Updates of LQTS

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Clinical Diagnosis of LQTS

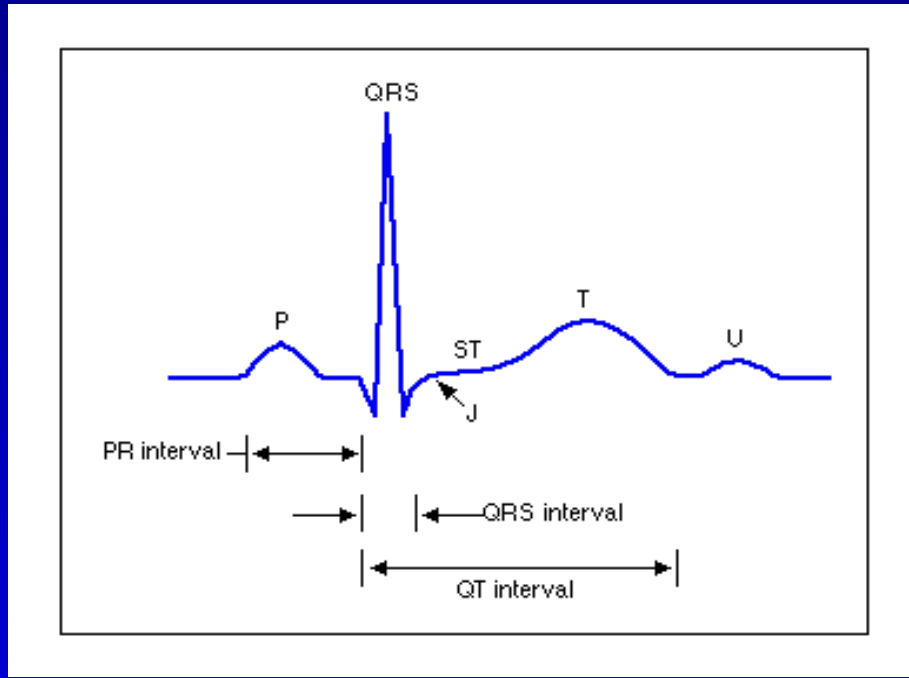
- **Sudden death, syncope, or QT prolongation on an incidental ECG.**
- **When QTc prolongation is identified following a syncopal event, the diagnosis of LQTS is certain**

ECG Findings in LQTS

- **QT interval should be measured from the onset of Q wave to the end of T wave in an ECG leads, usually lead II.**
- **QTc=QT/√RR**
- **QTc prolonged**

  Men > 0.45 s

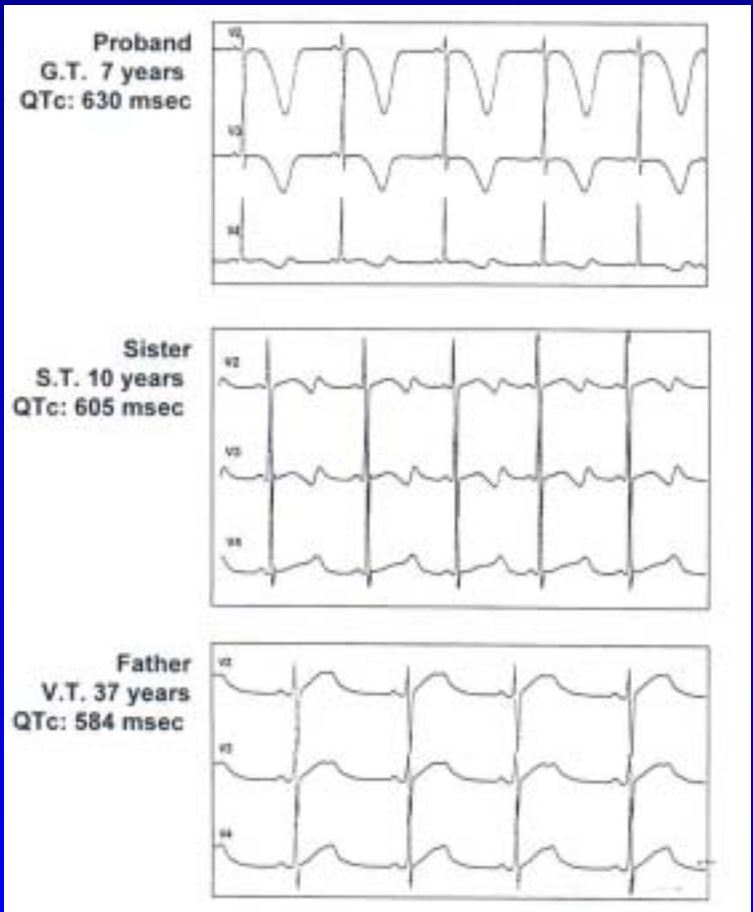
  Women > 0.46 s



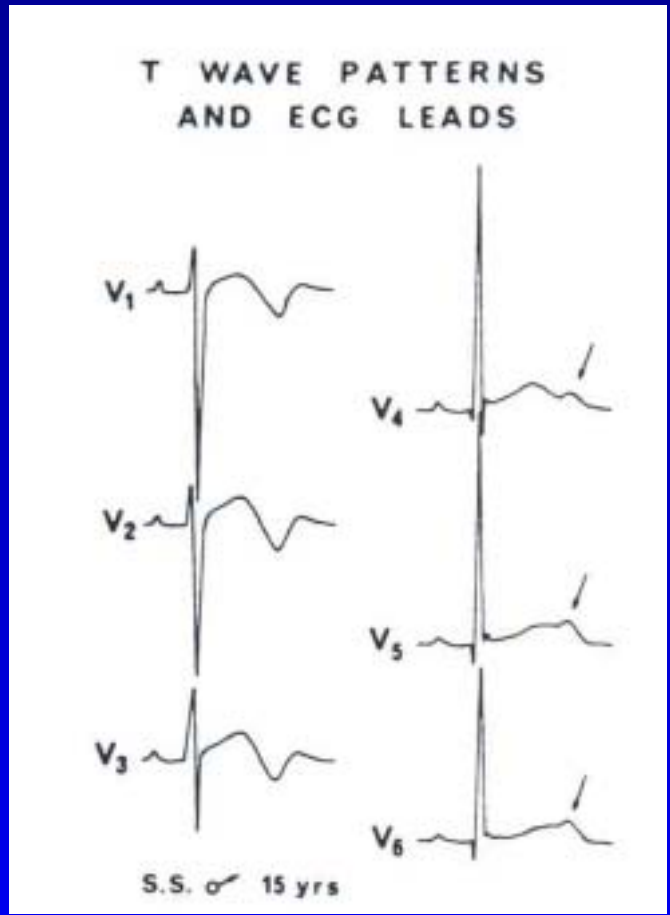
ECG abnormalities

- Notched or bifid T wave in the V_2 - V_5
- Repolarization abnormalities: more frequent in those patients with cardiac events.
- Notched T wave in recovery phase of exercise

T wave morphology

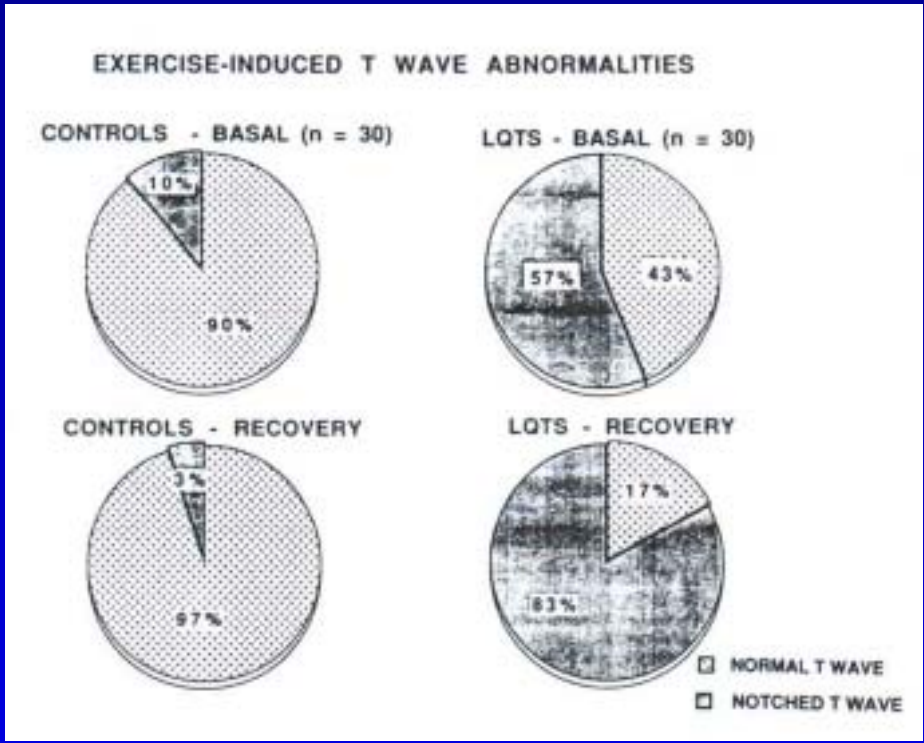


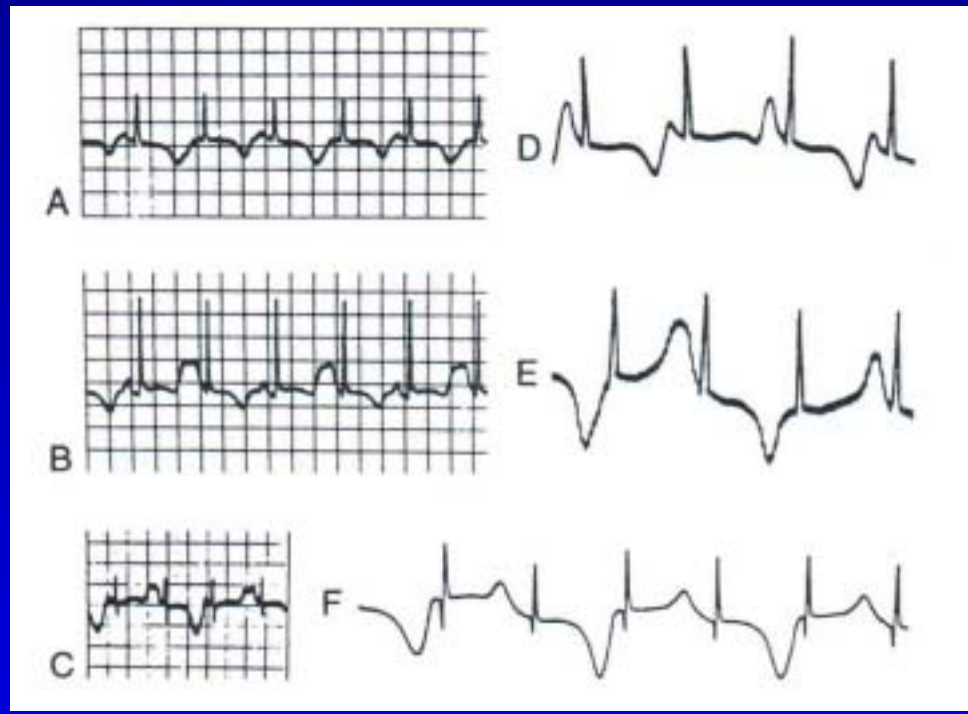
Schwartz PJ et al. Cardiac electrophysiology 2000:597-615



Malfatto G et al. J Am Coll Cardiol 1994;23:296-301

T wave abnormalities





Jervell A. et al. Adv Intern Med 1971;17:425-438

Heart rate abnormalities

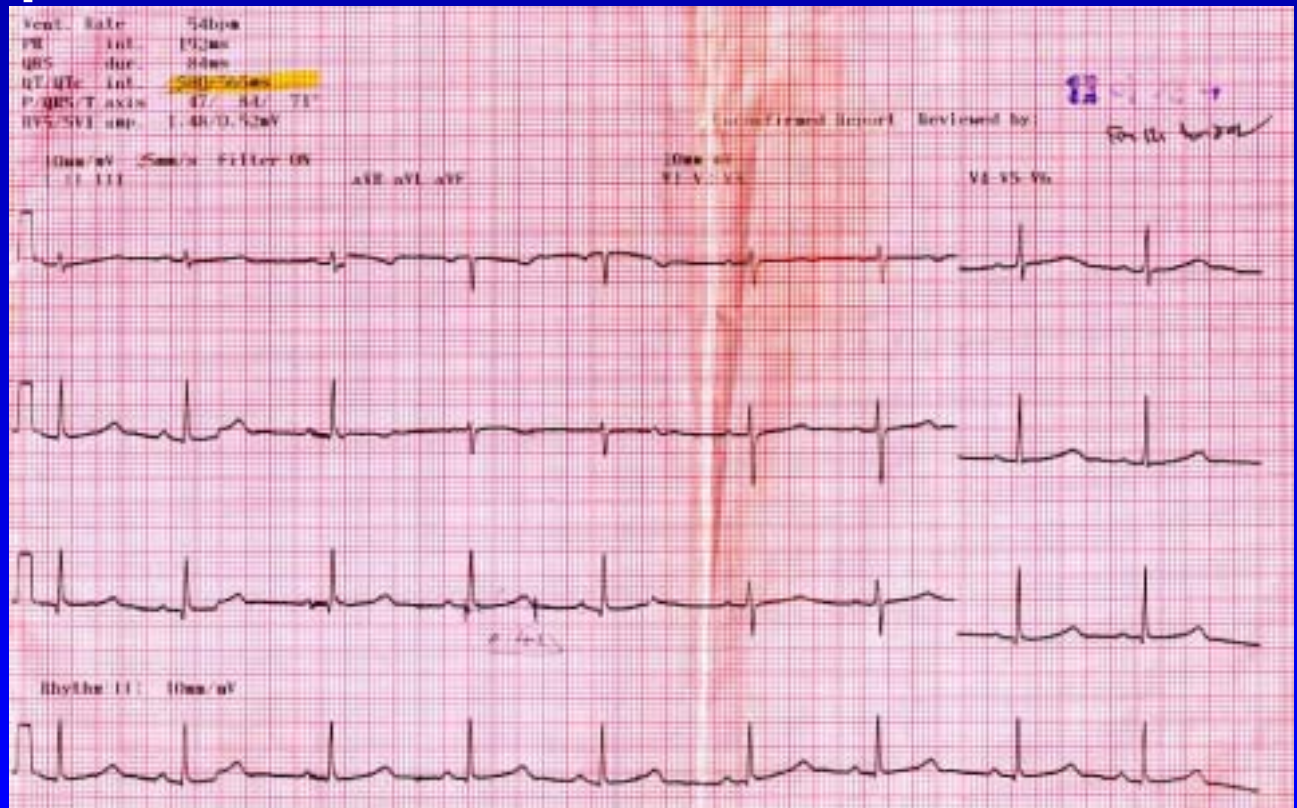
- Sinus pauses; usually followed by the appearance of a notch on the T wave
  - precede the onset of TdP
- Heart rate: lower than normal heart rate esp, children and evident at rest and during exercise.

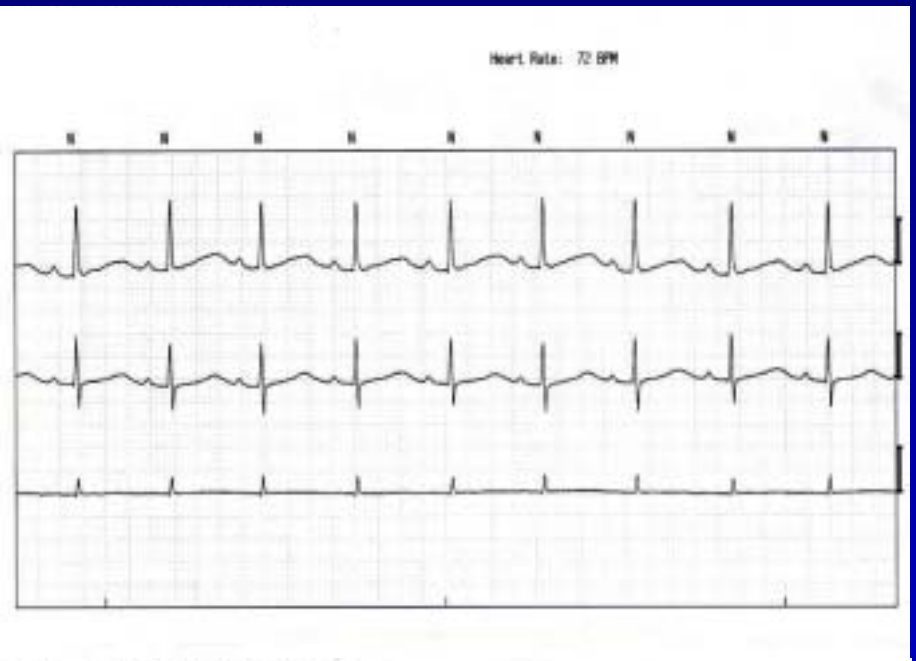
Case (1)

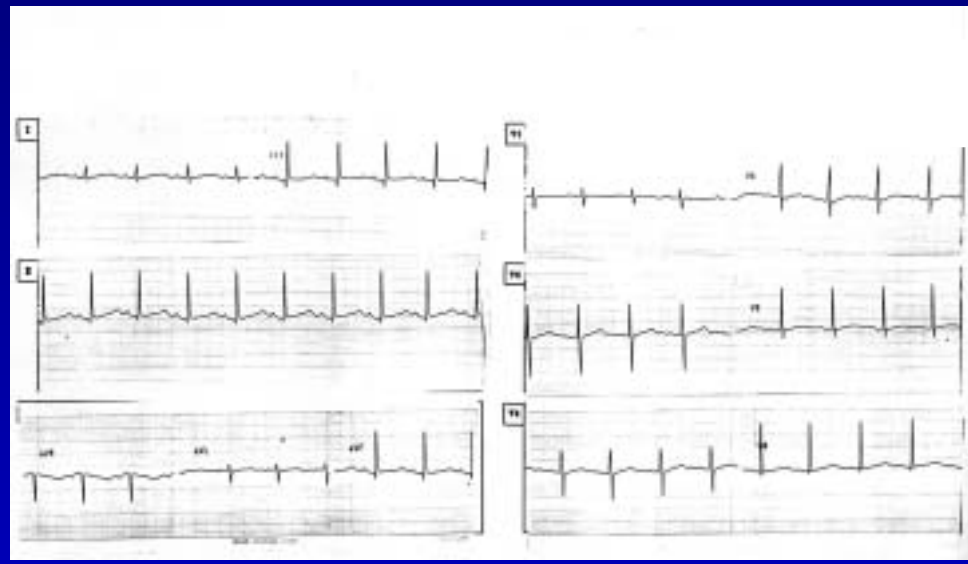
- 21 yr old woman, transferred to cardiology department
- Patient has frequent syncopal attack since childhood, it was managed by dilantin
- Patient complained intermittent chest discomfort for 1 month
- Family history negative for syncope, palpitation, premature deafness. But elder sister has mental retardation
- ECG of her mother and brother shows unremarkable findings.
- Normal K^+ & Mg level
- ECG; long QT intervals.
- What is next step?

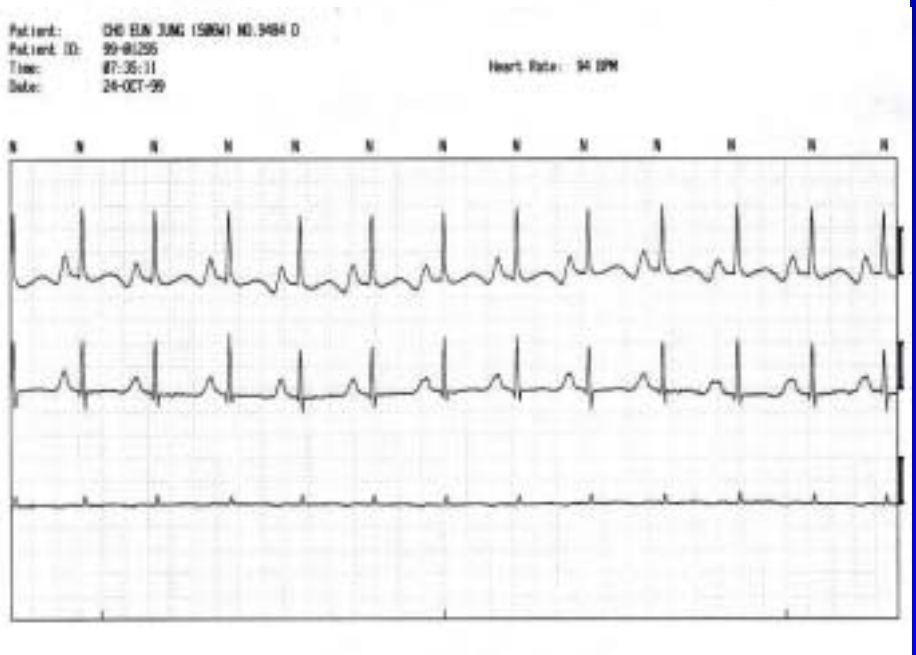
Diagnostic Procedure to LQTS

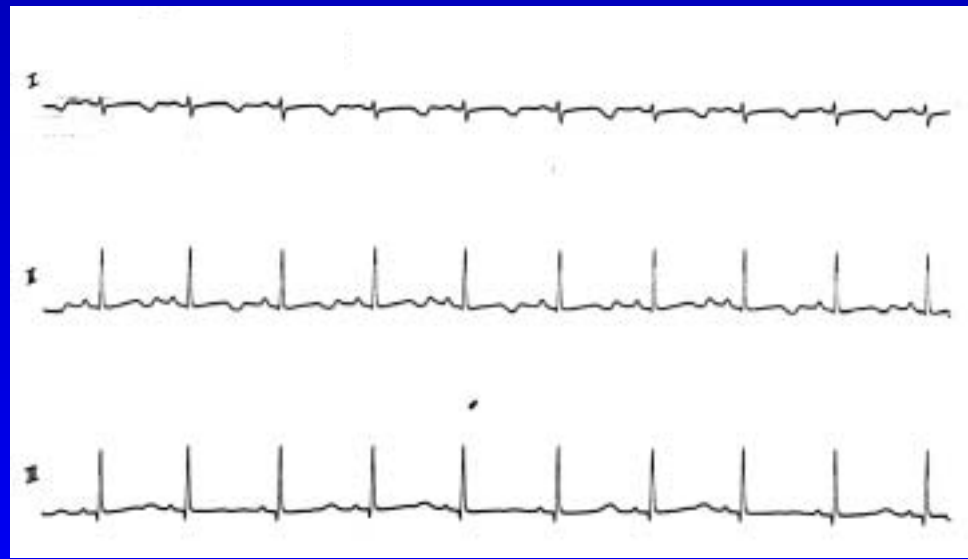
- Treadmill test; increased QT interval during and after exercise
- Holter monitoring; T wave changes
- Head up tilt test; T wave alternans, TdPs after isoproterenol infusion

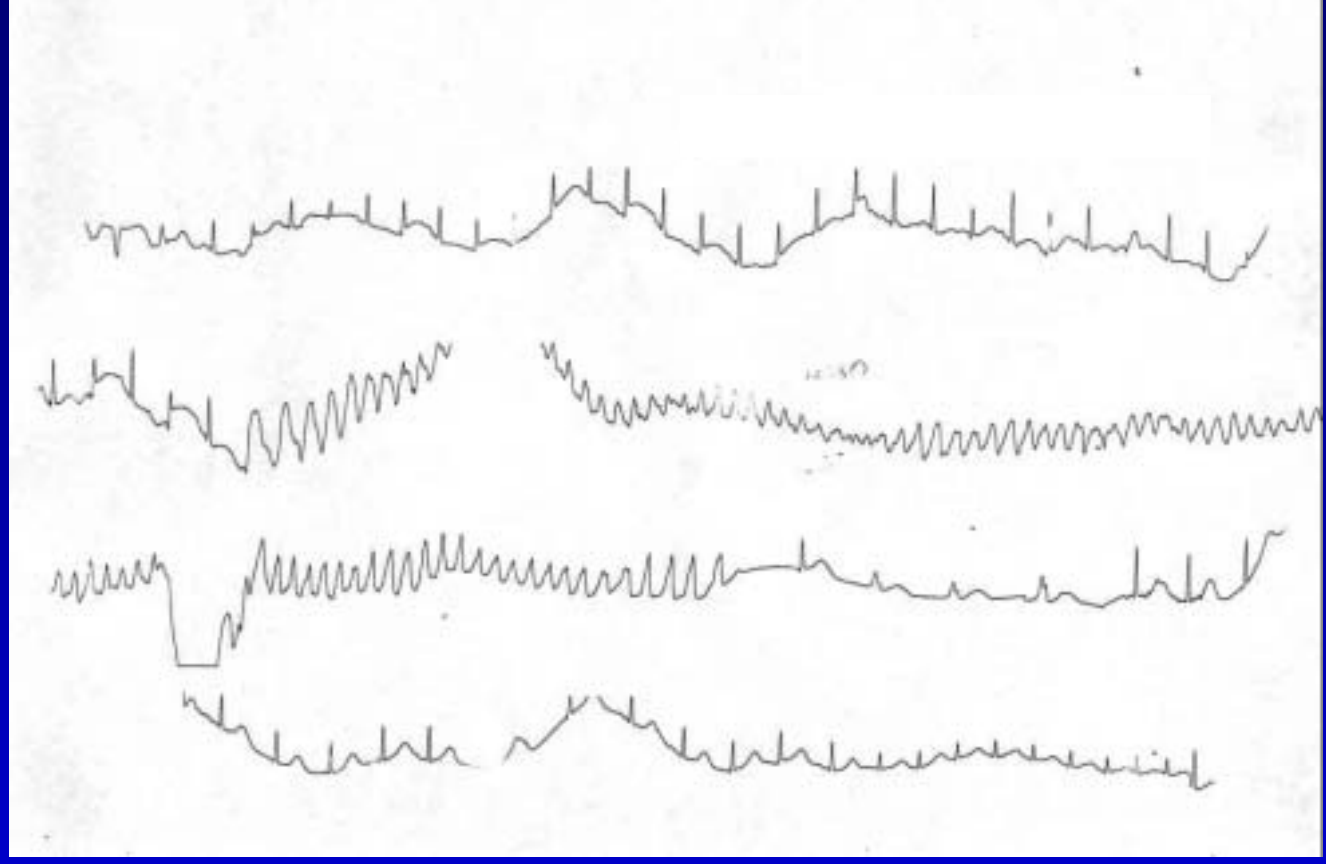


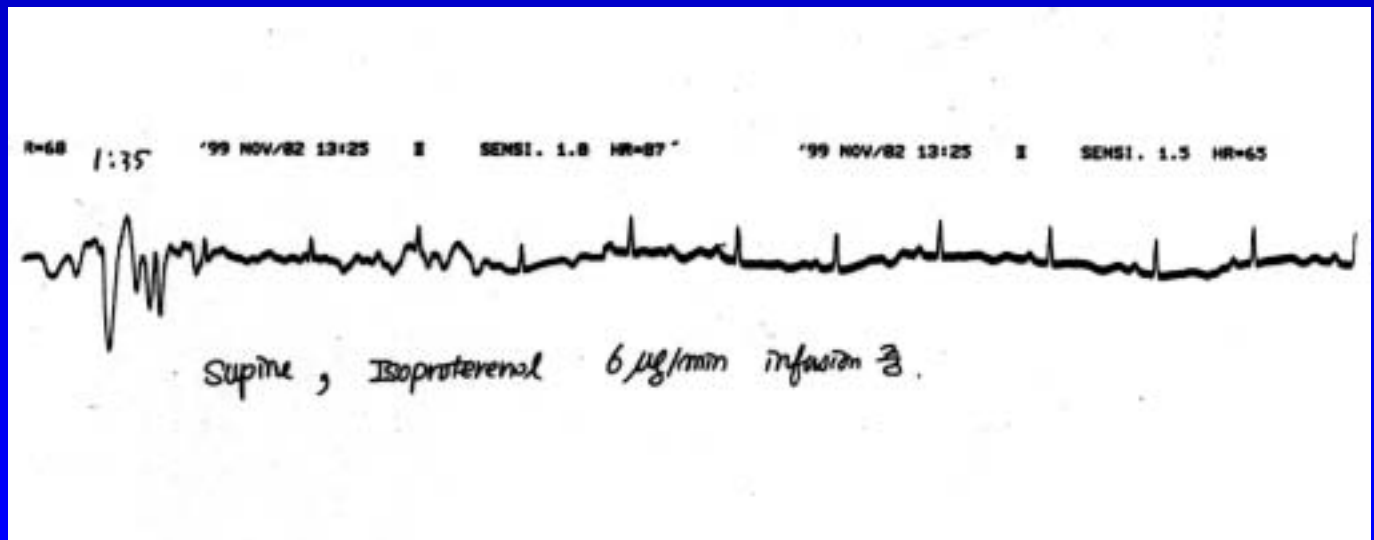

Heart Rate: 72 BPM




Patient:
Patient ID:
Time:
Date:
24-OCT-99
Heart Rate: 94 BPM

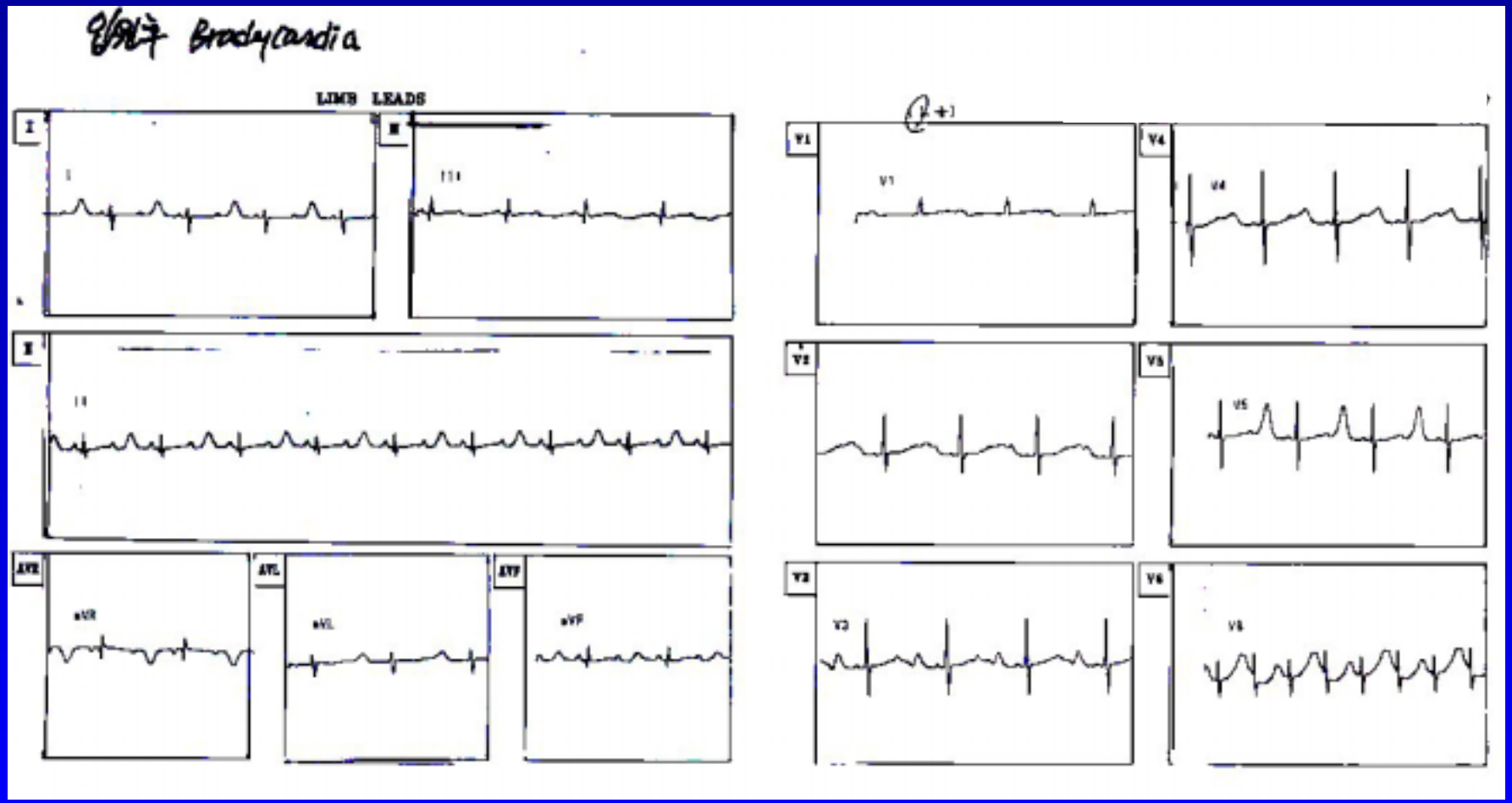

I
II
III

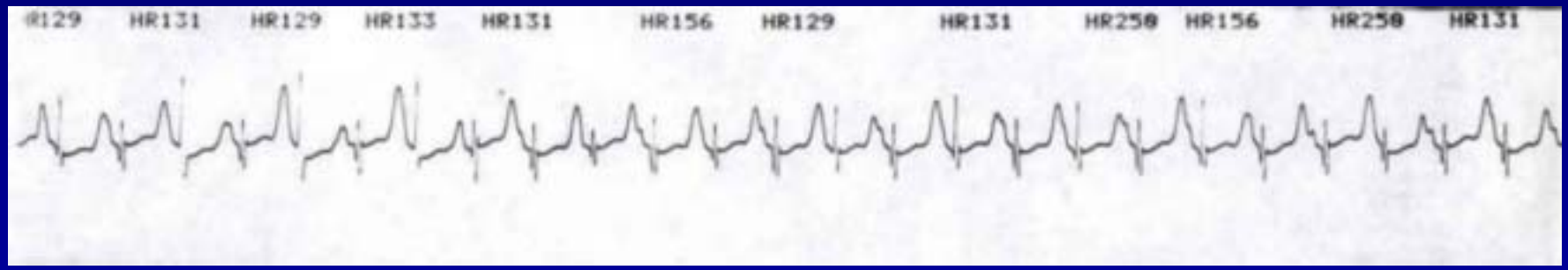


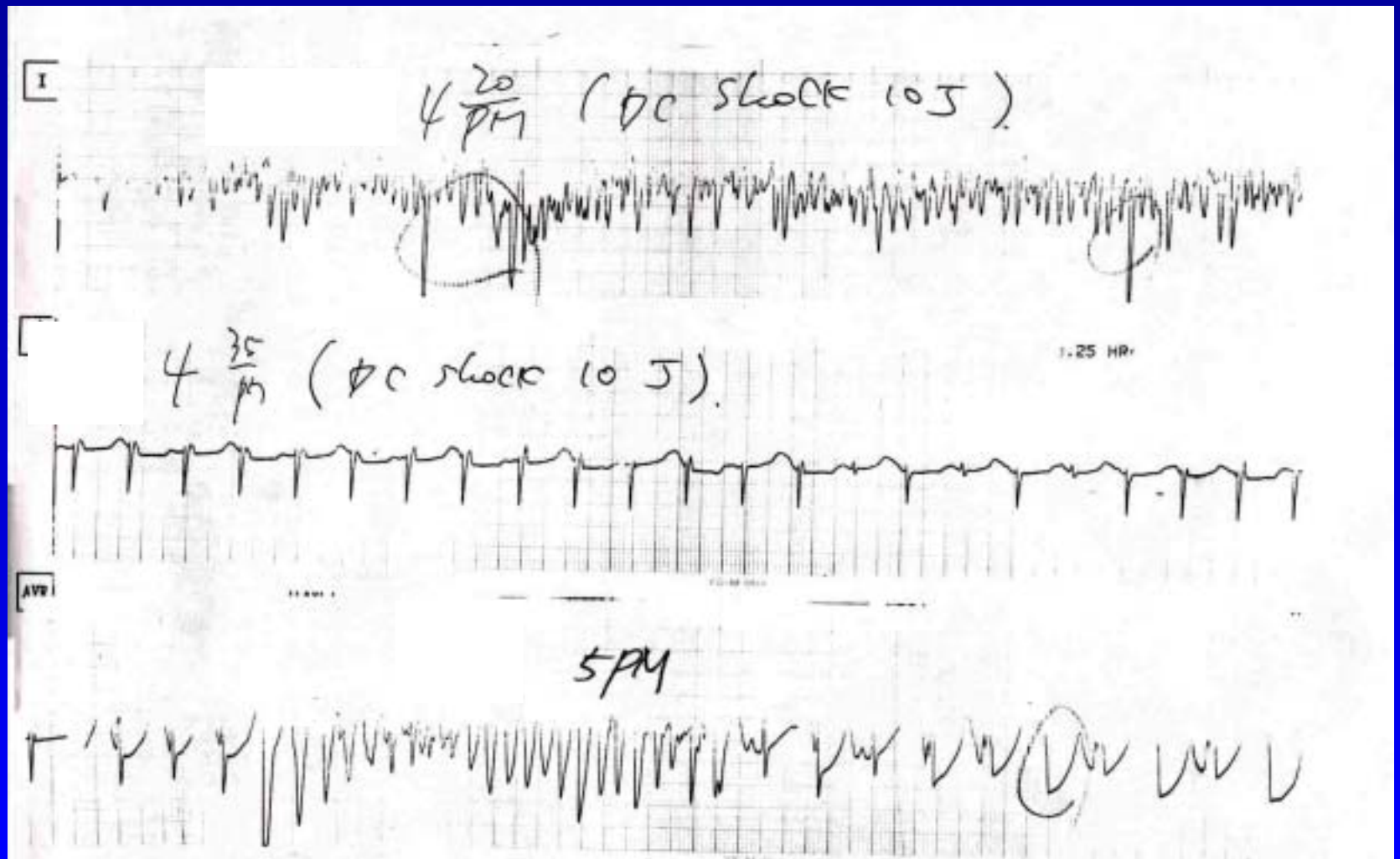

R=68 1:35 '99 NOV/02 13:25 I SENSI. 1.0 HR=87' '99 NOV/02 13:25 I SENSI. 1.5 HR=65
Supine, Isoproterenol 6 μg/min infusion 중.

Case 2

- 3 months male infant : frequent episode of seizure, whole body cyanosis,
- ECG : 2:1 AV block




HR129
HR131
HR129
HR133
HR131
HR156
HR129
HR131
HR250
HR156
HR250
HR131


I
4 20 PM (DC shock 10 J)
4 35 PM (DC shock 10 J)
1.25 HR
AVR
5PM

LQTS Diagnostic Criteria

Electrocardiographic Finding	Points
– QTc	
>480 ms	3
460-470 ms	2
450 (male) ms	1
– Torsade de pointes	2
– T wave alternans	1
– Notched T wave in 3 leads	1
– Low heart rate for age	0.5

Clinical History	Points
– Syncope	
With stress	2
Without stress	1
– Congenital deafness	0.5
Family History	
– (+) family Hx of LQTS	1
– Unexplained sudden death < 30	0.5

<2 points: low probability

2 to 3 points: intermediate probability

>4 points: high probability of LQTS

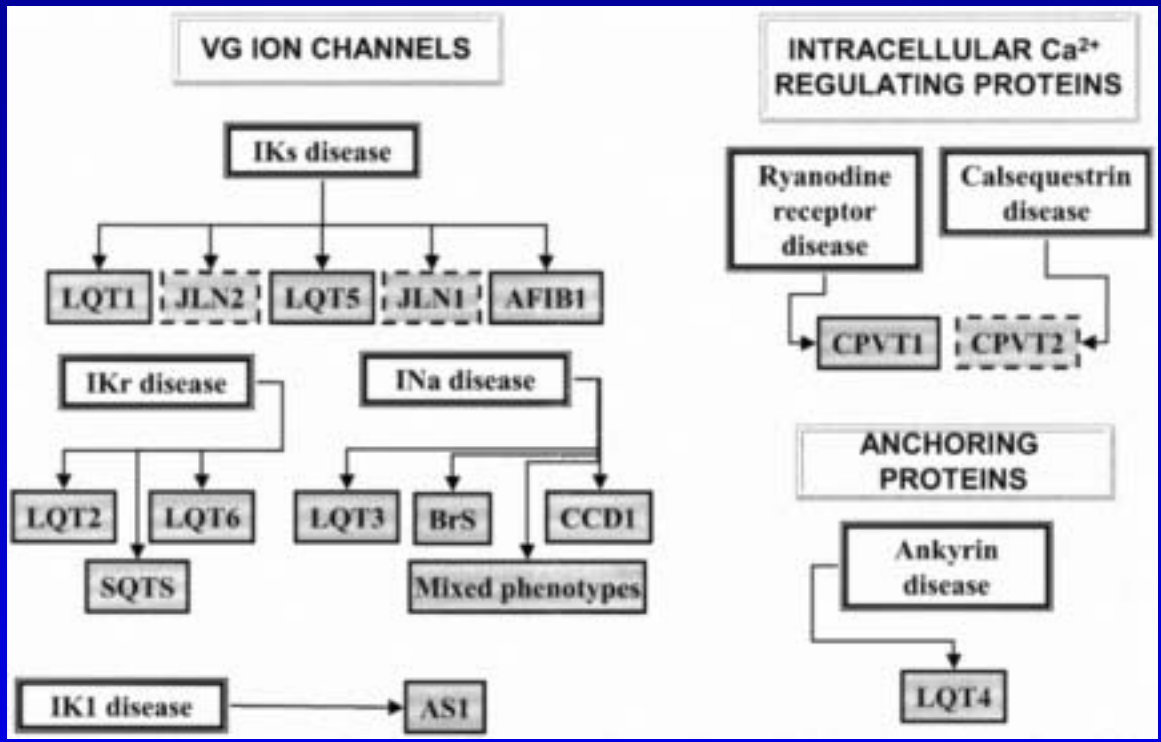
Inherited long QT syndrome

- **Autosomal dominant**
  - **Romano and Ward (1960).**
  - **Prolongation of QT interval and predisposition to torsades de pointes**
  - **No other obvious physical abnormalities**
- **Autosomal recessive**
  - **Jervell and Lange-Neilsen (1957)**
  - **Congenital neural deafness.**
  - **1 % of congenital deaf children had prolongation of the long QT interval**

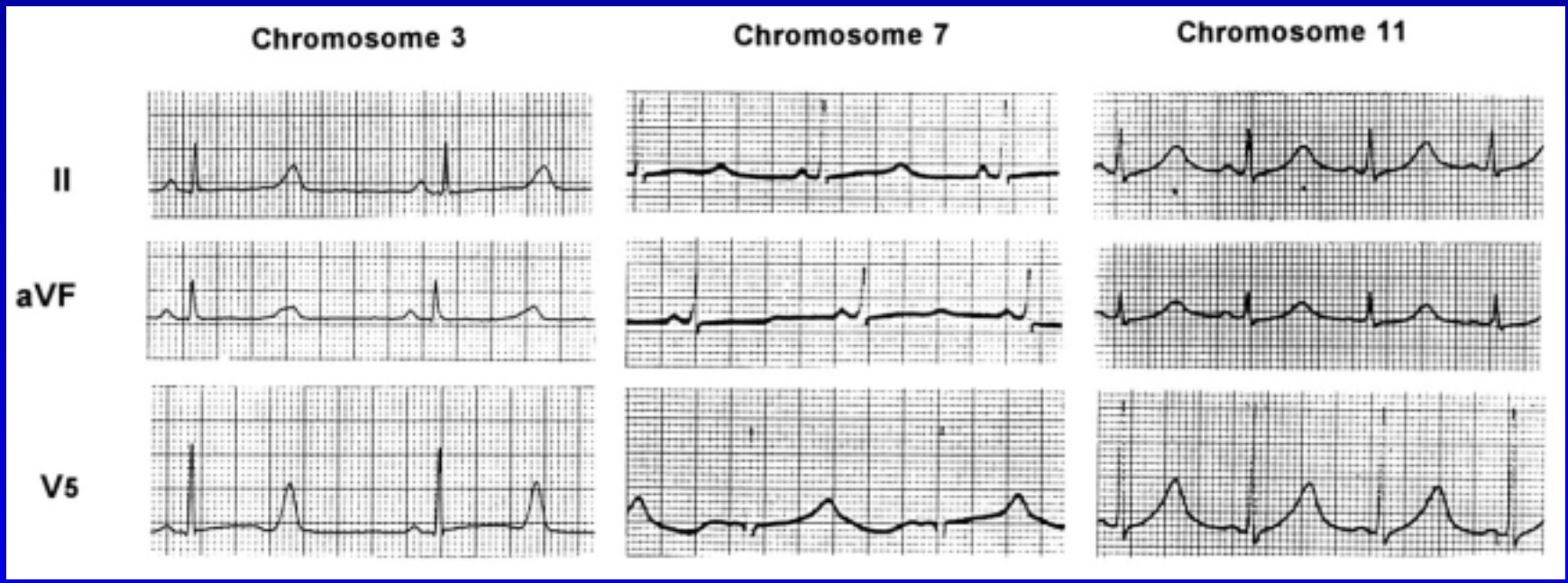
Molecular Genetics of LQTS

LQTS Type (Years Discovered)	Chromosomal Locus	Mutant Gene (Alternate Name)	Ion Currents	Frequency
LQT1(1991)	11p15.5	*KCNQ1 (KVLQT1)*	I_{Ks}	~ 50%
LQT2 (1994)	7q35-36	HERG	I_{Kr}	30-40%
LQT3 (1994)	3q21-24	SCN5A	Increased Na^+ current (I_{Na})	5-10%
LQT4 (1995)	4q25-27	Ankyrin B	Possibly increased late Na^+ current (I_{Na})	rare
LQT5 (1997)	21q22.1-22.2	*KCNE1* (minK)	I_{Ks}	rare
LQT6 (1999)	21q22.1-22.2	*KCNE2* (MiRP1)	I_{Kr}	rare
LQT7 (2001)	17q23	*KCNJ2*	I_{K1}	rare

Moss AJ et al. JAMA; 2003, 289: 2041-2044

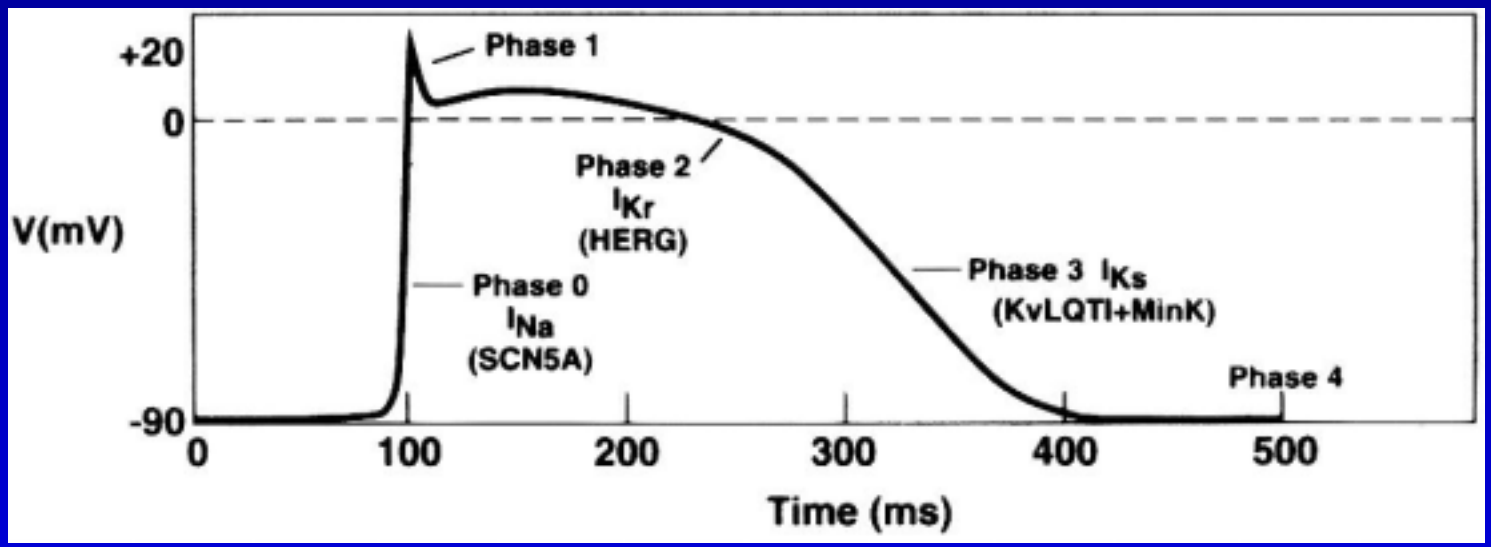


Priori SG. *Circ Res.* 2004;94:140-145



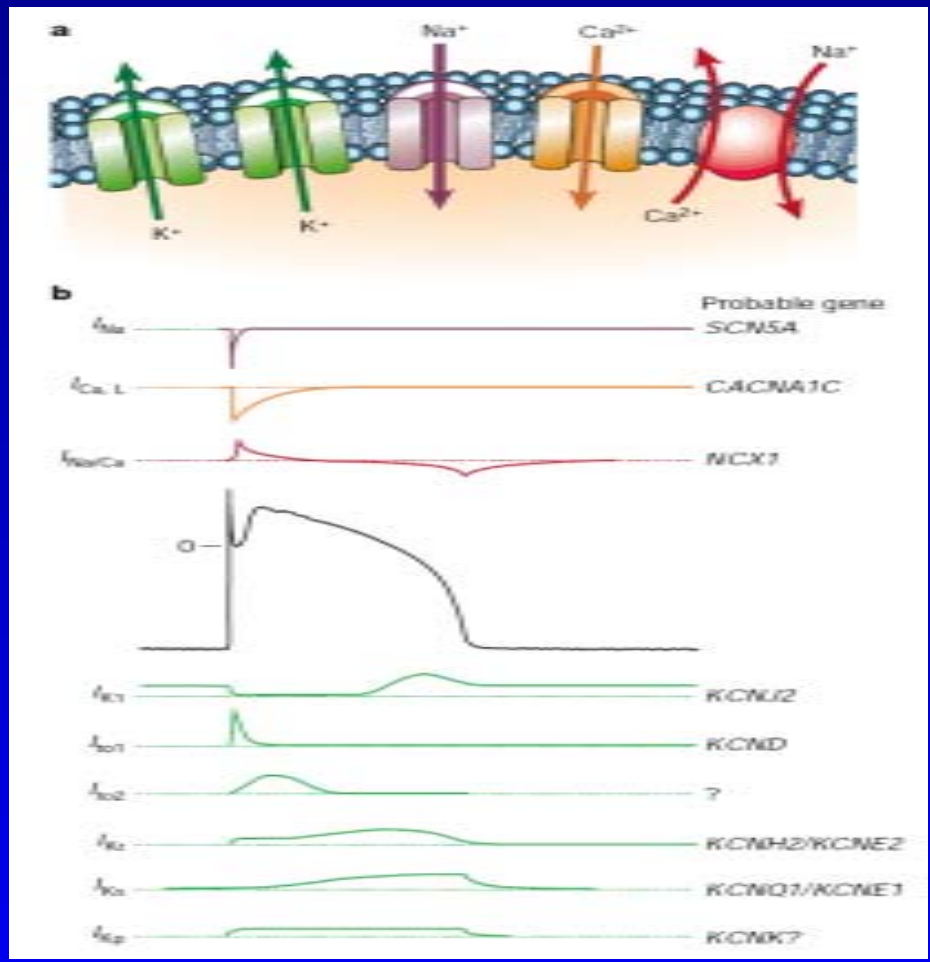
LQT3 LQT2 LQT1

Moss et al. Circulation 1995,92:2929-2934

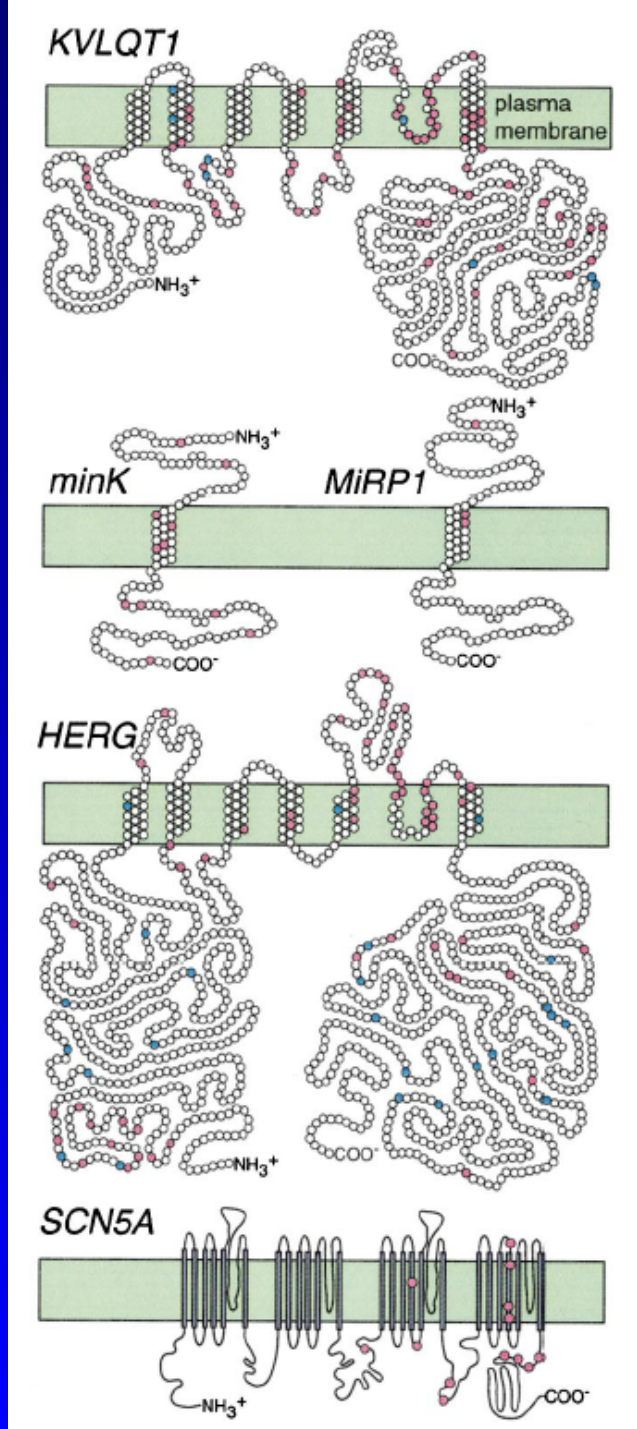


Towbin: Am J Med, 2001: 110 0(5)..385-398

Ion Channels Underlie Cardiac Excitability

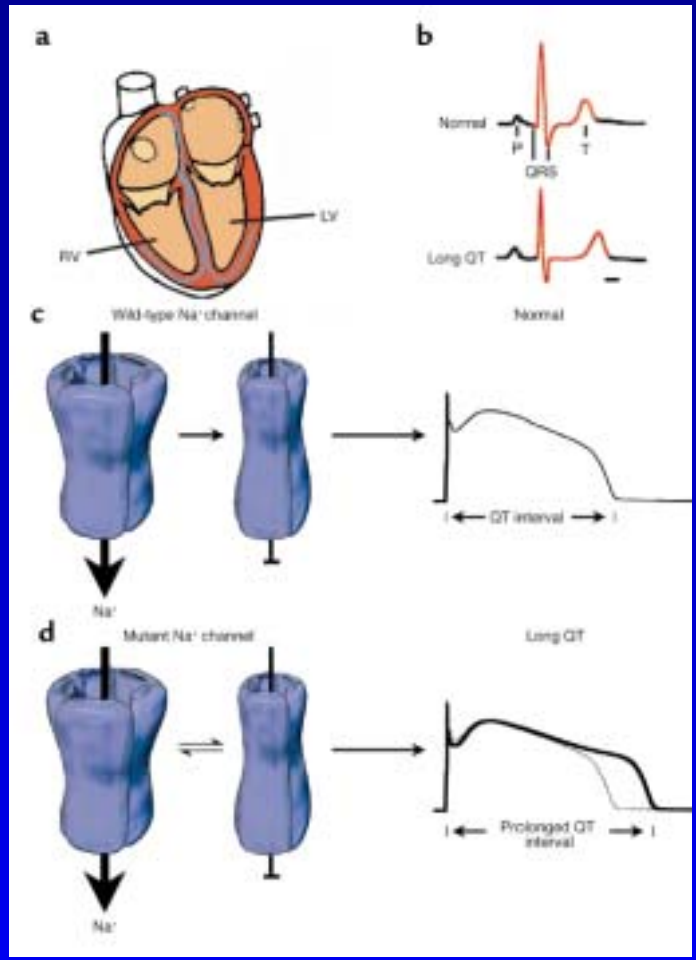


Marbán E. Nature 2002, 415, 213-218

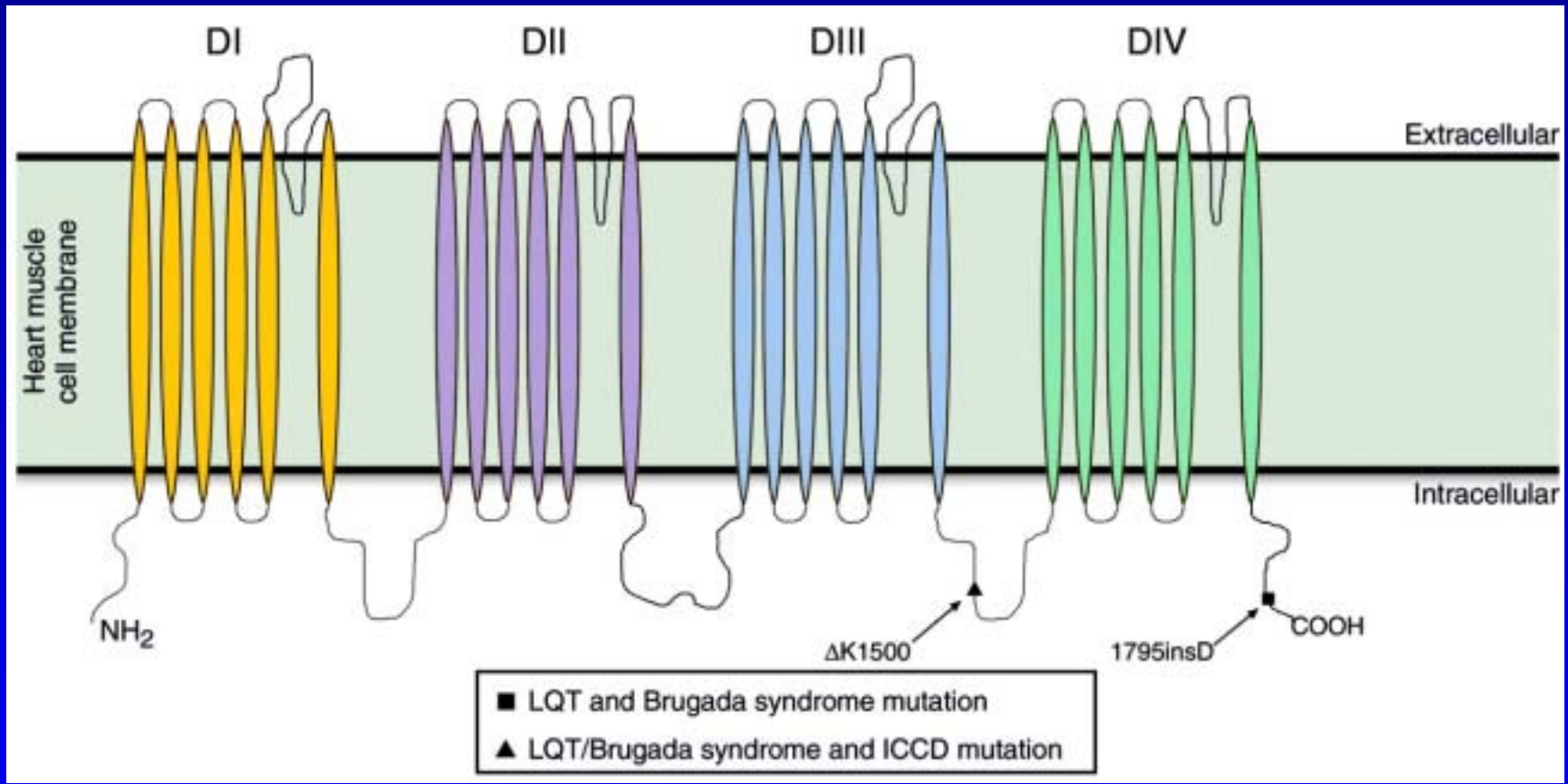


Cell 2001:104:569

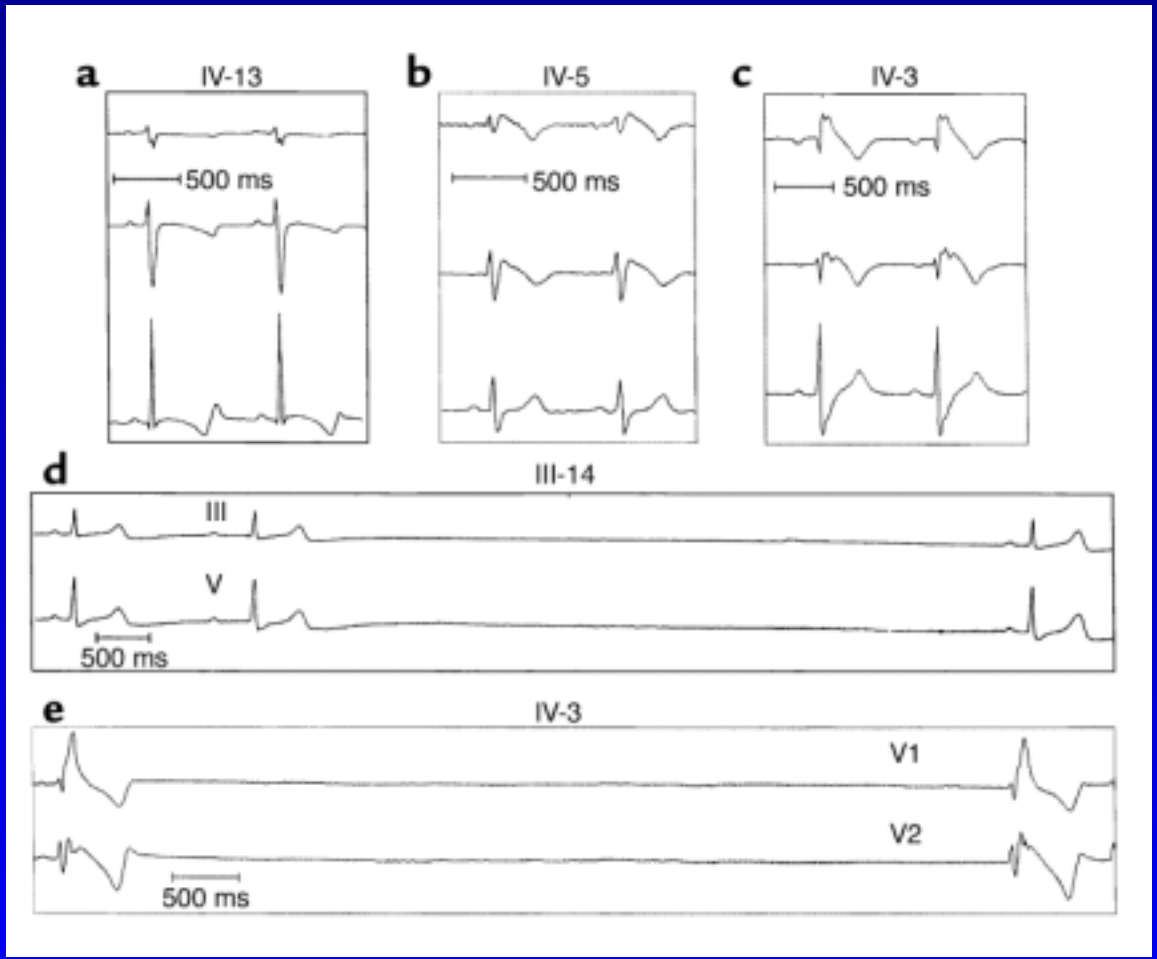
Mutation-altered Na^+ channel inactivation underlies the LQT-3 phenotype.



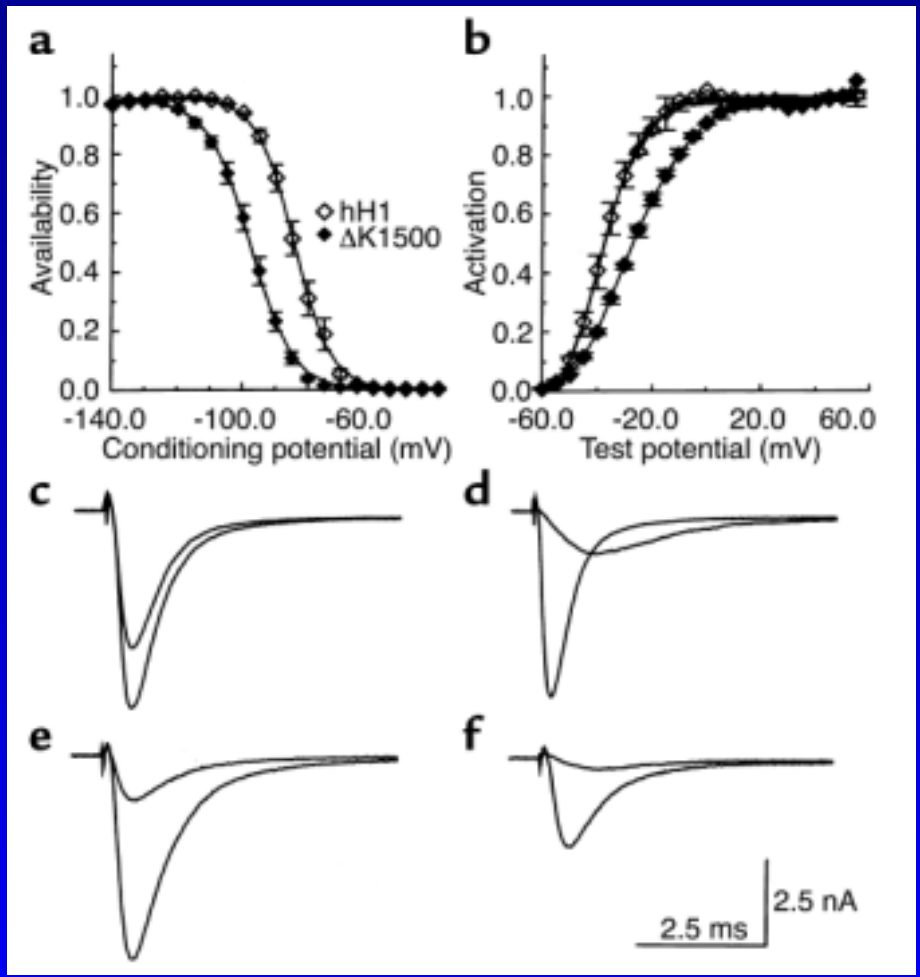
Cell 2001:104:569

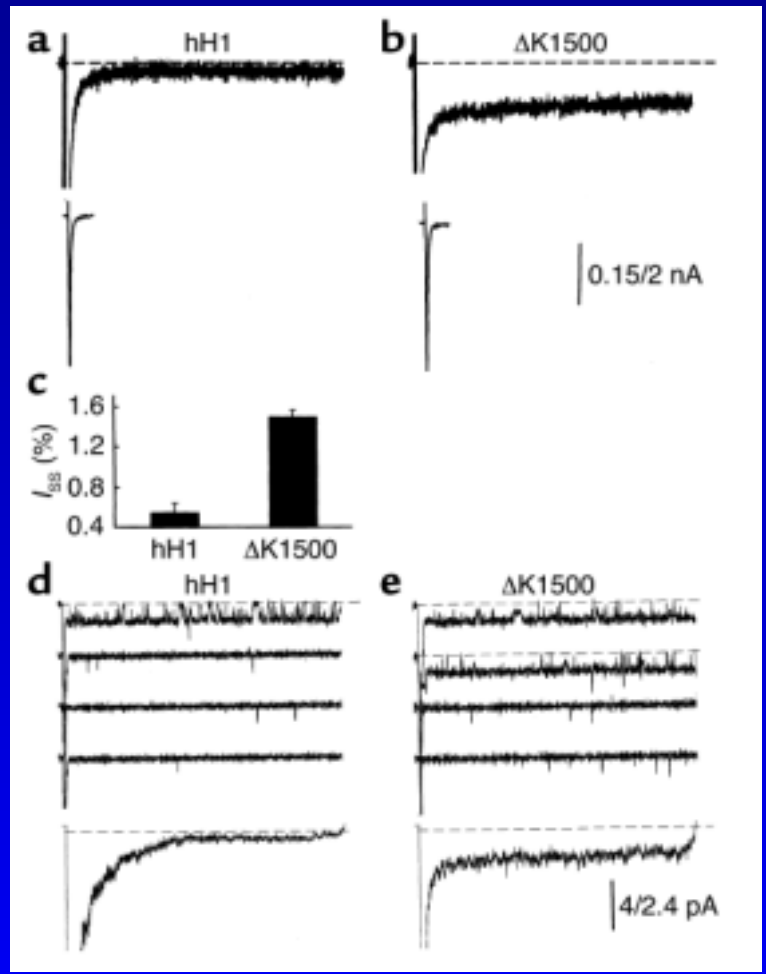


Colleen E. Clancy and Robert S. Kass *J. Clin. Invest.* 2002 110:1075-1077



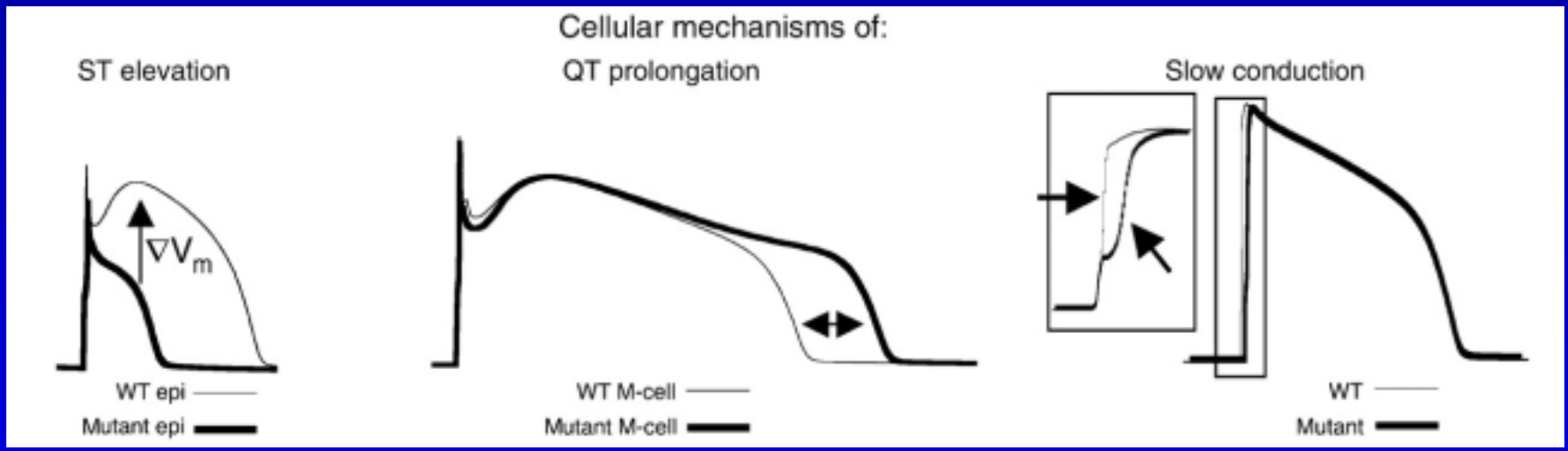
Grant AO, Priori S et al. *J. Clin. Invest.* 2002:110:1201–1209





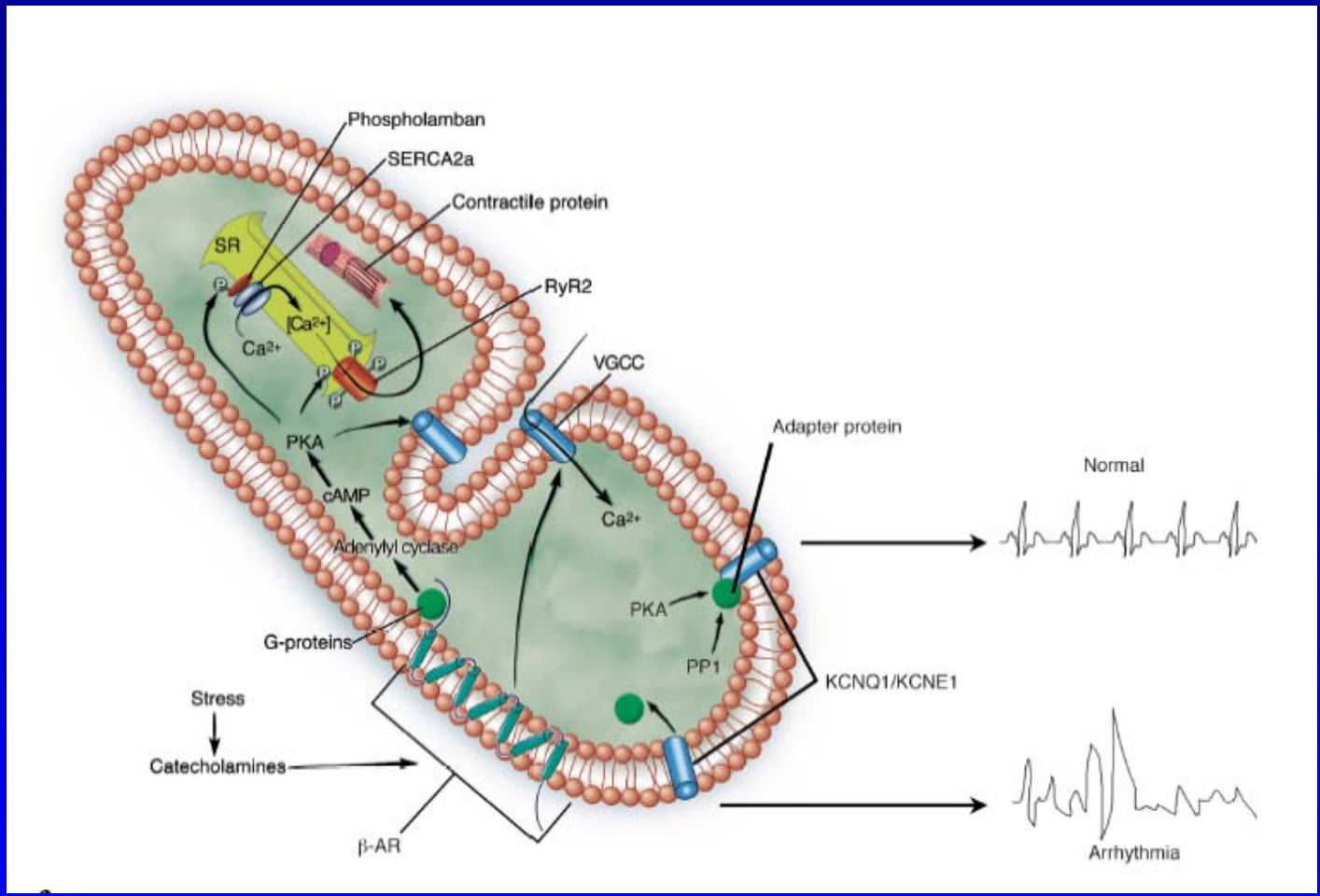
Grant AO, Priori S et al. *J. Clin. Invest.* 2002:110:1201–1209

Cellular electrical abnormalities and their relation to changes in the ECG



Colleen E. Clancy and Robert S. Kass *J. Clin. Invest.* 2002 110:1075-1077

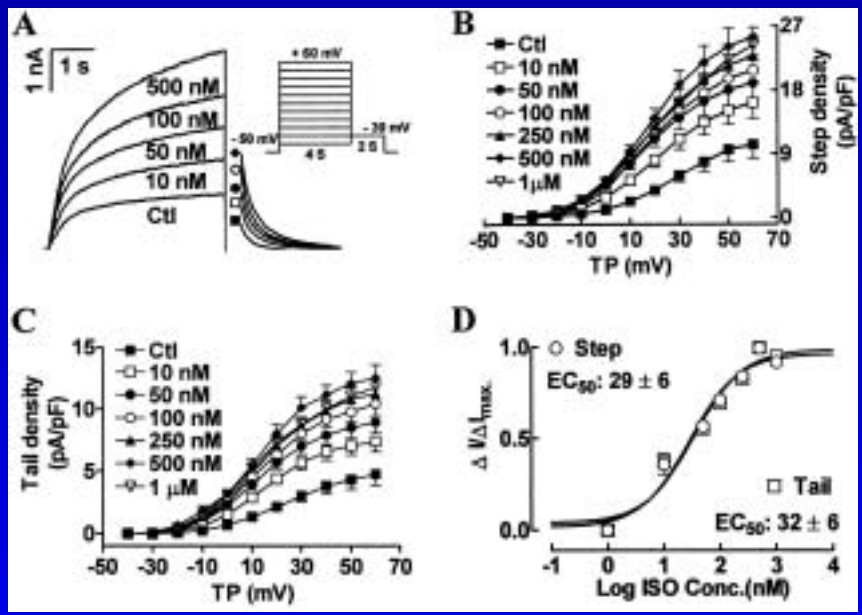
Disruption of local signaling domains occurs in LQT-1



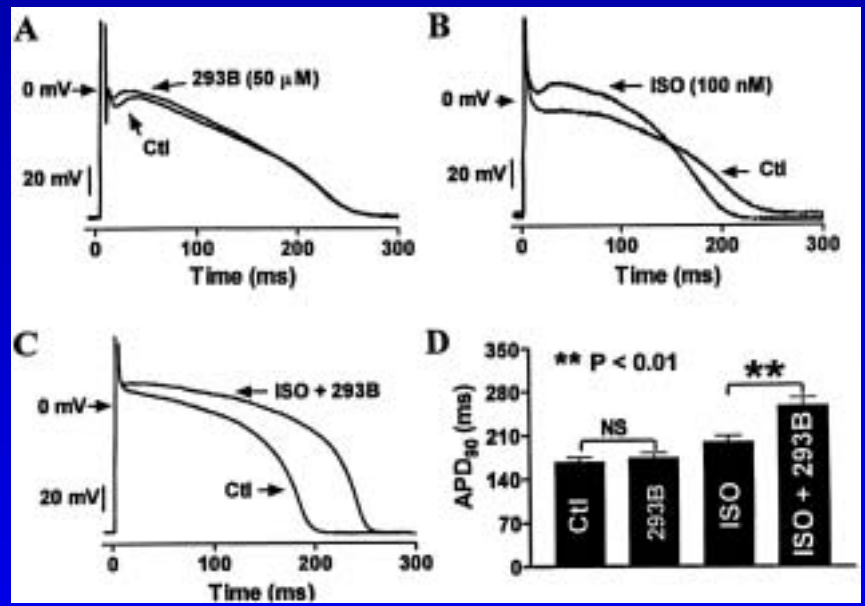
Cell 2001:104:569

Slow delayed rectifier current and repolarization in canine cardiac Purkinje cells

Effects of β-adrenergic stimulation on I_{Ks}

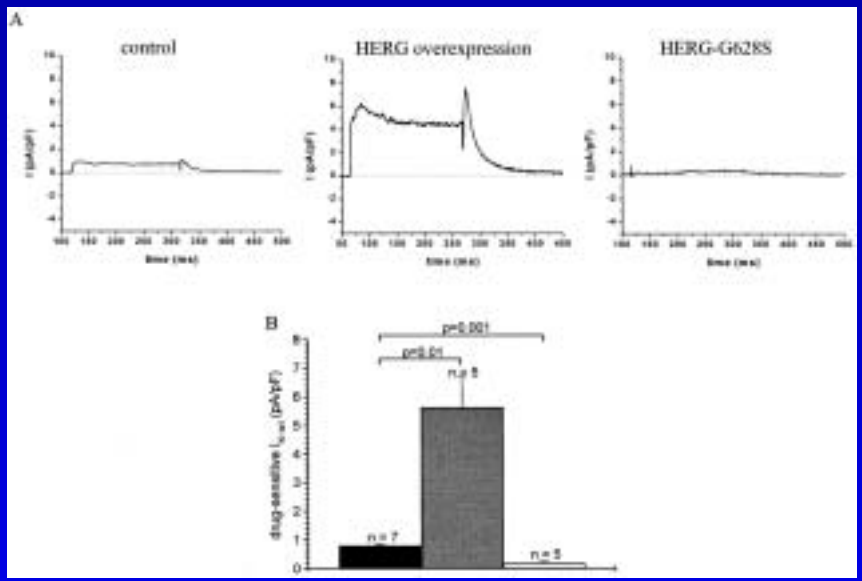


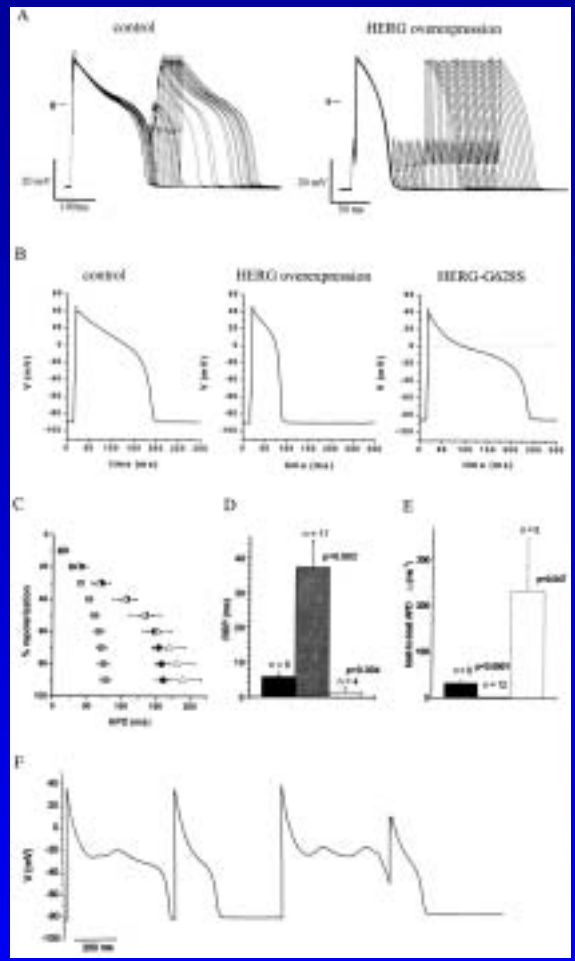
Effects of β-adrenergic stimulation and I_{Ks} inhibition on the AP.



Han W. et al. Am J Physiol 2001; **280: H1075-H1080**

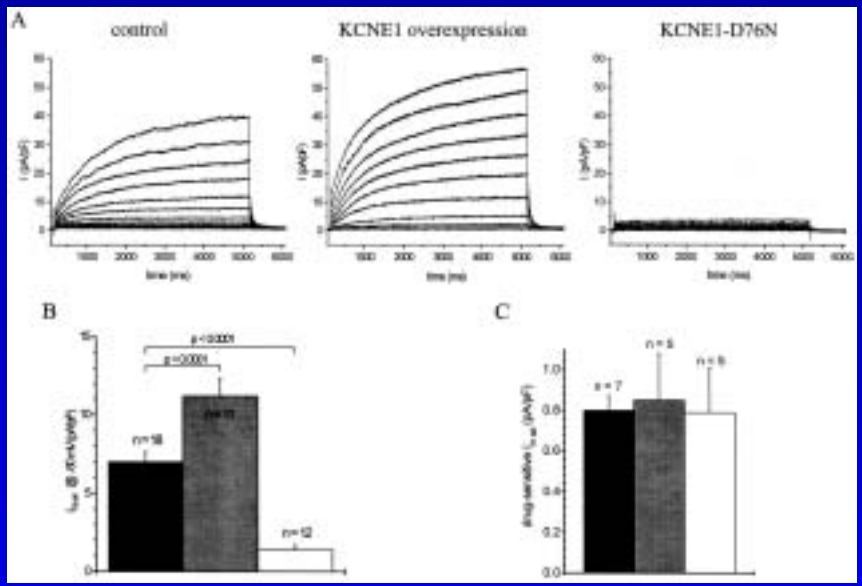
Distinct gene-specific mechanisms of arrhythmia revealed by cardiac gene transfer of two long QT disease genes, HERG and KCNE1

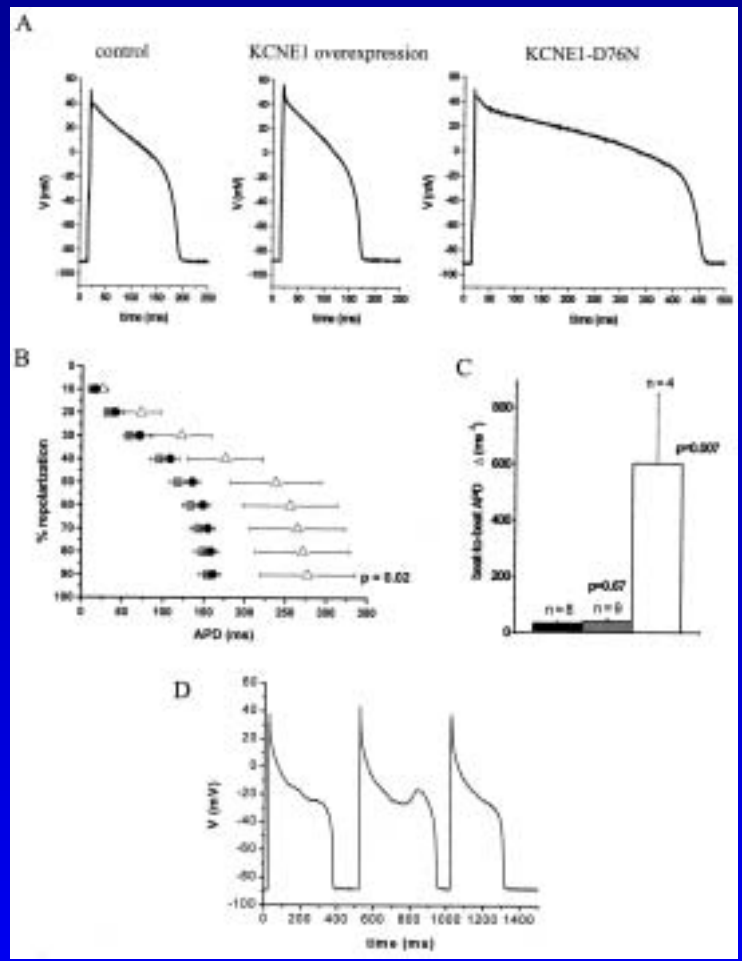




Hoppe U. et al. PNAS 2001: 98 5335–5340

Distinct gene-specific mechanisms of arrhythmia revealed by cardiac gene transfer of two long QT disease genes, HERG and KCNE1





Hoppe U. et al. PNAS 2001: 98 5335–5340

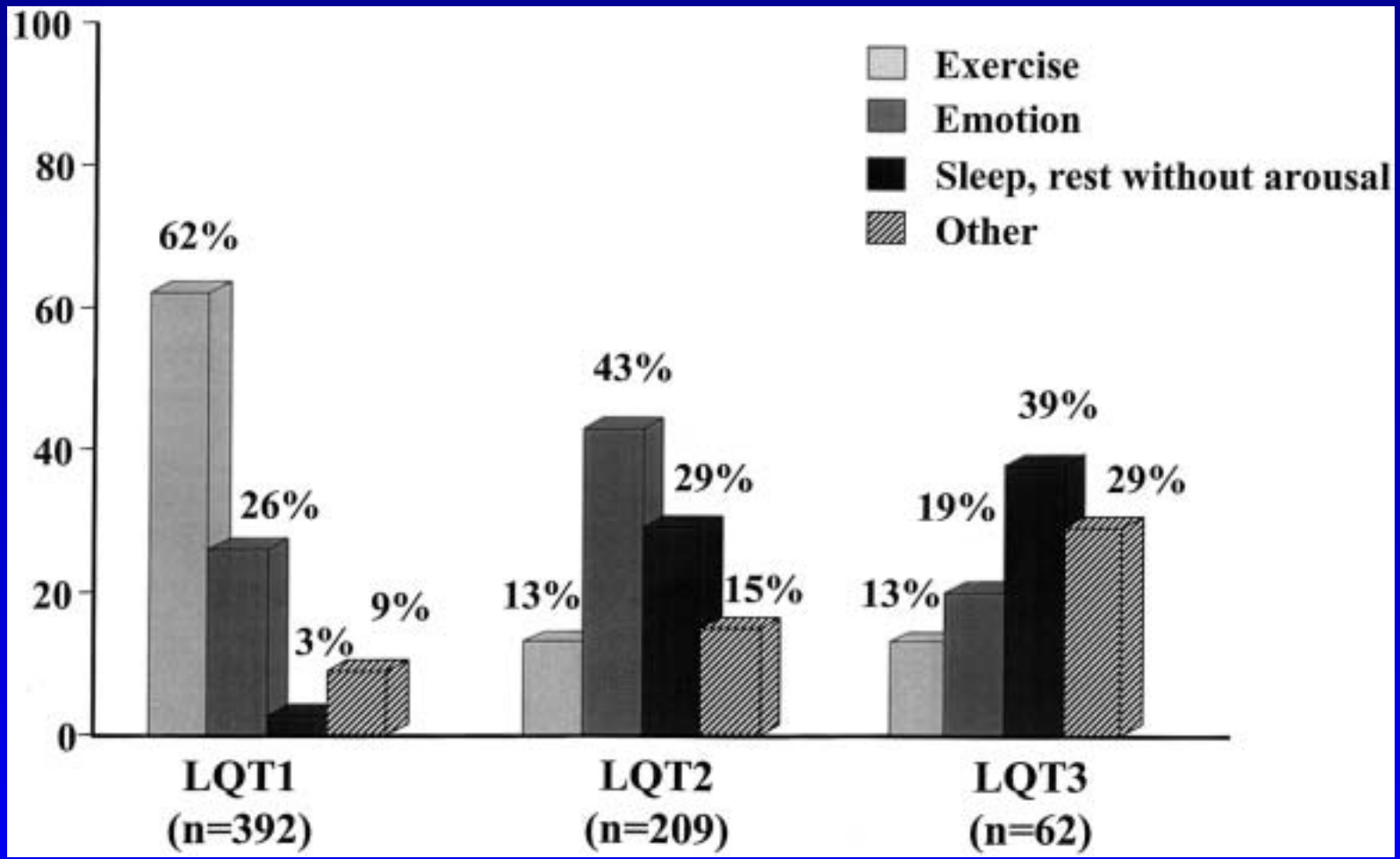
Triggers for Cardiac Events

- **LQT1: during exercise**
- **LQT2: acute arousal-type emotions**
- **LQT3: experience events without emotional arousal during sleep or at rest.**

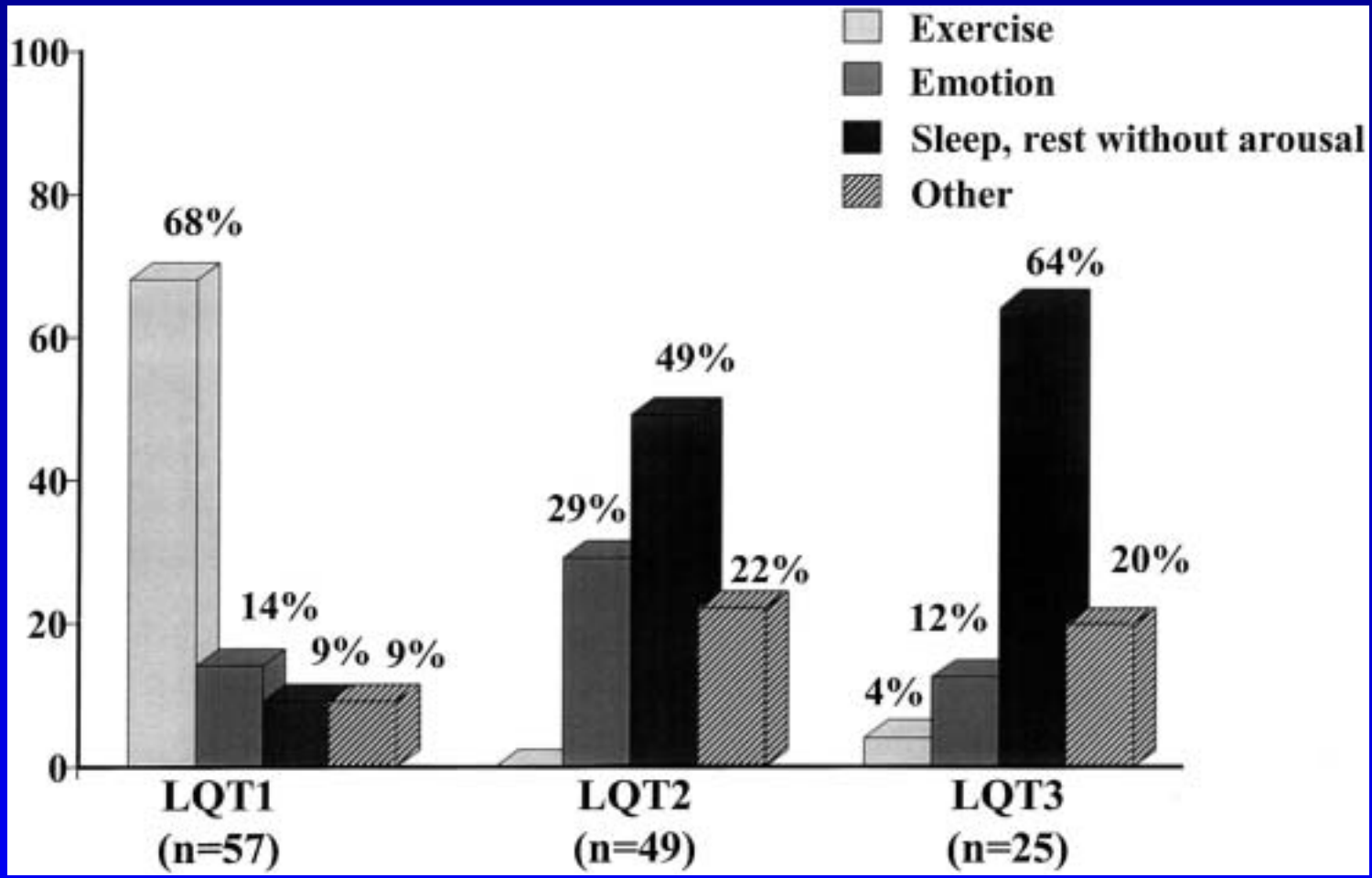
Trigger for EADs

- Reopening of $I_{Ca.L}$ during the prolonged plateau phase of the cardiac action potential.
- The beneficial effect of β-adrenergic blockers in individuals with LQTS may be caused by a blunting of the increase in L-type calcium current by sympathetic nerve stimulation.

Triggers for cardiac events according to 3 genotypes



Lethal cardiac events according to 3 classified triggers in 3 genotypes

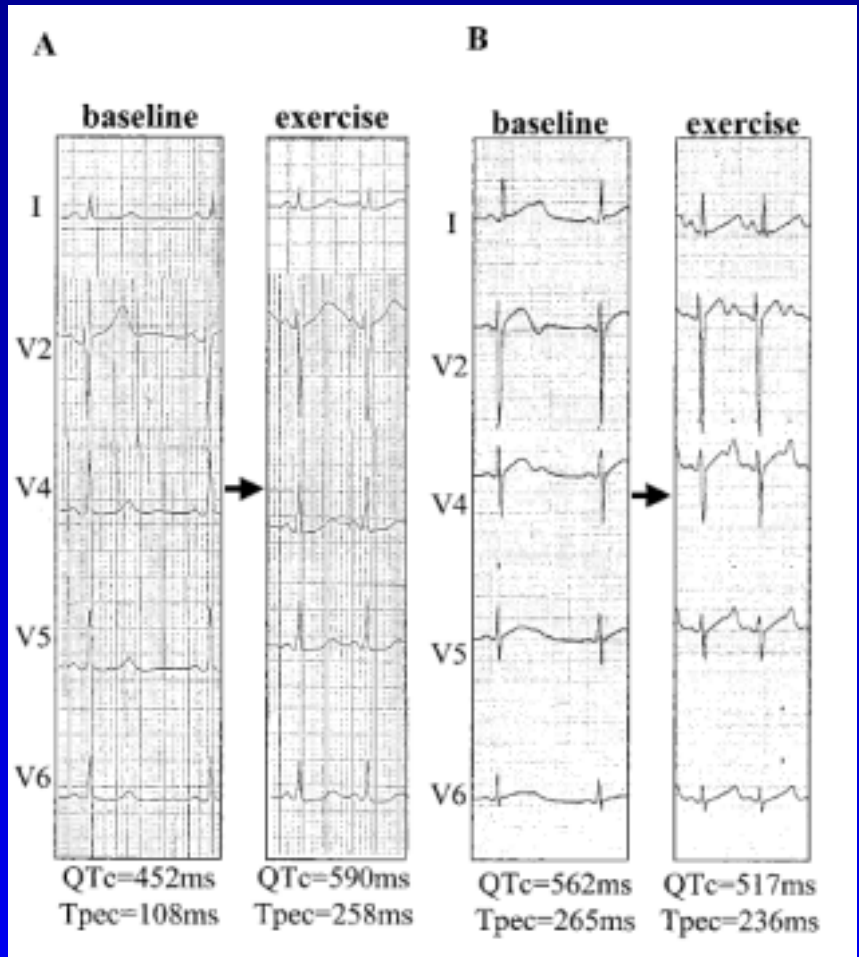


Exercise Stress Test Amplifies Genotype-Phenotype Correlation in the LQT1 and LQT2

TABLE 3. ECG Data Before and During Exercise in LQT1, LQT2, and Control

	Baseline	Peak Exercise	*P*
R-R, ms			
LQT1	888±155	461±146	*P*<0.001‡
LQT2	1020±184	514±134	*P*<0.001‡
Control	816±188	475±64	*P*<0.001‡
P	NS*†	NS*†	
QTc, ms			
LQT1	511±64	599±54	*P*<0.001‡
LQT2	513±55	502±82	NS‡
Control	402±36	418±17	NS‡
P	NS*/*P*<0.001†	NS*/*P*<0.001†	
Tpec, ms			
LQT1	142±46	215±46	*P*<0.001‡
LQT2	197±70	163±86	NS‡
Control	127±59	98±21	NS‡
P	*P*<0.001*†	NS*/*P*<0.001†	

*Between LQT1 and LQT2, †LQT1 and LQT2 group compared with control, respectively, ‡between baseline condition and peak exercise.



Takenaka K. et al.*Circulation.* 2003;107:838

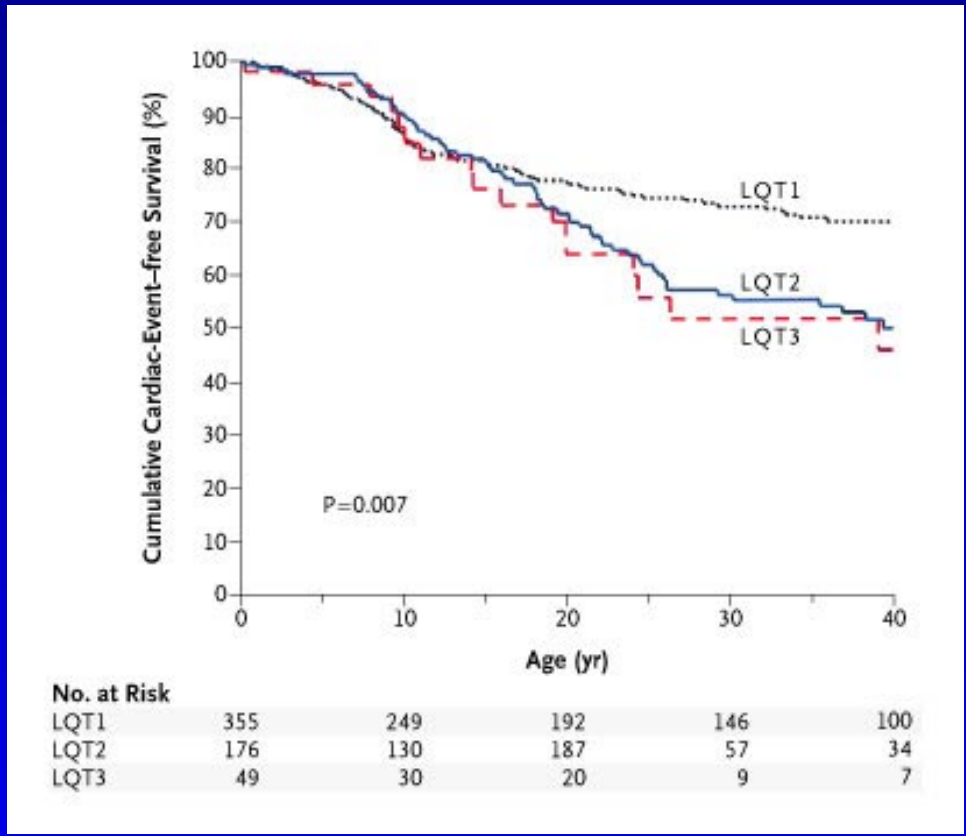
Clinical course of LQTS

- Risk of cardiac events is higher in males before puberty and higher in females during adulthood.
- The most significant risk factor for cardiac events is the length of the QTc interval, with the risk an exponential function of the QTc duration.

Evaluation of patients with suspected or definitive LQTS

- Frequent follow-up ECGs at monthly
- Holter
- Exercise test: useful if the activity precipitates a diagnostic arrhythmia or if the QTc interval becomes unequivocally prolonged during recovery after exercise.

Kaplan–Meier Estimates of Survival Free of Cardiac Events among the 580 Patients with the Long-QT Syndrome in the Risk-Stratification Analysis,



No. at Risk					
LQT1	355	249	192	146	100
LQT2	176	130	187	57	34
LQT3	49	30	20	9	7

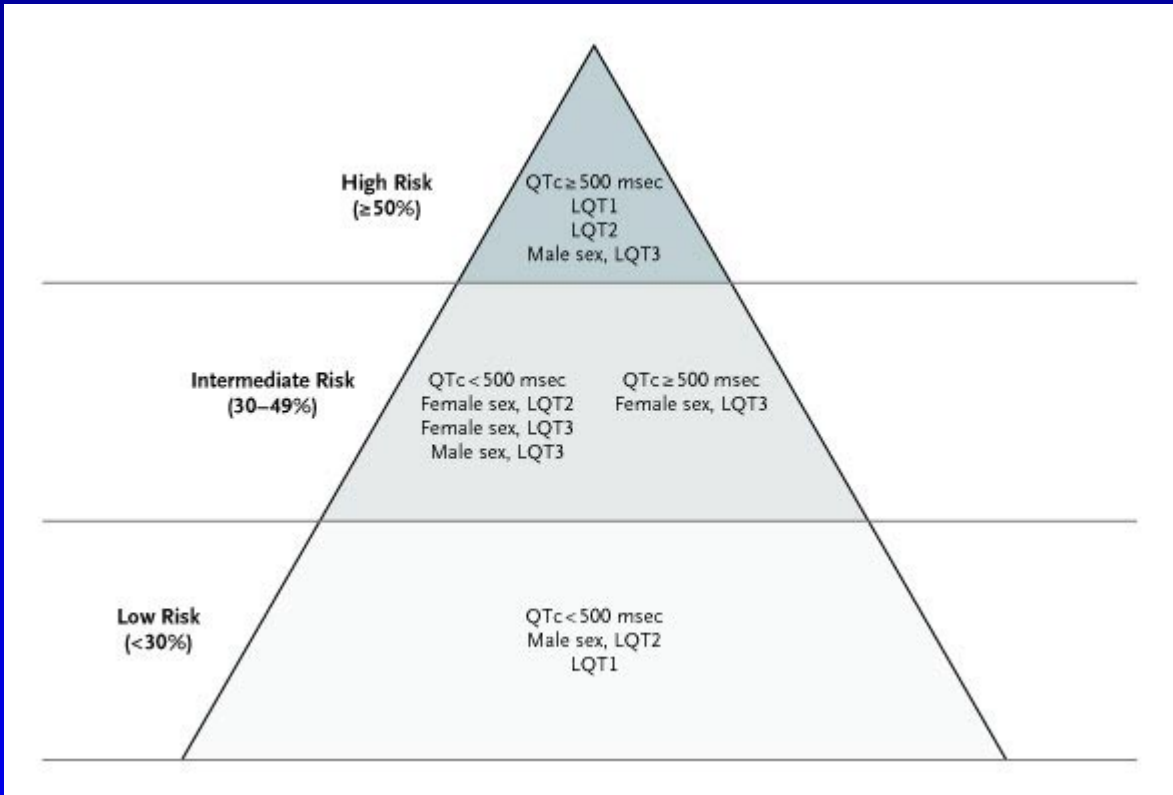
Priori SG et al. N Engl J Med 2003. 348: 1866-1874

Table 1. Incidence of a First Cardiac Arrest or Sudden Death before the Age of 40 Years and before Therapy among Patients with the Long-QT Syndrome, According to the Genetic Locus of the Mutation.

Locus and Sex	All Patients	Patients with Sudden Death or Cardiac Arrest	Incidence
	number		*%/yr*
LQT1			
Female sex	217	20	0.28
Male sex	169	17	0.33
Total	386	37	0.30
LQT2			
Female sex	125	30	0.82
Male sex	81	11	0.46
Total	206	41	0.60
LQT3			
Female sex	30	3	0.30
Male sex	25	6	0.96
Total	55	9	0.56

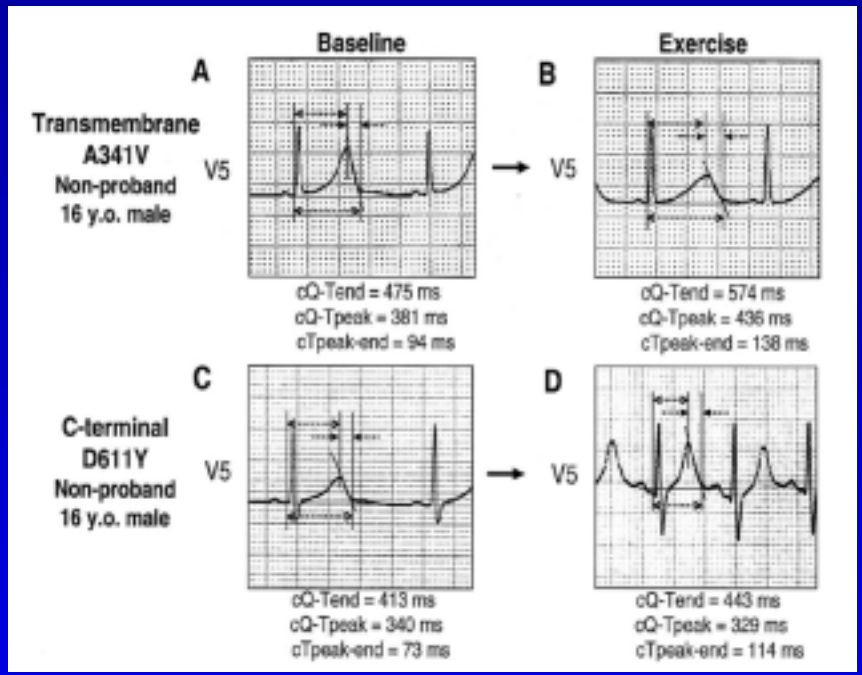
Priori SG et al. N Engl J Med 2003. 348: 1866-1874

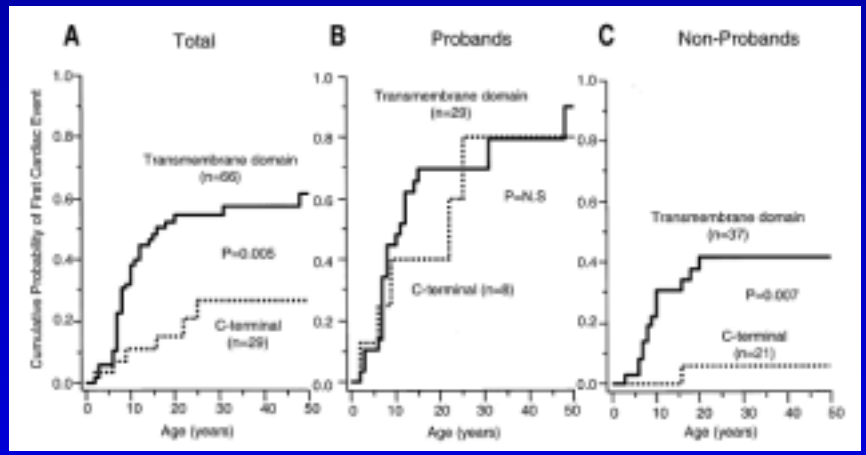
Risk Stratification among Patients with the LQTS According to Genotype and Sex



Priori SG et al. N Engl J Med 2003. 348: 1866-1874

Mutation Site-Specific Differences in Arrhythmic Risk and Sensitivity to Sympathetic Stimulation in the LQT1 Form of Congenital Long QT Syndrome





Shimizu W. J Am Coll Cardiol 2004;44:117–25

Acquired long QT syndrome

- **Drug-induced long QT syndrome; MC**

  Antiarrhythmic or psychoactive drug, such as quinidine and thioridazine;
- **In the setting of braycardia, neurologic trauma or surgery, intracranial bleeding, and electrolyte abnormalities, such as hypomagnesemia and hypokalemia**

Patients Carrying mutations or polymorphism associated with drug-provoked LQTS

- Mutation in the KCNE2 subunit of I_{Kr} potassium channel or mutation in the KCNQ1 subunit of the I_{Ks} channel
- Polymorphism in the KCNE1 gene
- Polymorphism in KCNE2

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Editorial

Acquired delayed rectifier channelopathies: how heart disease and antiarrhythmic drugs mimic potentially-lethal congenital cardiac disorders

Stanley Nattel*

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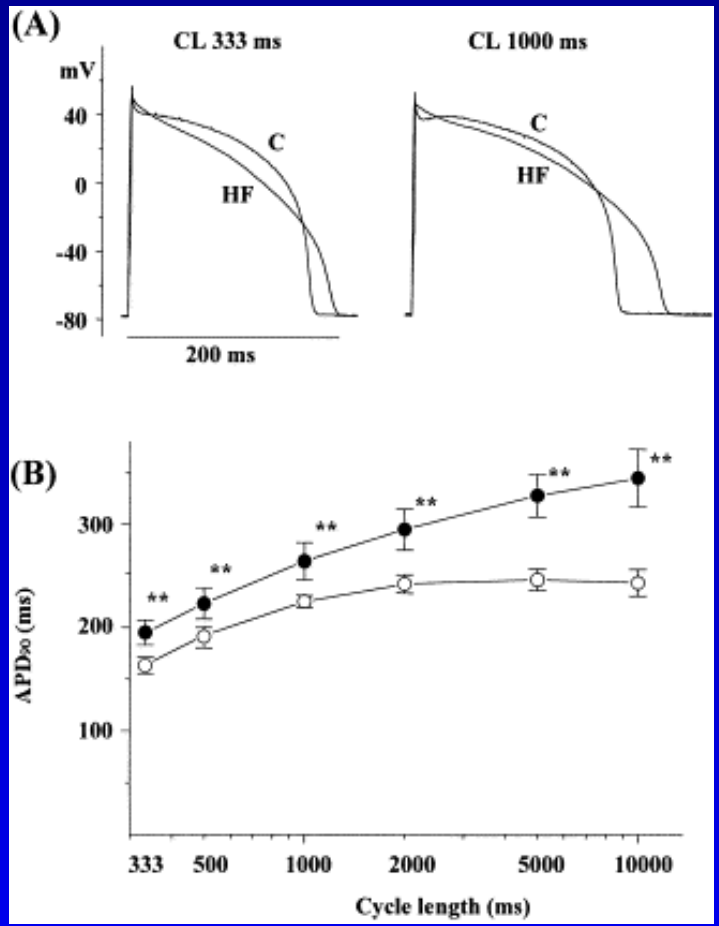
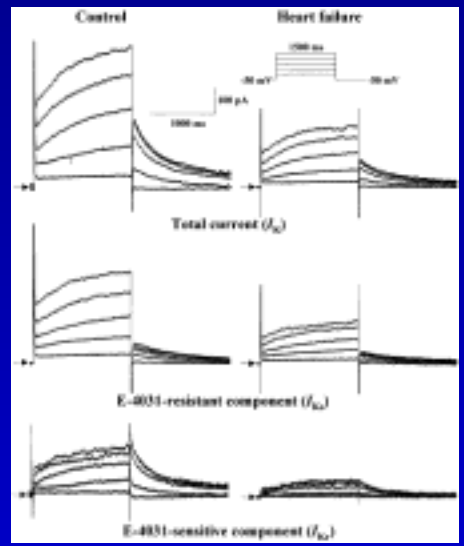
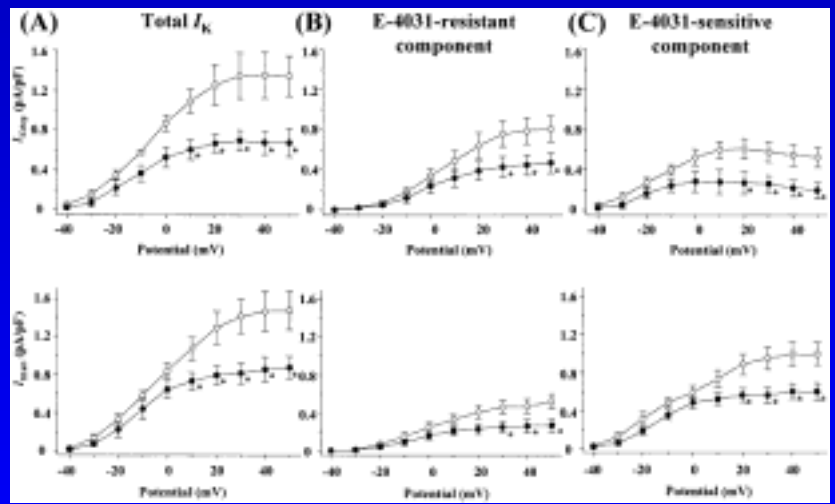
Received 28 June 2000; accepted 28 June 2000

Pacing-induced HF causes a reduction of I_K along with decreases in $I_{Ca.L}$ and I_{to} in rabbit ventricle







Tsuji Y. et al. *Cardiovasc Res.* 2000; 48: 300–309

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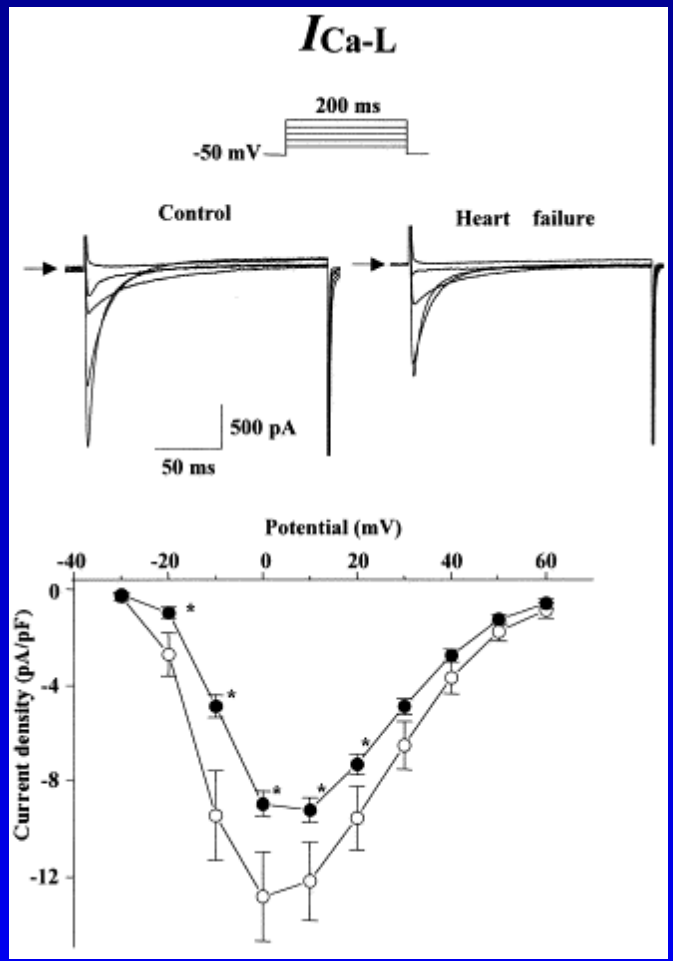
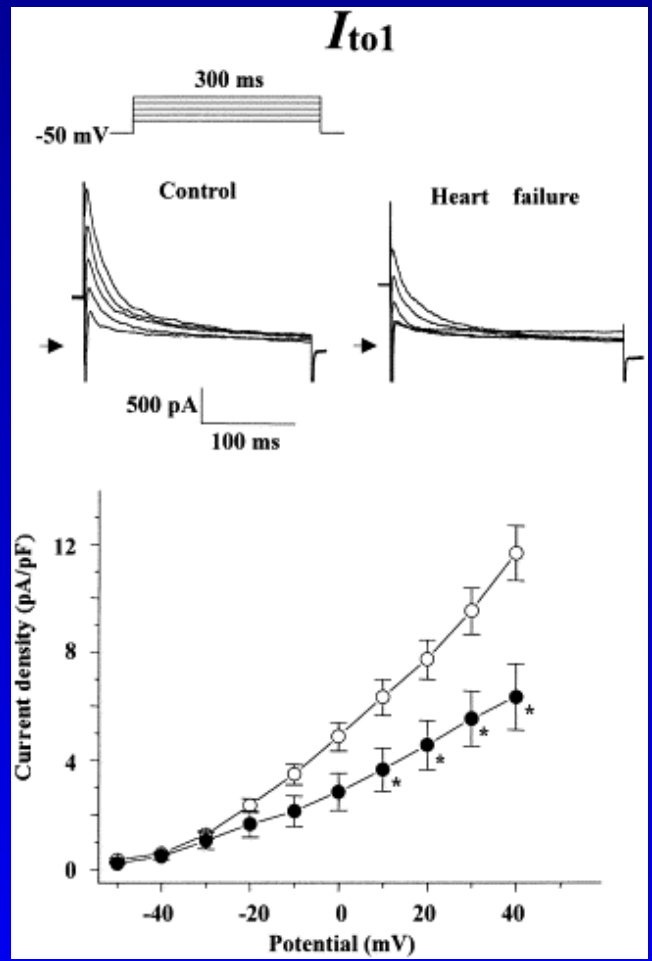
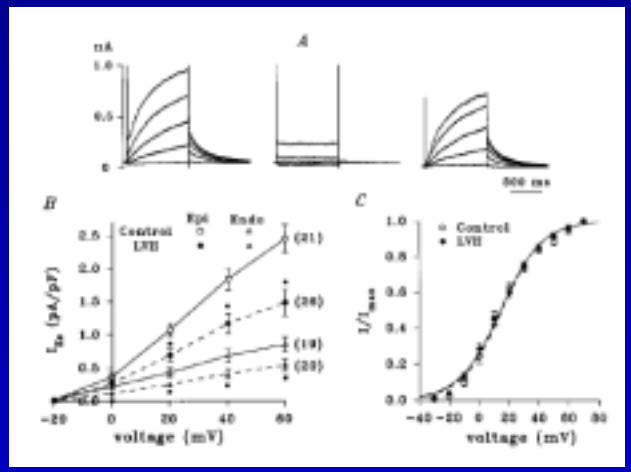
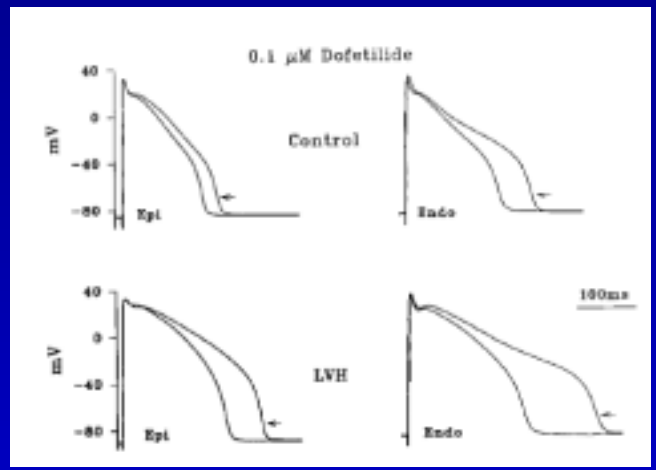


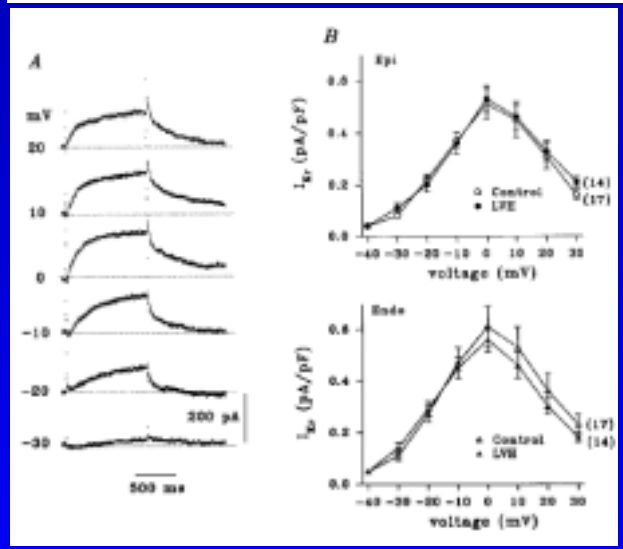


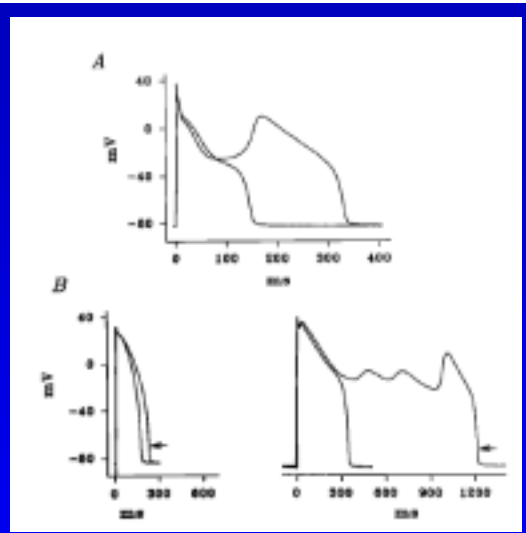
Tsuji Y. et al. *Cardiovasc Res.* 2000; 48: 300–309

Effects of LVH on I_{Ks} Currents in Rabbits



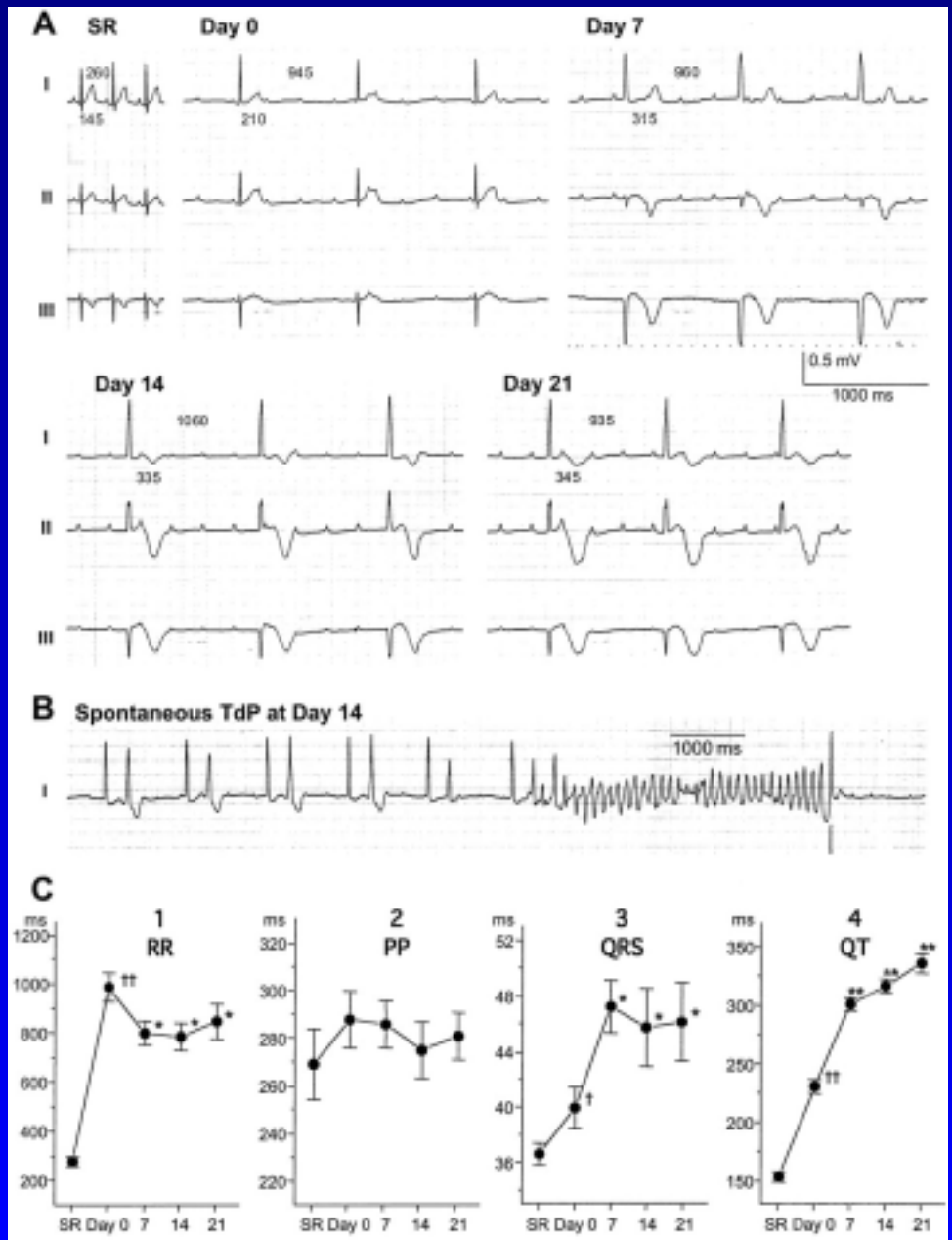






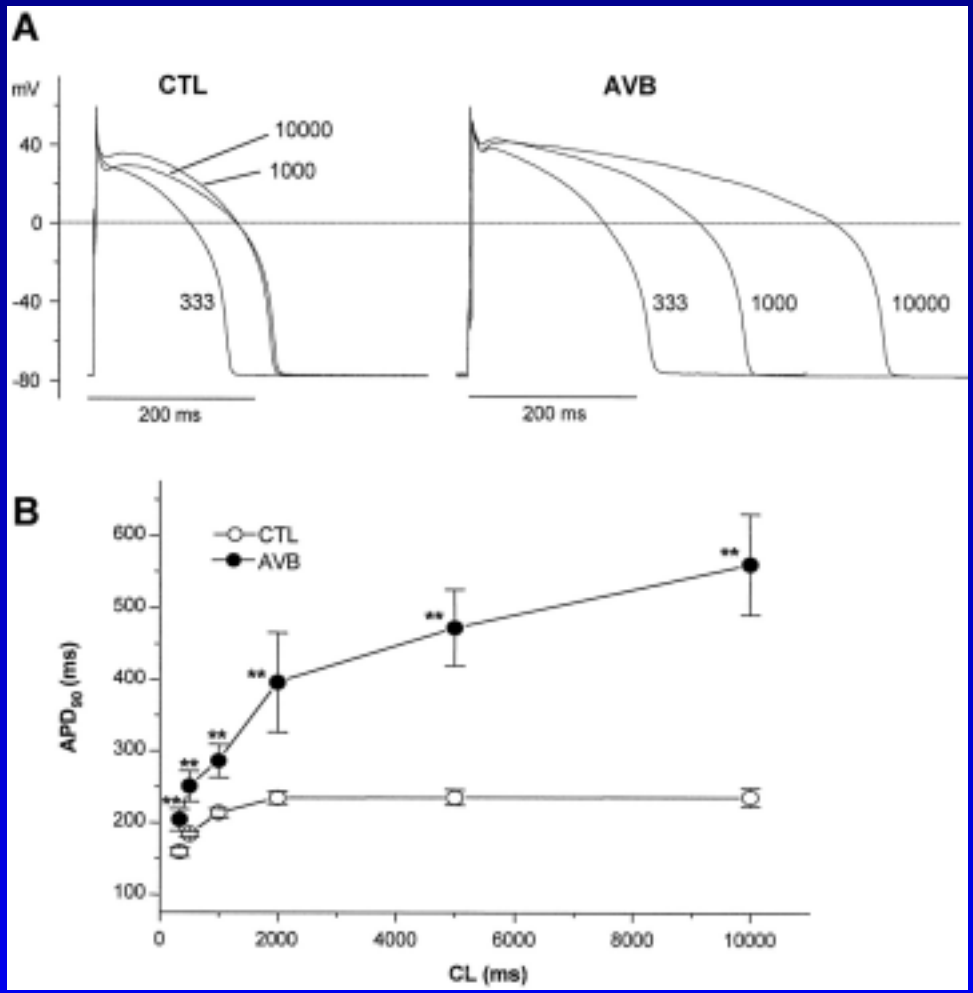
Xu et al. *Circulation*. 2001;103:1585-1590

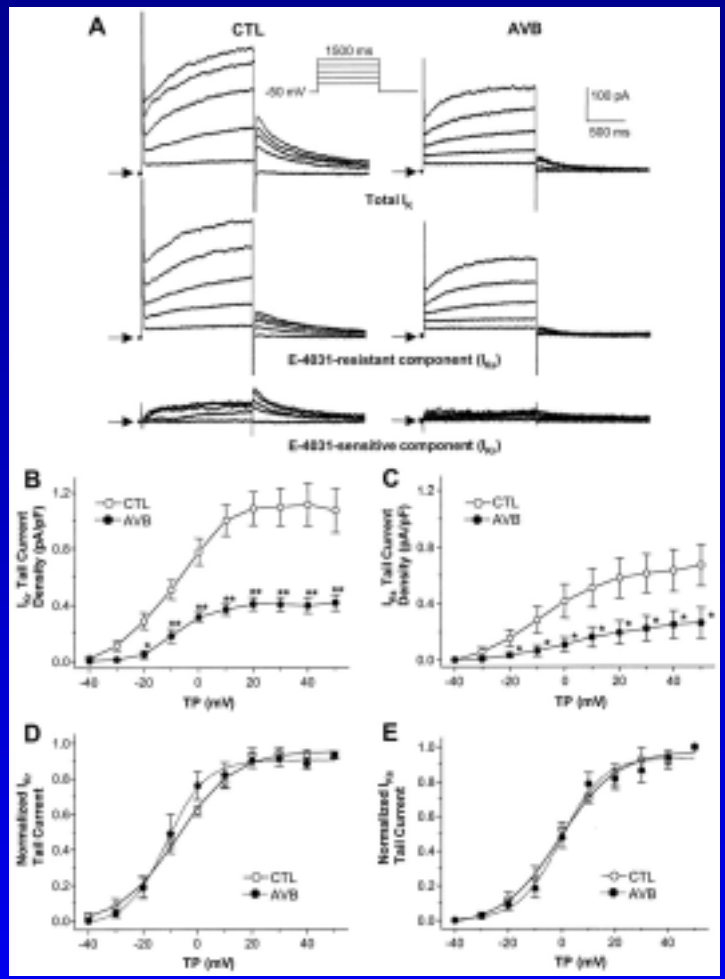
Acquired QT Prolongation and TdPs in Rabbits With Chronic Complete AV Block



Tsuji Y. et al.
***Circulation*. 2002;106:2012-2018**

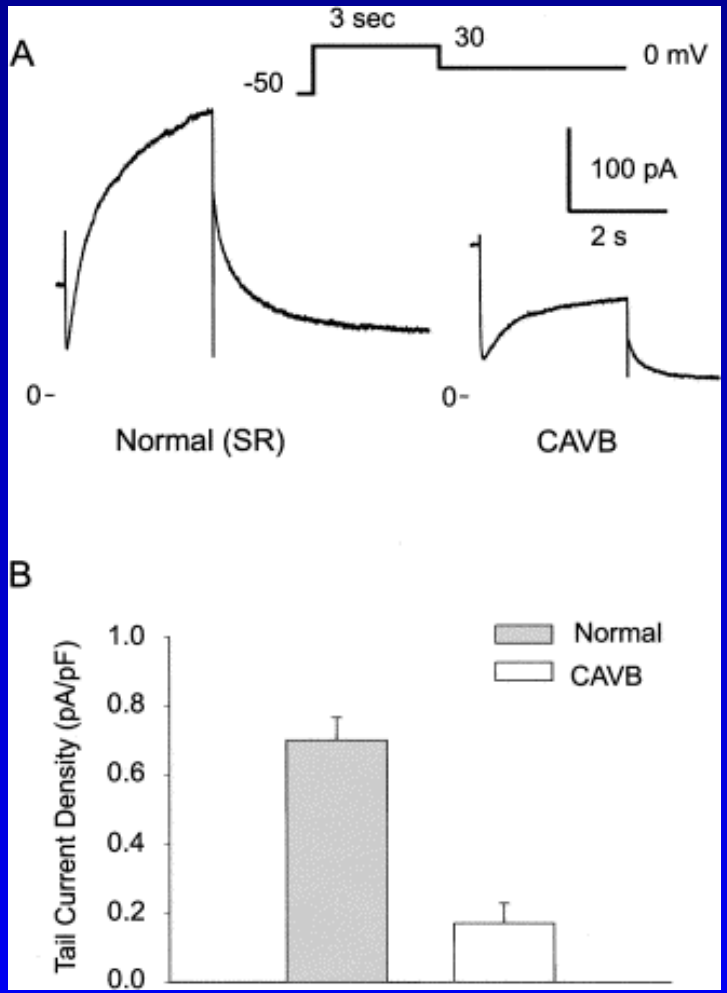
Acquired QT Prolongation and TdPs in Rabbits With Chronic Complete AV Block

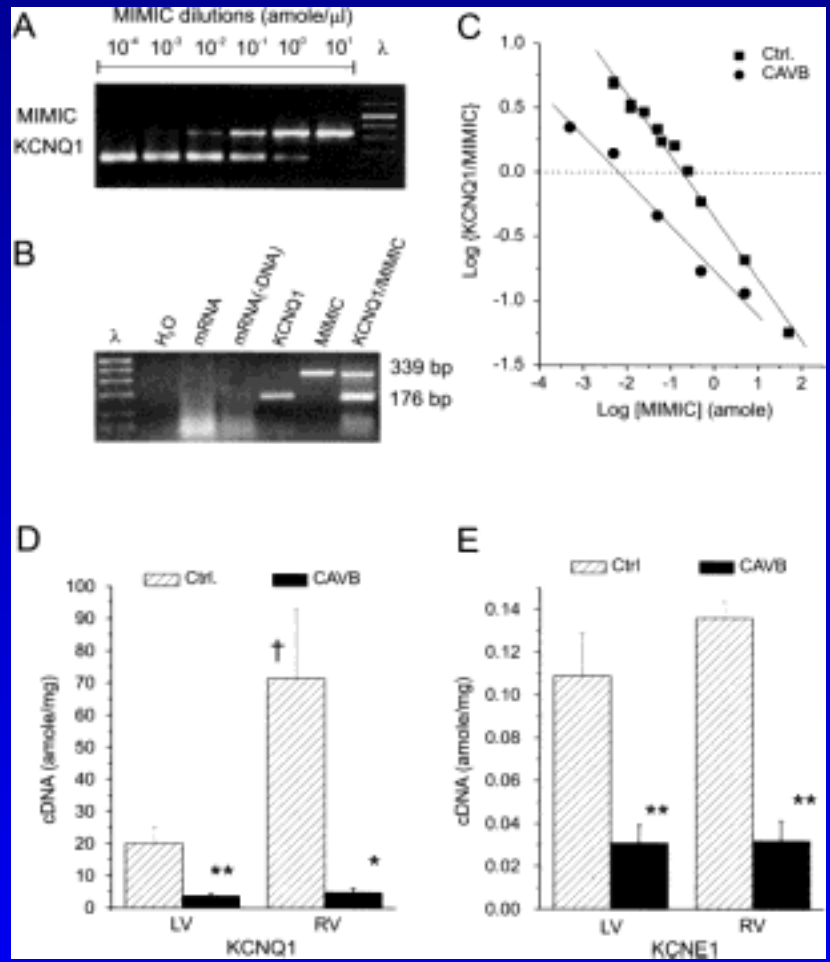




Tsuji Y. et al. ***Circulation*. 2002;106:2012-2018**

Coordinated down-regulation of KCNQ1 and KCNE1 expression contributes to reduction of I_{Ks} in canine hypertrophied hearts





Ramakers C. et al. Cardiovascr Res 2003; 57. 486–496

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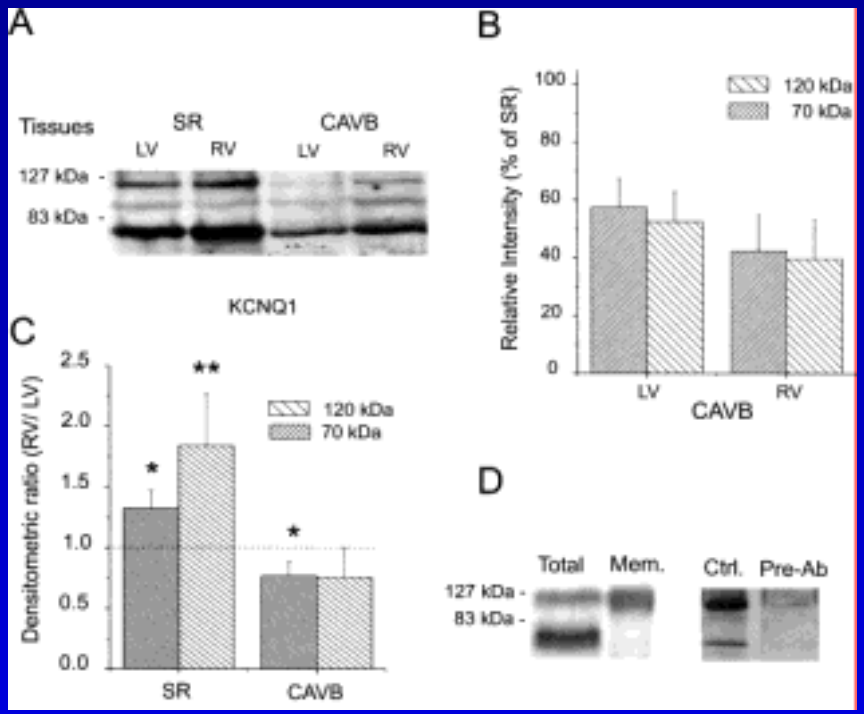
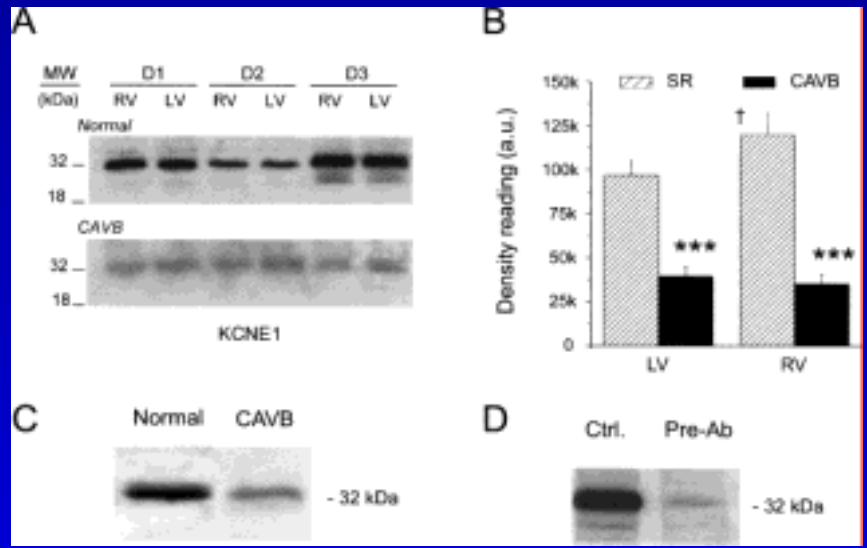
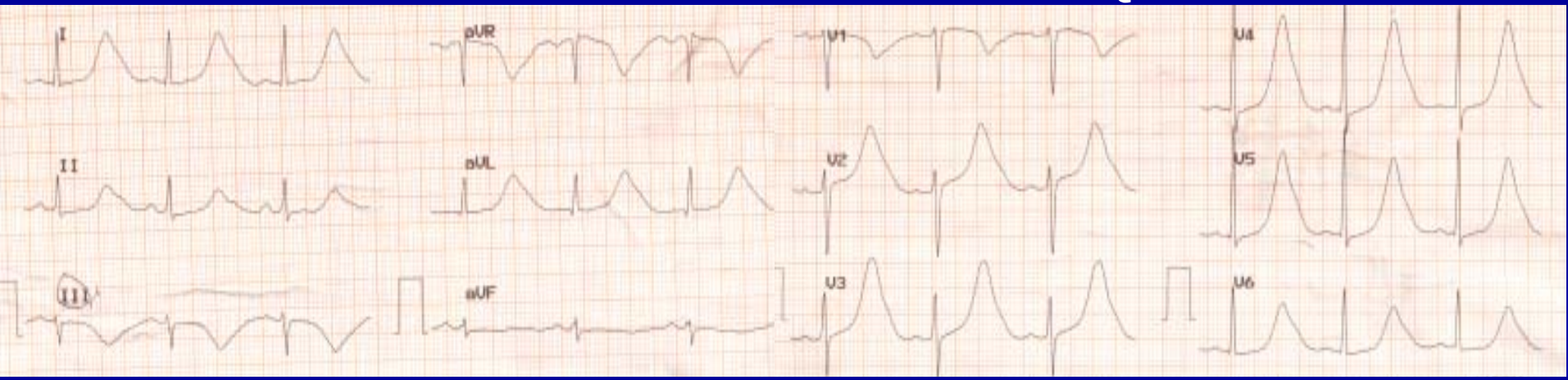




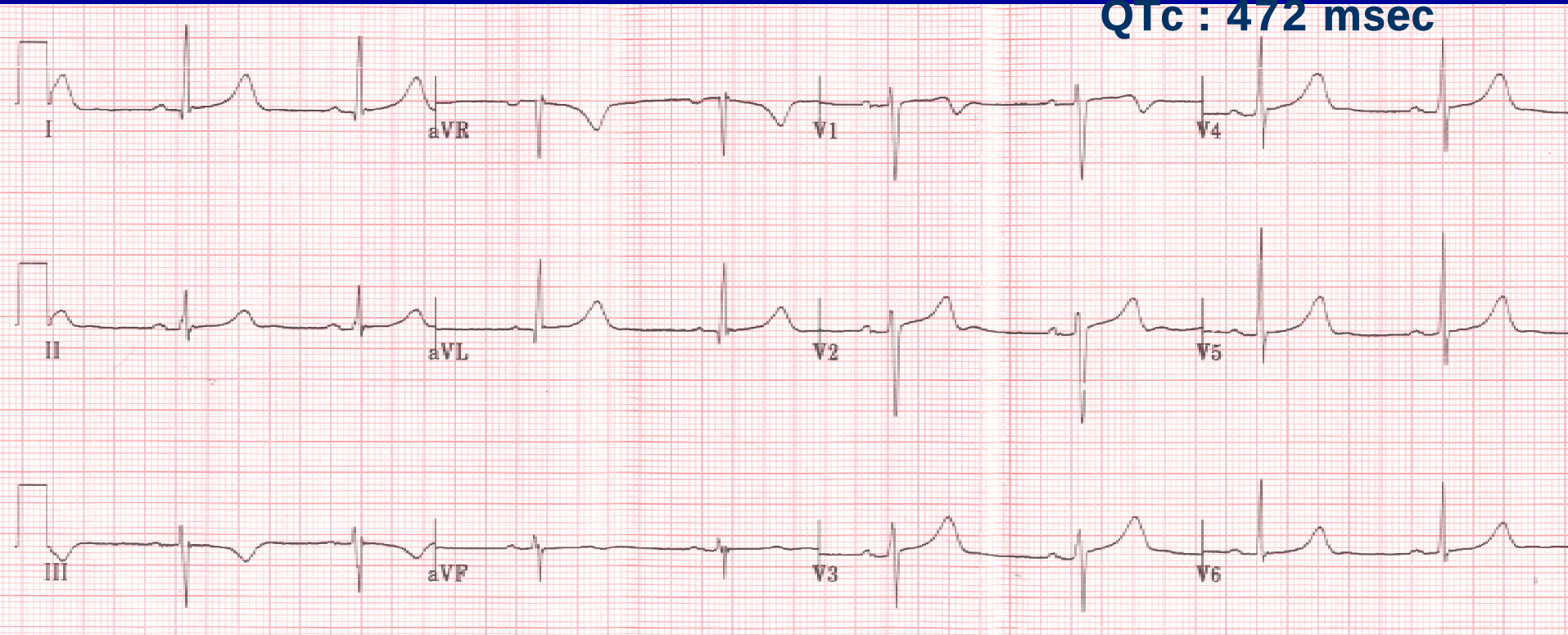
Ramakers C. et al. Cardiovascr Res 2003; 57. 486–496

50 years old female, syncope after 2 month tinea pedis Tx.

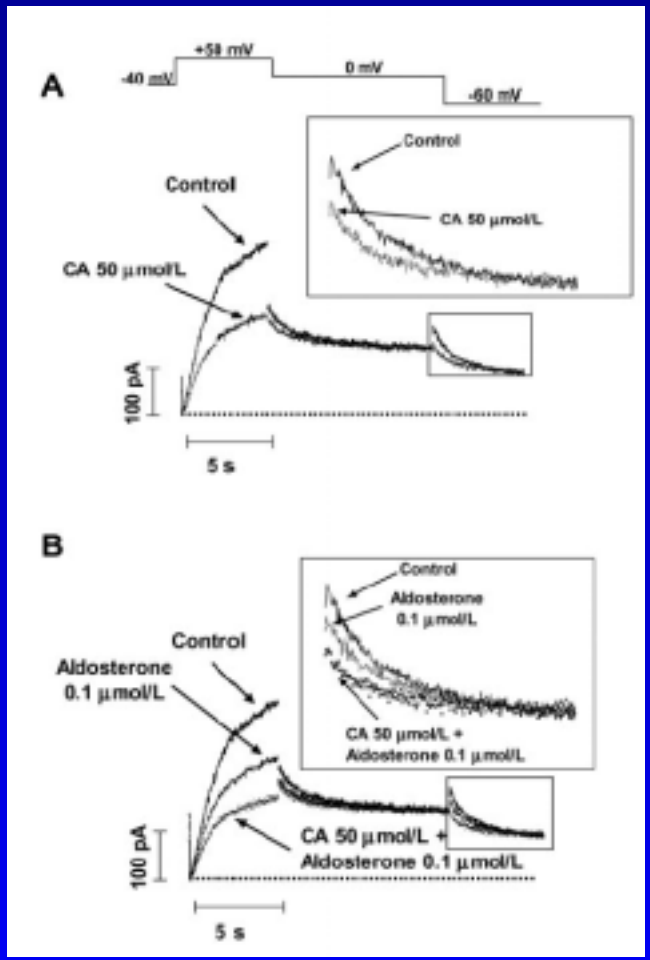
QTc : 760 msec

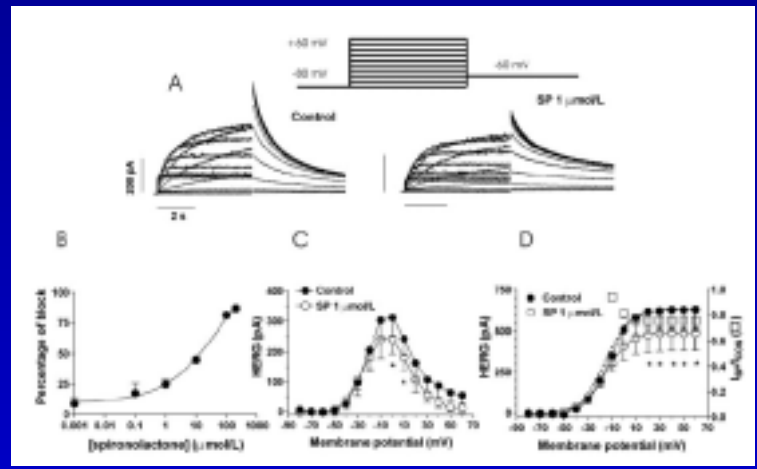


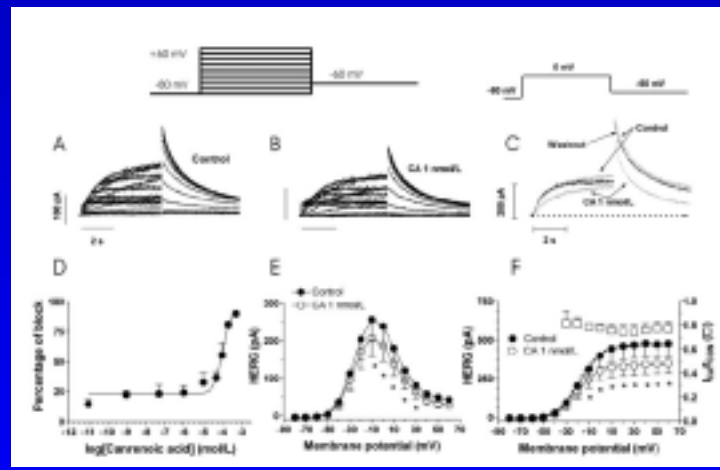
QTc : 472 msec



Spironolactone and Its Main Metabolite, Canrenoic Acid, Block Human Ether-a-Go-Go–Related Gene Channels

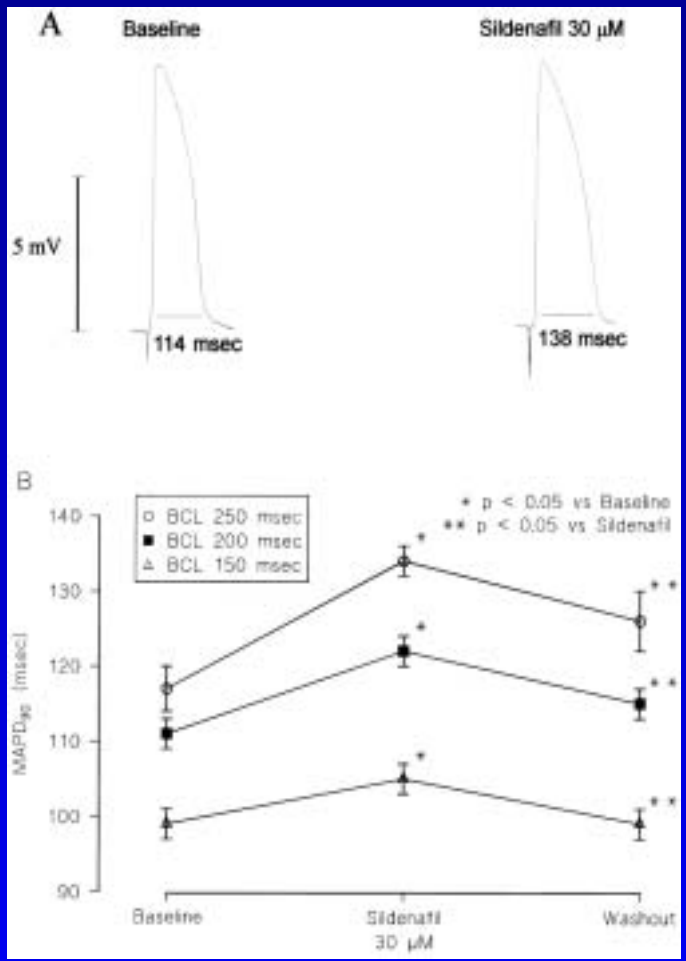


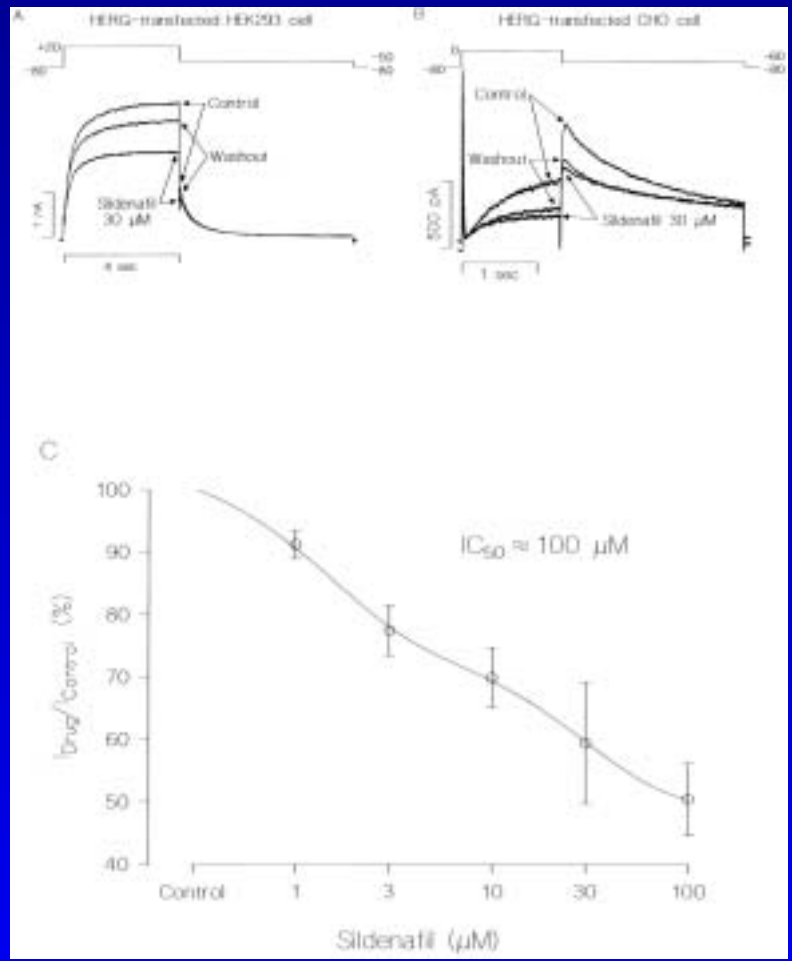




Caballero R. et al.*Circulation*. 2003;107:889-895

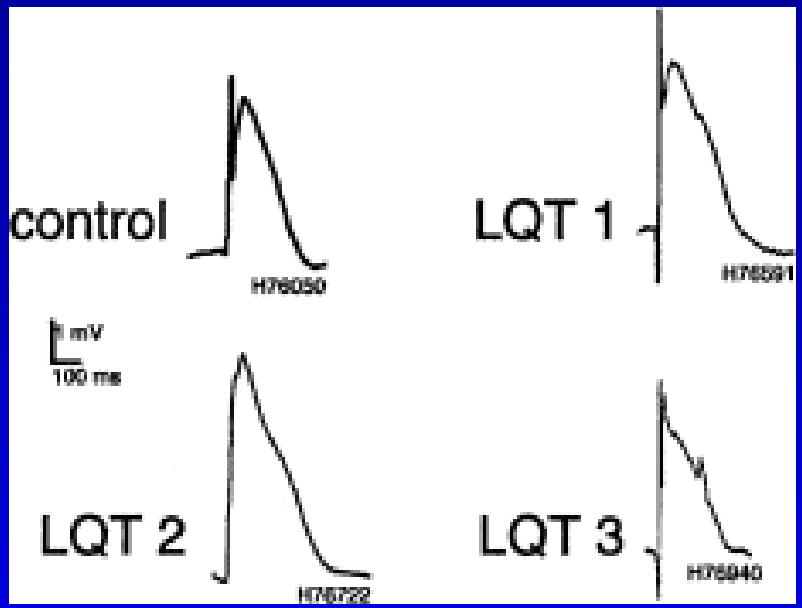
Sildenafil (Viagra) Prolongs Cardiac Repolarization by Blocking the IKr Current

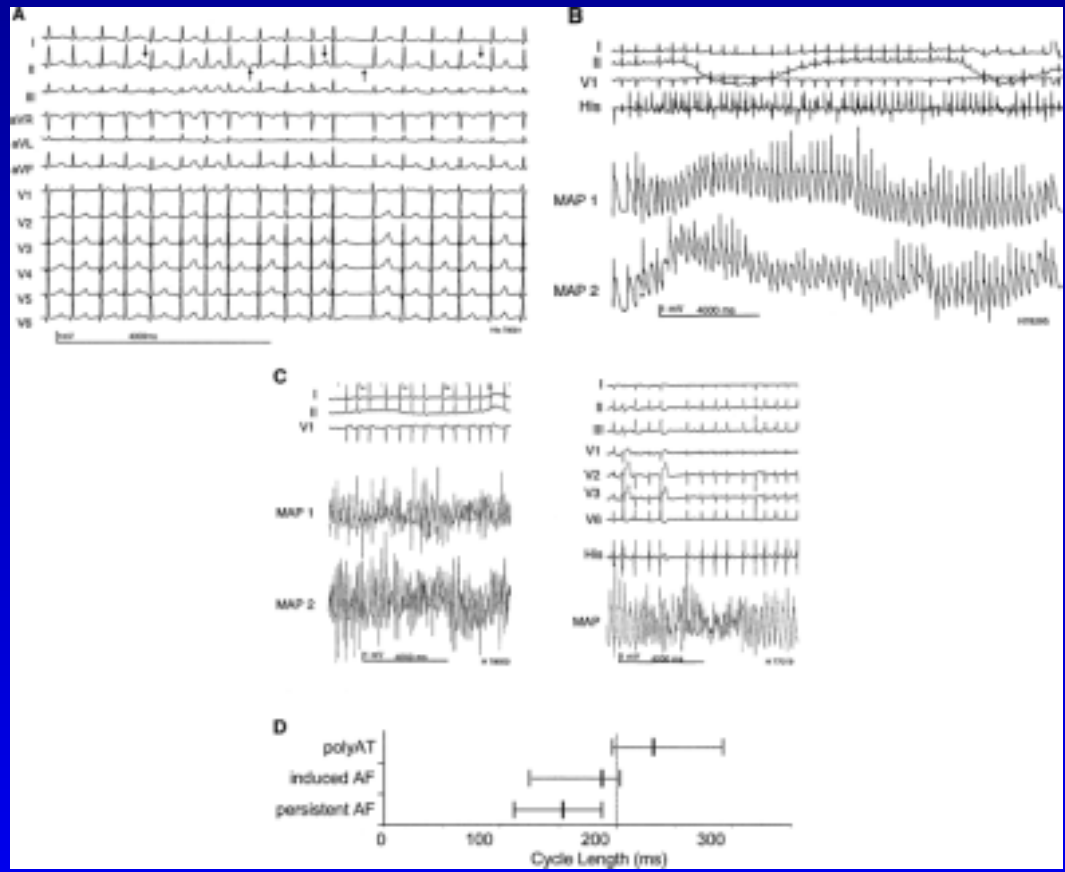




Geelen P. et al. *Circulation*. 2000;102:275-277

Prolonged atrial APD and polymorphic AT in patients with LQTS





J Cardiovascular Electrophysiol 2003:14:1037-1033)

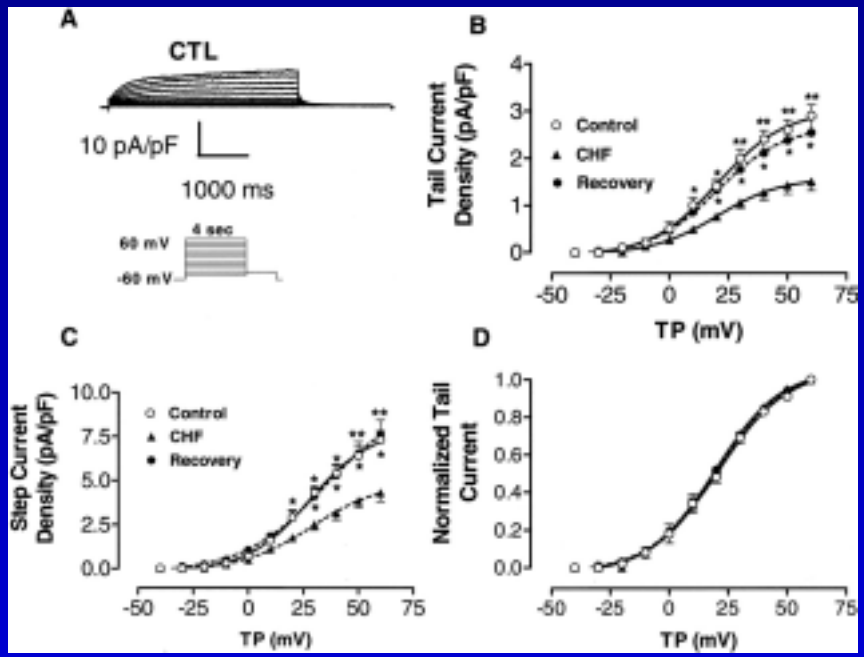
Dissociation Between Ionic Remodeling and Ability to Sustain Atrial Fibrillation During Recovery From Experimental Congestive Heart Failure

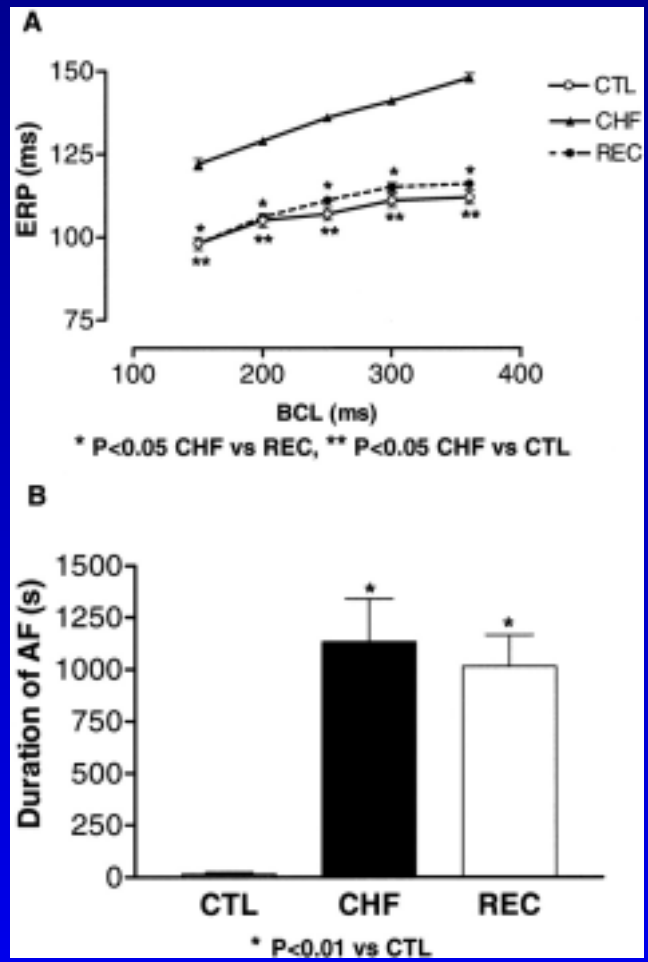
Tae-Joon Cha, MD; Joachim R. Ehrlich, MD; Liming Zhang, MSc; Yan-Fen Shi, MD; Jean-Claude Tardif, MD; Tack Ki Leung, MD; Stanley Nattel, MD

Background—Congestive heart failure (CHF) downregulates atrial transient outward (I_{to}), slow delayed rectifier (I_{Ks}), and L-type Ca^{2+} (I_{CaL}) currents and upregulates Na^+-Ca^{2+} exchange current (I_{NCX}) (ionic remodeling) and causes atrial fibrosis (structural remodeling). The relative importance of ionic versus structural remodeling in CHF-related atrial fibrillation (AF) is controversial.

Methods and Results—We measured hemodynamic and echocardiographic parameters, mean duration of burst pacing–induced AF (DAF), and atrial-myocyte ionic currents in dogs with CHF induced by 2-week ventricular tachypacing (240 bpm), CHF dogs allowed to recover without pacing for 4 weeks (REC), and unpaced controls. Left ventricular ejection fraction averaged 58.6±1.2% (control), 36.2±2.3% (CHF, $P<0.01$), and 57.9±1.6% (REC), indicating full hemodynamic recovery. Similarly, left atrial pressures were 2.2±0.3 (control), 13.1±1.5 (CHF), and 2.4±0.4 (REC) mm Hg. CHF reduced I_{to} density by ≈65% ($P<0.01$), decreased I_{CaL} density by ≈50% ($P<0.01$), and diminished I_{Ks} density by ≈40% ($P<0.01$) while increasing I_{NCX} density by ≈110% ($P<0.05$). In REC, all ionic current densities returned to control values. DAF increased in CHF (1132±207 versus 14.3±8.8 seconds, control) and remained increased with REC (1014±252 seconds). Atrial fibrous tissue content also increased in CHF (2.1±0.2% for control versus 10.2±0.7% for CHF, $P<0.01$), with no recovery observed in REC (9.4±0.8%, $P<0.01$ versus control, P=NS versus CHF).

Conclusions—With reversal of CHF, there is complete recovery of ionic remodeling, but the prolonged-AF substrate and structural remodeling remain. This suggests that structural, not ionic, remodeling is the primary contributor to AF maintenance in experimental CHF. **(*Circulation*. 2004;109:412-418.)**





Cha TJ et al. *Circulation*. 2004;109:412-418

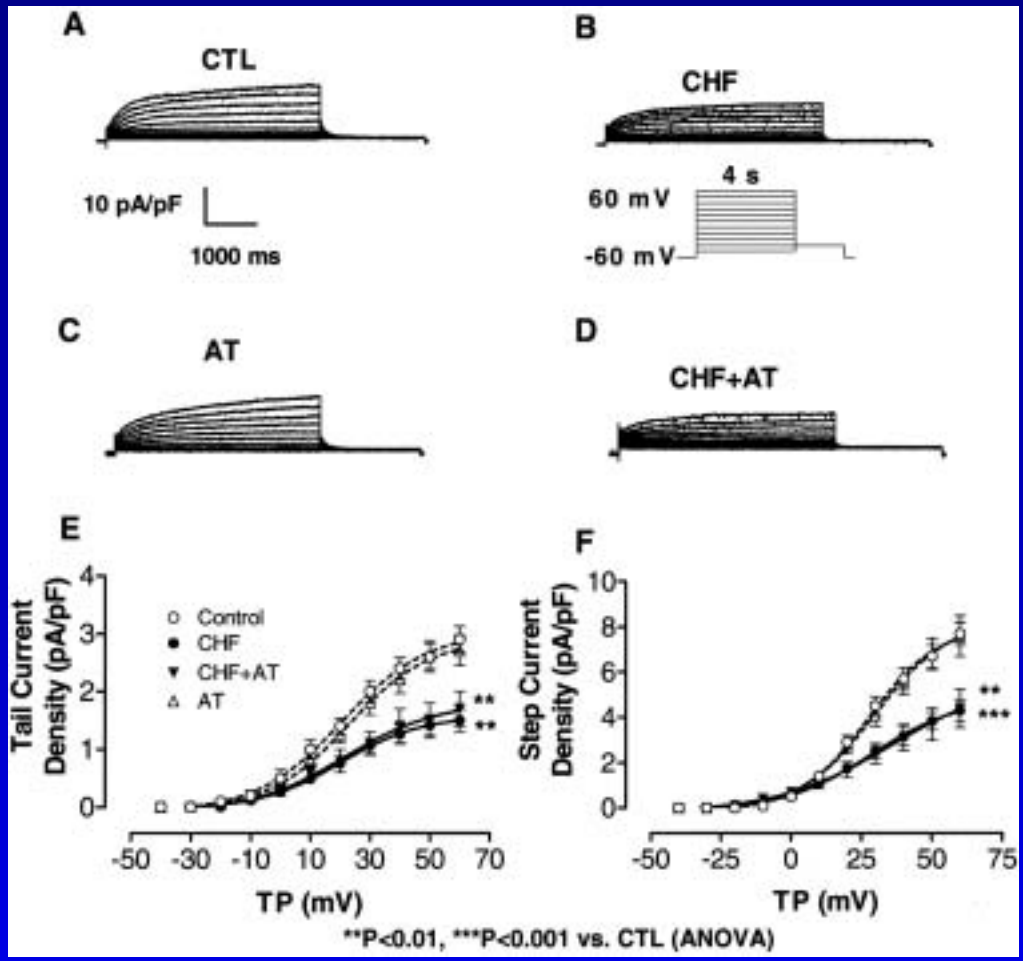
Atrial Ionic Remodeling Induced by Atrial Tachycardia in the Presence of Congestive Heart Failure

Tae-Joon Cha, MD; Joachim R. Ehrlich, MD; Liming Zhang, MSc; Stanley Nattel, MD

Background—Atrial fibrillation (AF) and congestive heart failure (CHF) produce discrete forms of atrial ionic remodeling. The in vivo effects of atrial tachycardia (AT) remodeling are altered by CHF. This study evaluated underlying mechanisms at the level of ionic remodeling.

Methods and Results—We studied 4 groups of dogs: (1) unpaced controls (CTLs); (2) CHF caused by 2-week ventricular tachypacing (VTP, 240 bpm); (3) AT (400 bpm ×7 days); and (4) CHF+AT (2-week VTP with AT for the last 7 days). CHF and CHF+AT groups equally increased left atrial pressure. AF duration was increased in all paced groups. Effective refractory period (ERP) was decreased by 42% in AT versus CTL but by only 24% in AT+CHF versus CHF. CHF reduced L-type Ca^{2+} (I_{Ca}), transient-outward (I_{to}), and the slow delayed-rectifier (I_{Ks}) currents while increasing the Na^{+}-Ca^{2+} exchanger (I_{NCX}) and not affecting the inward-rectifier (I_{K1}) current. AT reduced I_{to} and I_{Ca} while increasing I_{K1} and leaving I_{Ks} unaltered. The addition of AT to CHF failed to alter I_{to}, I_{Ks}, or I_{NCX} beyond the effect of CHF alone, decreased I_{Ca} slightly compared with CHF alone, but had smaller effects on I_{Ca} and I_{K1} compared with AT alone. Thus, CHF+AT, as would occur in a CHF patient who develops AF, produced an ionic remodeling pattern different from that of CHF or AT alone and from what would have been predicted from additive effects of CHF and AT.

Conclusions—The presence of CHF alters AT-induced ionic remodeling. Thus, the ionic remodeling caused by cardiac arrhythmias in the presence of cardiac pathology is not necessarily predictable from the effects of either alone, with important potential implications for understanding the pathophysiology of arrhythmias in the diseased heart.
(*Circulation.* 2004;110:1520-1526.)



Cha TJ et al. *Circulation.* 2004;110:1520-1526

Therapy for LQTS

- Beta-blocker: LQT1
- Left cervical sympathetic ganglionectomy
  - Reserved for high-risk LQT patients who can not be effectively treated with drugs and devices
- Pacemaker
- ICD; combined with β-blocker are the safest form for high risk LQTS patients.
- Mexiletine, flecainide; LQT3
- Potassium therapy: LQT2

Social Life Modification

- Avoid adrenergic-type stimuli that can trigger life-threatening arrhythmia.
- Competitive athletics should be prohibited.
- Alarm clocks should be removed.
- Good β-blocker compliance is important.