Rett Syndrome and Long QT

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Topics to cover

What is the QT interval?

What is the QTc (corrected QT interval)?

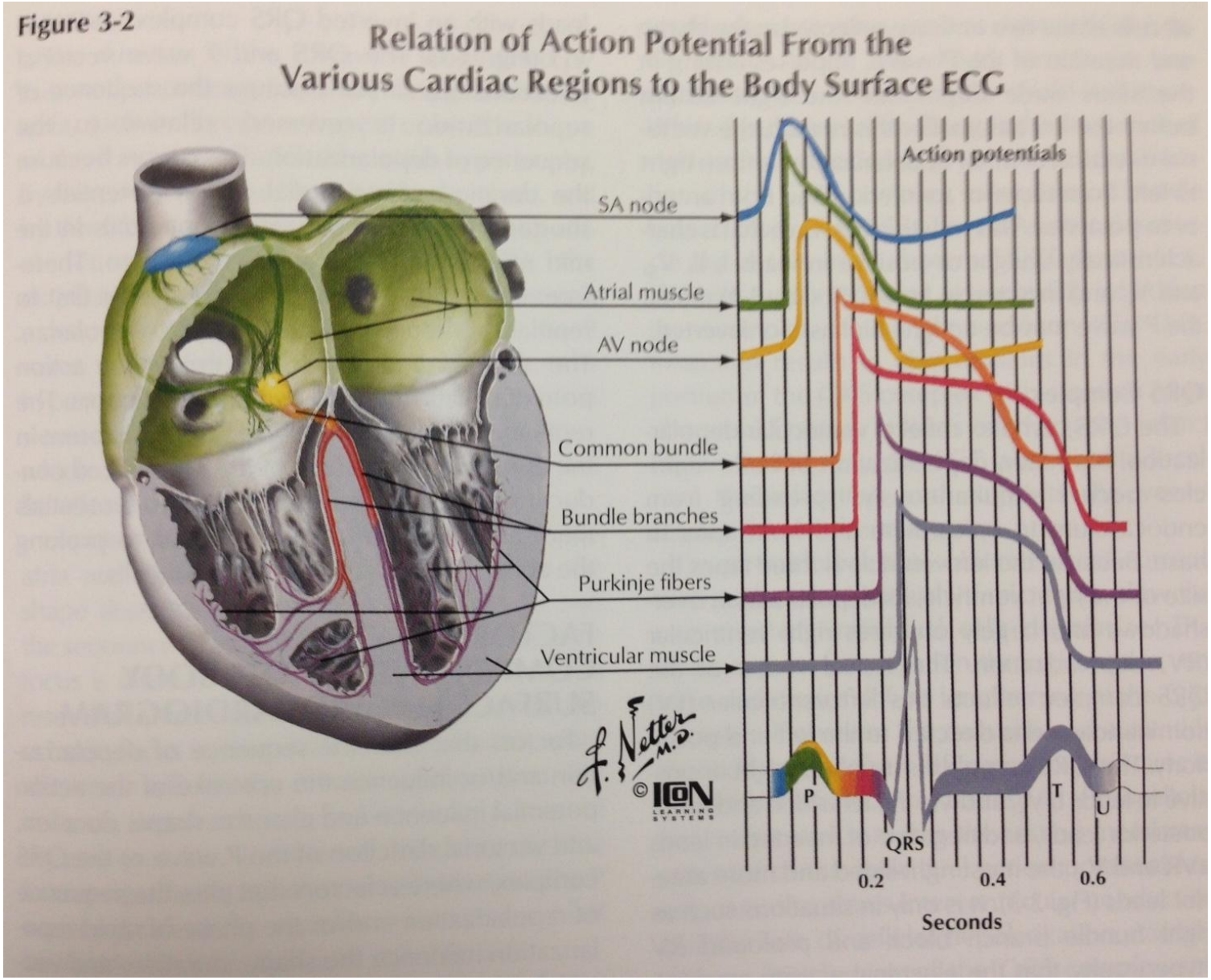
Why does it get prolonged?

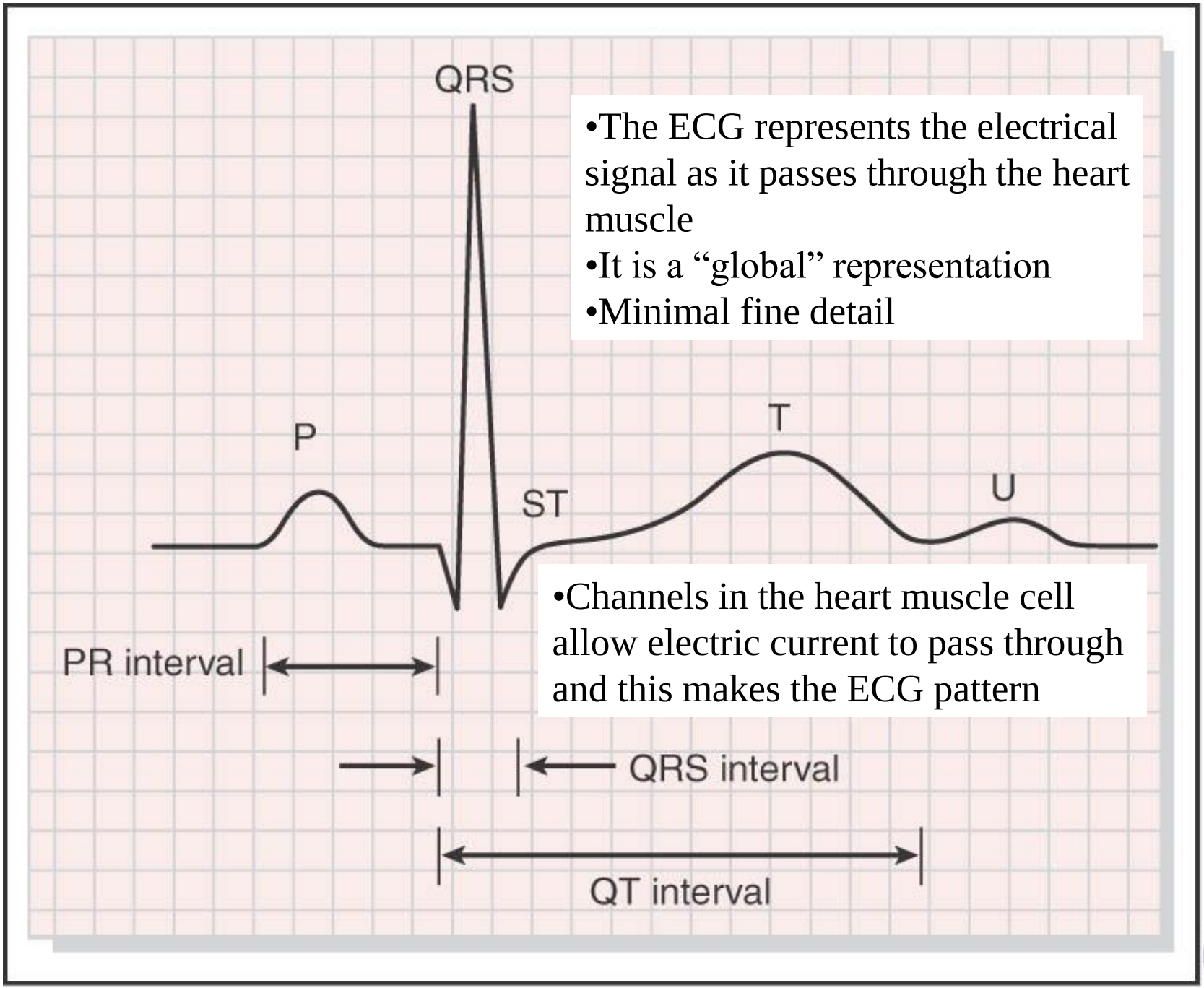
Why do we care?

What is the relationship to Rett Syndrome?

What should be done?

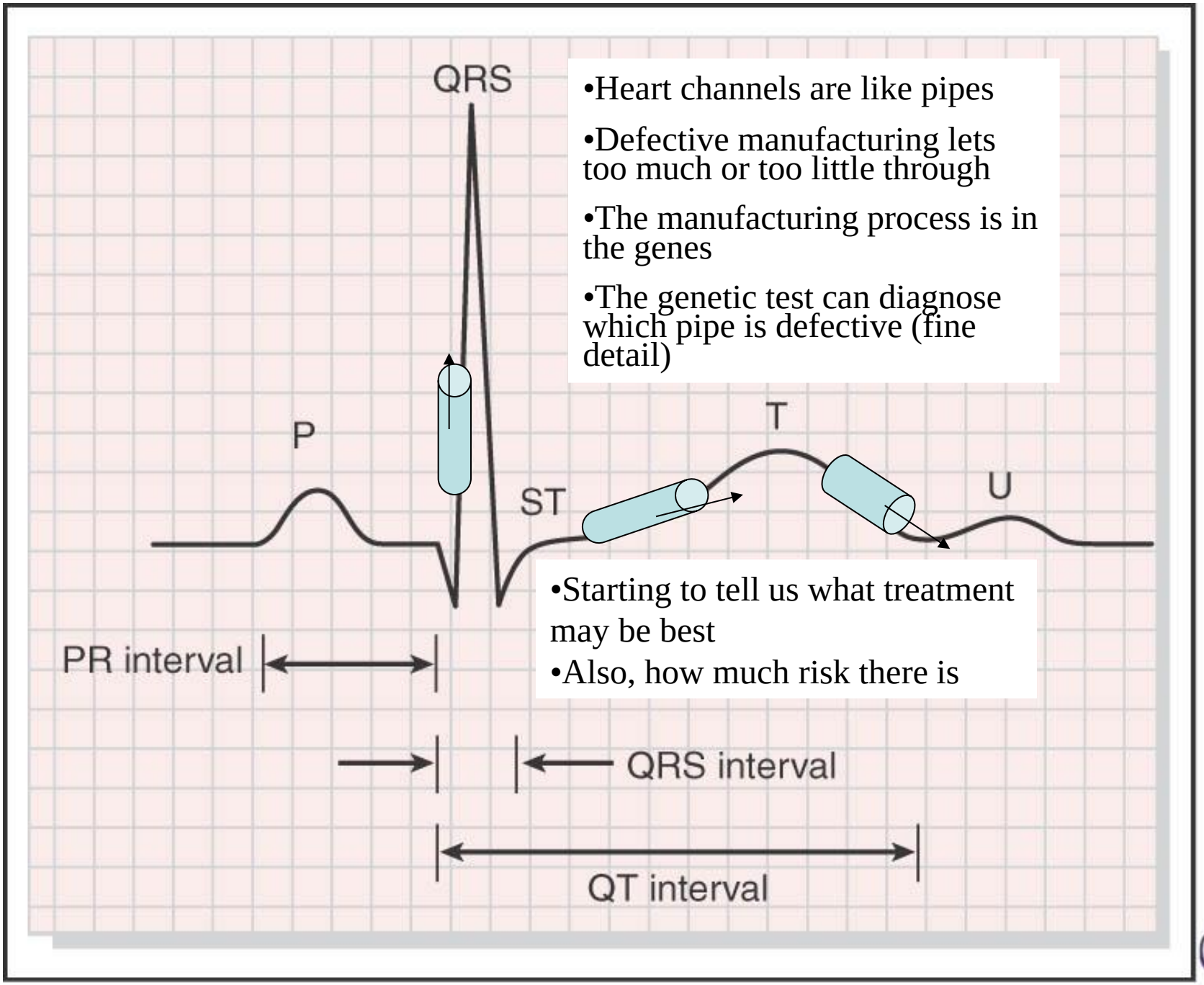
What is the QT interval?





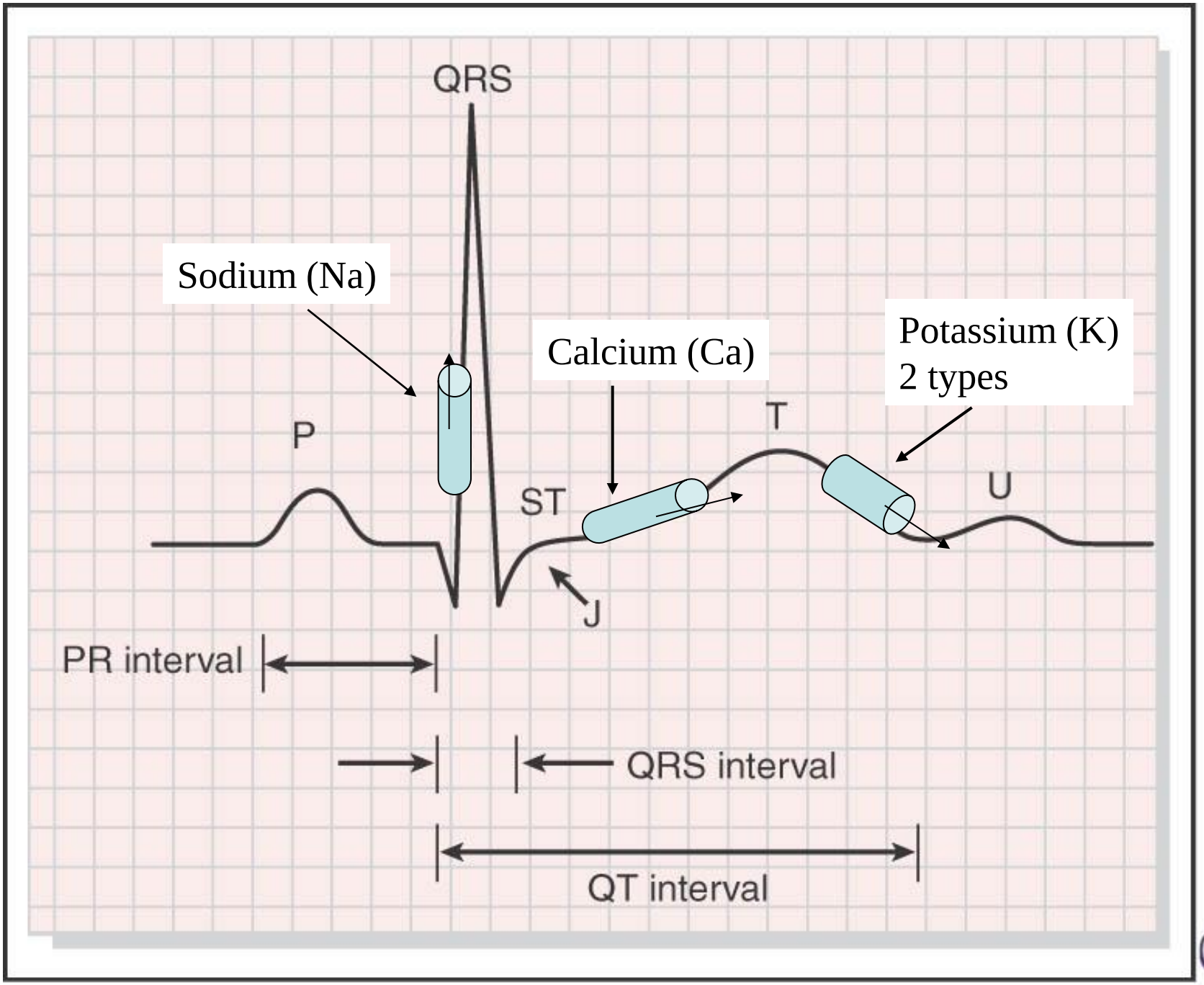
•The ECG represents the electrical signal as it passes through the heart muscle
•It is a "global" representation
•Minimal fine detail

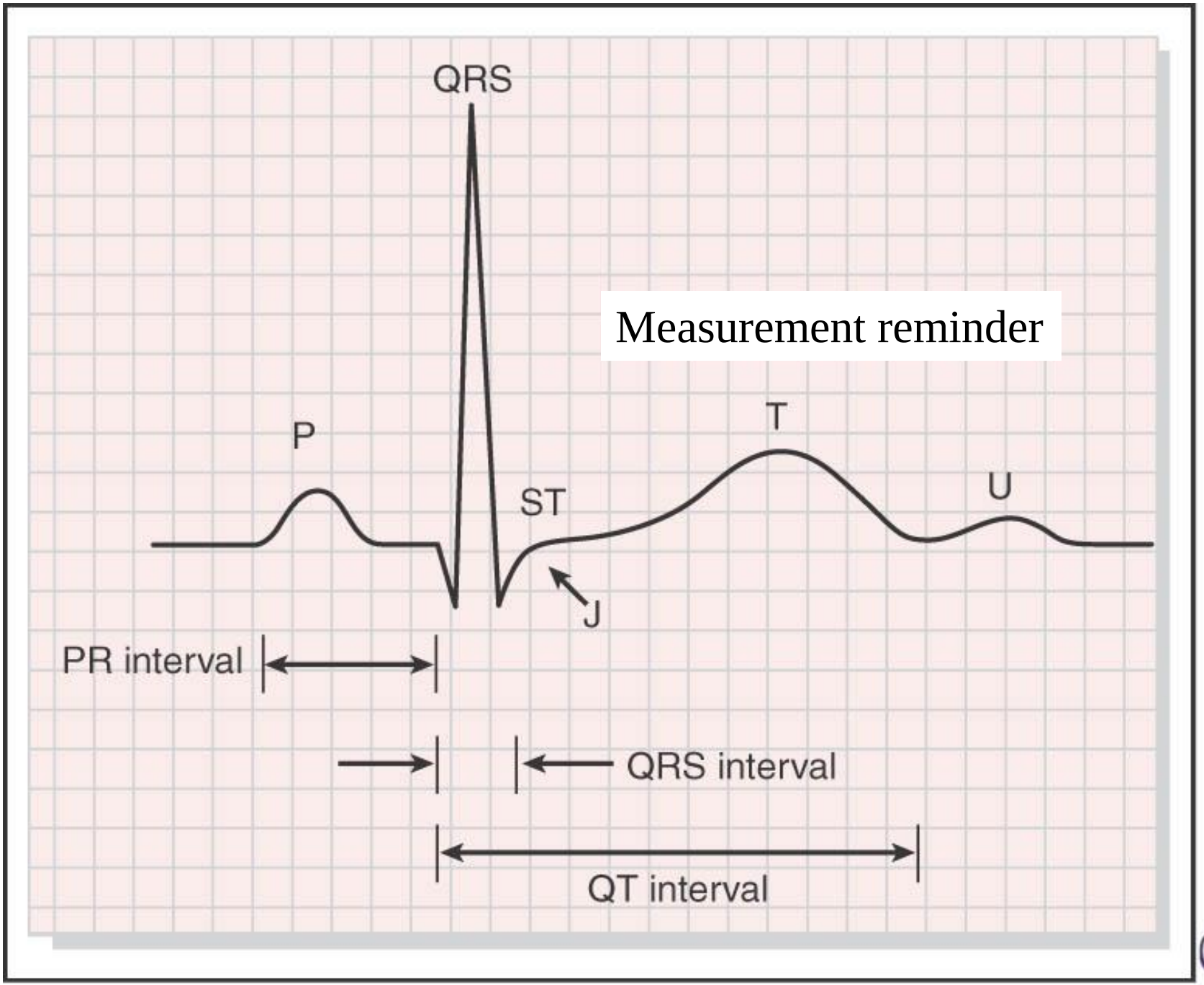
•Channels in the heart muscle cell allow electric current to pass through and this makes the ECG pattern



- Heart channels are like pipes
- Defective manufacturing lets too much or too little through
- The manufacturing process is in the genes
- The genetic test can diagnose which pipe is defective (fine detail)

- Starting to tell us what treatment may be best
- Also, how much risk there is





What is the QTc (corrected QT) and why do we need it?

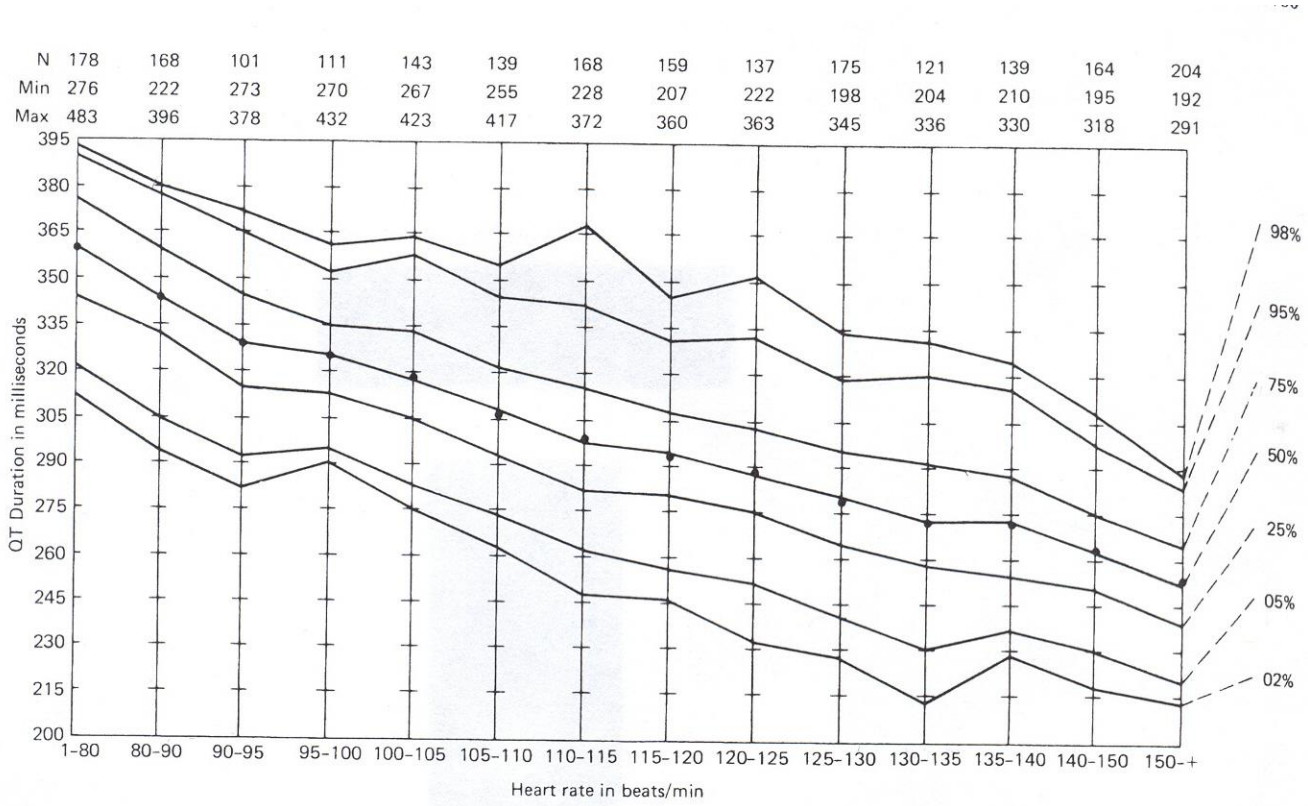


Fig. 6. QT duration vs. heart rate in lead V5 (● = mean)

QT gets shorter as heart rate increases – therefore no single "number" which defines normal

Bazett formula: $QTc = QT/(HR/60)^{1/2}$

Normal QT/QTc intervals

Not ≤ 440 msec (in old books etc)

Rijnbeck et al (now most commonly used)

(98^{th} %ile)

	0-1m	1-3m	3-6m	6-12m	1-3y	3-5y	5-8y	8-12y	12-16y
M	448	458	453	449	455	443	443	440	449
F	462	454	448	446	447	447	449	447	457

Mason et al (large population based study)

	98^{th} %ile	Mean (SD)	Overall
M 0-9	452	409 (21)	407 (22)
M 10-19	448	405 (23)	
F 0-9	461	408 (21)	
F 10-19	457	402 (23)	

What about measuring the QTc and how do we get measurements?

Automatically from the ECG printout

relies on an algorithm to detect end point of T wave

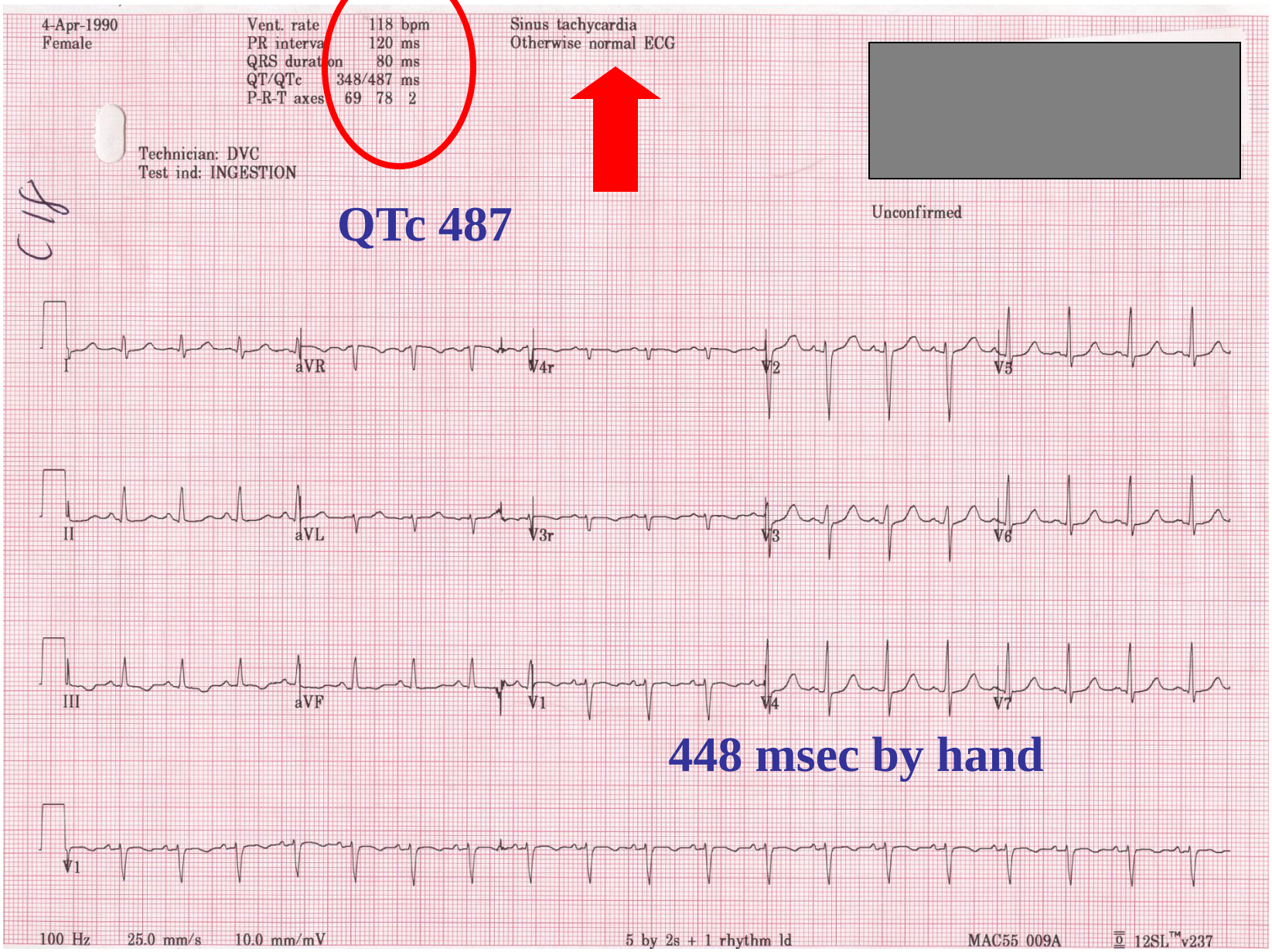
Hand measuring

there are reliable methods to measure

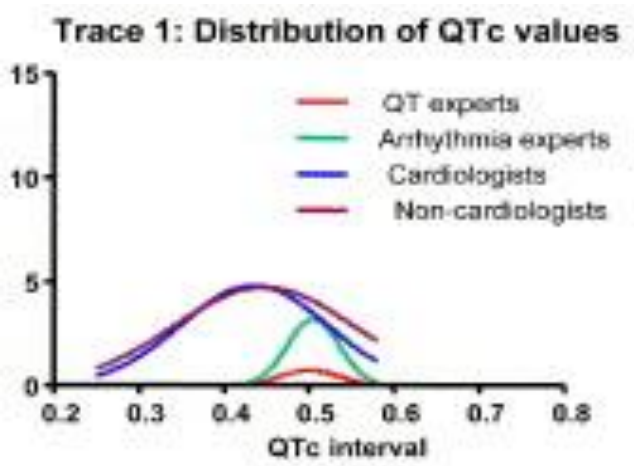
Studies show that most physicians cannot measure the intervals correctly, or interpret the data

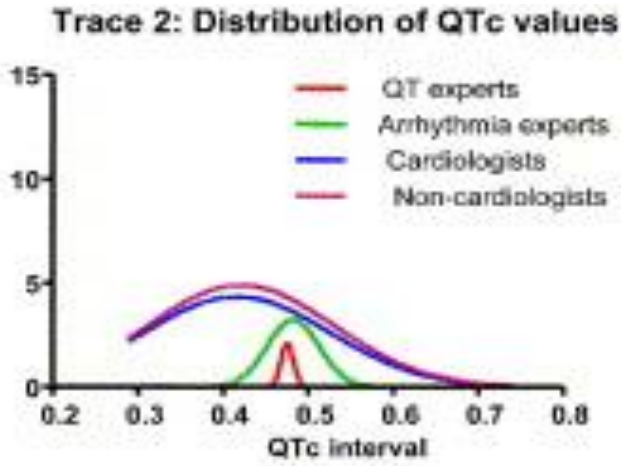
this is a specialized area of cardiology

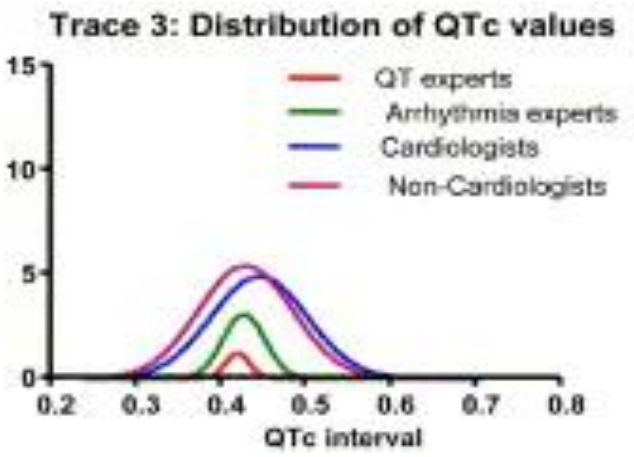
Even physicians who are “expert” will get slightly different Numbers each time they measure the ECG

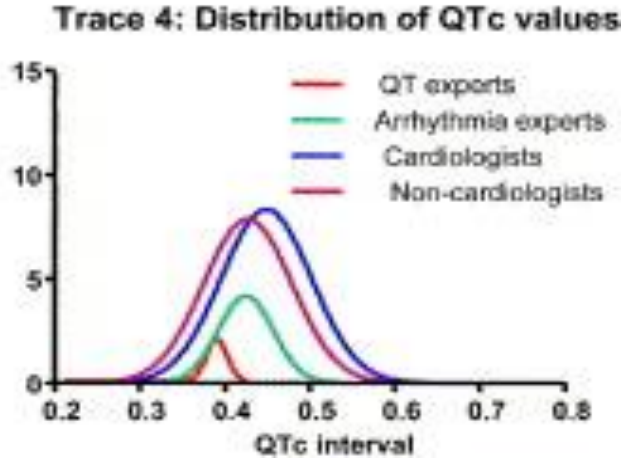


QTc above normal limits; HR > 100/m


Trace 1: Distribution of QTc values
QT experts
Arrhythmia experts
Cardiologists
Non-cardiologists
15
10
5
0
0.2
0.3
0.4
0.5
0.6
0.7
0.8
QTc interval


Trace 2: Distribution of QTc values
QT experts
Arrhythmia experts
Cardiologists
Non-cardiologists
15
10
5
0
0.2
0.3
0.4
0.5
0.6
0.7
0.8
QTc interval


Trace 3: Distribution of QTc values
QT experts
Arrhythmia experts
Cardiologists
Non-Cardiologists
15
10
5
0
0.2
0.3
0.4
0.5
0.6
0.7
0.8
QTc interval


Trace 4: Distribution of QTc values
QT experts
Arrhythmia experts
Cardiologists
Non-cardiologists
15
10
5
0
0.2
0.3
0.4
0.5
0.6
0.7
0.8
QTc interval

Viskin et al

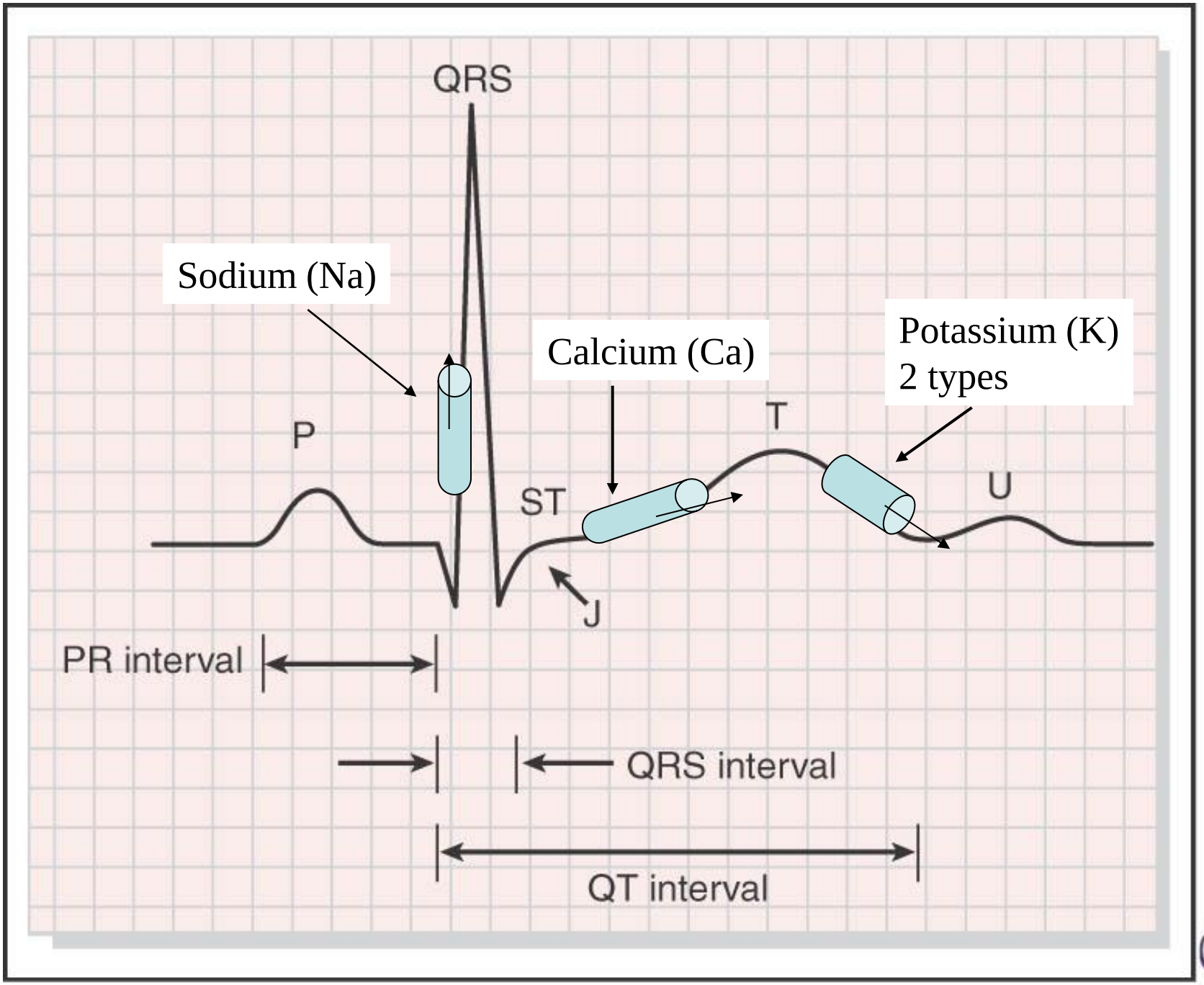
Why does the QT get prolonged?

Congenital

- Mutations in genes that control the manufacture of genes that make the channels
  - direct effects or secondary effects
- (3 main types: 1,2,3)

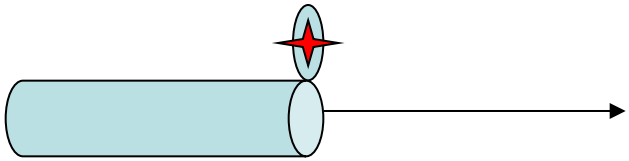
Acquired

- Function of channels changed by extraneous forces
  - medication
  - heart failure
  - electrolyte problems (K, Ca)
  - abnormal muscle



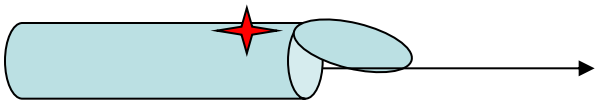
Main problems are Na channel and K channel

Na channel



- should close quickly
- does not in LQTS3
- current last longer than it should
- activation lasts longer

K channel



- should open fully
- does not in LQTS1, LQTS2
- delays current flow for recovery
- recovery takes longer

Manufacturing changes in congenital form
Acquired form – think of something building up to change the function

Medications that lengthen the QT/QTc

Antibiotics		
	azithramycin	zithromax
	ciprofloxacin	cipro
	erythromycin	erithrocin
	trimeth/sulf	bactrim/septra
Seizure medication		
	felbamate	felbatol
Psychological medication		
	fluoxitine	prozac
	imipramine	tofranil
	trazadone	desyrel
Antiviral		
	amantadine	symmetril
GI		
	domperidone	motilium
Antihistamines		
	diphenhyramine	benadryl
	hydroxyzine	atarax

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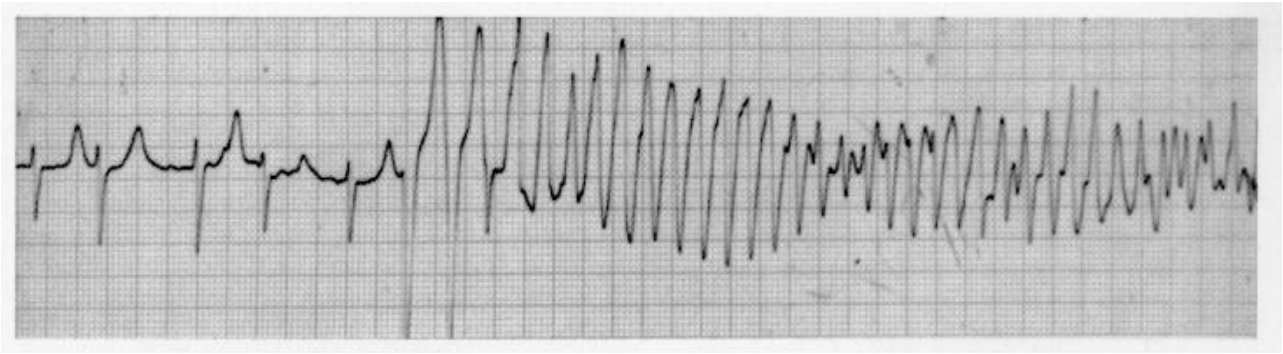
Why do we care about a prolonged QT/QTc?

LQTS and Torsade de Pointes



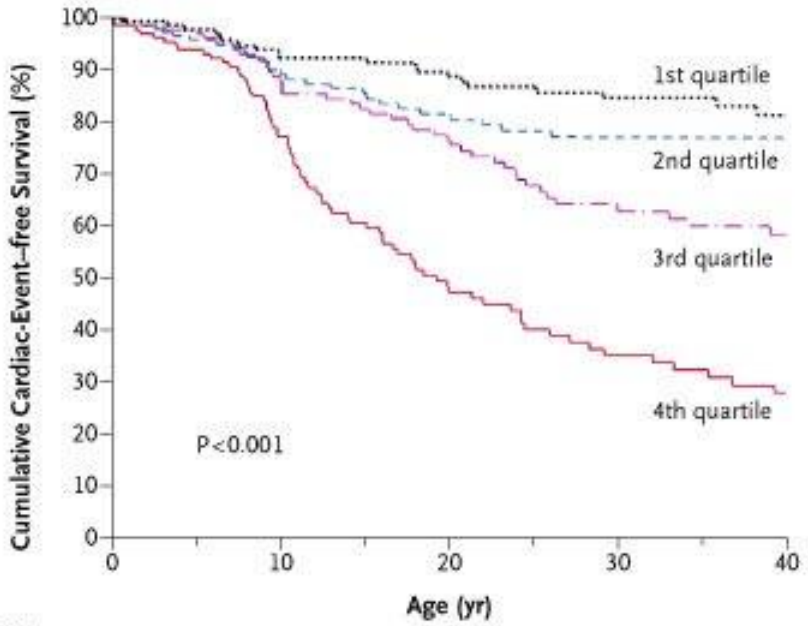
Potentially lethal arrhythmia

If brief it causes sudden fainting with quick recovery

May be seizure like activity – brief if recovery

Sudden death if prolonged

Prolonged seizure with recovery is not a LQT arrhythmia



No. at Risk					
1st quartile	148	112	96	76	45
2nd quartile	150	104	80	62	45
3rd quartile	140	103	78	49	33
4th quartile	142	92	45	28	18

Event free survival by QTc quartile -1st < 446 msec

- 2nd <468 msec

Priori et al

Congenital LONG QT syndrome

Found in 1 person per 2000 to 2500 people in the community

One of the leading causes of sudden death in otherwise healthy young people who die suddenly and unexpectedly when nothing found to explain death at an autopsy

Most forms are inherited (from parents to children)

Traditionally diagnosed on electrocardiogram

The electrocardiogram may be inconclusive in 20% to 40% of cases

In these, the diagnosis may only be confirmed or excluded by genetic testing

In those people with a known causative gene defect, the genetic test will be conclusive in other family members

Congenital LONG QT syndrome

Individuals with LQTS have an increased risk of sudden death compared with general population (10 to 40 times) depending on multiple factors (including specifics from genetic test)

Relatively simple measures can substantially reduce the risk in most

- medicines called beta blockers (block adrenalin's effect)
- avoiding certain prescription or over-the counter medicines
- avoiding dehydration
- modification of activity in many

People with the highest risk profile often require a multidisciplinary approach

Long term outlook is excellent with modern management

Probability of a female having these 2 independent conditions (RTT and cLQTS) is 1 in 25-30 million live female births)

What is the relationship between LQTS and Rett Syndrome?

Sudden unexplained death in RS

26% in Registry

Clinical associations

Sekul et al 1994

34 patients with Rett Syndrome

QTc $\geq$ 0.45

14/34 (41%)

Ellaway et al 1999

34 girls with RS

QTc > 0.45

9/34 (26%)

McCauley et al 2011

379 females

QTc > 0.45

18.5 % long QT

What is the relationship between LQTS and Rett Syndrome?

Experimental data

McCauley et al 2011

Mouse model

Put MeCP2 gene in males and females

QT was longer

Heart irregularities induced (death)

Na channel function abnormal

Prolonged current (like LQTS3)

even when mutation only in brain

Corrected by phenytoin (dilantin)

Hara et al 2015

Mouse model

MeCP2 produces structural changes in heart cells

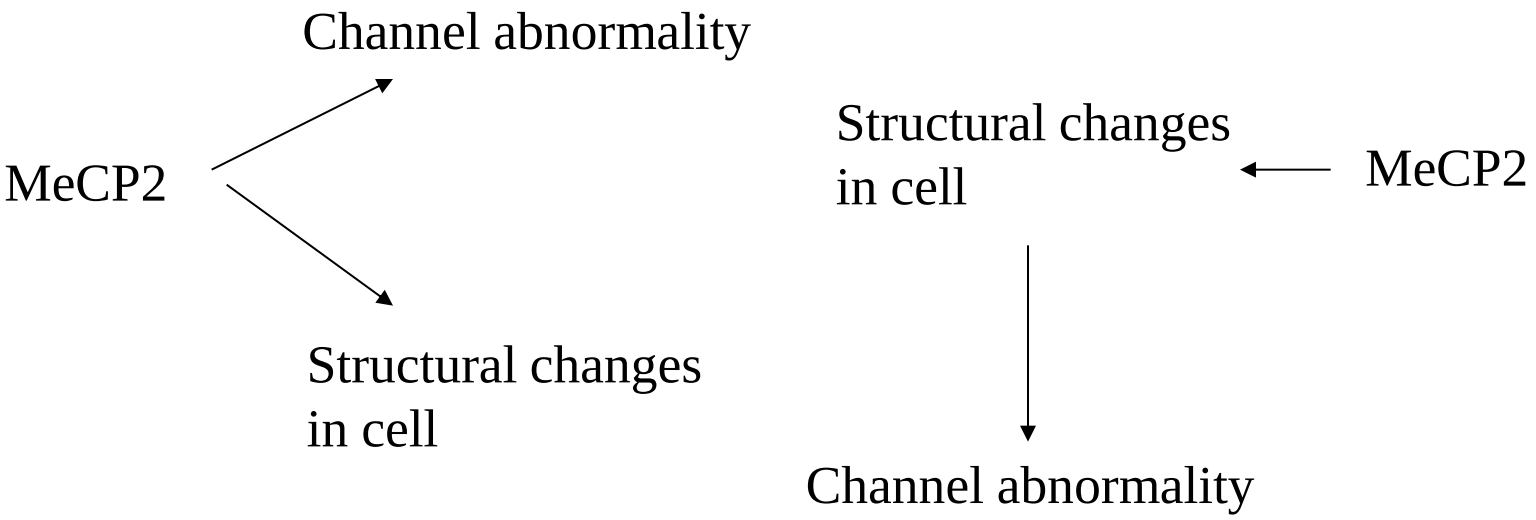
De Felice et al 2012

Subtle changes in heart contraction and relaxation in patients

What is the relationship between LQTS and Rett Syndrome?

Is the association true?

Too early to say



Long term follow-up studies have not (as yet) confirmed a causal relationship between QTc and increased risk of death

What is the relationship between LQTS and Rett Syndrome?

Two things being associated does not establish a causal link

There are very specific criteria to “establish” a causal link

The way this is studied is different

In this case:

Do ECGs on all people diagnosed with RTT (very early)
Follow them for a long time
Need large numbers to balance out many factors
See if QTc longer in those who died compared with those who did not
Make sure all “confounders” are balanced
medicine, seizures

Not established so far

OK, now what?

How should this be managed?

ECGs at diagnosis and during follow-up

If QTc prolongation (age, gender, heart rate) is suspected from a single ECG, repeated 2-3 times over one to two months

If able, an exercise test to examine the dynamics of the QT interval (possibly a standing test, rarely drug challenge test – eg adrenaline)

If “confirmed” management depends on length of QTc

(in individuals without heart related symptoms, the international guidelines state LQTS should not be diagnosed unless QTc > .48 (and usually .5))

Therefore marginal lengthening is usually NOT considered a sign of increased risk

OK, now what?

How should this be managed?

- Differentiate fainting from seizures
- Prudent to avoid medication that further prolongs the QT interval (if medically possible)
- Follow-up and keep an open mind
- I would not recommend β-blockers except under exceptional circumstances (open to discussion)
- Further research needed

Questions?