Prolonged QT Interval

January, 2004

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UTHSCSA and ALMMVAH

Measurement of QT interval

- Lead with large T wave with distinct end
- Best: maybe V2-V3
- Varies with heart rate, longer in women, longer in evening and night
- Bazett formula
  - QTc = QT/SQRT(RR interval)
- QTc ~0.40 for men, ~0.415 for women, ULN ~0.44 or 0.46 for men and 0.47 for women
  - Not universally accepted
- Marked PQT is >125% (0.50 men, 0.52 women), moderate PQT is 115-125% (0.46, 0.48)

Surawicz B et al. Chou's 5th ed. P. 22-3, 555

Causes of Prolonged QT interval

- Congenital
  - Jervell-Lange-Nielson
  - Romano-Ward
  - Sporadic
- Acquired
  - Ischemia*, infarction*
  - MVP, cardiomyopathy*
  - CNS dz*, esp ICH
  - Autonomic NS surg
- Acquired (contd)
  - Metabolic (lo Ca*, Mg, K*, liquid protein diet, intracoronary contrast
  - Drugs (I-A*, III*, I-C, Amio, phenothiazine, tricyclic, antihistamine-combo, pentamidine)
  - lo thyroid*, temp, pheo, organophosphate

* = may show less severe prolongation

Causes of Short QT Interval

- High Ca, K, digoxin, acidosis, ? beta-blockade

Causes of Abnormal U Wave

- Prominent U Wave
  - Definition: >1.5-2mm
  - Lo HR, K, Mg, hi Ca,
  - I-A, III, digoxin, phenothiazine, Epi
  - CNS disease
  - LVH
  - Hi thyroid
  - MVP, Long QT syndrome
- Inverted U Wave
  - Specific for heart disease
  - LVH (I, V5, V6)
  - RVH (V1, V2, II, III)
  - Ischemia/infarction
    - resting ECG
    - during anginal episode
    - exercise-induced

T and U Waves and Fusion

- Normal: U wave begins at end of T at baseline, synchronous with S2, with early beat, T and U may fuse
- If QT lengthens by less than about 0.10 sec, U is still discernable
- Notched T vs T-U:
  - Notch generally has short distance between peaks, where aT-aU interval is usually 0.17-0.22 sec
  - Notch nadir generally > 2mm, and U onset usually < 2 mm above baseline
  - Look at I aVL and aVR where there is usually no U to evaluate end of T wave

Surawicz B et al. Chou's 5th ed. P. 561

Electrolyte Disturbances with Significant ECG Effects

- Hyperkalemia, hypokalemia
- Hypercalcemia, hypocalcemia
- Hypothermia
- Hypermagnesemia (depress AV and IV conduction)
- Acidosis or alkalosis usually have altered K or Ca, independent effects uncertain

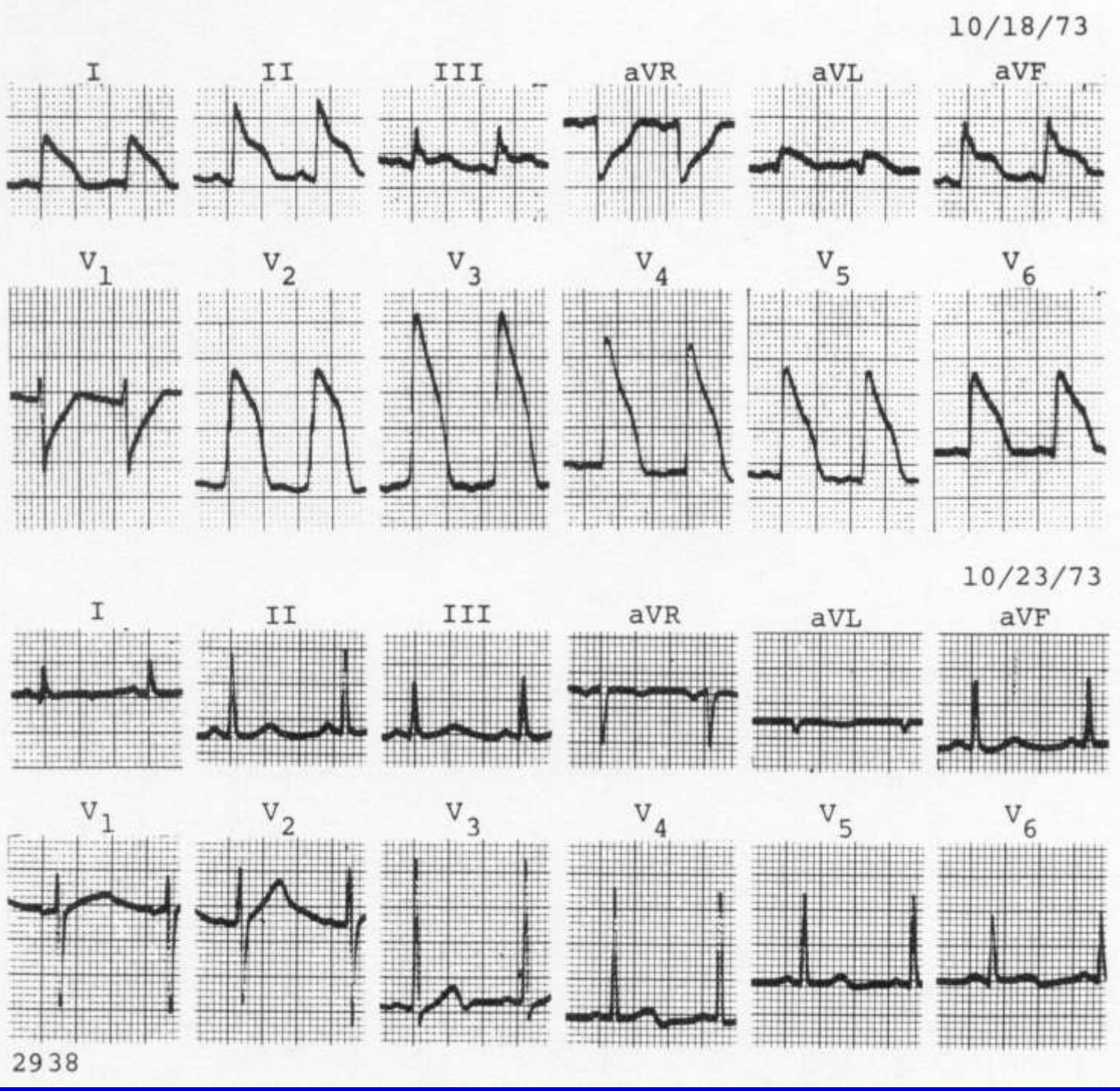
Hyperkalemia

- T waves become tall and peaked (>5.5)
- QRS widens uniformly (>6.5)
- QRS axis may shift either left or right
- Advanced hyperkalemia is indistinguishable from dying heart
- Advanced hyperkalemia may give ST elevation
- P wave amplitude decreases, PR interval prolongs
- Sinoventricular conduction
- Concomitant hypercalcemia mitigates changes
- Concomitant hyponatremia worsens changes and hypernatremia mitigates

Hyper-kalemia with ST elevation

Pt with DKA and K 6.9, morphology resembles monophasic action potential

Surawicz, p. 520

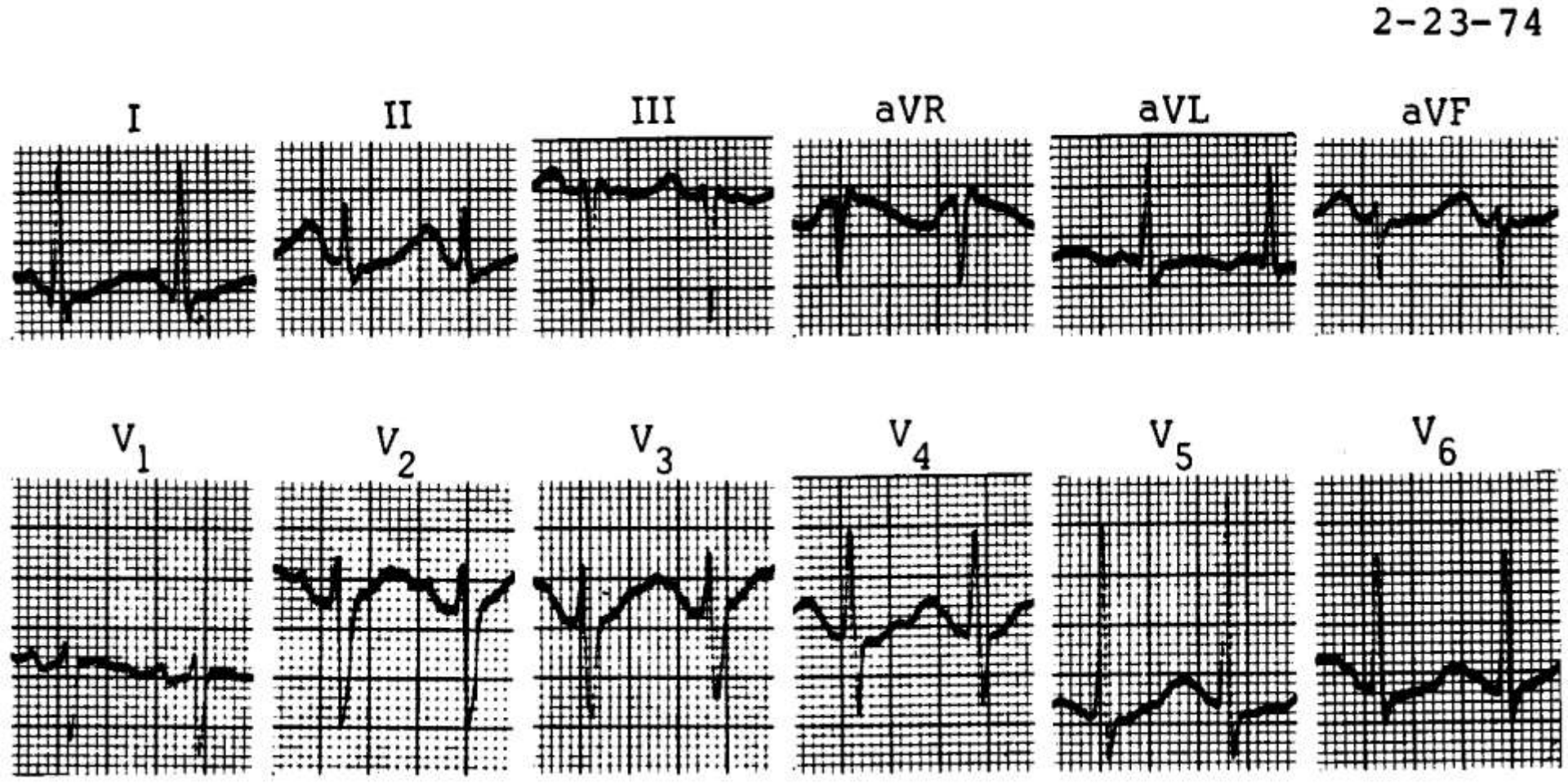


Hypokalemia

- Progressive ST segment depression > 0.5 mm
- Decrease in T wave amplitude
- Increase in U wave amplitude
  - >1 mm
  - >T wave height in same lead
- If K<2.7, ECG is “typical” (all 3 features) in 78% and “compatible” in 11%
- If K 2.7-3.0, ECG is “typical” in 35% and “compatible” in 35%
- No change in QT interval if measured before U wave
- Advanced hypokalemia – T and U are fused
- Concomitant hypocalcemia: aggravates findings

Surawicz, p. 523

Hypokalemia



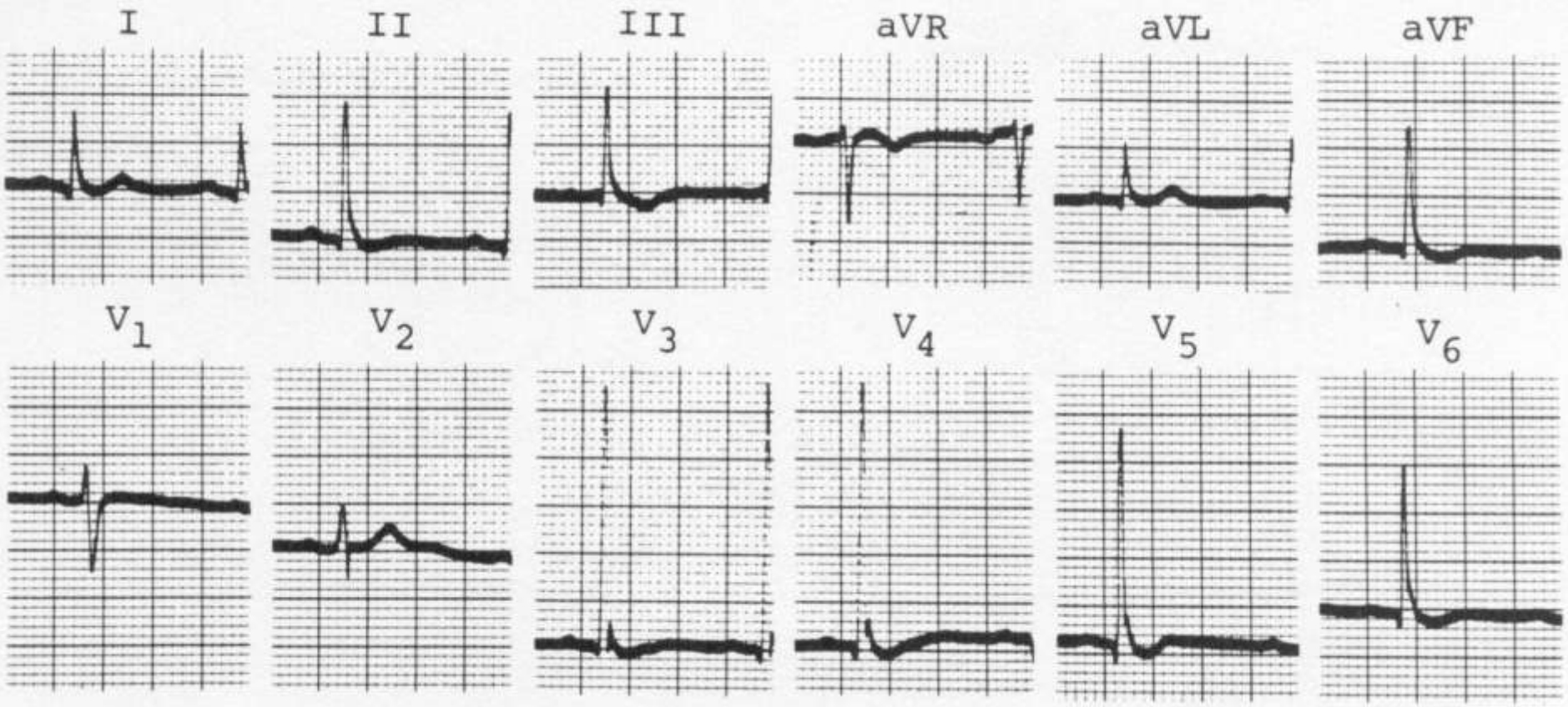
K = 2.4

Surawicz,
p. 525

Calcium

- Ionized calcium, so correct for albumin level
- Mainly change in ST segment duration, little change in T wave morphology or P or QRS or PR or U
- Hypercalcemia shortens ST segment, so shortens the QaT (onset of QRS to apex of T)
  - If QaTc is 0.27 sec or less, then Ca is high 90% of time
- Hypocalcemia lengthens ST segment (rarely more than 140% normal)

Hypercalcemia

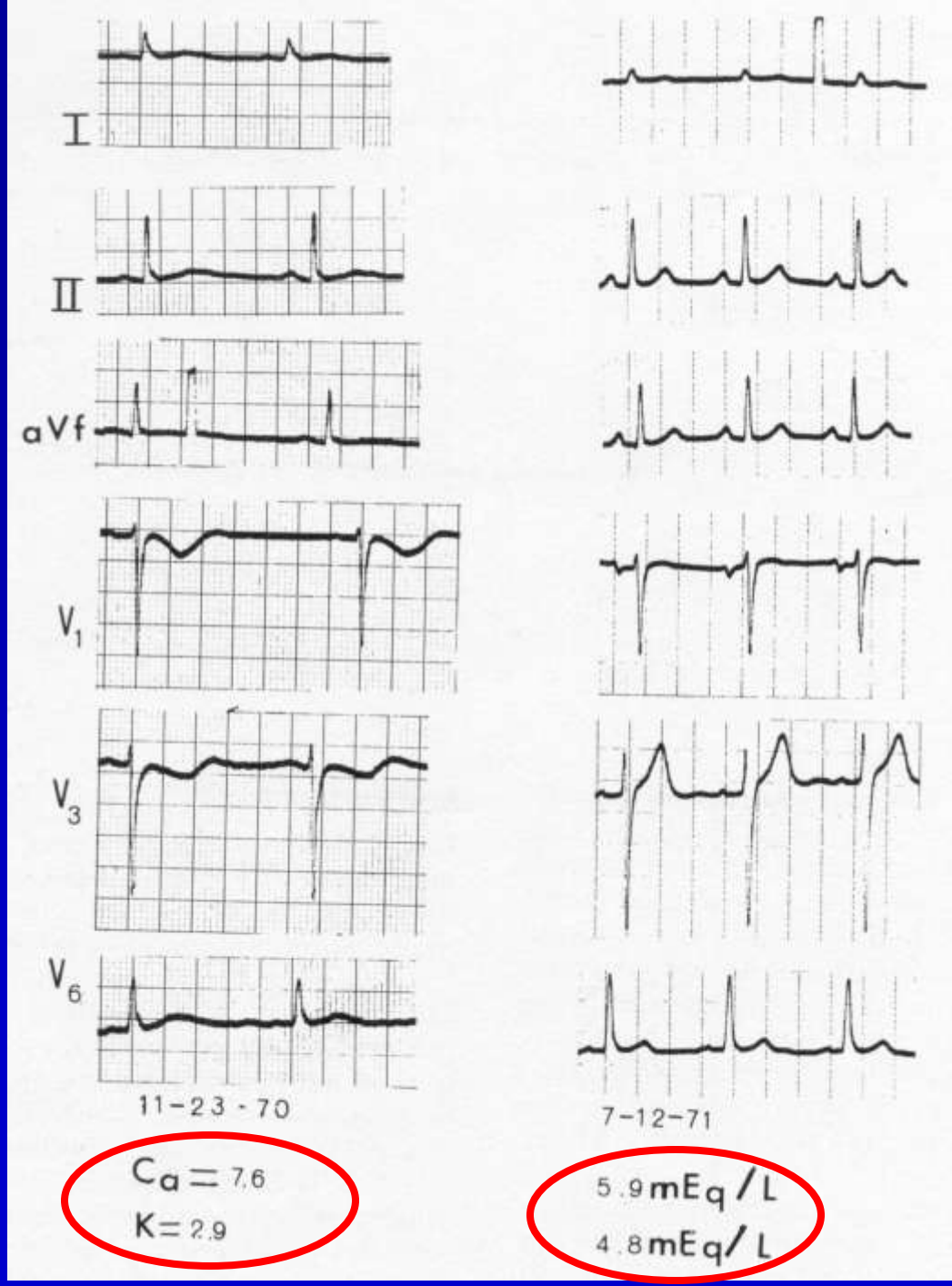


29-year old woman with lymphoma and bone involvement with Calcium 17.4; heart normal at autopsy, short QT interval, ST segment almost absent, flat T waves may or may not be related to hypercalcemia

Surawicz, p. 529

Hypercalcemia and Hypokalemia

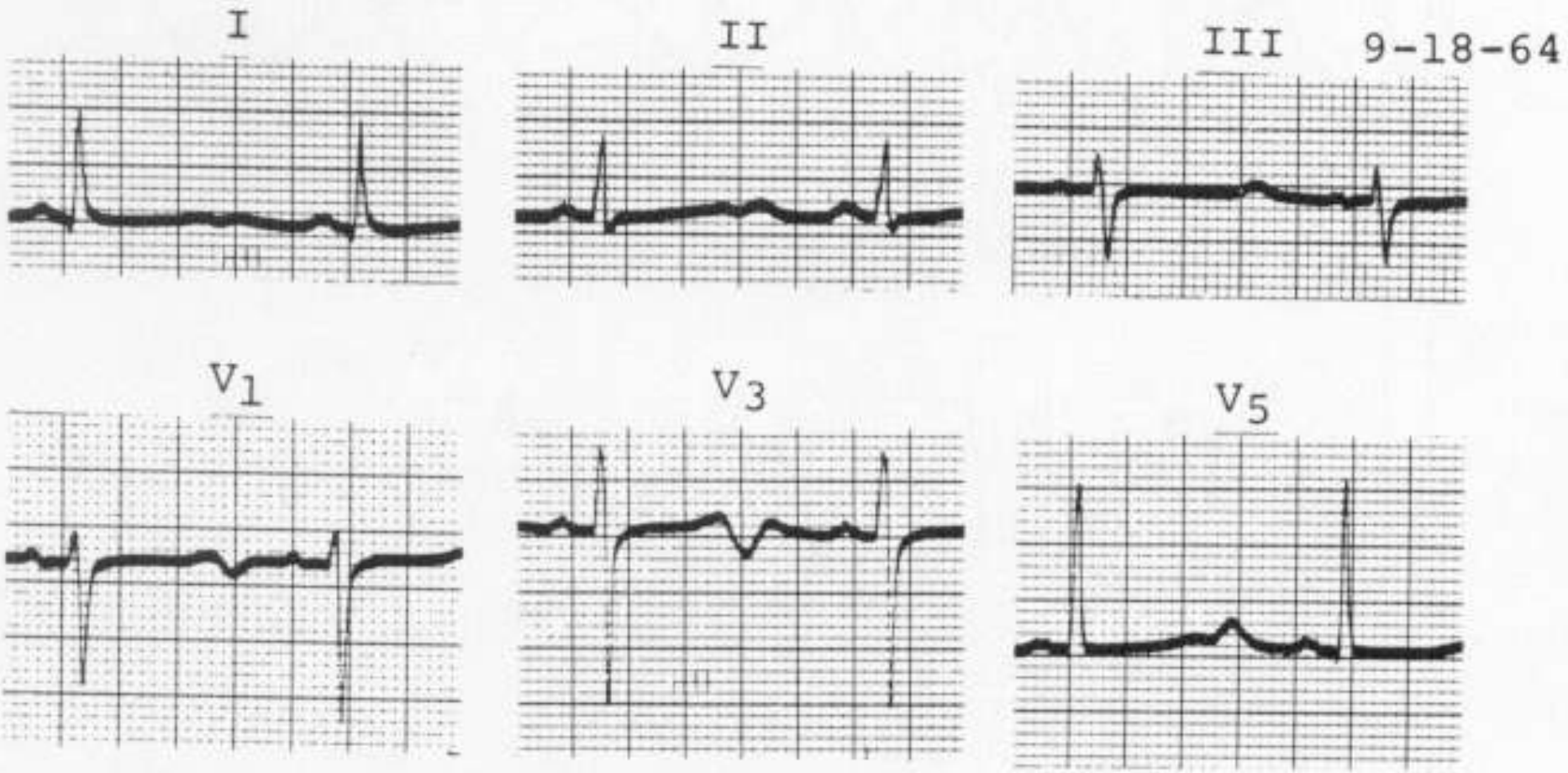
41-year old man with multiple myeloma with absent ST segment and prominent U wave (V3), later normal K and Ca and ECG



Surawicz, p. 530

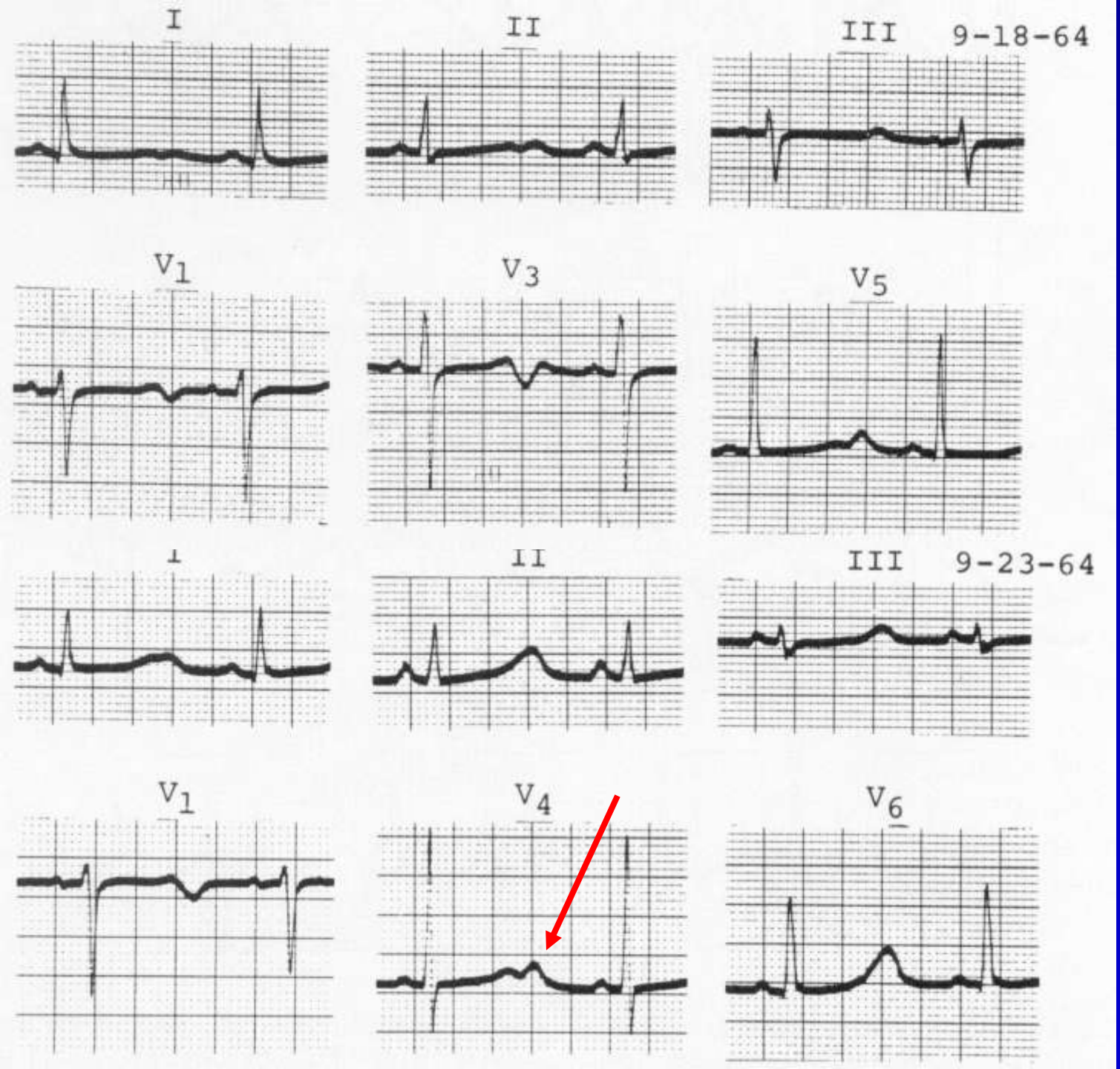
Hypocalcemia

31-year old man with chronic renal failure
Calcium 5.8 and K 3.3



PQT, esp ST segment, prominent U waves

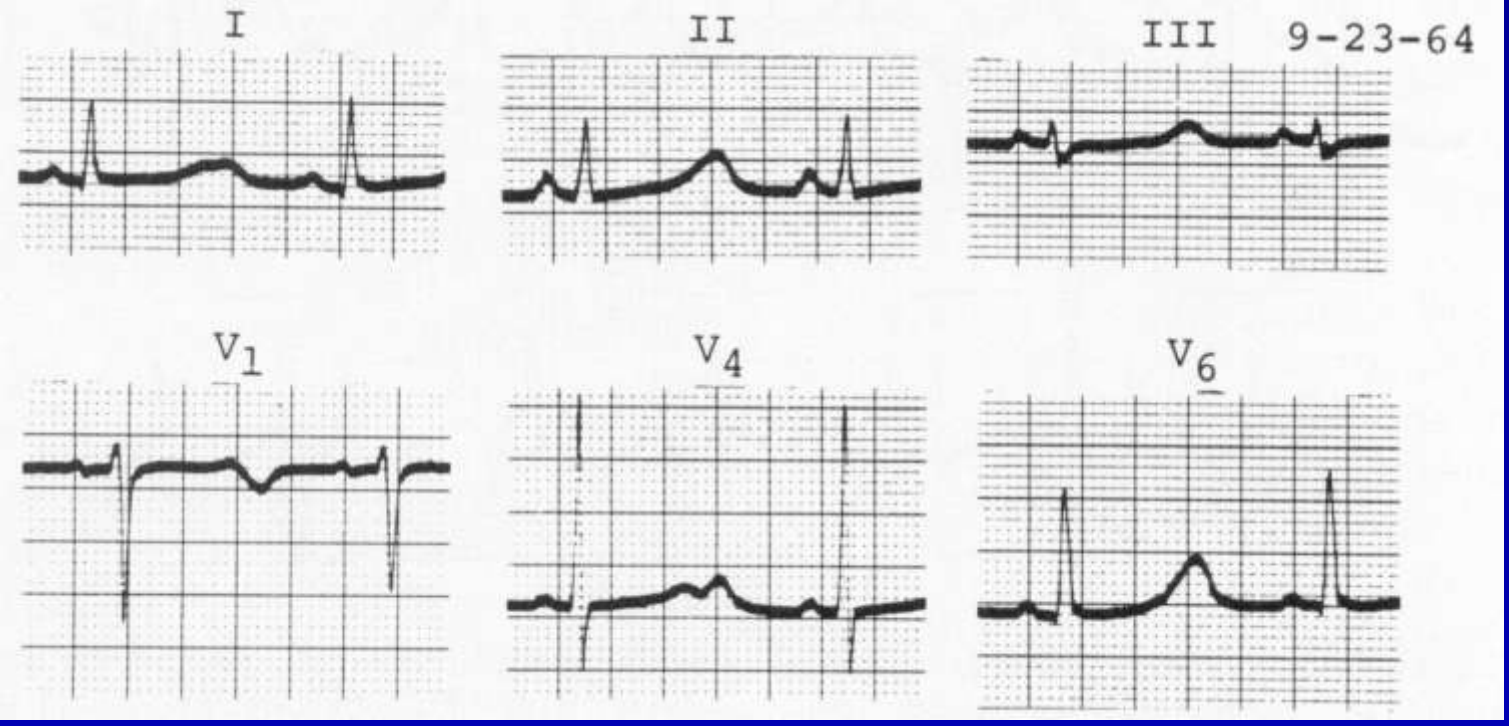
Surawicz, p. 528

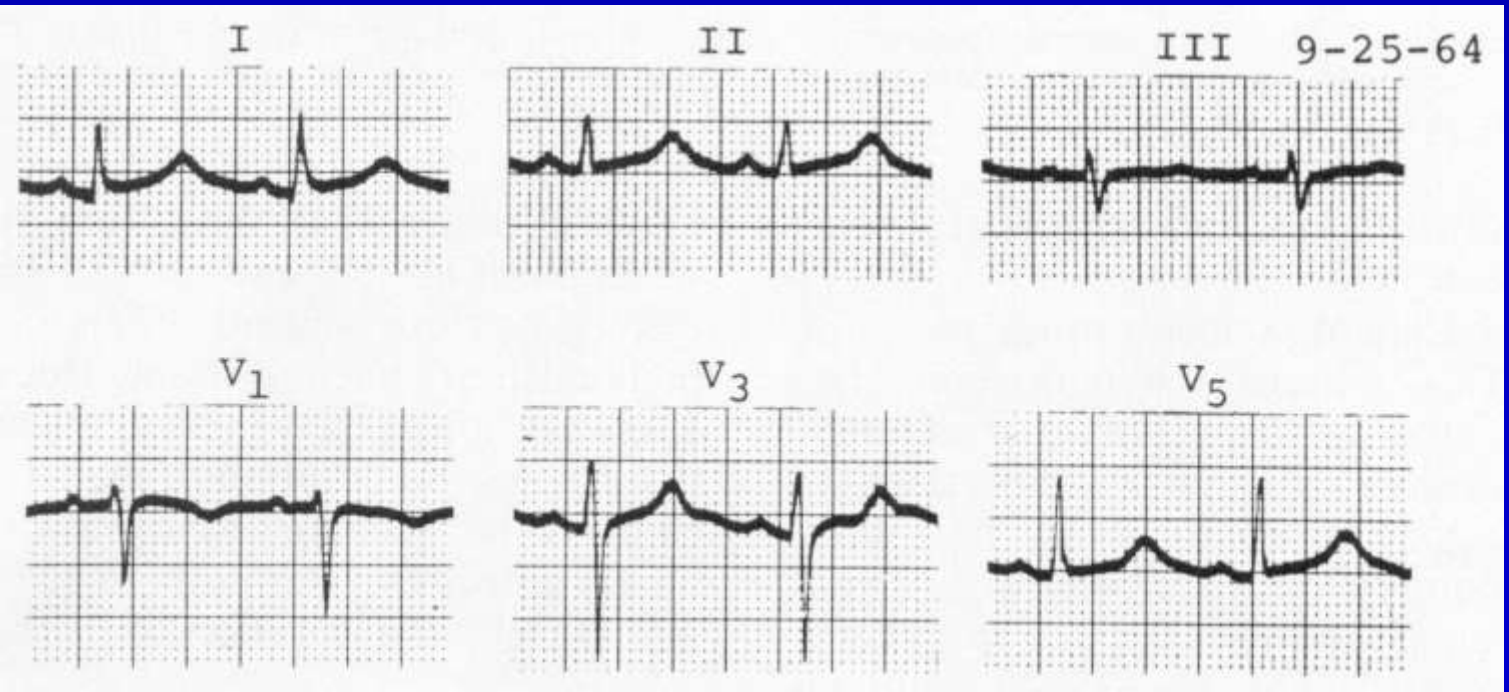


31-year old man with chronic renal failure
Calcium 5.8 and K 3.3

K now down to 2.8, U waves more prominent and mostly superimposed on T wave

Surawicz, p. 528





K now up to 3.5 and Calcium up to 6.5; ST segment is shorter and U less prominent

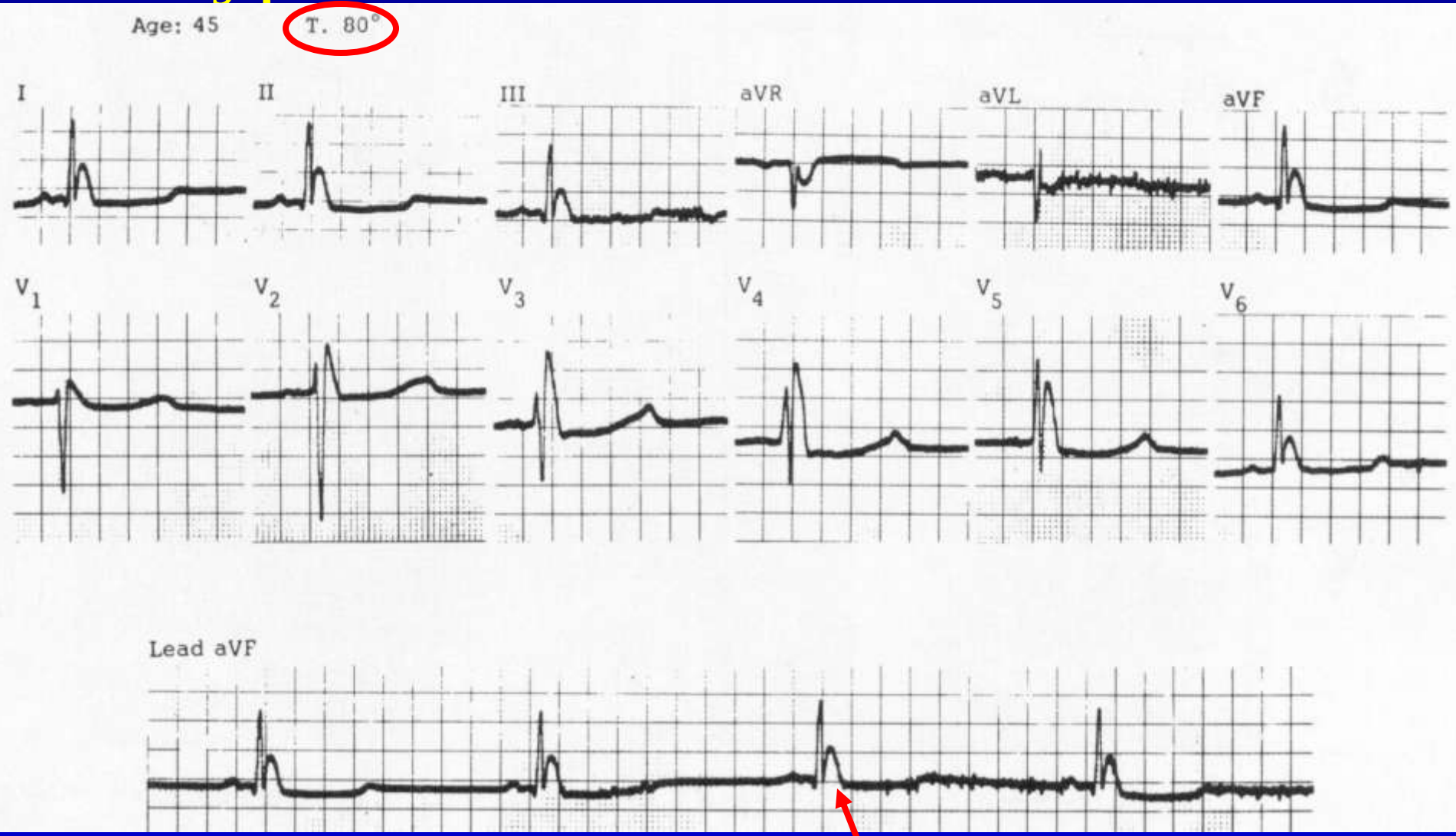
Surawicz, p. 528

Situations that Don’t Affect the ECG

- Hyponatremia, hypernatremia
- Hypomagnesemia, hypermagnesemia
- Hyperthermia
- Alkalosis, acidosis
- Alcohol, coffee, tobacco

Hypothermia

Surawicz, p. 533



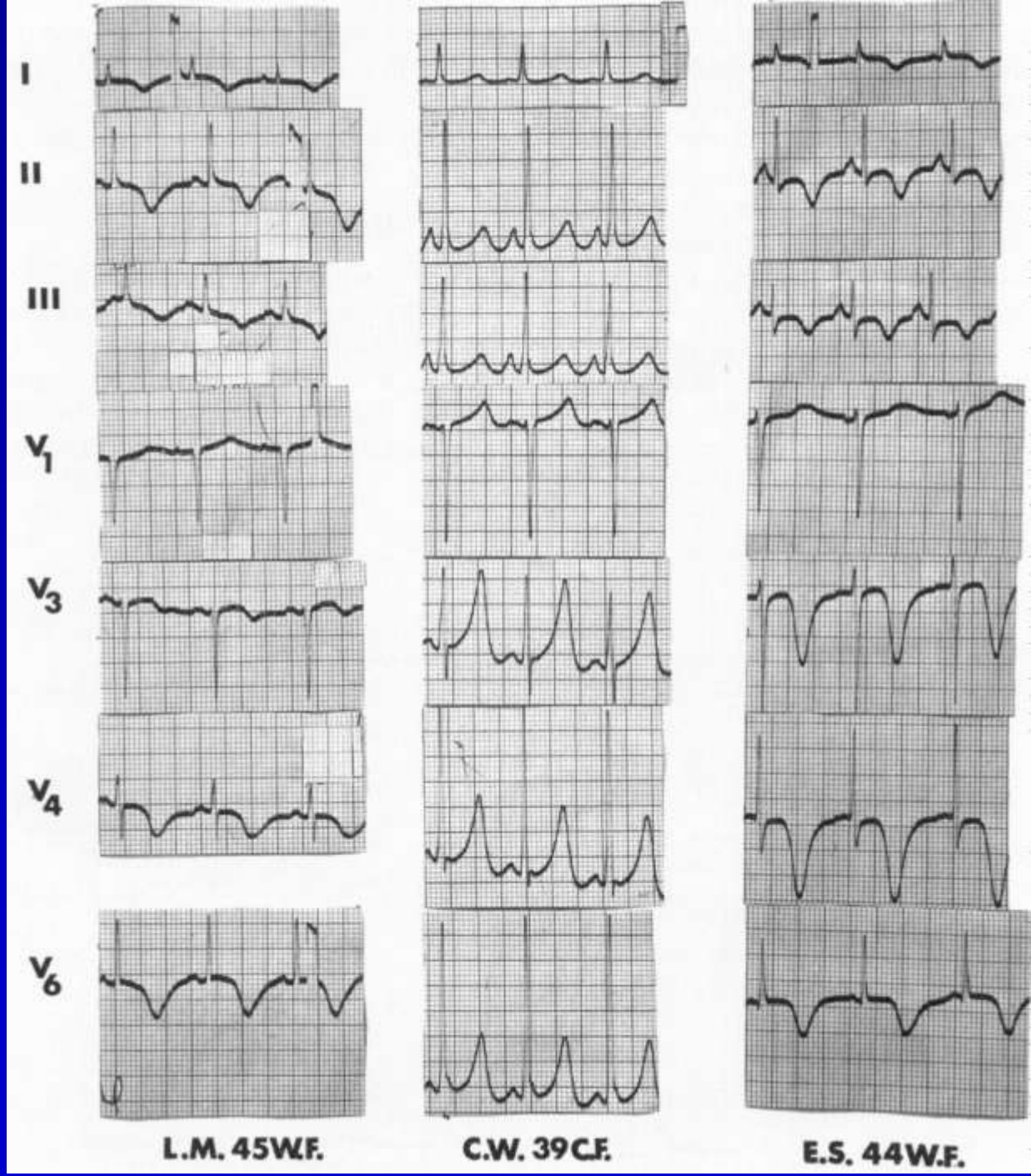
Heart rate 32, some baseline oscillation is somatic muscle tremor; long QT and ST depression as well as J wave ("Osborne wave")

CNS Disorders

- Diffuse T inversion
- Particularly giant T inversion in precordial leads
- Prolongation of QT interval
- Can also have ST segment elevation or depression
- LV wall motion abnormalities have been described

CNS: Subarachnoid Bleed

3 women with subarachnoid hemorrhage, prolonged QT and increased amplitude of an upright or inverted T wave



Surawicz p. 534

Tricky ECG

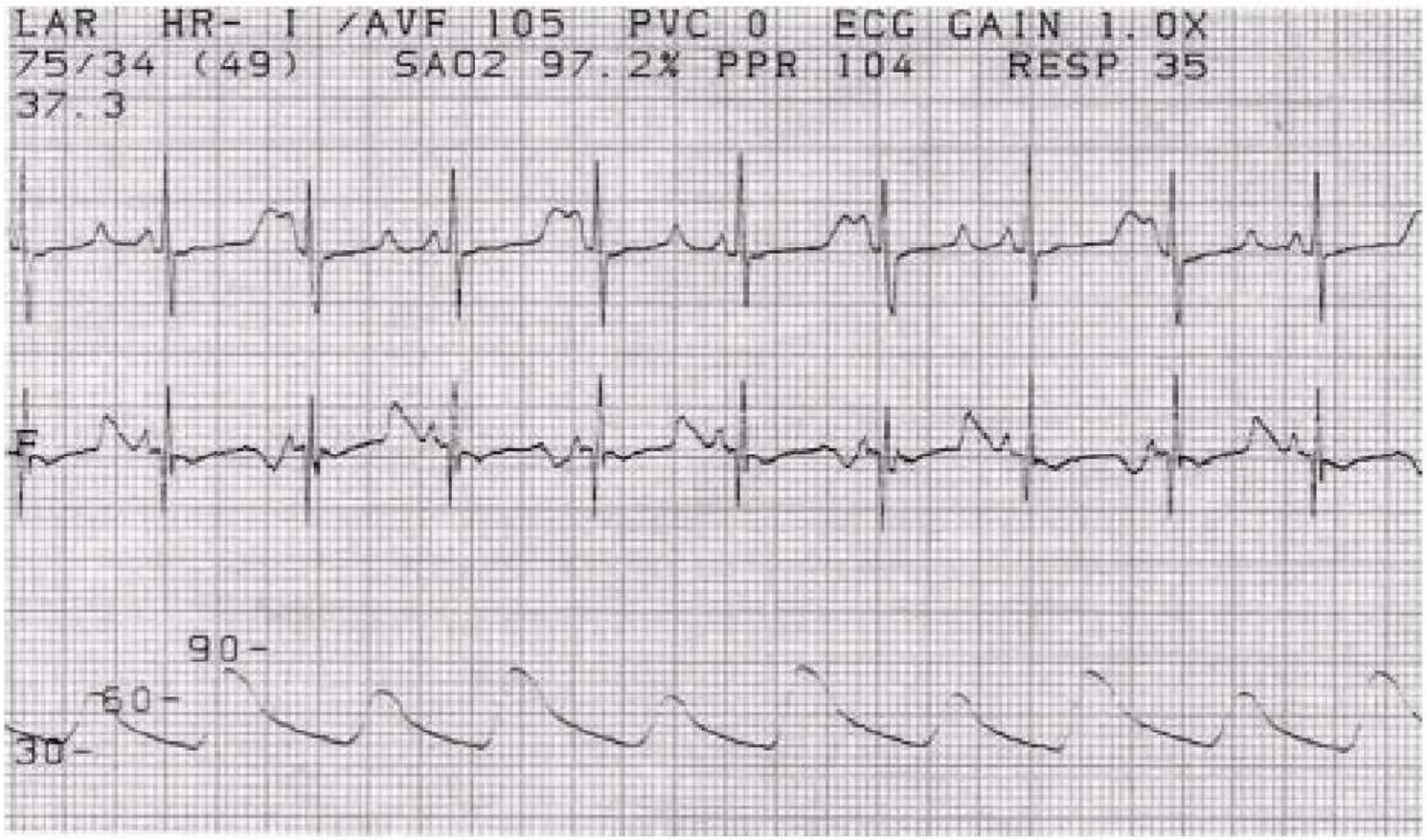


Figure 1. Prolonged QT and QTc intervals, T wave alternans, and pulsus alternans.

Suys B et al. Circulation 2003;108:e36

Tricky ECG

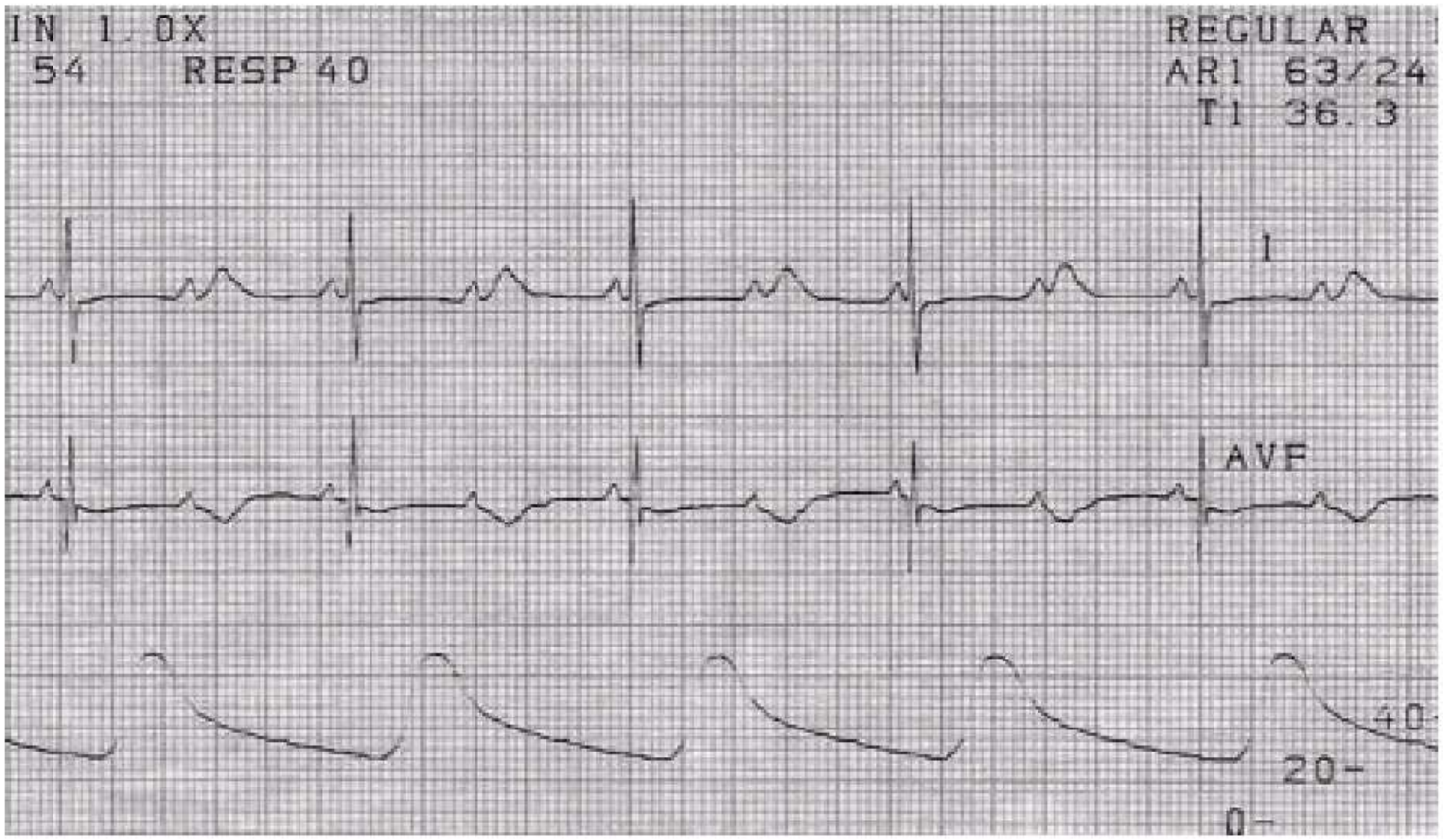
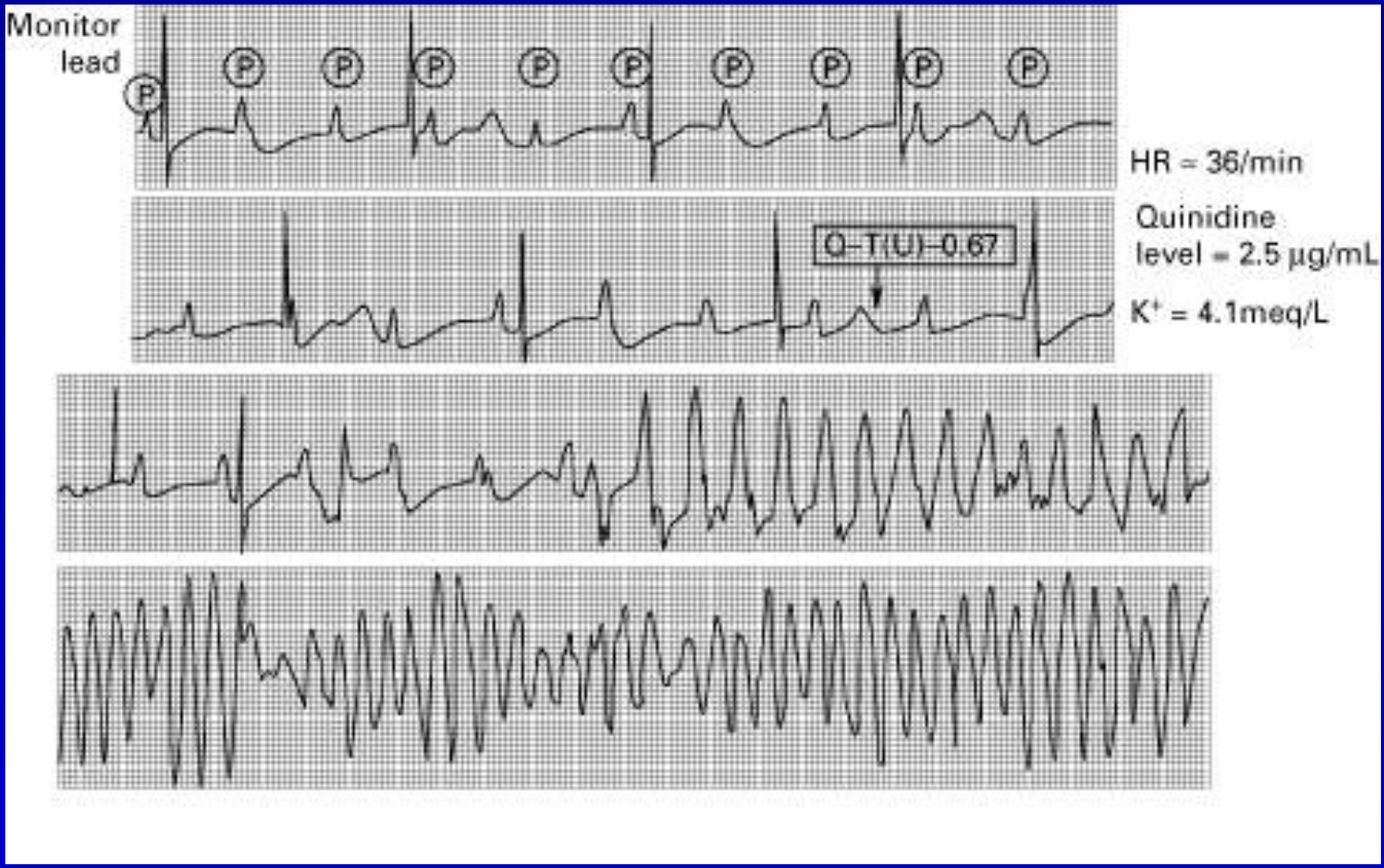


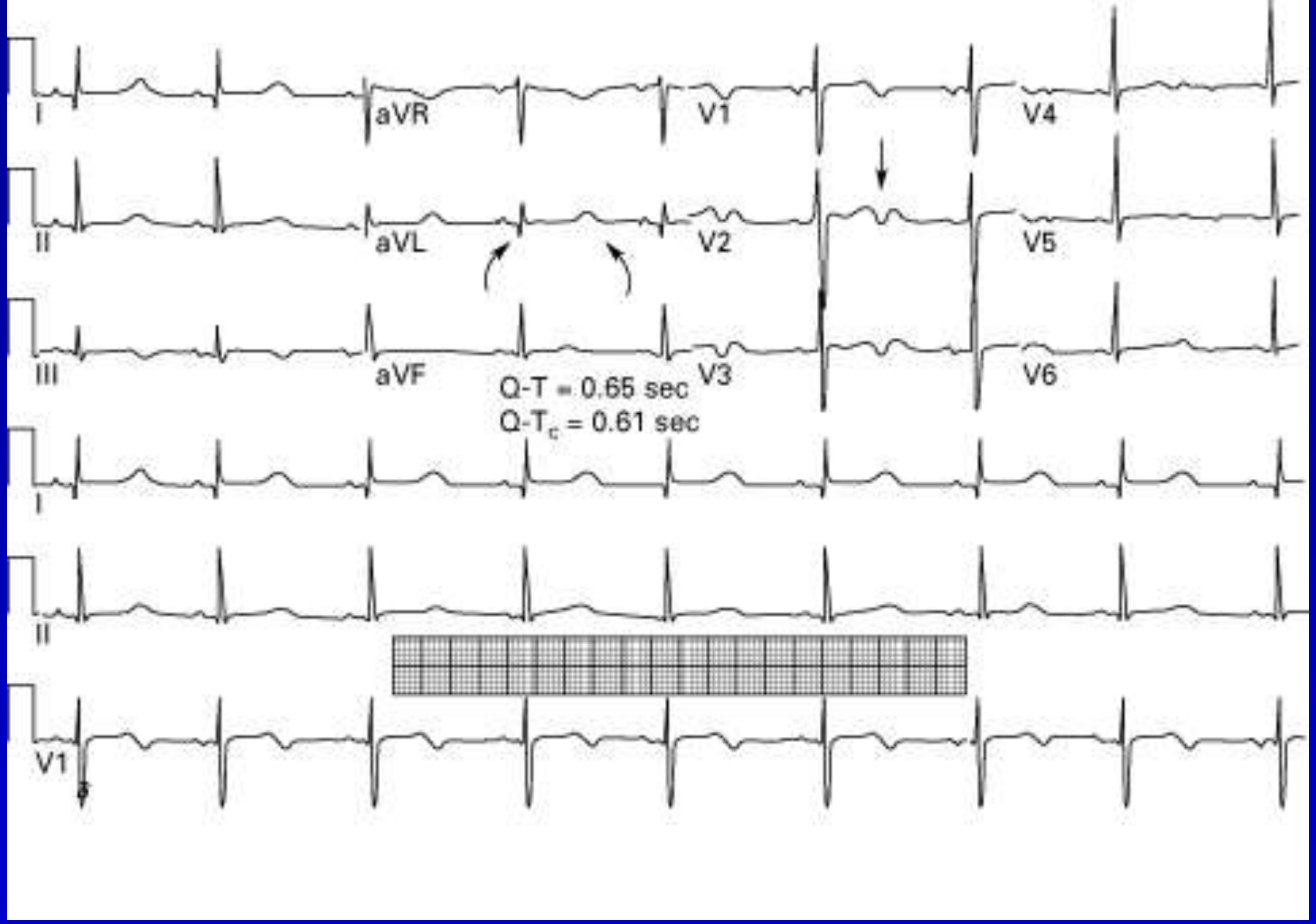
Figure 2. Pseudo 2:1 AV block with hypotension.

Suys B et al. Circulation 2003;108:e36



49 year old woman with complete heart block receiving quinidine for ventricular arrhythmia

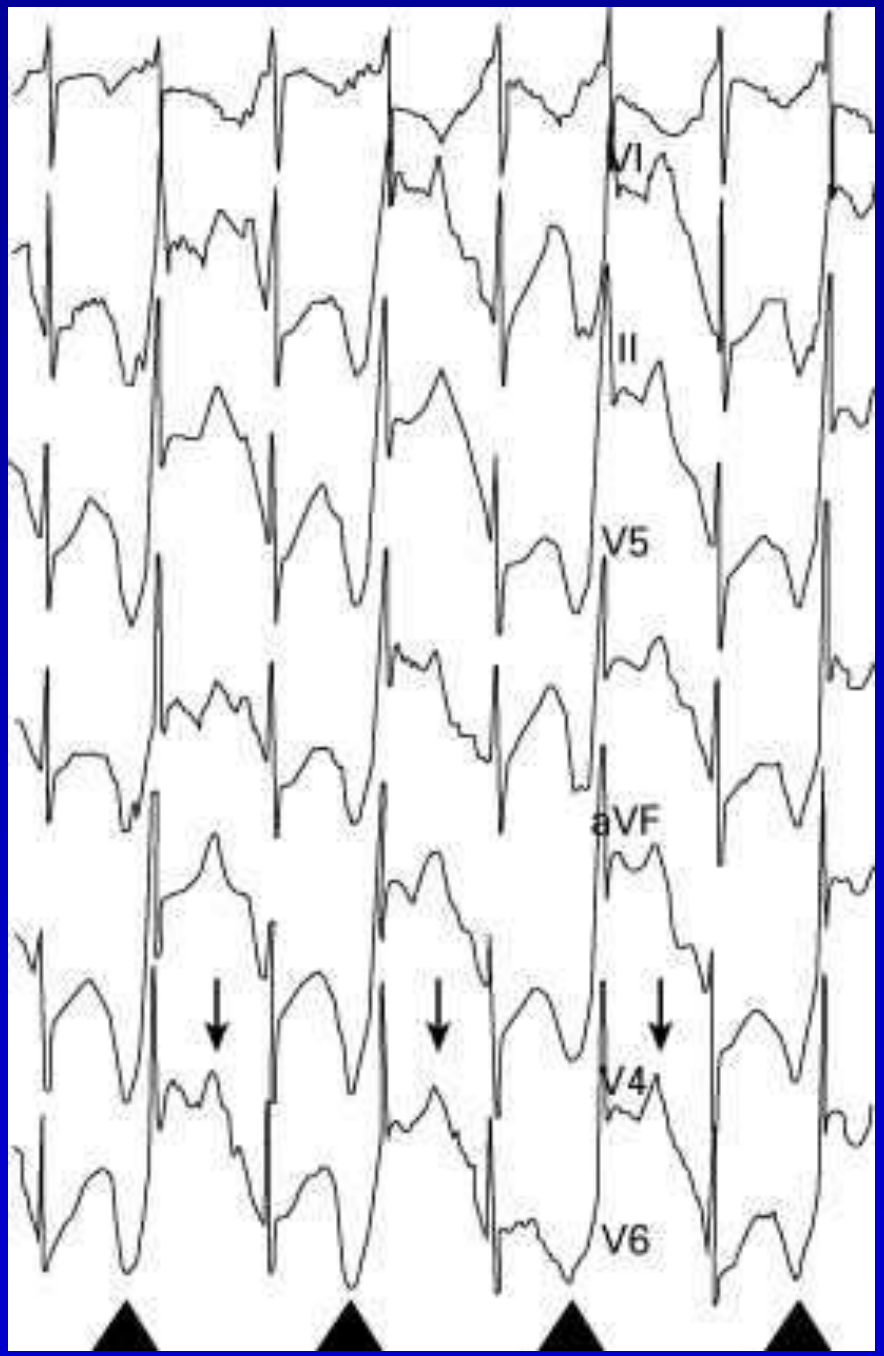
Hurst, 1998, Myerburg et al. P. 923



25 year old woman with Jervell and Lange-Neilson, and exercise-induced palpitations and syncope. Note the QTc of 610msec

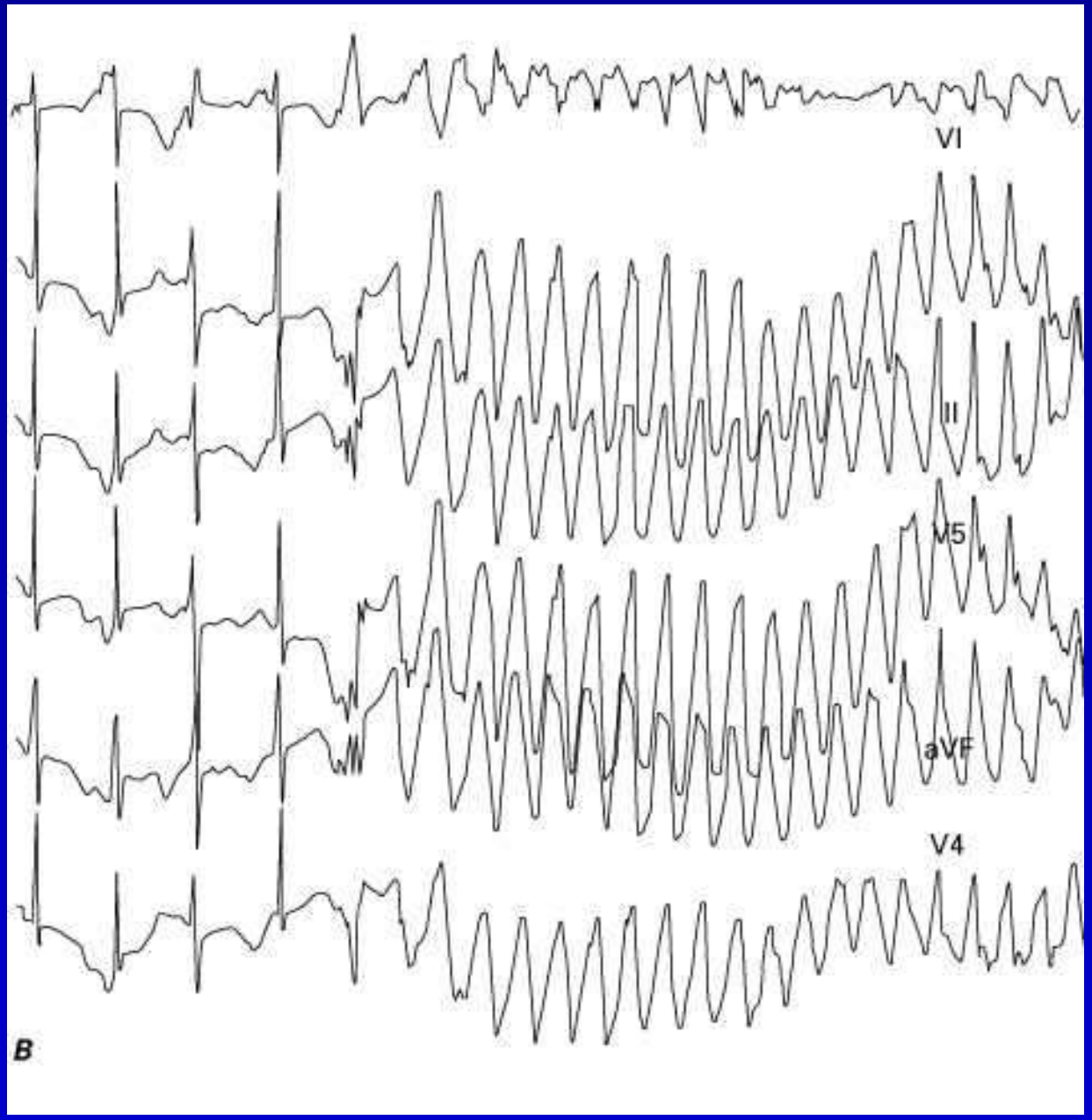
Hurst, 1998, Myerburg et al. P. 923

25 year old woman with Jervell and Lange-Neilson, and exercise-induced palpitations and syncope.
Note on this treadmill tracing
T wave alternans induced by exercise

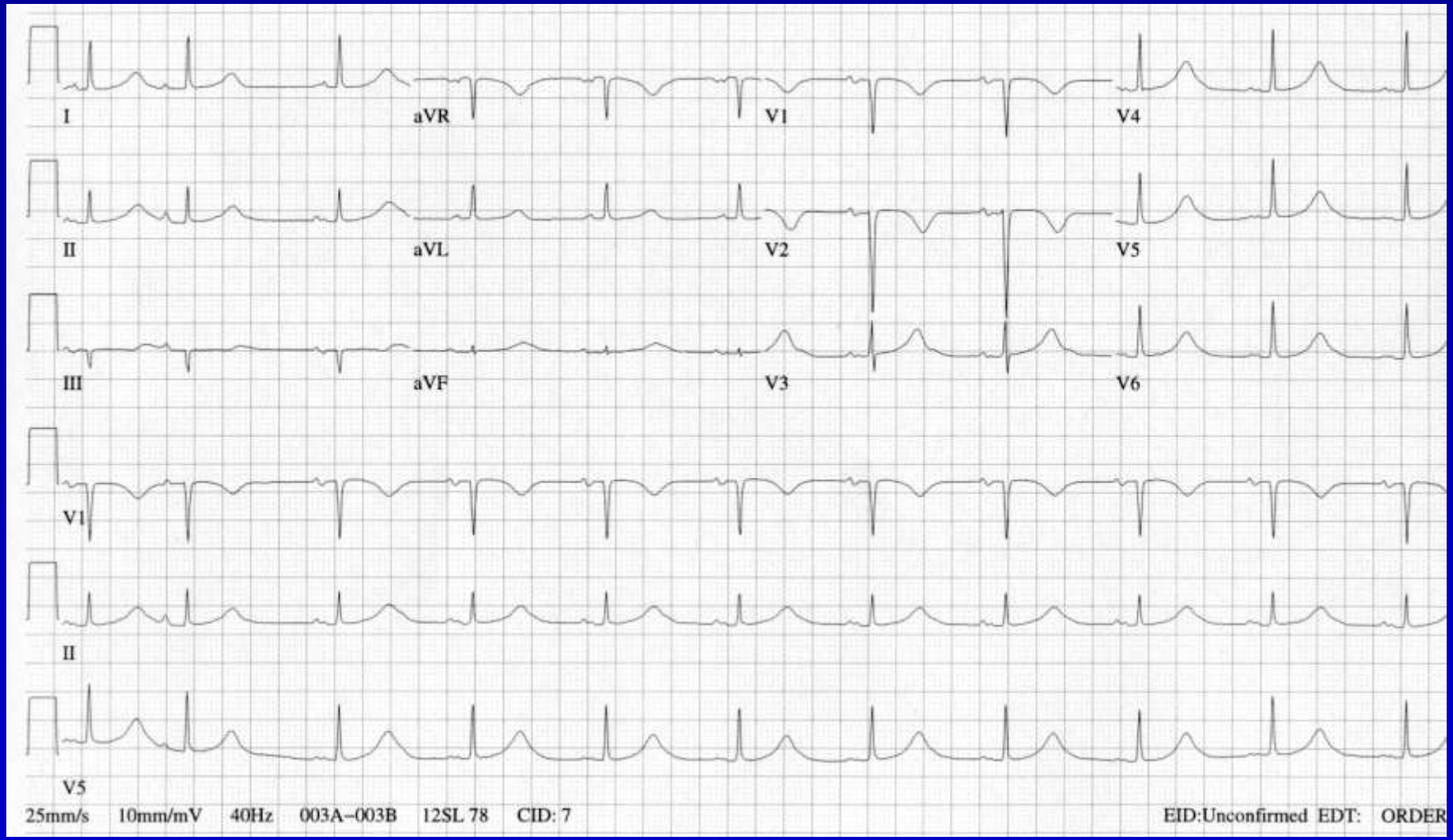


Hurst, 1998, Myerburg et al. P. 924

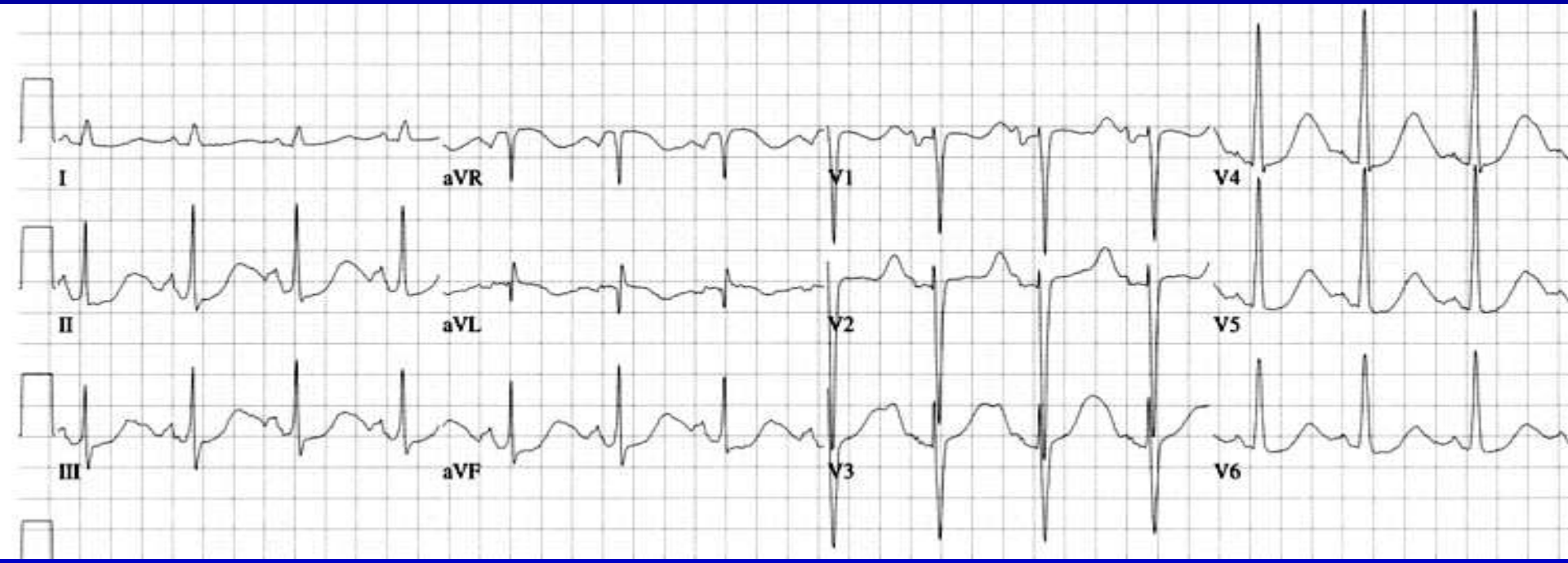
25 year old woman with Jervell and Lange-Neilson, and exercise-induced palpitations and syncope.
Note on this treadmill tracing T wave alternans followed by Torsades de Pointes



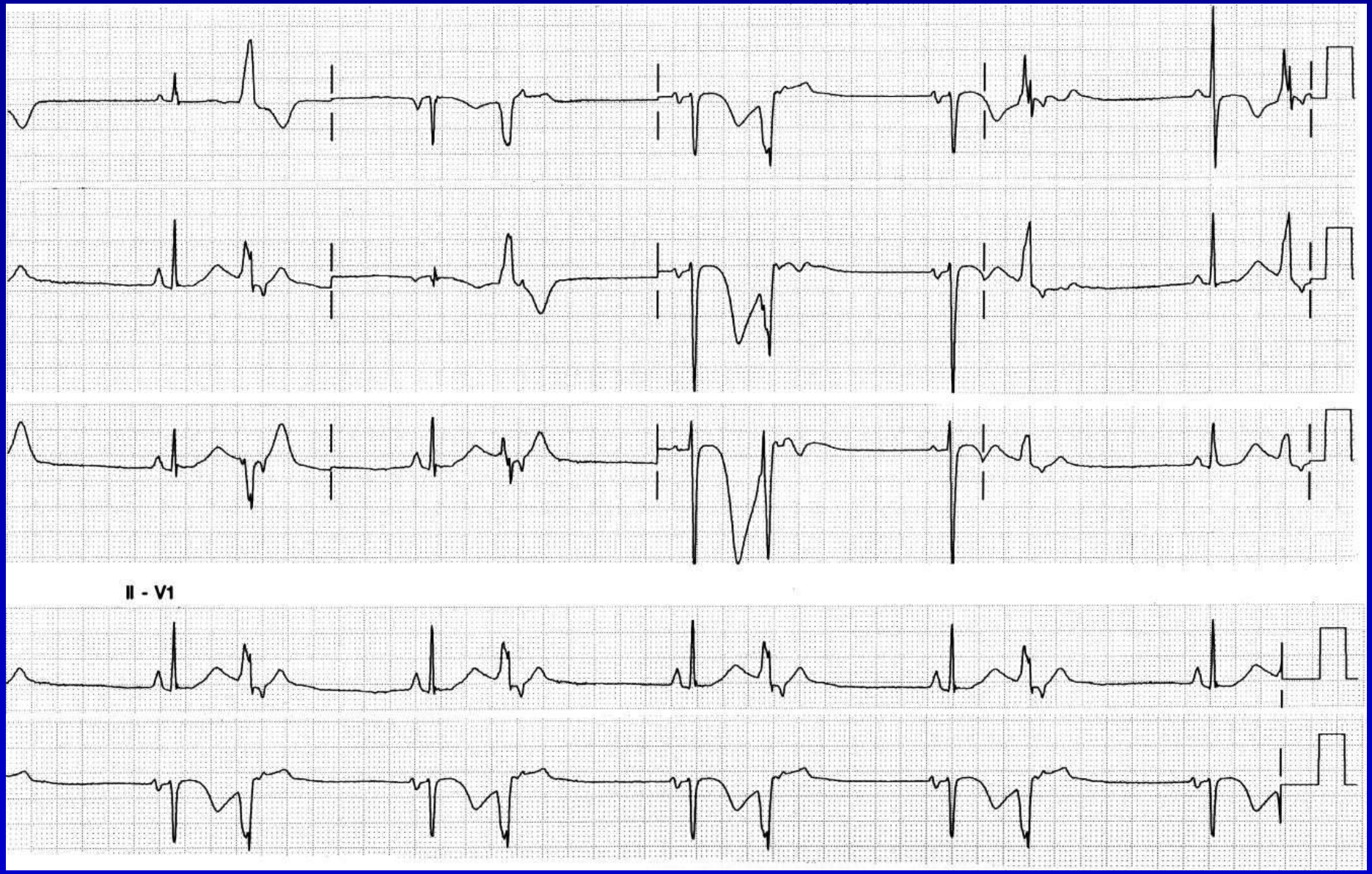
Hurst, 1998, Myerburg et al. P. 924



78 year old woman on telemetry service.

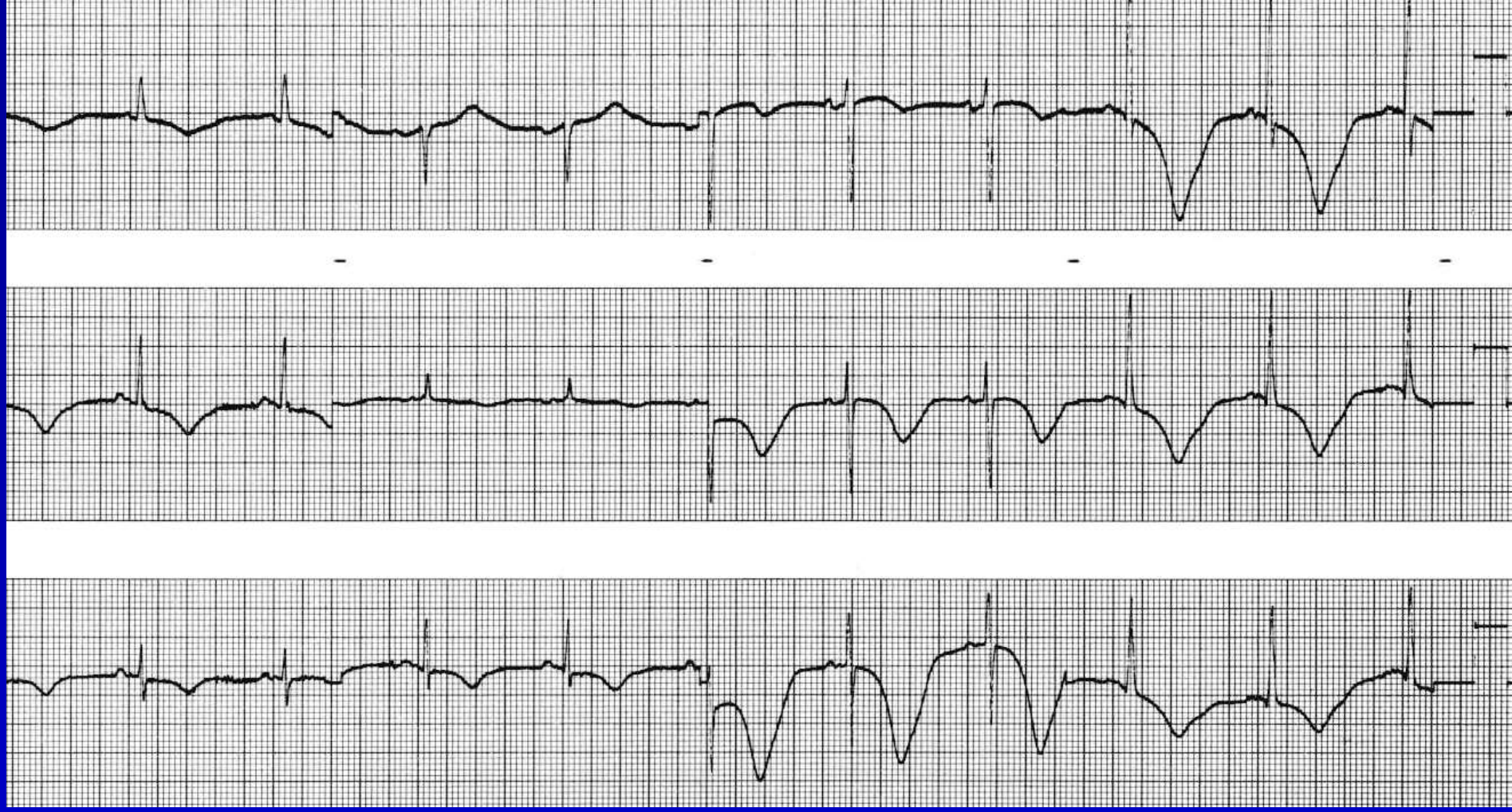


43 year old man in emergency center.



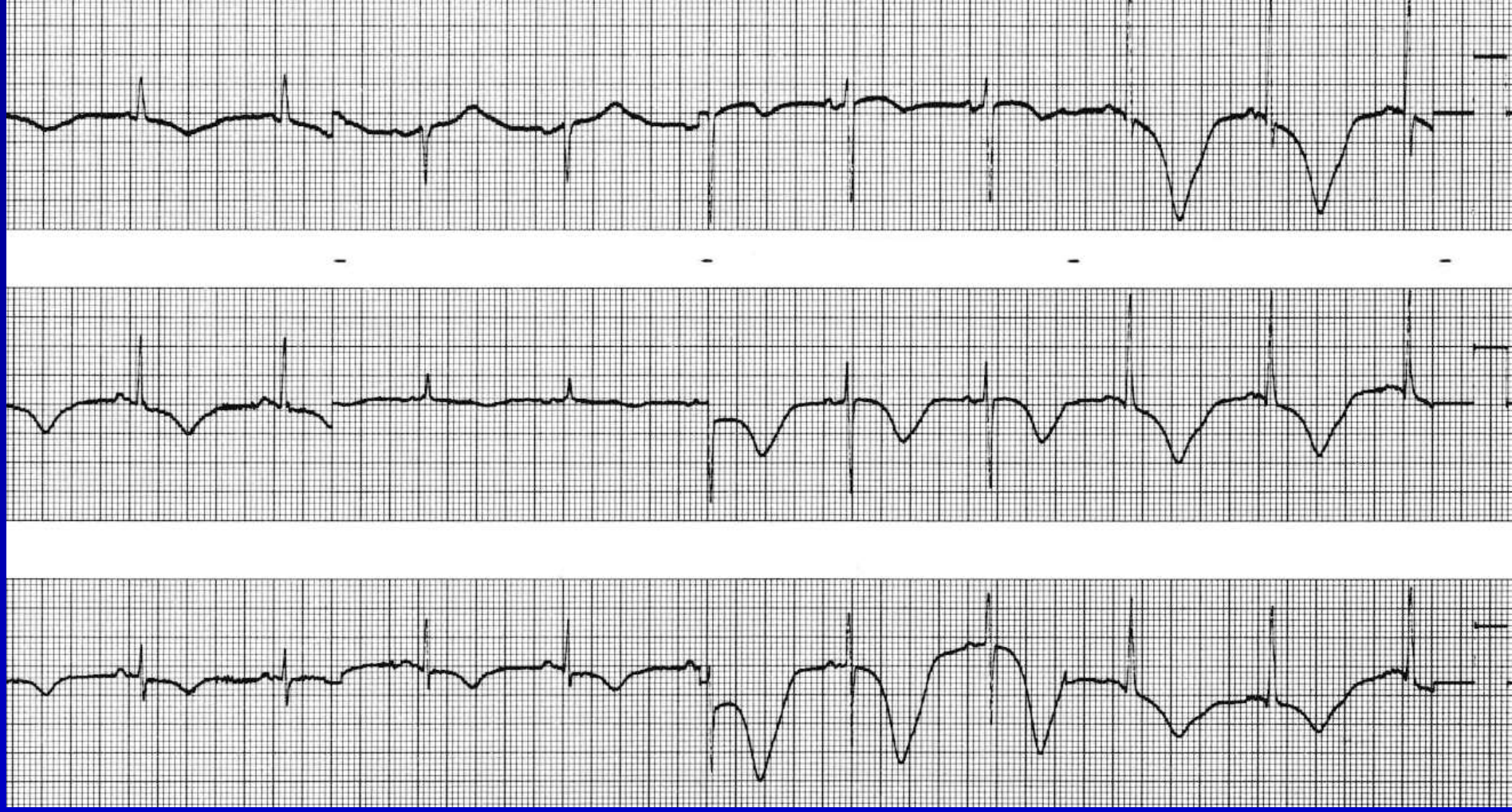
73 year old woman with COPD with chest discomfort.
History of atrial arrhythmia on digoxin and quinidine

ECG-SAP 1995, p. 56



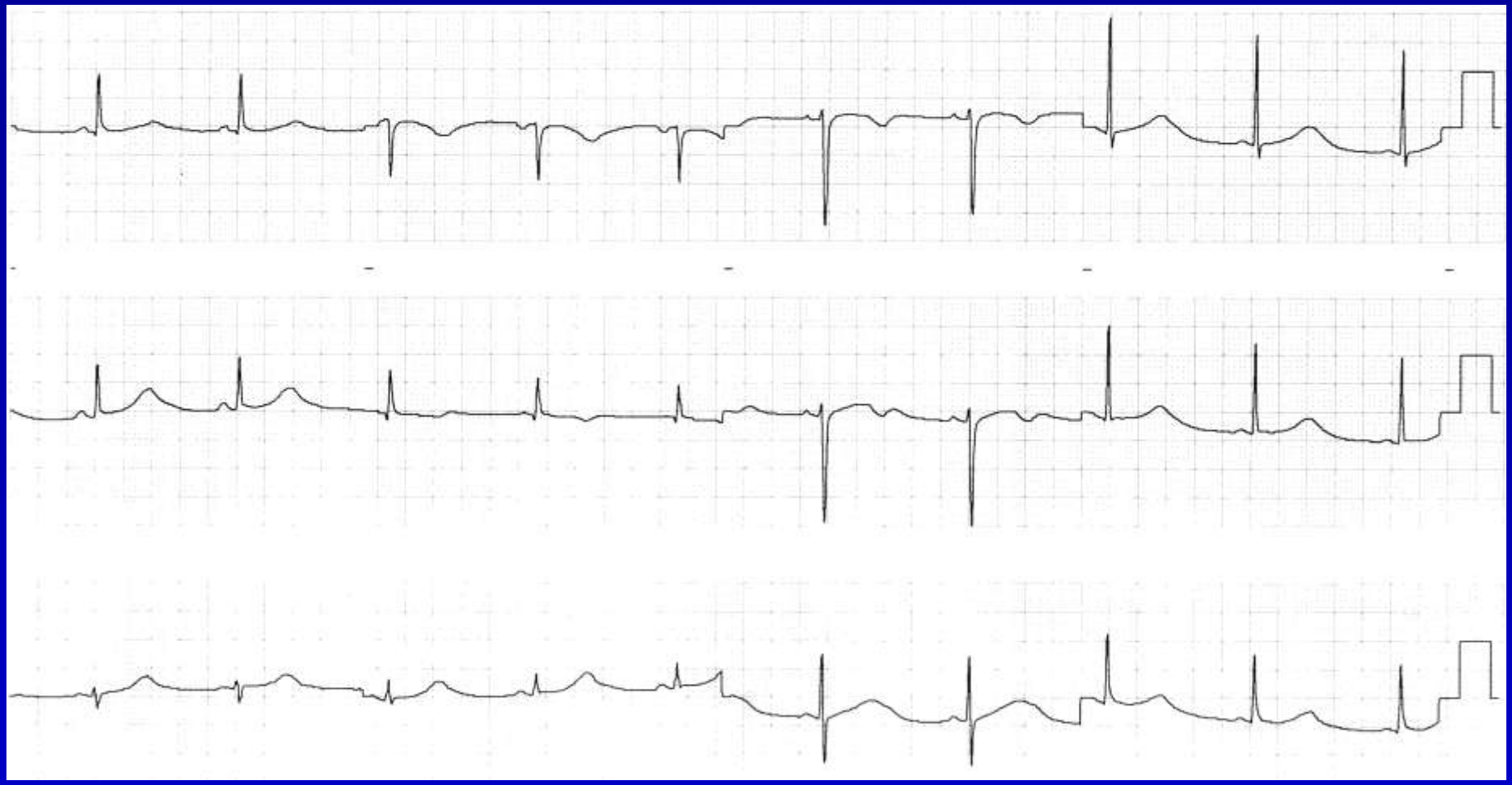
85 year old woman found unresponsive at home, brought to the ED

ECG-SAP 1995, p. 28



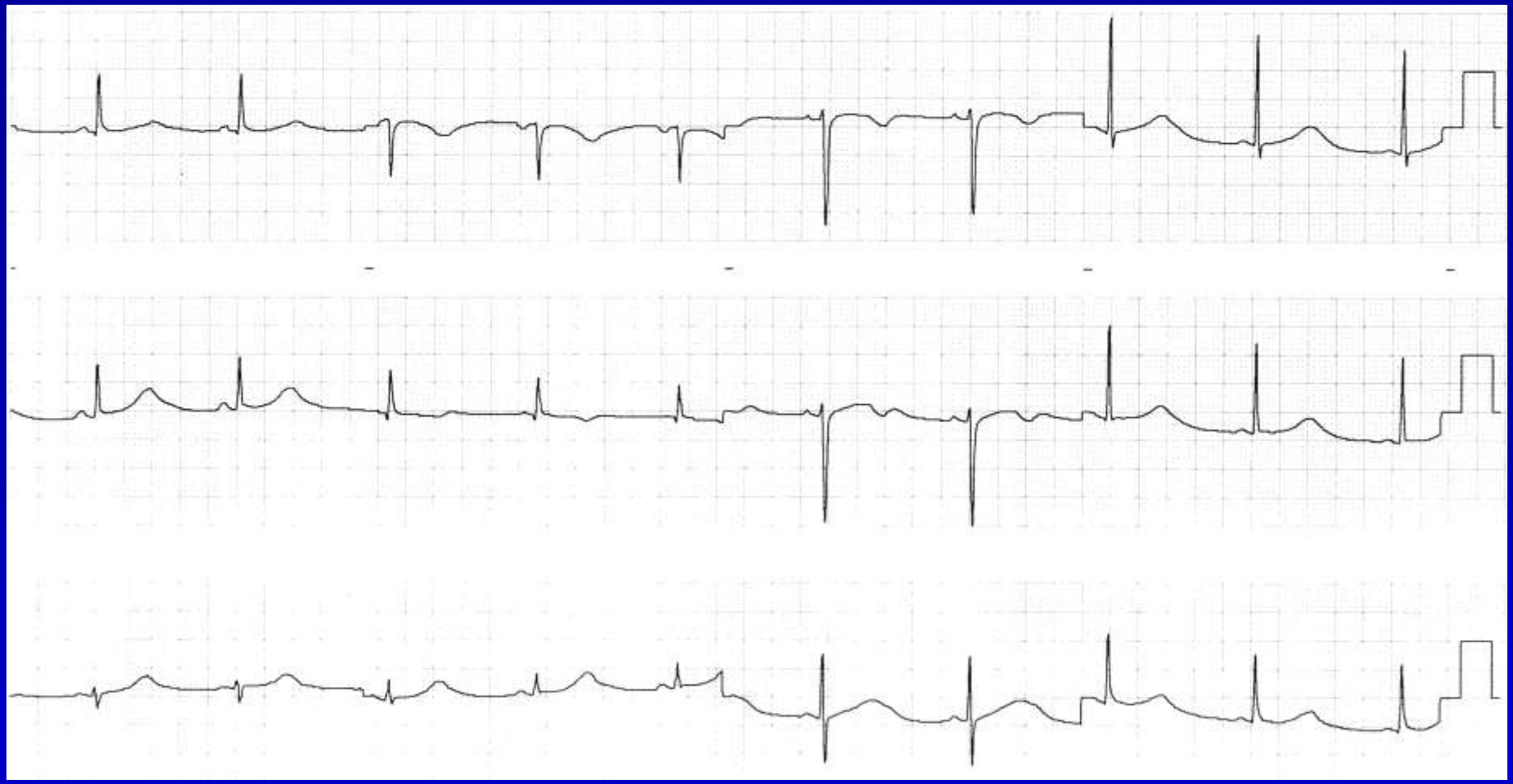
85 year old woman found unresponsive at home, brought to the ED. QT interval 0.62. Intracerebral hemorrhage (neurogenic or "CNS T-wave" pattern), maybe from overactivity of the sympathetic NS. Catecholamine-induced myocardial necrosis. DDX: NQMI, quinidine.

ECG-SAP 1995, p. 28



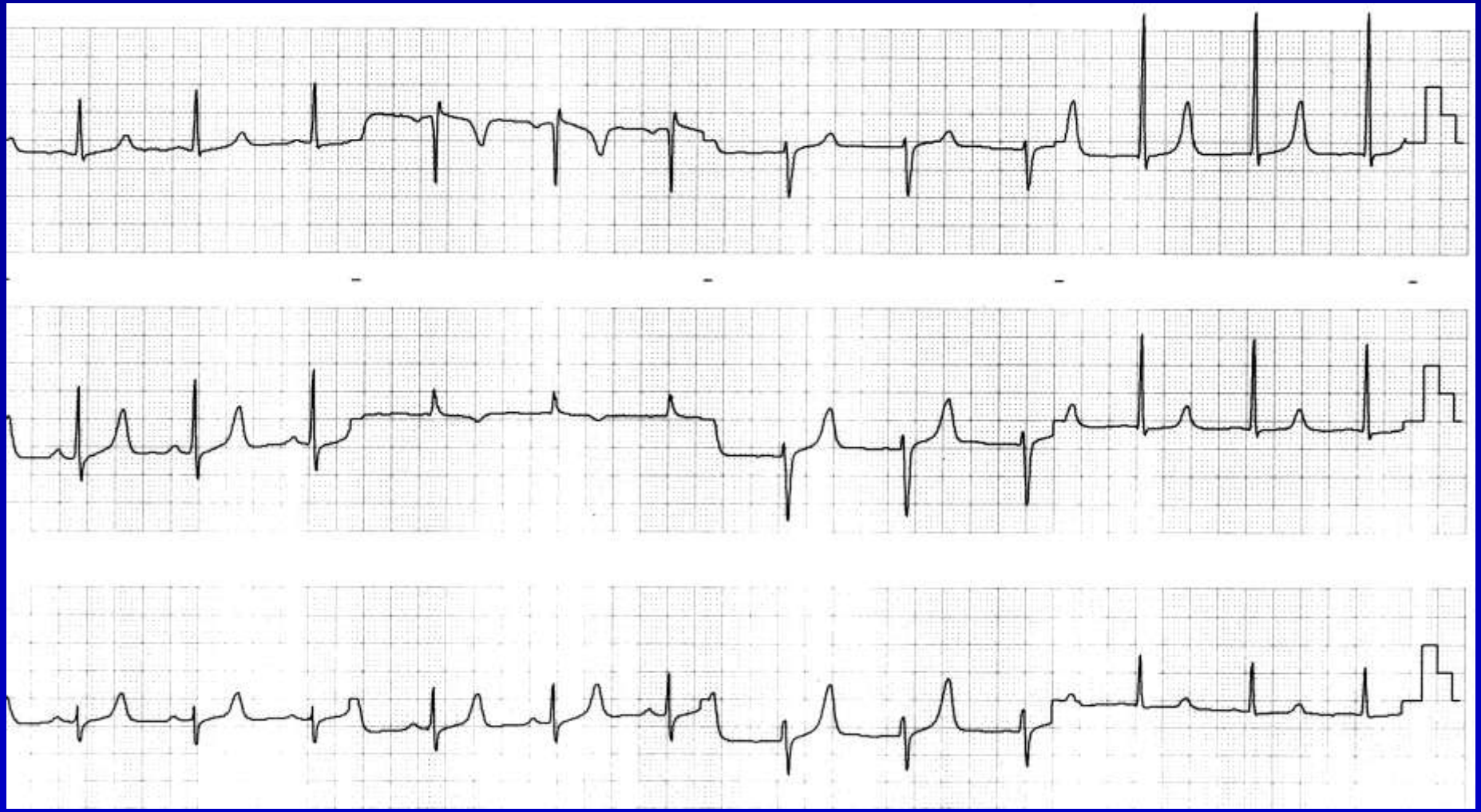
56 year old woman receiving diuretic therapy presents to the ER

ECG-SAP 1995, p. 36



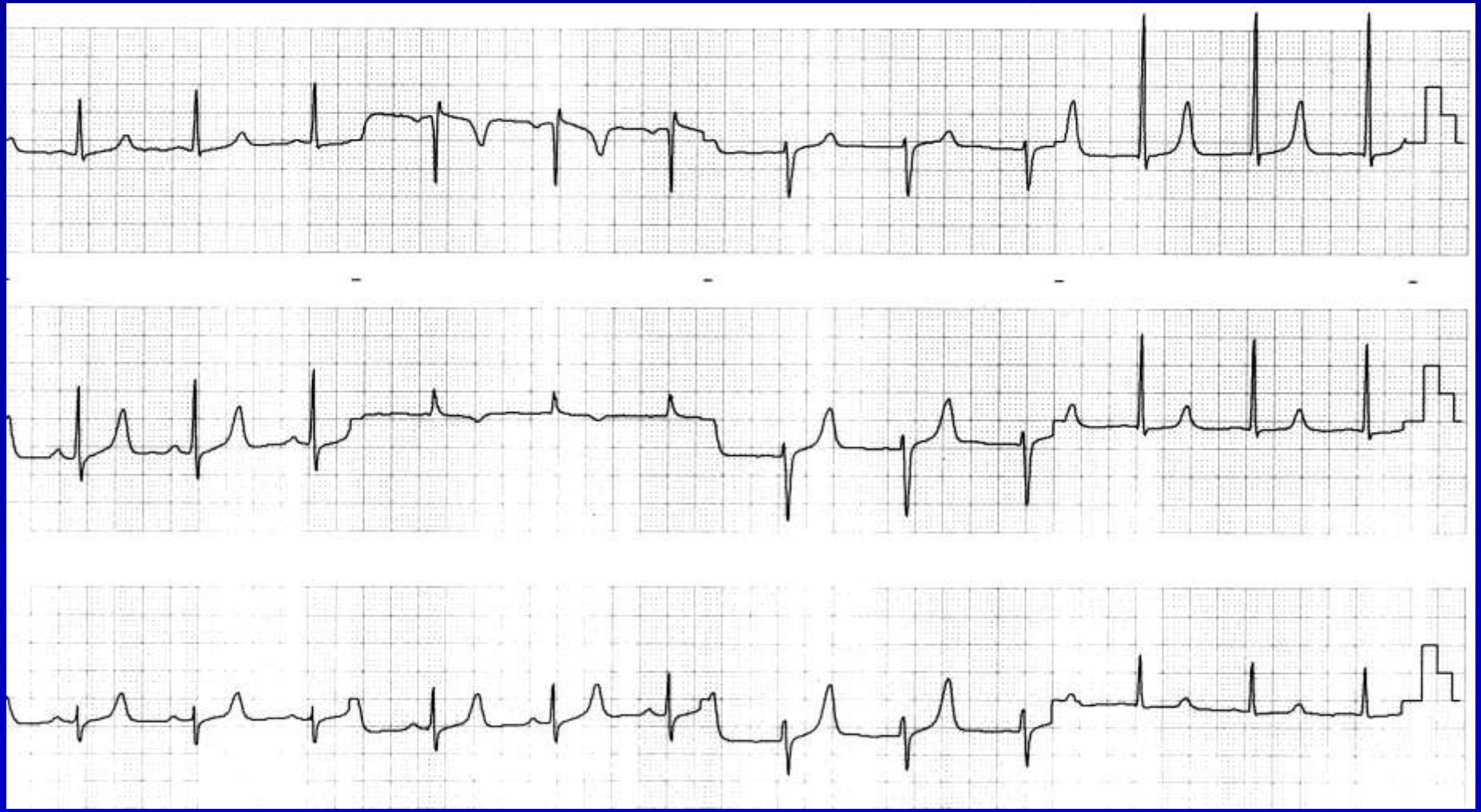
56 year old woman receiving diuretic therapy presents to the ER. QT 0.60. V2-3 with prominent U or bifid T, hypokalemia.

ECG-SAP 1995, p. 36



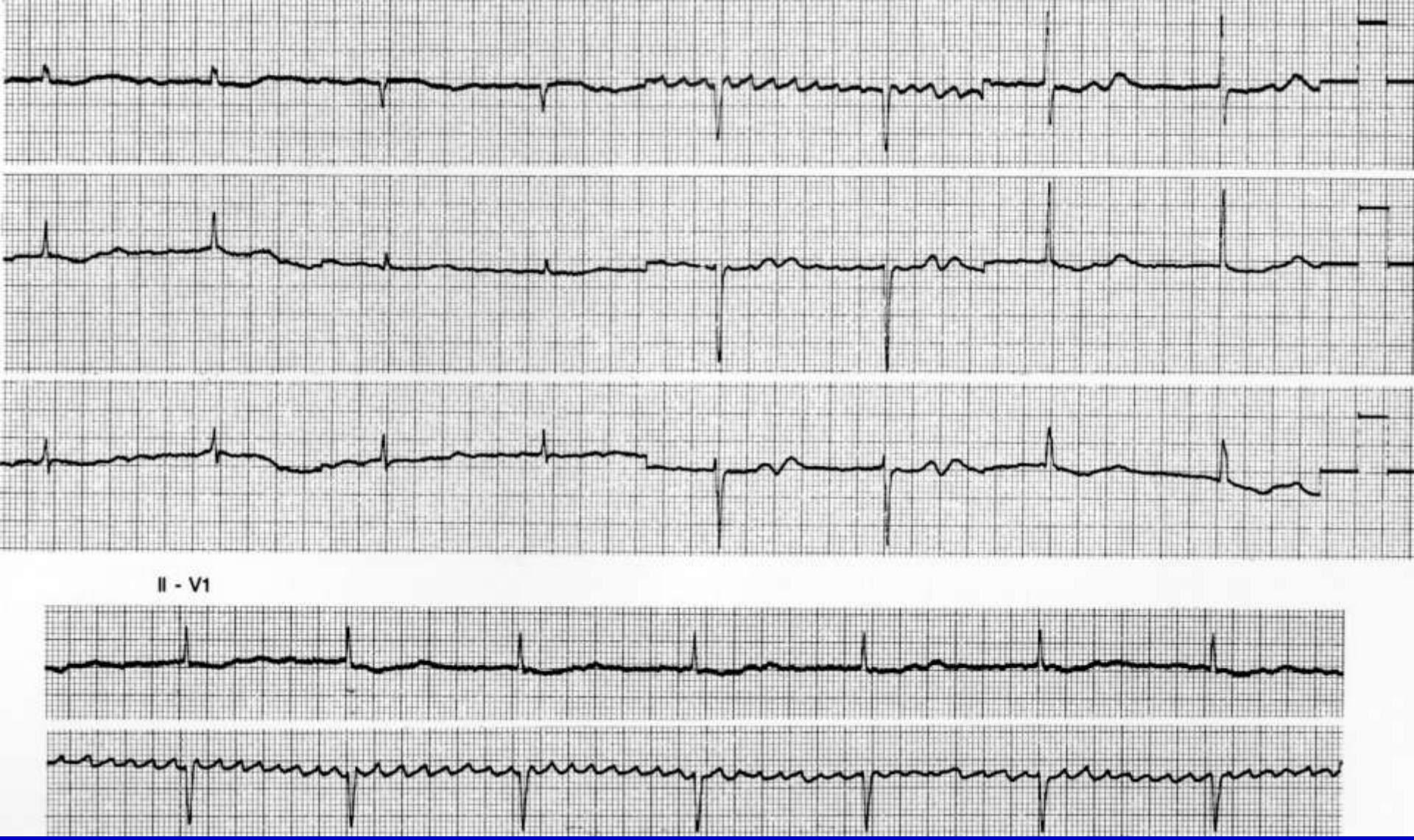
23 year old man on chronic hemodialysis.

ECG-SAP 1995, p. 38



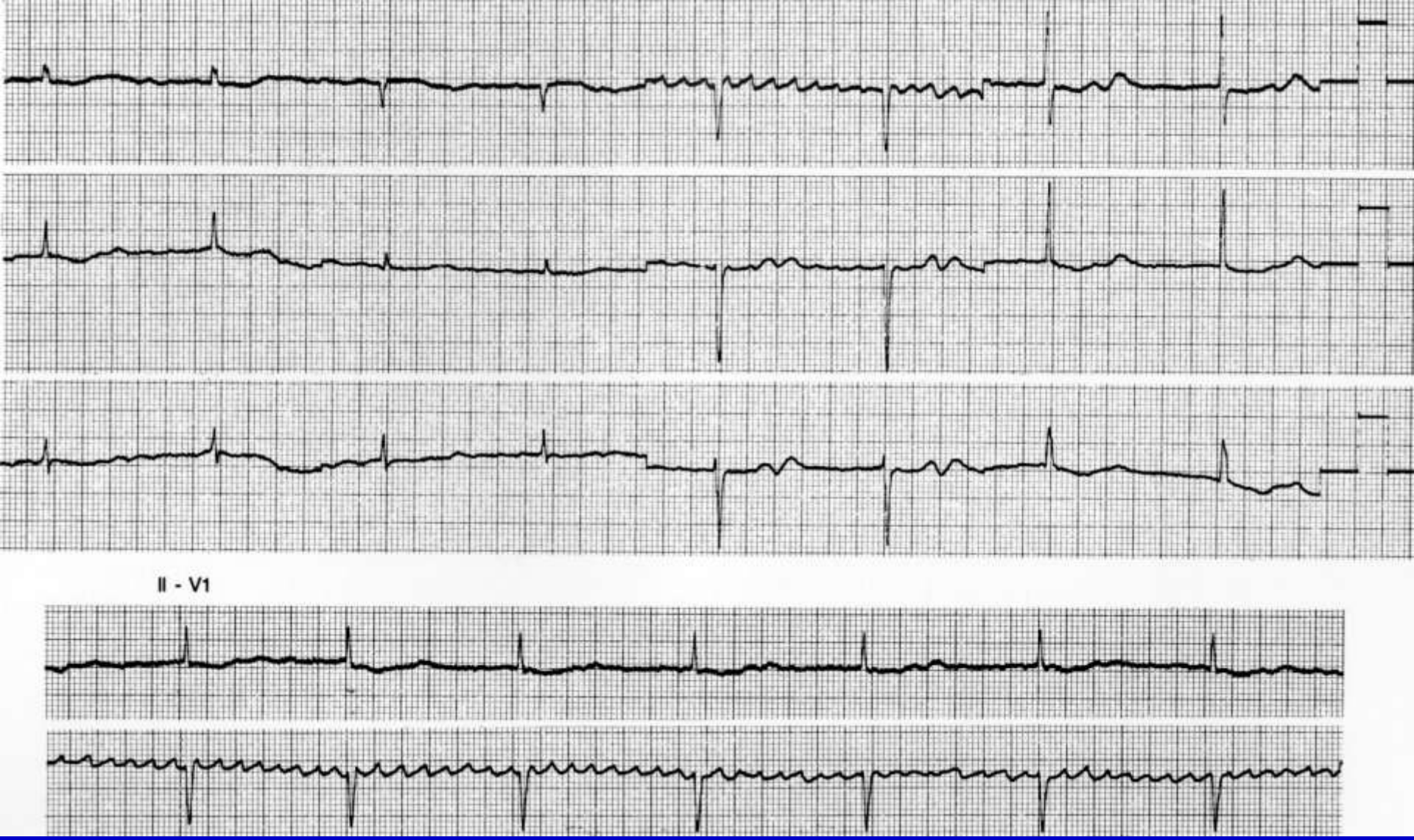
23 year old man on chronic hemodialysis. QT borderline 0.44.
ST segment prolonged but T wave normal duration. Hypocalcemia.
T's are peaked suggesting hyperkalemia (chest leads half standard.)
ECG for hyperkalemia is 0.85 spec, sens only 0.60.

ECG-SAP 1995, p. 38



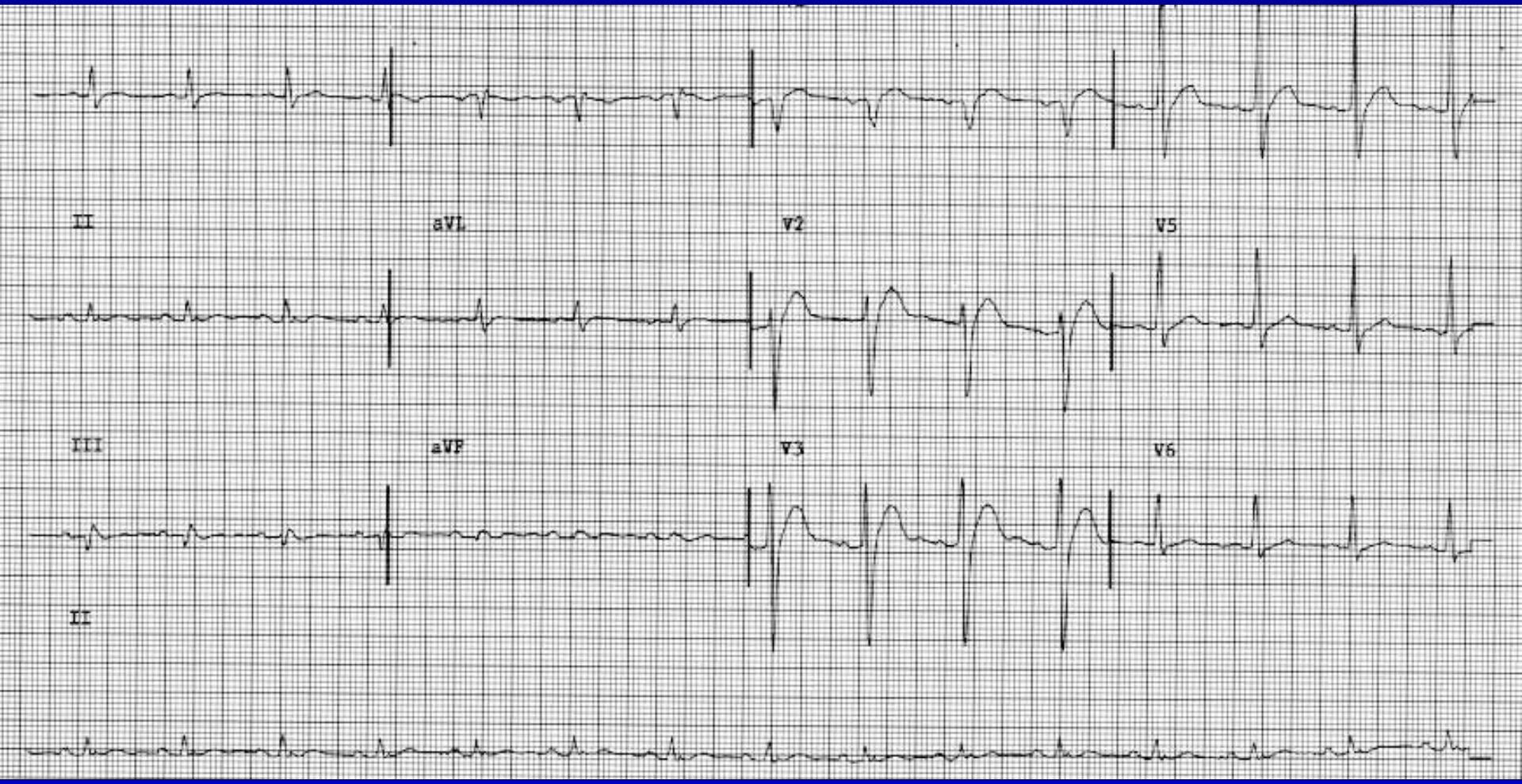
77 year old woman: CHF, palpitations and weakness, digitalis, diuretics

ECG-SAP 1995, p. 86



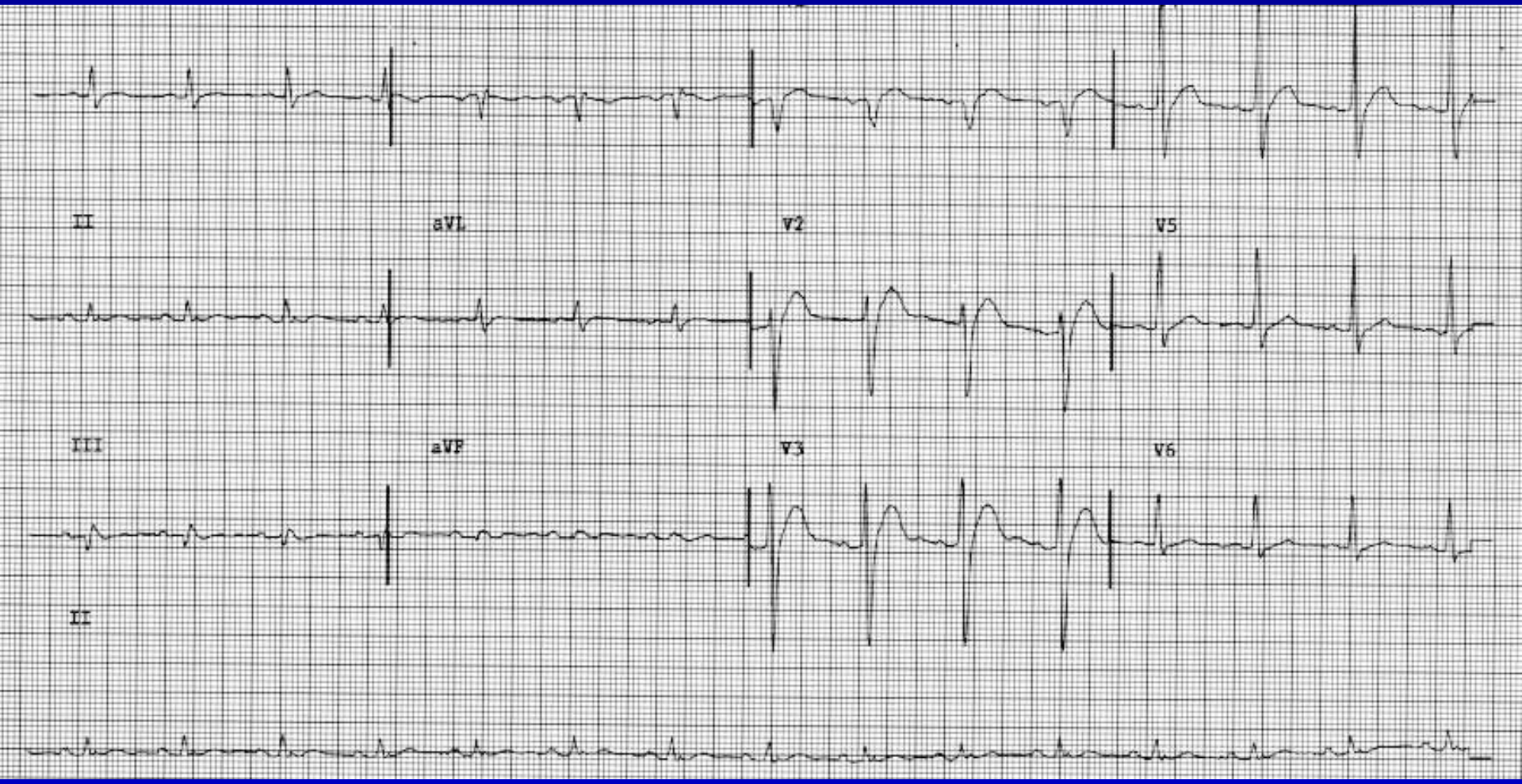
77 year old woman: CHF, palpitations and weakness, digitalis, diuretics
AFib, Junctional rhythm, AV block, low K+, long QT, digitalis toxicity

ECG-SAP 1995, p. 86



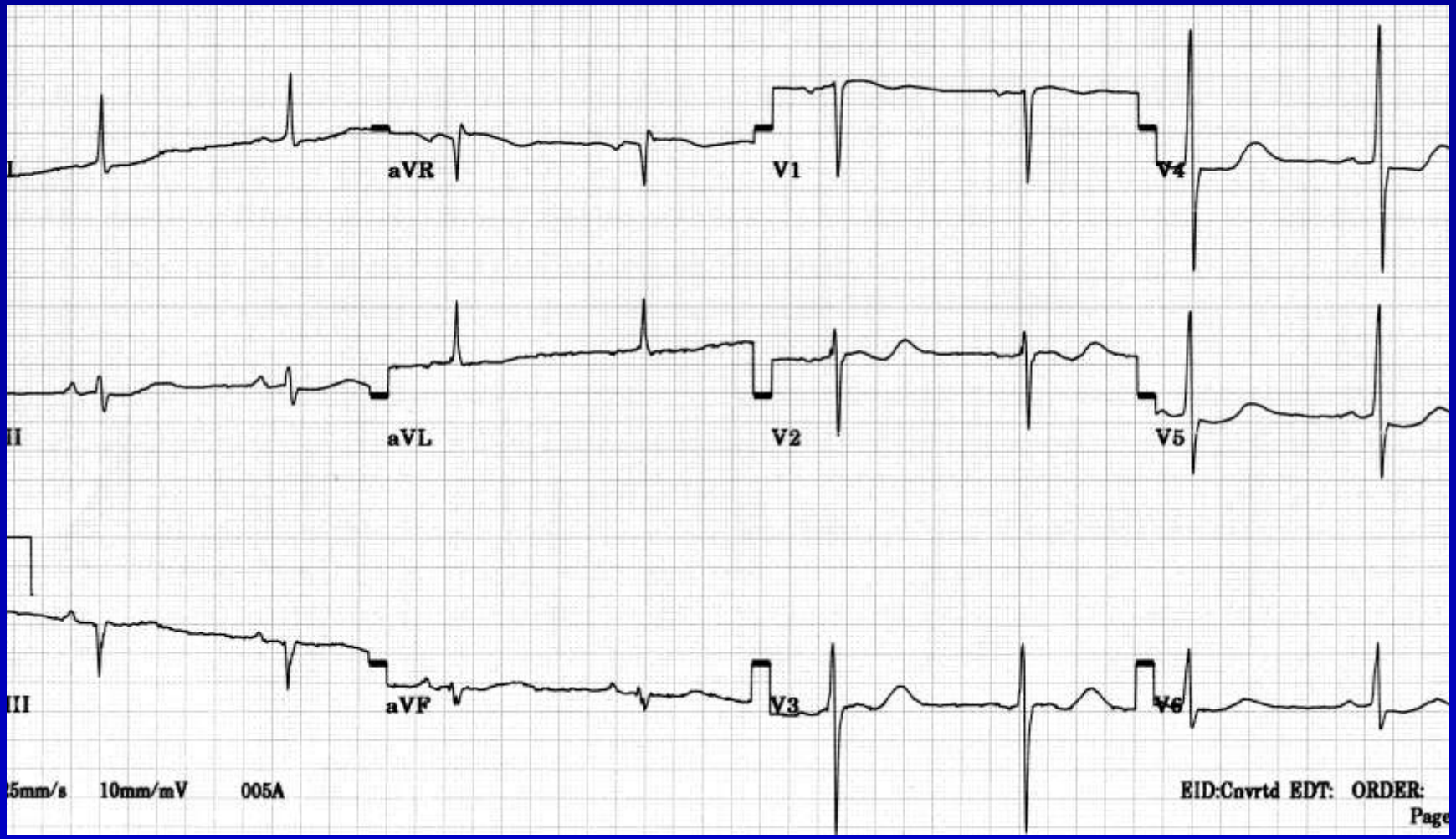
69 year old man with low back pain in the Emergency Department

ECG-SAP 1995, p. 82

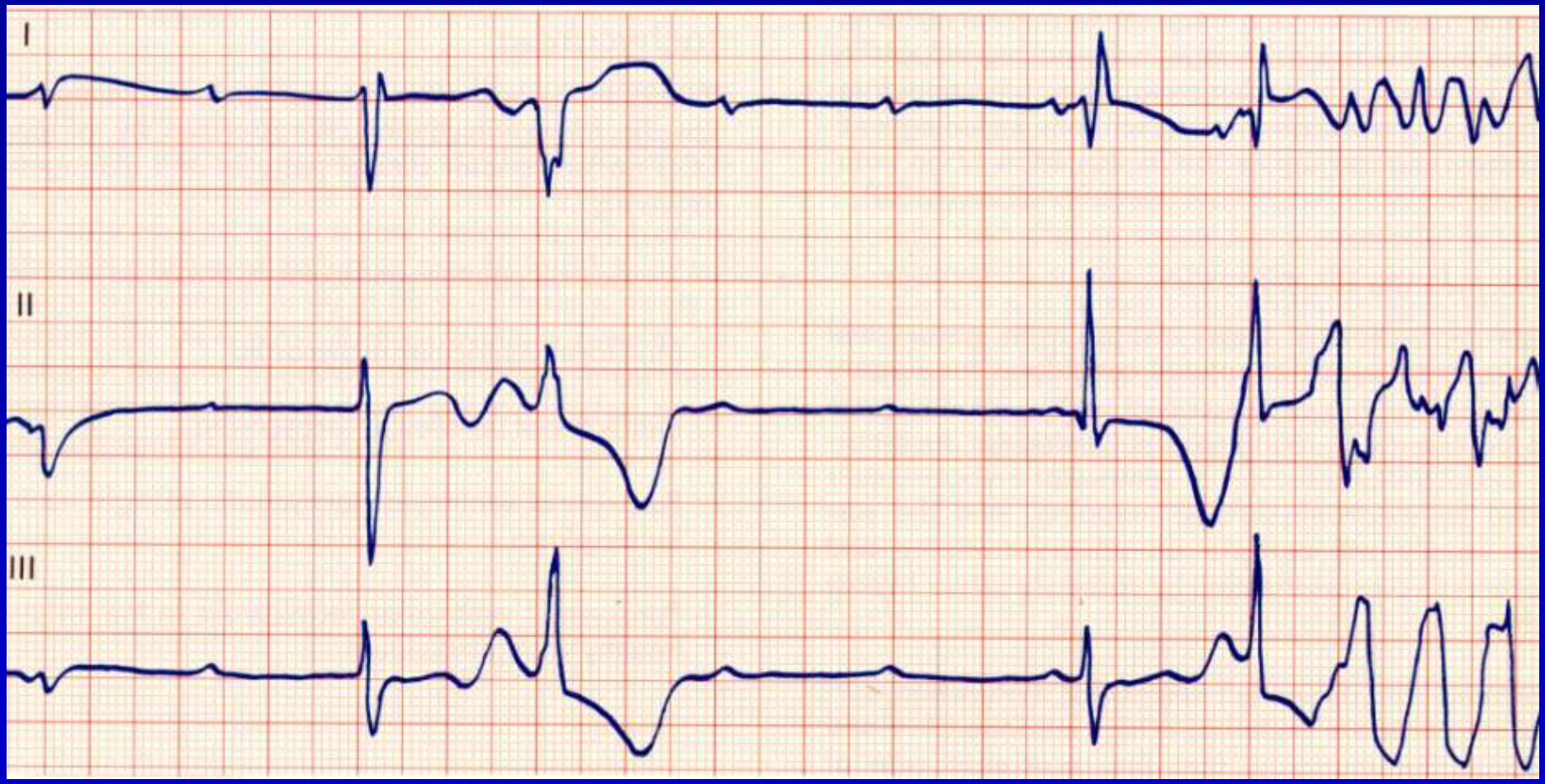


69 year old man with low back pain in the Emergency Department
Short QT 0.32, low P amplitude, absent ST segment, normal T, normal U
Hypercalcemia from Multiple Myeloma Ca >12 mg/dl shortens phase 2 of action potential

ECG-SAP 1995, p. 82



65 year old man in MICU



80 year old man with syncope for 2 weeks, with ECG showing complete AV block. No MI. K 3.8. Cure: pacemaker.

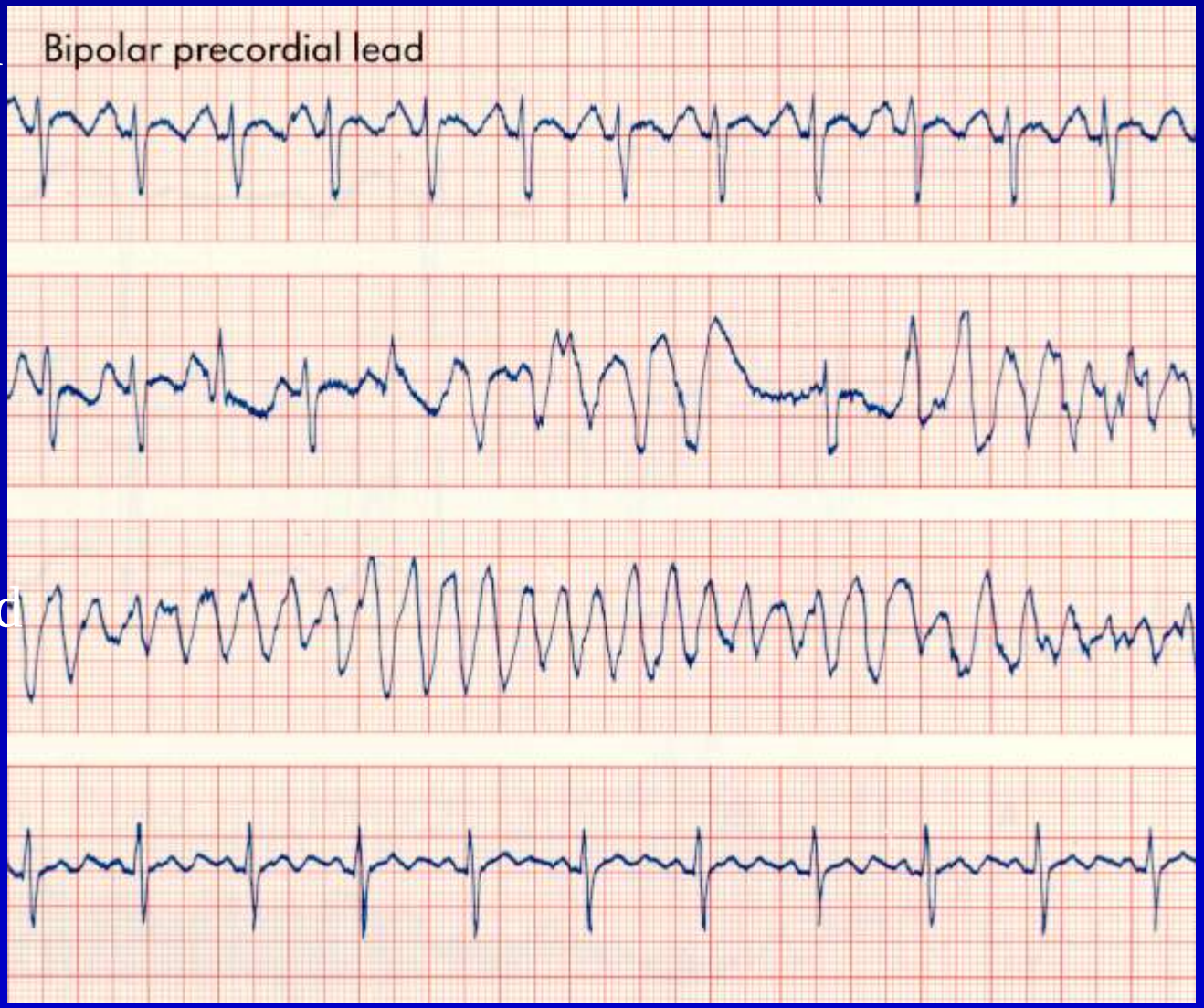
Sandoe, Sigurd, Arrhythmia - A guide to clinical electrocardiology 1991

Stable sinus rhythm
Long QT

Short torsade de pointes and longer

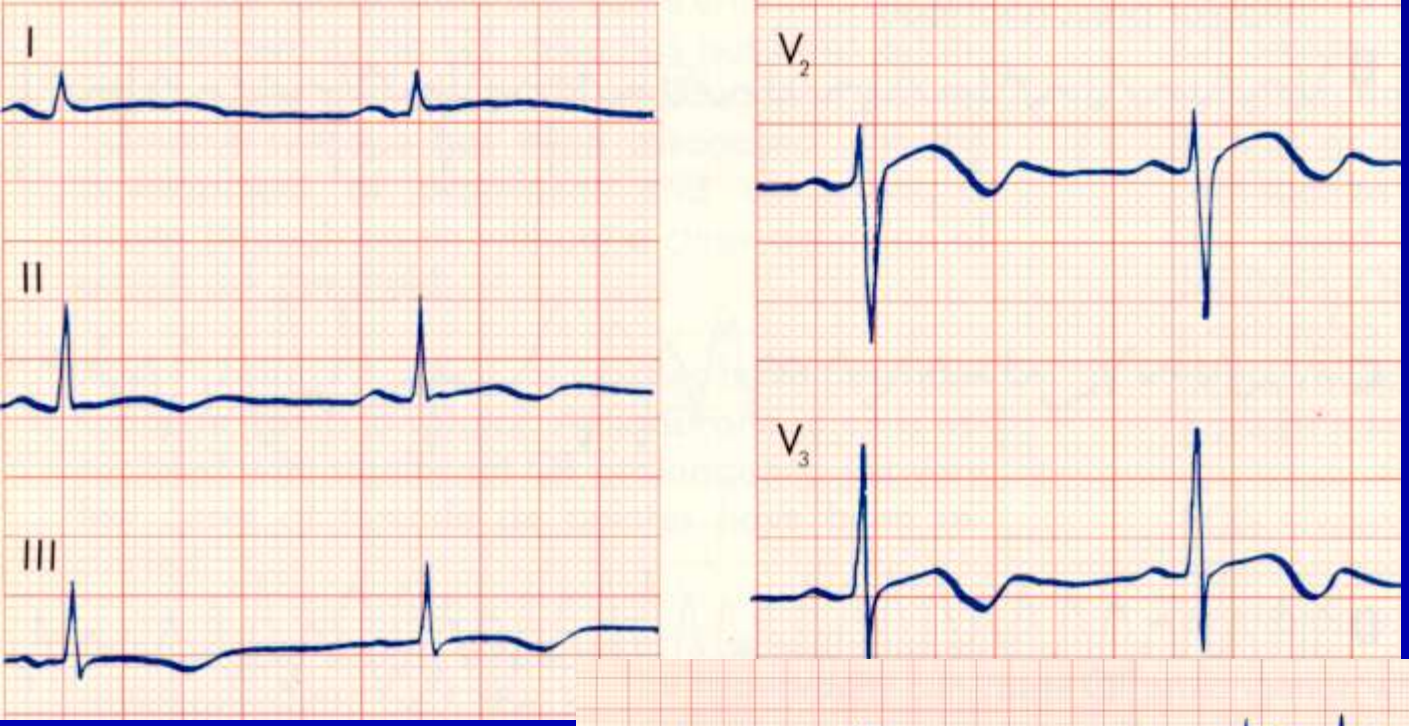
continued, needed shock. Later needed second shock

sinus rhythm



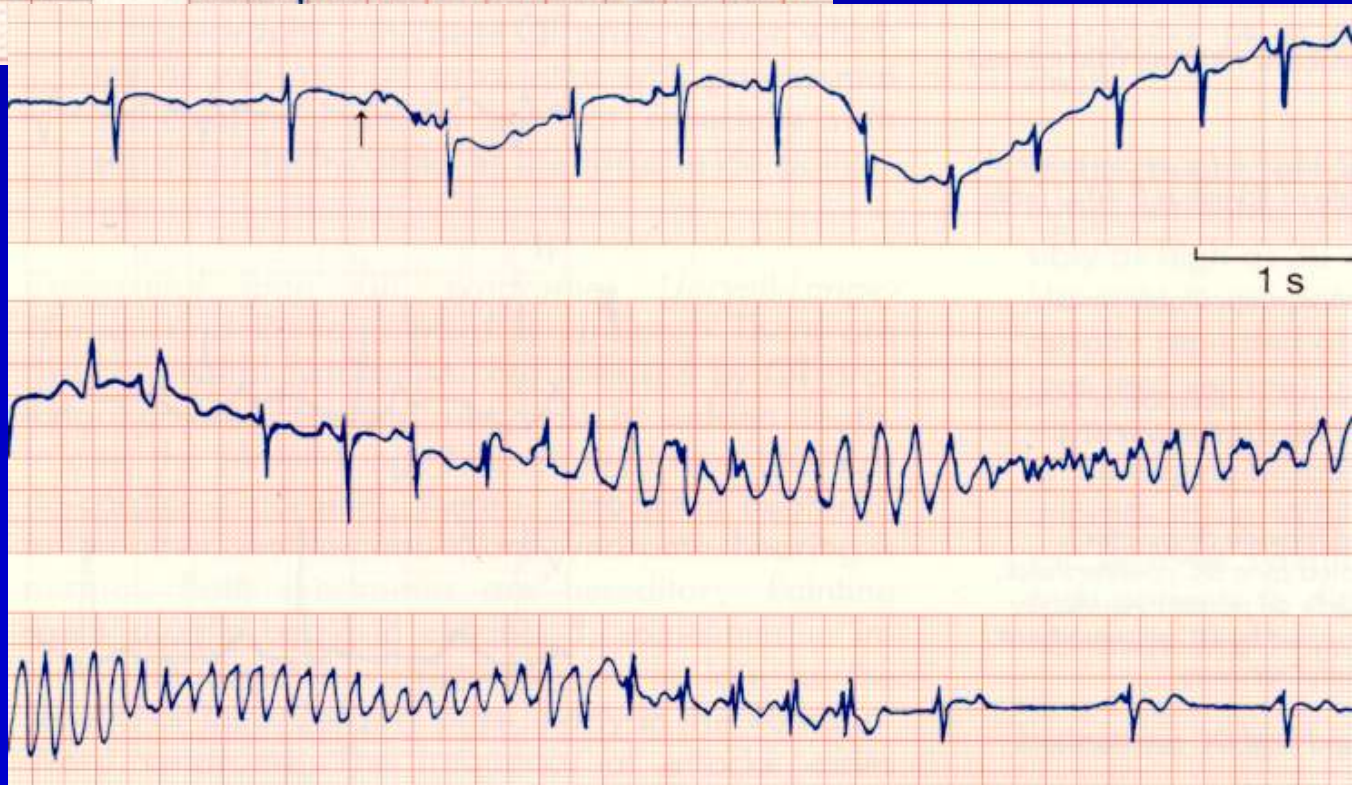
25 year old woman with 1000 mg thioridazine overdose (100 pills). Third day, QT normalized.

Sandoe, Sigurd, Arrhythmia - A guide to clinical electrocardiology 1991



13 year old girl with syncope: alarm clock: Romano-Ward

betablocker ended symptoms



Alarm clock ring - sinus rate rises

torsade onset

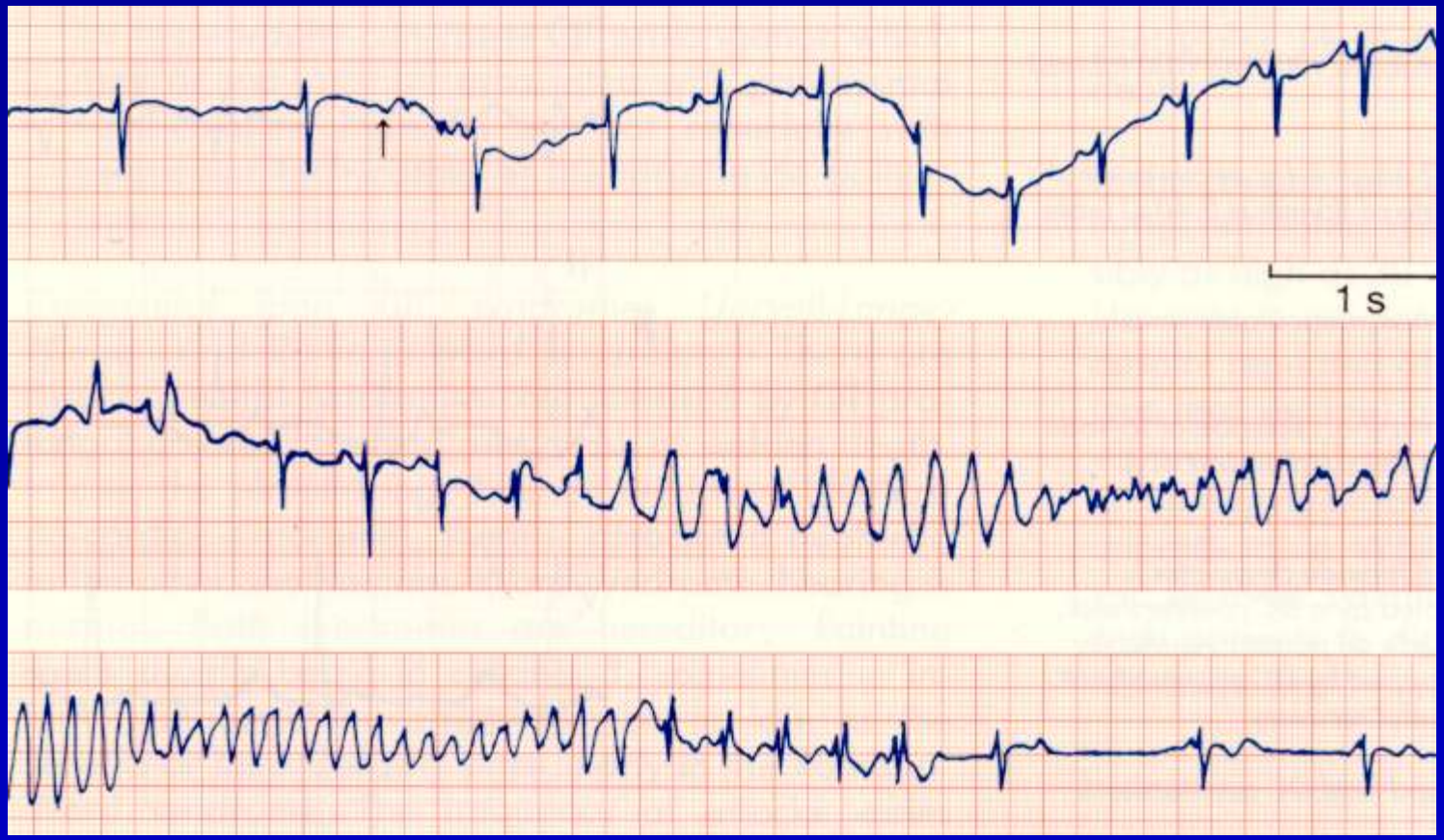
termination
30 sec later

Sandoe, Sigurd

Alarm clock ring - sinus rate rises

torsade onset

termination 30 sec later



No symptoms for at least 8 years after initiation with beta-blocker

Sandoe, Sigurd, Arrhythmia - A guide to clinical electrocardiology 1991

Treatment of Torsade de Pointes

- Depends on cause: remove offender of drug or bradycardia or lyte disturbance for acquired
- Acute and chronic: beta-blockade, Mg++ (2gm over 2 min, then 2-20 mg/min), Pacing, lidocaine, potential K+ channel opener, possibly Left cardiac sympathetic denervation, ICD if resistant, possibly mexilitene

Ion Channel and Action Potential

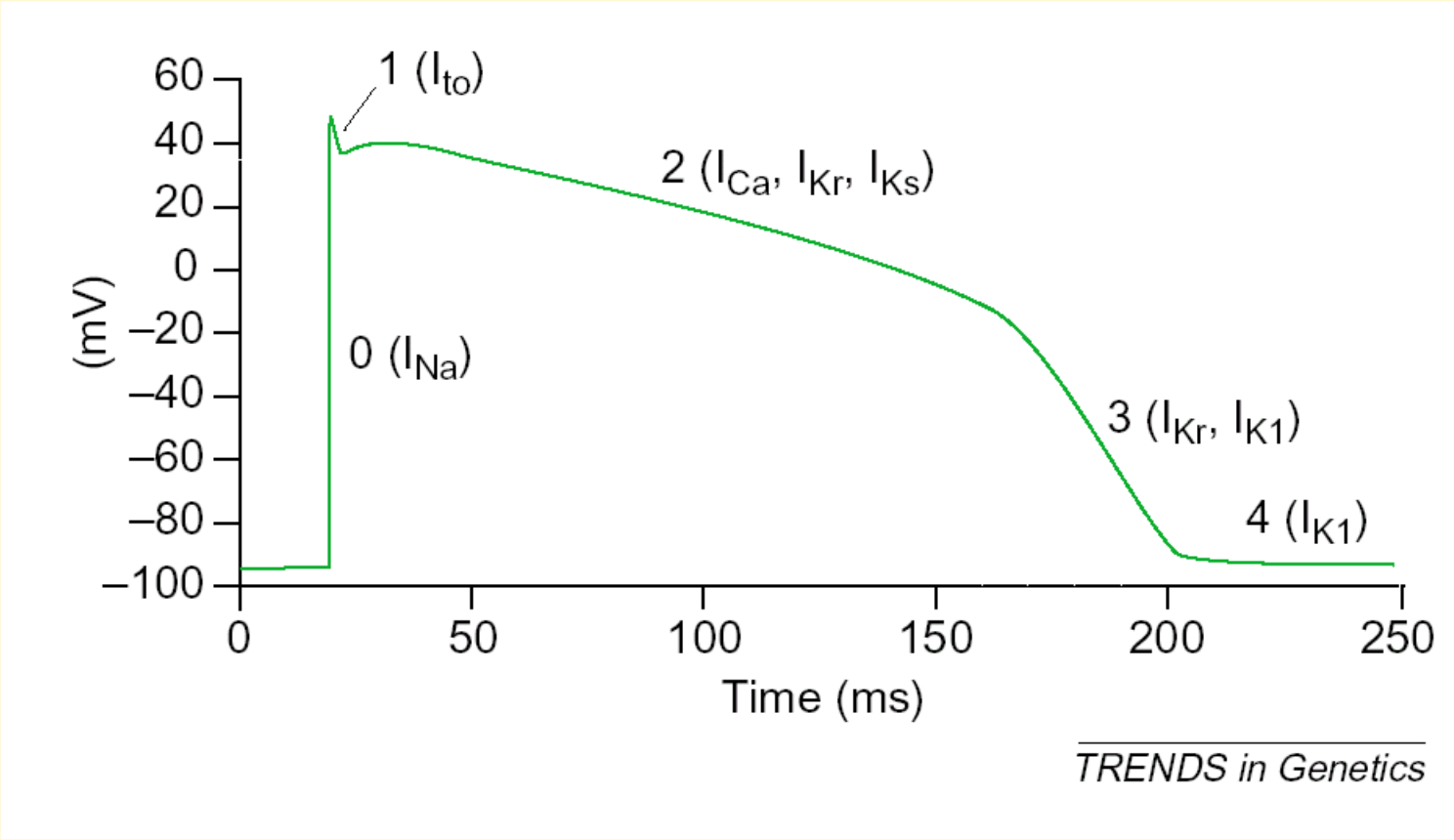


Fig. II. A simplified representation of the cardiac myocyte action potential and the role and timing of the currents implicated as causatory in the long QT syndrome (LQTS). Abnormalities of I_{Ca}, the L-type inward Ca^{2+} ion current, and I_{to}, the transient outward K^+ current, have not been identified as yet in congenital LQTS. Figure was supplied by Michael C. Sanguinetti. Reproduced, with permission, from Cell Press [30].

Behr ER et al. Trends in Genetics. 2003;19:470

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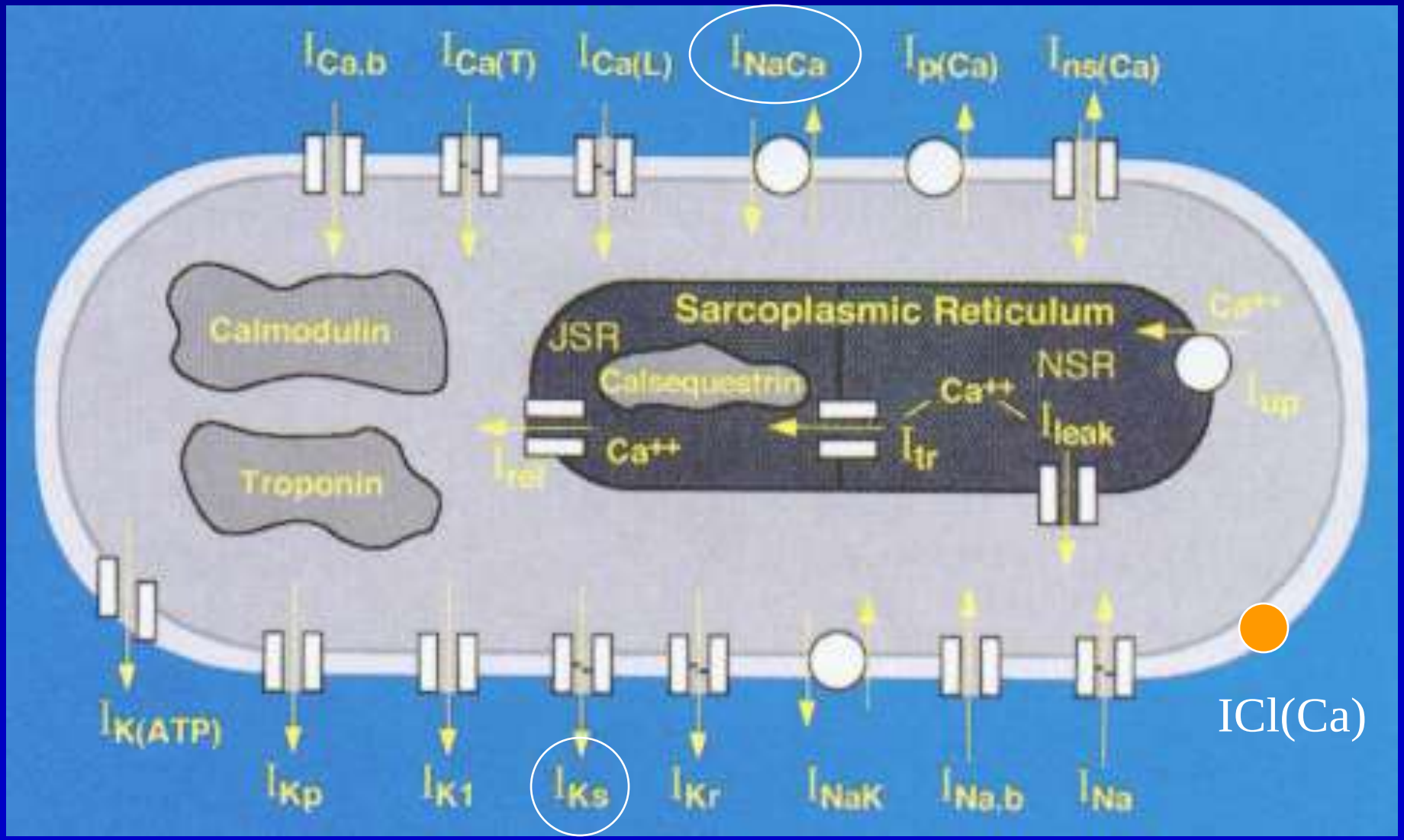


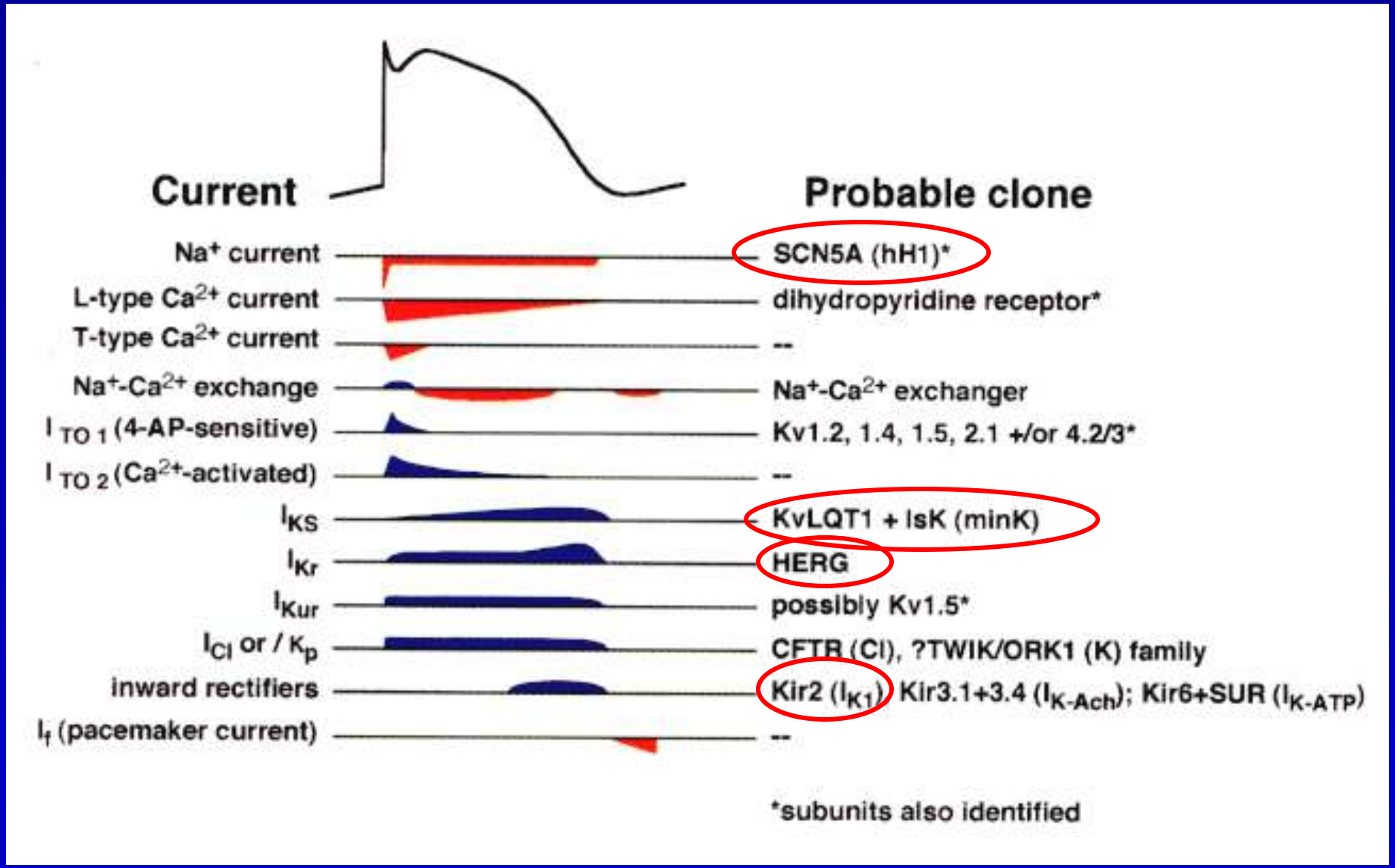
Model of Cardiac Ventricular Cell, with Ion Channels and Pumps
Circles indicate beta adrenergic augmentation

Priori SG, et al. Circulation 1999;99:674-81.

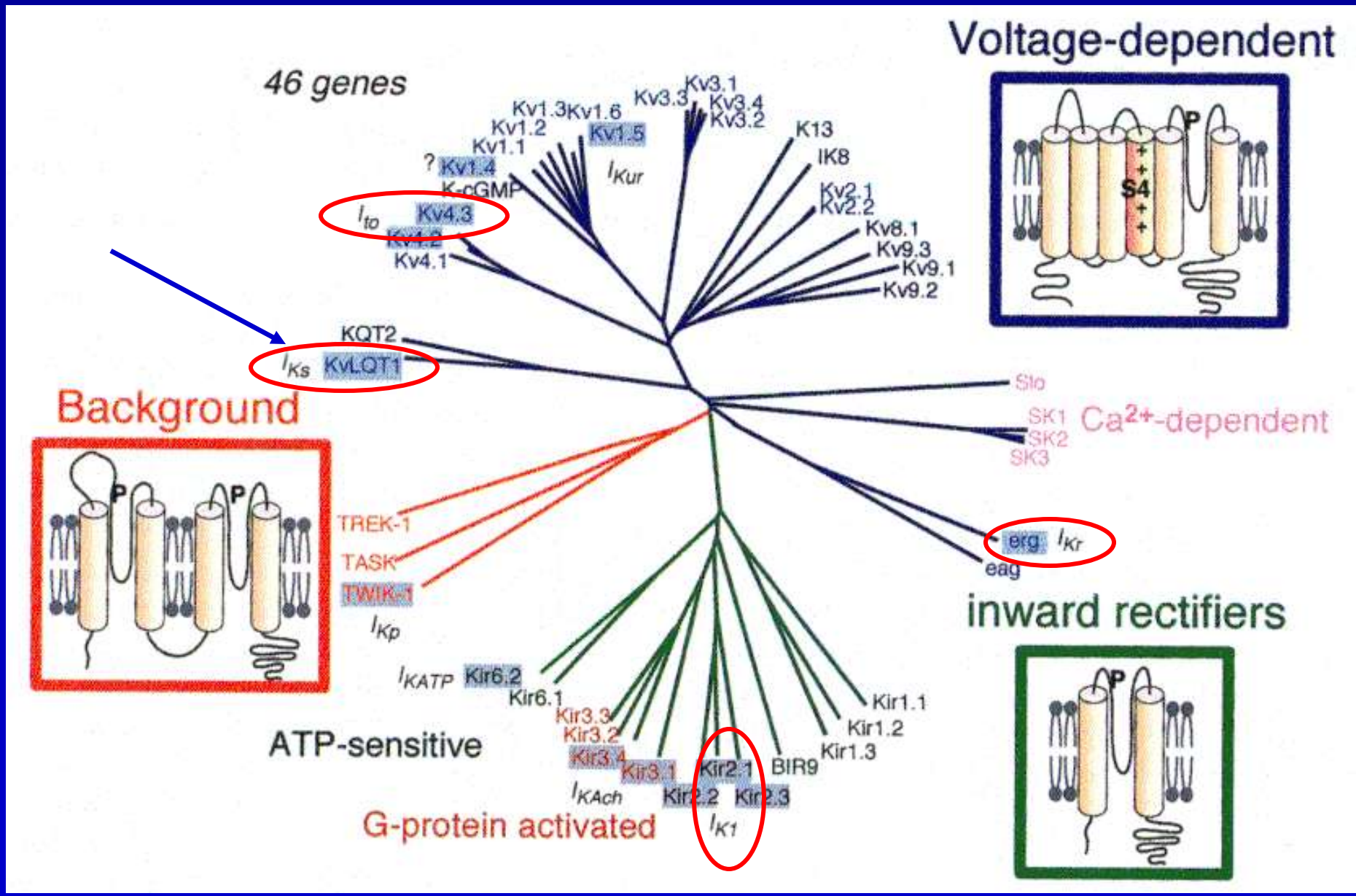
18 Currents in a Cardiac Ventricular Cell:

INa indicates fast sodium current;
ICa(L), calcium current through L-type calcium channels;
ICa(T) calcium current through T-type calcium channels;
IKr, fast component of delayed rectifier potassium current;
IKs, slow component of delayed rectifier potassium current;
IK1, inward rectifier potassium current;
IKp, plateau potassium current;
IK(ATP), ATP-sensitive potassium current;
INaK, sodium-potassium pump current;
INaCa, sodium-calcium exchange current;
Ip(Ca), calcium pump in sarcolemma;
INa,b, sodium background current;
ICa,b, calcium background current;
Ins(Ca), nonspecific calcium-activated current;
Iup, calcium uptake from myoplasm to network sarcoplasmic reticulum (NSR);
Irel, calcium release from junctional sarcoplasmic reticulum (JSR);
Ileak, calcium leakage from NSR to myoplasm; and
Itr, calcium translocation from NSR to JSR.
Calmodulin, troponin, and calsequestrin are calcium buffers.

Priori SG, et al. Circulation 1999;99:674-81.



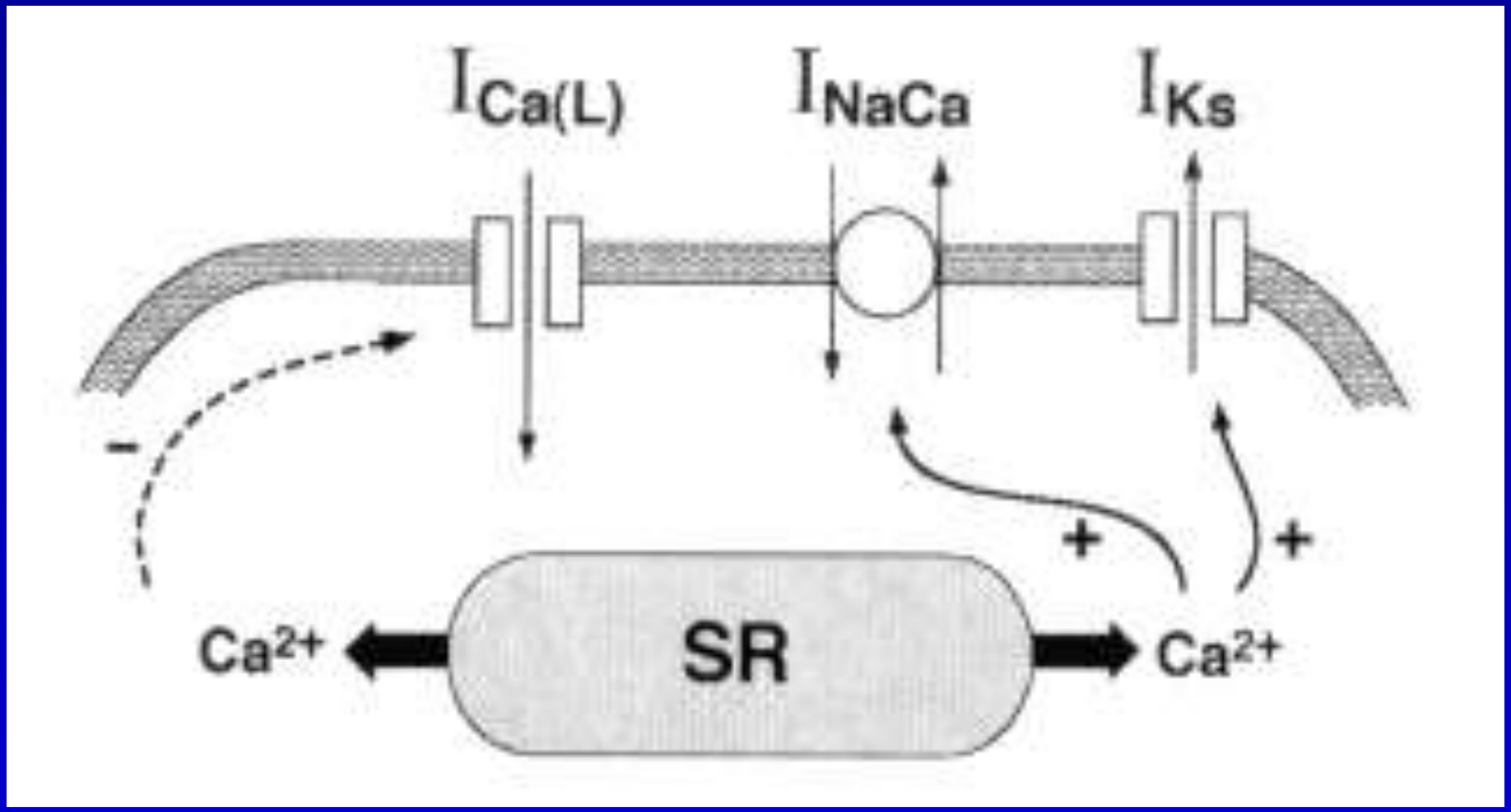
Priori SG, et al. Circulation 1999;99:674-81.



Pore-forming K+ channel subunits in man and rodent. grey box=heart

Priori SG, et al. Circulation 1999;99:674-81.

Interactive Processes in a Cell



Priori SG, et al. Circulation 1999;99:674-81.

Congenital QT Prolongation

- Diagnostic Criteria:
  - Asymptomatic patient, QTc>470msec
  - OR: Male with QTc>440 or female with QTc>460 PLUS:
    - Stress-related syncope
    - Torsade de pointes
    - Family history of early (<35yo) SCD
  - These criteria are neither totally sensitive or specific

Priori SG et al. Circulation 1999;99:529-33

Congenital QT Prolongation (LQTS)

Table 1
Diagnostic criteria for long QT syndrome

Features	Points
ECG findings[A]	
QTc	
≥0.48 s	3
0.46-0.47 s	2
0.45 s	1
Torsade de pointes[B]	2
T wave alternans	1
Notched T wave in three leads	1
Low heart rate for age[C]	0.5
Clinical History	
Syncope[B]	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history	
Family members with definite LQTS[D]	1
Unexplained sudden cardiac death before age 30 among immediate family members[D]	0.5

Scoring: ≤ 1 point, low probability of LQTS; 2–3 points, intermediate probability of LATS; ≥ 4 points, high probability of LQTS. [A]Findings in the absence of medications or disorders known to affect these ECG findings. QTc calculated by Bazett's formula, where QTc = QT/√RR. [B]Mutually exclusive. [C]Resting heart rate below the second percentile for age. [D]The same family member cannot be counted for both of these criteria. Reprinted with permission from ref. 6.

Kass RS &Moss AJ. J Clin Invest. 2003;112:810

Congenital QT Prolongation (LQTS)

Table 2

Molecular and cellular mechanisms of cardiac arrhythmias

Disease	Gene (alternate name)	Protein	Reference
LQT-1	*KVLQT1 (KCNQ1)*	I_{Ks} K^+ channel α subunit	28
LQT-2	*HERG (KCNH2)*	I_{Kr} K^+ channel α subunit	29
LQT-3	*SCN5A*	I_{Na} K^+ channel α subunit	30
LQT-4	*ANKB*	ANKRIN-β	31
LQT-5	*minK (KCNE1)*	I_{Ks} K^+ channel β subunit	32
LQT-6	*MiRP1 (KCNE2)*	I_{Kr} K^+ channel β subunit	33
LQT-7	*KCNJ2*	I_{Kr} K^+ channel α subunit	34

Kass RS & Moss AJ. J Clin Invest. 2003;112:810

Congenital QT Prolongation (LQTS)

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LQT-4	*ANKB*	ANKRIN-β	31
LQT-5	*minK (KCNE1)*	I_{Ks} K^+ channel β subunit	32
LQT-6	*MiRP1 (KCNE2)*	I_{Kr} K^+ channel β subunit	33
LQT-7	*KCNJ2*	I_{Kr} K^+ channel α subunit	34

Subtype of LQTS	Chromosome	Gene	Current (I)
LQT1	11	*KCNQ1*	I_{Ks} α-subunit
LQT2	7	*KCNH2*	I_{Kr} α-subunit
LQT3	3	*SCN5A*	I_{Na} α-subunit
LQT4	4	*AnkyrinB*	Unknown
LQT5	21	*KCNE1*	I_{Ks} β-subunit
LQT6	21	*KCNE2*	I_{Kr} β-subunit
LQT7 (Andersen's)	17	*KCNJ2*	I_{K1}

[a]Abbreviation: LQTS, long QT syndrome.

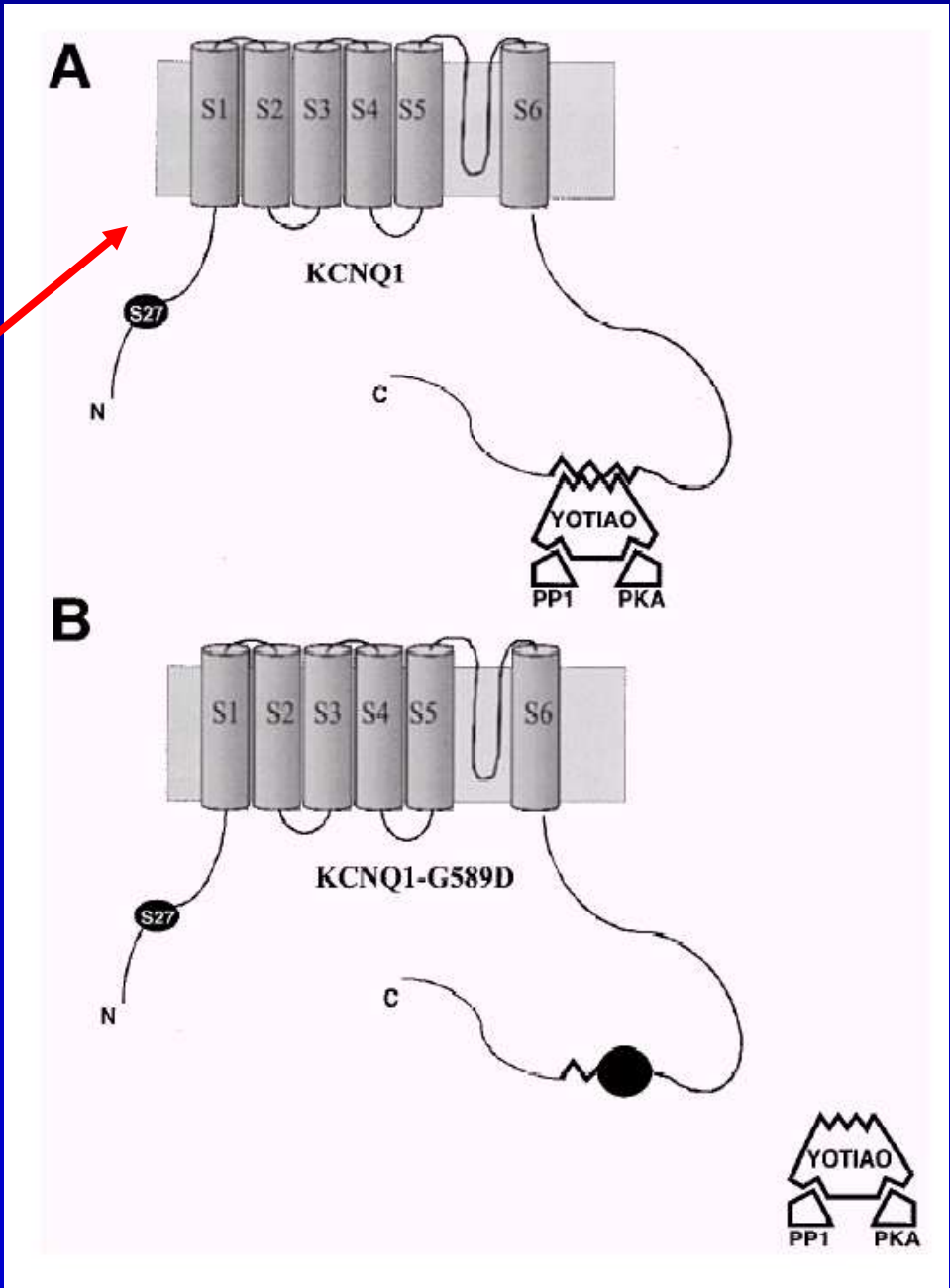
Kass RS & Moss AJ. J Clin Invest. 2003;112:810, Behr ER et al.Trends in Genetics. 2003;19:470

LQTS1 Mechanism

Phosphorylation of S27 causes increase in function of I_{Ks}:

Increase current density with depolarization

Delayed inactivation after activation, so open channels can accumulate



Kass RS et al. Trends Cardiovasc Med. 2003;13:52.

LQTS1 Mechanism

A – normal association of KCNQ1 with yotiao and SNS-responsive elements

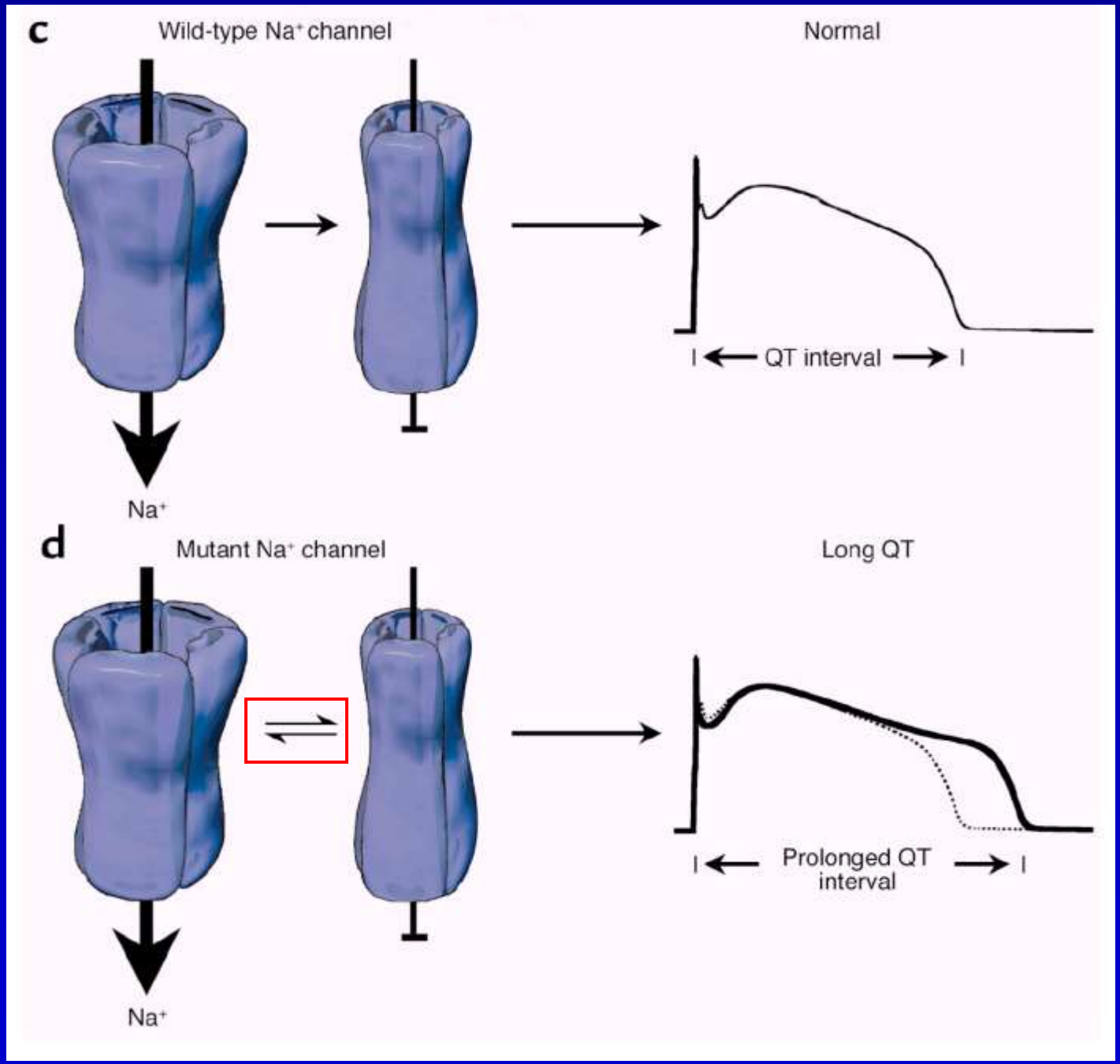
B – loss of association due to disruption of the LIZ motif, now not SNS-responsive

Kass RS et al. Trends Cardiovasc Med. 2003;13:52.

LQT3 Mechan-ism

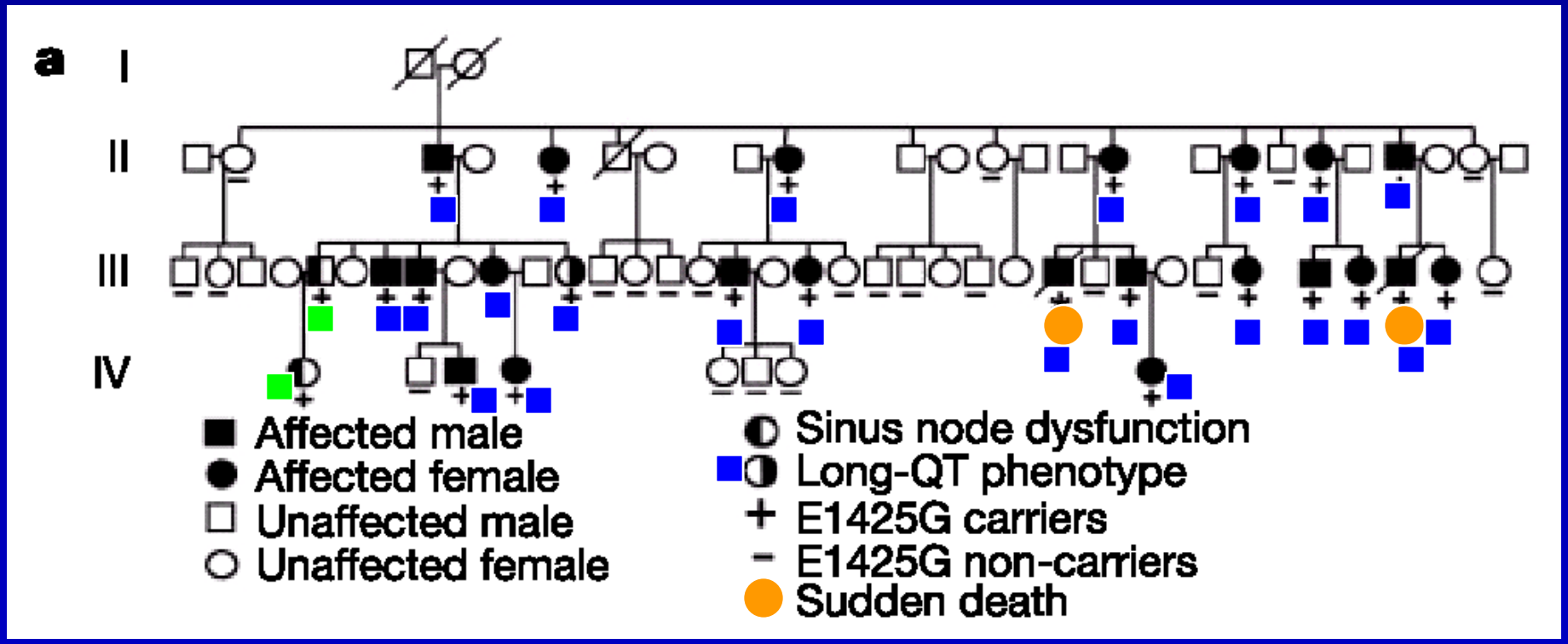
Gene SCN5A is cardiac Na channel, defect is incomplete inactivation

Gene SCN1A is neuronal Na channel, associated with epilepsy has similar functional abnormality



Kass RS & Moss AJ. J Clin Invest. 2003;112:810

LQTS4: Ankyrin dysfunction



- Autosomal dominant; one French kindred, 25 affected patients, SCD related to physical exertion or emotional stress (SCD in 2 pts)
- Phenotype: Sinus node dysfunction/bradycardia, LQTS and SCD, penetrance is high but not complete

Mohler PJ et al. Nature. 2003;421:634

Ankyrin Proteins

- Ankyrins are ubiquitously expressed intracellular adaptor proteins that target diverse proteins to specialized membrane domains, in 3 classes
  - Ankyrin R: restricted distribution (RBC, some neurons, striated muscle)
  - Ankyrin B: broadly expressed
  - Ankyrin G: giant size and general expression
- Structure: membrane-binding domain (24 ANK repeats), spectrin-binding domain, death domain, and C-terminal domain
- Ankyrins associate with ion channels, calcium release channels, cell adhesion molecules, and cytoplasmic proteins such as clathrin and tubulin

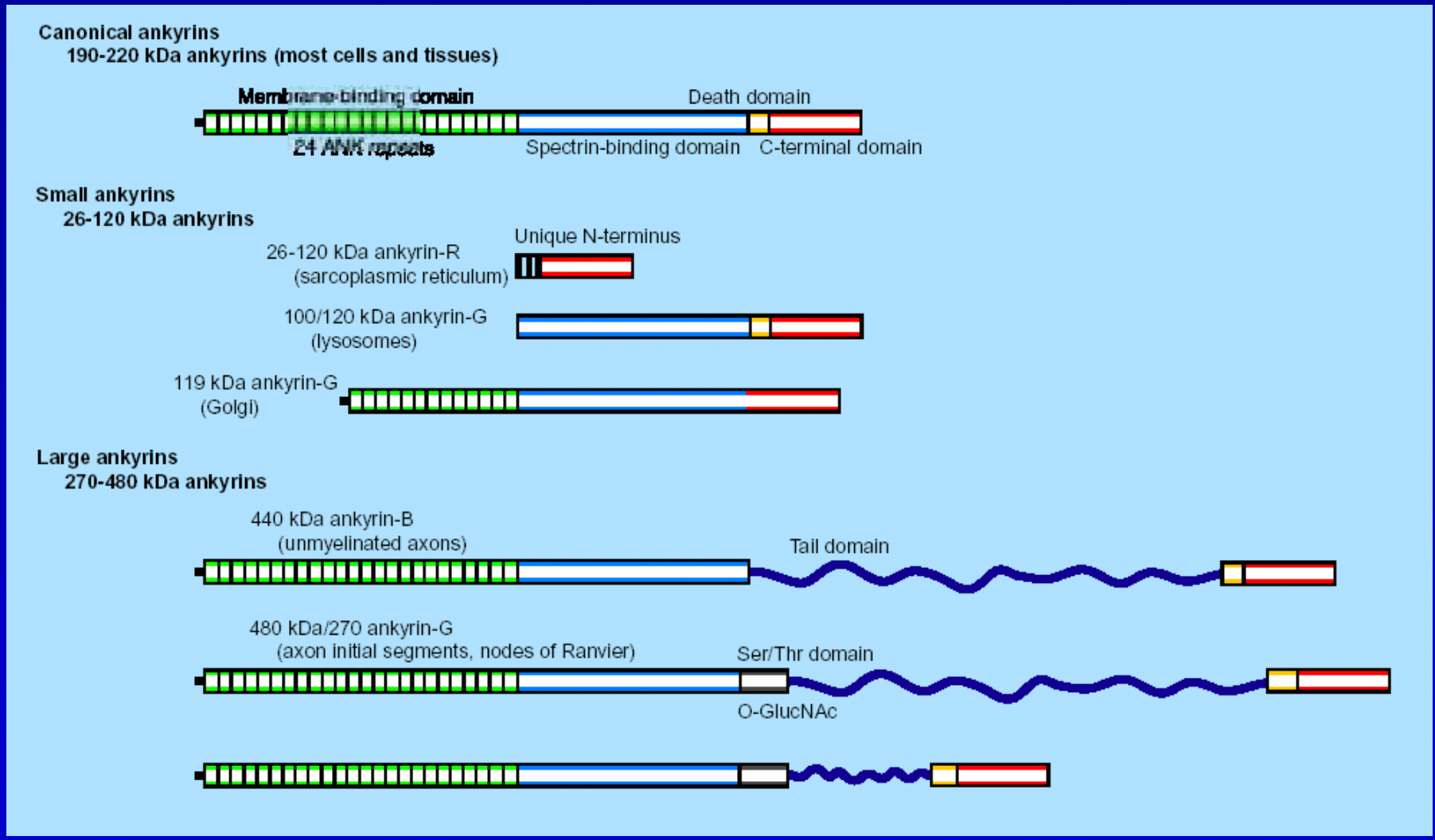
Mohler PJ et al. J Cell Sci. 2002;115:1565

Ankyrin Proteins

- ANK repeats: 33-AA motif involved in protein recognition, found in over 325 human proteins, they fold into stacks of antiparallel α-helices connected by exposed loops
- Membrane-binding domain (24 ANK repeats) are multivalent and can interact with multiple proteins so may assemble multiprotein complexes at specific sites: Ankyrin B -/- cardiomyocytes display downregulation and mis-sorting of Calcium release channels (ryanodine and I-P3 receptors) in the endoplasmic reticulum, mediated by the C-terminal domain

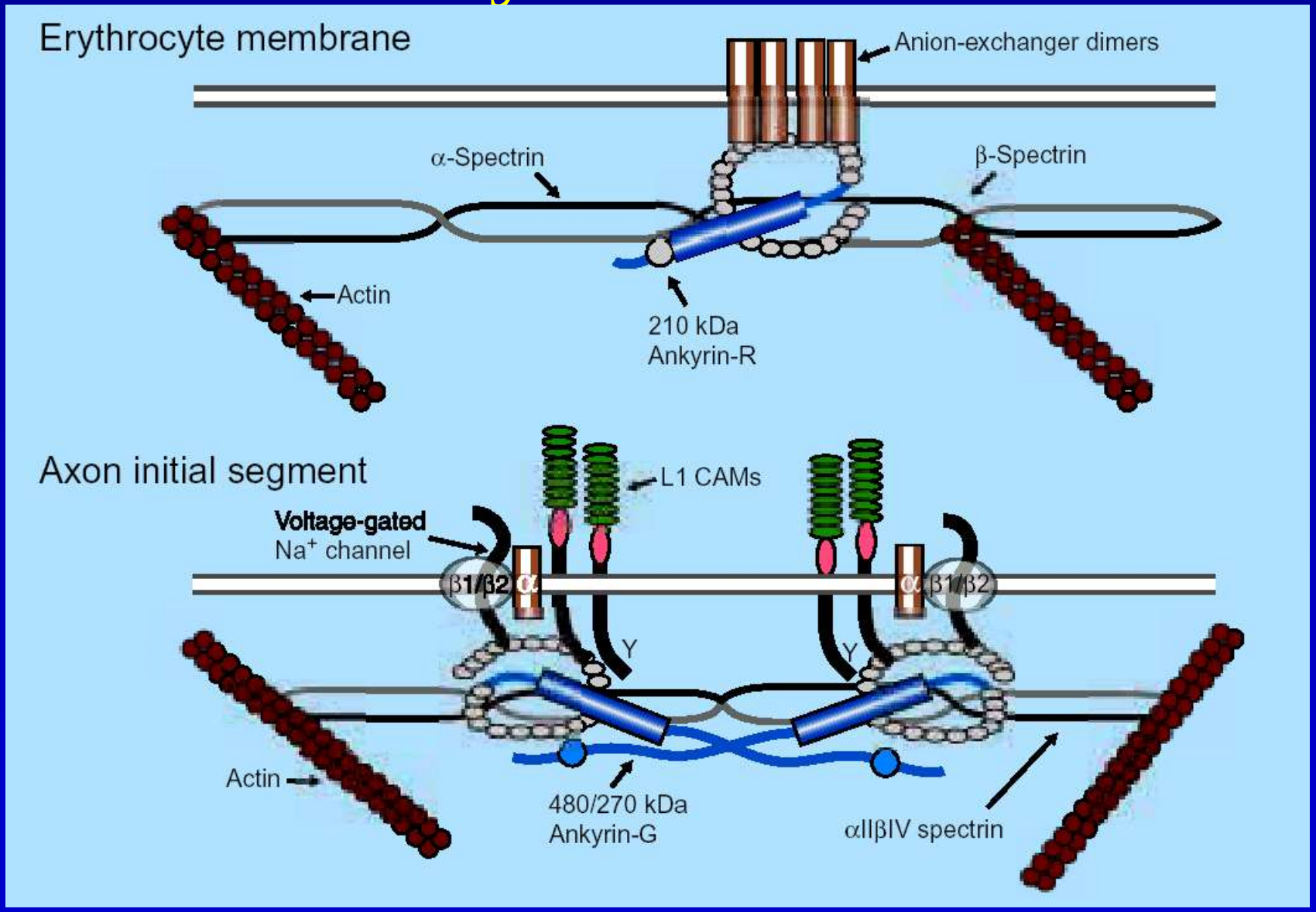
Mohler PJ et al. J Cell Sci. 2002;115:1565

Ankyrin Structure



Mohler PJ et al. J Cell Sci. 2002;115:1565

Ankyrin Structure



Mohler PJ et al. J Cell Sci. 2002;115:1565

Ankyrin Connections

Ankyrin-associated proteins

Cell adhesion molecules

CD44, L1CAMs: L1
LAD-1, NrCAM, NgCAM,
neuroglian, neurofascin

Ion channels

Anion exchanger (1-3)
Voltage-sensitive NaCh (β1,2)
Na^+/K^+-ATPase
H^+/K^+-ATPase
Na^+/Ca^{2+} exchanger

Calcium-release channels

Ryanodine receptor
Ins(1,4,5)P_3 receptor

Cytoplasmic

Tubulin
Clathrin
β spectrin I-IV

Mohler PJ et al. J Cell Sci. 2002;115:1565

LQTS4: Ankyrin dysfunction

- Autosomal dominant (heterozygote mice have disease phenotype)
- Disrupted cellular organization of:
  - Sodium pump
  - Sodium-Calcium exchanger
  - Inositol 1,4,5 triphosphate receptor
- Lower delivery to transverse tubules and lower protein level

Mohler PJ et al. Nature. 2003;421:634

K+ Channels

- The 2 key delayed rectifier currents are I_{ks} and I_{kr}, both potassium
- I_{ks} is α and β subunits, (LQTS1-KVLQT1=KCNQ1 and LQTS5-minK=KCNE1 respectively)
- I_{ks} is strongly regulated by SNS stimulation
- KCNQ1/KCNE1 channel forms a macromolecular signalling complex
  - Coupled to yotiao, an adaptor protein that binds to protein kinase A (PKA) and to protein phosphatase 1 (PP1) and facilitates phosphorylation of Ser^{27} and increase conductance
  - SNS stimulation > cAMP > increase I_{ks} > faster repolarization = shorter APD, balanced against PKA stimulation of L type Ca channels that prolong APD
  - Dysfunction of the channel leads to an arrhythmogenic inequity in SNS-stimulated phosphorylation of the channel, can give EADs

Kass RS & Moss AJ. J Clin Invest. 2003;112:810

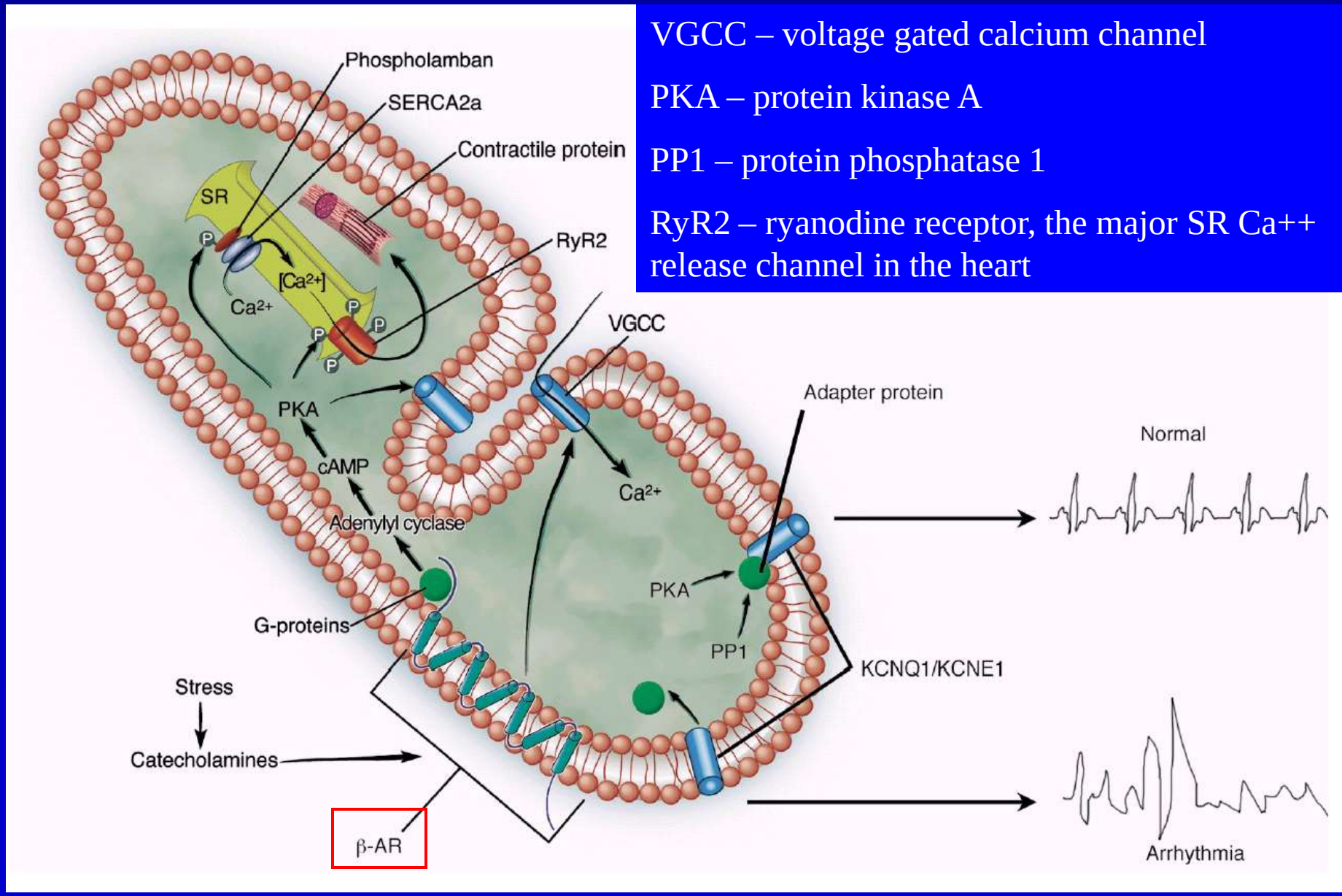
Potassium Channel Function

VGCC – voltage gated calcium channel

PKA – protein kinase A

PP1 – protein phosphatase 1

RyR2 – ryanodine receptor, the major SR Ca++ release channel in the heart



Kass RS & Moss AJ. J Clin Invest. 2003;112:810; Marks AR. J Clin Invest. 2003;111:597.

Ryanodine Receptor

- RyR1 is in skeletal muscle
- RyR2 is in cardiac muscle – has an extensive cytoplasmic domain that is a scaffold for regulatory proteins using LIZ (leucine-isoleucine zipper) motifs
  - FKBP12.6
  - PKA (reg and cat and mAKAP)
  - PP1 and spinophilin
  - PP2A and PR130
- Regulation is for the step of phosphorylation of Ser^{2809} that causes dissociation of FKBP12.6 and more activity of Ca++ release (similar to I_{ks})

Kass RS et al. Trends Cardiovasc Med. 2003;13:52.

LQTS7 Mechanism

Anderson's Syndrome is a triad of dysmorphic features, cardiac arrhythmias and LQT, and periodic paralysis, and expression is variable

Periodic paralysis syndromes are also channelopathies, but this syndrome shows combined abnormalities

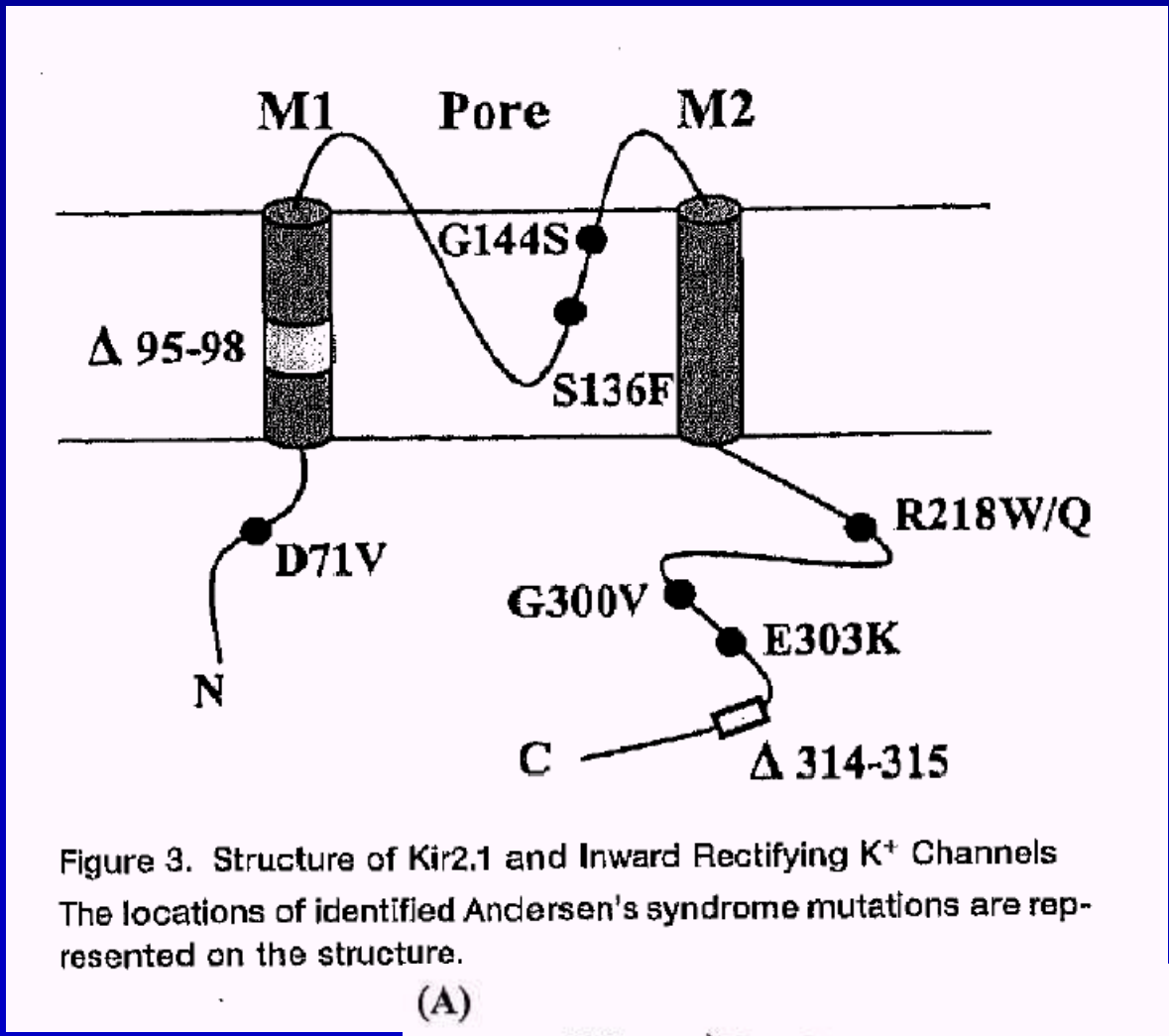
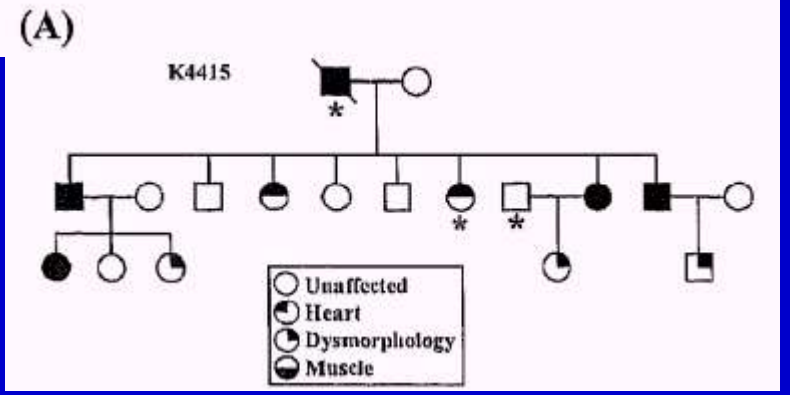


Figure 3. Structure of Kir2.1 and Inward Rectifying K^+ Channels
The locations of identified Andersen's syndrome mutations are represented on the structure.



Inward rectification means that inward flux of K+ ions at a potential below Keq for K+ occurs more readily than efflux at a potential above Keq for K+; Kir2.1 is a strong rectifier.

Plaster NM et al. Cell. 2001;105:511.

LQTS7 Mechanism

Kir1.1 mutation produces Bartter's syndrome and has analogous functional consequences as the Kir2.1 mutation explored.

Kir 2.1 has a pore region with a K+ selectivity filter GYG (gly-tyr-gly)

Kir 2.1 has been postulated to play an important, but not exclusive role as the inward rectifier current, I_{K1}.

Plaster NM et al. Cell. 2001;105:511.

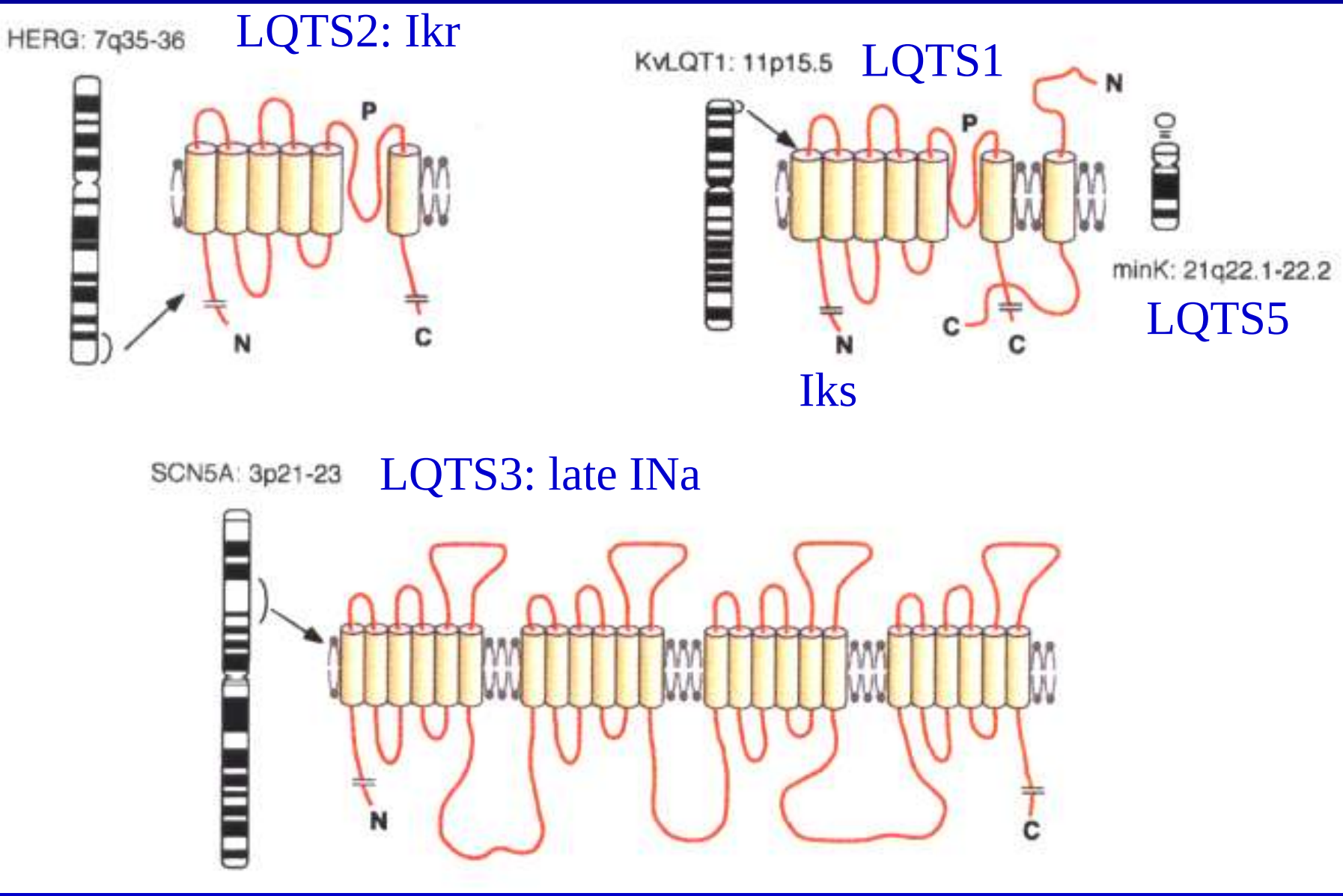
Congenital QT Prolongation

- Romano-Ward (1963, 1964): autosomal dominant, no deafness
- Jervell and Lange-Nielson (1957): autosomal recessive, with deafness (KVLQT1 and minK also control inner ear endolymph homeostasis)
- These 2 syndromes are disturbances in the same genes and channels, except Jervell and Lange-Nielson patients are homozygous, and the Romano-Ward patients are heterozygous with variable penetrance

Types of Congenital Prolonged QT interval

Syndrome	Gene	Chromosome	Current
LQTS1 (most common)*	KvLQT1	11p15.5	↓Iks (alpha subunit)
LQTS2	HERG	7q35-q36	↓Ikr
LQTS3 (rare)	SCN5A	3p21-p23	↑late INa
LQTS4	?	4q25-q27	?
LQTS5 (rare)*	minK (KCNE1)	21q22.1-q22	↓Iks (ancillary subunit)
LQTS6	KCNE2	?	↓Ikr

* Jervell and Lange-Nielson as well as Romano-Ward



Priori SG, et al. Circulation 1999;99:518-528.

Adrenergic Effects in Congenital Prolonged QT interval

Syndrome	Pharm Mimic	↑QT/ ↑TDR	Isoproterenol, +Propranolol	Current
LQTS1	chromanol 293B	+/-	↑/↑, n/n	↓Iks
LQTS2	dofetalide, E-4031, d-sotalol	+/+	↑/↑↓, n/n	↓Ikr
LQTS3	anthopleurin A, ATX-II	++/++	↓/↓, n/n	↑late INa

Experimentally: beta-blockade totally suppresses Tdp in LQT1, partially suppresses TdP in LQT2, and may provoke TdP in LQT3; but Na blocker may improve LQTS3, Mexiletine or flecainide

Shimizu, J Am Coll Cardiol 2000;35:778-86; Kass J Clin Invest 2003.

Mutations in LQTS Genes

- Each gene has multiple types of abnormalities, some are hot spots
- Modifier genes?: identical gene defects have variability in clinical features
- Modification of channel function:
  - Related to specific amino acid defect
  - KvLQT1, KCNE1 and HERG lose function
  - SCN5A gains function (defective inactivation)

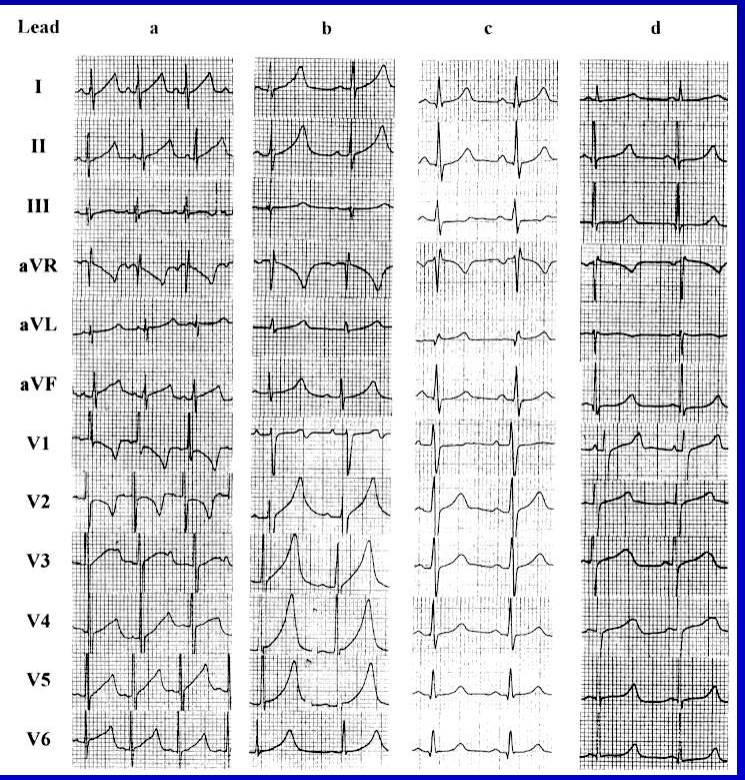
Clinical Correlation in Congenital LQTS

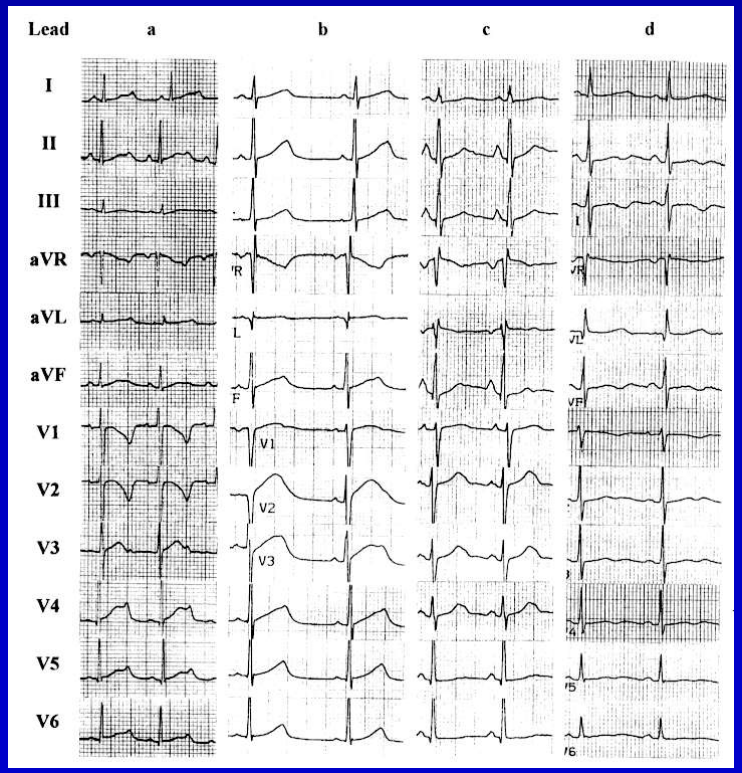
- Manifestations
  - LQTS1: trigger of exercise
  - LQTS3: trigger with sleep or rest, shorten QT with exercise
  - LQTS2: both rest and exercise
- Management
  - Beta-blocker is first choice therapy
  - LQT3 usually improve with mexiletine
  - LQT2 may improve with mexiletine

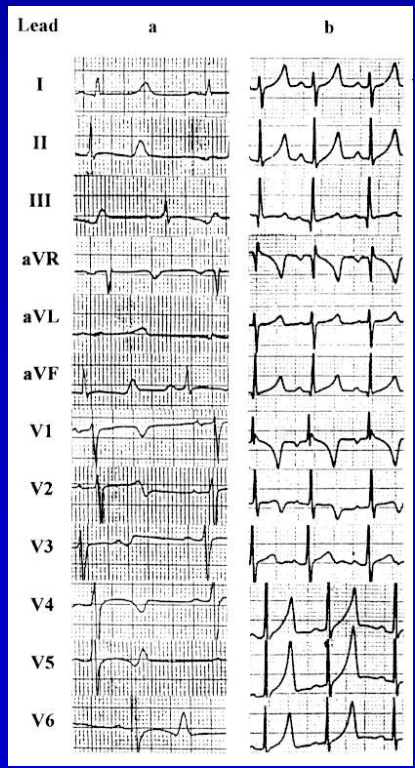
ECG manifestations of LQTS

- Vary with genotype

Type 1 Type 2 Type 3



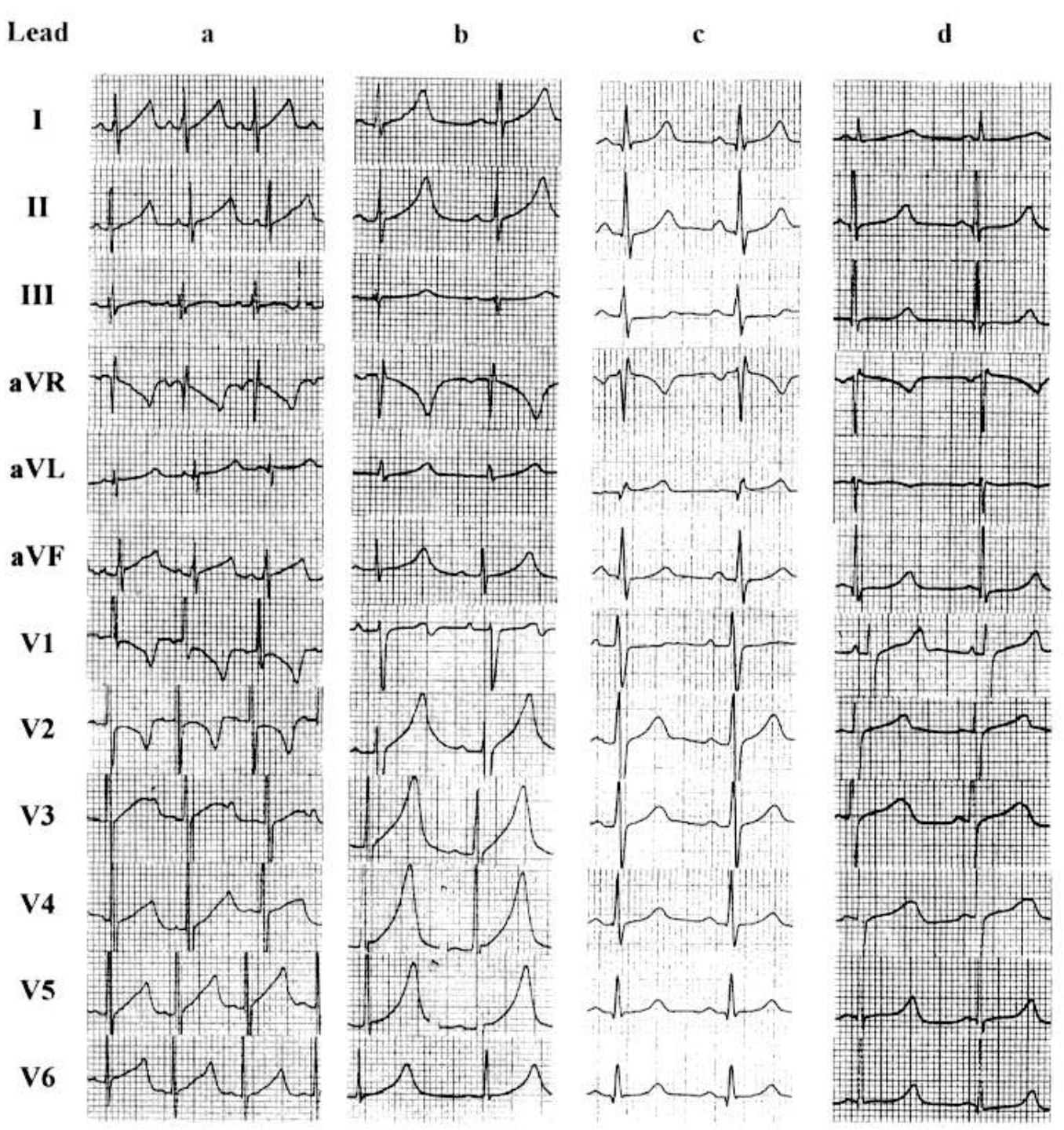




Circ, Dec 5, 2000… Wilde and Roden p 2797, Zhang et al, p.2849

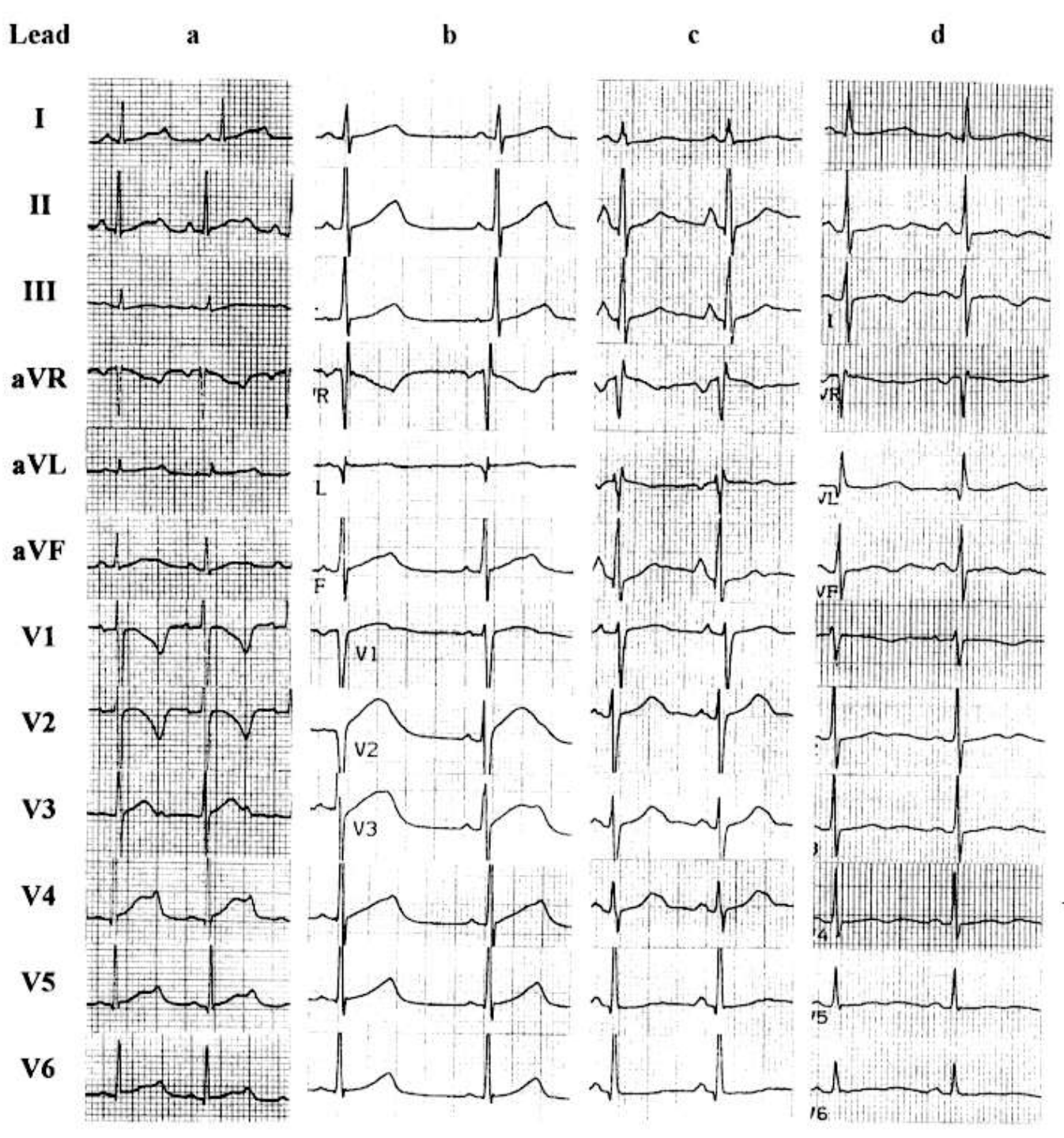
Type 1

Circ, Dec 5, 2000… Wilde and Roden p 2797, Zhang et al, p.2849



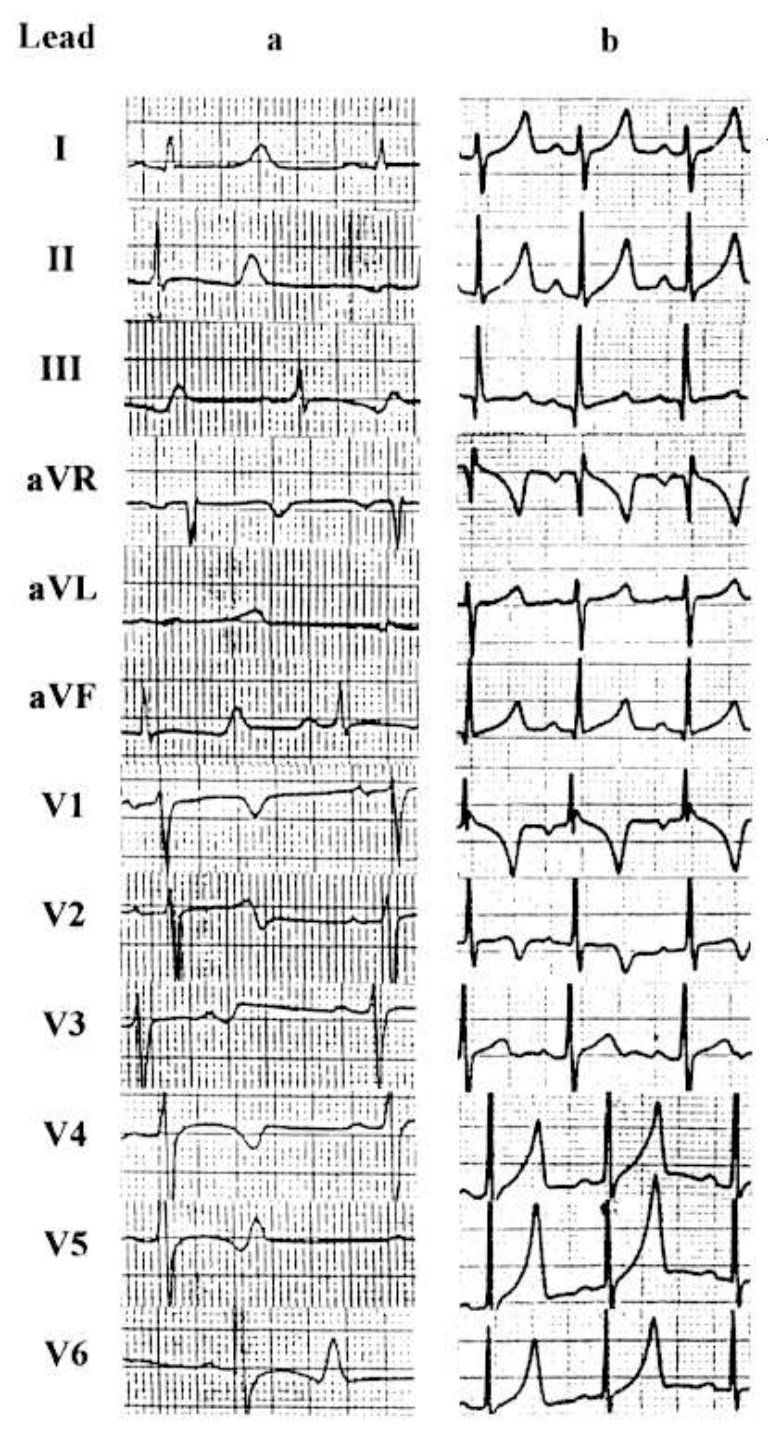
Type 2

Circ, Dec 5, 2000… Wilde and Roden p 2797, Zhang et al, p.2849



Type 3

Circ, Dec 5, 2000… Wilde and Roden p 2797, Zhang et al, p.2849



Clinical Characteristics in Common Forms of LQTS

	LQT1	LQT2	LQT3
Gene mutated	KCNQ1 (KvLQT1)	KCNH2 (HERG)	SCN5A
Current affected	I_{Ks}	I_{Kr}	I_{Na}
Estimated prevalence (%)*	45	40	10
Mean QTc†	490±43	495±43	510±48
% of events occurring with exercise or emotional stress‡	97	51	39
Exercise-related trigger	+++	+	+
Other triggers	Swimming	Loud noise	
% with events to age 10†	40	16	2
% with events to age 40†	63	46	18
Median age at 1st event†	9	12	16
QT shortening with exercise‡§	<Normal	Normal	>Normal
Efficacy of β-blockade to prevent events	+++	++	+(?)
Efficacy of mexiletine to shorten QT‡	−	+	+++

Circ, Dec 5, 2000… Wilde and Roden p 2797, Zhang et al, p.2849

References:

- Priori SG et al. Genetic and molecular basis of cardiac arrhythmias: impact on clinical management Parts I and II. Circulation 1999;99:518-28.
- Priori SG et al. Genetic and molecular basis of cardiac arrhythmias: impact on clinical management Part III. Circulation 1999;99:674-81.
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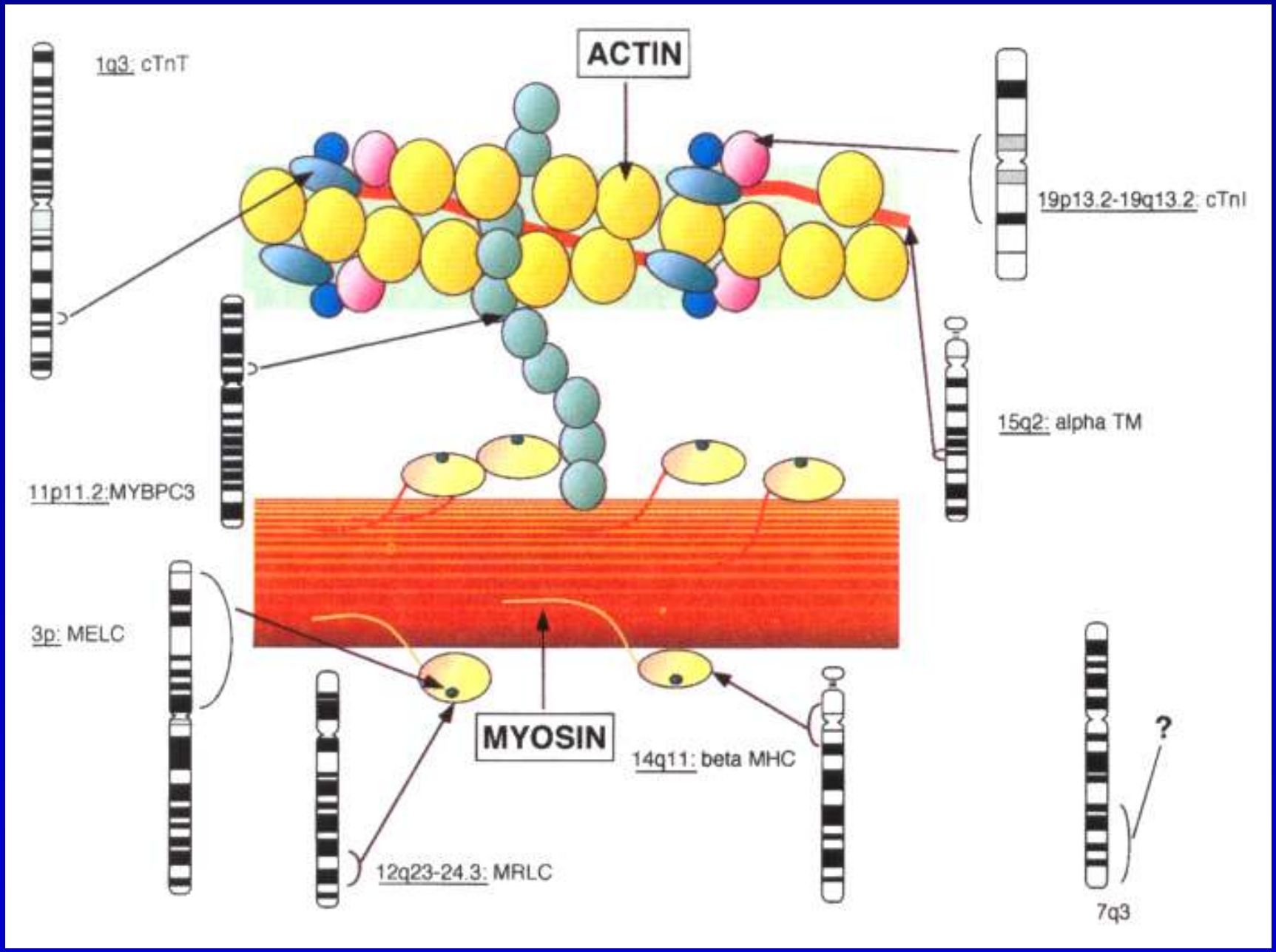
- Sandoe, Sigurd, Arrhythmia - A guide to clinical electrocardiology Publishing Partners Verlags GmbH 1991
- Zhang et al. Circulation 2000;102:2849-55
- Wilde et al. Circulation 2000;102:2799-2801



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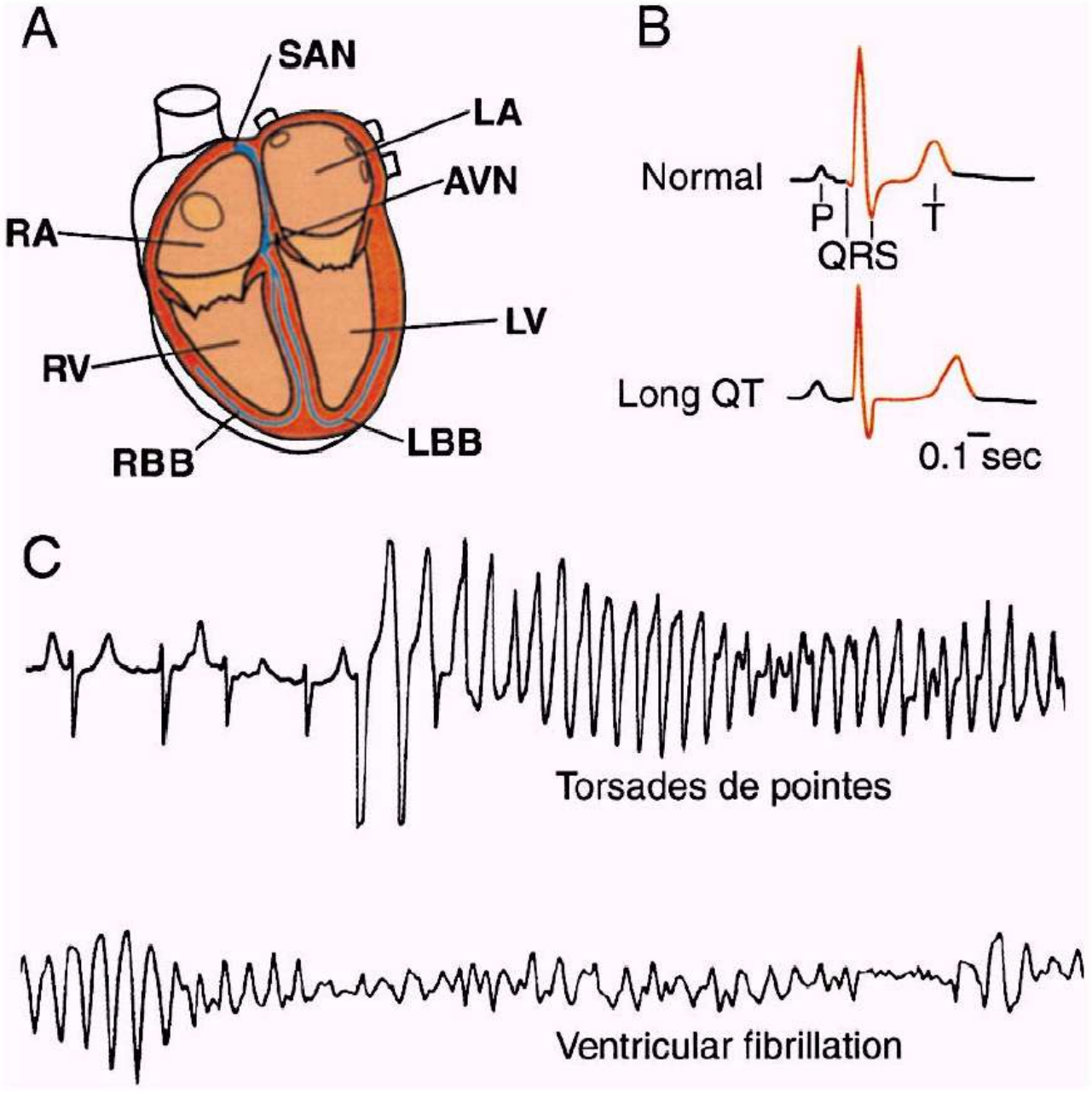
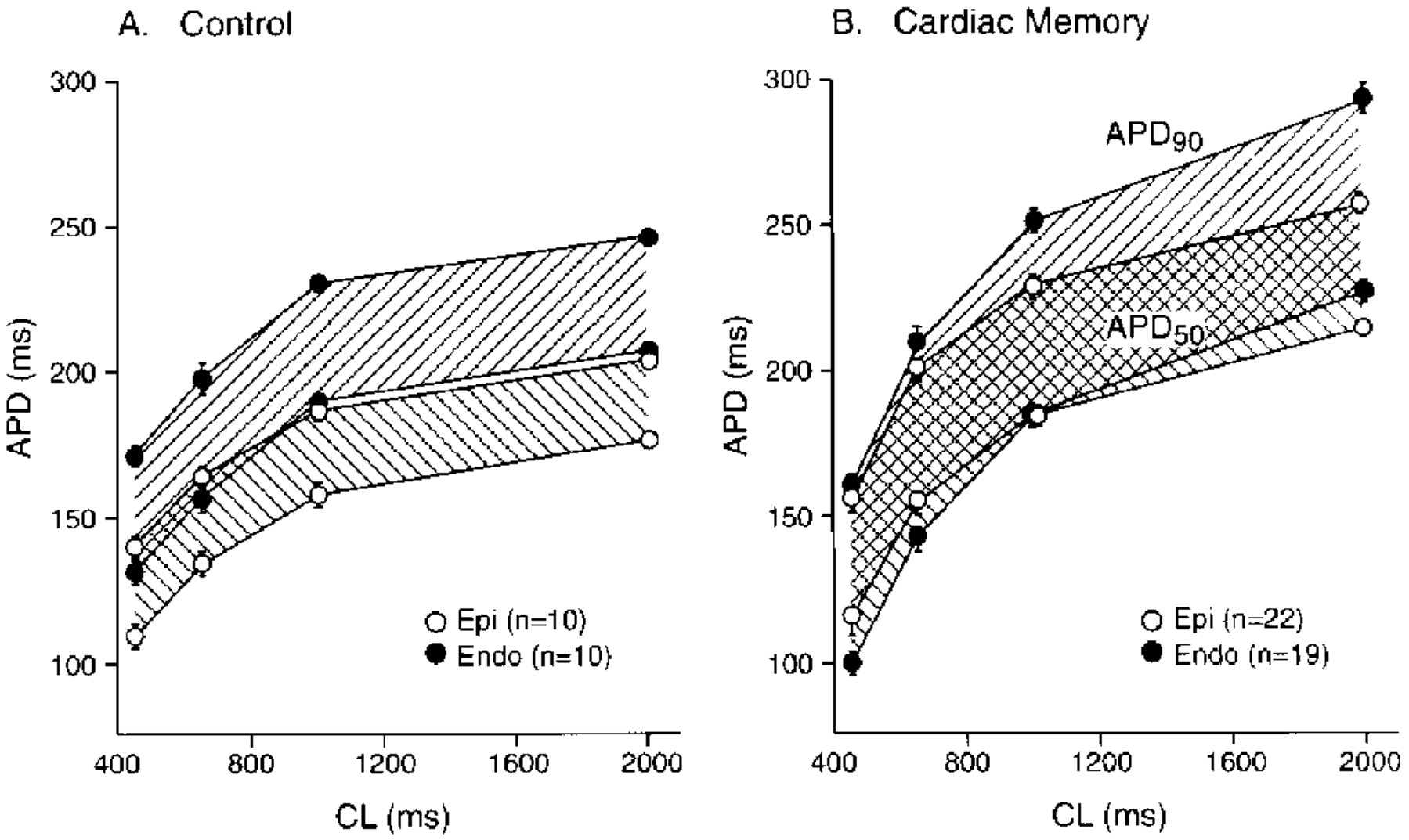
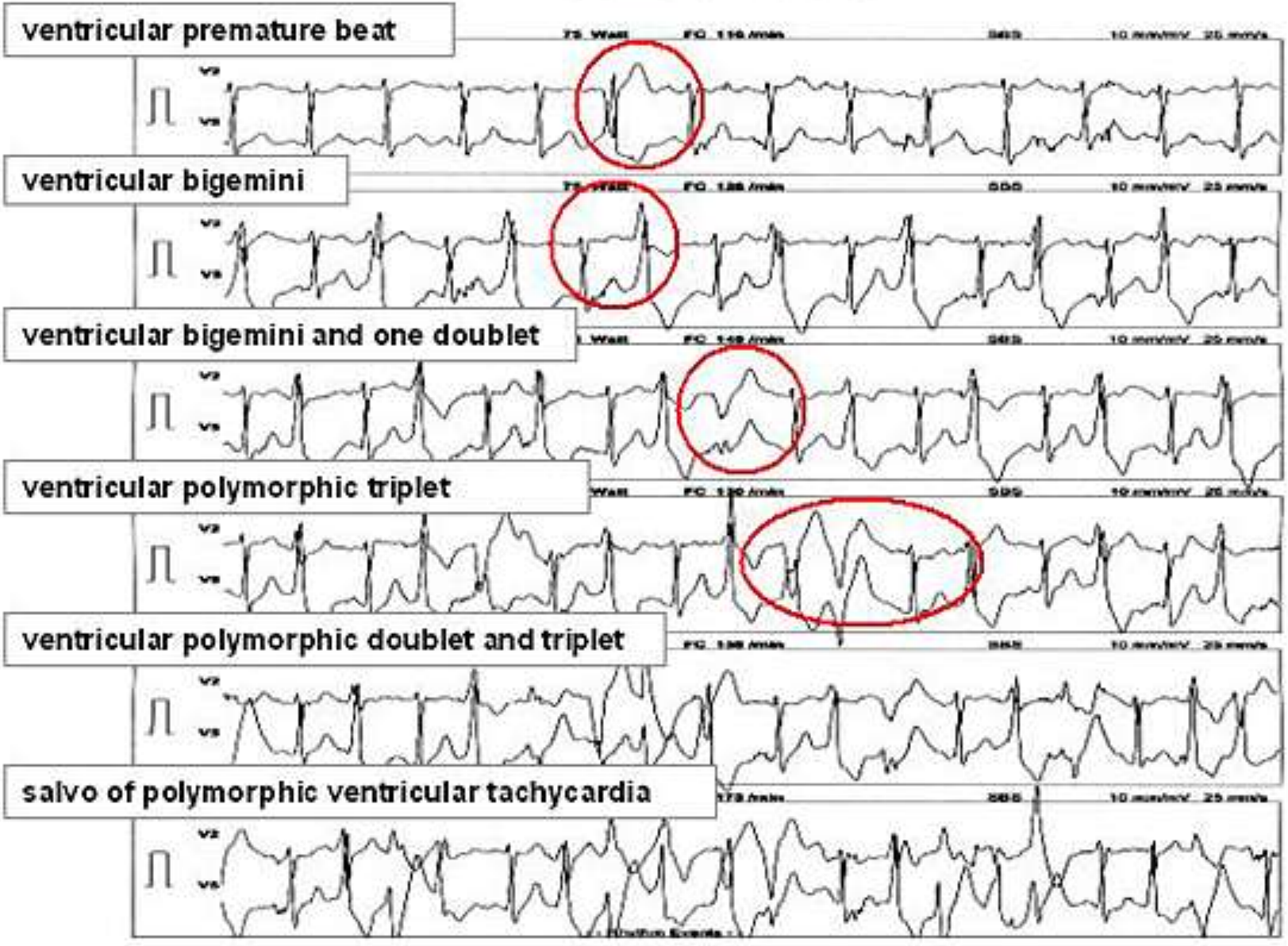


Keating M et al.
Cell 2001; 104:569



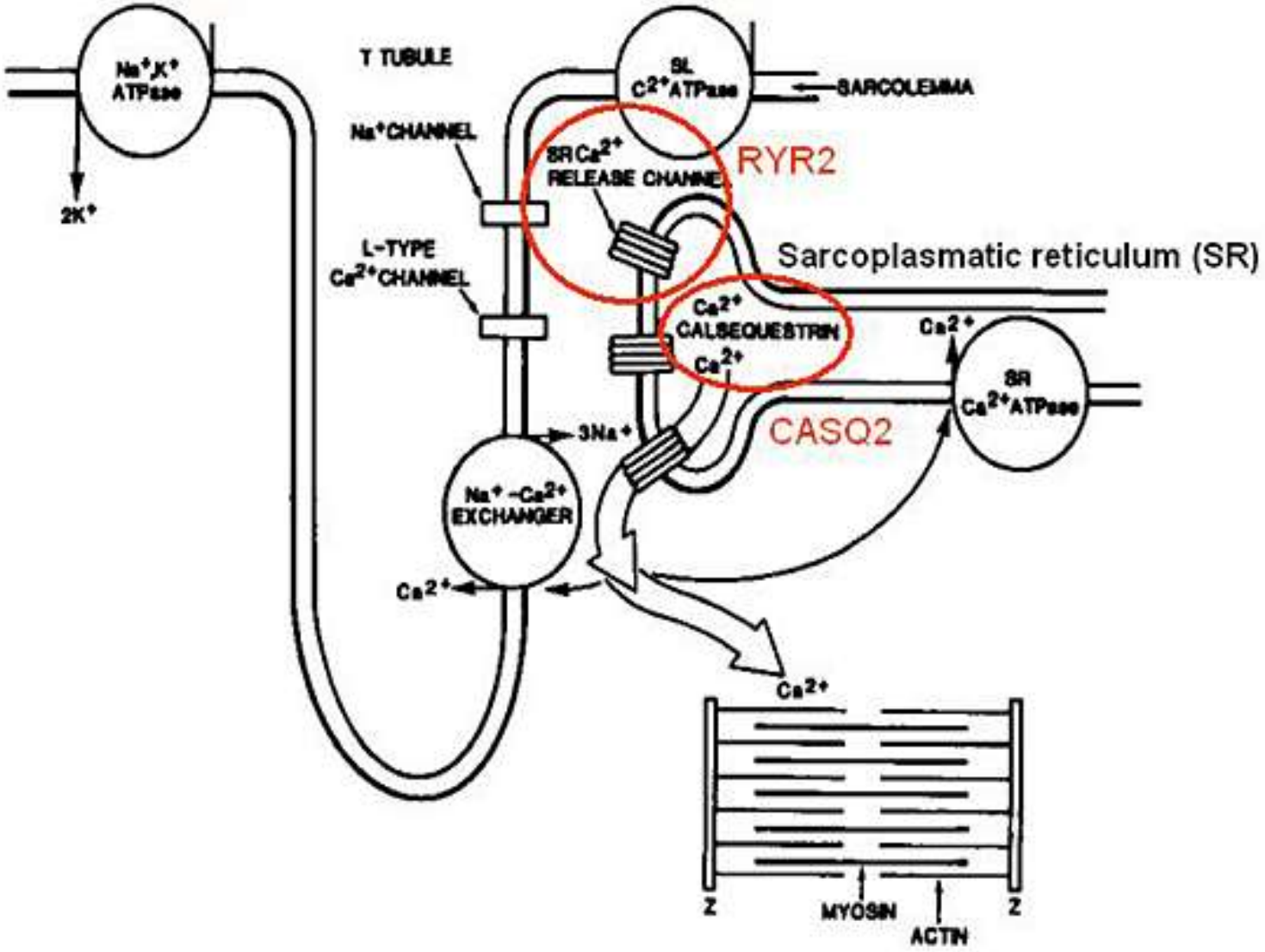
Shvilkin A et al. Circulation. 1998;97:1810

CPVT-ECG



Postma AV et al. Netherlands, presented at AHA Nov 2002

Ca^{2+} & excitation-contraction coupling



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