20170623 KHRS

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ECG in AVB

- Predicting Torsades de Pointes

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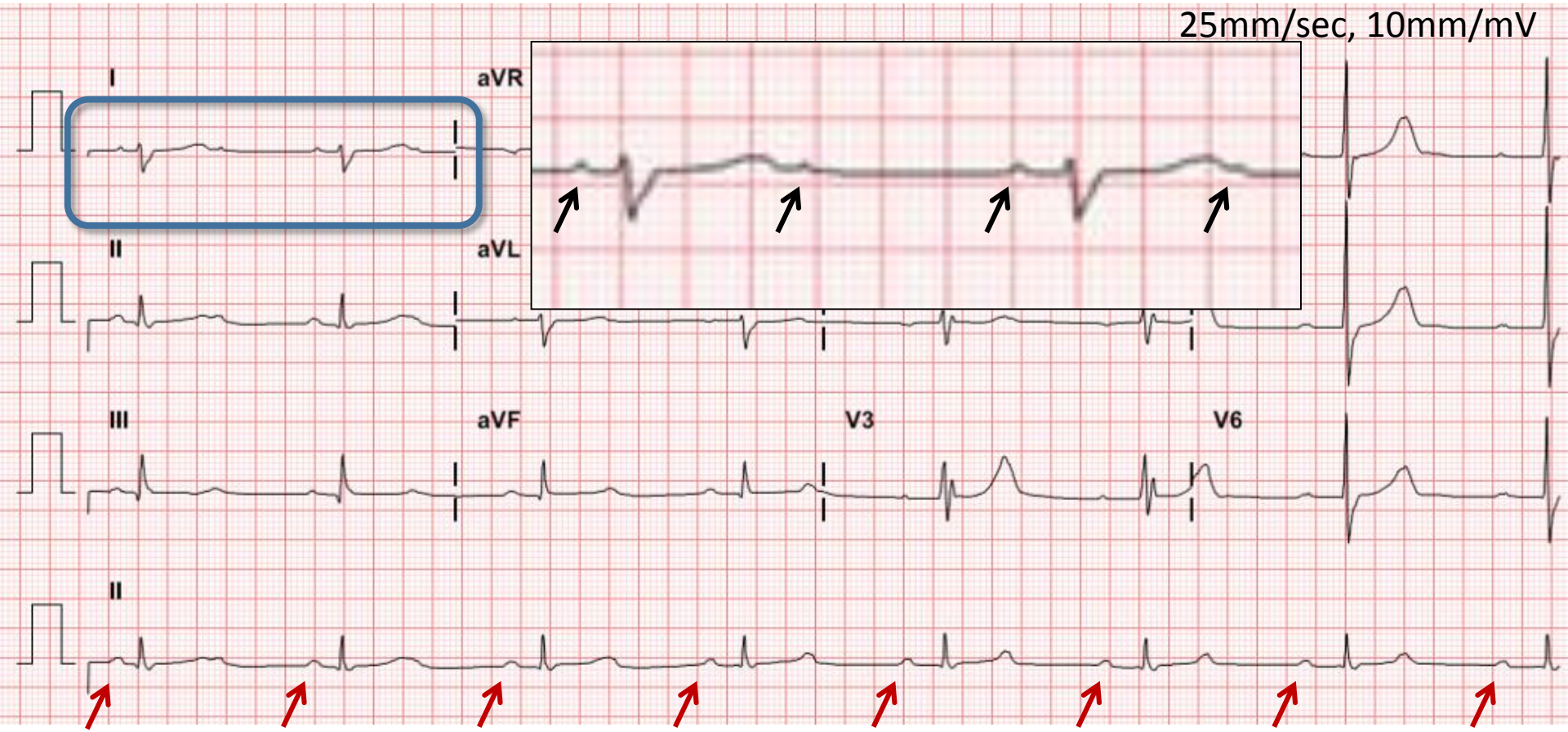
Case. Torsades de Pointes in CAVB

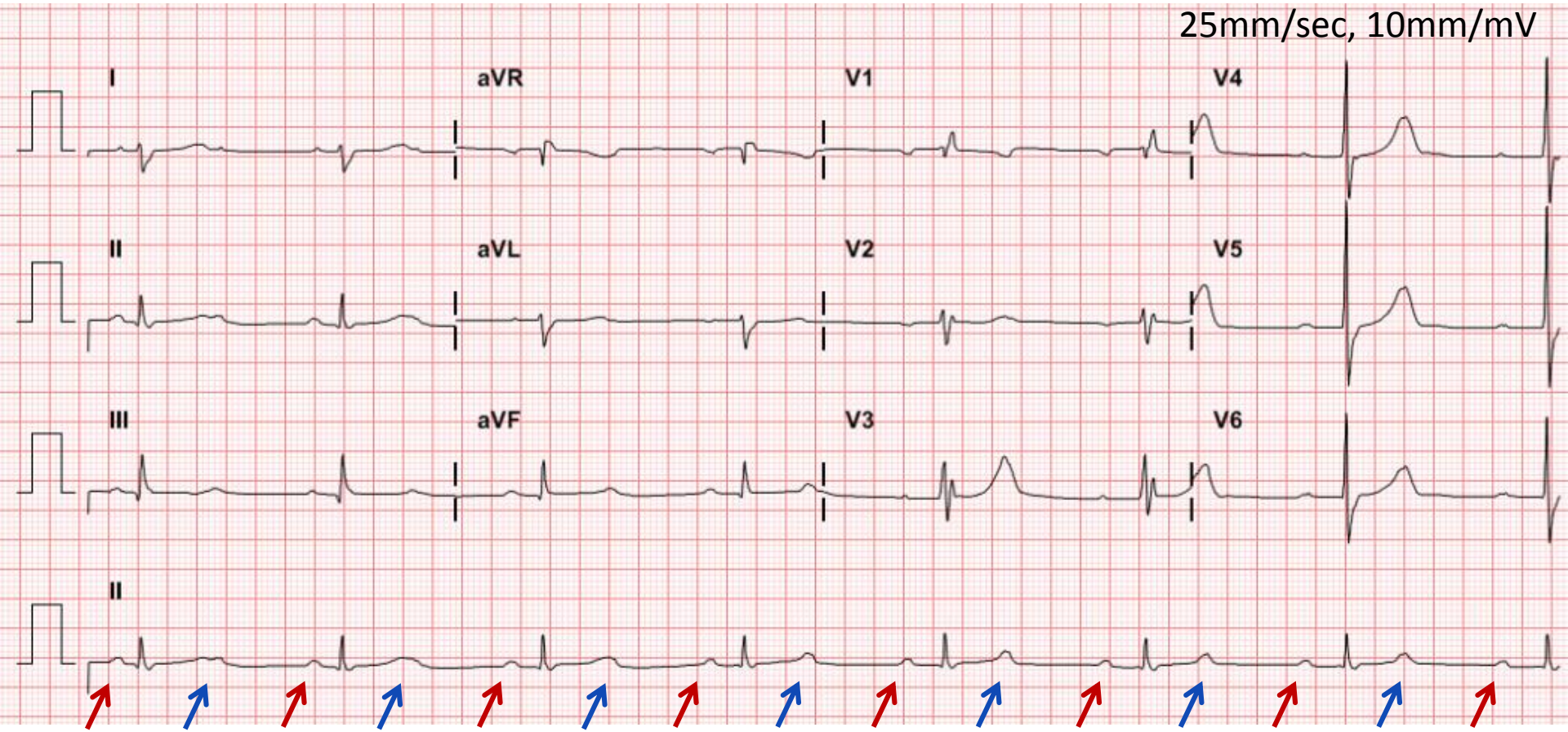
- F/78
- Underlying diseases
  - DM, HT, old CVA
- Spinal stenosis 수술 후 pneumonia 로 타원에서 supportive care 받던 분으로, dizziness 있어 본원 방문함.

내원시 심전도 (HR 44 bpm)



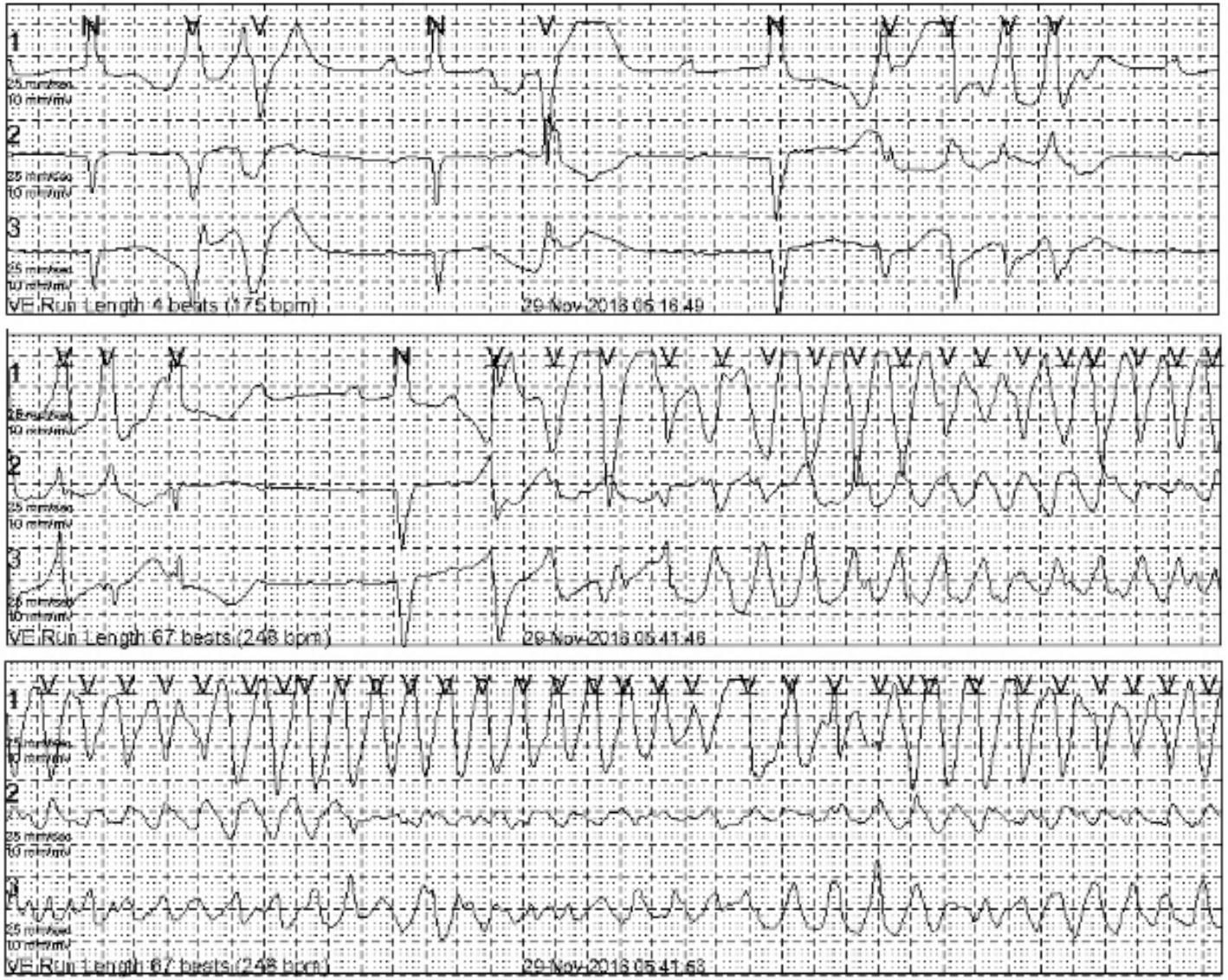
Sinus rhythm??

내원시 심전도 (HR 44 bpm)

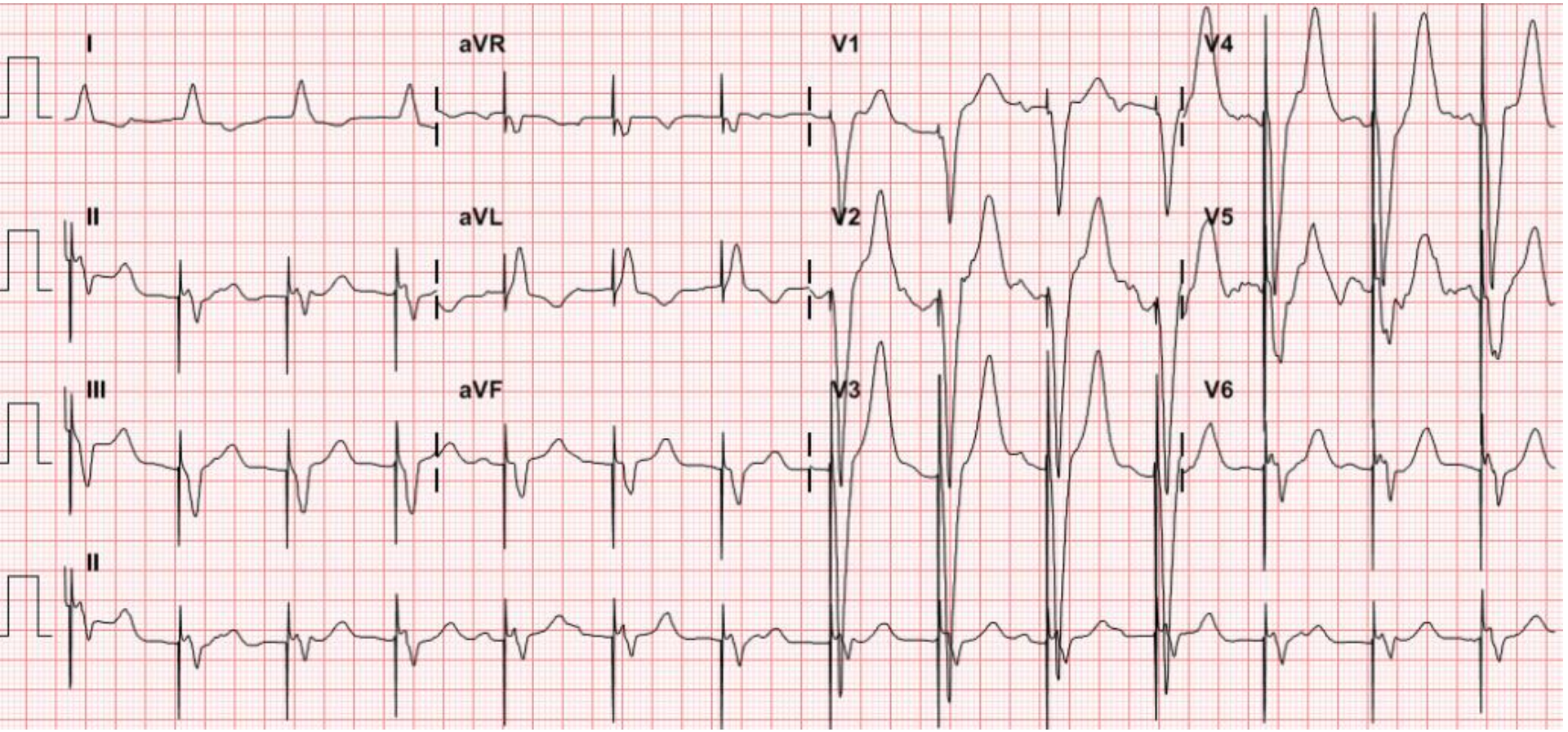


Complete AV block

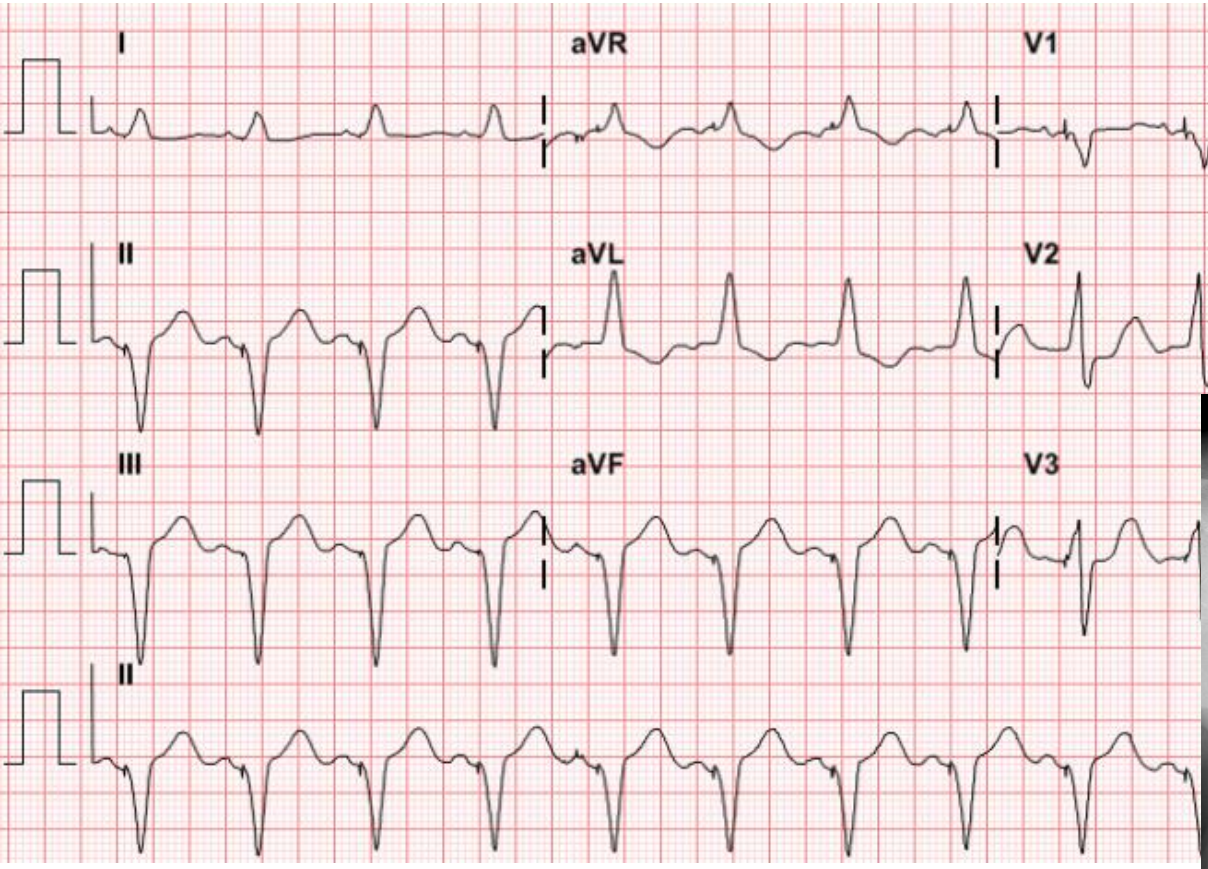
24hr Holter monitoring 중 syncope 발생

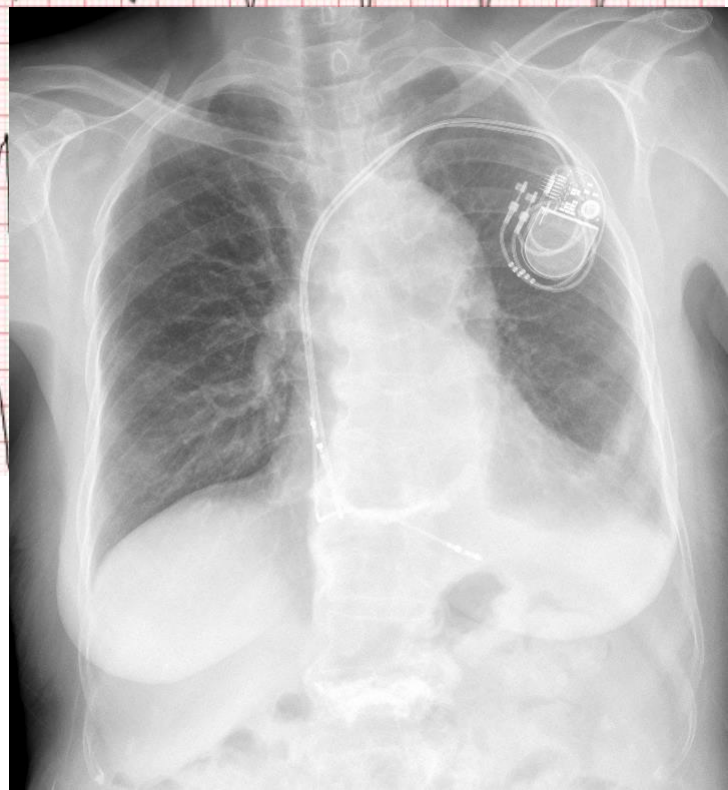


Temporary PM



Permanent PM implantation





No more dizziness / syncope

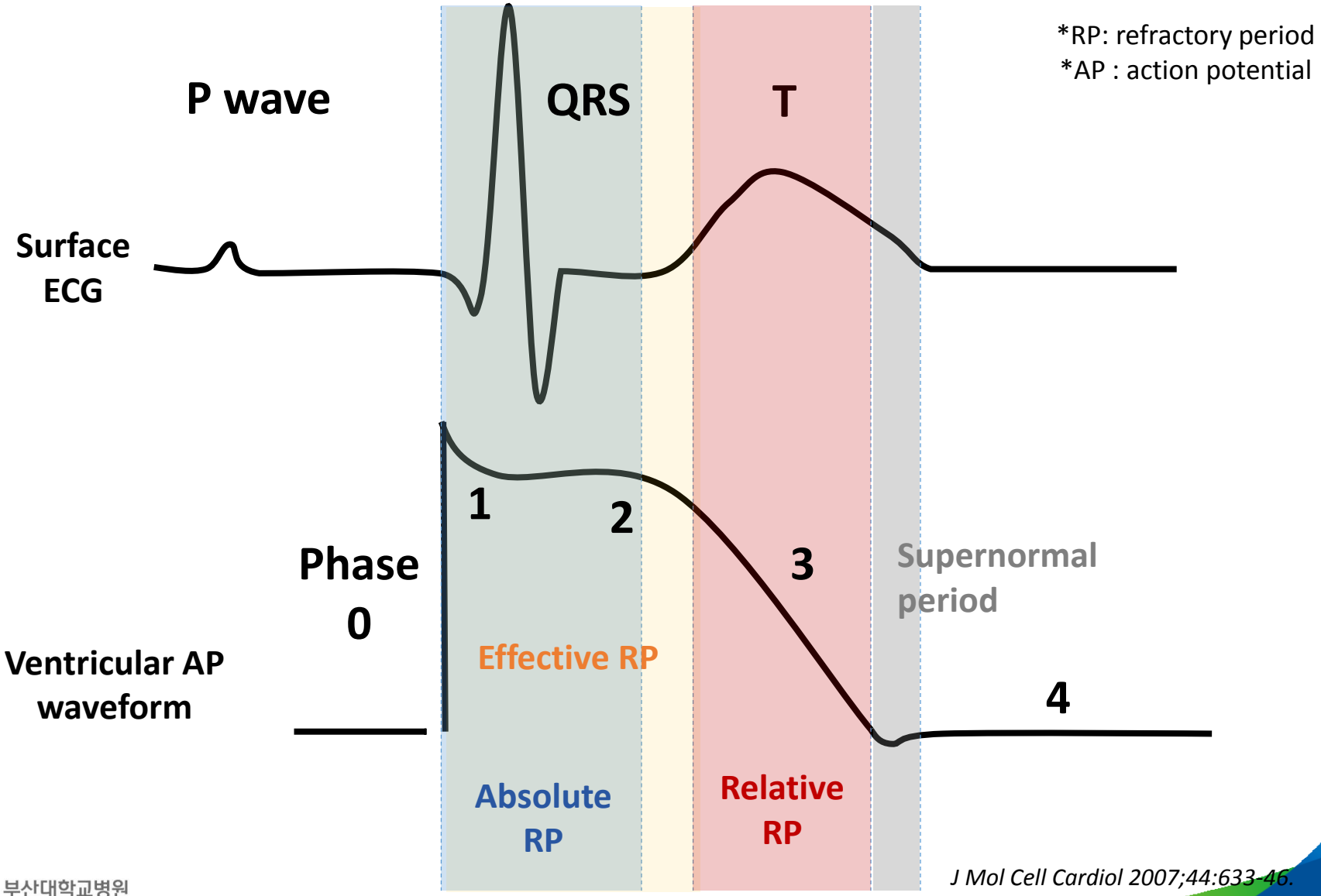
What is Torsades de Pointes (TdP)?

- A form of PMVT that occurs in the setting of QT interval prolongation.

- Terminologies to explain TdP
  - Long-short R-R cycle sequences
  - Transmural dispersion of repolarization
  - QT prolongation = prolongation of AP duration
  - Early afterdepolarization
  - PVC with R on T phenomenon
  - Twisting QRS complexes

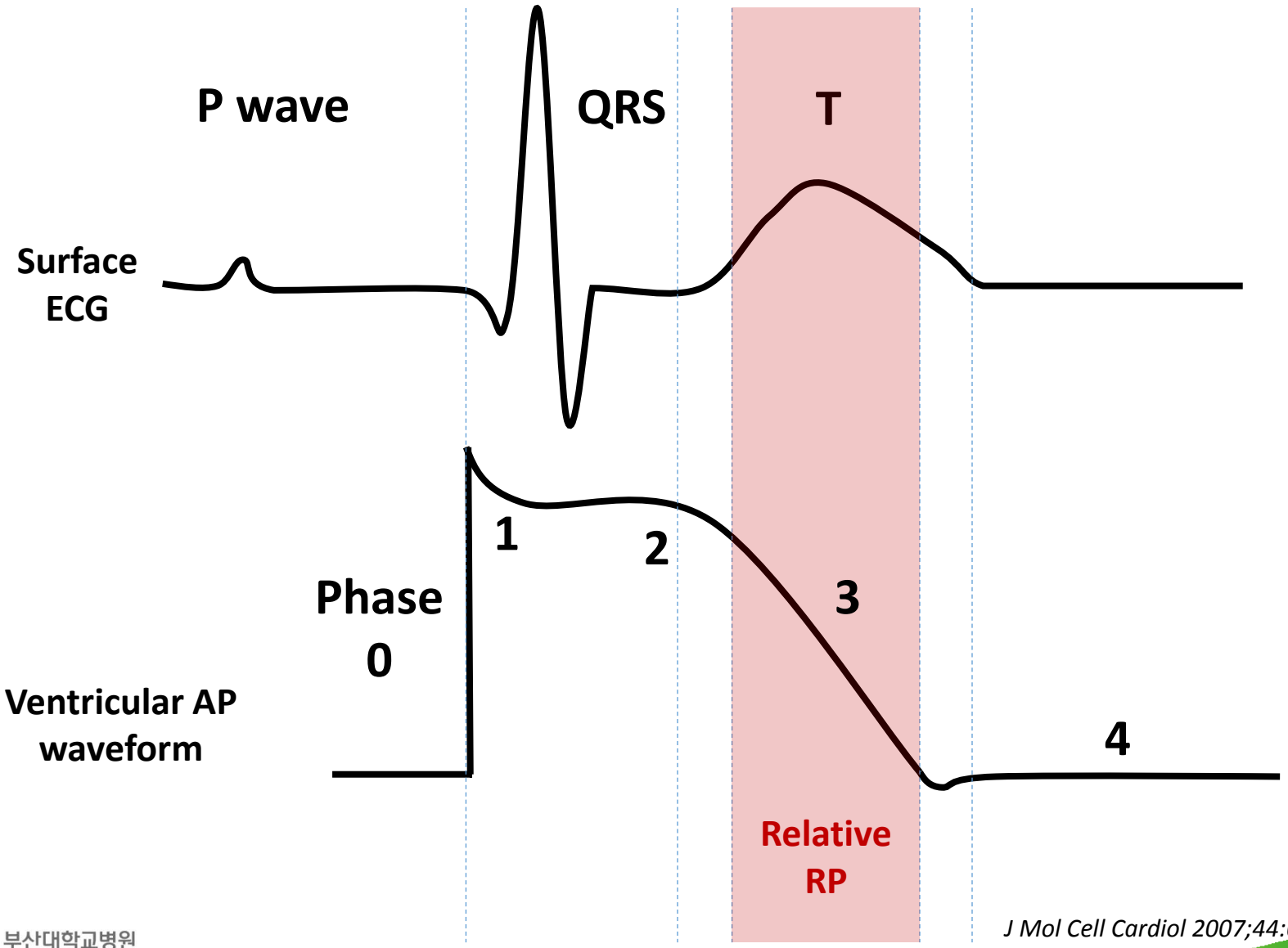
Braunwald's heart disease. 10th ed. Vol. 1. pp782.

Relation btw Ventricular Action Potential and ECG



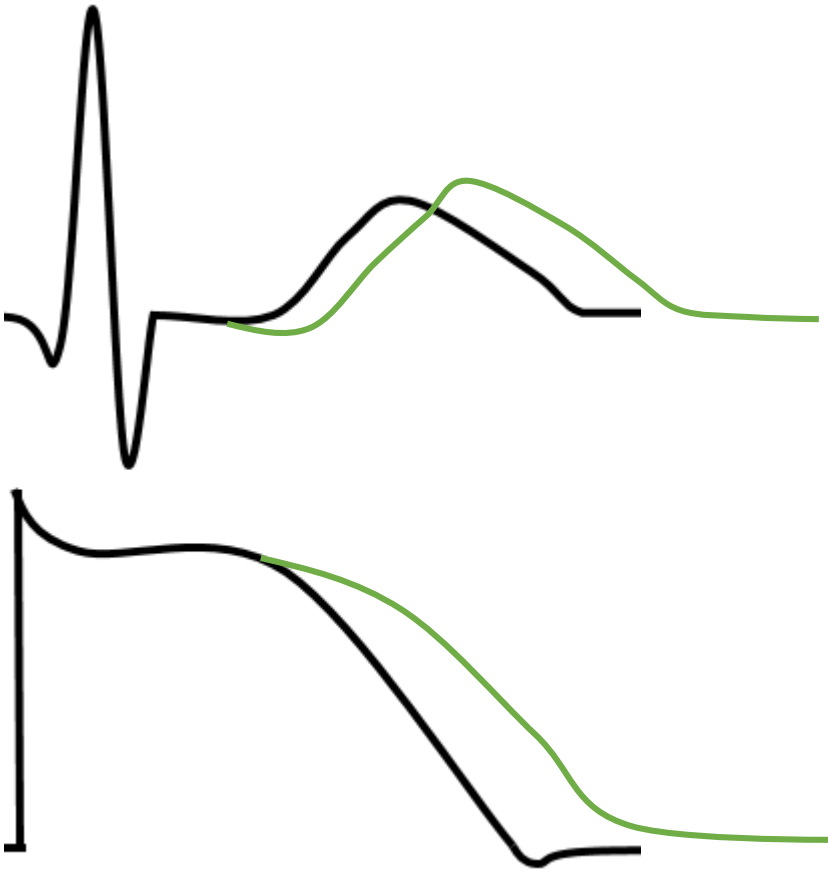
J Mol Cell Cardiol 2007;44:633-46.

Relation btw Ventricular Action Potential and ECG



J Mol Cell Cardiol 2007;44:633-46.

QT prolongation = prolonged AP duration



Outward repolarizing
K current

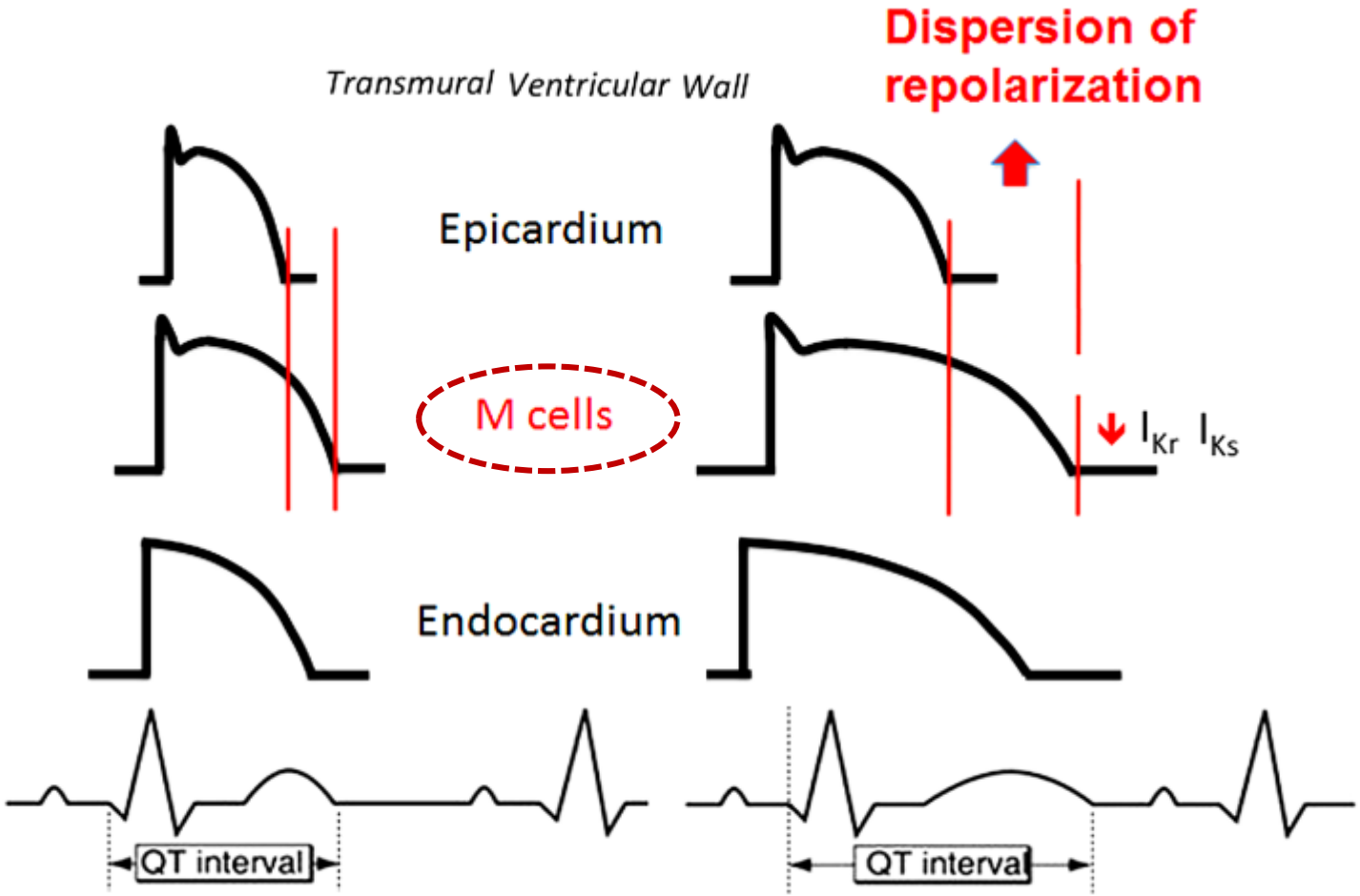
or

Inward depolarizing
Na or Ca current

J Mol Cell Cardiol 2007;44:633-46.

Transmural Dispersion of Repolarization

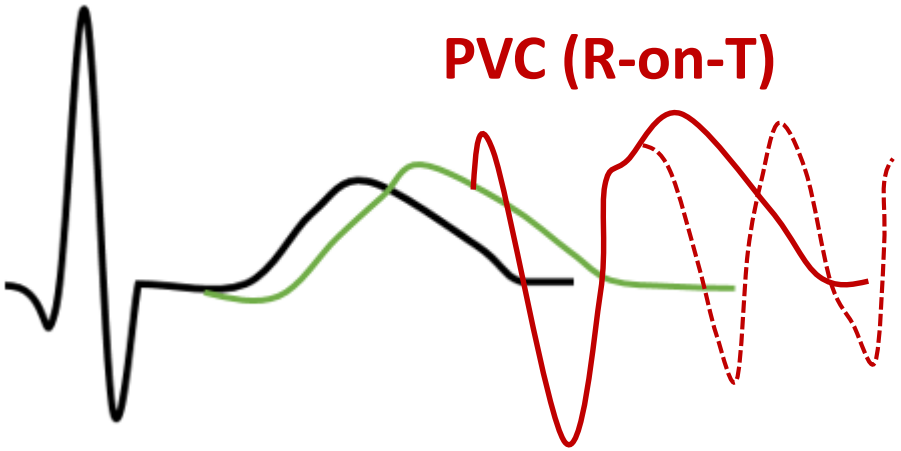
- AP duration difference between different myocardial layers
- Create a vulnerable window for development of reentry



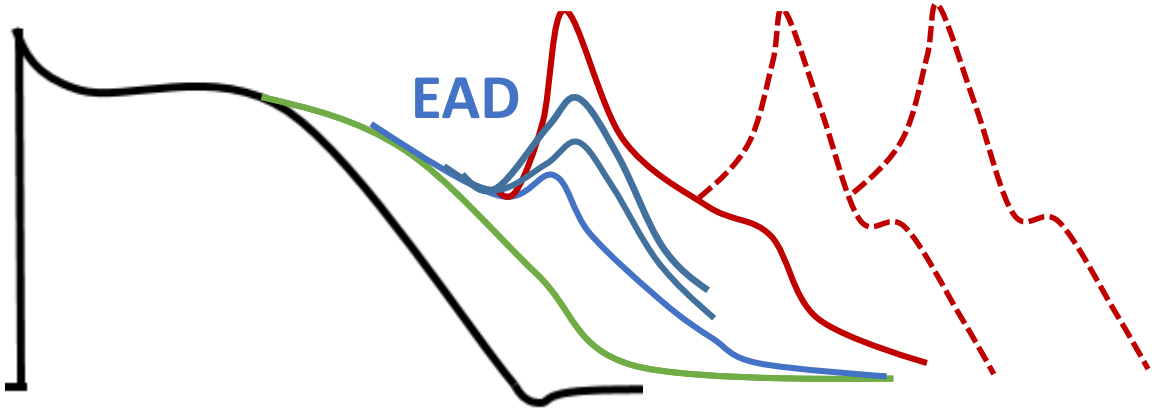
Postgrad Med J 2014;90:349-58.

Early Afterdepolarization → PVC → TdP

- Abnormal depolarization of Ca or Na → EAD → When reaching threshold potentials → generation of PVC (triggered beat) → initiation of TdP

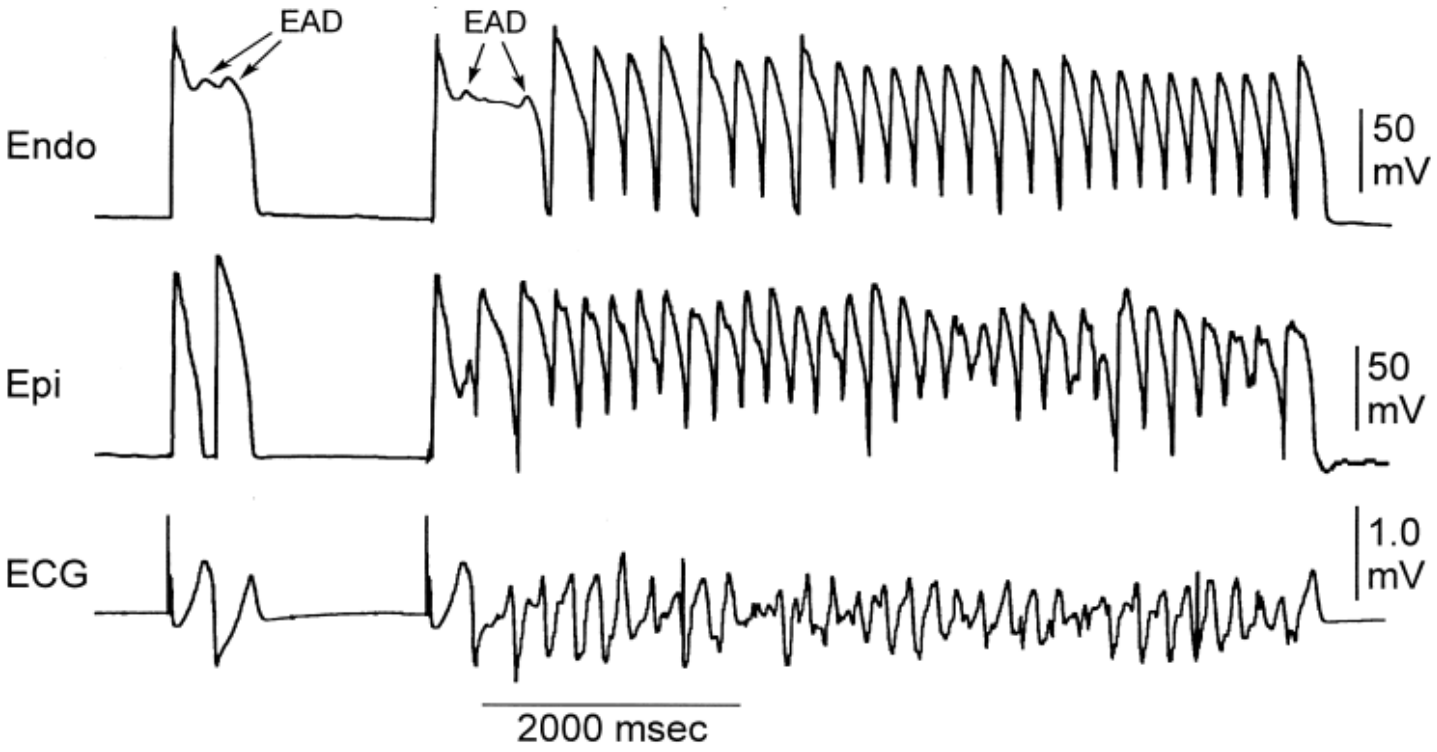


Perpetuation
: mainly d/t reentry

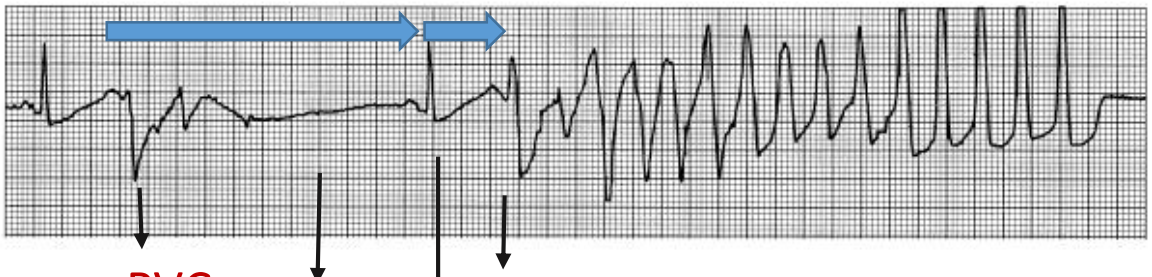


Cardiovasc Drugs Ther 1991;5:203-12.

TdP in an Isolated Arterially Perfused Rabbit Left Ventricle (dl-Sotalol 100 μM)



TdP in a Patient with Prolonged QT Interval Who was on Sotalol



PVC

Long pause

Longer QT interval

EAD → PVC (R on T) triggering → TdP

Long-short R-R sequence

J Am Coll Cardiol 2003;42:401-9.

Causes of TdP (QT prolongation)

1. Congenital long QT syndromes (see text for details)
   - Long QT syndrome type 1: Reduced repolarizing current I_{Ks} due to mutation in *KCNQ1* gene
   - Long QT syndrome type 2: Reduced repolarizing current I_{Kr} due to mutation in *KCNH2* gene
   - Long QT syndrome type 3: Delayed inactivation of the I_{Na} due to mutations in *SCN5A* gene
   - Others: Several other types of long QT syndromes have been described; long QT types 1, 2, and 3 account for 80–90% of cases
2. Acquired prolongation of QT interval
   - Electrolyte abnormalities
     - Hypokalemia
     - Hypomagnesemia
     - Hypocalcemia
   - Drugs
     - Antiarrhythmic drugs
       - Class IA: Quinidine, disopyramide, procainamide
       - Class III: Sotalol, amiodarone (QT prolongation common but torsade ventricular tachycardia is rare), ibutilide, dofetilide, almokalant
     - Antibiotics
       - Macrolides: Erythromycin, clarithromycin, azithromycin
       - Fluoroquinolones: Levofloxacin, moxifloxacin, gatifloxacin
       - Trimethoprim-sulfamethoxazole
       - Clindamycin
       - Pentamidine
       - Chloroquine
       - Antifungals: Ketoconazole, itraconazole
       - Antivirals: Amantadine
     - Antipsychotics
       - Haloperidol, phenothiazines, thioridazine, trifluoperazine, sertindole, zimelidine, ziprasidone
       - Tricyclic and tetracyclic antidepressants
     - Antihistamines (histamine 1-receptor antagonists)
       - Terfenadine, astemizole, diphenhydramine, hydroxyzine
     - Cholinergic antagonists: Cisapride, organophosphates
     - Citrate (massive blood transfusions)
     - Cocaine
     - Methadone
     - Fluoxetine (in conjunction with other drugs that prolong QT)
   - Cardiac conditions
     - Myocardial ischemia and infarction
     - Myocarditis
     - Marked bradycardia
     - Stress cardiomyopathy
   - Endocrine disorders
     - Hypothyroidism
     - Hyperparathyroidism
     - Pheochromocytoma
     - Hyperaldosteronism
   - Intracranial disorders
     - Subarachnoid hemorrhage
     - Thalamic hematoma
     - Cerebrovascular accident
     - Encephalitis
     - Head injury
   - Nutritional disorders
     - Anorexia nervosa
     - Starvation
     - Liquid protein diets
     - Gastroplasty and ileojejunal bypass
     - Celiac disease

Harrison's internal medicine. 19th ed. pp 1496.

ECG in AVB – factors predicting TdP

- Not everyone with AV block develops TdP.

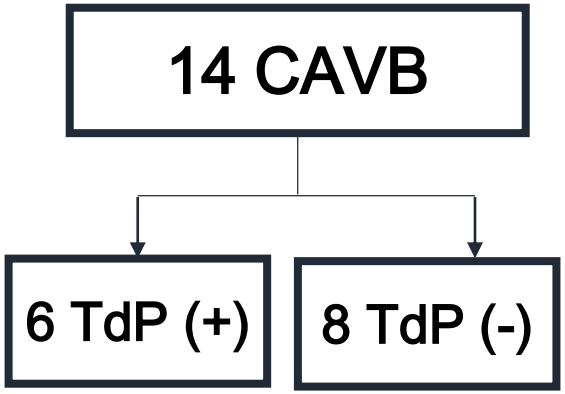
Who are in a higher risk of TdP?

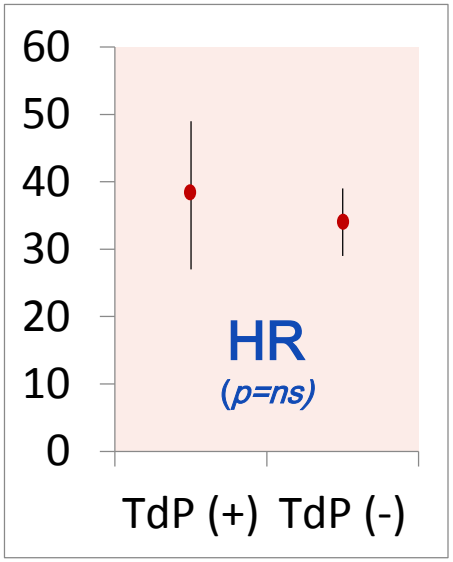
Clinical risk factors

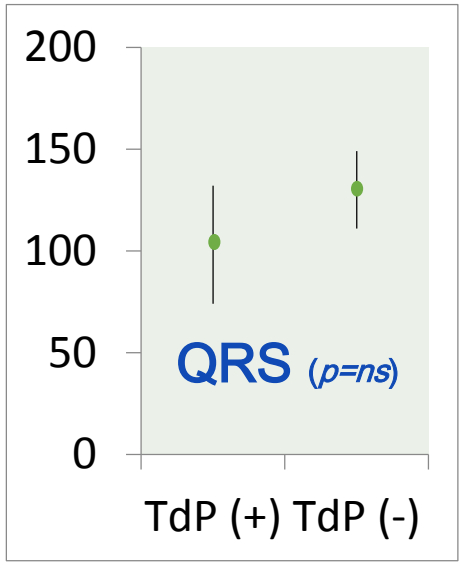
- Older age
- Female gender
- HypoK, HypoCa, HypoMg
- Exposure to QT prolonging drugs
- Underlying disease
  - Heart failure
  - Left ventricular hypertrophy
  - Thyroid disease
  - Myocardial infarction
  - Obesity
- Polymorphisms or mutations in genes
- Various ECG findings

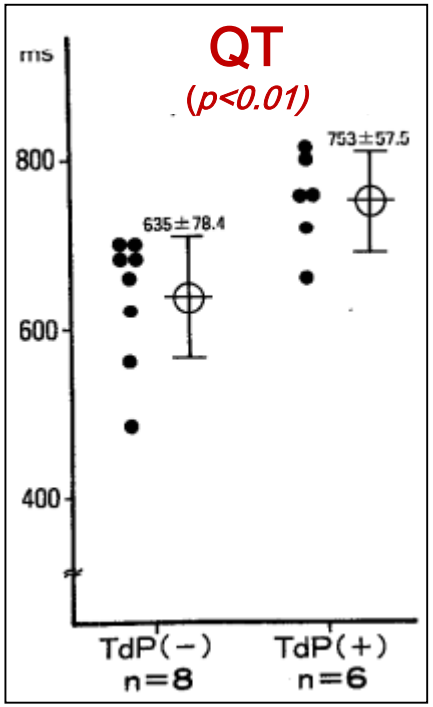
Eur Heart J 2003;24:1663-7.
J Intern Med 2006;259:59-69.
JAMA 1993;270:2590-7.
Eur J Cardiovasc Prev Rehabil 2005;12:363-8.

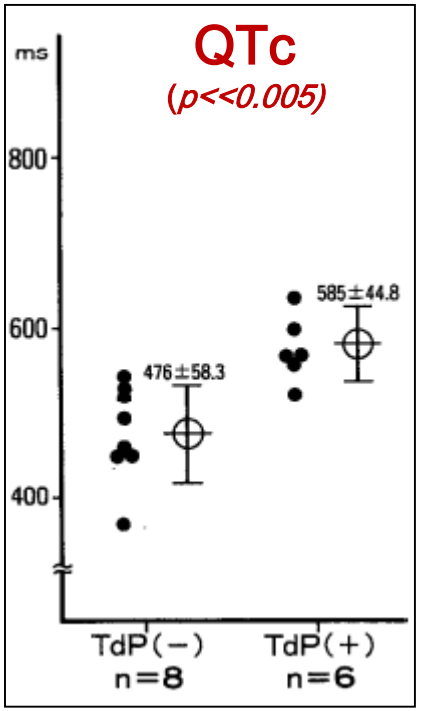
Bradycardia-Induced Abnormal QT Prolongation in Patients with Complete Atrioventricular Block with Torsades de Pointes





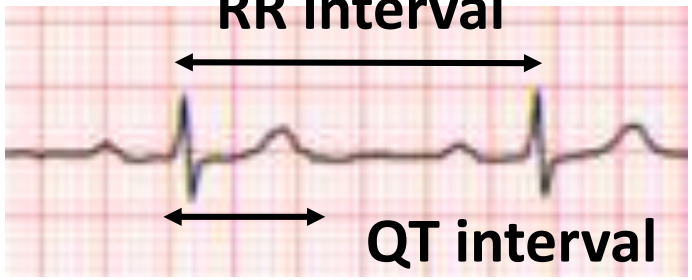






Am J Cardiol 1992;69:628-33.

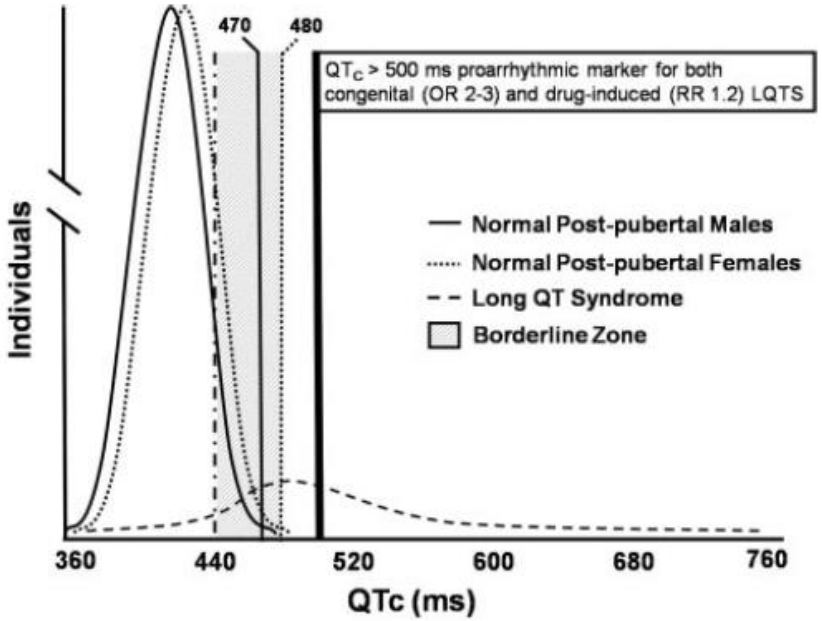
a. QT (QTc) prolongation



$$QTc = QT\ interval / \sqrt{RR}$$

Prevention of Torsade de Pointes in Hospital Settings

A Scientific Statement From the American Heart Association and the American College of Cardiology Foundation



***Upper limits of normal (99th percentile) for QTc**

- **470ms (M), 480ms (F)**

***QTc > 500ms**

- **Proarrhythmic marker**

Congenital (OR 2-3), acquired (OR 1.2)

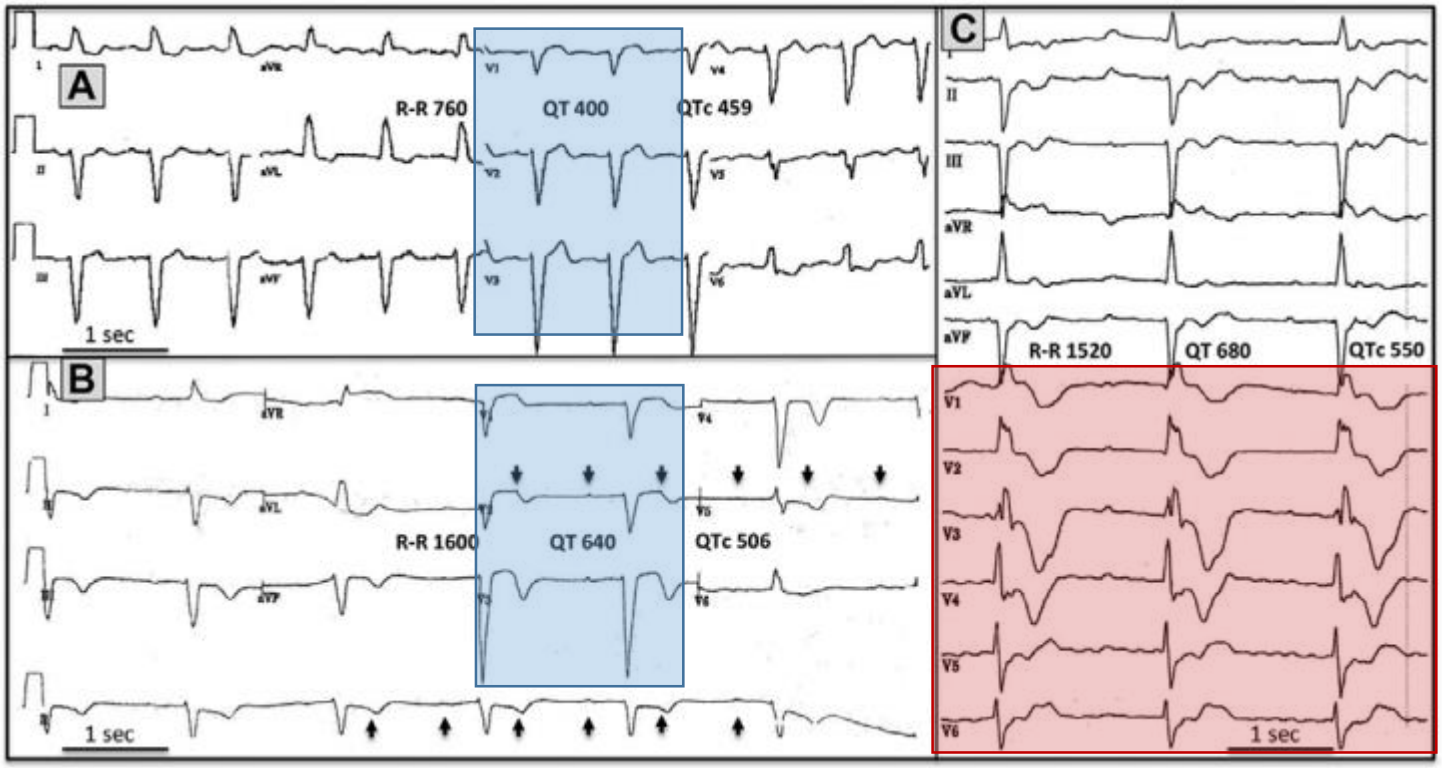
Circulation 2010;121:1047-60.

PNUH 부산대학 Pusan National Uni

b. QRS morphology change

Long QT Syndrome Complicating Atrioventricular Block

Arrhythmogenic Effects of Cardiac Memory



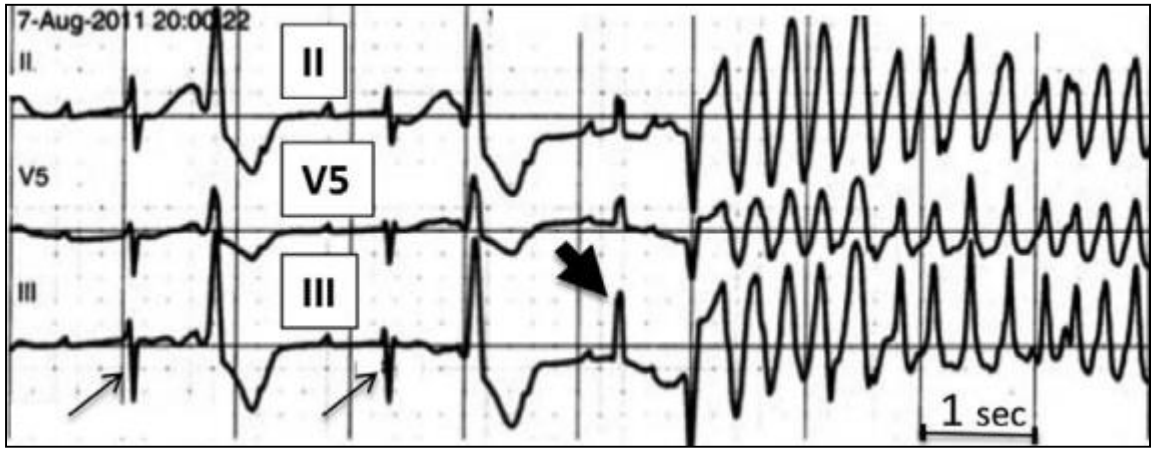
CAVB
(VR 38bpm)

2:1 AVB
(VR 36bpm)

Circ AE 2014;7:1129-35.

Long QT Syndrome Complicating Atrioventricular Block

Arrhythmogenic Effects of Cardiac Memory



Circ AE 2014;7:1129-35.

Holter of our case patient

Long QT Syndrome Complicating Atrioventricular Block

Arrhythmogenic Effects of Cardiac Memory

- **A change in QRS morphology at the time of AVB – in 1/3 patients**
- **T wave change, QT prolongation d/t cardiac memory → TdP risk**

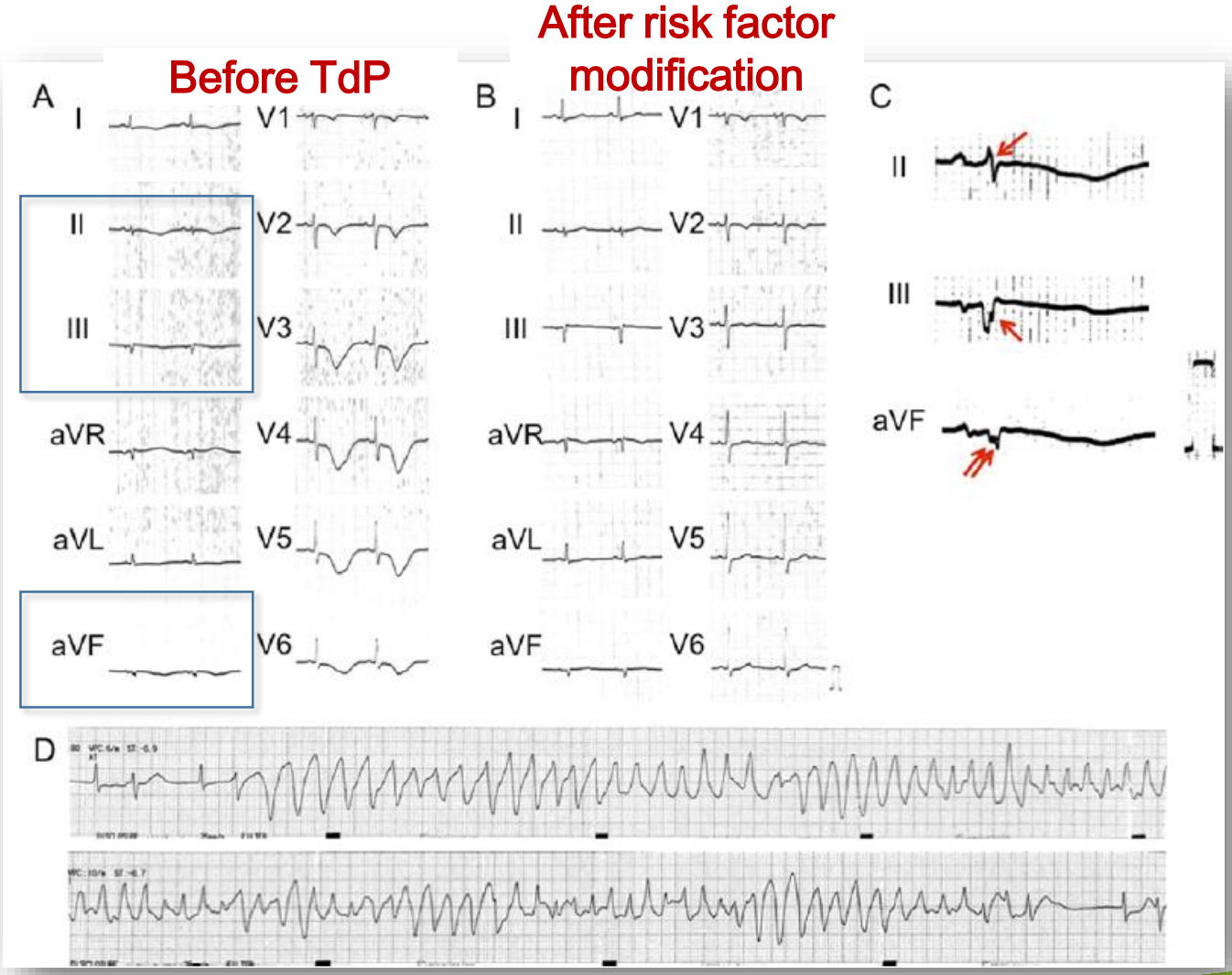
	No Change in QRS Axis	QRS Axis Change	*P* Value
ECG during AVB†			
QTc	442±62	501±89	0.001
QTcF	479±63	543±88	<0.001
ΔQT	153±82	222±96	<0.001
ΔQTc	−5±68	43±91	0.006
Long QT‡			
QT≥570 ms	31 (45%)	27 (73%)	0.008
QTc≥480 ms	19 (28%)	22 (60%)	0.002
Torsade de pointes	4 (6%)	8 (22%)	0.023

Predictor of TdP	Odds Ratio (95% Confidence Intervals)	*P* Value
Model 1 (without QTc)		
Female sex	9.6 (1.5–59.9)	0.016
Complete AVB*	2.1 (0.1–23.1)	0.54
R-R during AVB (for 100-ms increase)	1.1 (0.9–1.3)	0.46
QRS width during AVB (for 10-ms increase)	0.9 (0.7–1.0)	0.06
Change in QRS morphology	5.4 (1.4–21.3)	0.016
Change in QRS axis	3.1 (0.7–13.5)	0.130
Change in QRS morphology and axis	10.7 (2.0–57.6)	0.006

Circ AE 2014;7:1129-35.

Fragmented QRS is associated with torsades de pointes in patients with acquired long QT syndrome

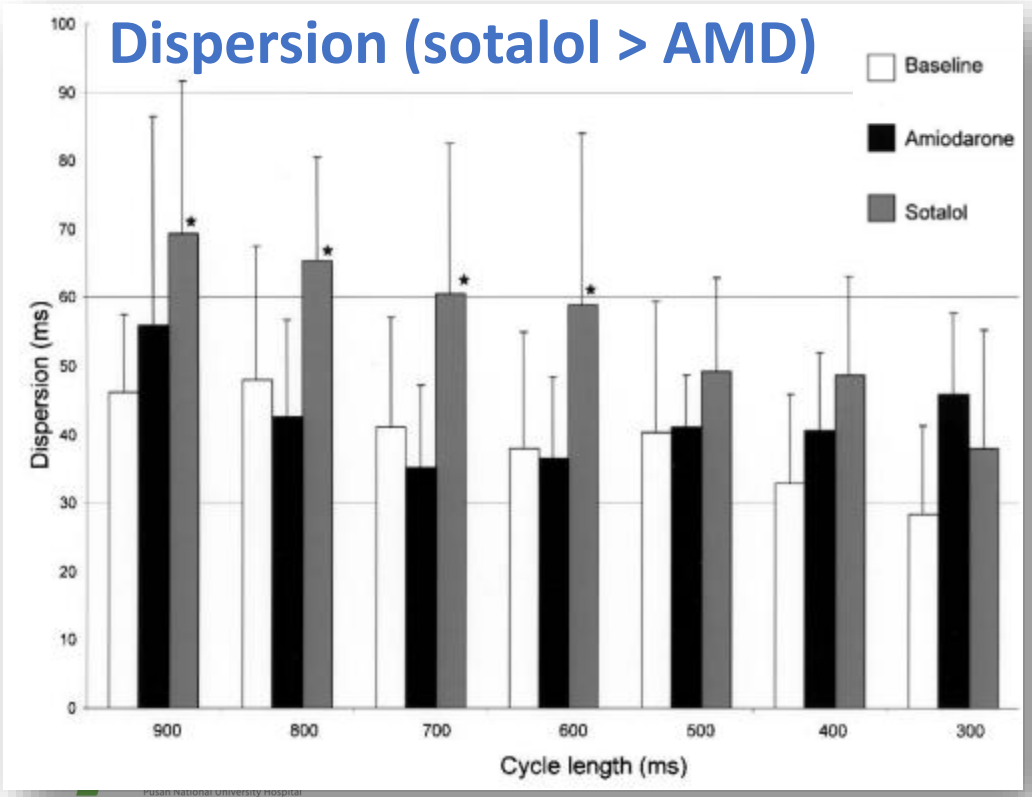
- **Fragmented QRS** - Depolarization abnormality
  - Substrate for reentrant circuit after TdP initiation

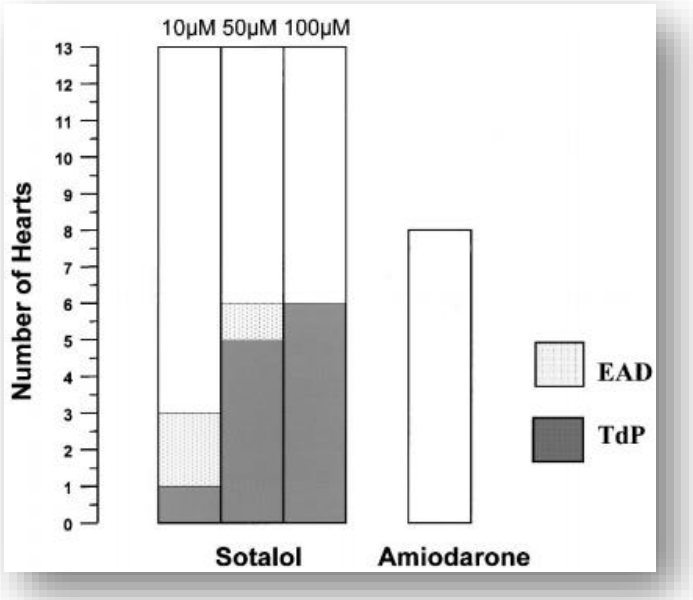


Heart rhythm 2010;7:1808-14.

c. Transmural dispersion of repolarization

- An increase in QT interval does not necessarily lead to TdP.
- Comparison of TdP induction between class III AAD.
  - In a rabbit model of acute AV block
  - **sotalol** vs. **amiodarone**



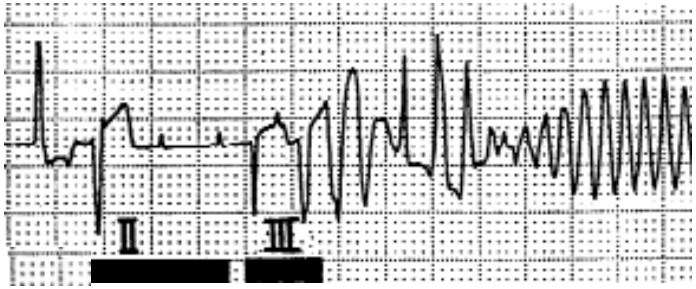


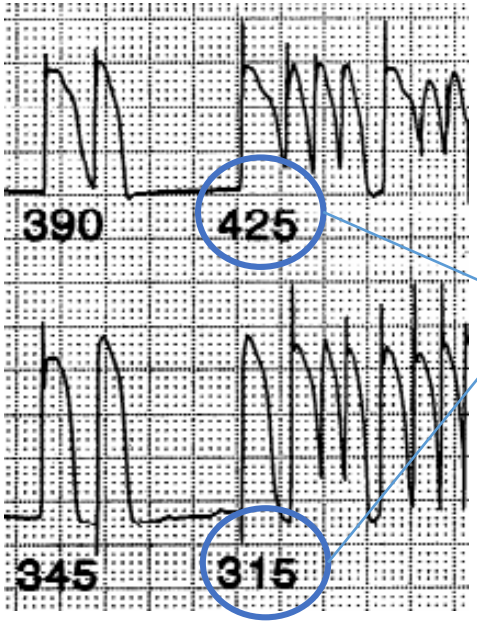
EAD, TdP (sotalol > AMD)

J Cardiovasc Pharmacol 2004;44:278-86.

c-1. Interventricular dispersion of repolarization

- **Long-short sequence**





LV APD

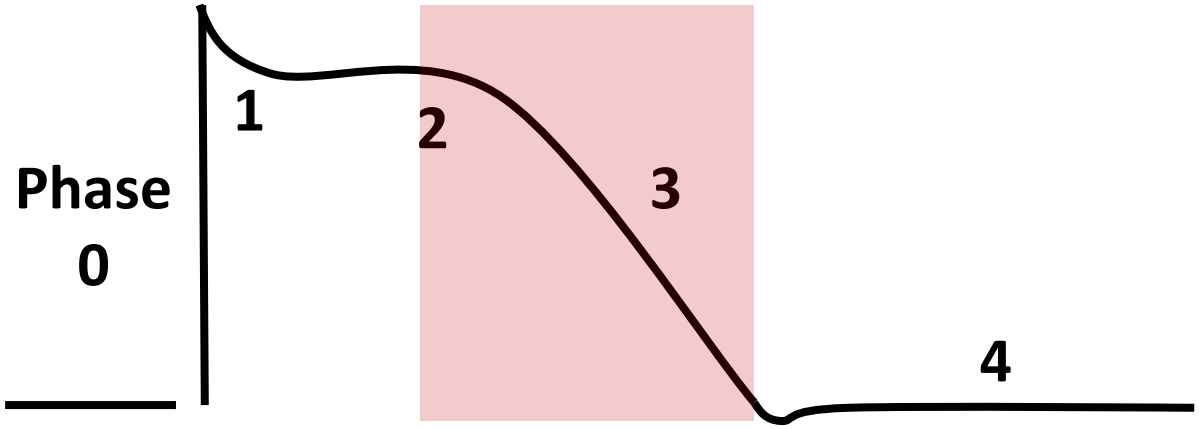
Interventricular dispersion of repolarization (110ms) → TdP

RV APD

Cardiovasc Res 2000;48:421-9.

d. T wave morphology

- Prolongation of AP duration
- Marked transmural dispersion of repolarization
- EAD triggering PVC, perpetuating TdP



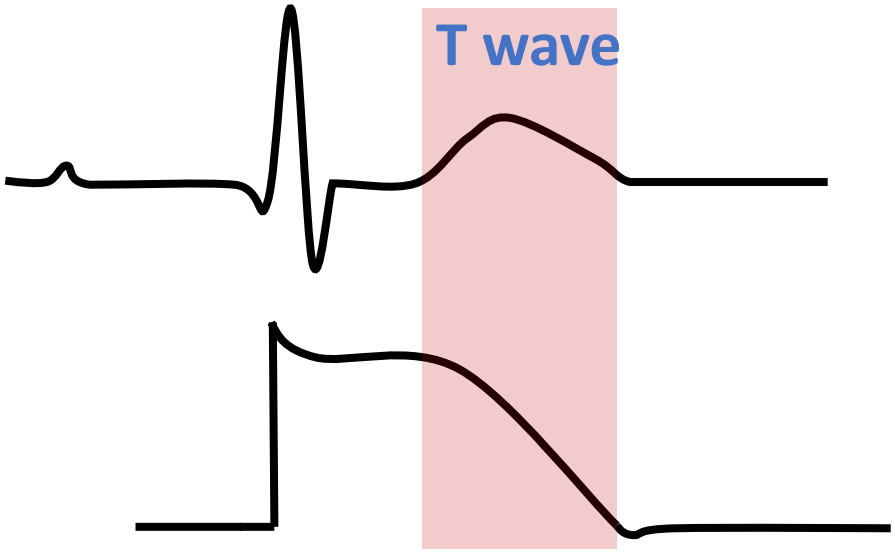
Repolarization problem

QT interval prolongation

T wave morphologic change

J Am Coll Cardiol 2007;49:320-8.

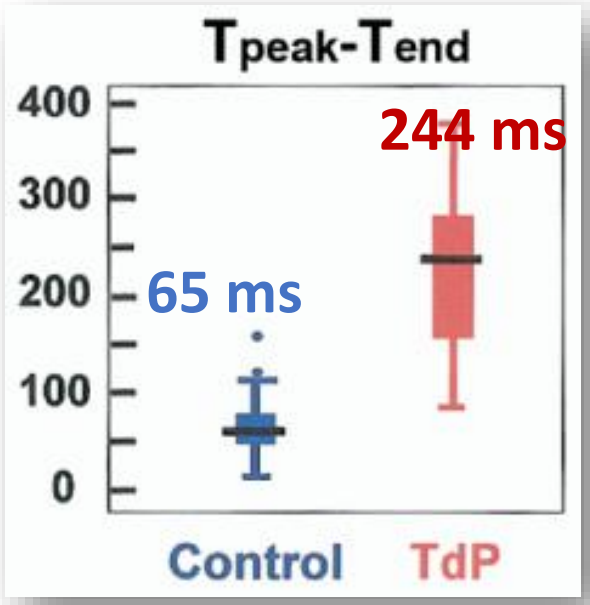
d. T wave morphology

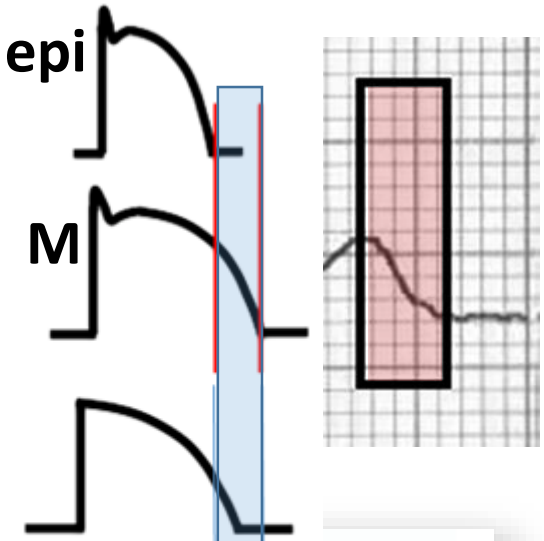


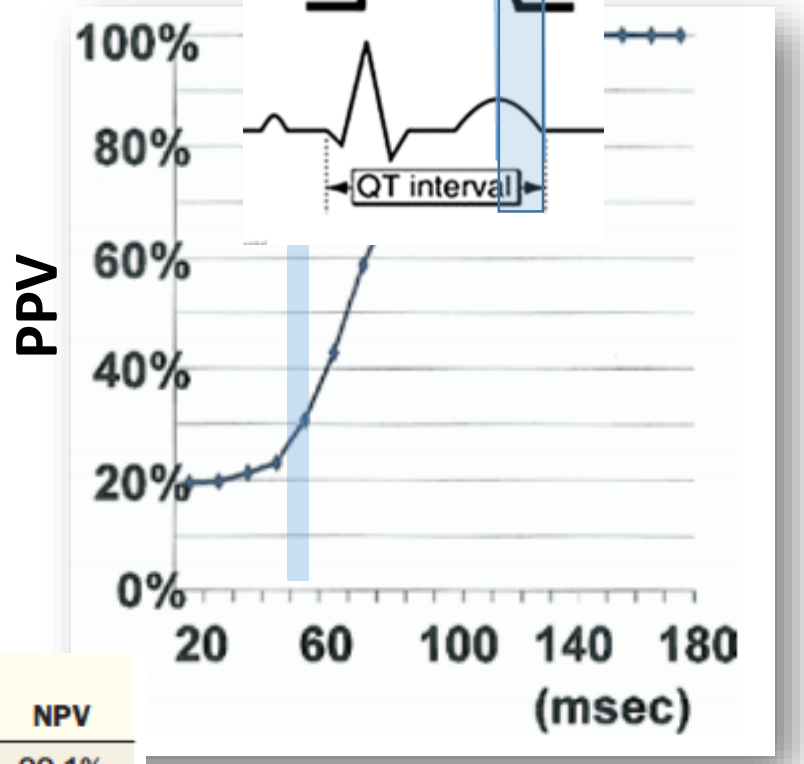
- T [peak] – T [end] interval
- Notched T wave (similar to LQT2)
- Complex (triphasic) T wave
- T wave alternans (macroscopic beat-to-beat alteration)
- Long QT with abnormal T-U wave

d-1. T [peak] – T [end] interval

- Comparison of Tpeak –Tend
- Pts with CAVB (TdP (-) vs (+))



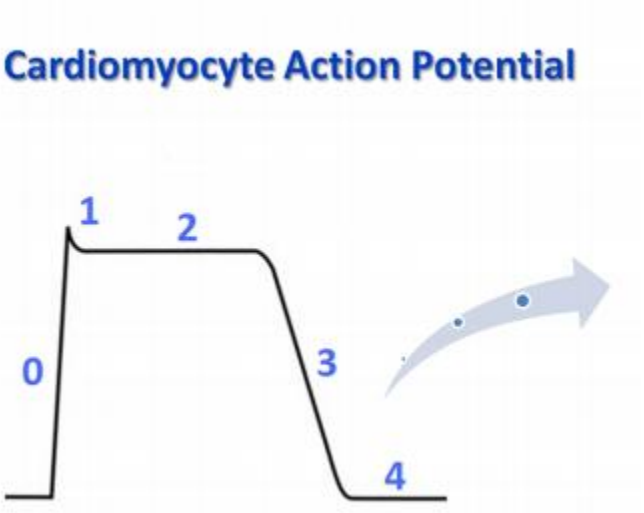




Parameter	Cutoff Value	Sensitivity	Specificity	PPV	NPV
T_{peak}–T_{end}	117 ms	96.6%	98.2%	93.3%	99.1%

J Am Coll Cardiol 2007;49:320-8.

d-2. Notched T wave (similar to LQT2)

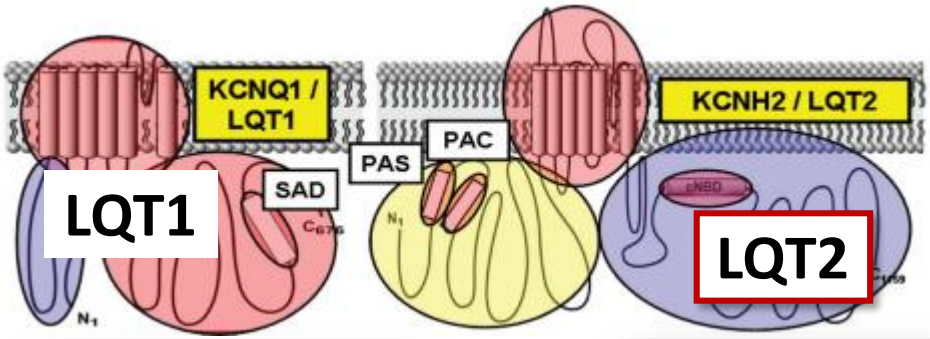


0	Na^+ (in) ✓I_{Na} (rapid)
1	K^+, Cl^- (out) ✓$I_{to1,2a}$ (transient outward)
2	Ca^{2+} (in), K^+ (out) ✓I_{Ca-L} (Ca long) ✓I_{KS} (K slow delayed rect.)
3	K^+ (out) ✓I_{KS} (K slow delayed rect.) ✓I_{KR} (K rapid delayed rect.) ✓I_{K1} (inward rect.)
4	K^+ (out) ✓I_{K1} (inward rect.)

Phase 3 : blocking delayed rectifier K current
→ QT prolongation

Iks (KCNQ1)

Ikr (KCNH2)



Broad T

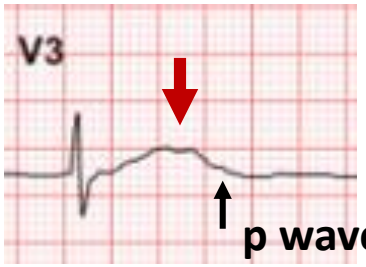
Bifid T

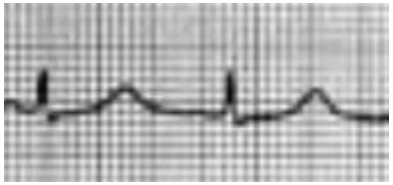
Circulation 2011;123:1021-37.
Postgrad Med J 2014;90:349-58.

LQT2-like T wave morphology

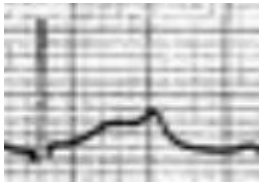
Table 1 Clinical and Electrocardiographic Characteristics of Patients With Bradyarrhythmias With and Without Torsade de Pointes

Variable	TdP n = 30	Control n = 113	p Value
QT morphology			
LQT1-like	4 (13.8%)	10 (8.8%)	0.426
LQT2-like	16 (55.2%)	3 (2.7%)	<0.001
LQT2 with T2>>T1	8 (27.6%)	0 (0%)	<0.001
LQT3-like	2 (6.9%)	6 (5.3%)	0.741
"Bumps-ahead sign"	17 (58.6%)	20 (17.7%)	<0.001

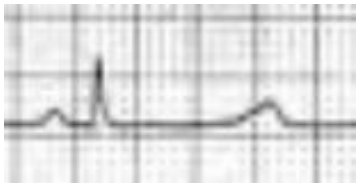




LQT1



LQT2



LQT3

J Am Coll Cardiol 2007;49:320-8.

Torsades de pointes complicating atrioventricular block: Evidence for a genetic predisposition

Tested gene

: HERG, KCNQ1, KCNE1, KCNE2, SCN5A

29 with CAVB, QT>600ms

VS.

22 with CAVB, QT<600ms

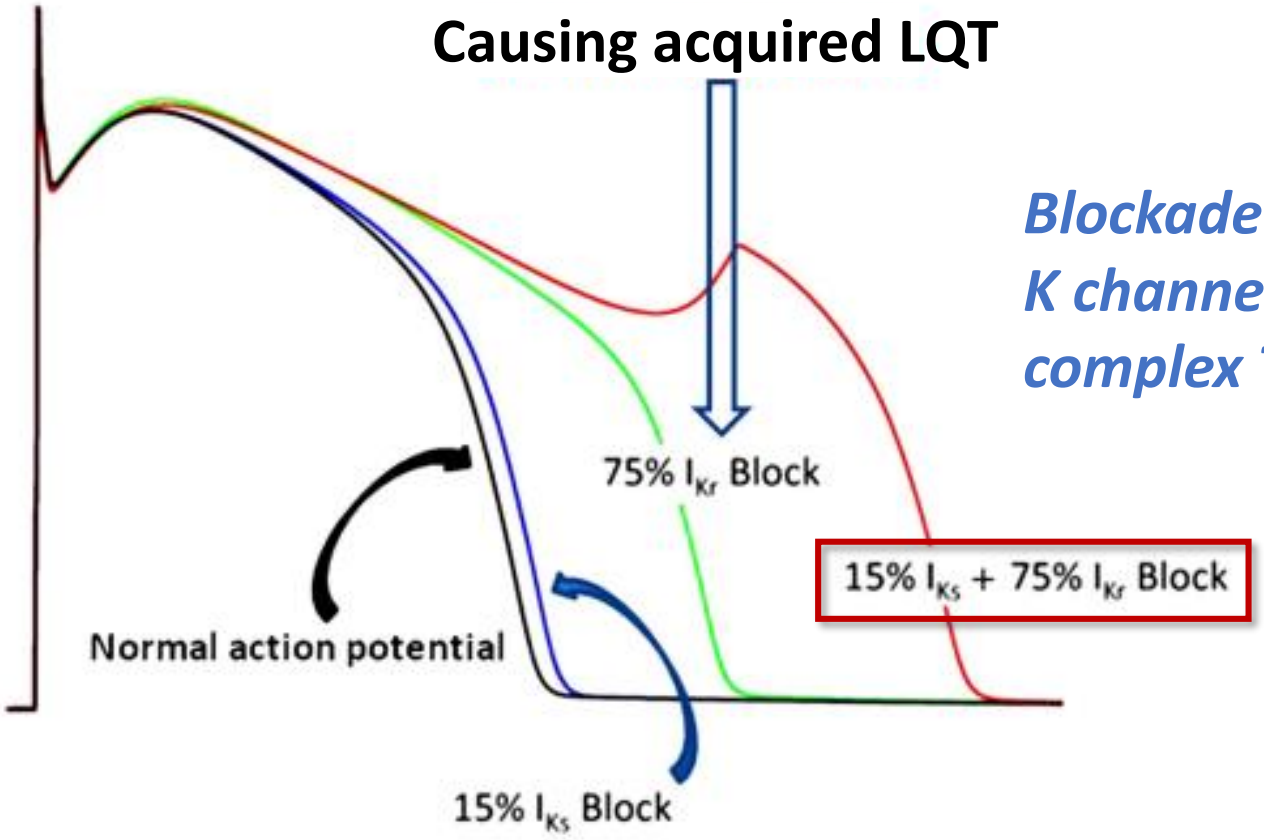
VS.

100 healthy controls

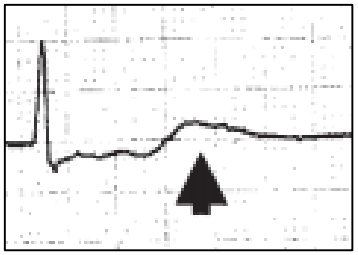
CAVB with LQT was associated with **HERG mutation in 17%** !

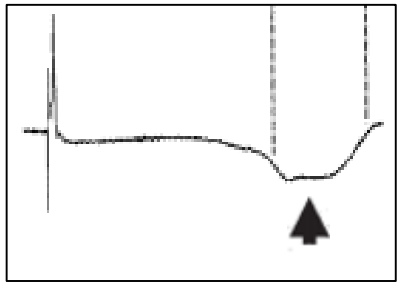
Heart rhythm 2007;4:170-4.

d-3. Complex T wave



Blockade of combined K channels → complex T waves





J Am Coll Cardiol 2007;49:320-8.
J Am Coll cardiol 2005;45:300-7.

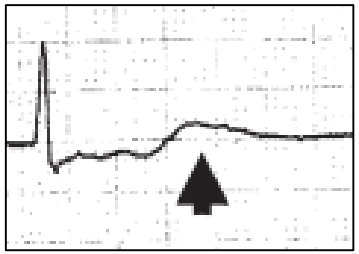
d-3. Complex (Triphasic) T wave

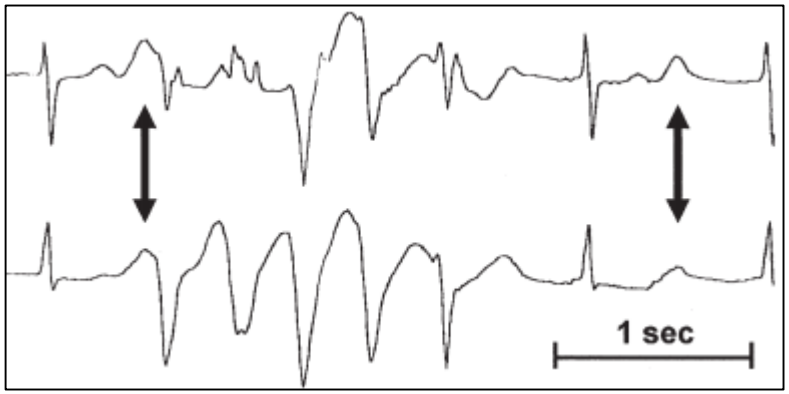
Table 1 Clinical and Electrocardiographic Characteristics of Patients With Bradyarrhythmias With and Without Torsade de Pointes

Variable	TdP n = 30	Control n = 113	p Value
QT morphology			
LQT1-like	4 (13.8%)	10 (8.8%)	0.426
LQT2-like	16 (55.2%)	3 (2.7%)	<0.001
LQT2 with T2>>T1	8 (27.6%)	0 (0%)	<0.001
LQT3-like	2 (6.9%)	6 (5.3%)	0.741
"Bumps-ahead sign"	17 (58.6%)	20 (17.7%)	<0.001

U wave?
Sign of EAD?

Triphasic T : late positive component

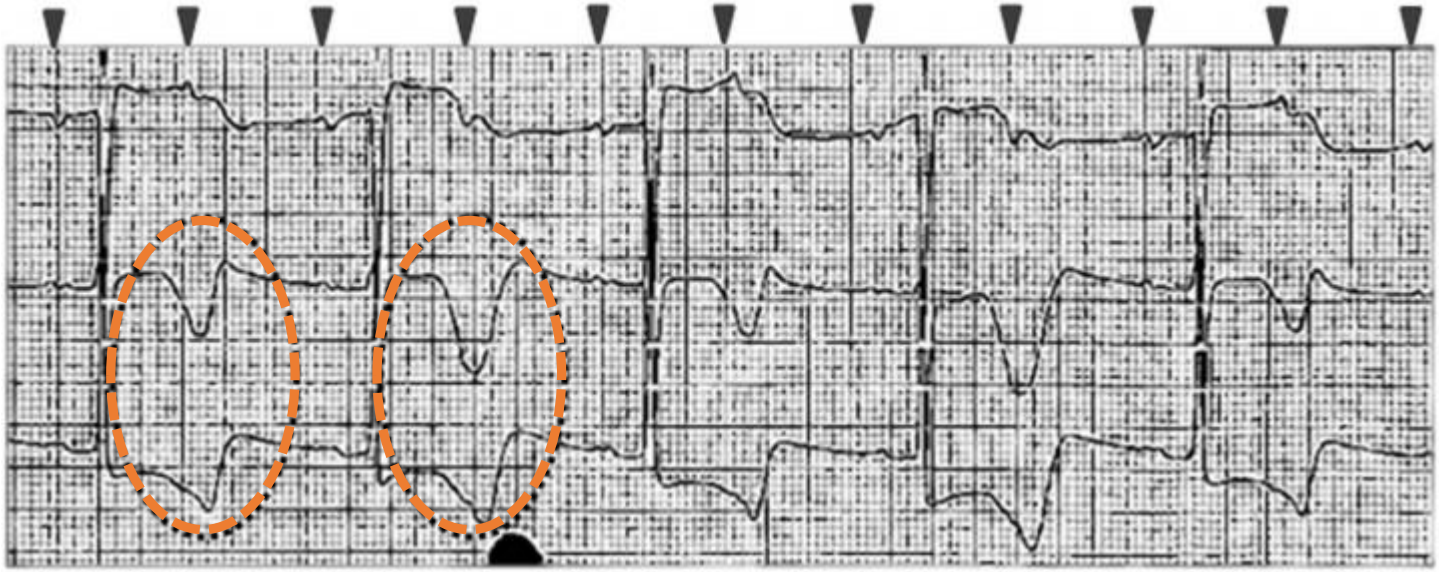




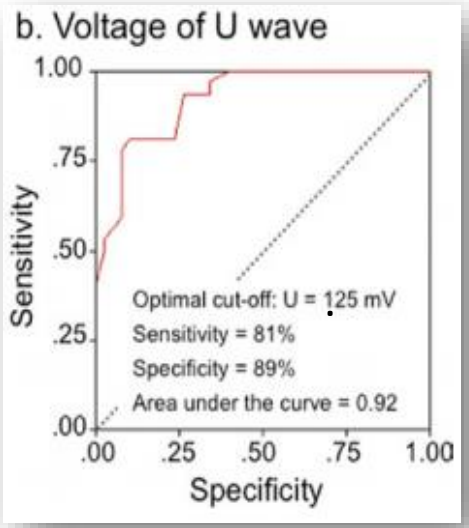
J Am Coll Cardiol 2007;49:320-8.

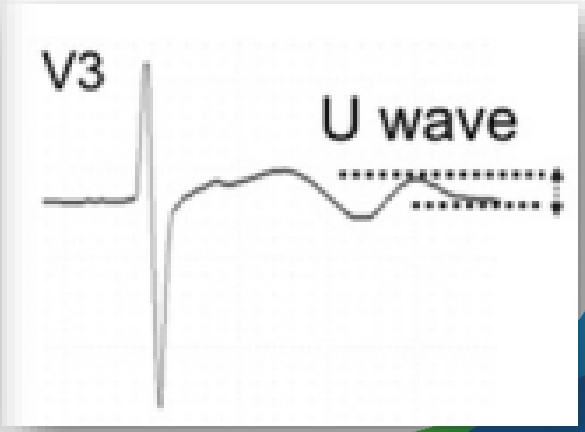
d-4. Others

- T wave alternans (macroscopic beat-to-beat alteration)



- **Long QT wave with abnormal T-U wave**





Heart Rhythm 2015;12:498-505
J Am Coll Cardiol 2009;54:143-9.

A 2-Step Model for predicting TdP

The Morphology of the QT Interval Predicts Torsade de Pointes During Acquired Bradyarrhythmias

Parameter	Cutoff Value	Sensitivity	Specificity	PPV	NPV
T_{peak}–T_{end}	117 ms	96.6%	98.2%	93.3%	99.1%
QTc interval	480 ms	96.6%	92.0%	75.7%	99.0%
QT interval	570 ms	90.0%	86.7%	64.3%	97.0%

Values derived from receiver-operating characteristic curves.
NPV = negative predictive value; PPV = positive predictive value; QTc = corrected QT interval.

QT interval > 510ms

LQT2-like T wave +

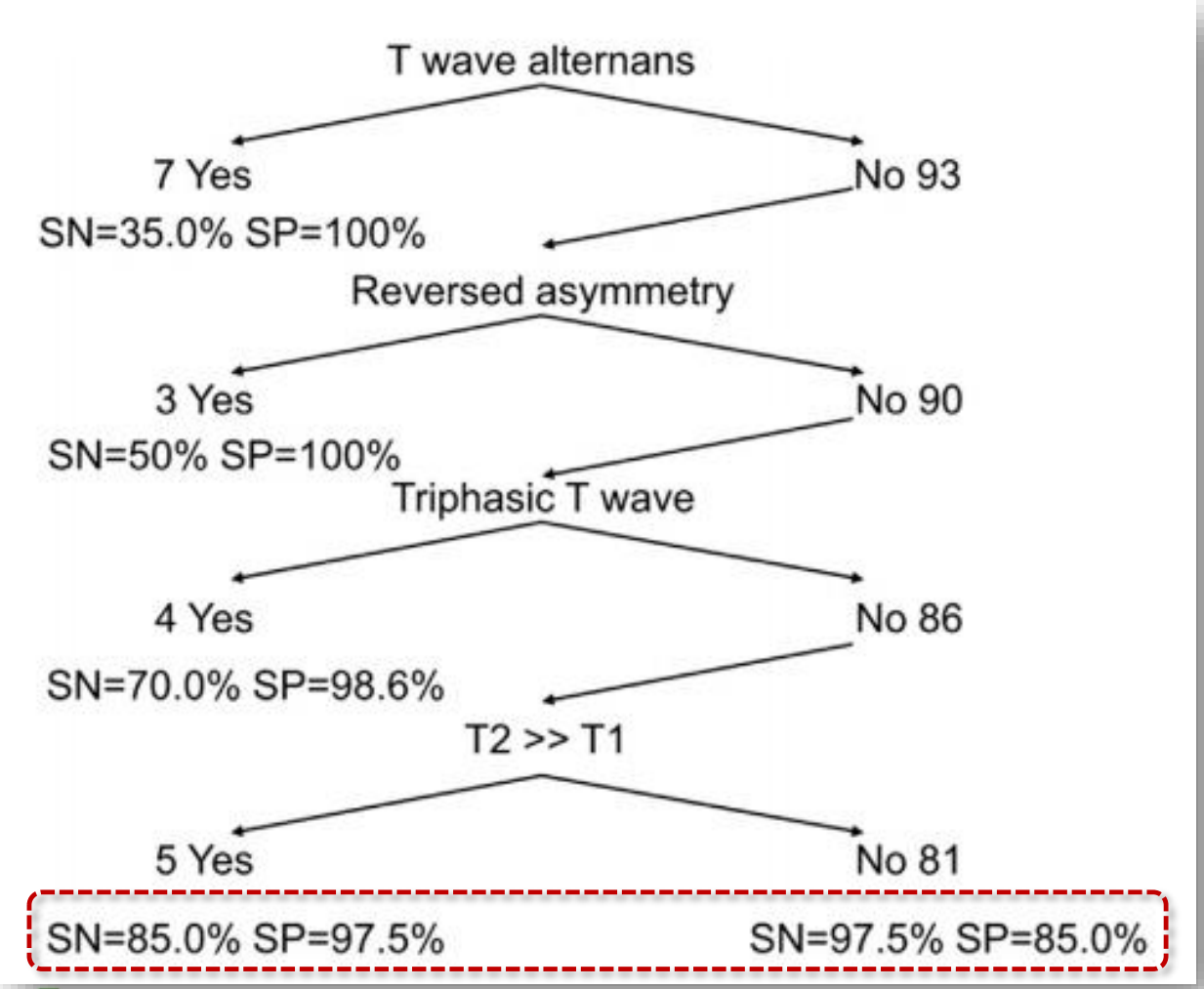
Tpeak-Tend > 85ms

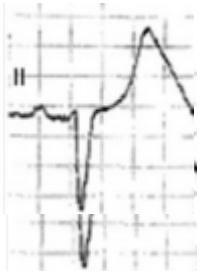
Specificity 97.3%
PPV 84.2%

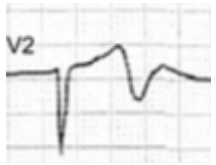
Specificity 99%
PPV 94%

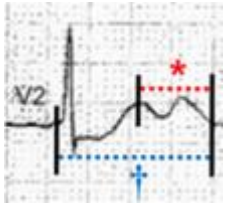
J Am Coll Cardiol 2007;49:320-8.

Electrocardiographic predictors of bradycardia-induced torsades de pointes in patients with acquired atrioventricular block









Heart Rhythm 2015;12:498-505.

Summary

- TdP is a polymorphic ventricular tachycardia caused by a long QT interval.

- Prolongation of AP (decrease in K^+ or increase in Na^+ or Ca^{++}) → transmural dispersion of repolarization → EAD (reactivation of L-type Ca^{++} or late I_{Na} or Na-Ca exchanger) → PVC when EAD reaching threshold → initiation of TdP → perpetuation (transmural reentry)

Predictors for TdP risk from ECG

- **QT prolongation**

  → heterogeneous dispersion of repolarization

- **PVC with long-short sequence, R-on-T**

- **Changes in QRS morphology and axis**

- **Changes in T wave morphology**
  - T [peak] – T [end] interval
  - Notched T wave (similar to LQT2) – genetic component (+)
  - Complex (triphasic) T wave
  - T wave alternans (macroscopic beat-to-beat alteration)
  - Long QT with abnormal T-U wave

Thank you for your attention !