QT prolongation

A clinician's perspective

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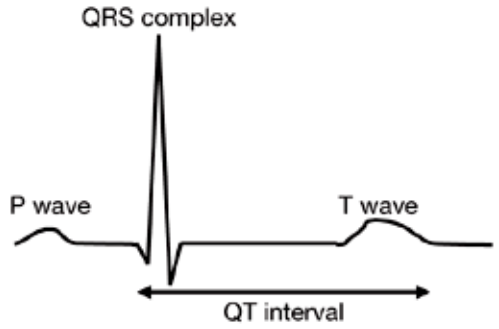
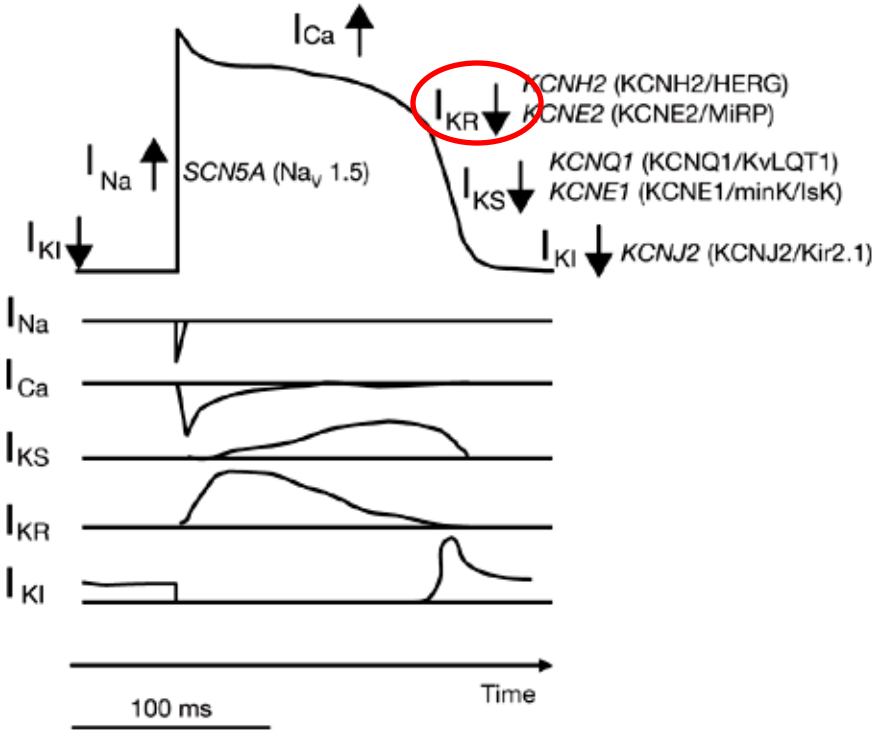
Electrophysiology of cardiac repolarization



Electrocardiogram (ECG)



Cardiac action potential and

(Names of genes implicated in long-QT syndrome are shown in brackets)

Different currents contributing to cardiac action potential.

Jentsch T, et al. *Nature Cell Biology* 2004;**6:**1039-1047

Possible mechanisms of APD / QT interval prolongation

- Delayed inactivation of inward sodium current
- Delayed inactivation of inward calcium current
- Increased activity of calcium channel (L-type Ca^{++} channel)
- Inhibition of slow activating K^+ channel (I_{Ks})
- Inhibition of rapid activating K^+ channel (I_{Kr})

- Mutations in ion channels resulting in one of these effects implicated in congenital LQTS
- >100 mutations in 10 genes are linked to LQTS – in some families – “private mutations”
- LQT1 = I_{Ks} channel; LQT2 = I_{Kr} channel; LQT3 = I_{Na} channel
- Variable penetrance – may have mutation but no clinical features or arrhythmia risk

Table 1. Common Forms of the Long-QT Syndrome.*

Variable	Genetic Subtype		
	LQT1	LQT2	LQT3
Disease-associated gene	*KCNQ1*	*KCNH2*	*SCN5A*
In vitro effect	Decreased I_{Ks}	Decreased I_{Kr}	Increased plateau I_{Na}
Setting of arrhythmia†	Emotional or physical stress, swimming, diving	Emotional or physical stress, sudden loud noise	Rest, sleep
Typical resting ECG‡	Broad T wave	Low-amplitude T wave with notching	Long isoelectric ST segment
ECG at onset of arrhythmia§	No pause	Pause	Not established
QT change with exercise	Failure to shorten	Normal	Supranormal
QT shortening with mexiletine¶	No	No	Yes
Clinical response to beta-blockers‖	Yes	Less than LQT1 response	Uncertain

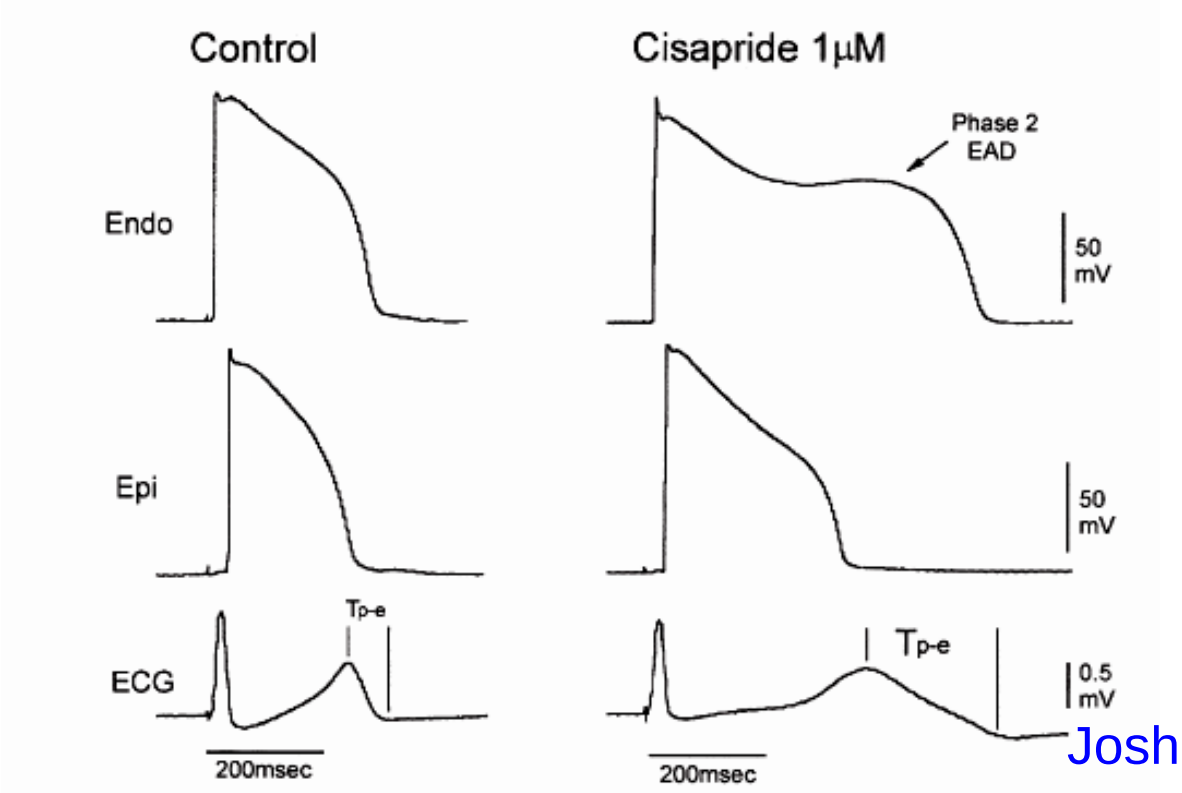
Table 2. Guidelines for Management of the Long-QT Syndrome.*

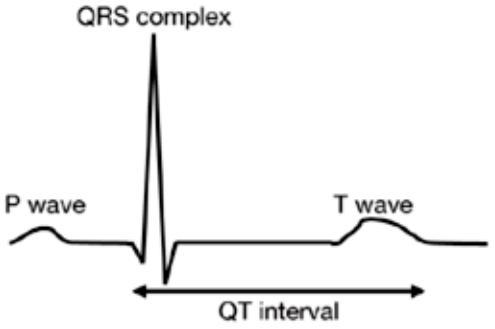
Recommendation	Level of Evidence†	Comment
No participation in competitive sports	I	Includes patients with the diagnosis established by means of genetic testing only
Beta-blockers	I	For patients who have QTc-interval prolongation (>460 msec in women and >440 msec in men)
	IIa	For patients with a normal QTc interval
Implantable cardioverter–defibrillator	I	For survivors of cardiac arrest
	IIa	For patients with syncope while receiving beta-blockers
	IIb	For primary prevention in patients with characteristics that suggest high risk; these include LQT2, LQT3, and QTc interval >500 msec‡

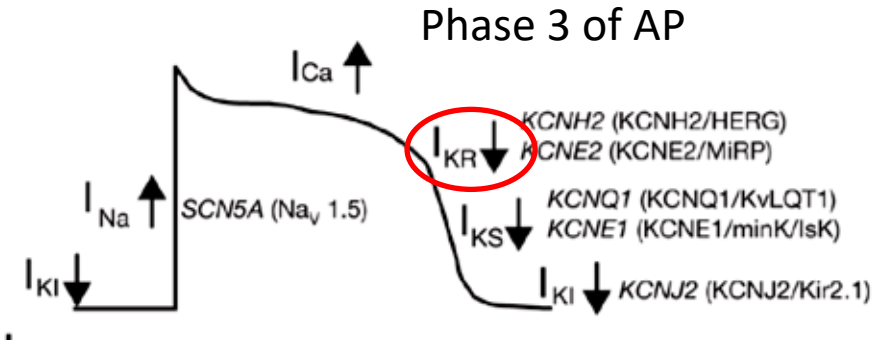
Roden DM. Long QT Syndtrome. N Engl J Med 2008;358:168-176

Drug-induced QT prolongation

- 500-1000 times more common than congenital LQTS
- Most drugs block rapidly activating delayed rectifier K channel (I_{Kr})
- Negative or Reverse use-dependency – bradycardia = longer QTc
- Transmural dispersion of repolarization
- Prolong duration of action potential (QT interval)

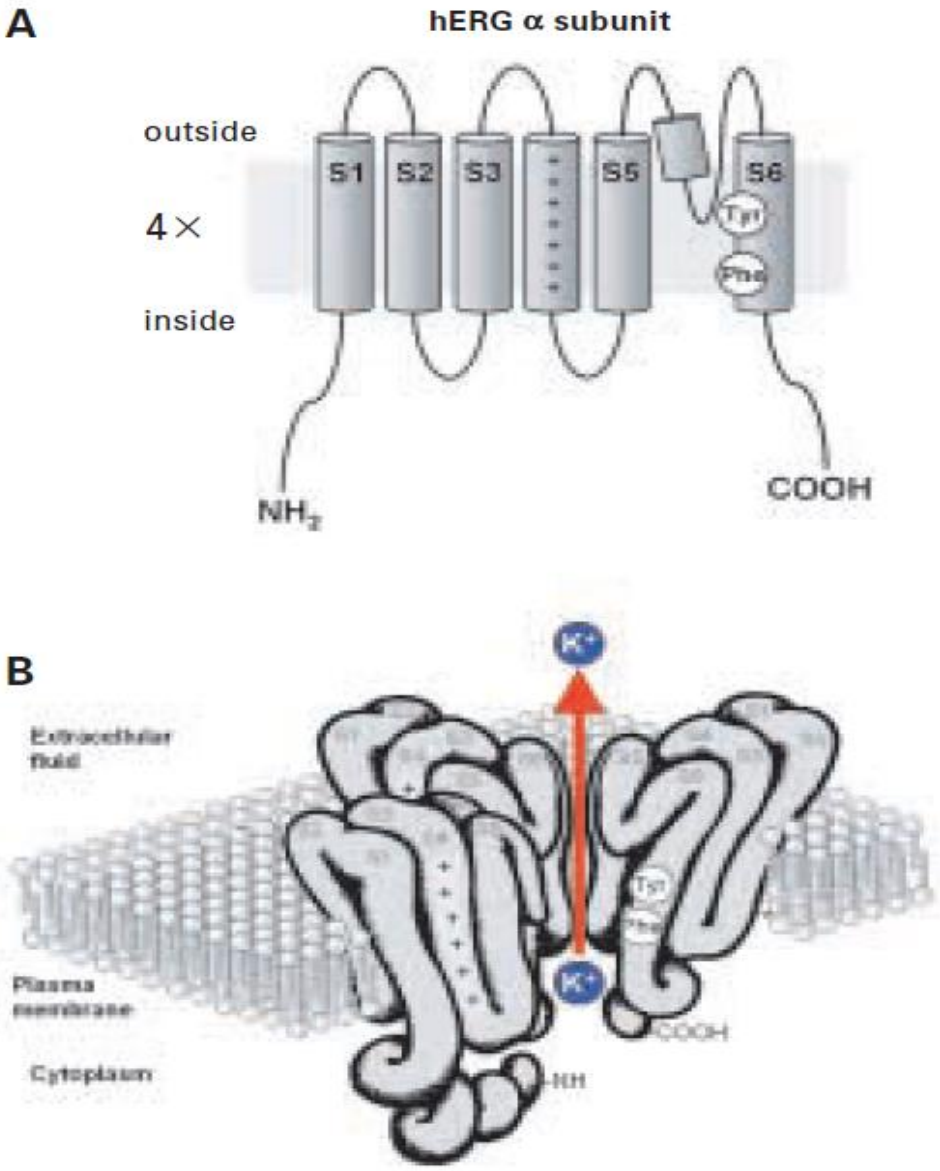






Joshi A et al. J Electrophysiol 2004;37 (Suppl):7-14

Structure of the Myocardial I_{Kr} channel

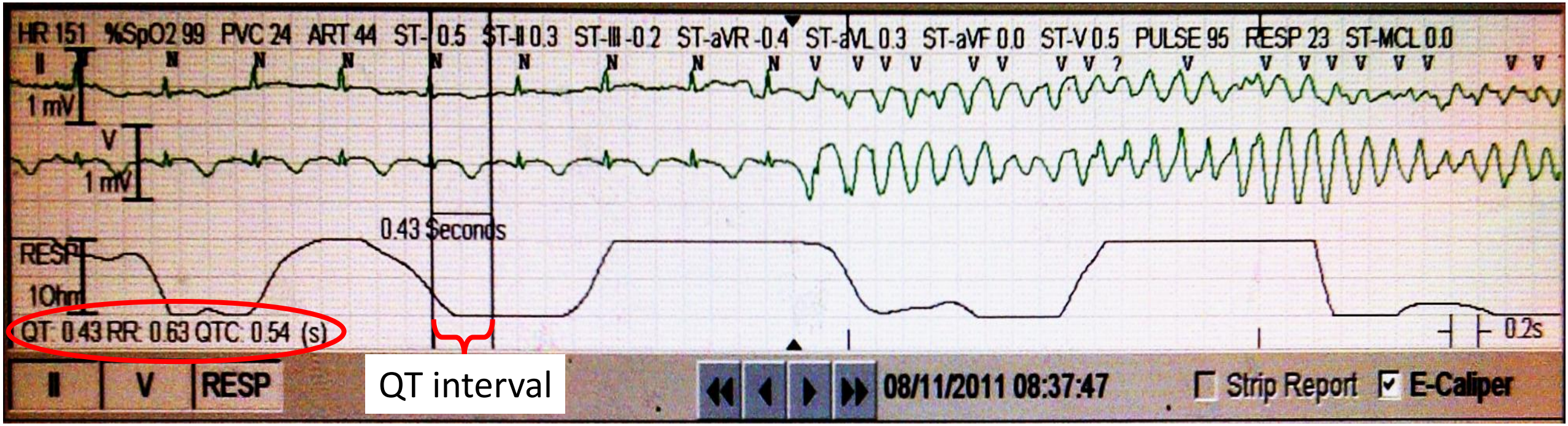


- Most drugs QT prolonging drugs block I_{Kr} channel
- Funnel-shaped channel
- Wide mouth on intra-cellular aspect
- Easily blocked by drugs
- Drug must enter cell first
- Can it be blocked from outside?
  - ? monoclonal antibodies
  - ? Large protein compounds
    - e.g. Scorpion venom

QT prolongation leads to Torsades de Pointes

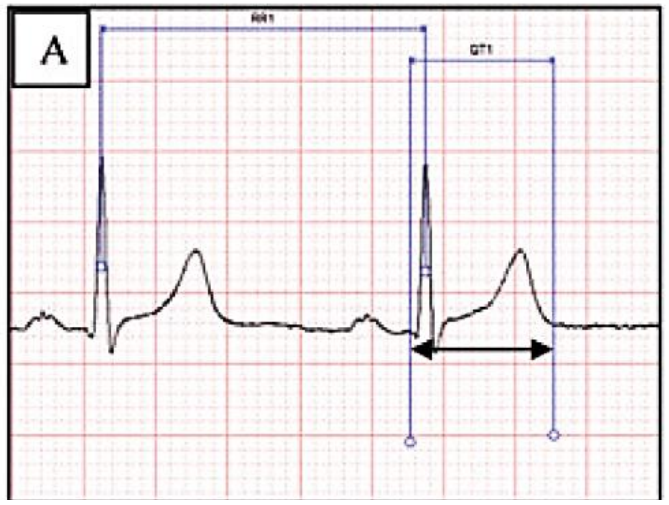
- QT prolongation followed by Early After-Depolarization (EAD)
- EAD predisposes to triggered activity - VPC
- VPC followed by long compensatory pause
- Beat after long cycle has more prolonged QT interval and exaggerated U wave
- VPC coincidentally falling on U wave triggers TdP

Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart 2003;***89**:1363–1372.



How to measure QT interval manually?

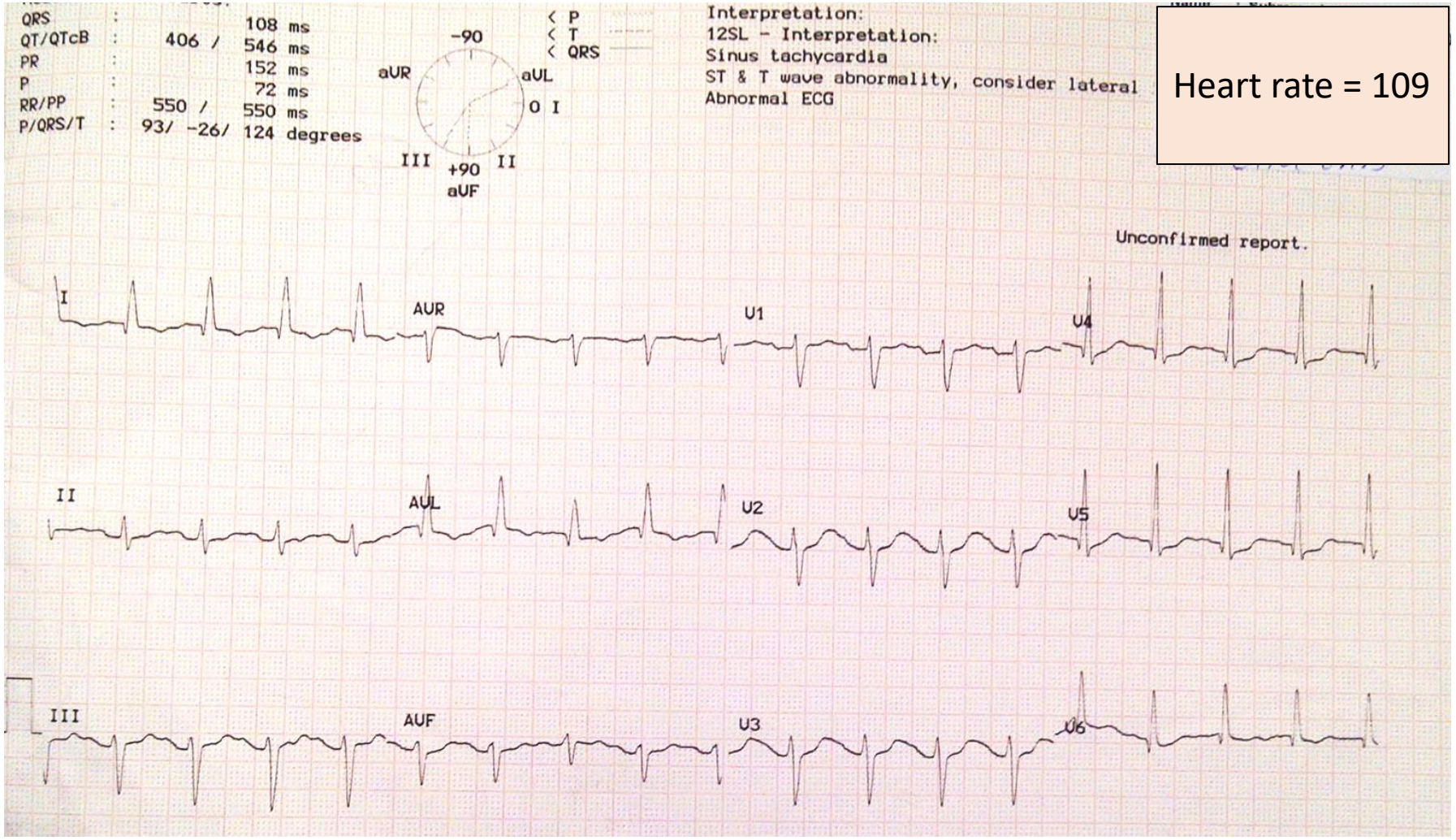
Threshold method



Tangent method

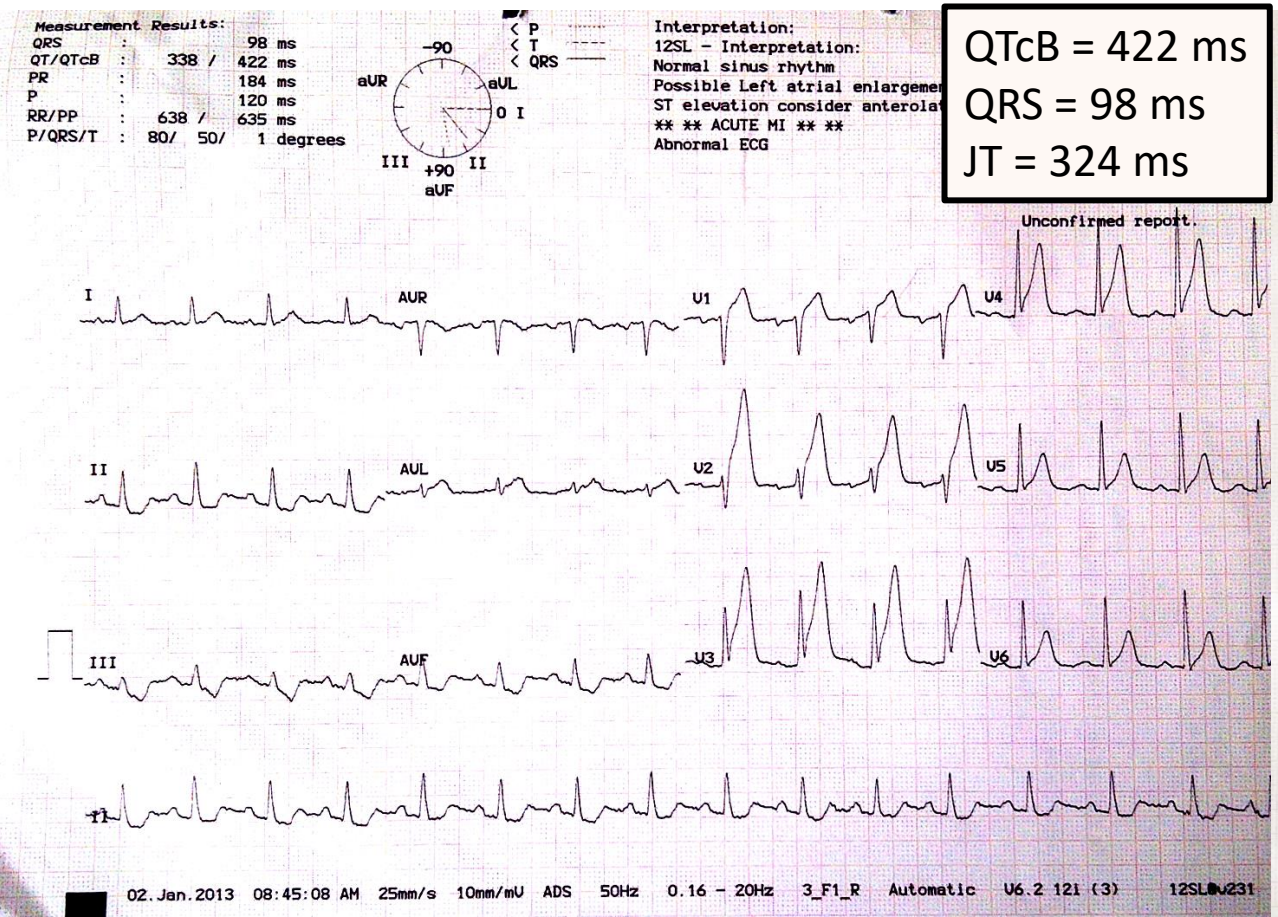
Tangent method useful when end of T obscured by other waves:

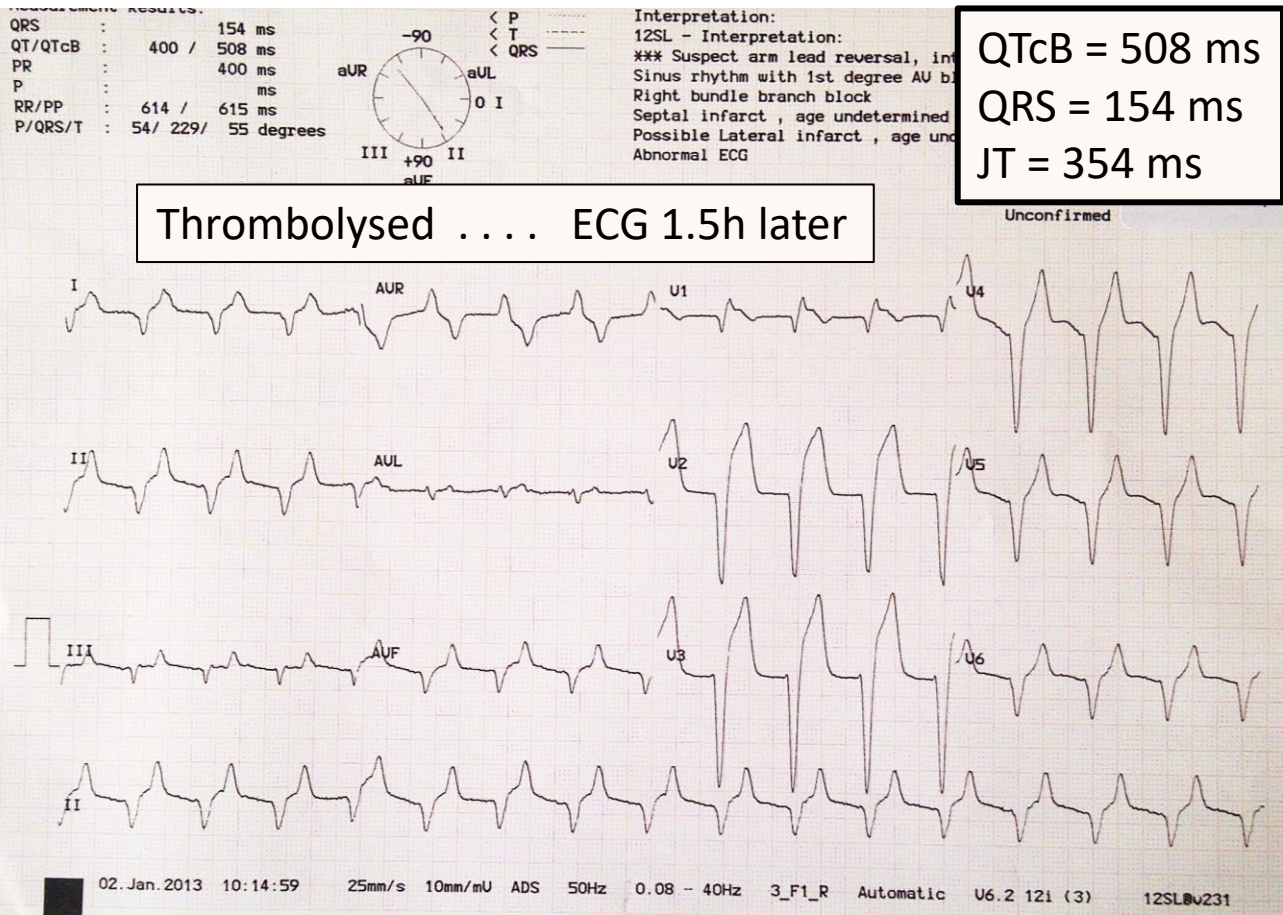
- Prominent U wave
- P wave if HR is fast



Causes of QT prolongation

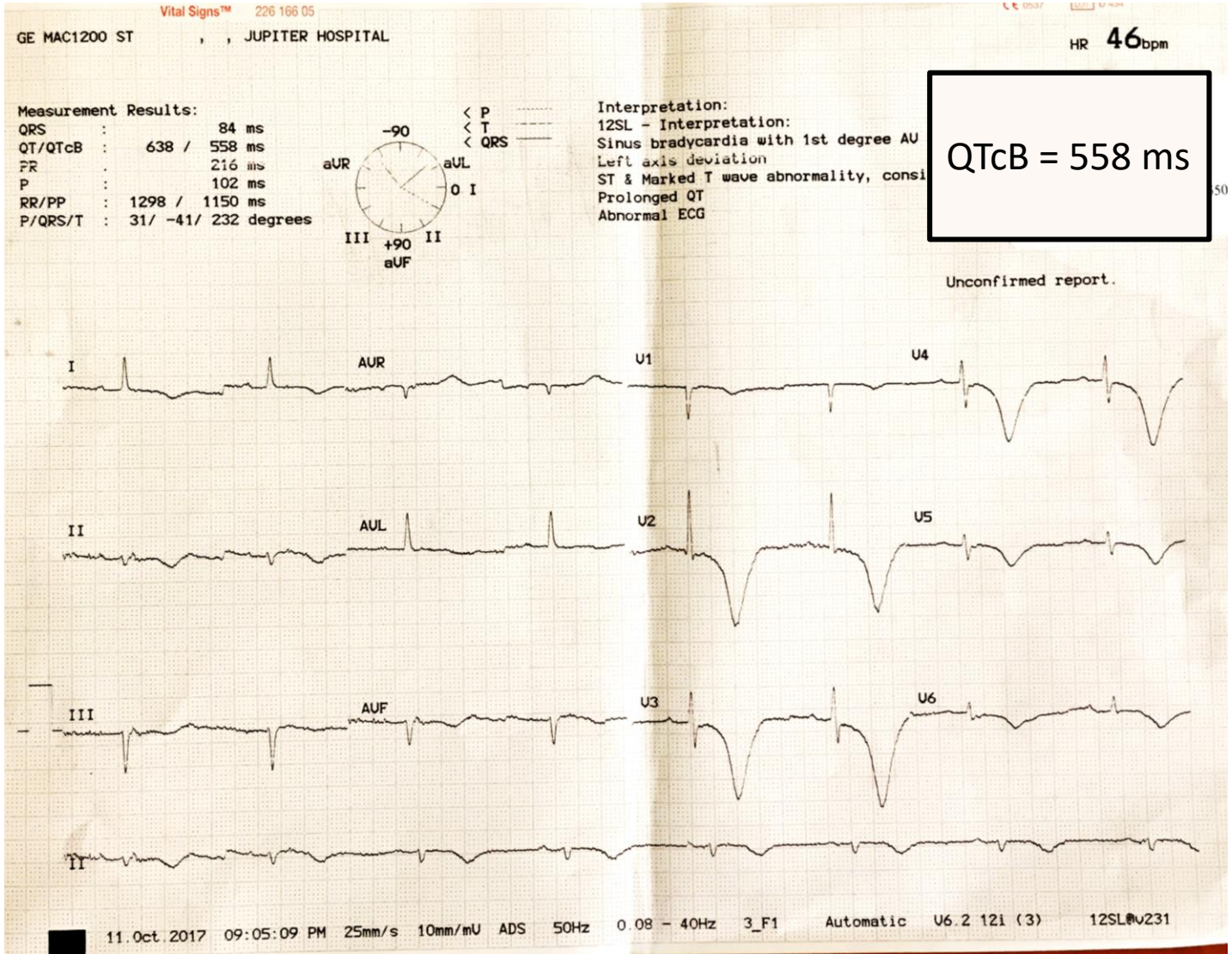
- Pseudo-prolongation – when QRS widens - Bundle branch blocks, IVCD
- End of QRS to end of T (also called JT interval) is not prolonged





Causes of QT prolongation

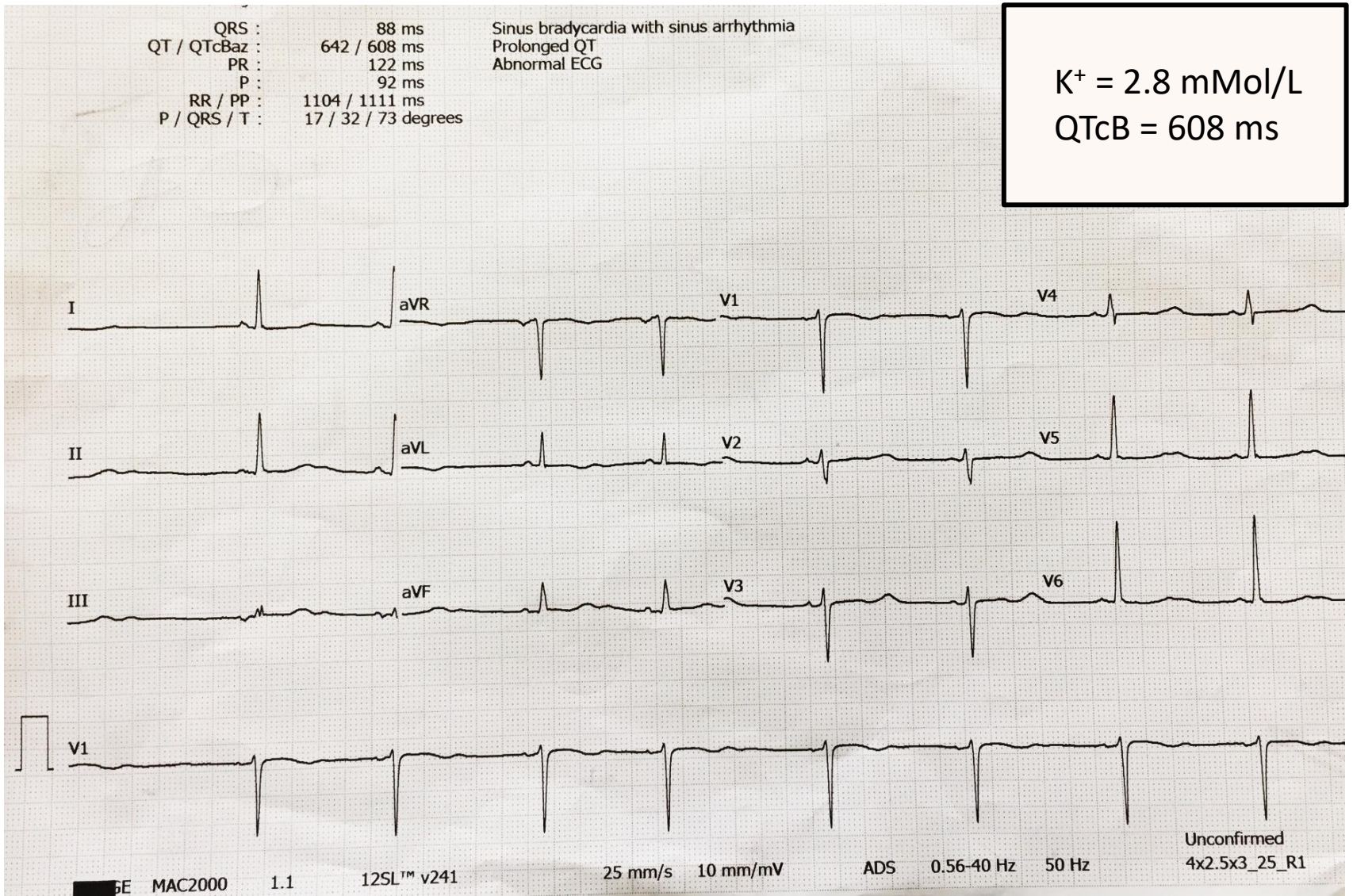
Heart Disease - Acute coronary syndrome, Myocarditis



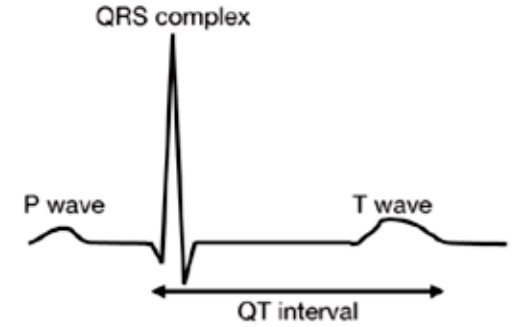
Causes of QT prolongation

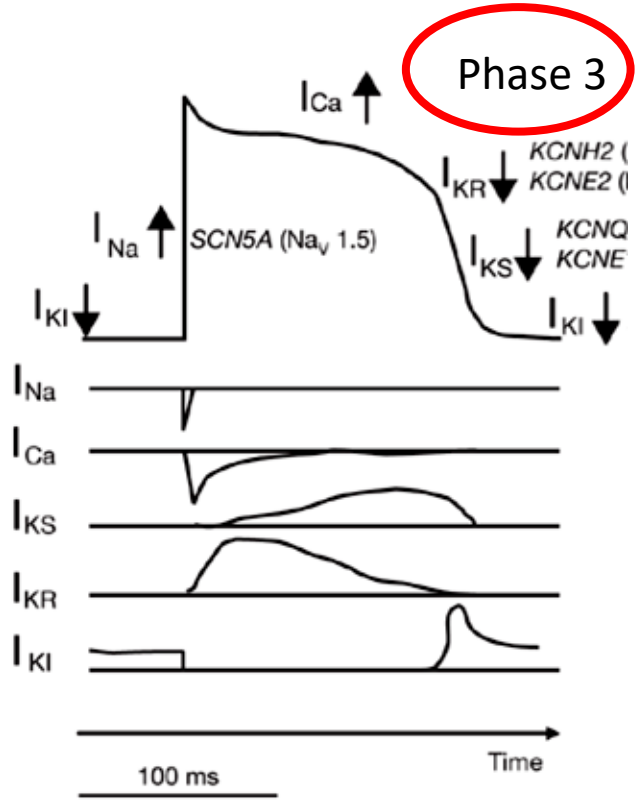
Metabolic causes

Hypokalemia – Long QT, Flat T, U waves



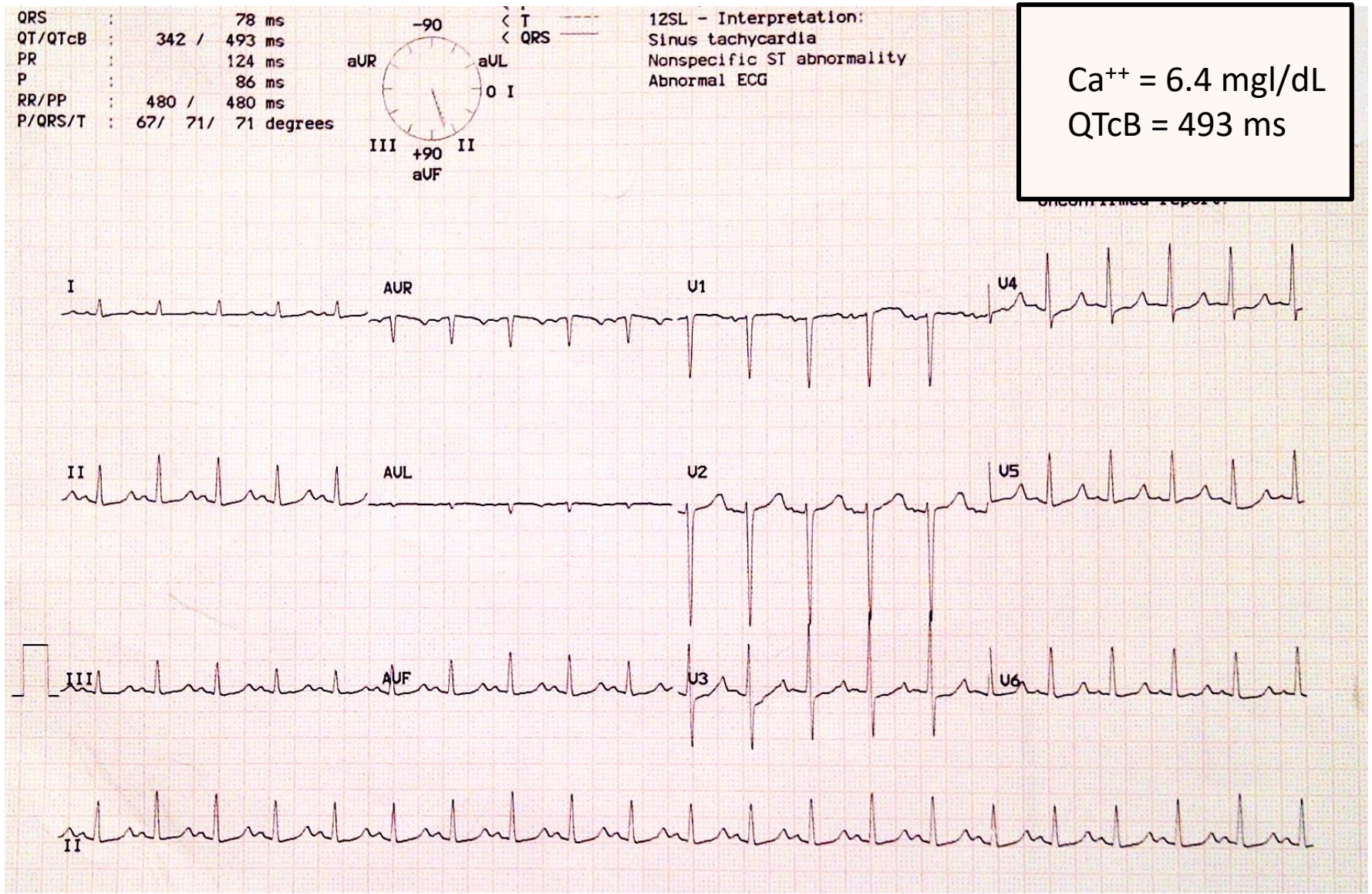
K^+ = 2.8 mMol/L
QTcB = 608 ms



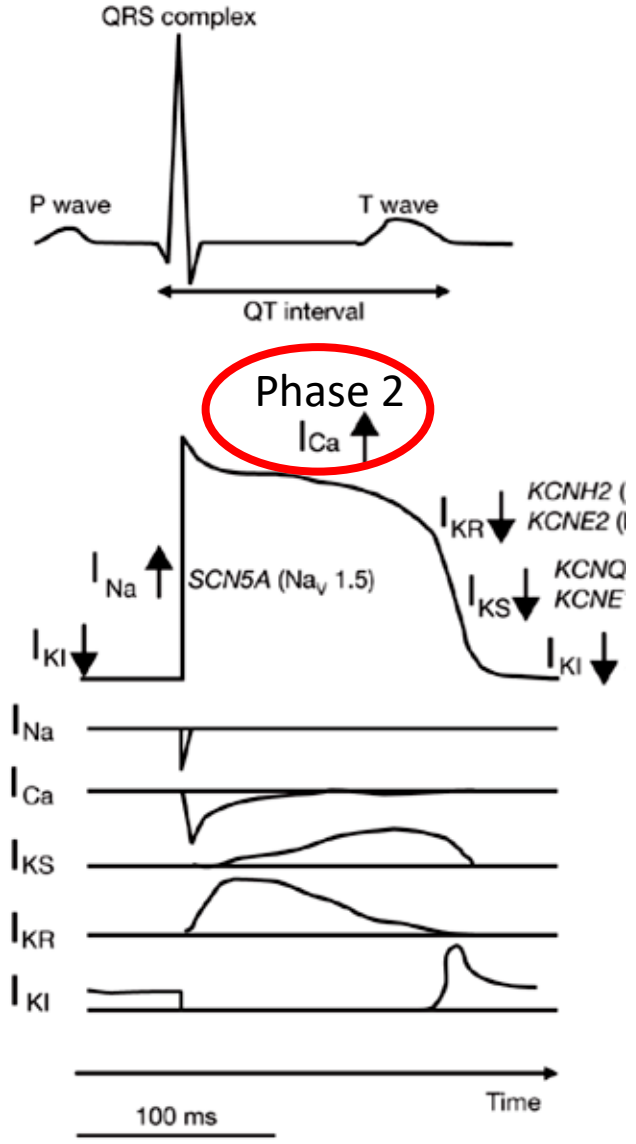


Causes of QT prolongation

Metabolic causes <u>Hypocalcemia</u> – Long ST segment, Narrow T waves

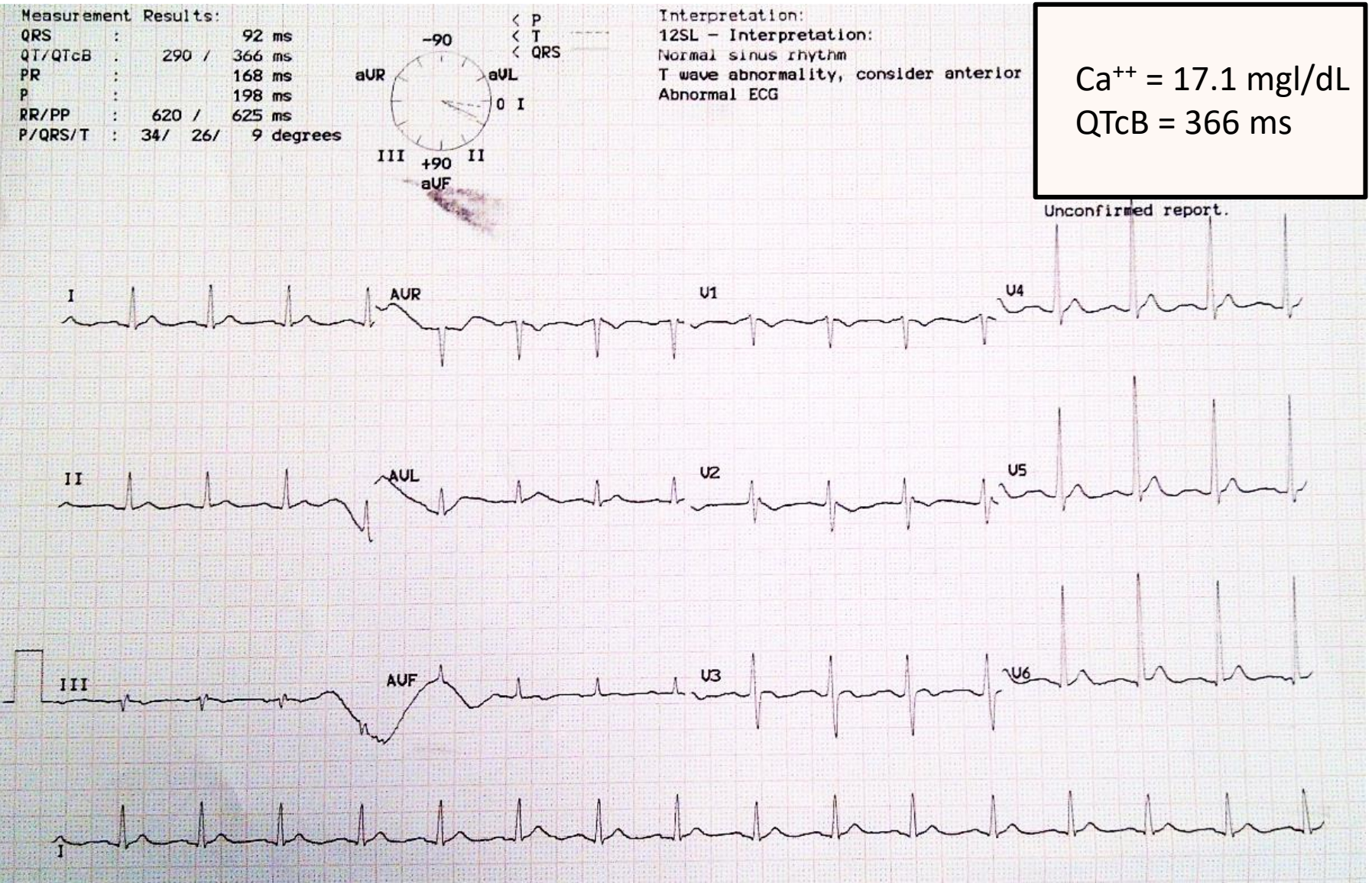


Ca^{++} = 6.4 mgl/dL
QTcB = 493 ms

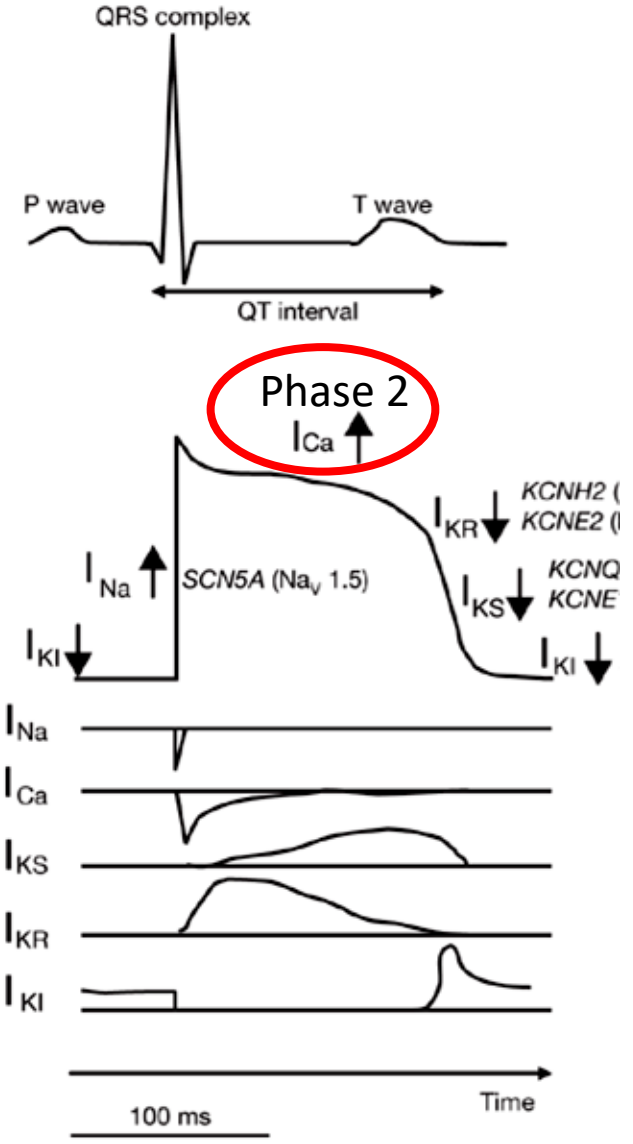


Causes of QT shortening

Metabolic causes Hypercalcemia – Very short ST segment, Narrow T waves



Ca^{++} = 17.1 mgl/dL
QTcB = 366 ms



Causes of QT prolongation

Drugs & Toxins - Mechanisms

IKr ion channel blockade	Most drugs that prolong QT interval Anti-emetics, antibiotics, antipsychotics, GI prokinetic drugs
Ion channel trafficking	Arsenic trioxide Pentamidine Geldanamycin Potassium antimony tartrate Probucol Fluoxetine

Table 1 Non-class III drugs reported to cause QT interval prolongation and/or torsade de pointes.

Non-class III cardiovascular drugs		*Non-cardiovascular drugs*		
Sodium channel blockers	Neuroleptics	Antidepressants	Antimicrobials	Anticancer drugs
Quinidine	Chlorpromazine	Amitriptyline	Erythromycin	Anthracycline
Disopyramide	Trifluprom azine	Protriptyline	Co-trimoxazole	Aclarubicin
N-acetyl-procainamide	Promazine	Nortriptyline	Sulfamethoxazole	5-fluorouracil
Lorcainide	Perphenazine	Butriptyline	Pentamidine	Acodazole
3-Methoxy-O-desmethyl-encainide (MODE)	Fluphenazine	Desipramine	Amantidine	Adriamycin
Ajmaline	Prochlorperazine	Imipramine	Grepafloxacin	Tamoxifen
	Trifluoperazine	Lofepramine	Levofloxacin	S9788
Antianginals	Triethylperazine	Clomipramine	Moxifloxacin	502U83
Prenylamine	Haloperidol	Doxepin	Sparfloxacin	Arsenic trioxide
Fendiline	Trifluoperidol	Maprotiline	Gatifloxacin	Efavirenz
Lidoflazine	Droperidol	Dothiepin	Clarithromycin	
Bepridil	Penfluridol	Citalopram	Spiramycin	Miscellaneous
Aprindine	Fluspirilene	Zimeldine	Fluconazole	Vincamine
Terodiline	Risperidone	Fluoxetine	D0870	Probucol
Perhexiline	Ziprasidone		Antimoniates	Glibenclamide
Amiodarone	Amisulpride	H_1-Antihistamines		Epoprostenol
Tedisamil	Chlorprothixene	Terfenadine	Serotonin (5-HT_2)-antagonists	Chloral hydrate
Mibefradil	Thiothixene	Astemizole	Ketanserin	Amiloride
	Thioridazine	Diphenhydramine	Amperozide	Bromocriptine
α_1/β blockers	Sertindole	Promethazine	Retanserin	Sevoflurane
Sotalol	Pimozide	Hydroxyzine	Pipamperone	Cisapride
Oxprenolol	Zotepine			Tacrolimus
Nifenalol	Quetiapine	Antimalarials	Serotonin (5-HT_3)-antagonists	Levacetylmethadol
Indoramin	Olanzapine	Halofantrine	Dolasetron	Lubelozole
Melperone		Chloroquine	Zatosetron	Tiapride
Amosulalol		Arteether		Tizanidine
				Rivastigmine
Inotropic agents				Cocaine
Dobutamine				Domperidone
				Bupivacaine

Shah RR. Br J Clin Pharmacol 2002;54:188-202

Clinical significance – Drug-induced TdP

- Only occurs if QT prolonged – usually >500 ms
- Prerequisites
  - Prolonged QT interval
  - VPCs
  - Bradycardia
- Not all drugs that prolong QT interval cause torsades
  - Amiodarone
  - Ranolazine
  - Verapamil
  - Sodium pentobarbital

Who is at risk of drug-induced TdP?

- QTc prolongation>500ms
- Female gender
- Multiple drugs (interactions)
- Electrolyte derangements
  - Hypokalemia
  - Hypomagnesemia
- Heart disease – especially IHD
- Age > 65 years
- Congenital LQTS

  and family members

Medicine. 82(4):282-290, JUL 2003
DOI: 10.1097/01.md.0000085057.63483.9b, PMID: 12861106
Issn Print: 0025-7974
Publication Date: 2003/07/01

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Torsade de Pointes Due to Noncardiac Drugs: Most Patients Have Easily Identifiable Risk Factors

David Zeltser; Dan Justo; Amir Halkin; Vitaly Prokhorov; Karin Heller; Sami Viskin

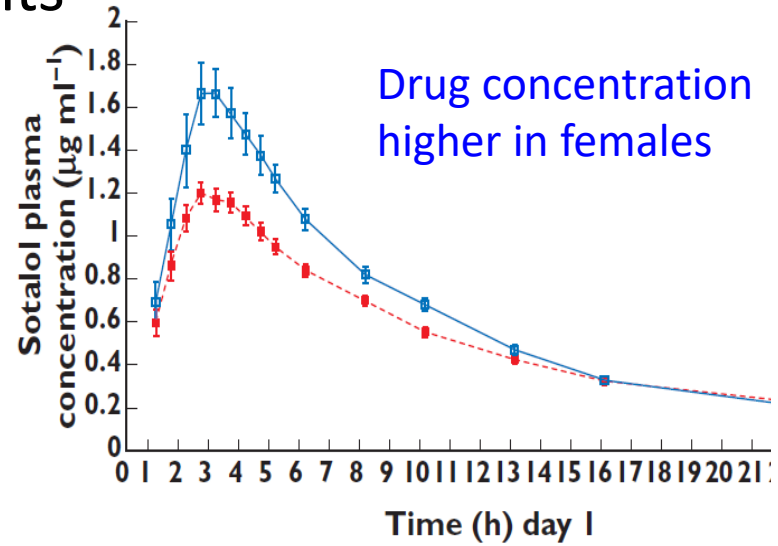
Abstract

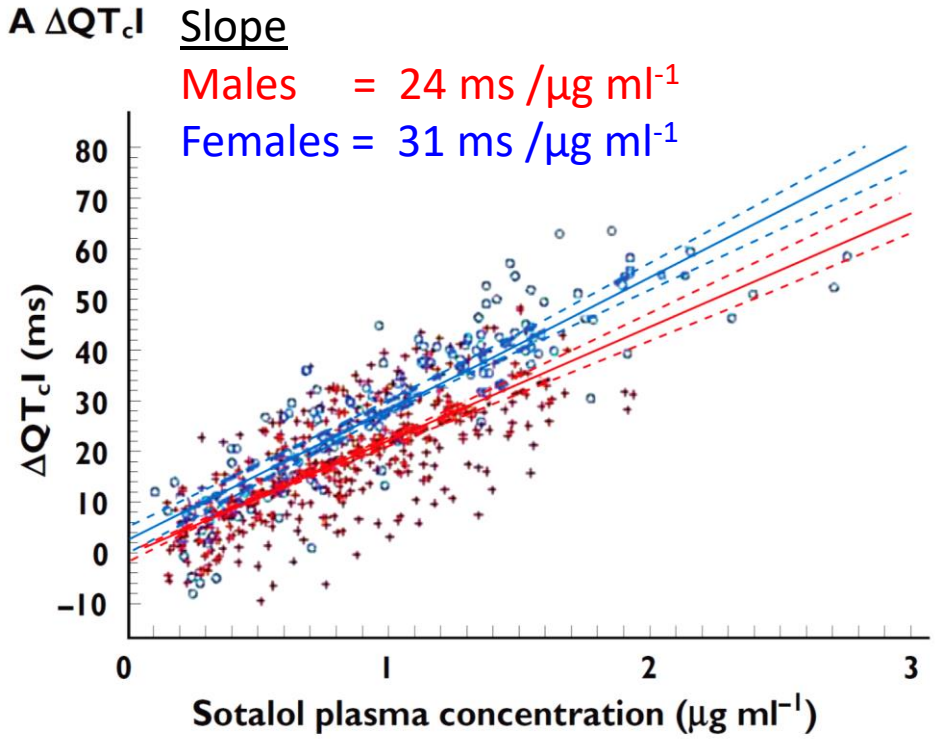
Numerous medications, including drugs prescribed for noncardiac indications, can lead to QT prolongation and trigger torsade de pointes. Although this complication occurs only rarely, it may have lethal consequences. It is therefore important to know if patients with torsade de pointes associated with noncardiac drugs have risk factors that are easy to identify. We reviewed reports of drug-induced torsade de pointes and analyzed each case of torsade de pointes associated with a noncardiac drug for the presence of risk factors for the long QT syndrome that can be easily identified from the medical history or clinical evaluation (female gender, heart disease, electrolyte disturbances, excessive dosing, drug interactions, and history of familial long QT syndrome). We identified 249 patients with torsade de pointes caused by noncardiac drugs. The most commonly identified risk factor was female gender (71%). Other risk factors were frequently present (18%-41%). Virtually all patients had at least 1 of these risk factors, and 71% of patients had 2 or more risk factors. **Our study suggests that almost all patients with torsade de pointes secondary to noncardiac drugs have risk factors that can be easily identified from the medical history before the initiation of therapy with the culprit drug.**

Who is at risk of drug induced TdP?

- Drug-induced QT prolongation
- **Female gender**
- Multiple drugs (interactions)
- Electrolyte derangements
  - Hypokalemia
  - Hypomagnesemia
- Heart disease
- Age > 65 years
- Congenital LQTS and family members

- >70% of TdP cases are in women
- Higher baseline QTc – 20-30ms longer than males





Darpo B, et al. Br J Clinical Pharmacol 2014;77:522-531

Who is at risk of drug-induced TdP?

- Drug-induced QT prolongation
- Female gender
- **Multiple drugs (interactions)**
- Associated metabolic derangements
  - Hypokalemia
  - Hypomagnesemia
- Heart disease – especially IHD
- Age > 65 years
- Congenital LQTS and family members

- Interaction – Ketoconazole (Prolongs QT & inhibits CYP metabolism)+ Astemizole (prolongs QT)
- Halofantrine (Prolongs QT) especially if given after Mefloquine (long half-life) failure
- 2 QT prolonging drugs given together e.g. antipsychotic medications, antibiotics

- 43 years old female
- Breast Ca with brain metastasis
- Vomiting
- Suddenly became unconscious

28.10.2017 21:10:57
JUPITER HOSPITAL

Location:
Order Number:
Visit:
Indication:
Medication 1:
Medication 2:
Medication 3:

Room:

54 bpm
-- / -- mmHg

Technician:
Ordering Ph:
Referring Ph:
Attending Ph:

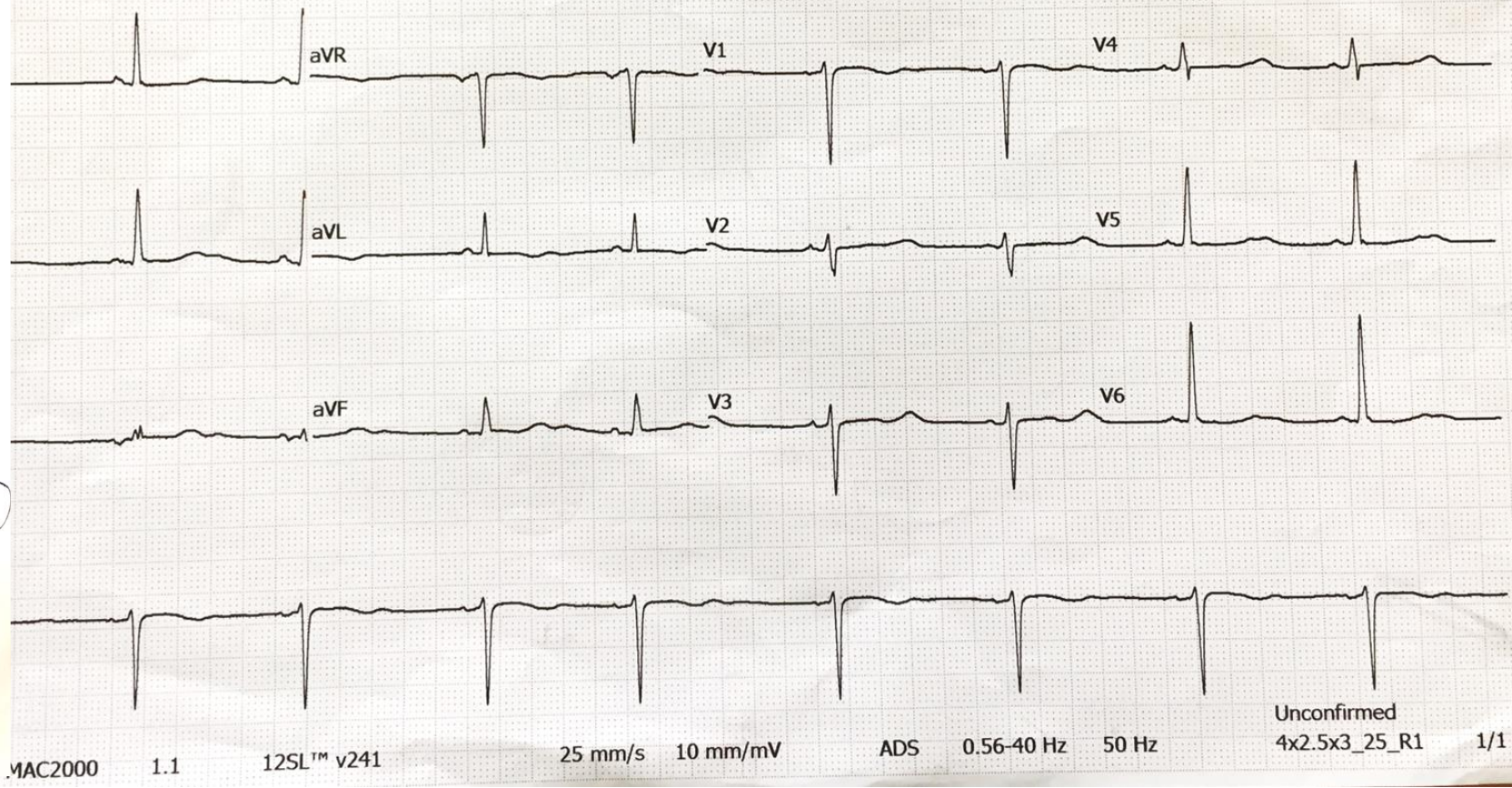
QRS :	88 ms	Sinus bradycardia with sinus arrhythmia
QT / QTcBaz :	642 / 608 ms	Prolonged QT
PR :	122 ms	Abnormal ECG
P :	92 ms	
RR / PP :	1104 / 1111 ms	
P / QRS / T :	17 / 32 / 73 degrees	

K^+ = 2.8 mMol/L

QTcB = 608 ms

Allergies: None. Date: 28/10/17.

Medication	Dose	Route	Freq	Omit	Administration Record
INJ. LEVETIRACETAM	500 mg	IV	1-0-1		8AM prime / 8 P.M
INJ. DEXA	8 mg	IV	1-1-1	(CANCELLED)	11am / 6pm / 12MN
INJ. ESOMAC	40 mg	IV	1-0-1		7AM Pantop / 7P.M.
INJ. EMESET (W/H)	4 mg	IV	1-1-1	omit 5:30 PM stat	6AM Pantop / 10P.M Prime / 6P.M.
INJ. PCM	1 gm	IV	1-1-1		6AM Pantop / 10P.M Prime / 10AM
T. ULTRACET (W/H)		po	sos	omit 5:30pm	10 am Prime (14)
SYP. DUPHALAC	20 ml	po	0-0-1		10pm
INJ. MANNITOL	100 ml	IV	1-1-1		6AM Pantop / 10P.M Prime / 10 P.M.
D2 INJ. MONOCEF	2 gm	IV	1-0-1		10AM Prime / 8AM Prime
STEAM INHALATION			1-0-1		8 P.M. Prime
P. C. ENEMA		PR	Daily OD		12pm Prime
		(TILL	completely B/O).		
W/H INJ. PERINORM (in 10 cc NS)	10 mg	iv	1-1-1		6pm Stat / 12am
STAT ORDERS					
5pm INJ EMESET	4mg	IV	Stat		5pm Prime
~~INJ DEXA~~	~~8mg~~	~~IV~~	Stat 7:15pm		7:15 pm Prime
GRANICET (W/H)	20mg 3mg	IV	Stat 7:15pm		7.15pm Prime



Who is at risk of drug-induced TdP?

- Drug-induced QT prolongation
- Female gender
- Multiple drugs (combinations)
- **Associated metabolic derangements**
  - Hypokalemia
  - Hypomagnesemia
- Heart disease – especially IHD
- Age > 65 years
- Congenital LQTS and family members

- Hypokalemia prolongs QTc
- Hypokalemia
  - Diuretics
  - Vomiting
- Predisposes to ectopy
- Hypomagnesemia
- Magnesium used for treatment of drug-induced TdP

Who is at risk of drug-induced TdP?

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  - Hypomagnesemia
- **Heart disease – especially IHD**
- Age > 65 years
- Congenital LQTS and family members

Heart disease

- Predisposes to ventricular ectopy
- Disease itself may prolong QTc
- Drugs
  - Diuretic use – Hyopkalemia, hypomagnesemia
  - Antiarrhythmic drugs that prolong QTc e.g. sotalol
  - Drugs that cause bradycardia

Who is at risk of drug-induced TdP?

- Drug-induced QT prolongation
- Female gender
- Multiple drugs (combinations)
- Associated metabolic derangements
  - Hypokalemia
  - Hypomagnesemia
- Heart disease – especially IHD
- **Age > 65 years**
- Congenital LQTS and family members

- Comorbidities – heart, renal, hepatic
- Altered drug pharmacokinetics – drug concentration may be higher than desired
- Risk of arrhythmias
- Multiple drugs

Who is at risk of drug-induced TdP?

- Drug-induced QT prolongation
- Female gender
- Multiple drugs (combinations)
- Associated metabolic derangements
  - Hypokalemia
  - Hypomagnesemia
- Ischemia
- Age > 65 years
- **Congenital LQTS and family members**

- Previously unrecognized long-QT syndrome can be identified in 5 to 20% of patients with drug-induced TdP
- Family history of
  - Sudden death
  - Drowning
  - Sudden infant death syndrome
  - Death while driving

Roden DM. Long QT syndrome. N Engl J Med 2008;358:169-76.

Conclusions

- QT prolongation common in clinical practice
- QTc prolongation in 20-30% of ICU patients
- Most patients at risk of TdP can be identified before hand
  - Age, females, electrolyte disturbance, heart disease, family history of LQTS
- Avoid using drugs that prolong QT interval if alternative is available
- Multiple drugs increase risk of QT prolongation – interaction, synergy
- Monitor QT interval on daily ECG
- Correct electrolyte imbalance
- Avoid bradycardia if QT is prolonged