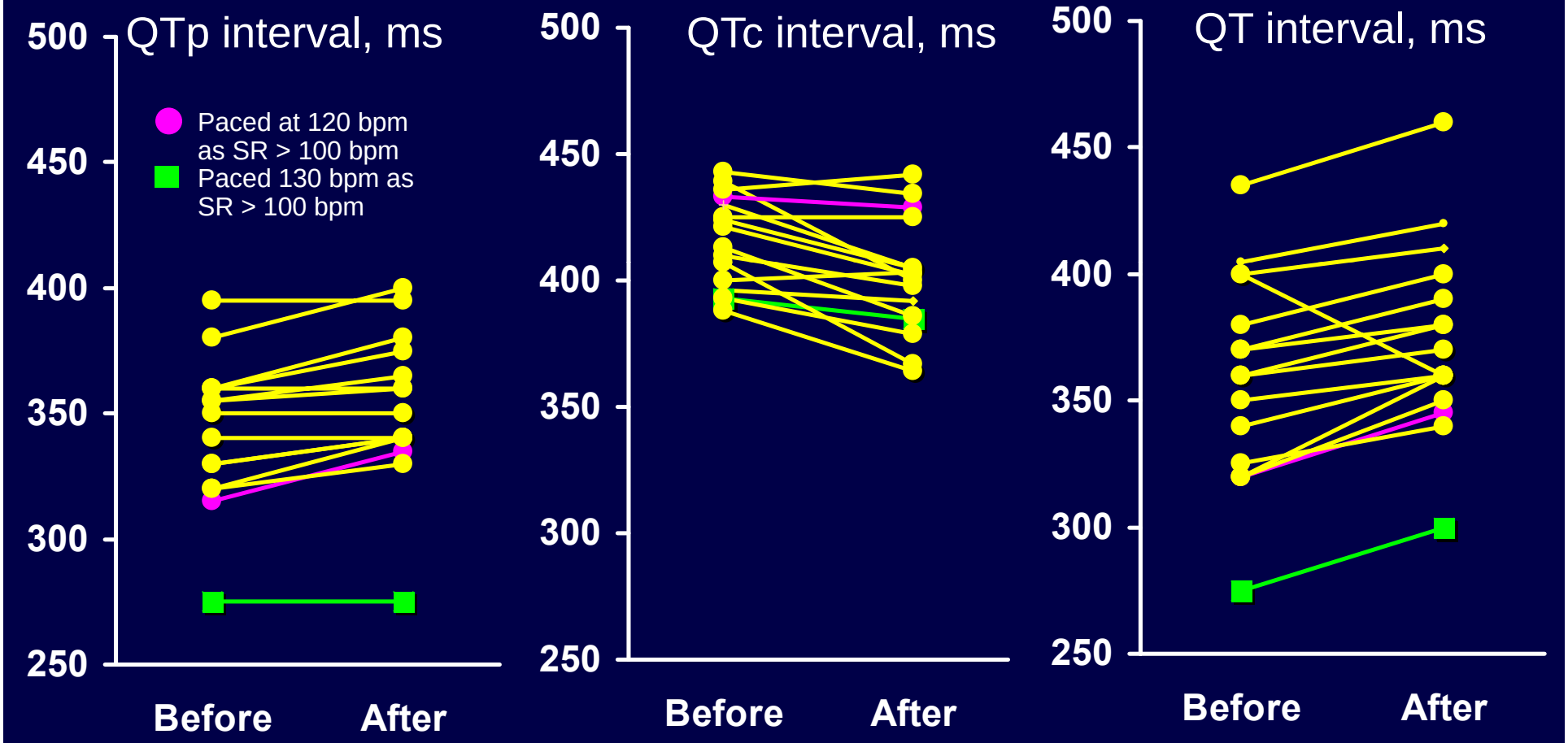
Effect of i.v. Propranolol on QT at Identical Paced Rates



In the case of propranolol, which produces a significant relative bradycardia, that the application of a correction factor, in these cases Bazett's formula, may give rise to spurious results, and the formal assessment of drug induced QT interval changes should be made at identical [atrial paced] rates

Milne JR, et al. Br H J 1980;43:1-6

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Assessment of the EP Effects of Class I Drugs During Atrial and Ventricular Pacing

European Heart Journal (1984) **5**, 99–107

Class 1 antiarrhythmic drugs — Characteristic electrocardiographic differences when assessed by atrial and ventricular pacing

J. R. MILNE, K. J. HELLESTRAND, R. S. BEXTON, P. J. BURNETT*, N. M. G. DEBBAS, A. JOHN CAMM†

Department of Cardiology, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, U.K.

Class 1 antiarrhythmic drugs have been subdivided into Ia, Ib and Ic according to their effect on the action potential duration. The effects on the surface electrocardiogram of one drug from each subgroup were investigated in nine patients. Electrocardiographic recordings were taken during sinus rhythm and at identical atrial and ventricular paced rates. Disopyramide (Ia) significantly prolonged the QT interval during sinus rhythm and at the identical paced rates, by increasing both the QRS duration and JT interval. Lignocaine (Ib) significantly reduced the Q T interval during sinus rhythm and at the identical paced rates, by reducing the JT interval. Lignocaine had no effect on the QRS duration. Flecainide (Ic) significantly prolonged the QRS duration during sinus rhythm, but not the Q Tc. However the Q T interval at the paced rates prolonged significantly, due entirely to an increase of the QRS duration. Flecainide had no effect on the JT interval. These characteristic electrocardiographic differences support the differentiation of class 1 drugs into three separate subgroups

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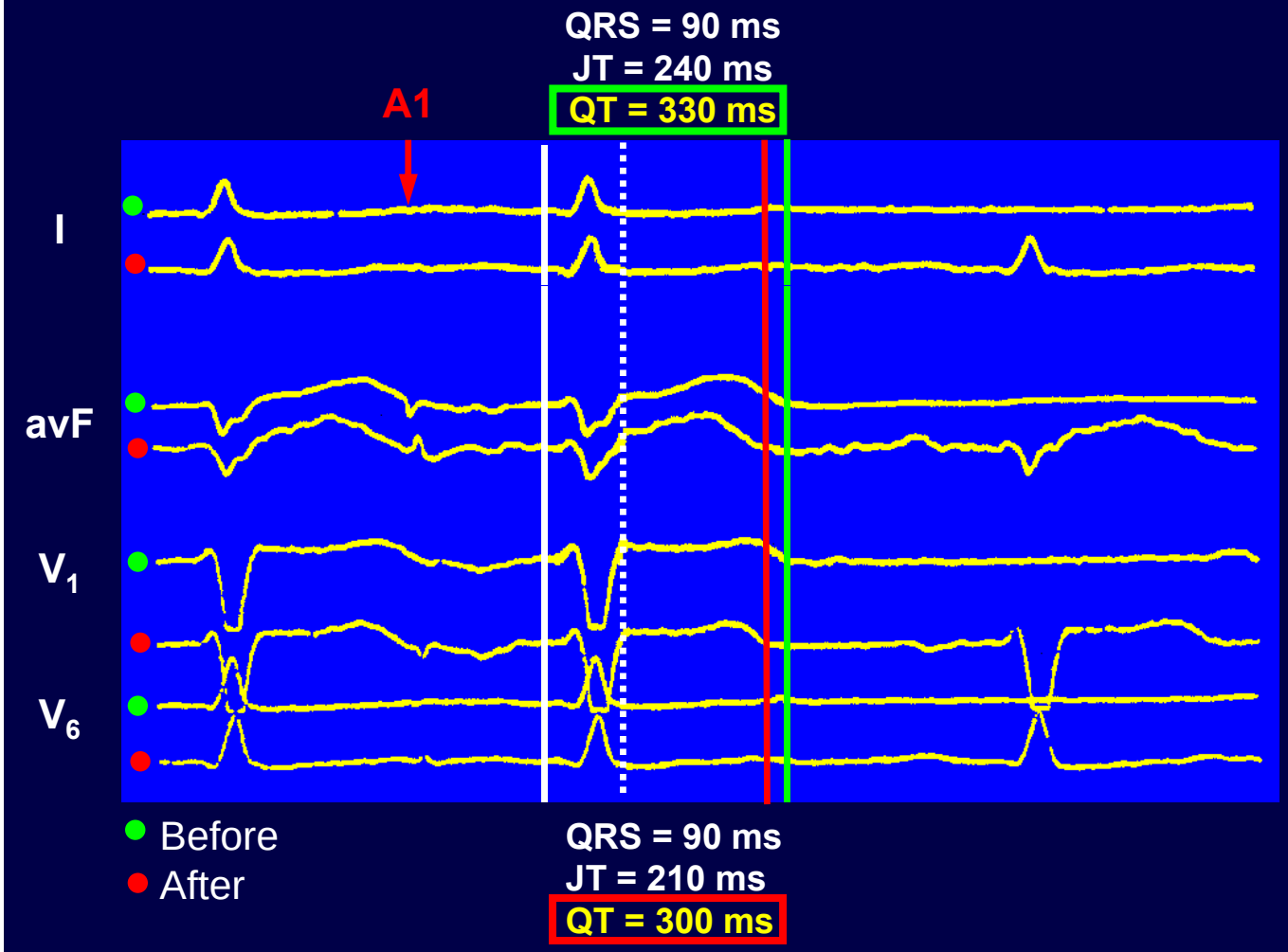
Assessment of the EP Effects of Class I Drugs During Atrial and Ventricular Pacing



Superimposed ECGs for leads I, avF, V_1 and V_6 recoreded during atrial pacing at 110 bpm and after the administration of lignocaine. Lignocaine has shortened the QT interval from 330 ms to 300 ms by shortening the JT interval from 240 ms to 210 ms. The QRS duration is unchanged

Camm AJ, et al. EHJ 1984;5:99-107

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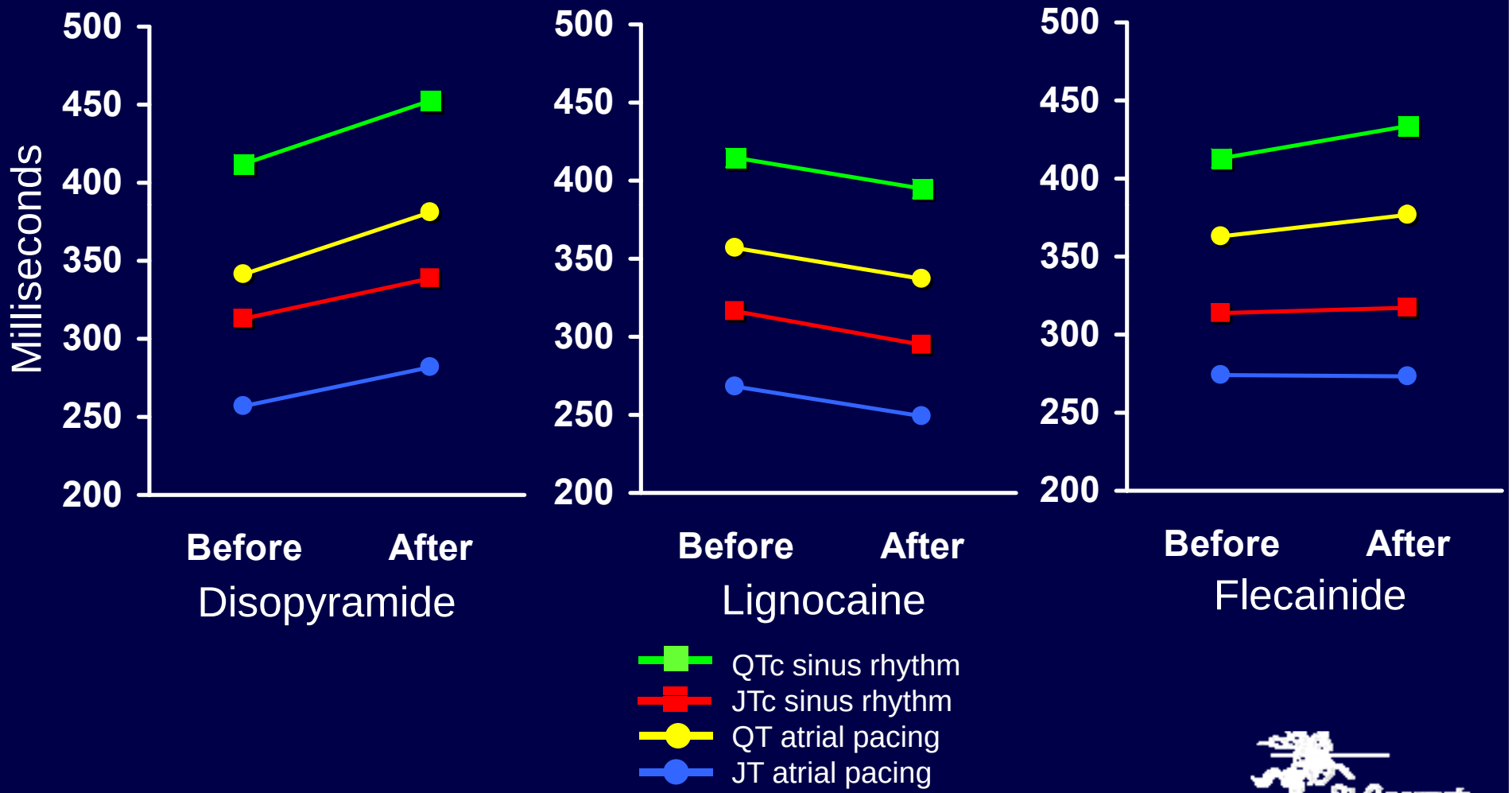
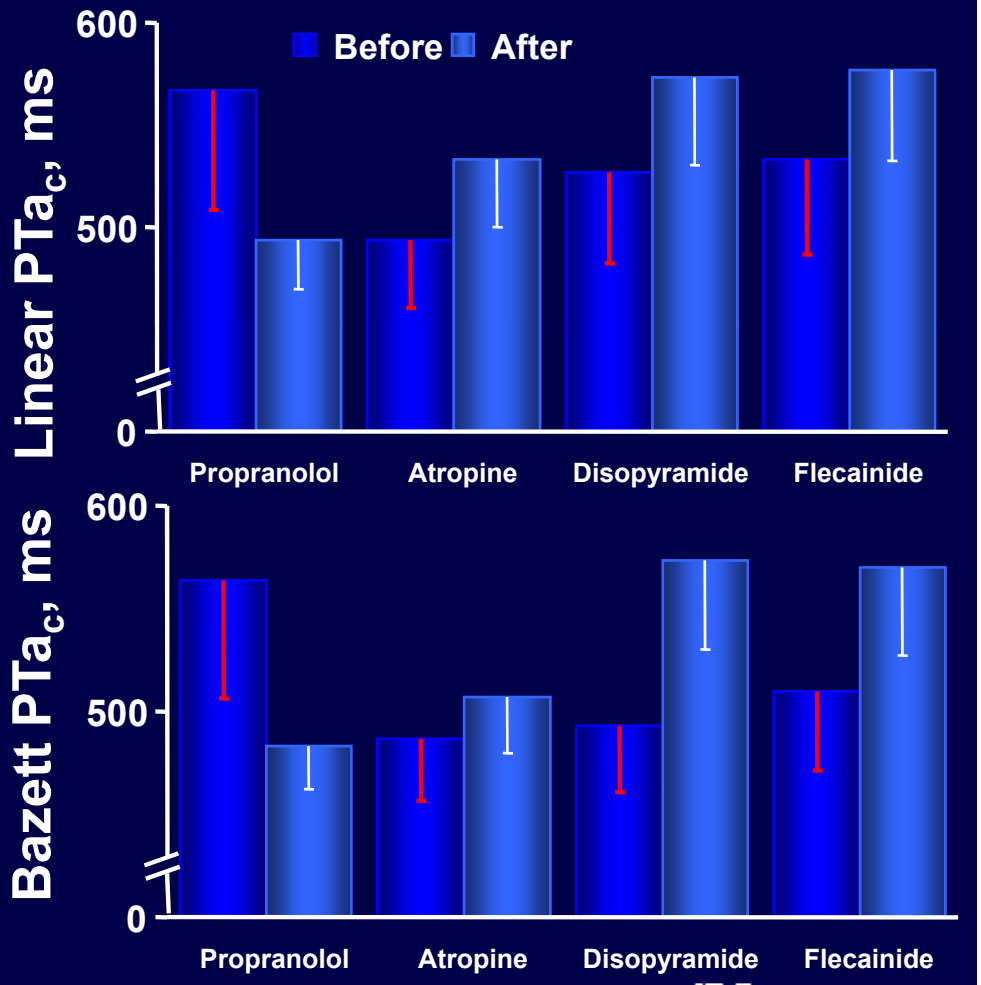
Assessment of the Effects of Class I Drugs on QT and JT Intervals During Sinus Rhythm and Atrial Pacing



Camm AJ, et al. EHJ 1984;5:99-107

Assessment of the Effects of Antiarrhytmic Drugs on ECG Under Atrial Pacing Conditions

In the group of 20 patients with atrial pacing electrodes, the effect of pacing the atrium at pacing intervals varying between 863 and 381 ms (rates varying between approximately 70 and 150 bpm) was determined. Each patient was paced at two to nine different rates. The atrium was paced for 3 min at each rate before any recording was made to allow steady state to be reached. The PTa and Ta intervals and the P wave duration were correlated with the paced PP intervals. A linear regression equation was derived to predict the effect of changes in PP intervals on PTa, P and Ta.
Using this formula allowed determination of the intrinsic effect of chronotropic drugs on atrial depolarization and repolarization. It should also permit future investigation of the intrinsic effect of biophysical, pharmacologic, pathologic phenomena on atrial depolarization and repolarization, eliminating their potential effect on atrial rate



Propranolol significantly decreased the PTa interval, whereas atropine had no significant effect on it. Disopyramide and flecainide significantly prolonged the PTa interval

Debbas NMG, et al. JACC 1999';33:358-65

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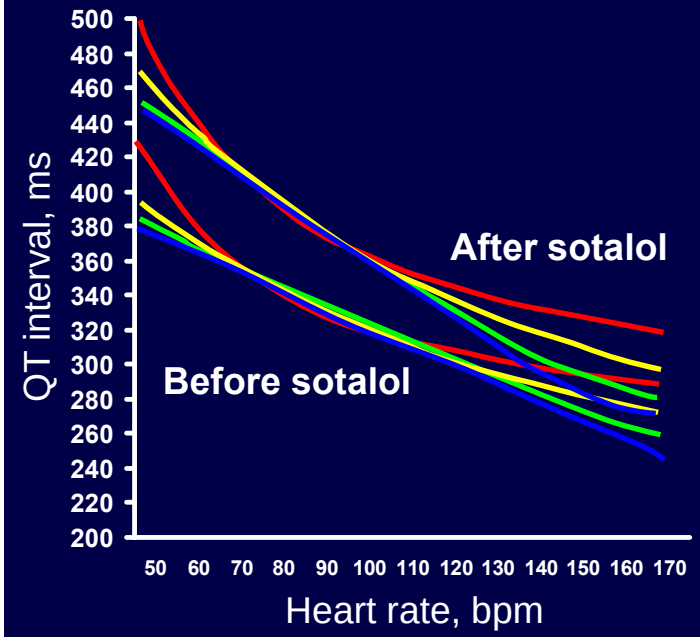
Effects of Rate-Slowing Drugs on the QT/RR Relationship: Assessment Using Atrial Pacing

- 10 healthy volunteers
- RA pacing at 70, 85, 100, 130, 145, 160 bpm
- Duration of pacing 180 s
- Protocol repeated after sotalol 2 mg/kg i.v.



Mean deviation of calculated from the observed QT values with 4 equations tested during atrial pacing before and after sotalol administration

Time point	Equation I	Equation II	Equation III	Equation IV
Before sotalol				
30 s pacing	52.5	62.2	91.8	50.0
60 s pacing	48.5	57.3	85.3	47.1
120 s pacing	46.1	48.2	64.1	48.2
180 s pacing	31.8	30.3	42.6	34.5
After sotalol				
30 s pacing	52.2	56.6	72.3	55.2
60 s pacing	47.7	50.8	65.3	50.6
120 s pacing	63.4	65.8	74.4	65
180 s pacing	45.7	46.8	58.8	47.7
Mean	48.5	52.2	69.3	49.8
Mean difference to Equation I (SEM)	-	3.7 ± 1.5	20.8 ± 4.5	1.3 ± 0.8

Equation I: $QT = a\, e^{-b(HR-60)}$ (Exponential)

Equation II: $QT = e_o e^{\frac{-f\sqrt{60/HR}}{}}$ (modified Bazett)

Equation III: $QT = c\sqrt{60/HR} + d(\sqrt{60/HR})^2$ (Sarma)

Equation IV: $QT = g\,HR + h$ (Kovacs)

Dickhuth HH, et al. PACE 1991;14:793-9

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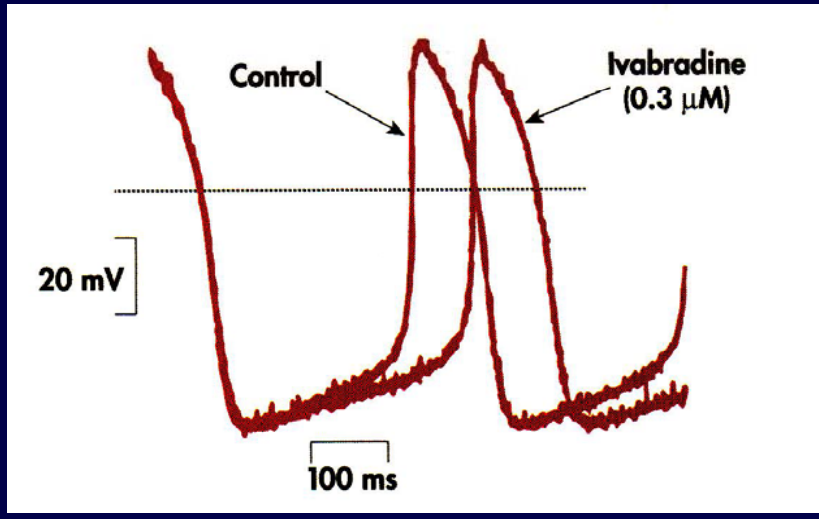
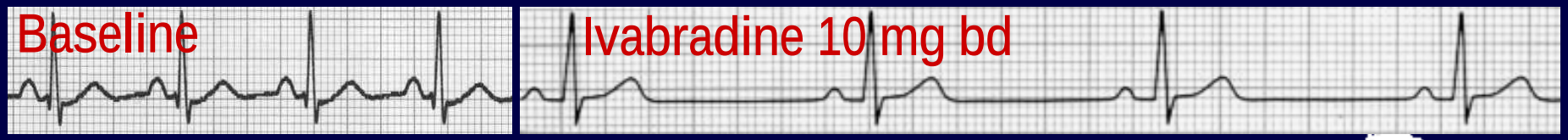
Ivabradine - Mechanism of Action

- Ivabradine is the first pure heart rate lowering agent approved for the symptomatic treatment of stable angina in patients with coronary artery disease. The mechanism of action is selective blockade of the I_f current in sinoatrial cells leading to prolongation of the slow diastolic depolarisation phase of the action potential of the sinus node and as a result, a reduction in the sinus node discharge rate. Ivabradine has no or little direct effect on systemic haemodynamics, blood pressure, and myocardial contractility. Ivabradine has no or little effect on repolarisation currents and theoretically should not prolong the duration of cardiac repolarisation

AP of an isolated SA cell





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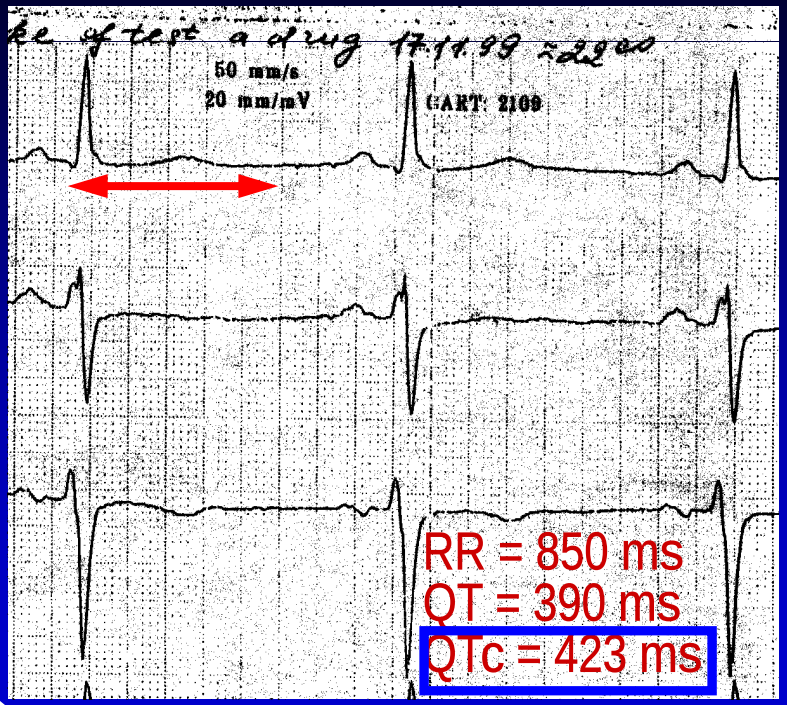
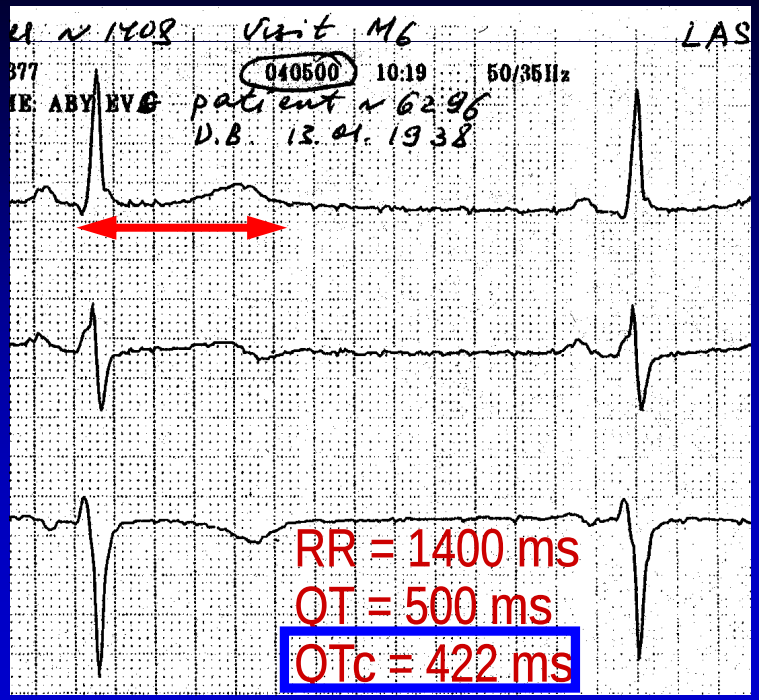
Ivabradine – Potential Concern

- Bradycardia and relative QT prolongation
- No changes in the QTc (Bazzett) interval

Baseline



Ivabradine 10 mg bd



NESI

Non-invasive Electrophysiological Study of Ivabradine (NESI)

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Rationale

- The facility of non-invasive programmed stimulation (NIPS) incorporated in many modern pacemakers and defibrillators can provide limited information on cardiac electrophysiology. The NIPS feature allows atrial and ventricular effective refractory periods to be measured, and the sinus node recovery time, and measures of atrioventricular conduction to be assessed

Study Design

- Prospective, randomised, double-blind, parallel group, single-centre study
- Group 1: Ivabradine 5 mg b.i.d
- Group 2: Ivabradine 10 mg b.i.d.
- Group 3: Placebo
- Duration of treatment 3½ days
- Non-invasive EP study & digital 12-lead Holter at baseline and at the end of treatment period

Patients with complete heart block, baseline QTc (Bazett) interval > 450 ms (men) and > 470 ms (women); history of sustained supraventricular and ventricular tachyarrhythmias, drug-induced proarrhythmias, concurrent administration of QT prolonging drugs including class I and III antiarrhythmic drugs and amiodarone, and AV node blocking agents (digoxin, nondihydropyridine calcium antagonists), and electrolyte disturbances were excluded. All patients gave informed consent and did not participate in another study within 3 months prior to inclusion

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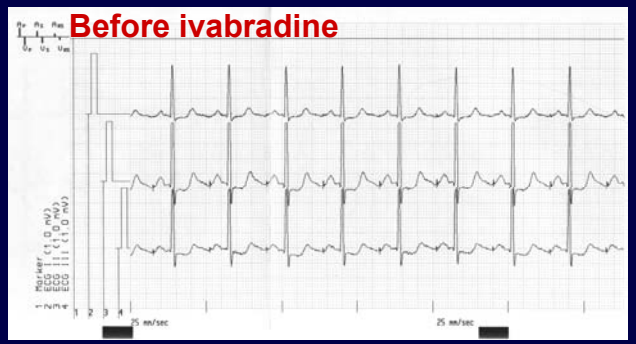
Patient Characteristics

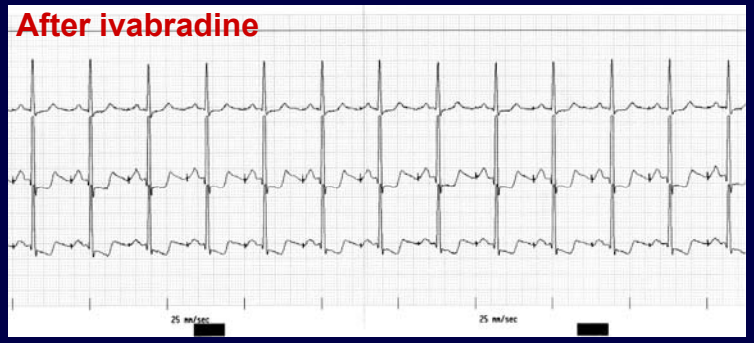
Dual chamber pacemakers with NIPS	
Total	25
Age, years	63 ± 10
M/F	16/9 (36%)
Sick sinus syndrome	14 (56%)
1º-2º AV block	11 (44%)
Including IV block	5 (45%)

Pacing Protocol

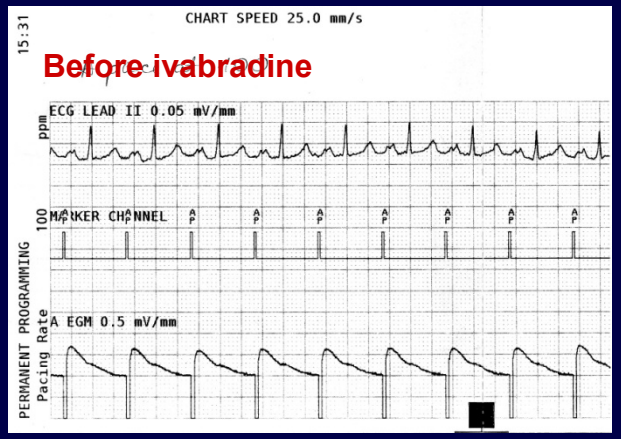
For the purpose of atrial pacing at four fixed rates, the pacemaker was programmed to AAI mode. Atrial pacing at ascending rates of 80, 90, 100, and 110 bpm was performed at baseline and at the end of a 3½ days' treatment period at the trough of drug activity. Pacing at each rate continued for four minutes which allowed the stability of AV conduction to be visually ensured and any hysteresis of the QT interval to have occurred. Approximately 30 seconds were allowed between the pacing steps in order to program the pacemaker to pace at the appropriate rate

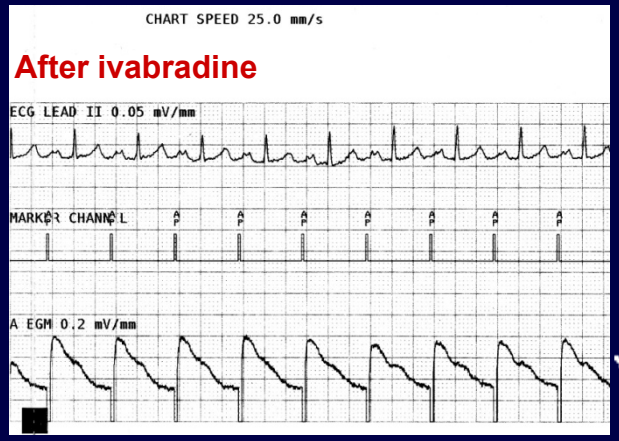
Example 1
Atrial pacing at 80 bpm





Example 2
Atrial pacing at 100 bpm





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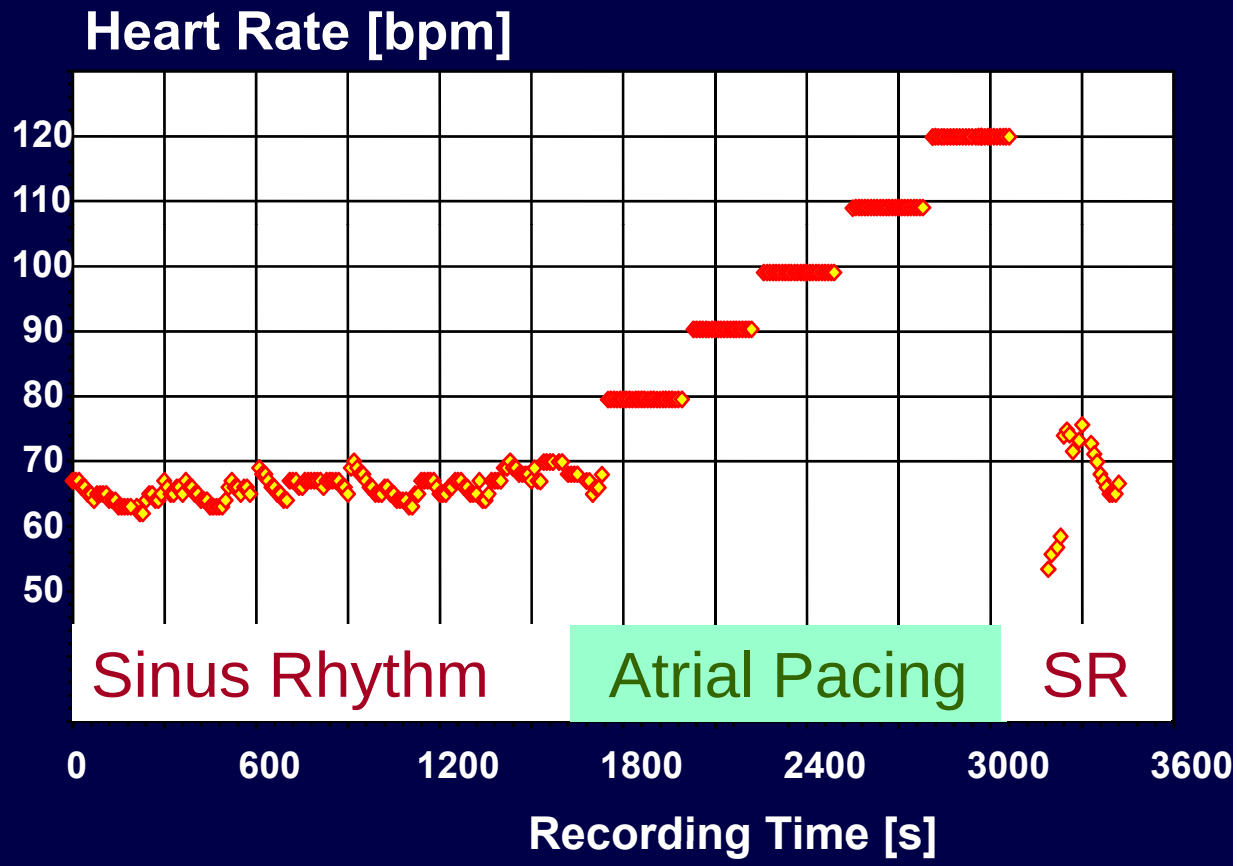
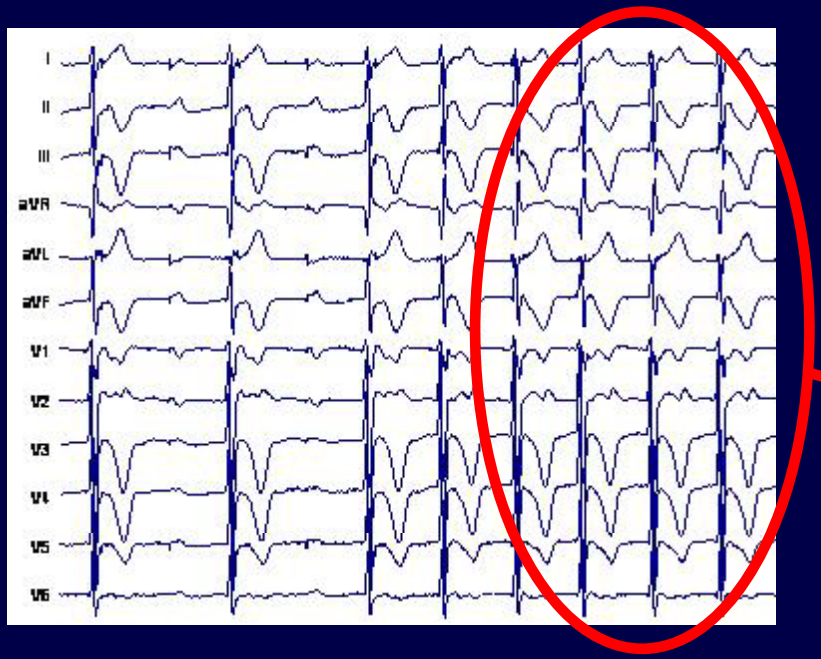
Data Acquisition

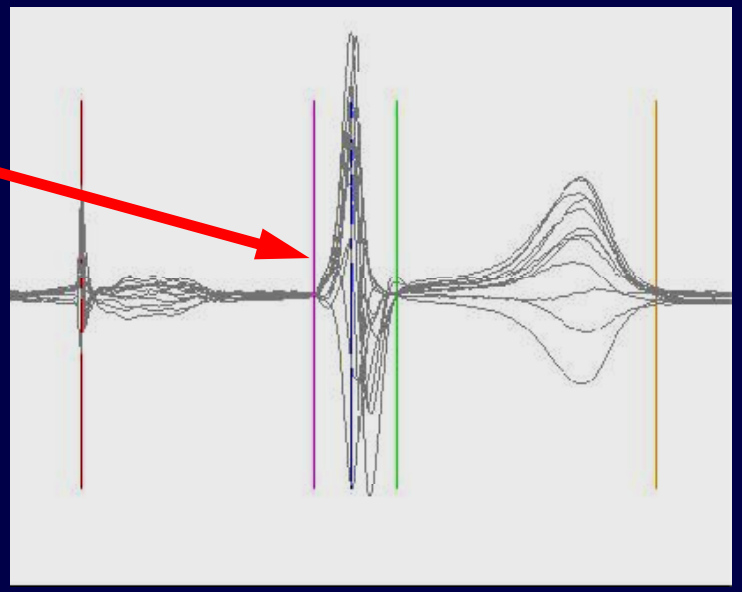
A continuous 12-lead high resolution (250 Hz) digital Holter ECG recording (SEER MC recorders, GE Medical Systems, Milwaukee, Wisconsin, USA) was used for QT analysis. The recorders were programmed to acquire individual 10-second ECGs every 10 seconds. Thus effectively, the signal obtained from the recorders was continuous since no ECG samples were lost between adjacent 10-second elementary ECG recordings. For each session, the heart rate sequence was plotted and provided that effective pacing and AV conduction was uninterrupted the QT interval was measured in the last 3 ECGs at each pacing rate. Episodes where stable 1:1 AV conduction failed to maintain were excluded from the analysis as were episodes where the detection of the T wave was impossible because of the superimposition of the atrial spike



Data Processing



Median beat



In each of the selected ECGs, the images of individual cardiac cycles were identified and the so-called median beat was created for each lead. The averaged images of individual leads were superimposed on a computer screen matching their baseline. Subsequently, using manual positioning of vertical trigger points, the following points were identified in each superimposed image: atrial pacing spike, onset of the QRS complex, peak of the R wave, offset of the QRS complex, and offset of the T wave

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Results: Absolute QT Values, ms

Atrial pacing, bpm	Study	Ivabradine	Placebo
80	Baseline	373 ± 26	366 ± 26
	Drug	372 ± 22	362 ± 21
90	Baseline	357 ± 23	341 ± 23
	Drug	356 ± 24	339 ± 20
100	Baseline	342 ± 24	324 ± 22
	Drug	342 ± 24	326 ± 20
110	Baseline	327 ± 24	315 ± 18
	Drug	330 ± 17	320 ± 21

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Conclusions

- The study demonstrated the feasibility of using NIPS incorporated in implantable devices as a method for assessing cardiac electrophysiologic effects of oral agents
- Direct comparisons of the QT interval when the influence of heart rate was controlled by atrial pacing at a series of identical rates before and after drug administration showed that ivabradine had no direct effect on the QT interval
- These findings suggest that the torsadogenic potential of ivabradine is probably low, and other than for QT prolongation directly consequent on bradycardia, ivabradine does not appear to have any direct proarrhythmic effect

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Assessment of QT During Atrial Pacing: Need for Discussion

- Selected patient population (e.g., implanted with DDD pacemakers, preserved native AV conduction, relatively low percetage of ventricular pacing in order to avoid the effect of “cardiac memory” on the native T wave, baseline heart rates < 60 bpm to allow for a wide range of pacing rates)
- After the administration of a drug with a potential heart rate slowing effect, it is necessary to overpace the atria by a proportionately greater increment in order to achieve the same paced rate for comparison
- Technical issue to discuss (what pacing rate range should be, what minimum duration of pacing at each rate should be)

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