

# Repolarization and the ECG – Selected Topics

December 18, 2007

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UTHSCSA and STVAHCS

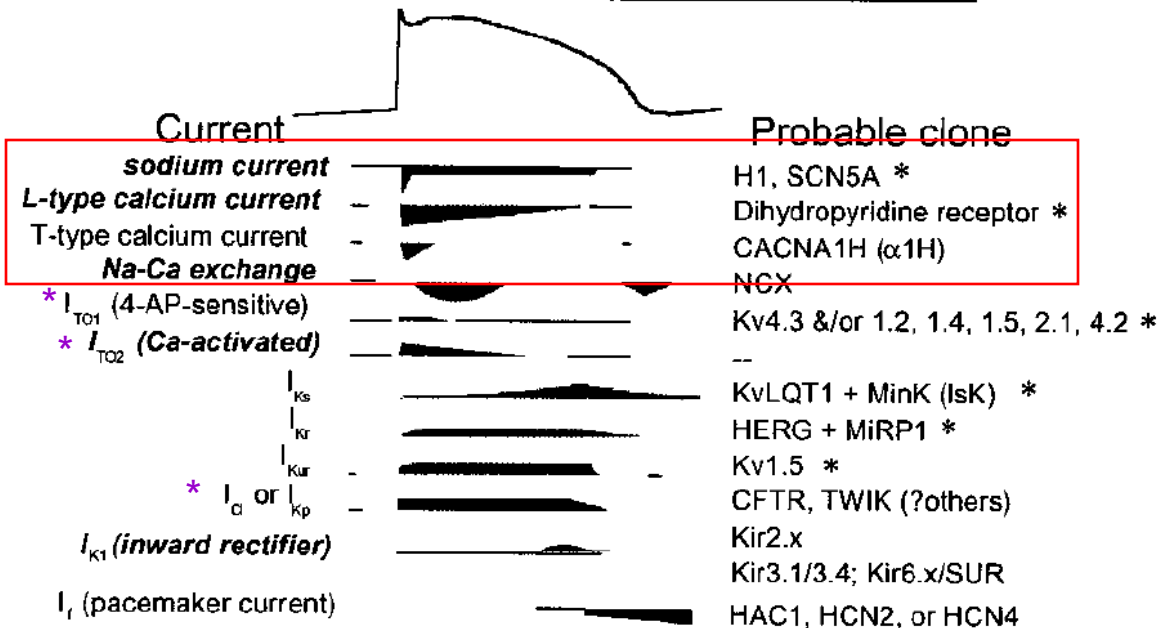
# 2001 Surawicz Text Chapters

- Ch. 1: Normal ECG
- Ch. 3: Ventricular enlargement
- Ch. 4: LBBB
- Ch. 5: RBBB
- Ch. 7: Acute Ischemia
- Ch. 8: Myocardial Infarction
- Ch. 9: Non-Q Wave MI, UA, Myocardial ischemia
- Ch. 11: Pericarditis and Cardiac Surgery
- Ch. 21: Effect of Drugs on the electrocardiogram
- Ch. 22: Electrolytes, temperature, CNS disease
- Ch. 23: T wave abnormalities
- Ch. 24: QT interval, U wave abnormalities, and cardiac alternans

# ECG Repolarization Topics

- Fundamental Considerations
- Early Repolarization, ?Normal variant?
- Primary and Secondary abnormalities
- Nonspecific ST-T changes
- Cardiac Memory
- T wave alternans
- Mechanism of ST elevation
- Post Extrasystolic T wave alterations
- QT interval and arrhythmia

# Ion currents and ion channel clones



## Fundamental Considerations: Ion Currents

Ionic currents and coding genes responsible for the configuration and duration of the AP. Approximate relative current magnitude, direction, and duration of each current are indicated by the darkened deviations from baseline. The AP upstroke is primarily determined by the  $Na^+$  current; however, repolarization is the result of the interplay of many inward currents (marked by down-going shapes) and outward currents (marked by up-going shapes). Current names are printed in bold italics where there is experimental evidence for regulation by intracellular  $Ca^{2+}$ . Asterisks indicate that modifier subunit proteins are thought to be important contributors to the ionic current linked to the listed clone.  $K^+$  currents are the largest source of repolarizing outward current and are carried by a variety of ion channels. These repolarizing  $K^+$  currents include the first component of the transient outward current ( $I_{to1}$ ), the slow ( $I_{Ks}$ ), rapid ( $I_{Kr}$ ), and ultra-rapid ( $I_{Kur}$ ) components of the delayed rectifier current, and the inward rectifier ( $I_{K1}$ ). Reduction in repolarizing outward current or increases in depolarizing inward current can each result in prolongation of AP repolarization.

# Normal ST Segment

- Limb leads: less than 0.1 mV elevation or depression is normal, elevation is more common in II, III, and aVF
- Precordial leads:
  - elevation in >90% of normal subjects,
    - more in men and in younger,
    - more in V2-V3 up to 0.3 mV,
    - seldom >0.1 mV in left precordial,
    - seldom >0.2 mV in >40 y.o.
  - Any depression in precordial leads is abnormal

# ST Segment Deviation

- Baseline reference by convention is line connecting beginning of QRS on 2 consecutive beats
- Sinus tachycardia (overlap with atrial repolarization)
- Delayed repolarization from slow depolarization (hypertrophy, BBB, pre-excitation)
- Myocardial ischemia

# T Wave

- Ventricular gradient:
  - If depolarization and repolarization have identical progress through the heart, the area of the QRS plus the area of the T wave should be equal to zero (T wave would be opposite the QRS)
  - Since QRS and T are generally in the same direction, the progress of repolarization must be different than that of depolarization
- Normal:
  - T inversion in V1 in 50% women and <1% men
  - T inversion in  $\geq 2$  right precordial – persistent juvenile pattern
  - Limb leads T is generally  $\leq 0.6$  mV, and I and II,  $\geq 0.05$  mV
  - T in left precordial abnormal if <10% of R height

# U Wave

- Time from end of T to apex of U (aU) is 90-110 ms (HR 50-100); from end of T to end of U is 160-230 ms
- Normally ascent steeper than descent (opposite of T wave)
- Usually largest in V2-3 (3-24% of T height)
- Usually  $<0.2$  mV
- DDX U vs notched T wave:
  - Notched T usually has  $<0.15$  sec between peaks, and T-U has more



# Origin of U Wave

- U waves come from M cells – Antzelevitch 1996
  - Antzelevitch 2006 – “While delayed repolarization of the M cells contributes to the inscription of the second component of the T2 (pathophysiologic U wave), it is unlikely that it is responsible for the normal U wave.”
- U waves come from Purkinje cells
- U waves come from mechanoelectric feedback from myocardial stretch
  - Dramatic separation of T and U in short QT syndrome is evidence

# Early Repolarization

- Benign (maybe 1-2% of the population)
- Minnesota Code definition (AJC 2002):
  - $\geq 1$  mm ST elevation in I, II, III, aVL, aVF,  $V_5$  or  $V_6$ , or  $\geq 2$  mm ST elevation in  $V_1$ ,  $V_2$ ,  $V_3$ , or  $V_4$ , needed in 2 subsequent leads, compared to the TP segment
- Diffuse ST elevation generally less than 2 mm (but can be up to 5 mm), concave up, especially precordial, especially  $V_2$ - $V_4$ , notched or slurred terminal QRS, concordant large T waves, constancy over time (or waxing and waning)
- Increased vagal tone
  - Lower resting HR
  - Seen in spinal cord injury at C5-6 (disruption of cardiac sympathetic) and reversed by isoproterenol
  - Decreases with deconditioning
  - No ethnic differences (prior African American prevalence now disproved)
  - Normalizes with exercise
- T usually tall, so ST/T in  $V_6$  is  $<0.25$  (contrast with pericarditis)

# Early Repolarization



Figure 4. Representative example of electrocardiographic complex depicting BER. The complex demonstrates STE with elevation of the J point. The initial portion of the ST segment/T wave complex is concave. The ST segments of BER appear to have been lifted evenly off the baseline, thereby preserving the normal upward concavity of the J point.

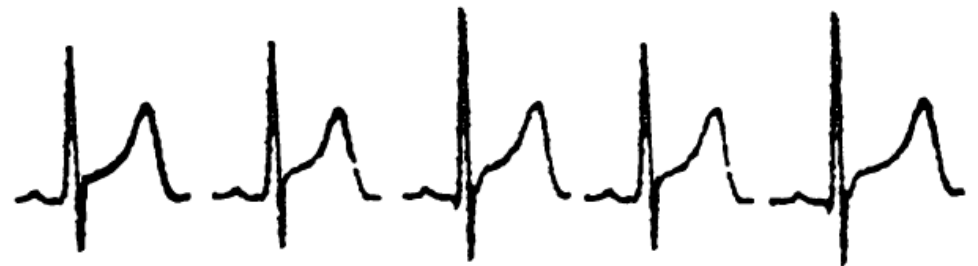


Figure 2. Lead II is shown, obtained from sequential EKGs performed approximately every 10 min in the patient from Case One. Initially, with ongoing pain, no evolution of the STE was seen. With resolution of the discomfort, the EKG remained unchanged, once again suggesting that the STE resulted from BER and not from AMI.

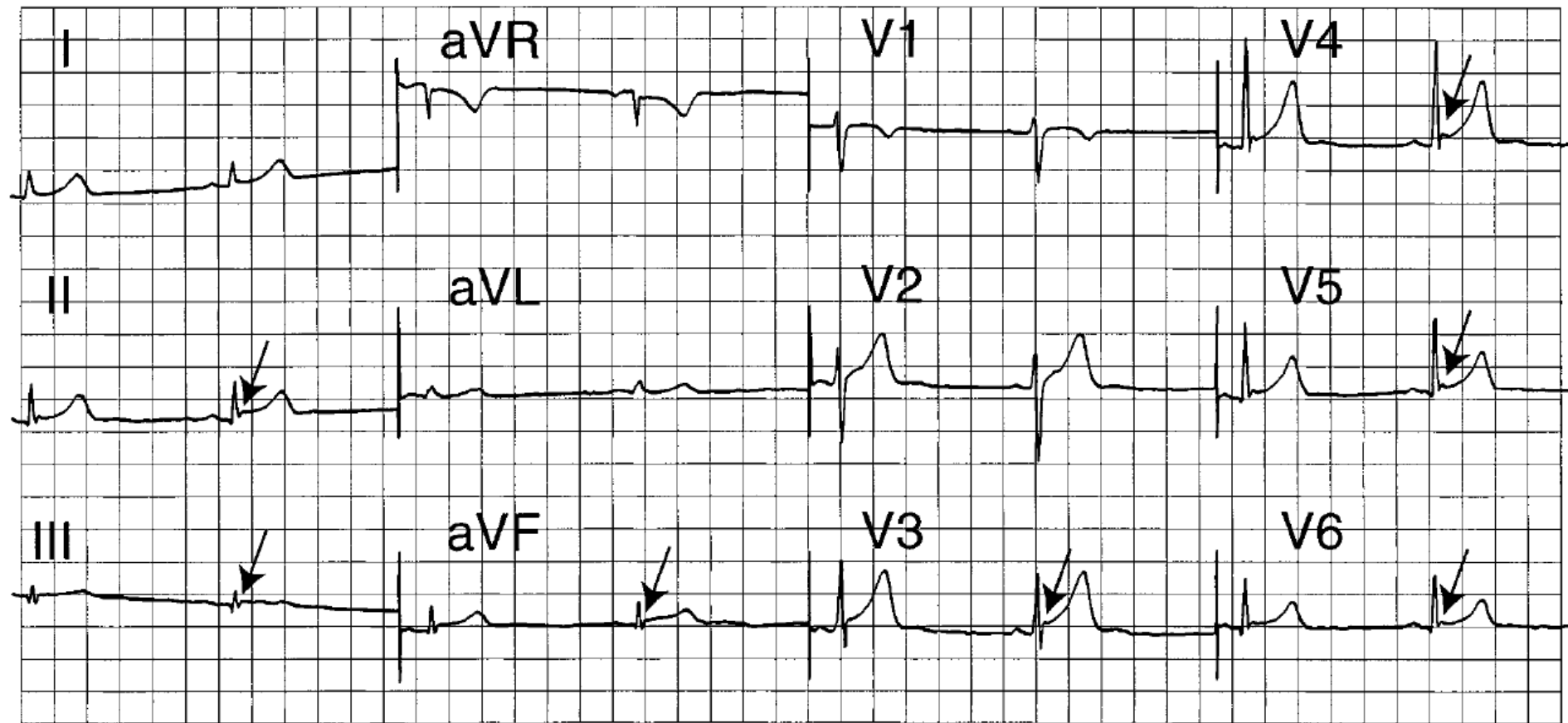
# Early Repolarization



# Early Repolarization Mechanisms

- Response to maneuvers is similar to Brugada:
  - Increase in ST elevation with sodium channel blockade and beta blockade, and
  - decrease in ST elevation with isoproterenol and exercise, and
  - no effect with nitroglycerin
- In Brugada, there is a prominent transient outward current, maybe also in Early Repolarization

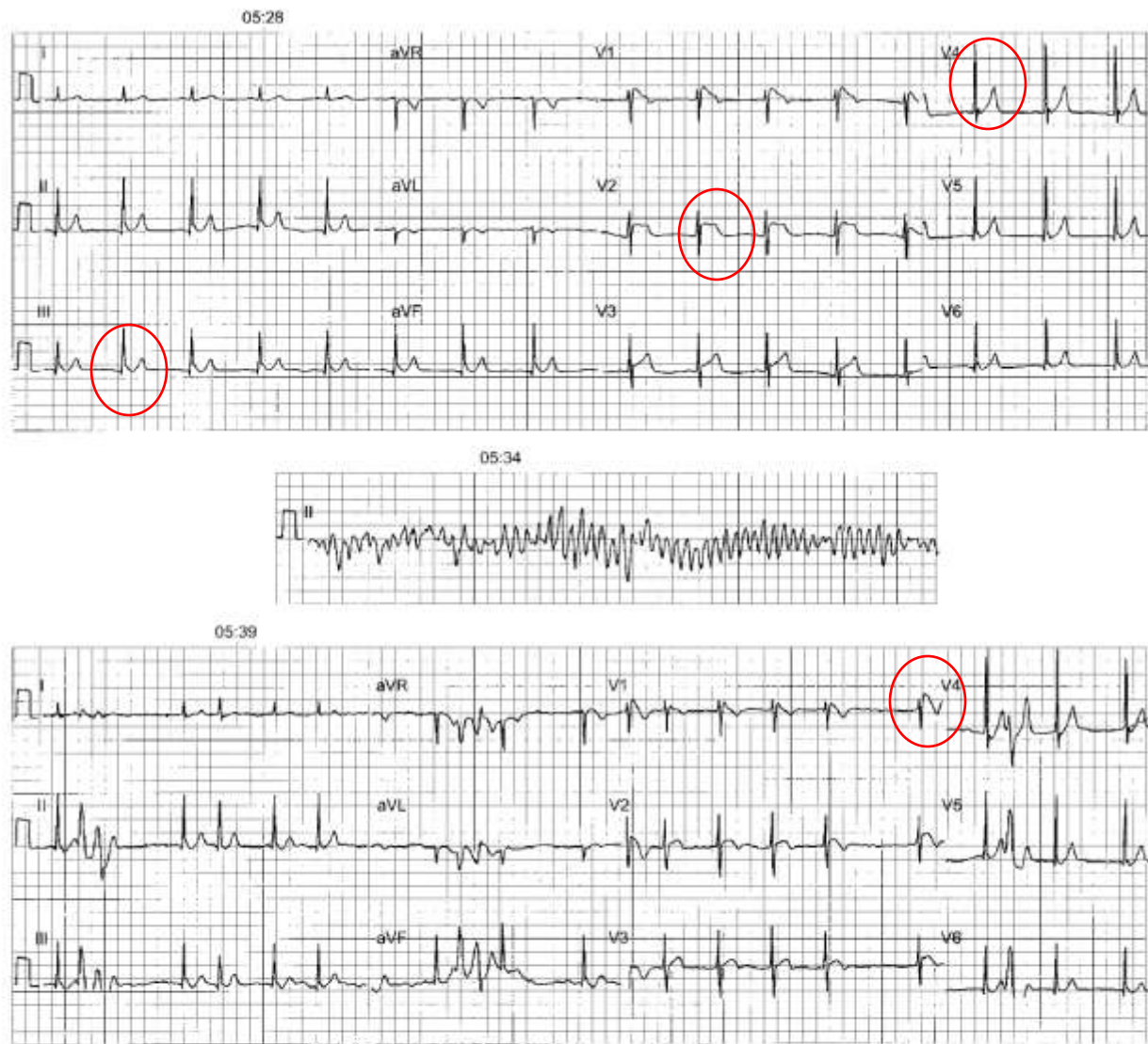
# Early Repolarization Mechanisms



**Fig. 1.** ECG manifestation of the early repolarization syndrome in a 12-lead ECG in an apparently healthy individual. An elevated notch is apparent on the downsloping limb of the QRS complex and is followed up by an upsloping ST-segment elevation that is most prominent in leads V<sub>3</sub>-V<sub>6</sub>. These changes are also seen in the inferior leads, but to a lesser extent.

# Early Repolarization (ER) vs Brugada Pattern (Br)

- ER: mostly V2-V4(5), notched J, positive T with upward concavity (also high cervical spinal cord injury)
- Br: prominent J elev, downsloping ST elev, negative T in V1-3



**Fig. 2.** Twelve-lead ECGs of a patient with the Brugada syndrome before (upper panel) and after (lower panel) an episode of ventricular fibrillation (middle panel). Upper panel (05:28), note prominent J-point elevation followed up by: (1) downsloping ST-segment elevation in leads V<sub>1</sub>, horizontal ST-segment elevation in lead V<sub>2</sub>, (2) upsloping ST-segment elevation and positive T wave in lead V<sub>3</sub>, (3) without ST-segment elevation in lead V<sub>4</sub>, and (4) slurring downsloping limb (late delta wave) of the QRS complex in inferior and lateral leads. Middle panel (05:34), spontaneous episode of ventricular fibrillation. Lower panel (05:39), atrial fibrillation with a short run of PVCs, with a short coupling interval after termination of ventricular fibrillation by direct current discharge. Note rate (deceleration)—dependent prominence of elevation of the J point and following downsloping ST-segment elevation in leads V<sub>1</sub>–V<sub>3</sub> and appearance of the negative T waves in the right precordial leads. (Courtesy of Kiyotaka Matsuo, MD, National Cardiovascular Center, Osaka, Japan.)

# Secondary T wave Abnormalities

- T wave direction is opposite
  - Main QRS: LVH or RVH or LBBB
  - Delta wave: WPW
  - Terminal delay: RBBB
- Secondary and primary T abnormality can coexist on the same recording



# Primary T Wave Abnormalities

- Uniform change in action potential with normal sequence of depolarization or repolarization: temperature, electrolytes, drugs
- Altered sequence of repolarization, generally sparing the ST segment but will usually prolong the QT
  - Ischemia or post-ischemia; pericarditis, myocardial disease, mitral prolapse, global T inversion, isolated adult midprecordial T inversion, autonomic nervous dysfunction, hyperventilation, orthostatic, postprandial, coronary contrast material, postextrasystolic abnormalities, post-tachycardic abnormalities, ventricular pacing, post LBBB and post preexcitation, rapidly reversible T wave abnormality

# Reading Nonspecific ST and T wave Abnormalities

- Define whether ST segment or T wave or both
- Assess as slight, moderate or marked
- Determine whether likely secondary to hypertrophy or interventricular conduction disturbance
- Assume terminal T inversion is probably primary that often indicates ischemia
- Probability of ischemia is greater if
  - Pattern of progression or regression on serial tracings
  - Pattern of lead involvement suggest localization
  - QT interval is prolonged
  - U wave is inverted
- Secondary and primary abnormalities can co-exist
- Tachycardia alone can precipitate ST depression and T abnormalities
- Negative T wave may be normal in III, aVL and V1, and V2 may be juvenile pattern
- Marked QT prolongation with ST depression and fusion of T and U may be drug or hypokalemia

# NSST-T in Hypertension

- 1970 Italian hypertensive patients without heart disease (70% new diagnosis)
  - 1355 normal repolarization
  - 504 minor repolarization changes
  - 111 typical LV strain pattern

Table 1 Electrocardiographic criteria for minor left ventricular repolarization changes and left ventricular strain [19]

	Minnesota code
<b>MINOR REPOLARIZATION CHANGES</b>	
One or more of the following:	
ST-J depression $< 0.05$ mV with ST-segment downward sloping and segment or T-wave nadir $\geq 0.05$ mV below P-R baseline, in any of leads I, II, aVL or $V_2 - V_6$	4-3
ST-J depression of $\geq 0.10$ mV and ST-segment upward sloping or U-shaped, in any of leads I, II, aVL or $V_2 - V_6$	4-4
T-wave amplitude zero (flat), negative or diphasic (negative-positive type only) with $< 0.10$ mV negative phase in lead I, II, $V_3 - V_6$ , or in lead aVL when R-wave amplitude is $\geq 0.5$ mV	5-3
T-wave amplitude positive and T- to R-wave amplitude ratio $< 1:20$ in any of leads I, II, aVL or $V_3 - V_6$ when R-wave amplitude in the corresponding leads is $\geq 1.0$ mV	5-4
<b>TYPICAL STRAIN</b>	
Coexistence, in any of leads I, II, aVL or $V_3 - V_6$ , of:	
ST-segment horizontal or downward sloping depression $\geq 0.05$ mV, <i>plus</i>	4-1 or 4-2
T-wave asymmetric inversion	5-1 or 5-2

# NSST-T in Hypertension

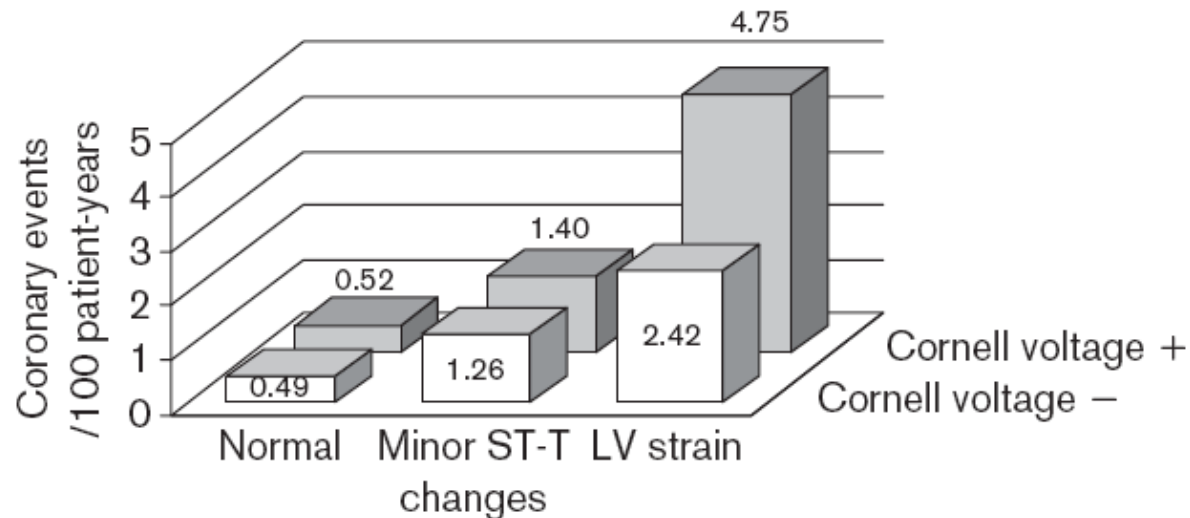
**Table 2** Clinical characteristics of study subjects with normal left ventricular repolarization, non-specific ST-T changes and typical left ventricular strain

	Normal (n = 1355)	Minor changes (n = 504)	LV strain (n = 111)
Age (years)	48.5 ± 12	53.0 ± 13*	54.3 ± 13*
Men (%)	58	43*	58†
Body mass index (kg/m <sup>2</sup> )	26.9 ± 4	26.6 ± 4	27.6 ± 4
Current smokers (%)	23	23	33†
Diabetes (%)	6	9*	12†
Duration of hypertension (years)	3.7 ± 5	4.4 ± 6	5.4 ± 7†
Office systolic BP (mmHg)	151 ± 9	158 ± 21*	167 ± 24†
Office diastolic BP (mmHg)	96 ± 10	96 ± 11	99 ± 13†
24 h systolic BP (mmHg)	133 ± 14	137 ± 17*	149 ± 21†
24 h diastolic BP (mmHg)	85 ± 10	86 ± 11	91 ± 13†
Cholesterol (mmol/l)	5.49 ± 1.1	5.65 ± 1.1*	5.73 ± 1.2
Left ventricular hypertrophy (%)	8	15*	100†
Cornell voltage (mV)	1.47 ± 0.5	1.51 ± 0.6	1.94 ± 0.8†

Except for those presented as percentages, the values are given as the mean ± SD. BP, blood pressure; LV, left ventricular. \**P* < 0.05 versus normal; †*P* < 0.05 versus normal and minor changes.

# NSST-T in Hypertension

Fig. 1



Incidence of coronary heart disease in the study population grouped by the presence or absence of increased Cornell voltage (S wave in  $V_3$  plus R wave in  $aVL \geq 2.4$  mV in men and  $\geq 2.0$  mV in women) and by left ventricular repolarization abnormalities. LV, left ventricular.

# Cardiac Memory – Gap Junction - 1

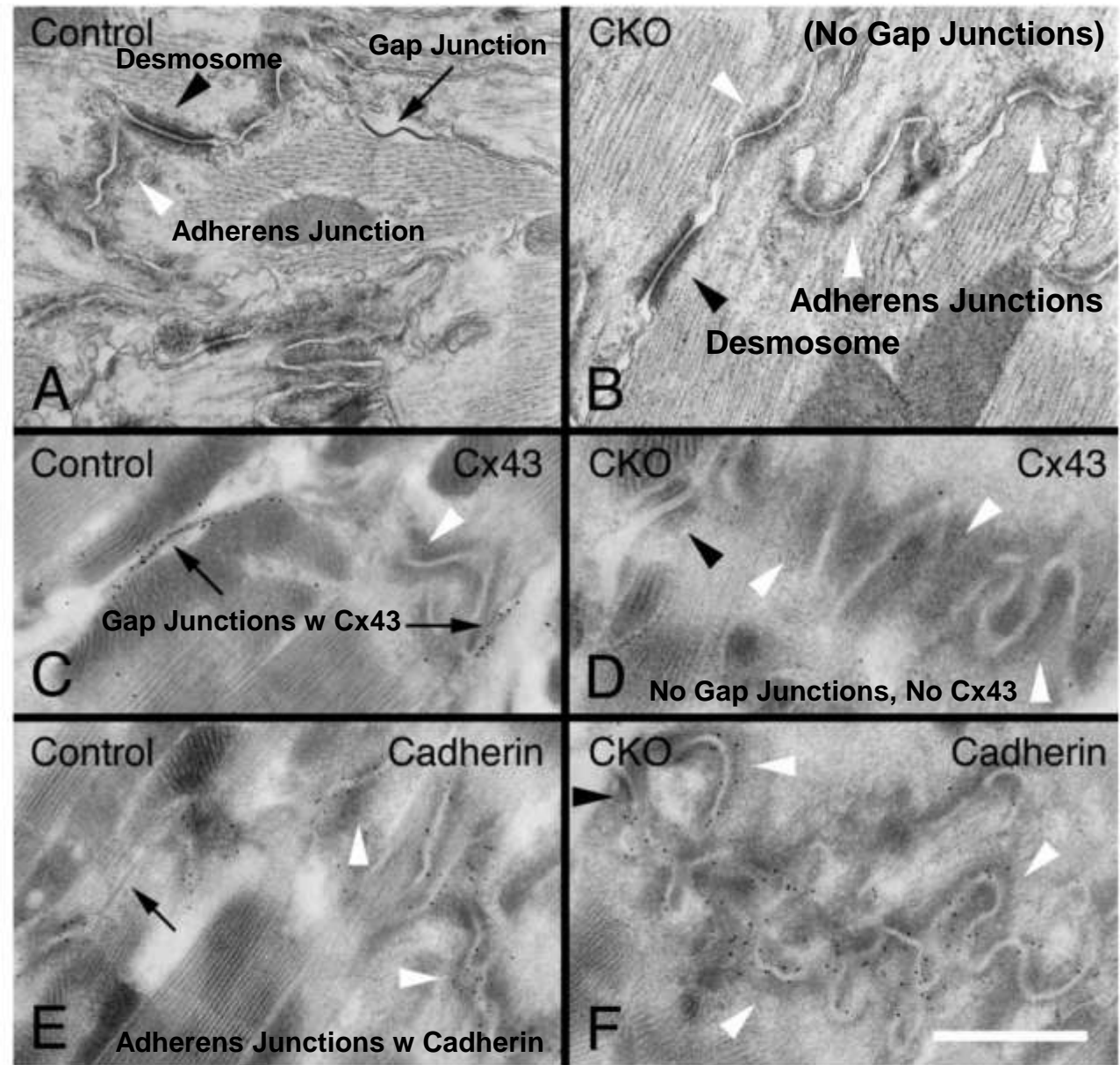
- The heart is structurally a collection of individual cells, but electrically functions as a syncytium
- The syncytial function is due to the presence of gap junctions
- A gap junction is a narrowing of the intercellular space to about 20 Angstroms
- Gap junction contains a large number of hexagonally arrayed particles
- Each particle protrudes about 14 Angstroms from the extracellular surface of the membrane, and has a pore size of about 38 Angstroms
- Each particle is a hexamer of connexin protein molecules and is called a connexon
- Each connexon is a hemichannel
- 2 hemichannels, one from each cell, dock in the extracellular space forming a gap junction channel

# Cardiac Memory – Gap Junction - 2

- Human genome contains 20 connexin isotypes, different tissues have different populations of these isotypes, and the differences are functionally very significant
- Connexin43 is most abundant in heart



# Cardiac Memory – Gap Junction Basics - 3

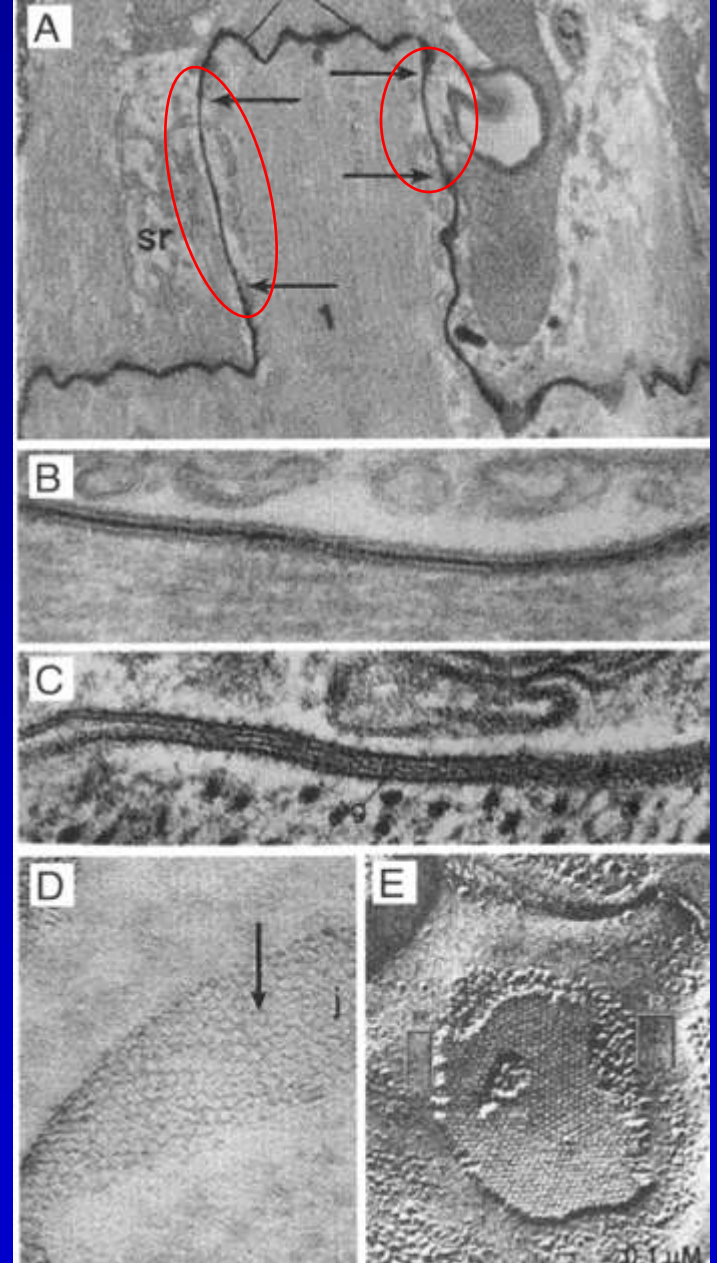


**Fig. 9.** Electron microscopy of the intercalated disc in control and CKO mice. Electron microscopy of the intercalated disc in a control mouse heart (A) shows a gap junction (arrow) in close proximity to adherens junctions (white arrowheads) and desmosomes (black arrowheads), while a representative intercalated disc in a CKO heart (B) shows no gap junctions but intact architecture of the remaining structures. Immuno-electron microscopy for Cx43 in a control heart (C) confirms the presence of Cx43 in the cardiac gap junction and demonstrates the absence of Cx43 label at the intercalated disc of a CKO mouse (D). Immuno-electron microscopy for cadherin in controls (E) and CKO hearts (F) demonstrates intact adherens junctions in both samples. Bars, 50 nm (A,B); 140 nm (C); 70 nm (D); 95 nm (E); 70 nm (F).



# Cardiac Memory – Gap Junction Basics - 4

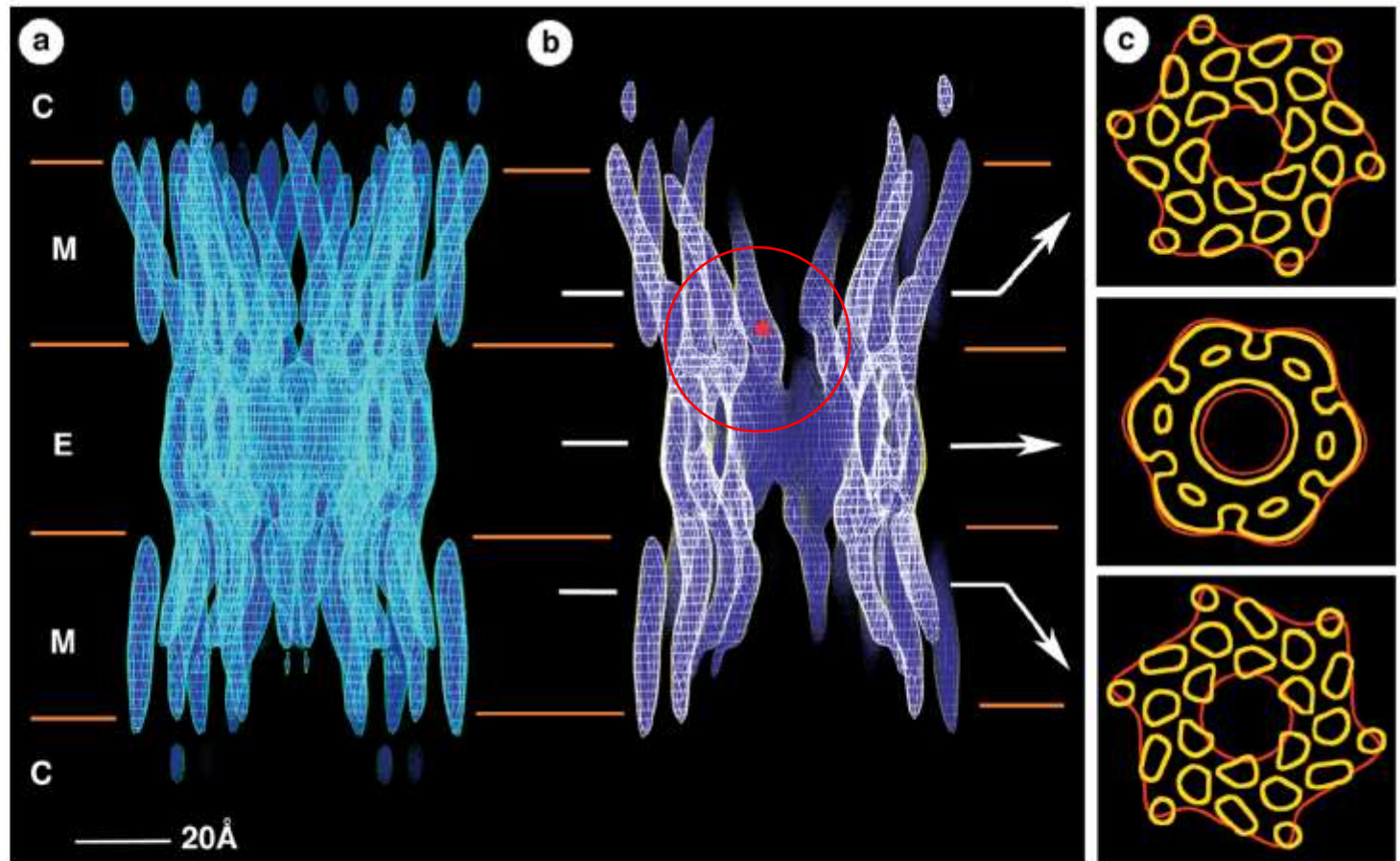
**FIGURE 8-1** ■ *A*, Longitudinal section of lanthanum-stained mouse heart showing the outline of the intercalated disc, including regions of close membrane apposition (between pairs of *horizontal arrows*). *B*, High-magnification view (200,000 $\times$ ) of a cross section of a “gap” junction showing the area of close membrane apposition in the pattern of three dense lines. *C*, Lanthanum-stained block section of mouse heart showing that the normal intercellular space is decreased to about 20 Å in the area of the junction (g). *D*, *En face* view of thin-section image of a mouse heart junction showing the hexagonally packed subunits, which later became known to be the hemichannels of the gap junction. *E*, Freeze-fracture image of a cardiac gap junction confirming the presence of particles within the junction that lie in hexagonal array, forming a junction between cells in the myocardium. (A to D, from Revel JP, Karnovsky MJ: Hexagonal array of subunits in intercellular junctions of the mouse heart and liver. *J Cell Biol* 33: C7–C12, 1967. E, from McNutt NS, Weinstein RS: The ultrastructure of the nexus. A correlated thin-section and freeze-cleave study. *J Cell Biol* 47:666–688, 1970.)



Delmar M et al. “Ch. 8: Molecular Organization and Regulation of the Cardiac Gap Junction Channel Connexin43”, pp 66-76 in Zipes and Jalife Cardiac Electrophysiology: From Cell to Bedside, 4<sup>th</sup> Ed. Saunders, 2004.

# Crystallography Cx43 Structure

**Fig. 2.** Molecular organization of a recombinant gap junction channel. (a) A full side view is shown, and (b) the density has been cropped to show the channel interior. The approximate boundaries for the membrane bilayers (M), extracellular gap (E), and the cytoplasmic space (C) are indicated. The white arrows identify the locations of (c) the cross sections that are parallel to the membrane bilayers. The red contours in (c) are at  $1\sigma$  above the mean density and include data to a resolution of 15 Å. These contours define the boundary of the connexon and can be compared to previous low-resolution structural studies of liver (16, 17) and heart (20) gap junctions. The yellow contours at  $1.5\sigma$  above the mean density include data to a resolution of 7.5 Å. The roughly circular shape of these contours within the hydrophobic region of the bilayers is consistent with 24 transmembrane  $\alpha$  helices per connexon. The maps in (a) and (b) were contoured at  $3\sigma$  above the mean, which tends to eliminate density that is less well defined, such as the cytoplasmic domains visualized in Fig. 3a, which are contoured at  $1.5\sigma$  above



the mean. The red asterisk in (b) marks the narrowest part of the channel where the aqueous pore is  $\sim 15$  Å in diameter, not accounting for the contribution of amino acid side chains that are not resolved at the current limit of resolution. The noncrystallographic twofold symmetry that relates the two connexons of a gap junction channel has not been applied to the map. Hence, the similarity of the two connexons provides an independent measure of the quality of this reconstruction.

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# Cardiac Memory

- Definition: Altered T wave during sinus rhythm, induced by prior alteration in ventricular depolarization
  - Ventricular pacing
  - Intermittent BBB
  - Ventricular tachycardia
  - Pre-excitation
- Short term (seconds to minutes) and long term (days to weeks) memory both exist and probably are due to different mechanisms, similar to CNS short term and long term memory

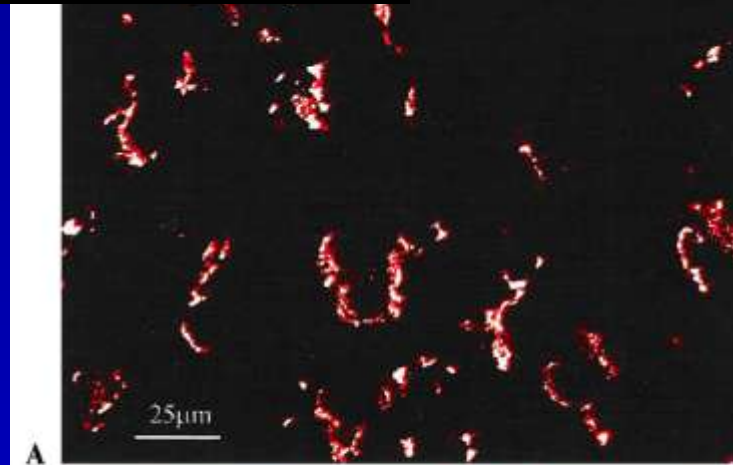


# Cardiac Memory - Mechanisms

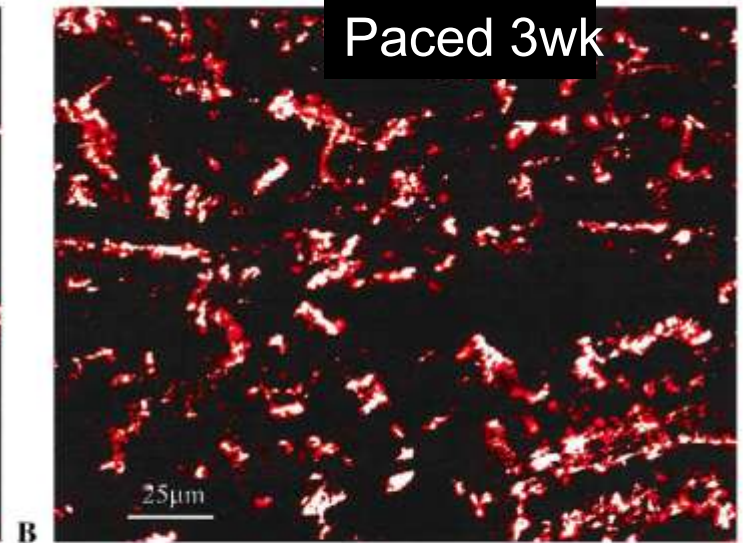
- Decrease in epicardial  $I_{to}$  (endocardium has less of this current) gives taller and longer plateau and smaller notch (reduced Kv4.3 gene expression for the alpha subunit and reduced KChIP2 gene expression for an accessory subunit)
- Change in the current of the large calcium channel ( $I_{Ca,L}$ ) current: nifedipine blocks this channel and blocks short term memory, and also channel kinetics are changed
- Connexin 43 (Cx43) is the major ventricular gap junction protein and it is redistributed and also diminished by change in depolarization
- Angiotensin II blockade also decreases cardiac memory, probably through changes in the calcium channel
- Changes in protein transcription are also likely involved, but this hypothesis is still being tested and refined

# Redistribution of Cx43

Control, Cx43 is in intercalated discs at transverse cell abutments



Paced 3wk



Paced 3wk, Cx43 in clusters along longitudinal borders



**Figure 2.** Confocal micrographs of the epimyocardial layer of the anterior left ventricular wall (~1 cm from pacing site) immunolabeled for connexin43, from an unpaced control animal (A) and from an animal paced for 21 days (B,C). All micrographs are of longitudinally sectioned myocardium, with the long axis of the constituent cells running horizontally, as clearly visible on overlaying immunoconfocal imaging with incident light interference microscopy (C). The transversely oriented clustering of connexin43 label confined to the intercalated discs at the transverse cell abutments in panel A is characteristic of normal ventricular myocardium (score 1 on the visual scale; see Results and Table 2). Panels B and C are illustrative examples of the abnormal pattern of connexin43 label distribution, with a significant proportion of the label spread in clusters along the longitudinal borders of the myocytes (score 4). Panels A and B are projection images of confocal optical slices spanning 5-μm depth of tissue, through which there is considerable overlapping of the labeling within the intercalated discs viewed edge on, particularly in panel A.

# Redistribution of Cx43

Angiotensin II has  
a role in synthesis  
and regulation of  
connexins

Connexins bind to  
proteins  
intracellularly,  
possibly regulating  
function

Patel PM et al. J  
Cardiovasc  
Electrophysiol.  
2001;12:570.

TABLE 2			
Visually Assessed Scores of Distribution of Connexin43 Label in LV Myocardial Layers Close to Pacing Site			
	Epi	Mid	Endo
Control			
Unoperated			
A	1	3	1
B	2	2	3
C	1	3	1
D	1	2	2
E	3	2	1
Sham-operated			
F	1	1	2
G	2	2	1
H	1	2	1
Mean	1.5	2.1	1.5
Paced			
I	4	2	1
J	4	1	1
K	4	2	2
L	3	2	1
M	5	—	1
Mean	4.0	1.7	1.2

A to H are control dogs (F, G, and H were sham-operated), and I to M are paced dogs (scale 1 to 5, where 1 = confined to transverse clusters and 5 = confined to longitudinal clusters).  
Endo = endomyocardium; Epi = epimyocardium; Mid = mid-myocardium.

# Redistribution of Cx43

**TABLE 3**

Relative Densitometric Quantification of Band Intensity of Western Blots of Connexin43 Expression in LV Myocardial Layers of Paced and Control Dogs

	Near to Pacing Site			Distant from Pacing Site		
	Epi	Mid	Endo	Epi	Mid	Endo
Control						
Unoperated						
A	59.8	82.9	102.8	64.7	83.0	58.0
B	100.0	96.2	136.7	86.1	123.3	108.4
C	178.3	49.4	79.3	52.2	40.4	66.5
D	101.8	99.7	118.0	99.9	80.2	102.0
E	96.0	90.2	109.3	74.4	73.4	91.7
Mean	107.2	83.7	109.2	75.5	80.0	85.3
SD	43.3	20.2	21.0	18.5	29.5	22.1
Sham-operated						
F	91.7	101.9	95.3	81.1	91.2	87.6
G	85.5	63.0	52.4	93.9	104.4	119.1
H	93.7	126.6	142.8	129.9	135.5	86.9
Mean	91.3	97.2	96.8	101.7	110.4	97.8
SD	4.3	32.1	45.2	32.28	22.73	18.37
Paced						
I	85.3	133.5	96.1	103.6	51.8	99.8
J	55.2	94.7	78.3	82.1	70.5	50.9
K	74.3	64.5	89.4	97.7	72.6	97.6
L	74.8	82.3	109.1	82.0	59.5	151.8
M	65.3	130.7	119.7	100.1	94.6	128.1
N	40.4	88.8	37.5	94.0	99.6	126.4
O	36.7	113.3	49.1	92.7	98.4	114.6
Mean	61.7*	101.1	82.8	93.2	78.1	109.8
SD	18.4	25.7	30.2	8.4	19.5	31.9

Values are corrected for protein loading using the actin band on a coomassie stained gel run in parallel.

\* Significant reduction compared with sham-operated ( $P < 0.01$ ), unoperated ( $P < 0.05$ ), or combined control groups ( $P < 0.02$ ).

p=0.18

# Cardiac Memory

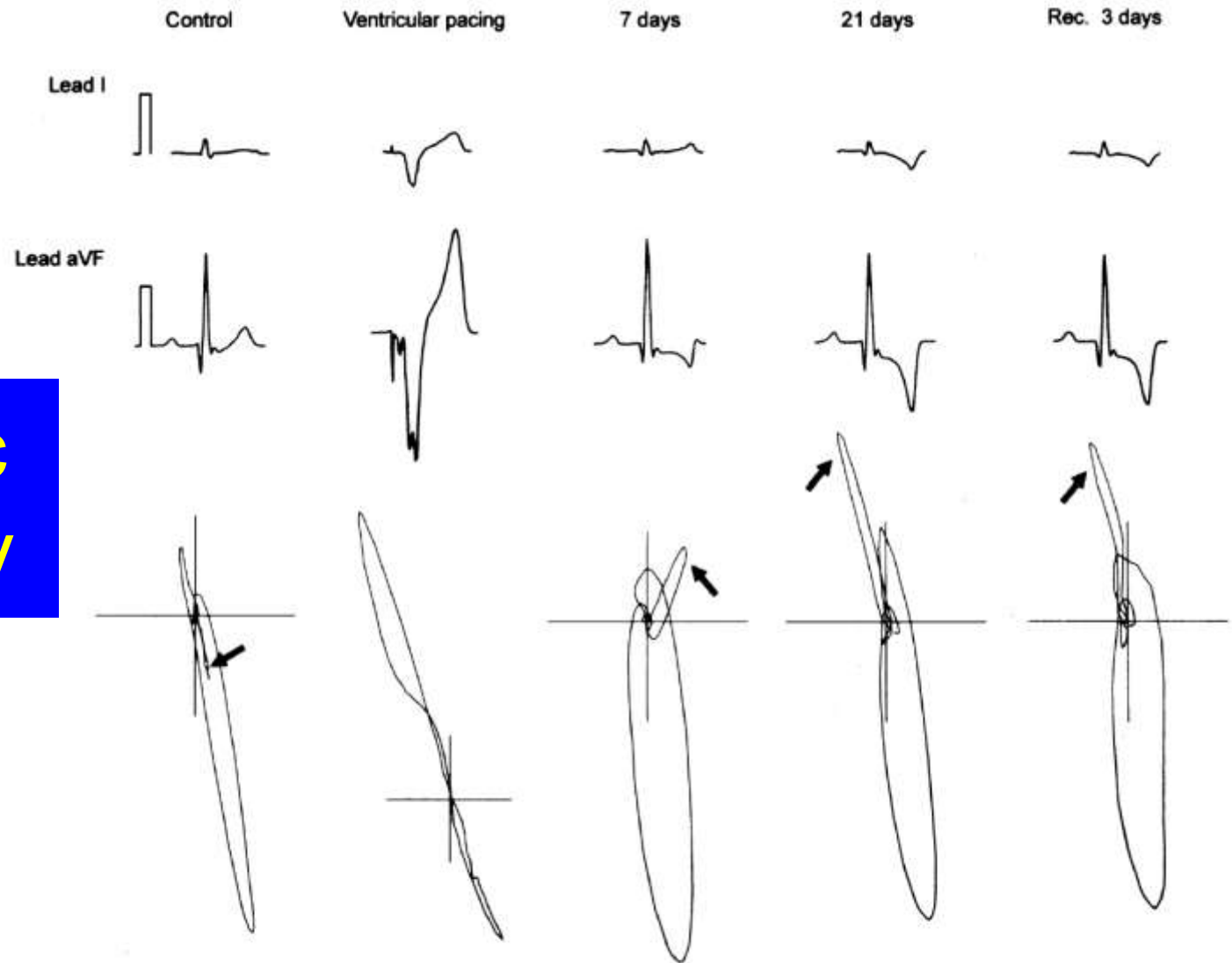


Fig. 1. Evolution of cardiac memory. Top: leads I and aVF of canine ECG in control (before ventricular pacing), during ventricular pacing, and 1 h after discontinuing pacing on days 7 and 21 (last day of pacing), and during recovery on day 3 after pacing was permanently discontinued (Rec). Paper speed, 25 mm/s; calibration, 1 mV. Bottom: frontal plane VCG from same animal. Crosshairs, 0.5 x 0.5 mm. Arrow indicates T-wave vector during sinus rhythm. Note evolution of a T-wave vector that tracks the paced QRS vector, as well as persistence of the day 21 T-wave and vector over 3 d after cessation of pacing (adapted from Yu et al. [14]).



# Cardiac Memory

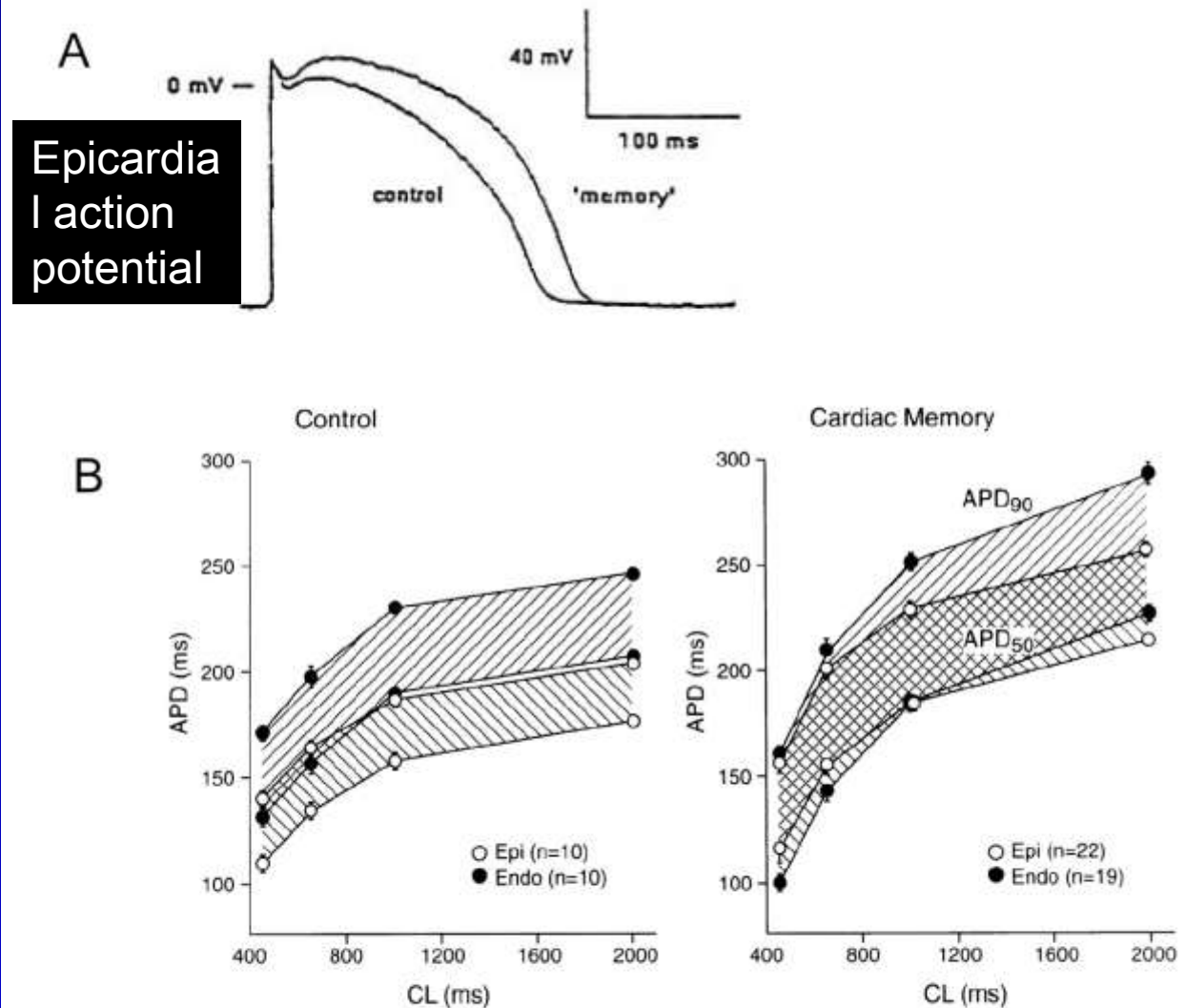
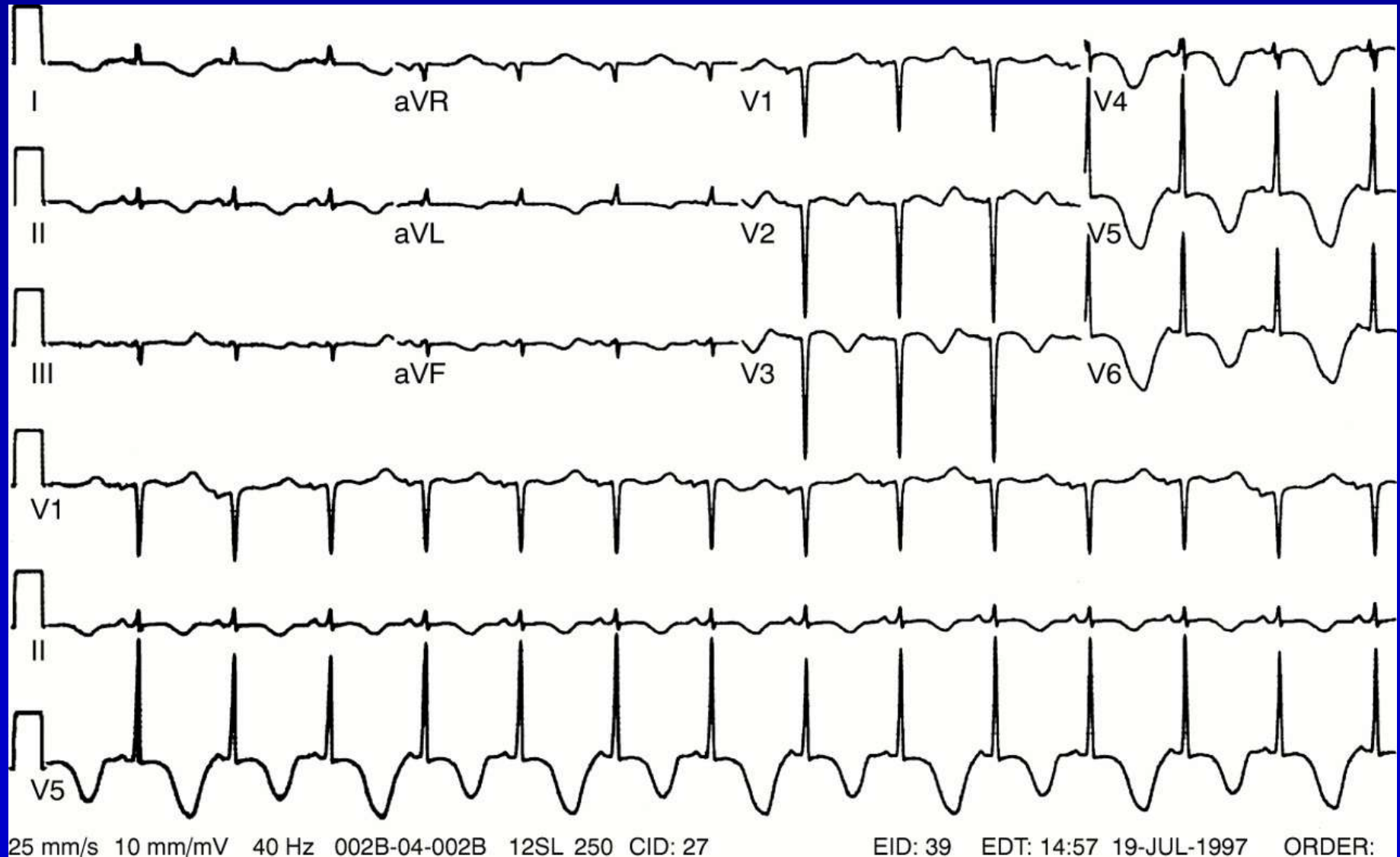


Fig. 3. Action potential characteristics and transmural left ventricular gradients in long-term cardiac memory. (A) Superimposed examples of epicardial action potentials from a control dog and a dog paced for 20 d to induce memory. Note that although maximum diastolic potential is identical in both, in the setting of memory, notch and plateau are more positive and APD is longer. Basic cycle length (BCL) = 650 ms (Adapted from Yu et al. [14]). (B) APD to 50% (APD<sub>50</sub>) and 90% (APD<sub>90</sub>) repolarization measured from epicardium (Epi) and endocardium (Endo) of LV in a control dog and a dog with cardiac memory. Preparations were paced over a range of cycle lengths (CL; horizontal axis) from 2000 to 400 ms. The shaded areas are those inscribed between APD<sub>50</sub> and APD<sub>90</sub> of the epicardial and endocardial preparations. In the control dog at almost all cycle lengths, almost all values for endocardium differ from those at corresponding cycle lengths in epicardium ( $P < 0.05$  for all). In the memory dog, statistical significance ( $P < 0.05$ ) was seen only for APD<sub>90</sub> at the two longest cycle lengths (adapted from Shvilkin et al. [10]).

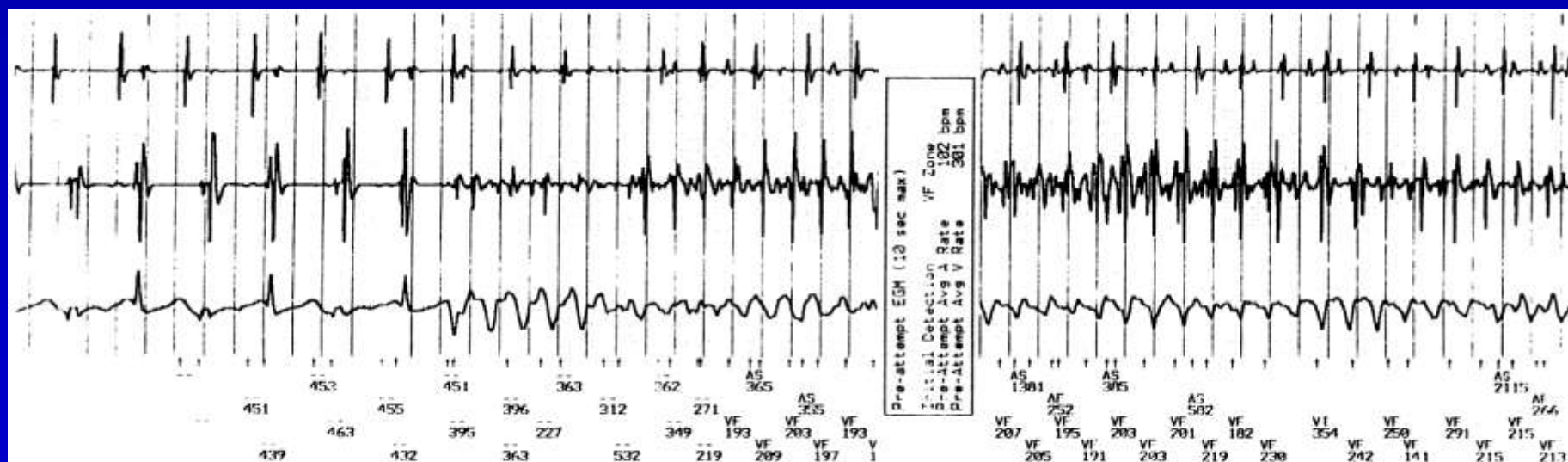
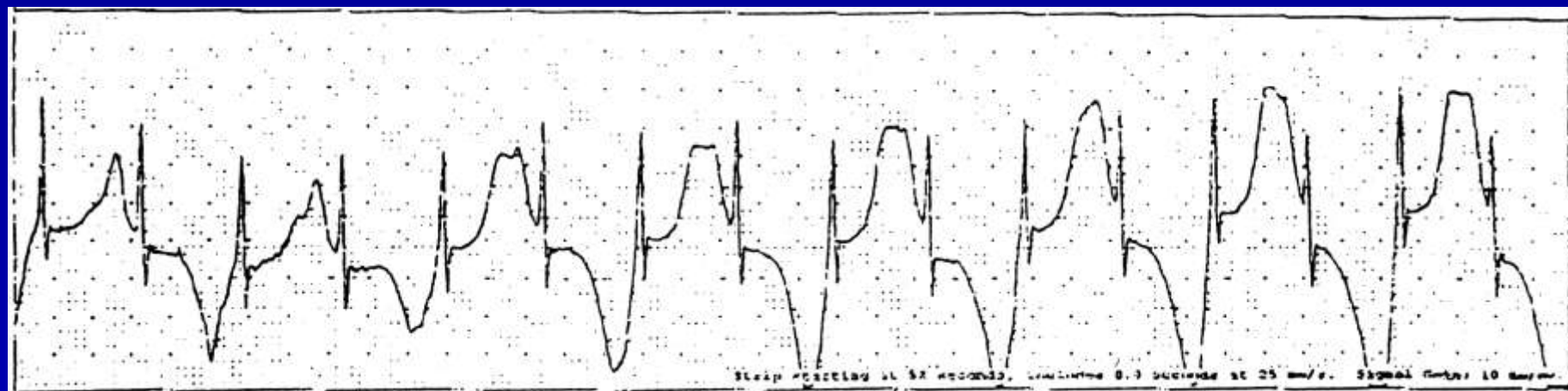
# Surawicz: T Wave Alternans

- Frequently associated with abrupt rate changes or prolonged QT interval
- Longer QT interval, longer the shortest cycle length at which alternans can occur
- Long QT interval also frequently reflects the presence of a substrate predisposing to torsade de pointes
- T wave alternans dependent on critical shortening of diastolic interval - frequently manifests when duration of action potential approaches or exceeds the cycle length
- Clinical associations: congenital long-QT syndrome, hypocalcemia, quinidine, hypokalemia, hypokalemia with hypocalcemia and hypomagnesemia, cardiomyopathy associated with hypomagnesemia after defibrillation, or unexplained

46 yo hypertensive woman with right hemispheric stroke and mass effect. Subsequent VF resuscitation.

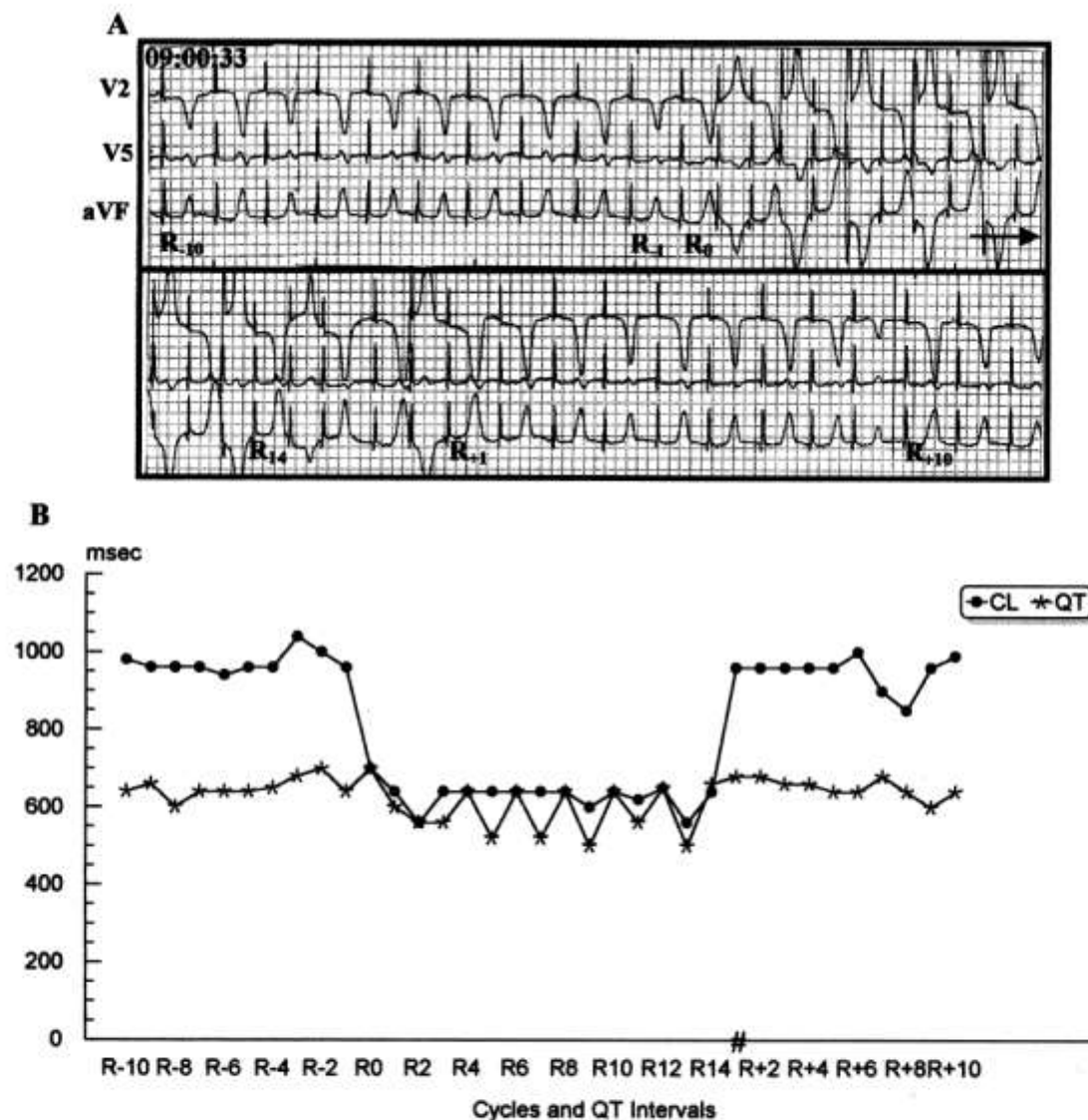


36 yo woman with “seizures” since childhood, son with syncope and prolonged QT, during anxious and hyperventilation on event monitor.

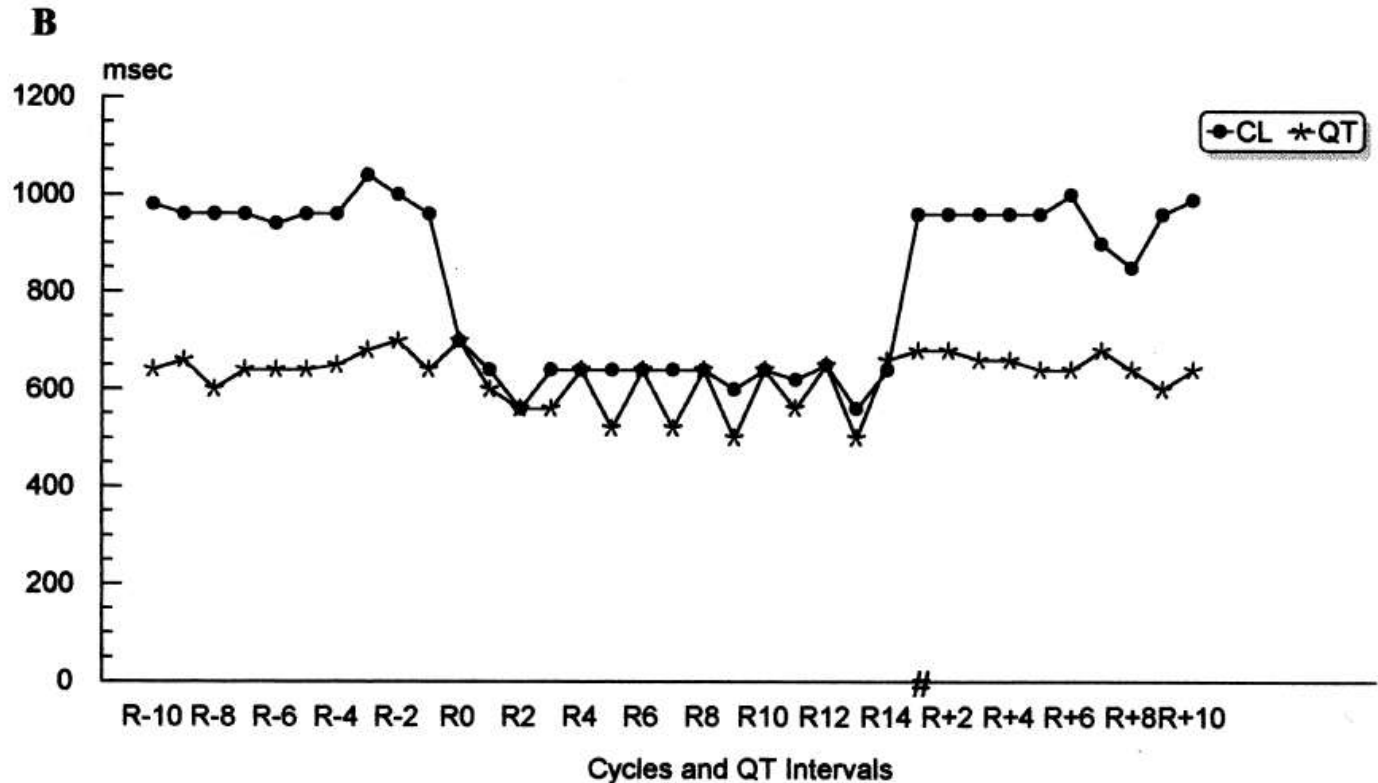
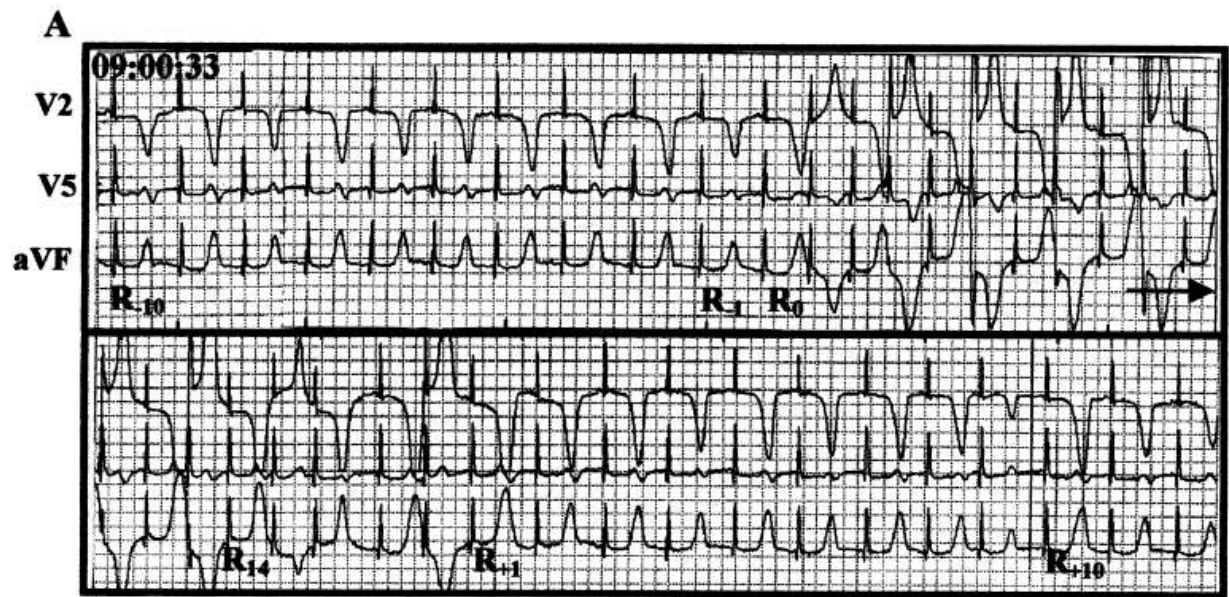


8 months later, during stressful situation, required multiple shocks





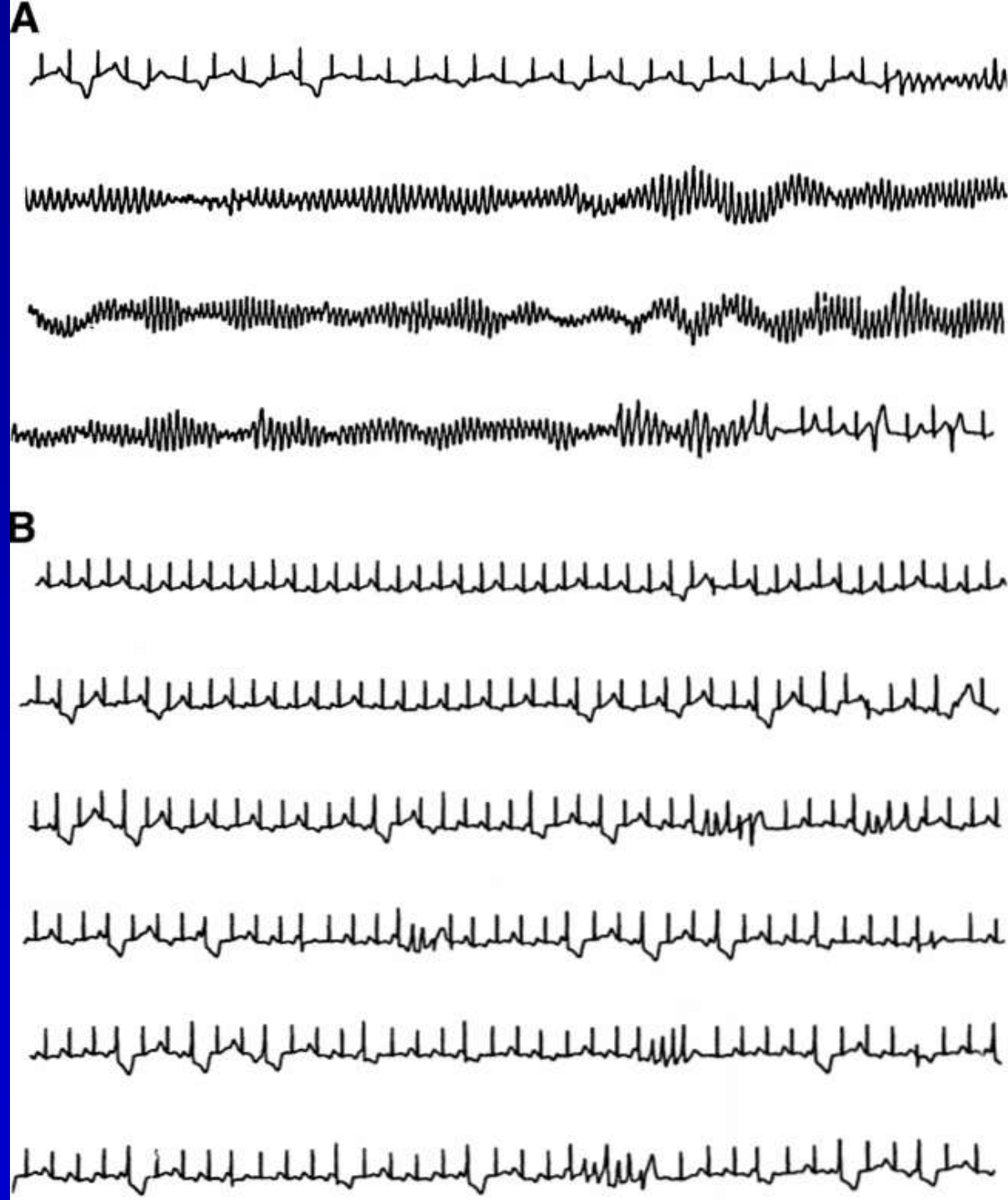
**Figure 1.** A typical episode of T-wave alternans (Case 1). (A)  $R_{(-)}$  refers to the 10 cycles immediately preceding the alternans episode (from  $R_{-10}$  to  $R_{-1}$ ).  $R$  refers to the alternans cycles ( $R_0$ , onset, and  $R_{+10}$ , the last measured alternans cycle).  $R_{(+)}$  refers to the 10 cycles immediately succeeding alternans episode ( $R_{+1}$ , the first, and  $R_{+10}$  the last cycle measured). (B) Graph showing the sequence of these cardiac cycles. Note that the alternans cycles (from  $R_0$  to  $R_{+10}$ ) are expressively shorter than the preceding and succeeding cycles. At the bottom (asterisk), a nice demonstration is shown of concomitant great variability of QT intervals, while TWPA is depicted. The transition of the last cycle of alternans and the first cycle after alternans is not continuous.



Cruz Filho FES et  
al. J Am Coll  
Cardiol  
2000;36:167.

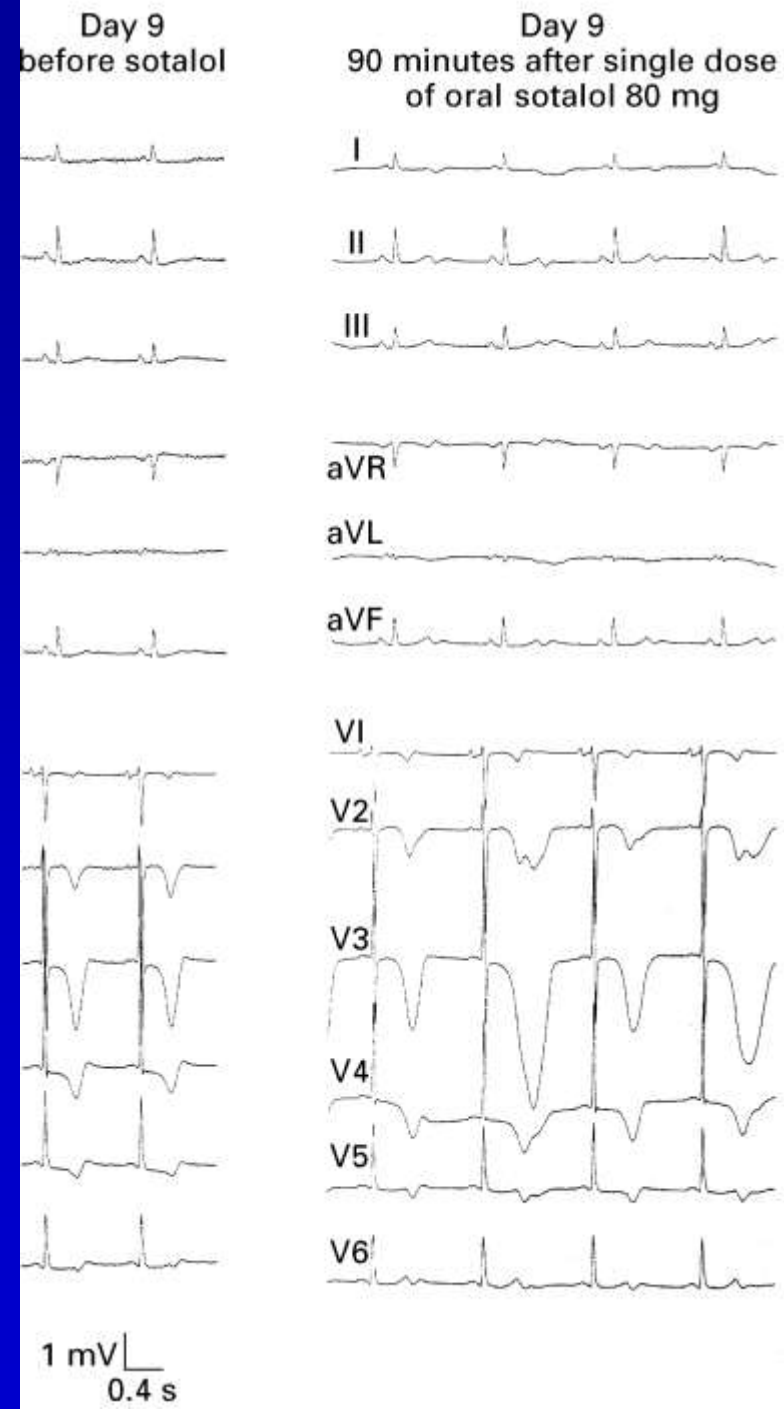
72 yo woman with multiple syncopal episodes with cardiac arrest in hospital waiting room. Subsequent Holter recording. ICD not available. SCD 4 months later.

Panel B: 3 minutes later



Armoundas AA et al.  
Circulation 2000;101:2550.

64 yo woman with paroxysmal AF  
reverted to NSR with 100 mg flecainide.  
Syncope one day after sotalol started.





53 yo woman taking fluoxetine for 16 mo suffered syncope twice in 48 h.

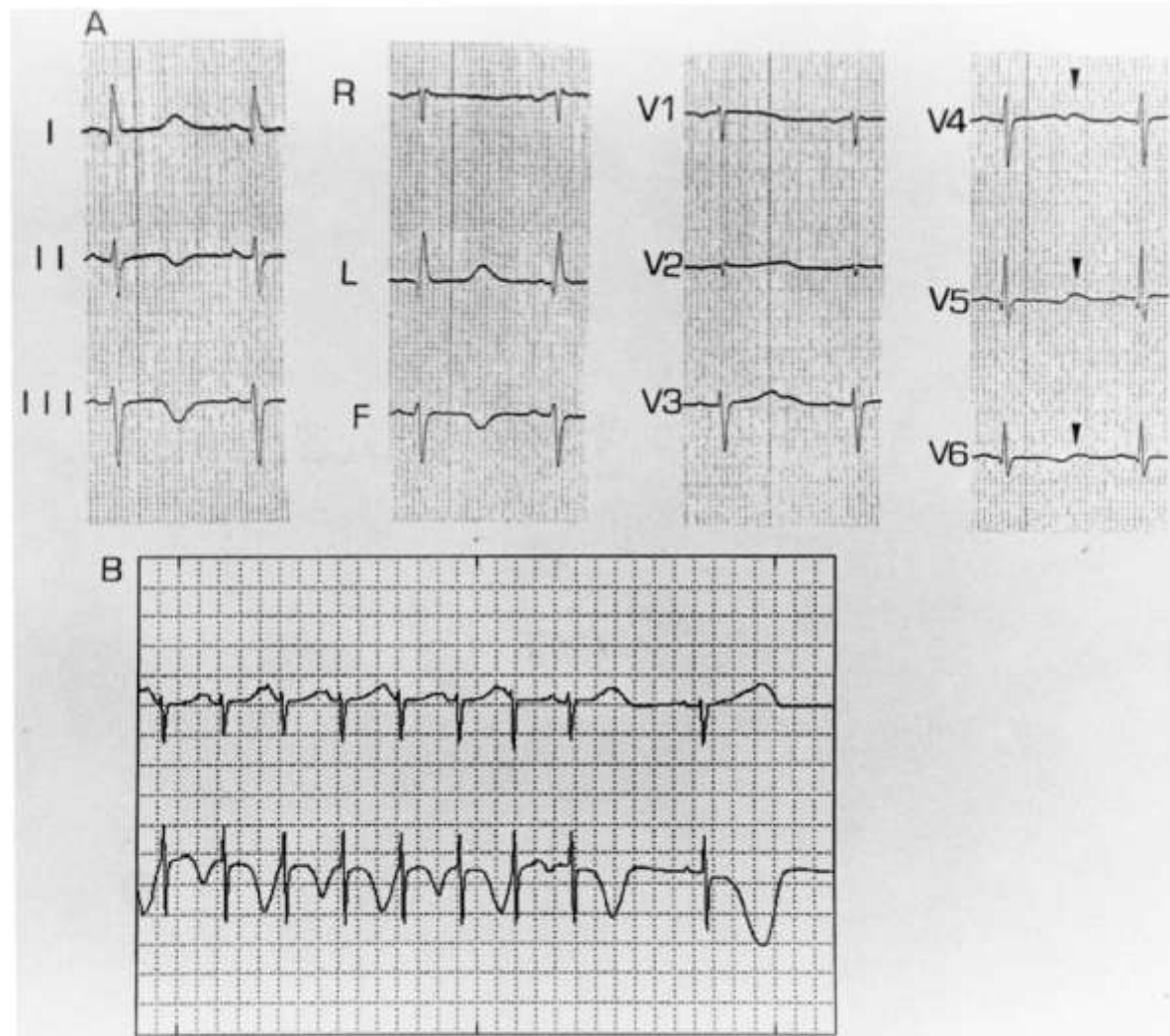
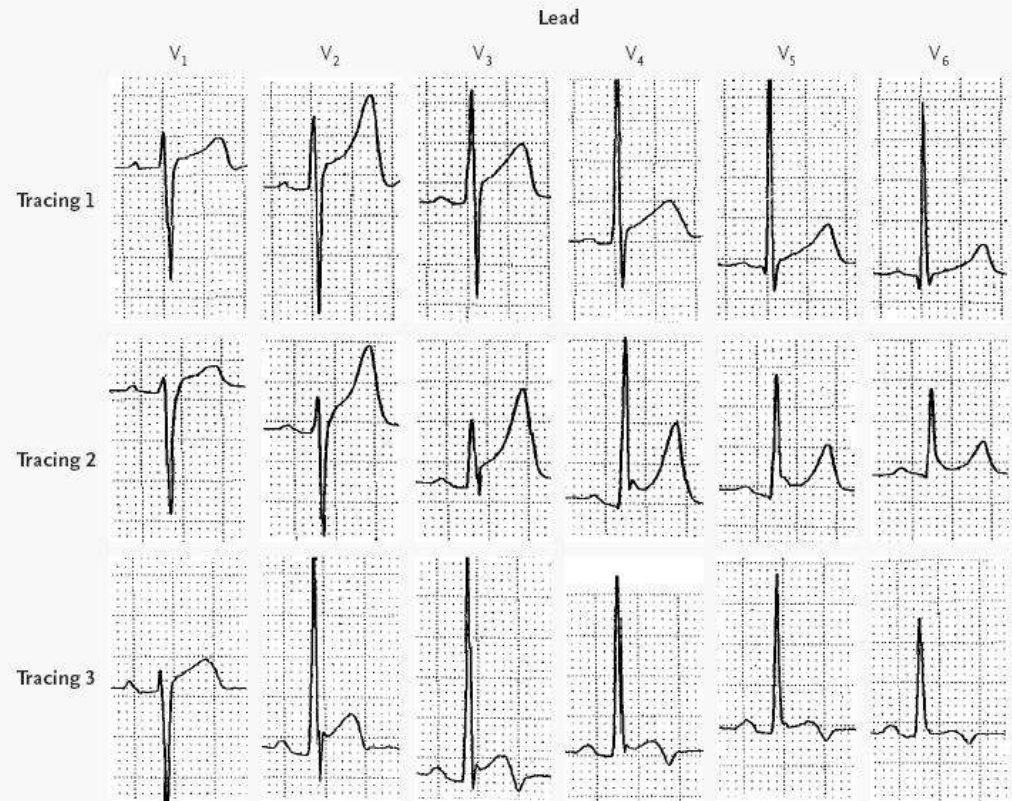


Fig. 1. (A) ECG on admission. The sinus rate is 65 beats/min, and the QTU interval is prolonged at 600 ms. U waves are marked by arrows. (B) Holter recording showing grossly distorted T waves. When the sinus rate increases to 100 beats/min, the QT interval (600 ms) equals the RR interval (the diastolic resting period is zero) and T wave alternans ensues.

# T Wave Alternans

- NOT pulsus alternans or electrical alternans
- T wave alternans has been associated with increased mortality since 1948 (in 5 of 6059 patients)
- Clinical associations: myocardial ischemia, coronary spasm, electrolyte disturbances, congenital long QT (chronotropic or metabolic stress)
- Intracellular calcium cycling plays a key role
- Discordant T wave alternans: some parts of the ventricle have longer AP duration on the same beat in which other parts have shorter duration
- Microvolt T wave alternans, MTWA, (computer algorithms), induce by increasing HR (pacing, but exercise is prognostically important in coronary disease with depressed LVEF); every patient has a HR above which MTWA appears, and in normal subjects the HR is >110

# Causes of ST Elevation - Normal

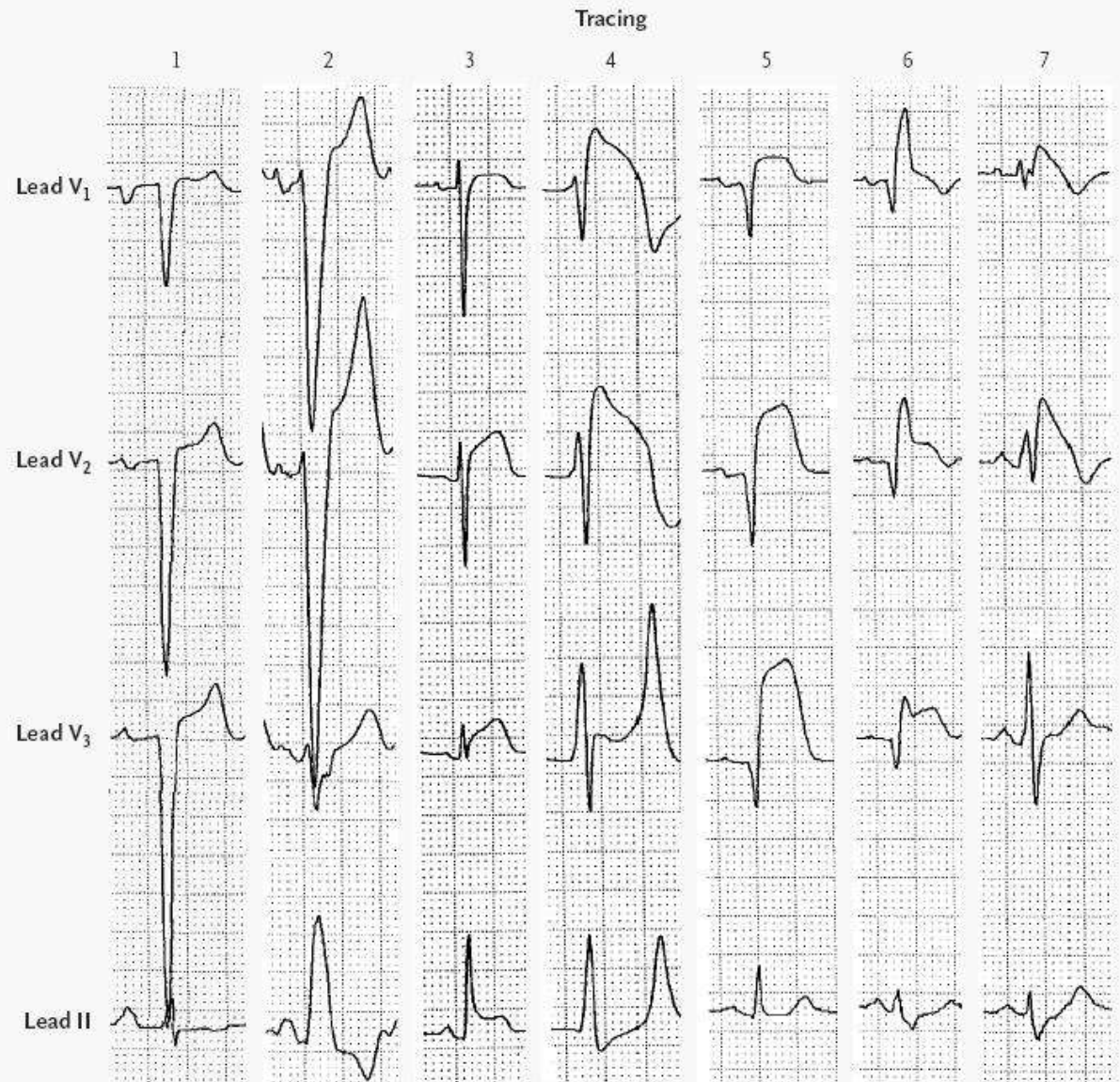


**Figure 1.** Electrocardiograms Showing Normal ST-Segment Elevation and Normal Variants.

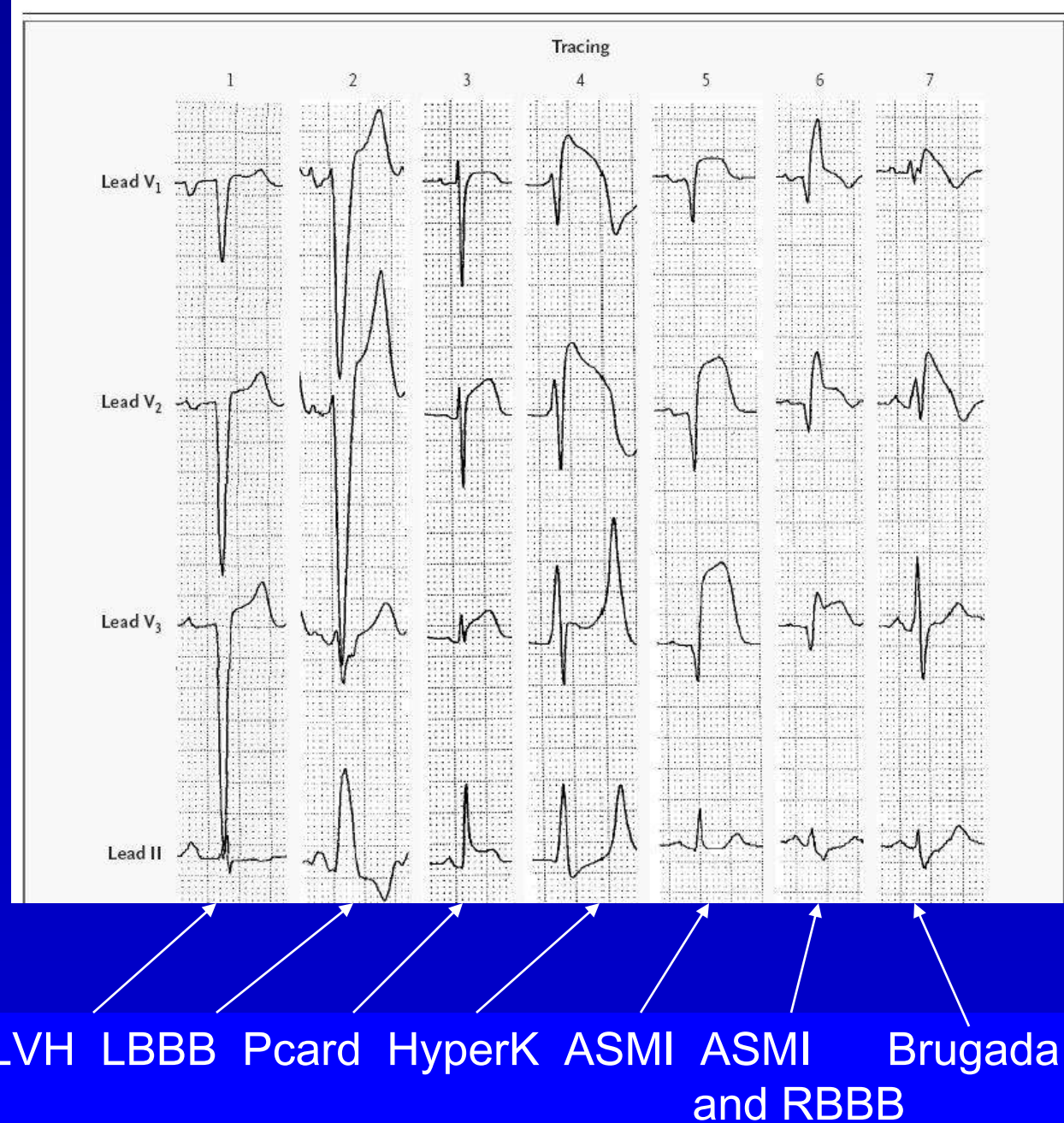
Tracing 1 shows normal ST-segment elevation. Approximately 90 percent of healthy young men have ST-segment elevation of 1 to 3 mm in one or more precordial leads. The ST segment is concave. Tracing 2 shows the early-repolarization pattern, with a notch at the J point in V<sub>4</sub>. The ST segment is concave, and the T waves are relatively tall. Tracing 3 shows a normal variant that is characterized by terminal T-wave inversion. The QT interval tends to be short, and the ST segment is coved.



# Causes of ST Elevation

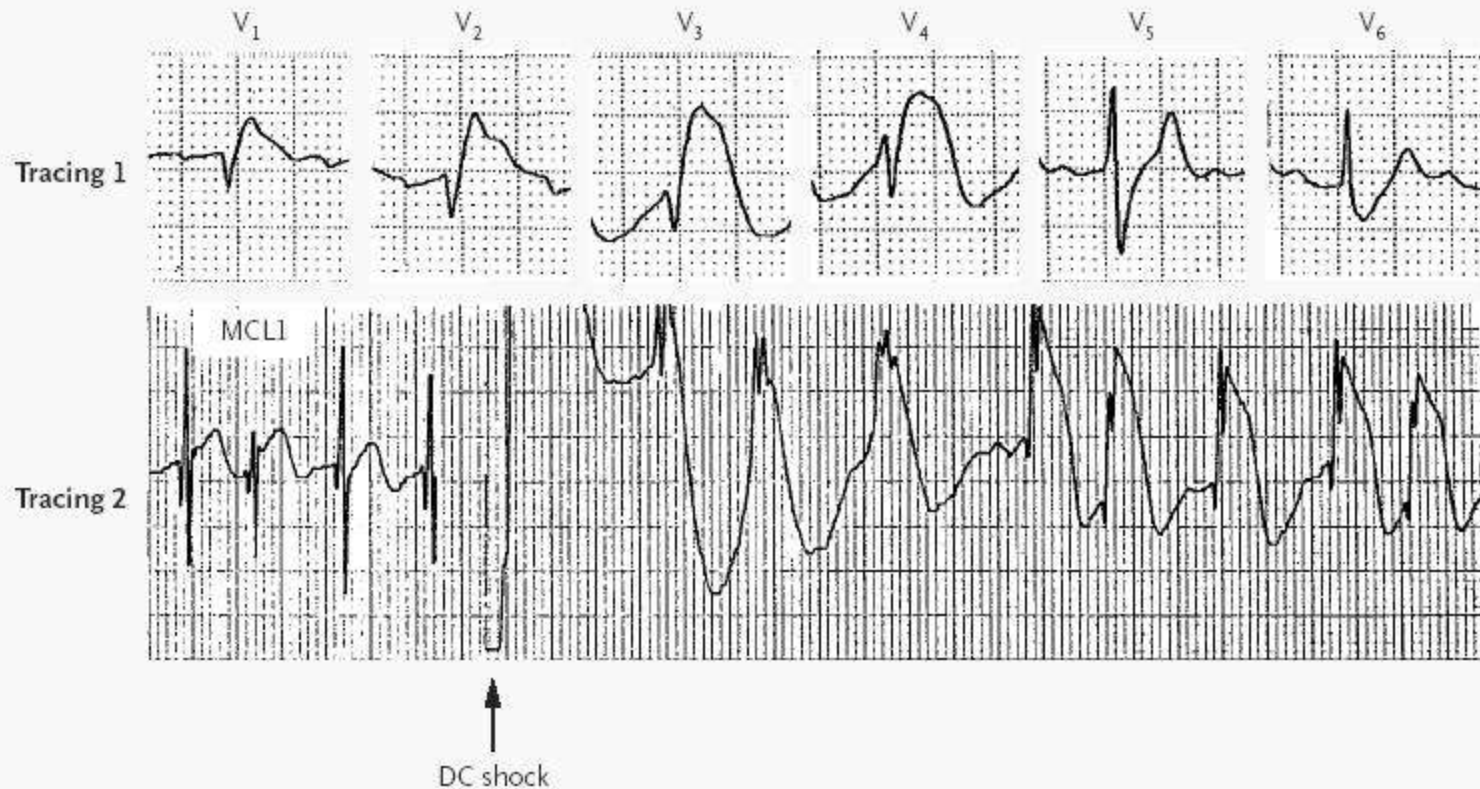


# Causes of ST Elevation





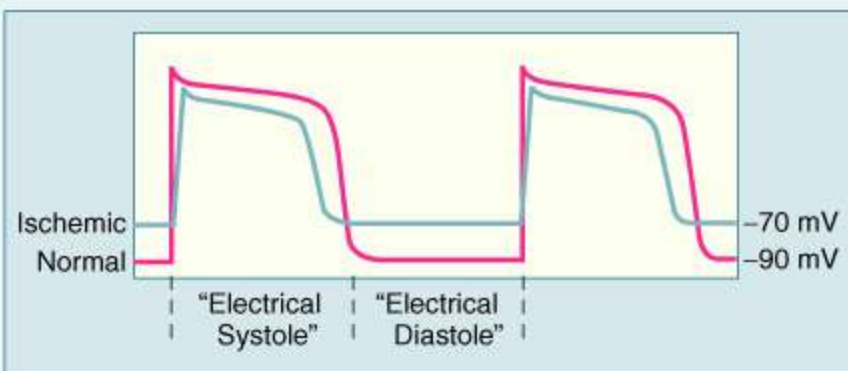
# Causes of ST Elevation – Pulmonary Embolism



**Figure 3.** Electrocardiograms from a Patient with Massive Pulmonary Embolism Who Had a Normal Coronary Angiogram (Tracing 1) and a Patient with Transient ST-Segment Elevation Immediately after Direct-Current (DC) Countershock to the Precordium (Tracing 2).

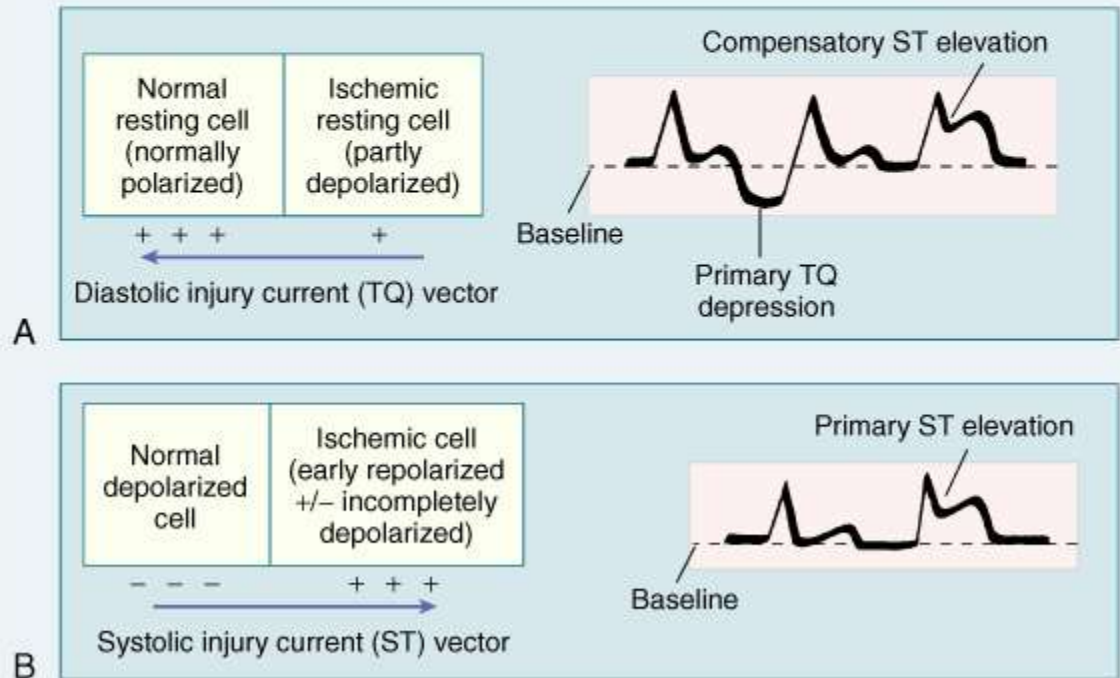
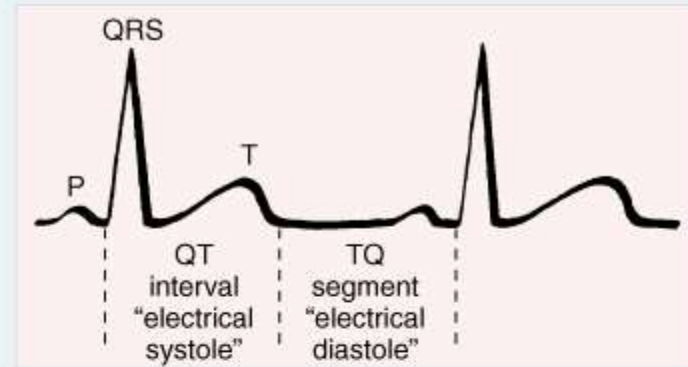


# Mechanism of ST Elevation



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- Classic theory
  - Current of Injury could be systolic (shorter AP duration of ischemic cell, lower slope of phase 0, or lower peak amplitude) or diastolic (lower resting potential of ischemic cell)

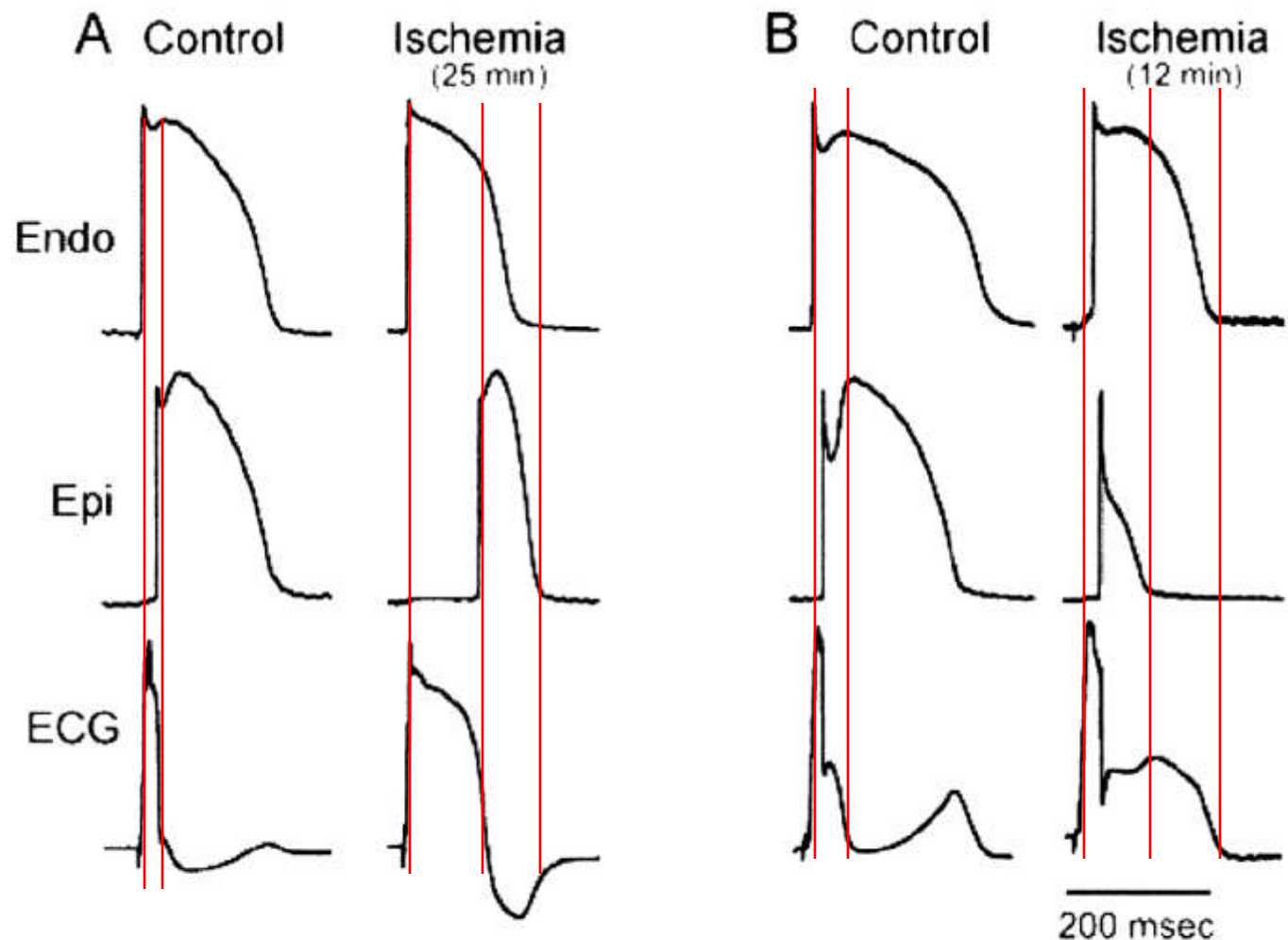


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# Mechanism of ST Elevation

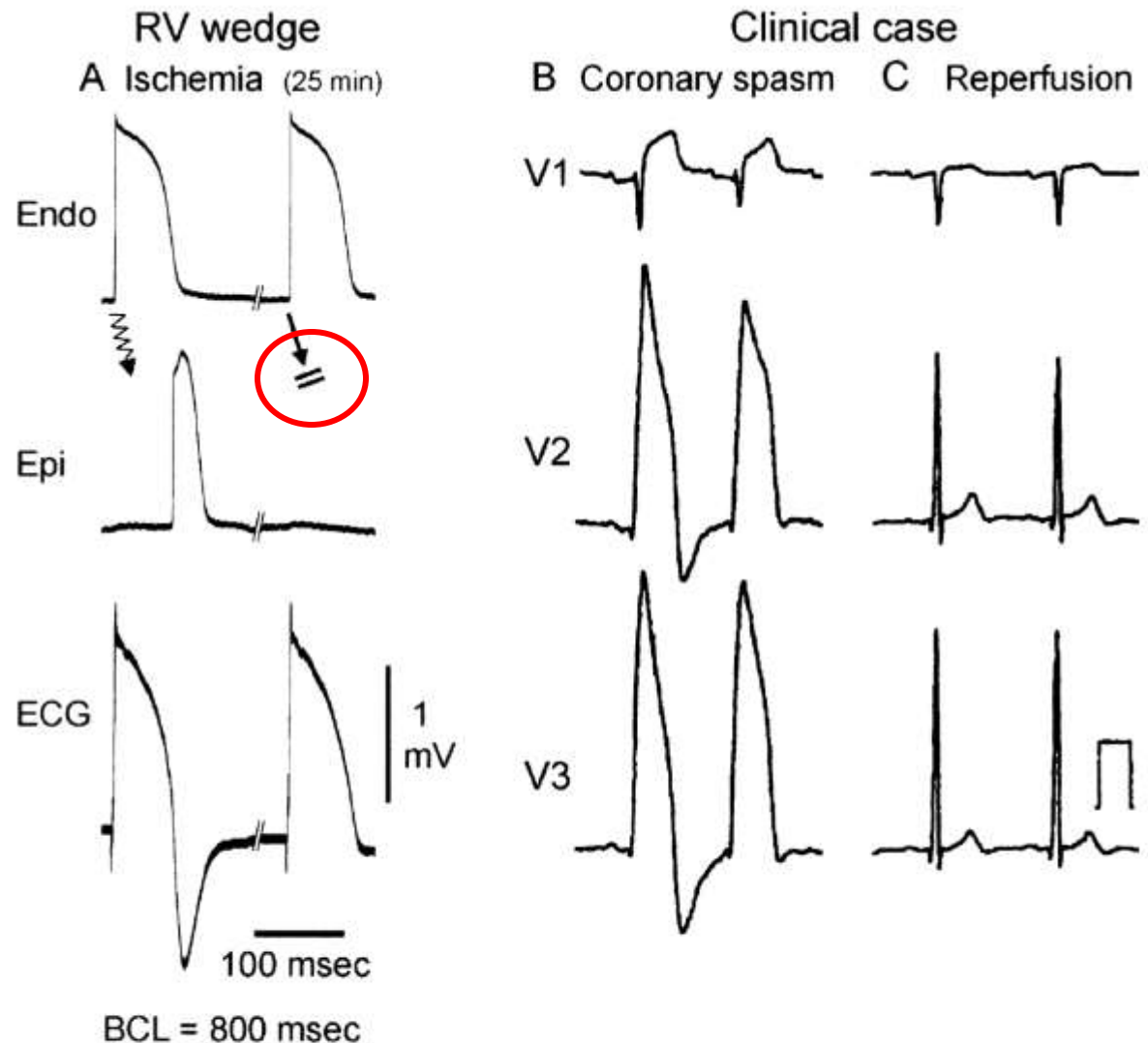
- Information in canine wedge preparations
- Possibly very slow transmural progression of depolarization
- Possibly loss of epicardial dome and very short epicardial action potential
- T inversion may be delayed depolarization of epicardium
- Here is the data – Dr. Moody is not sure whether it is clinically relevant

# Mechanism of ST Elevation



**Fig. 1.** Electrophysiologic effect of ischemia in the ventricular wedge model. Results are from 2 different preparations. Each panel shows (from top to bottom) simultaneous recordings of transmembrane action potentials from endocardium (Endo) and epicardium (Epi) and the ECG recorded across the bath along the same axis. (A) Recordings obtained under control conditions and after 25 minutes of ischemia. (B) Recordings obtained under control conditions and after 12 minutes of ischemia. BCL= 800 ms. Two distinctly different mechanisms involving 1) markedly delayed transmural conduction and 2) loss of the epicardial action potential dome underlie the apparent ST-segment elevation encountered during acute ischemia.

# Mechanism of ST Elevation

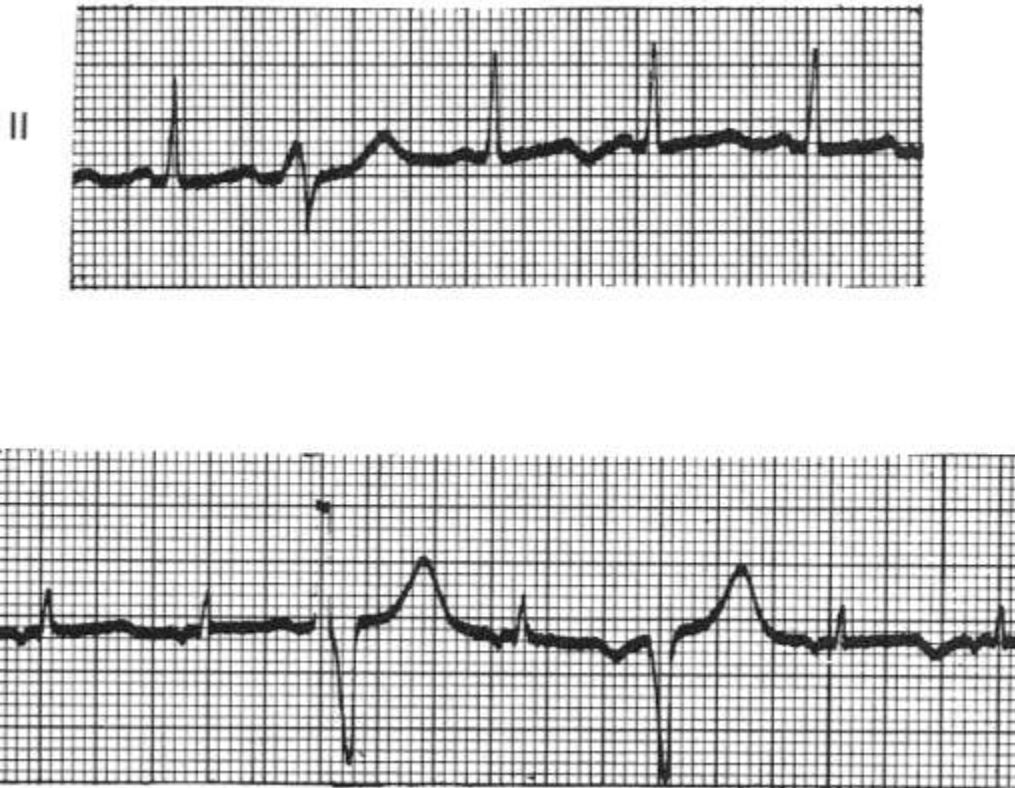


**Fig. 2.** Ischemia-induced tombstone morphology accompanied by T-wave alternans. (A) Recording from arterially perfused right ventricular wedge preparation after 25 minutes of ischemia. Shown are 2 consecutive beats at a BCL of 800 ms. Delayed transmural conduction gives rise to an apparent ST-segment elevation (tombstone morphology) and negative T wave. In the following beat, intramural conduction block leads to manifestation of a wide QRS, but disappearance of the T wave. (B) Clinical example of the tombstone effect and T-wave alternans appearing in the right precordial leads after vasospastic ischemia (C) Normalization of the ECG after spontaneous reperfusion [B and C are reprinted with permission (7)].

# Postextrasystolic Changes

- Occasional primary T wave change in the first and sometimes also the second or third postextrasystolic beat
- Cause unknown
- Association with prolonged QT
- Apparently more frequent in patients with heart disease
- Reason for this association is not obvious

# Postextrasystolic Changes



**Figure 23-7.** Postextrasystolic T wave inversion in a person with no evidence of heart disease and a normal ECG except for premature ventricular complexes. (From Surawicz B: ST-T abnormalities. In MacFarlane PW, Lawrie TD (eds): Comprehensive Electrocardiology. New York, Pergamon, 1989.)

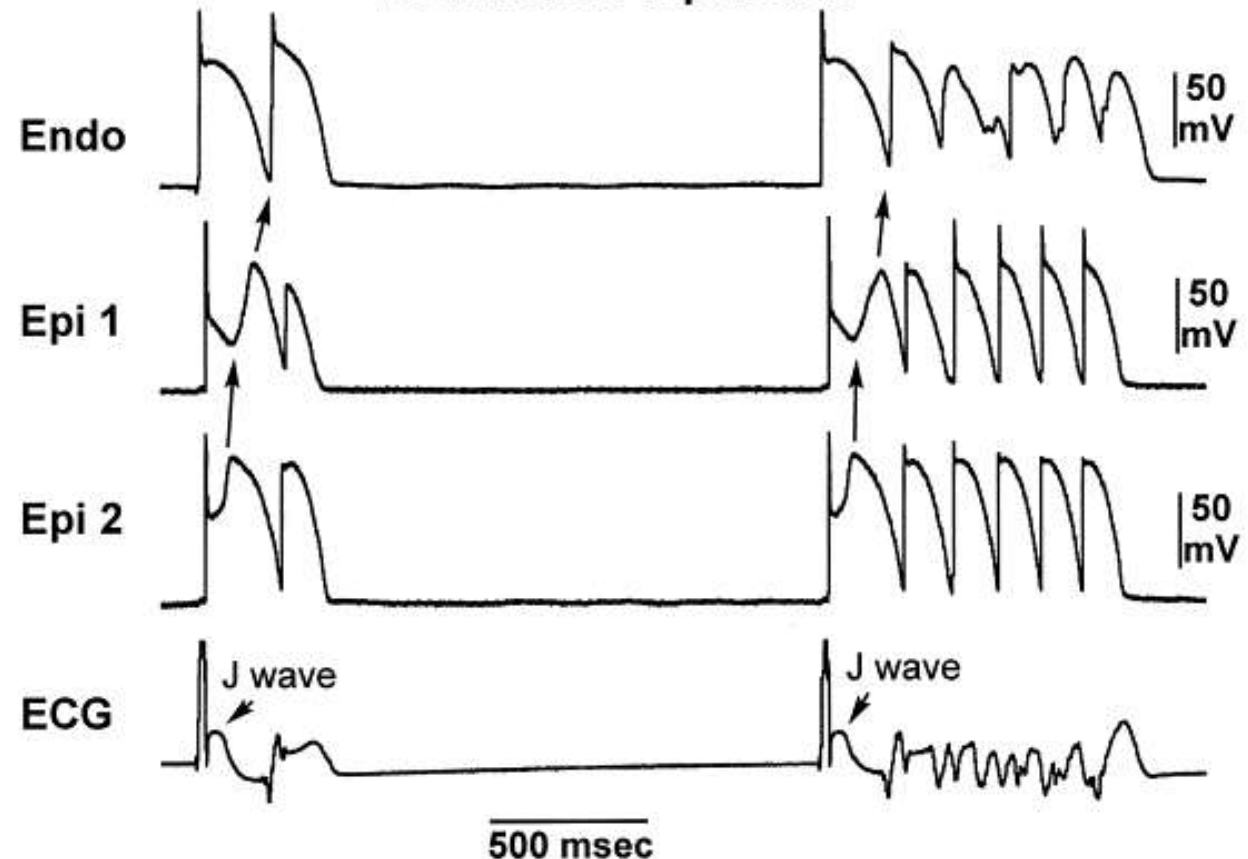


# Brugada Physiology

## A. J wave and Associated Ventricular Tachycardia in a Patient



## B. Phase 2 Reentry and Ventricular Tachycardia in a Canine Ventricular Preparation



- Transient outward current (also  $I_{to1}$  – calcium independent, 4-aminopyridine sensitive)
  - Rapidly activating, rapidly inactivating, relatively slow recovery from inactivation (so less prominent in tachycardia)
  - Outward potassium current
  - Responsible for Phase 1 of AP
  - Prominent in epicardial and M cells
  - Gives AP a notched or spike and dome appearance
  - Less in endocardial cells
  - Transmural and interventricular variations in the density of transient outward current are thought to contribute to J wave of ECG (hypothermia-“Osborn”, hypercalcemia), to early repolarization and to Brugada syndrome
  - An extremely prominent transient outward current can overwhelm the inward currents responsible for the plateau of the AP (chiefly  $I_{Ca}$ ), eliminate the plateau, resulting in a very abbreviated action potential in epicardium, so a potential difference endo-epi, so ST elevation
- The difference between early repolarization and Brugada may be related to the fact that the dome is not lost in early repolarization, and also that the LV is more involved in early repolarization than in Brugada, which may be more RVOT

$I_{to}$

# Brugada Syndrome

**Table I.**

Diagnostic Criteria for Brugada Syndrome (From 1<sup>st</sup> Consensus Document) ST-Segment Abnormalities in Leads V1-V3

	Type 1	Type 2	Type 3
J-point	$\geq 2$ mm	$\geq 2$ mm	$\geq 2$ mm
T-wave	Negative	Positive or biphasic	Positive
ST-T configuration	Coved type	Saddleback	Saddleback
ST segment (terminal portion)	Gradually descending	Elevated $\geq 1$ mm	Elevated $< 1$ mm

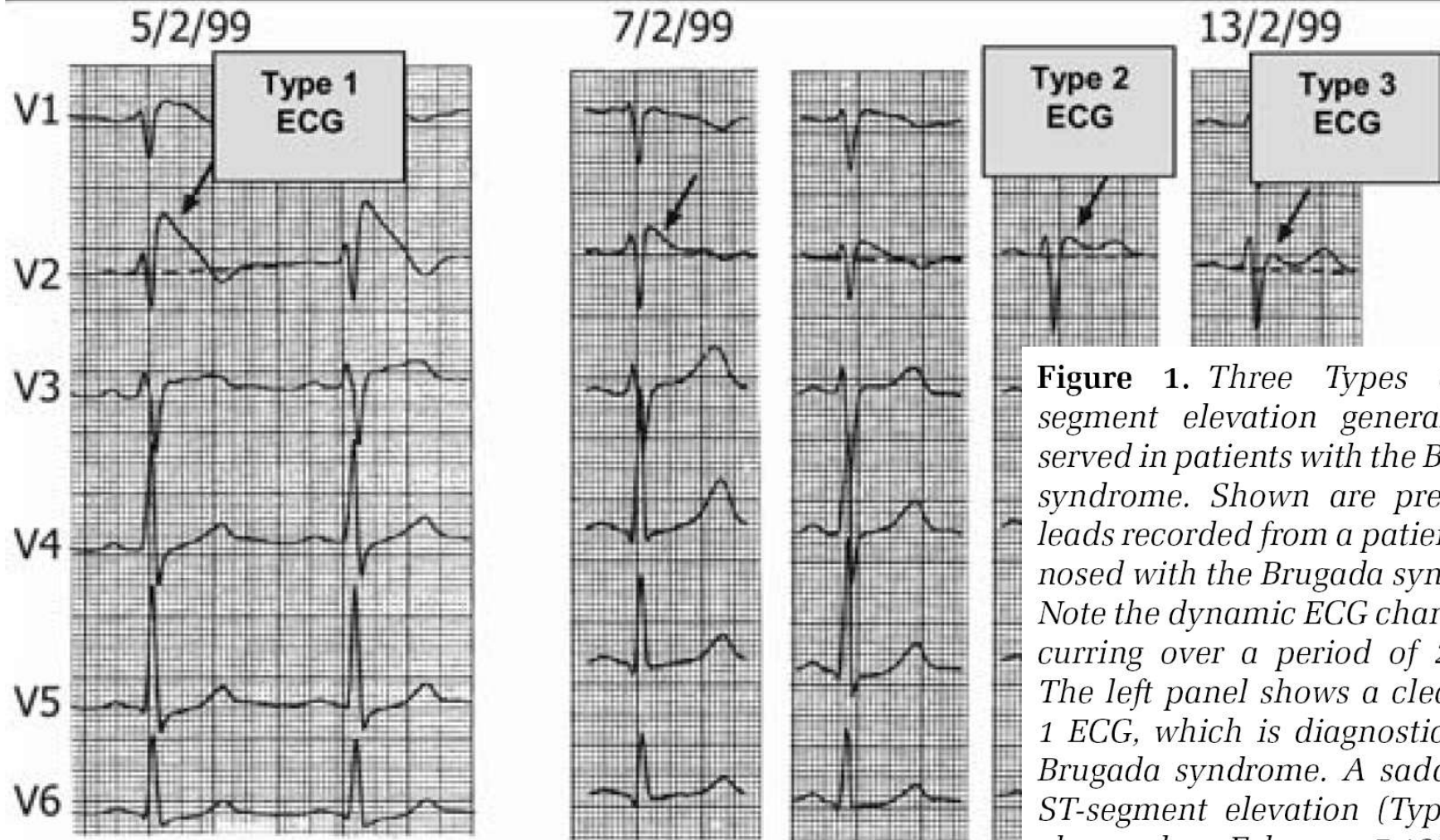
1 mm = 0.1 mV, the terminal portion of the ST segment refers to the latter half of the ST segment. From Wilde et al.<sup>3</sup> with permission.

**Table II.**

Drugs Used to Unmask the Brugada Syndrome

Ajmaline	1 mg/kg/5 min, i.v.
Flecainide	2 mg/kg/10 min, i.v. (400 mg, p.o.)
Procainamide	10 mg/kg/10 min, i.v.
Pilsicainide	1 mg/kg/10 min, i.v.

# Brugada ECGs



**Figure 1.** Three Types of ST-segment elevation generally observed in patients with the Brugada syndrome. Shown are precordial leads recorded from a patient diagnosed with the Brugada syndrome. Note the dynamic ECG changes occurring over a period of 2 days. The left panel shows a clear Type 1 ECG, which is diagnostic of the Brugada syndrome. A saddleback ST-segment elevation (Type 2) is observed on February 7, 1999. The ST segment is further normalized on February 13, 1999, showing a Type 3 ECG. Modified from Wilde et al.<sup>4</sup> with permission.

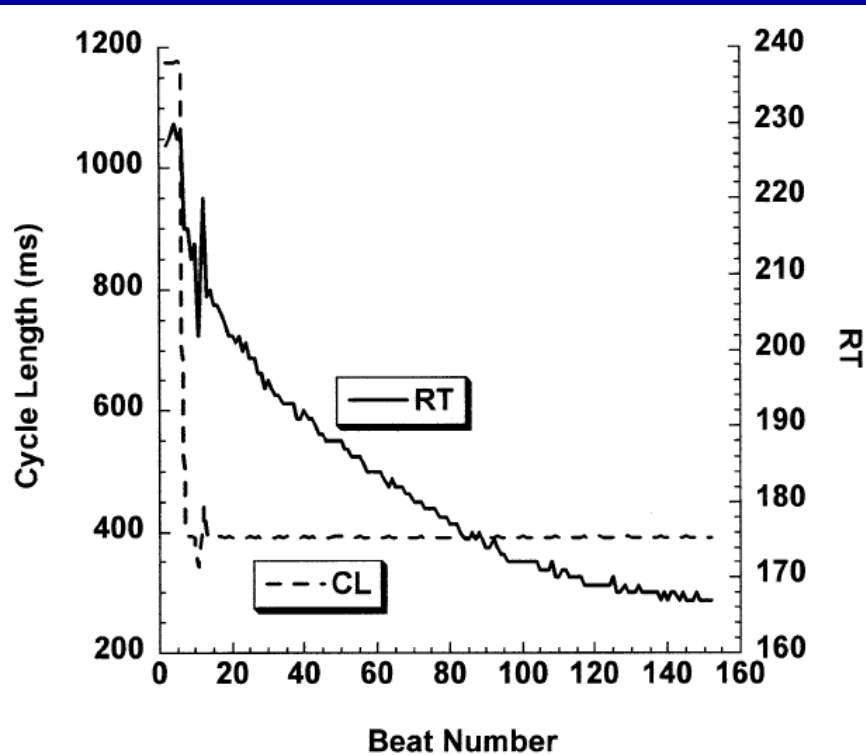


# QT Interval and Heart Rate

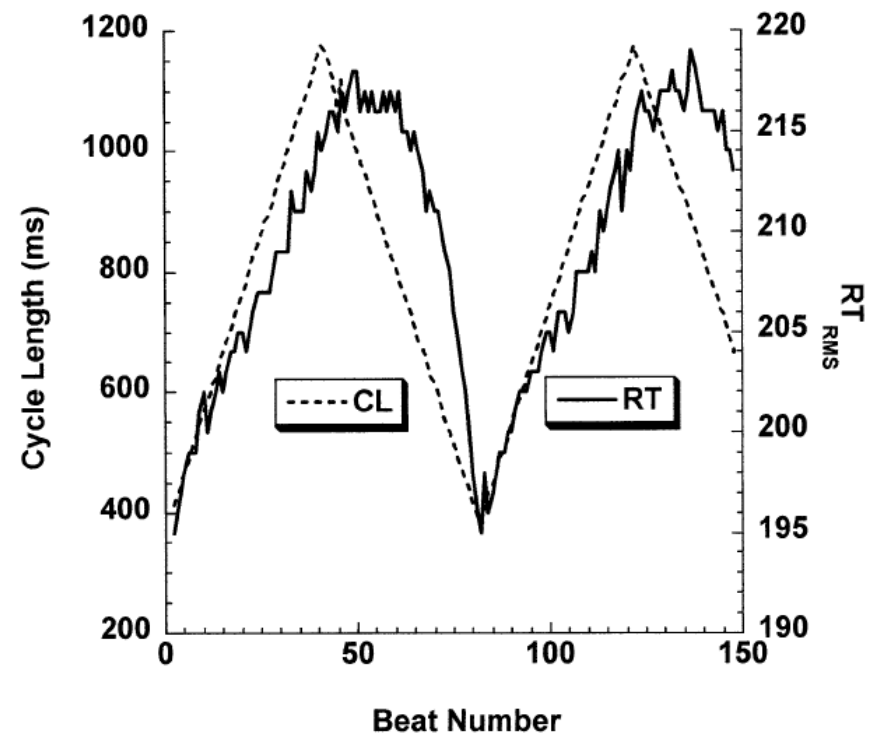
- Very complex
- Determinations include reason for RR interval change and history of prior RR intervals

# QT Interval vs RR interval

- Studies in acute canine preparations



**Fig. 1.** Cycle length and R-T interval obtained during a pacing sequence in which cycle length was abruptly shortened from 1,200 to 400 ms.

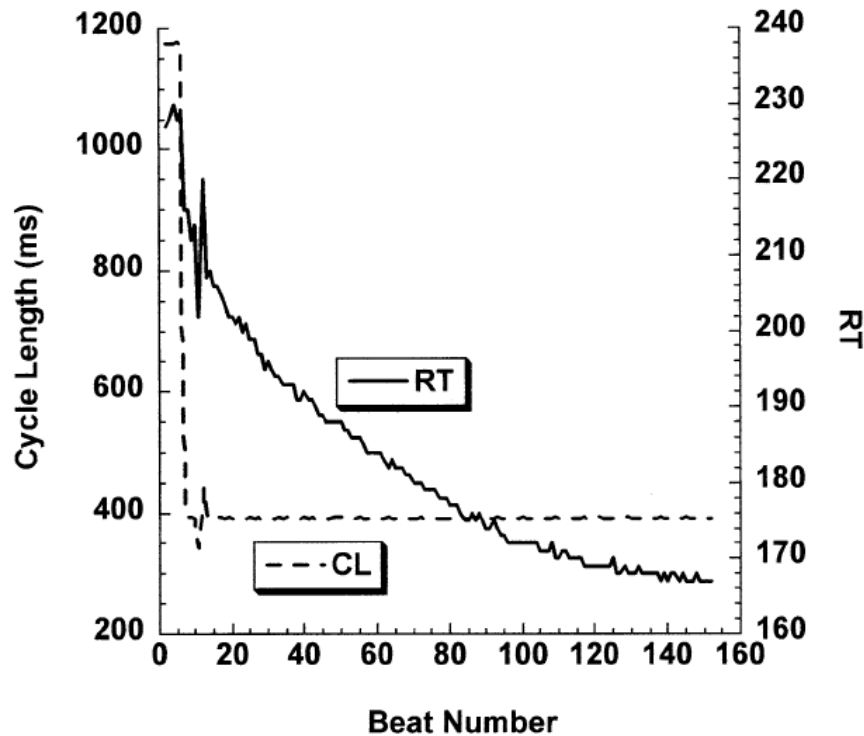


**Fig. 2.** Cycle length and R-T intervals obtained during a pacing sequence in which cycle length was increased and decreased linearly between 1,200 and 400 ms.

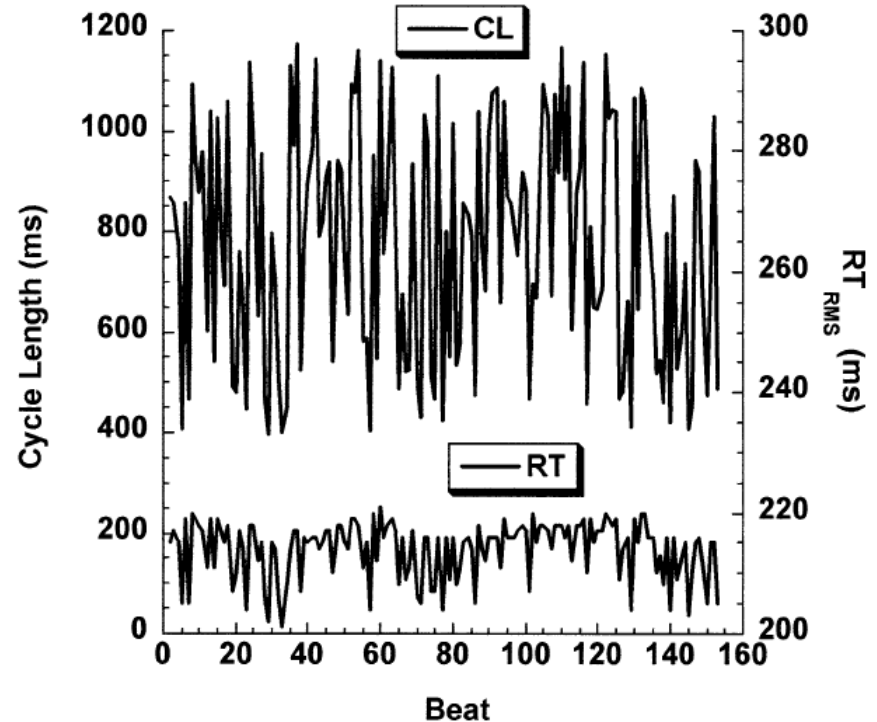


# QT Interval vs RR interval

- Studies in acute canine preparations



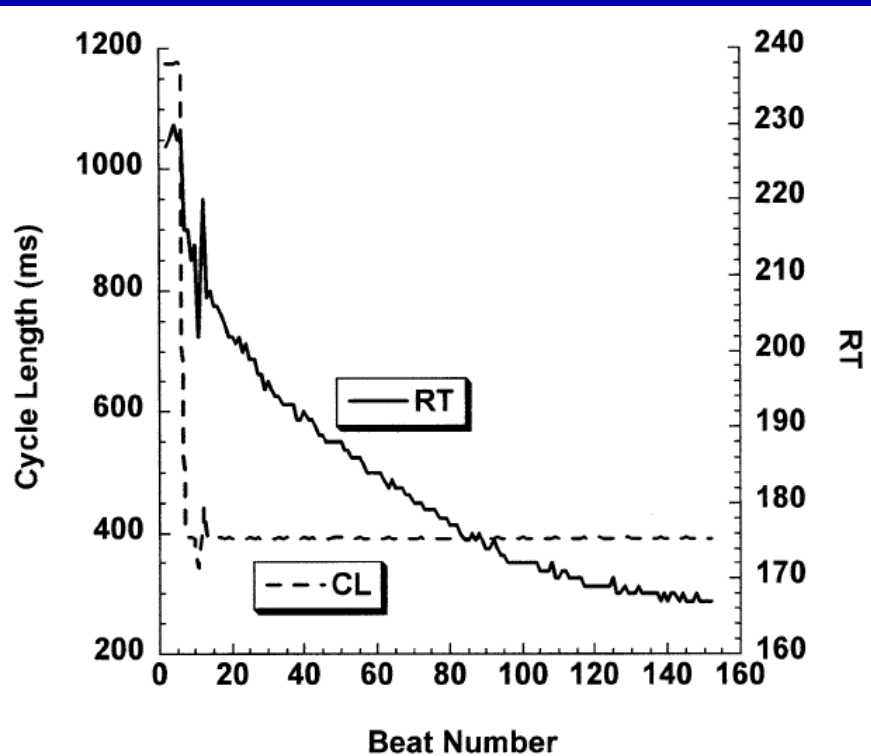
**Fig. 1.** Cycle length and R-T interval obtained during a pacing sequence in which cycle length was abruptly shortened from 1,200 to 400 ms.



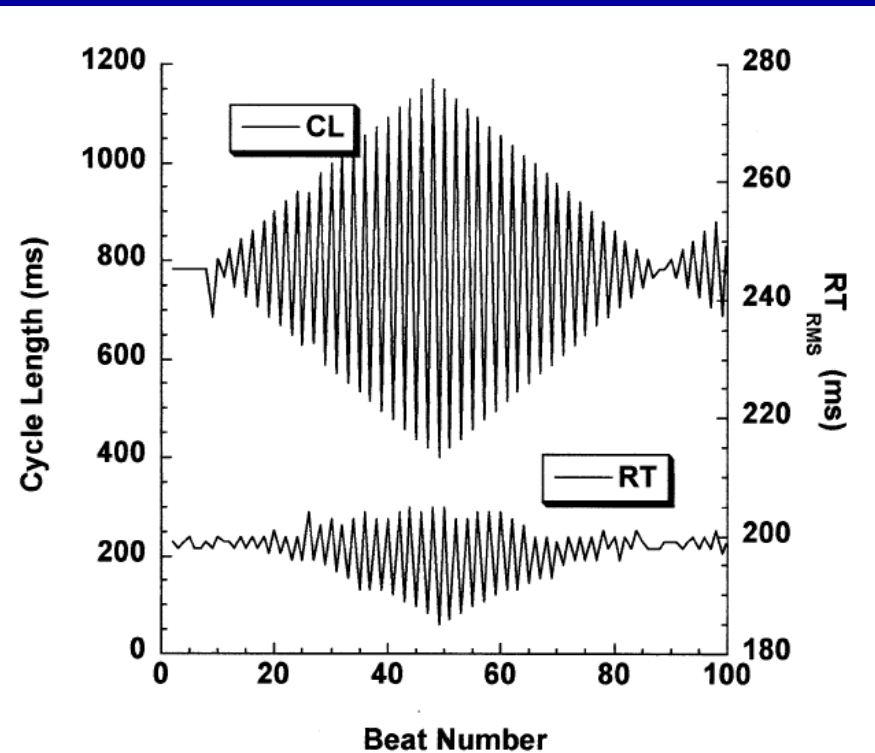
**Fig. 4.** Cycle length and R-T intervals obtained during a pacing sequence in which cycle lengths were random (uniformly distributed between 400-1200 ms).

# QT Interval vs RR interval

- Studies in acute canine preparations



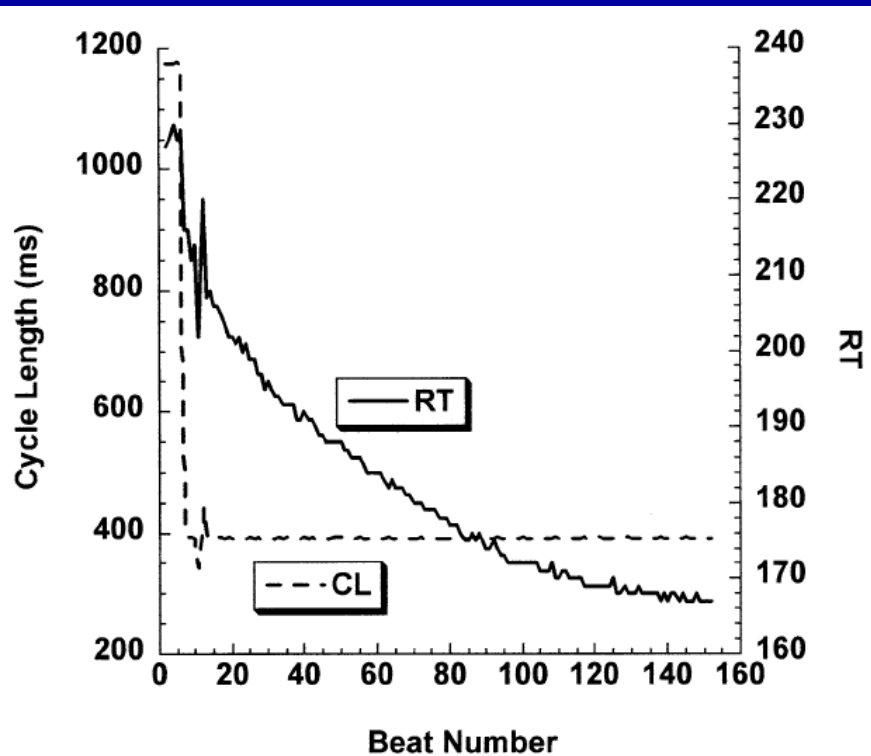
**Fig. 1.** Cycle length and R-T interval obtained during a pacing sequence in which cycle length was abruptly shortened from 1,200 to 400 ms.



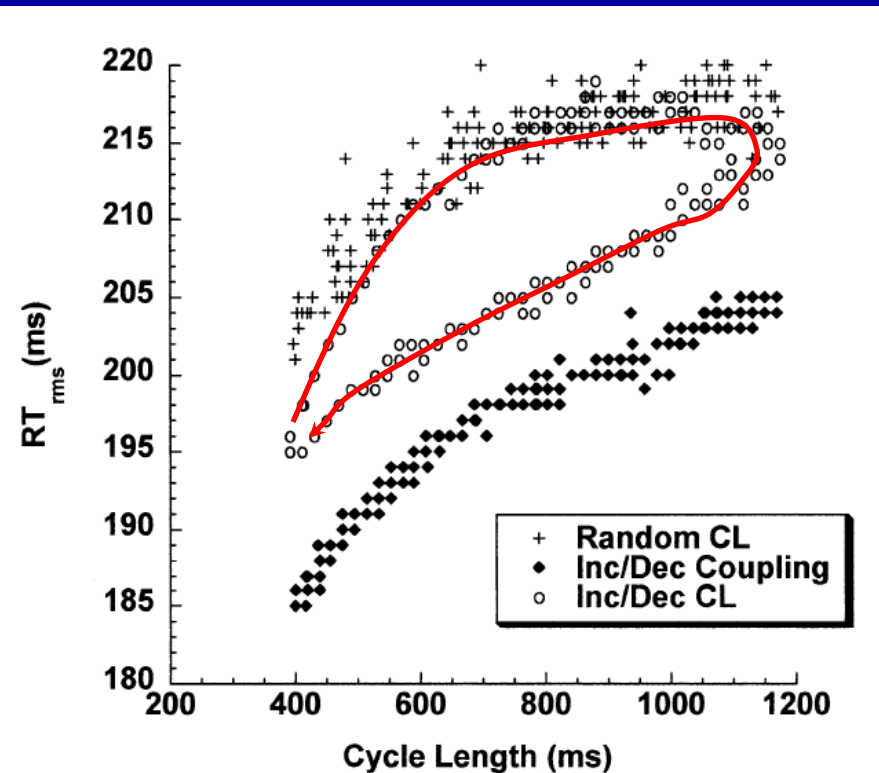
**Fig. 3.** Cycle length and R-T intervals obtained during a pacing sequence in which coupling interval was incremented and decremented by 10 ms on alternate beats, again within the range of 400-1,200 ms. The mean cycle length was the same as in the previous examples.

# QT Interval vs RR interval

- Studies in acute canine preparations

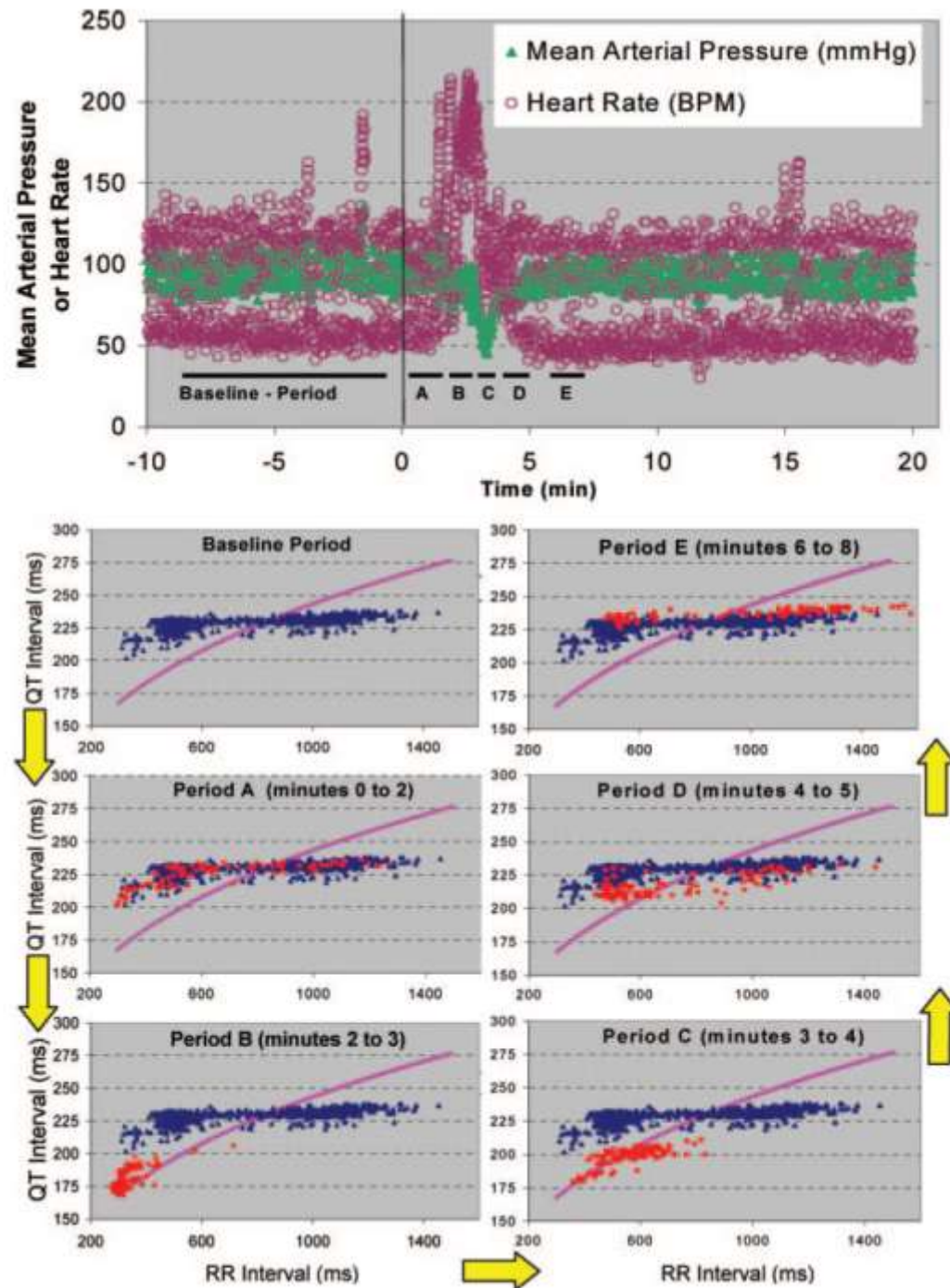


**Fig. 1.** Cycle length and R-T interval obtained during a pacing sequence in which cycle length was abruptly shortened from 1,200 to 400 ms.



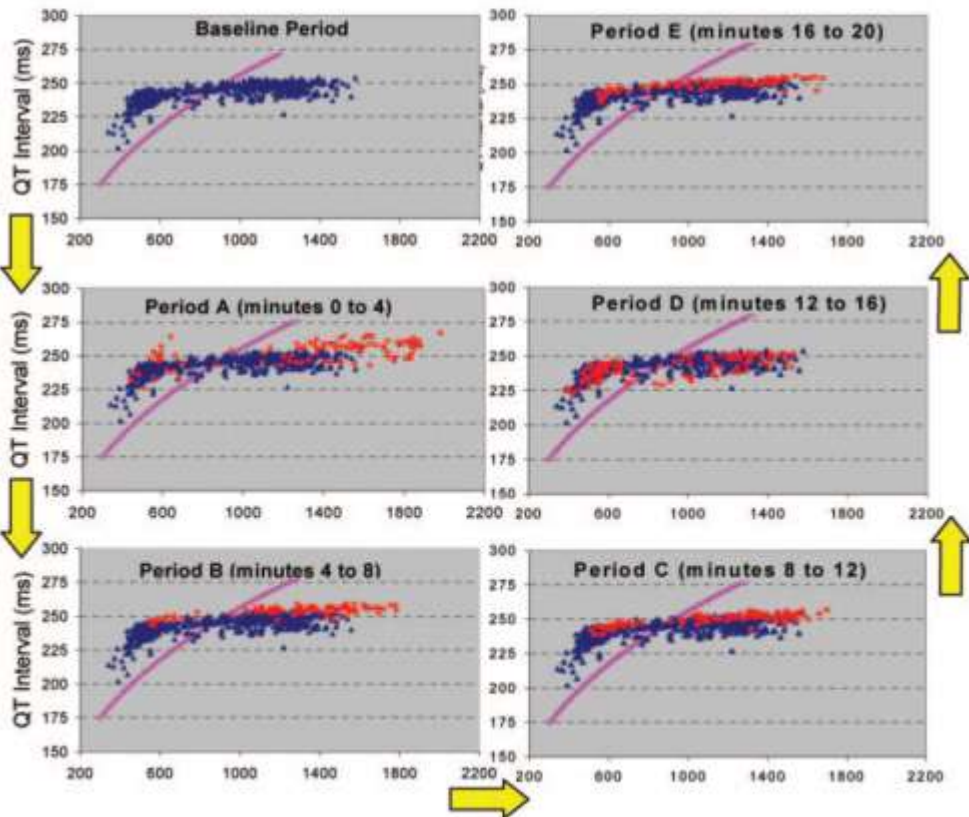
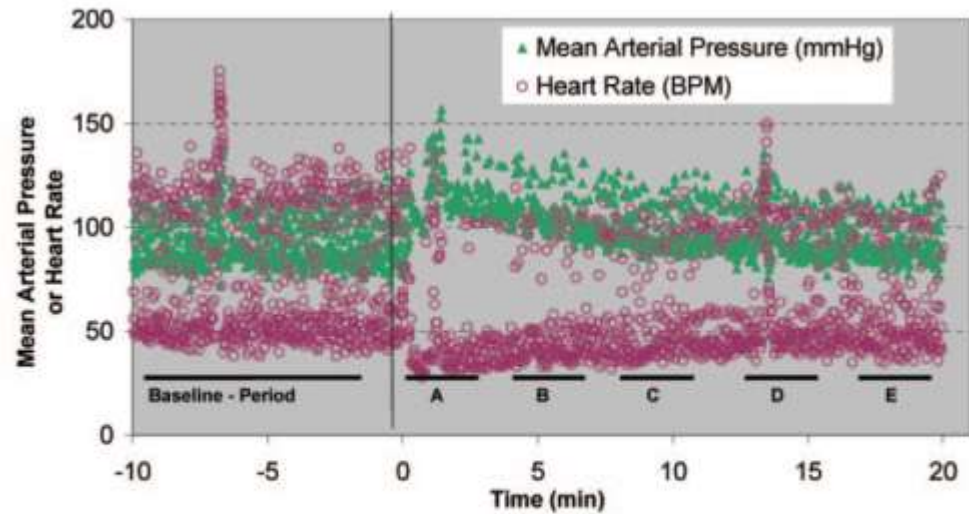
**Fig. 5.** Composite dynamic restitution scattergram—examples 2-4.

# Effect of Nitroprusside on a Dog



Fossa AA et al. J Pharm Exp Ther. 2005;312:1-11.

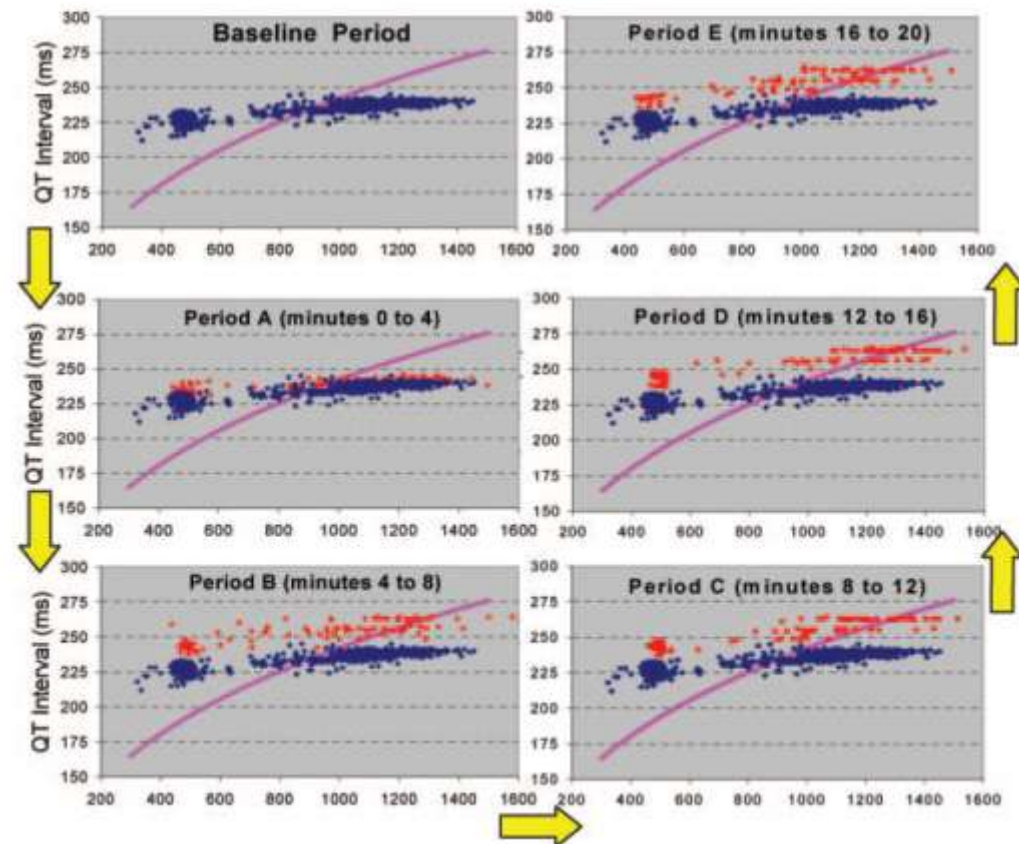
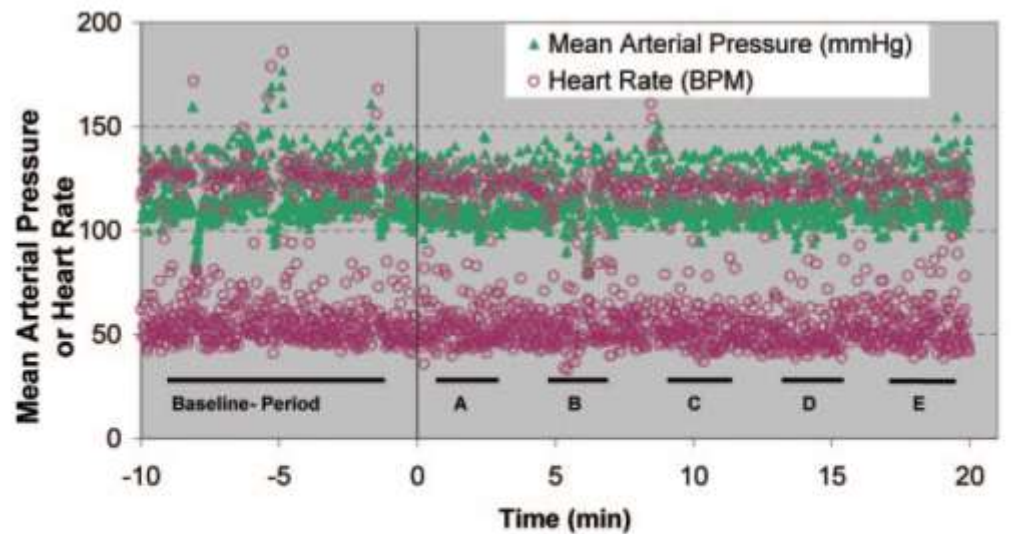
# Effect of Phenylephrine on a Dog



Fossa AA et al. J Pharm Exp Ther. 2005;312:1-11.



# Effect of E4031 on a Dog



Fossa AA et al. J Pharm Exp Ther. 2005;312:1-11.



# Effect of Isoproterenol on a Man

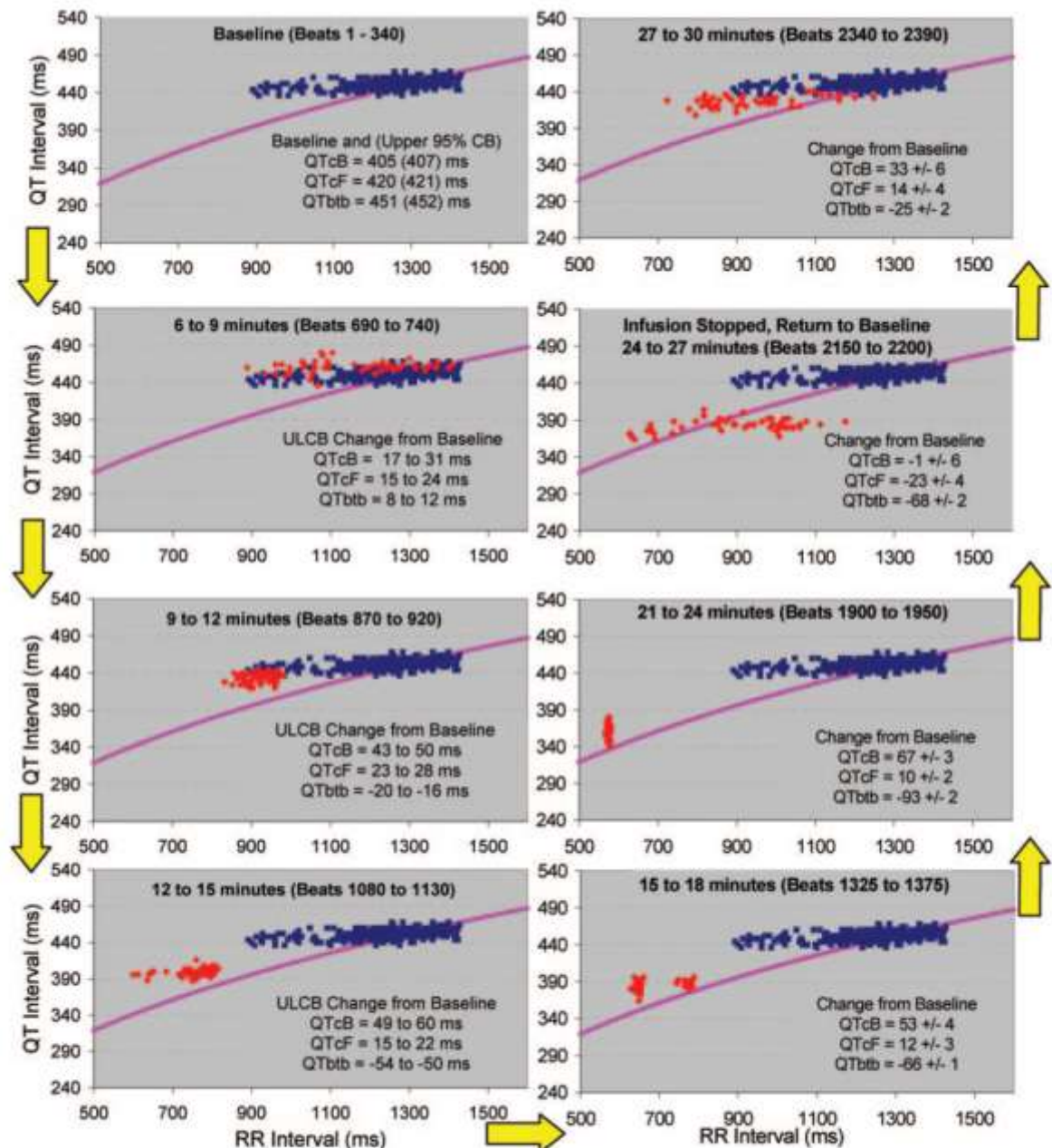
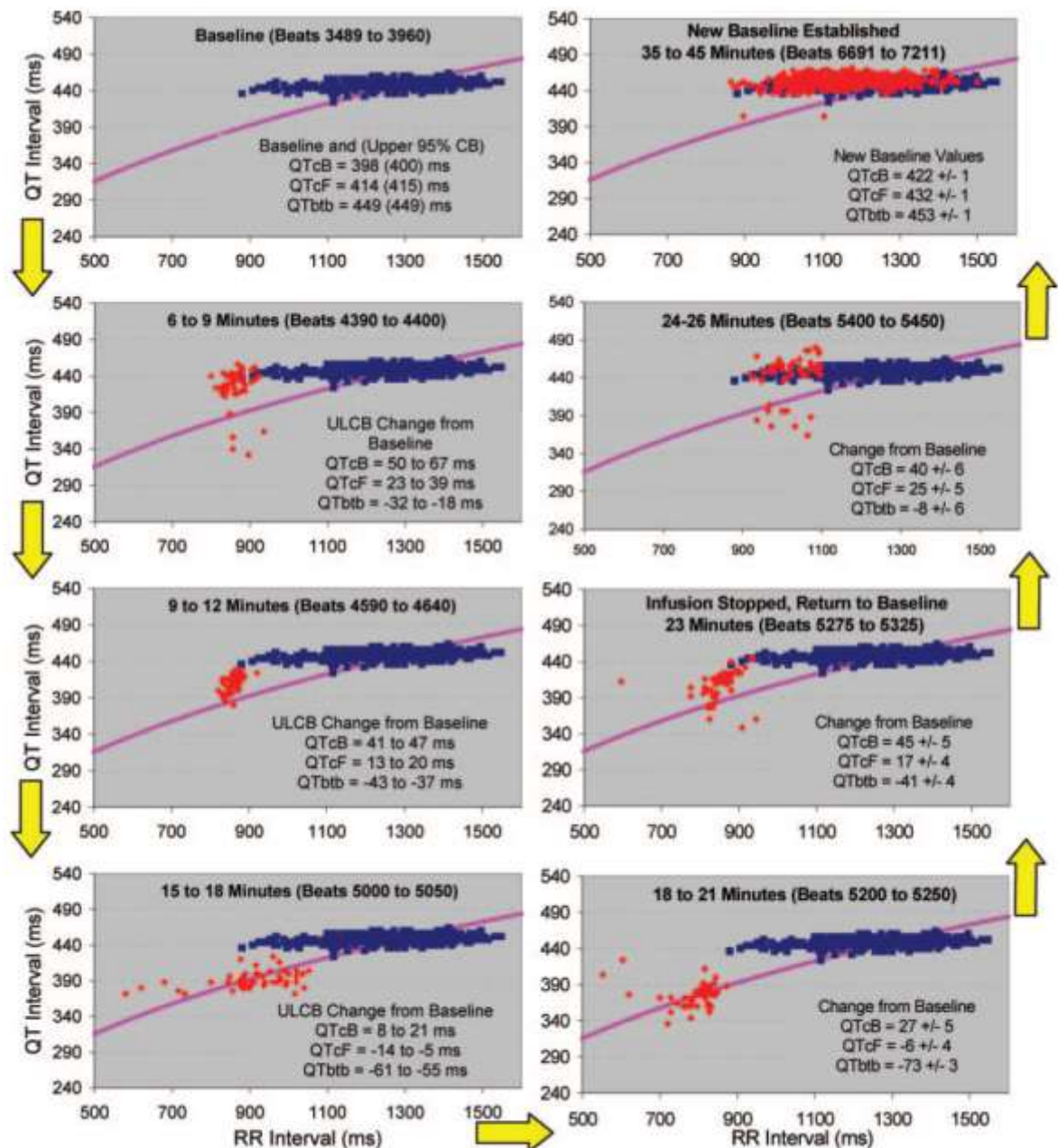


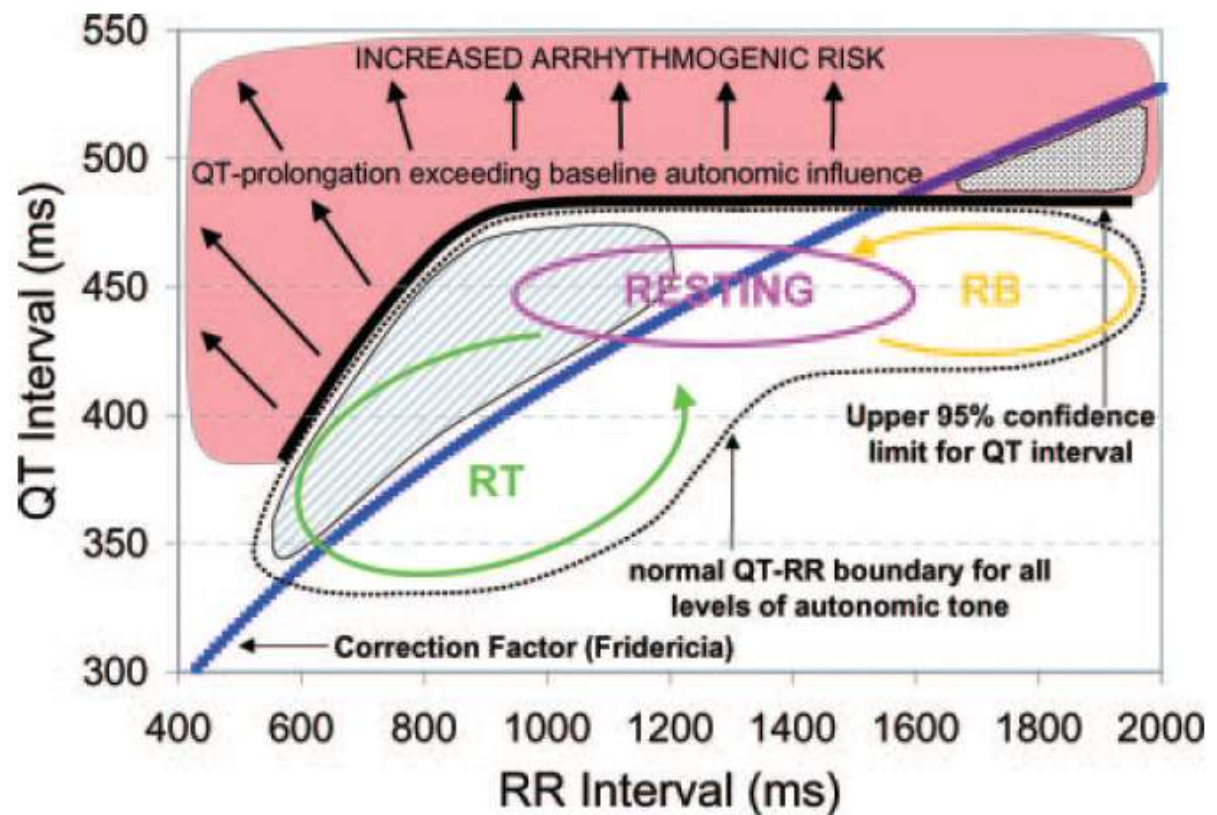
Fig. 5. Time-course effect of an isoproterenol infusion on the beat-to-beat QT-RR interval relationship from a single human male (see also Video Data Supplement 4). The RR interval range from 300 to 1500 ms, corrected each 10 ms using the Fridericia formula, is depicted (pink line) for visual perspective from the beat-to-beat QT-RR interval relationship. Median 100 beats during each time periods (red triangles) were compared with beats obtained at baseline (blue squares) using upper 95% confidence bounds (CB) generated from bootstrapping (see Materials and Methods). The upper and lower 95% confidence bounds (ULCB) for QTcB and QTcF values were calculated from the QTbtb values.

# Effect of Epinephrine in a Man



**Fig. 6.** Time-course effect of an epinephrine infusion on the beat-to-beat QT-RR interval relationship from a single human male (see also Video Data Supplement 5). The RR interval range from 300 to 1500 ms, corrected each 10 ms using the Fridericia formula, is depicted (pink line) for visual perspective from the beat-to-beat QT-RR interval relationship. Median 100 beats during each time periods (red triangles) were compared with beats obtained at baseline (blue squares) using upper 95% confidence bounds (CB) generated from bootstrapping (see *Materials and Methods*). The upper and lower 95% confidence bounds (ULCB) for  $QTcB$  and  $QTcF$  values were calculated from the  $QTbtb$  values.





**Fig. 1.** Normal dynamic QT-RR interval relationship (dotted-line forming asymmetric cloud) encompasses autonomic reflex responses such as tachycardia (RT) and bradycardia (RB) with hysteresis. The statistical outer boundary of the normal cloud is defined as the upper 95% confidence bounds. The Fridericia correction factor applied to the resting QT-RR interval relationship overcorrects dynamic responses in the normal range (striped area above correction line and below 95% confidence bounds) or underestimates QT prolongation at slow heart rates (shaded area above 95% confidence bounds but below Fridericia correction). QT prolongation of undefined arrhythmogenic risk (dark shaded area) occurs when exceeding the 95% confidence bounds of QT intervals during unstressed autonomic influence.

# Repolarization Abnormalities

- Primary T wave abnormality – Electrolyte imbalance or drug or temperature; ischemic or postischemic often have long QT and long aTeT interval; pericarditis; mitral valve prolapse syndrome; CNS disorders and CEA (nonhomogeneous sympathetic stimulation of the heart); pheochromocytoma, cocaine
  - Giant precordial T inversion usually subarachnoid hemorrhage or apical cardiomyopathy or myocardial ischemia
  - Cholecystitis, peritonitis, appendicitis, pancreatic necrosis, ileus
  - Fear, anxiety, hyperventilation
- Secondary T wave abnormality – an abnormality expected under a condition of altered depolarization sequence (RBBB, LBBB, LVH, WPW)

# Drug and Metabolic Abnormalities and ECG Effects

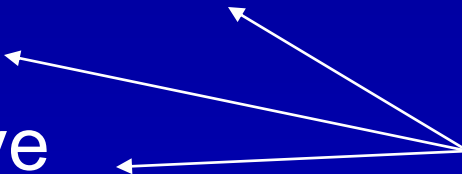
- Antiarrhythmic Agents
  - Class I (Mainly Na blocker; A, B, and C)
  - Class II (Beta-adrenergic blocking agents)
  - Class III (Mainly K blocker)
  - Class IV (Ca blocker)
  - Class V (specific bradycardia agents acting on the SA node)



# Class I Antiarrhythmic Agents and ECG Effects

- Class IA – quinidine, procainamide, disopyramide
  - block Na channel and K channel and Ca channel
  - Prolong P wave, QRS, and JT intervals
  - Prolongation of QRS more at rapid rates
  - Proarrhythmia from reverse use-dependent effect on refractoriness - Torsades
- Class IB – lidocaine, tocainide, mexiletine, phenytoin
  - Block Na current more at rapid rates and in depolarized (ischemic) tissue
  - No recognizable effect on ECG
  - Seldom proarrhythmic
- Class IC – encainide, flecainide, propafenone, moricizine, tricyclic antidepressants (imipramine and amitriptyline)
  - Block Na entry, strong use-dependent effect
  - Prolong QRS and QT but not JT particularly at rapid rates and in premature complexes, so SVT can mimic VT
  - Proarrhythmia – incessant VT from use-dependent conduction effects

# Quinidine – Class IA

- T wave amplitude decreased or inverted
  - ST depression
  - Prominent U wave
  - QTc prolongation
  - Notching and widening of P wave
  - Increased QRS duration (toxic is prolonged above 25%)
  - Procainamide similar to quinidine except it has no anticholinergic property, and less pronounced ECG changes
  - Disopyramide similar to quinidine, less pronounced ECG effects
- Mimics Hypokalemia
- Phenothiazines have similar effects
- 

# Class II Antiarrhythmic Agents and ECG Effects

- Beta-adrenergic blocking agents
  - Depress SA node automaticity - Slow sinus rate
  - Prolong AV conduction time (AH interval) - Prolong PR interval
  - Produce SA and AV conduction block
  - Depress escape and accelerated automatic rhythms
  - May actually shorten QT (not mentioned in Surawicz)
- Seldom proarrhythmic

# Class III Antiarrhythmic Agents and ECG Effects

- Prolong repolarization
  - Mainly by blocking a potassium channel, but other mechanisms possible
  - Potassium channel blocking drugs
    - Sotalol, amiodarone, bretylium, dofetilide, ibutilide, sotalilide, almokalant
    - ECG: prolong QT and JT without prolonging QRS (except amiodarone prolongs QRS)
    - Reverse use-dependence means more effect in bradycardia
    - Proarrhythmia from reverse use-dependent effect on refractoriness - Torsades

# Class IV Antiarrhythmic Agents and ECG Effects

- Calcium inward current blocker
- Depress SA and AV node automaticity, conduction, and refractoriness
- Verapamil and diltiazem decrease sinus rate and prolong AV conduction
- Seldom proarrhythmic



# Class V Antiarrhythmic Agents and ECG Effects

- “Specific bradycardia” agents acting on the SA node

# Digitalis effects

- Decrease SA automaticity
- Slow AV conduction but enhance junctional automaticity – prolongation of PR interval
- No effect on H-V interval
- Increase His-Purkinje automaticity with increasing Phase 4 slope
- ST depression and terminal T wave positivity, shortening QT interval, increase U wave amplitude

# Arsenic

- QRS widening 0.10-0.16 sec
- ST depression
- QT prolongation
- T wave flattening
- VT and VF reported
- Complete AV block attributed to Arsenic trioxide to treat leukemia

# Electrolyte Abnormality Effects on ECG

- Hyperkalemia
- Hypokalemia
- Hypercalcemia
- Hypocalcemia
- Hypothermia
- CNS disorders

# 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



# 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**
- No change in QT interval if measured before U wave
- Advanced hypokalemia – T and U are fused
- Concomitant hypocalcemia: aggravates findings

# Calcium

- Ionized calcium, so correct for albumin level
- Mainly change in ST segment duration, little change in T wave morphology
- Hypercalcemia shortens ST segment, so shortens the QaT (onset of QRS to apex of T)
- Hypocalcemia lengthens ST segment

# Situations that Don't Affect the ECG

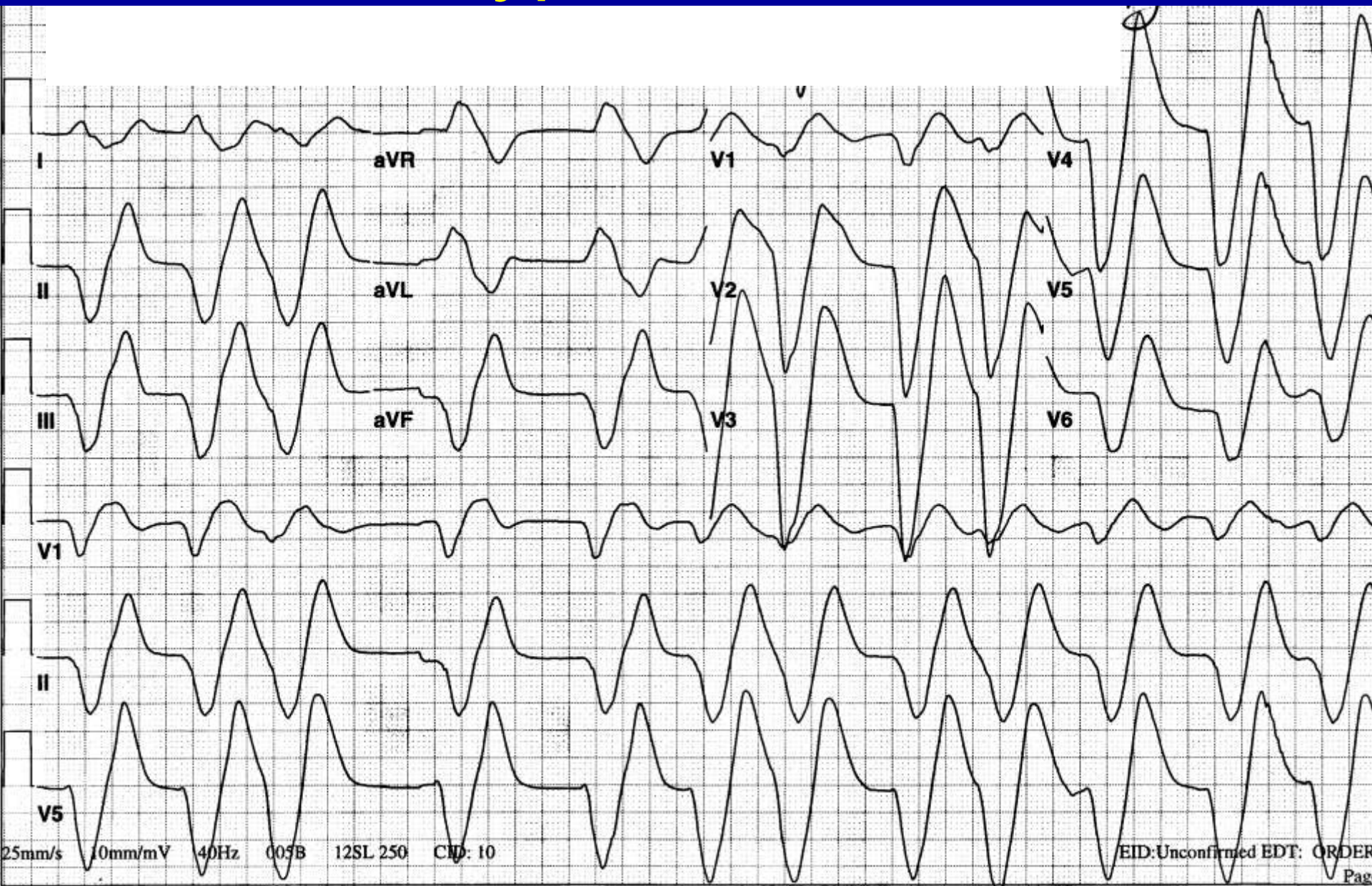
- Hyponatremia, hypernatremia
- Hypomagnesemia, hypermagnesemia
- Hyperthermia
- Alkalosis, acidosis
- Alcohol, coffee, tobacco

# 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

6:04

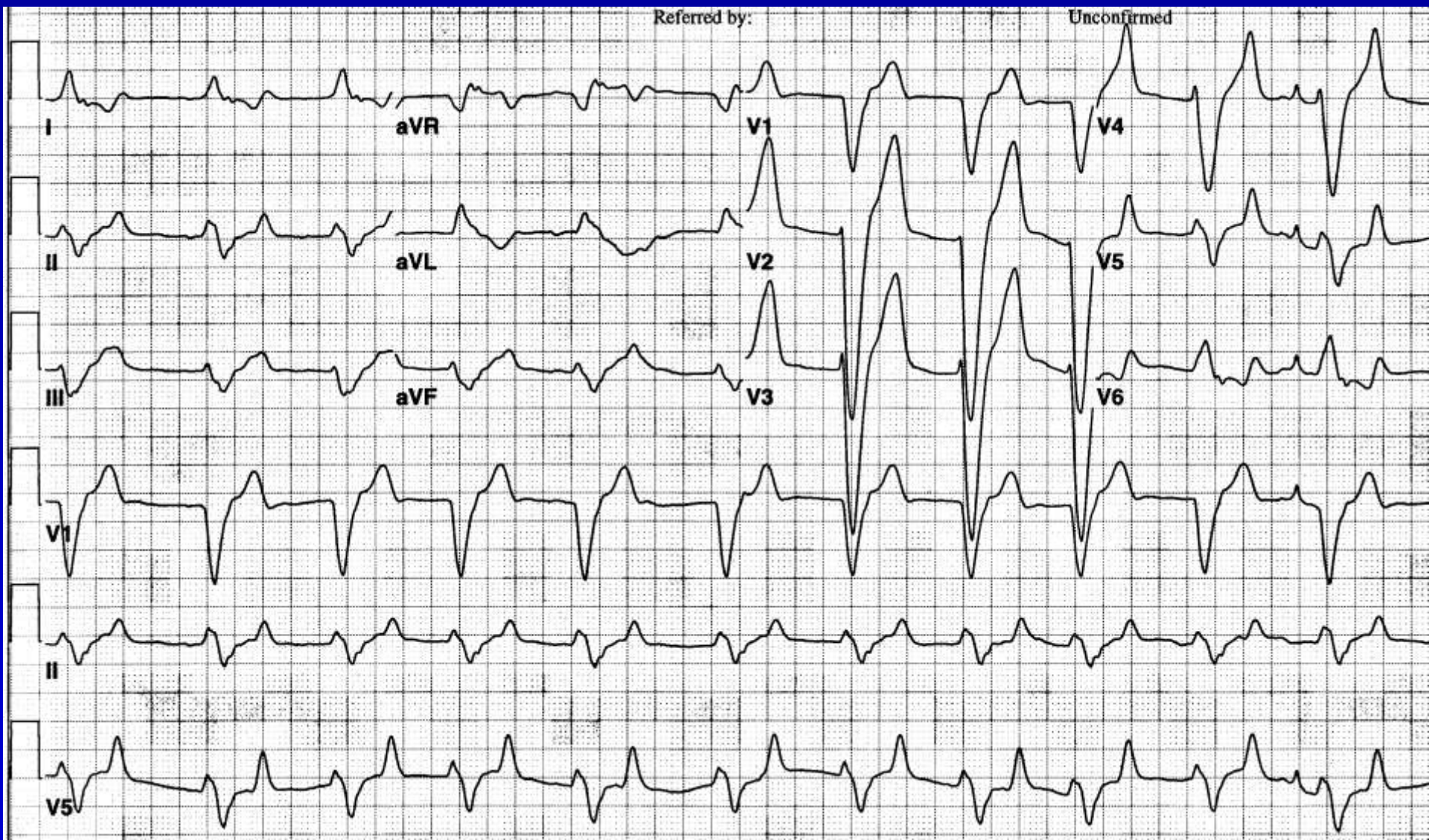
# Hyperkalemia





6:44

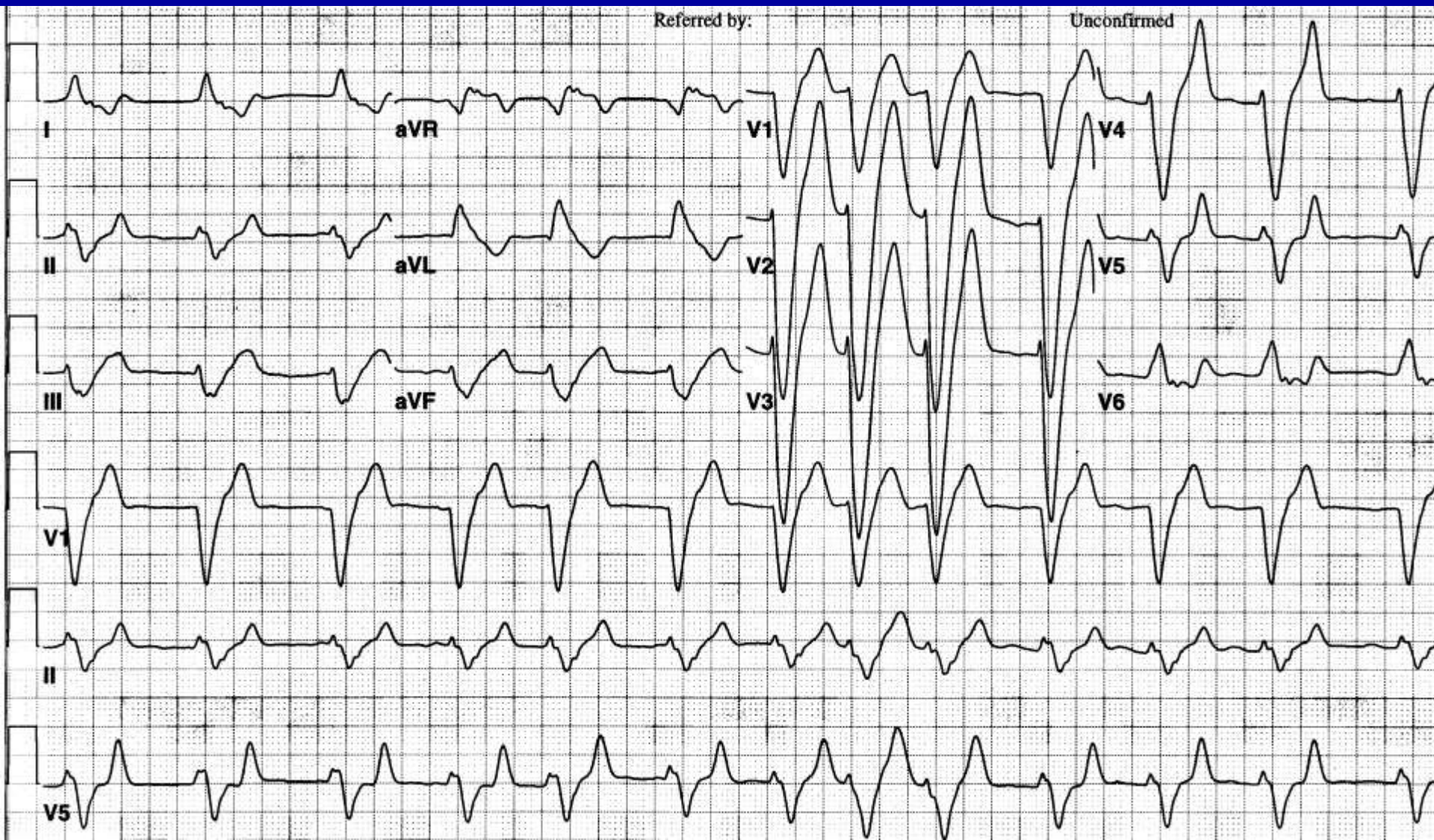
# Hyperkalemia





6:58

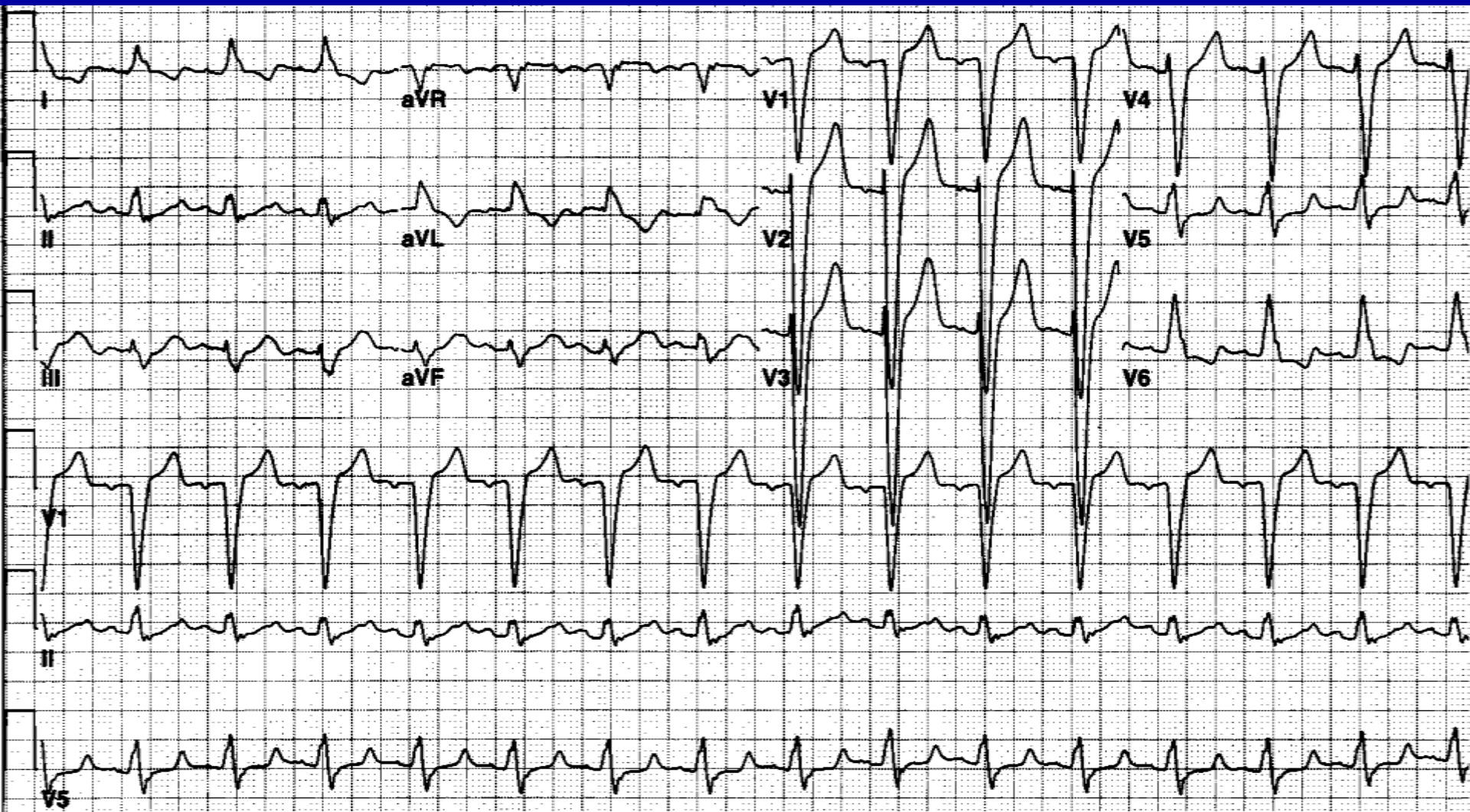
# Hyperkalemia





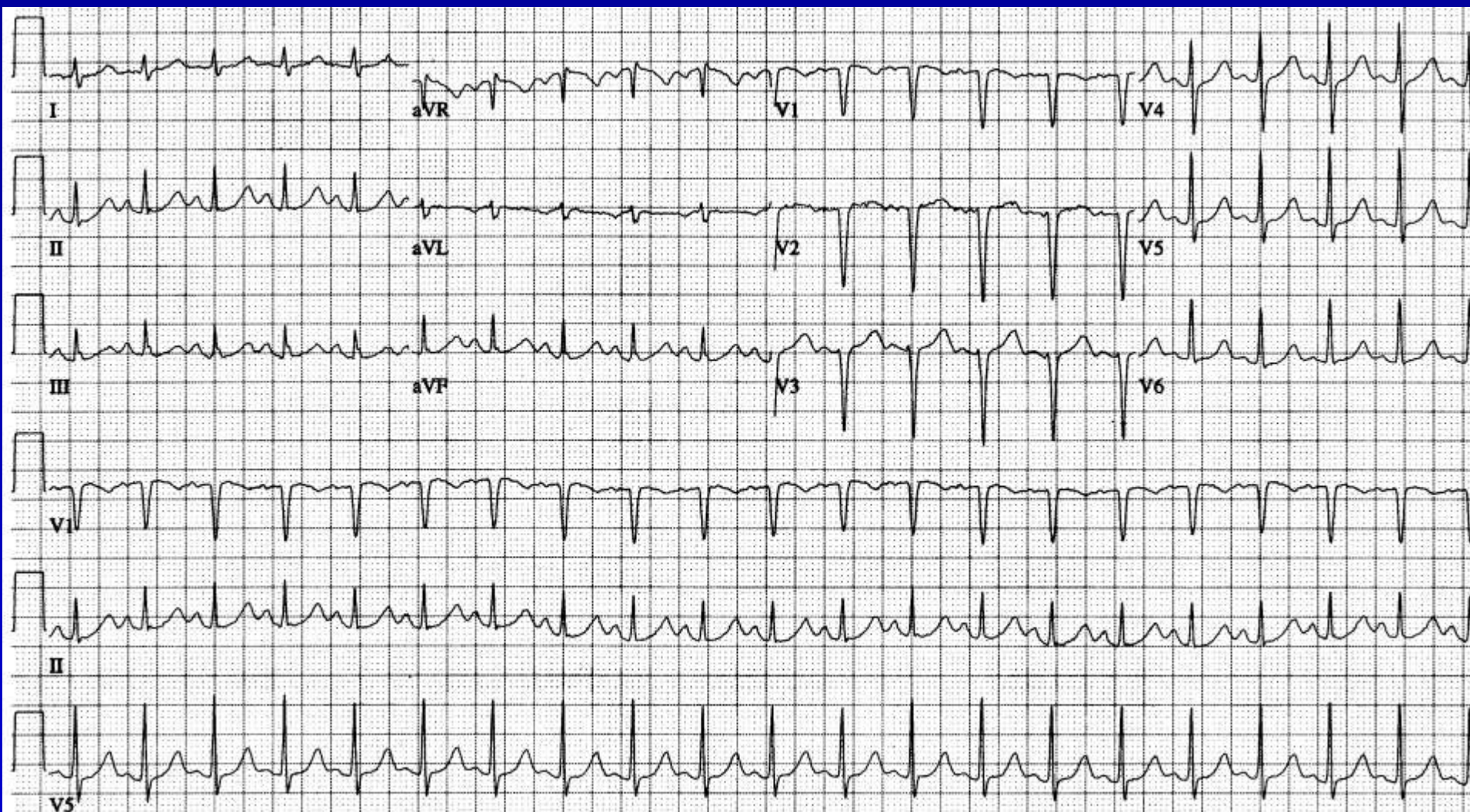
9:19

# Hyperkalemia



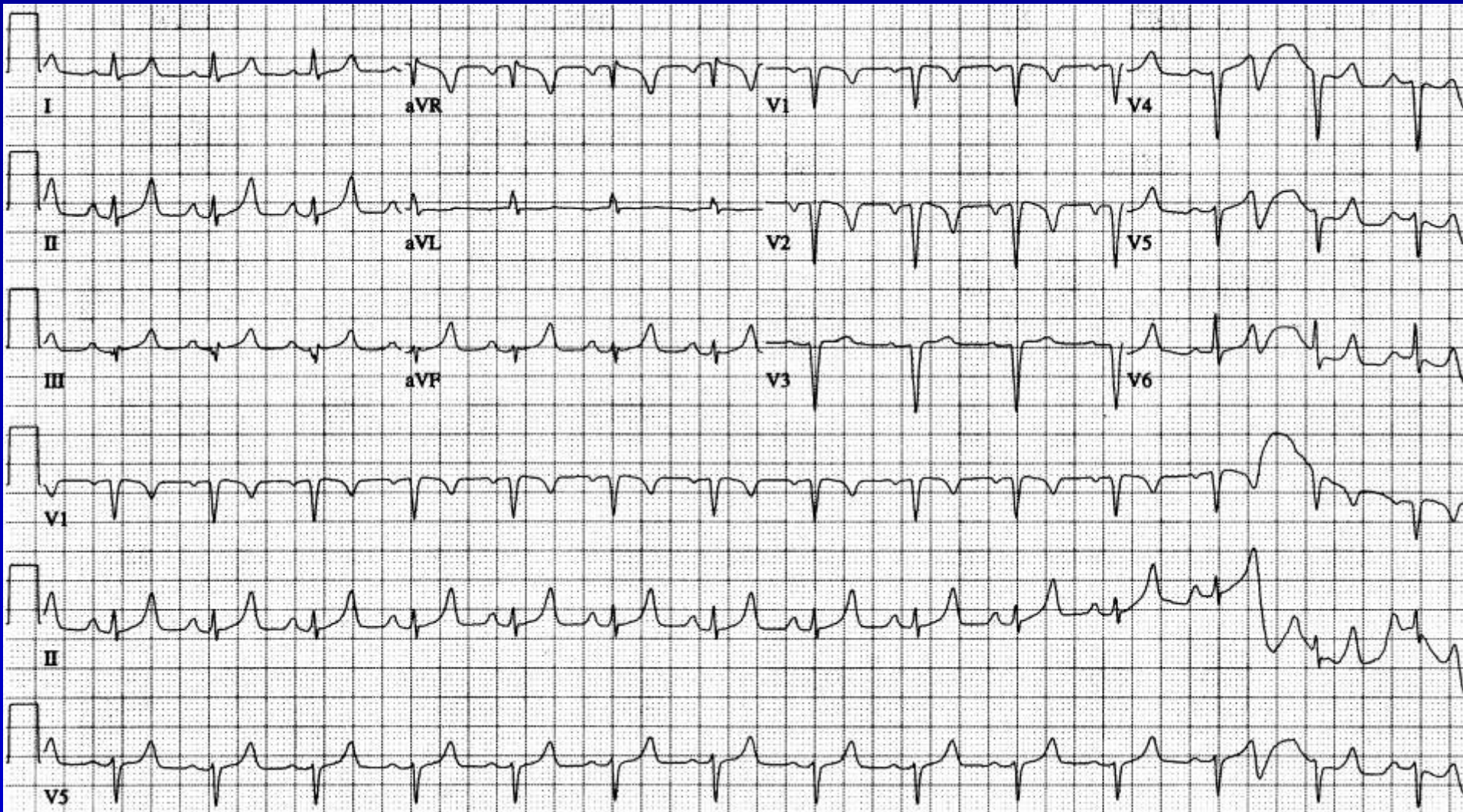


# 1996 Baseline Hyperkalemia case 2



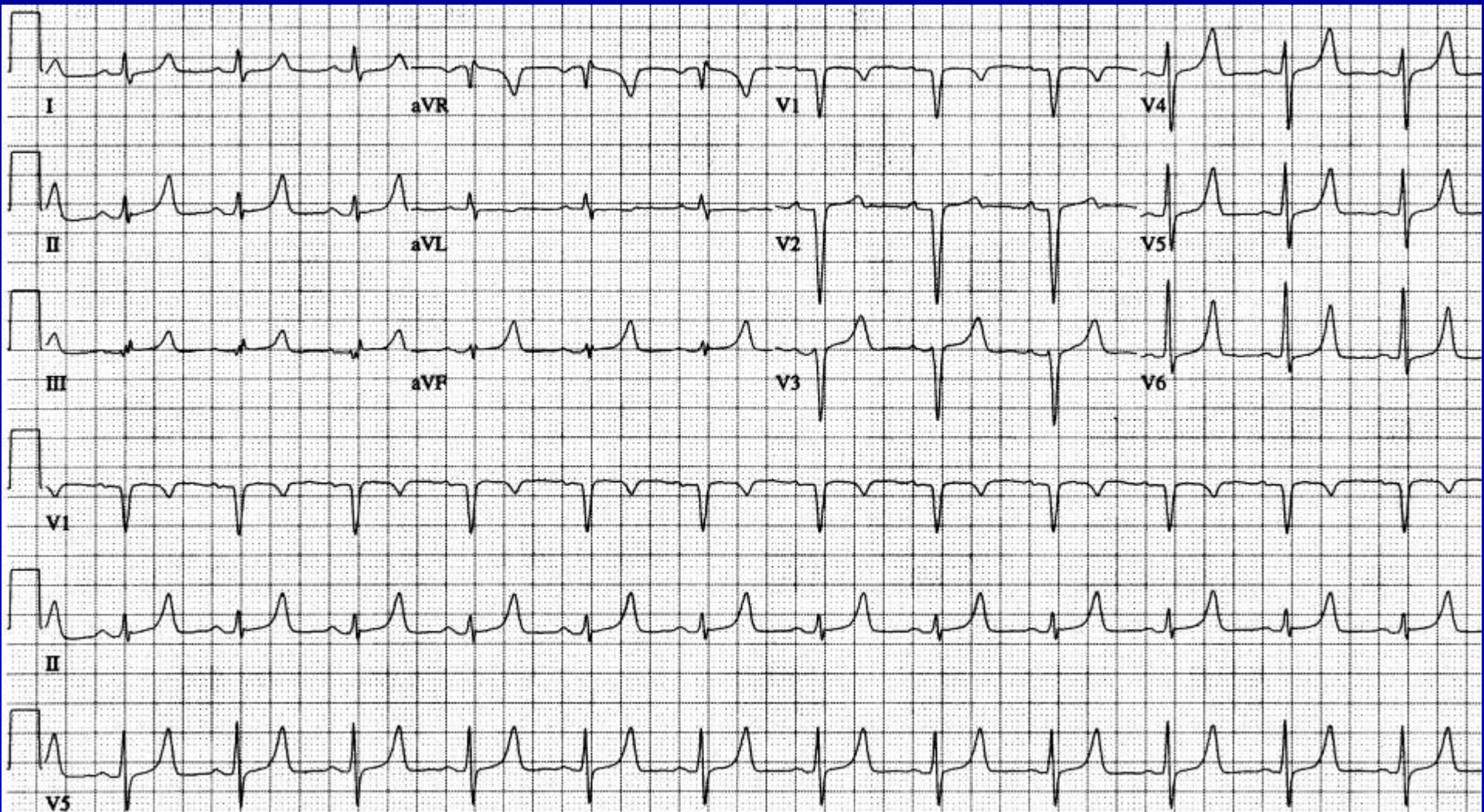


21 June 1998 **Hyperkalemia case 2**





23 June 1998 **Hyperkalemia case 2**





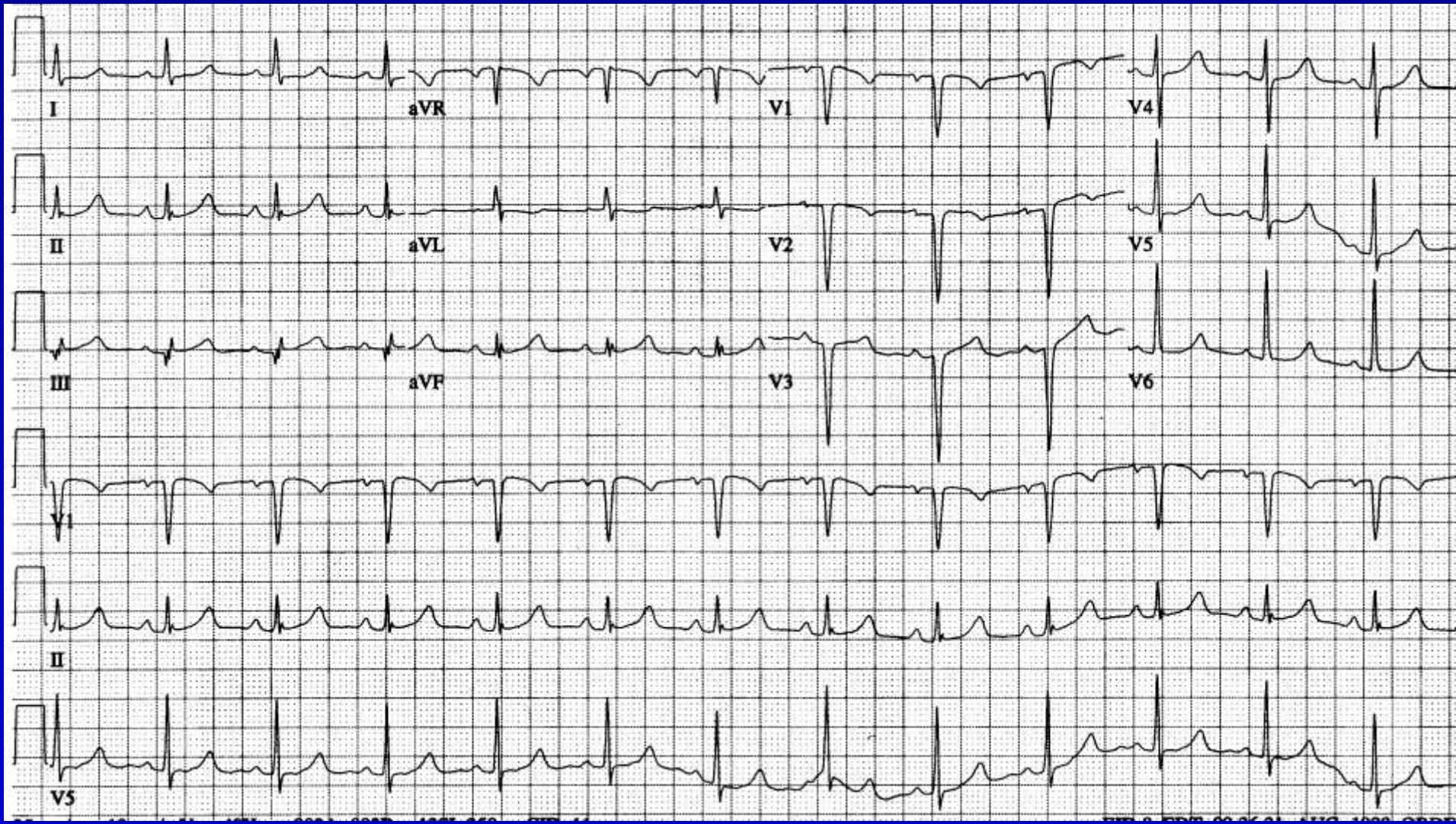
# 27 June 1998 Hyperkalemia case 2





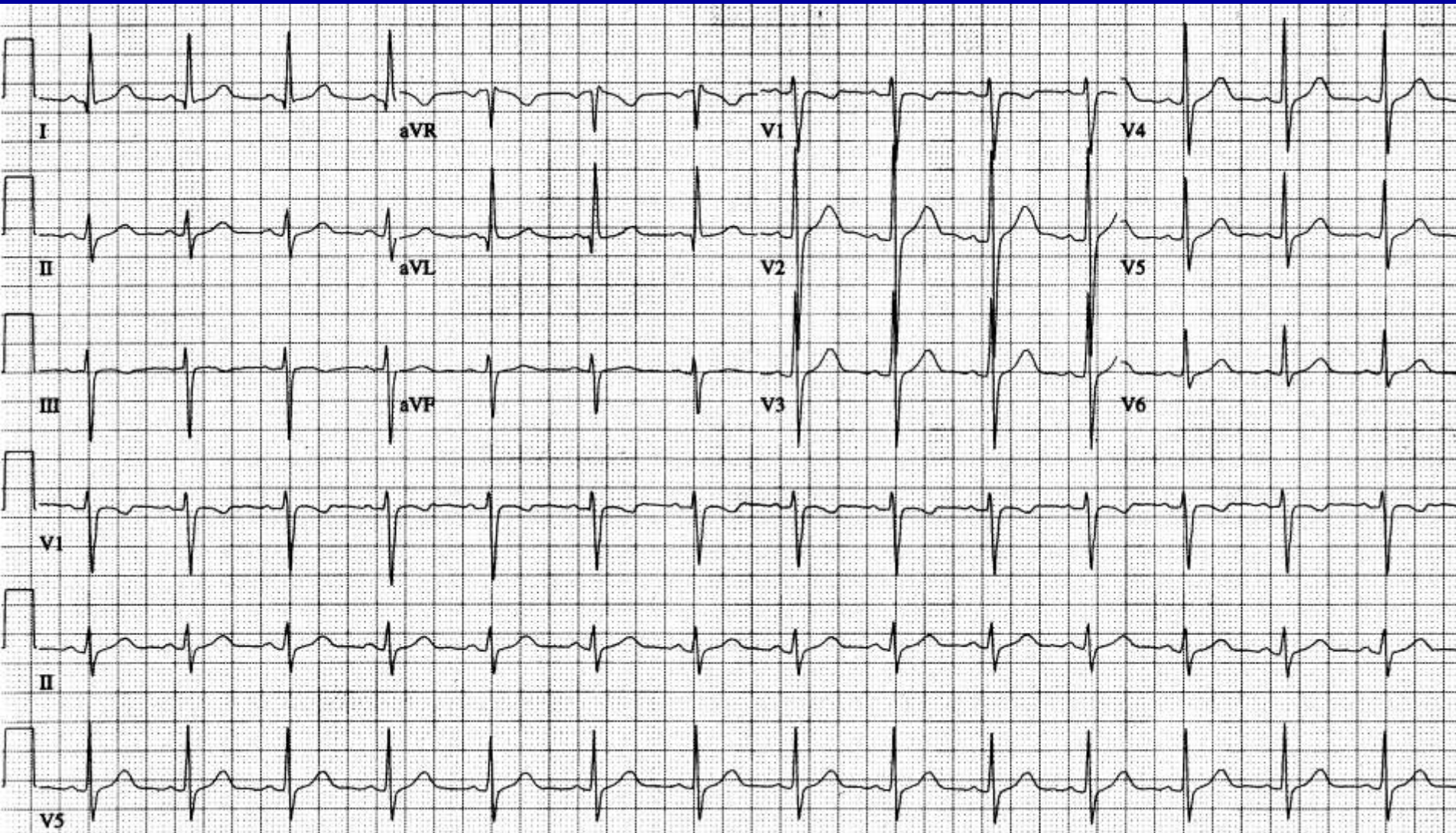
24 July 1998

# Hyperkalemia case 2





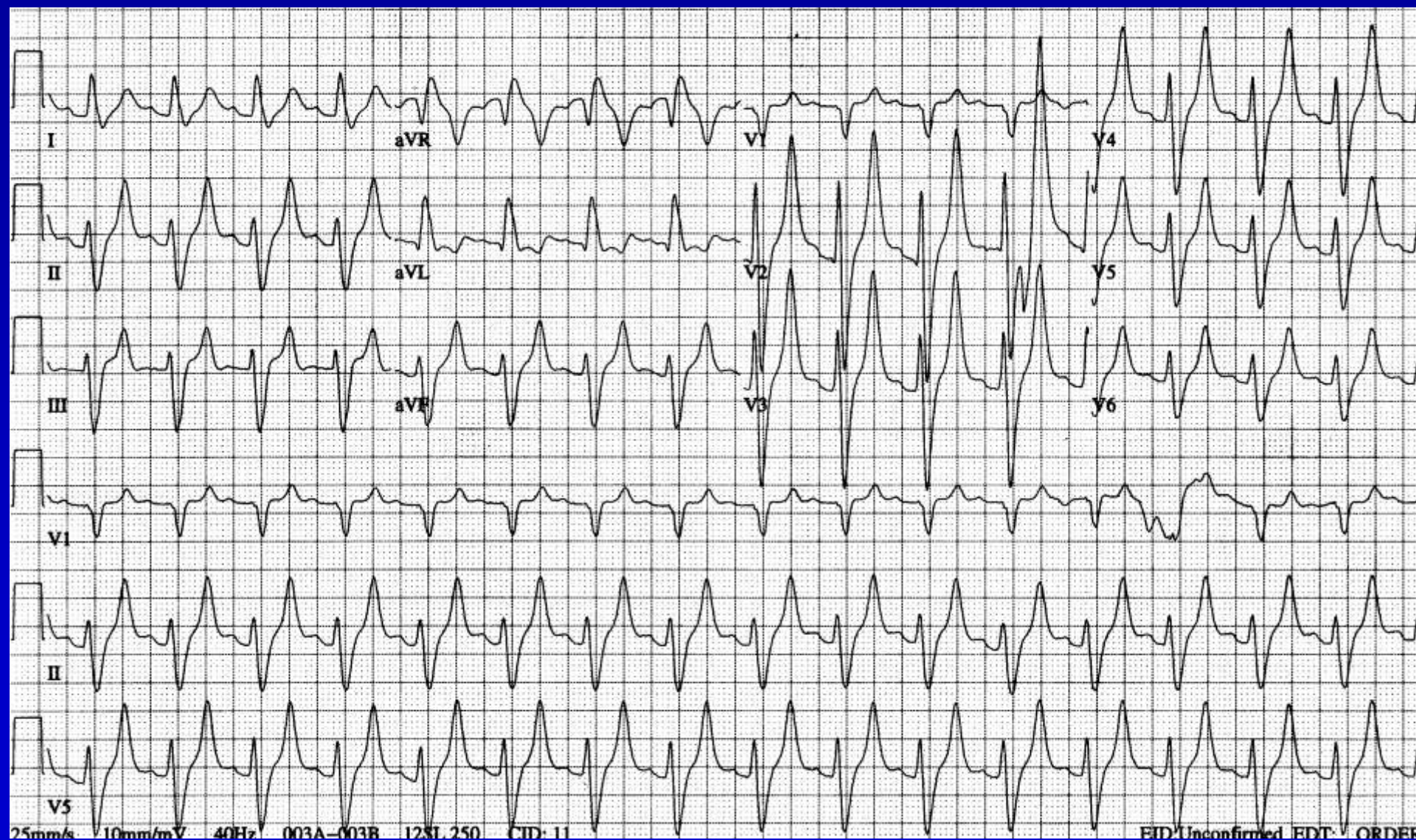
# Baseline 1997 Hyperkalemia case 3





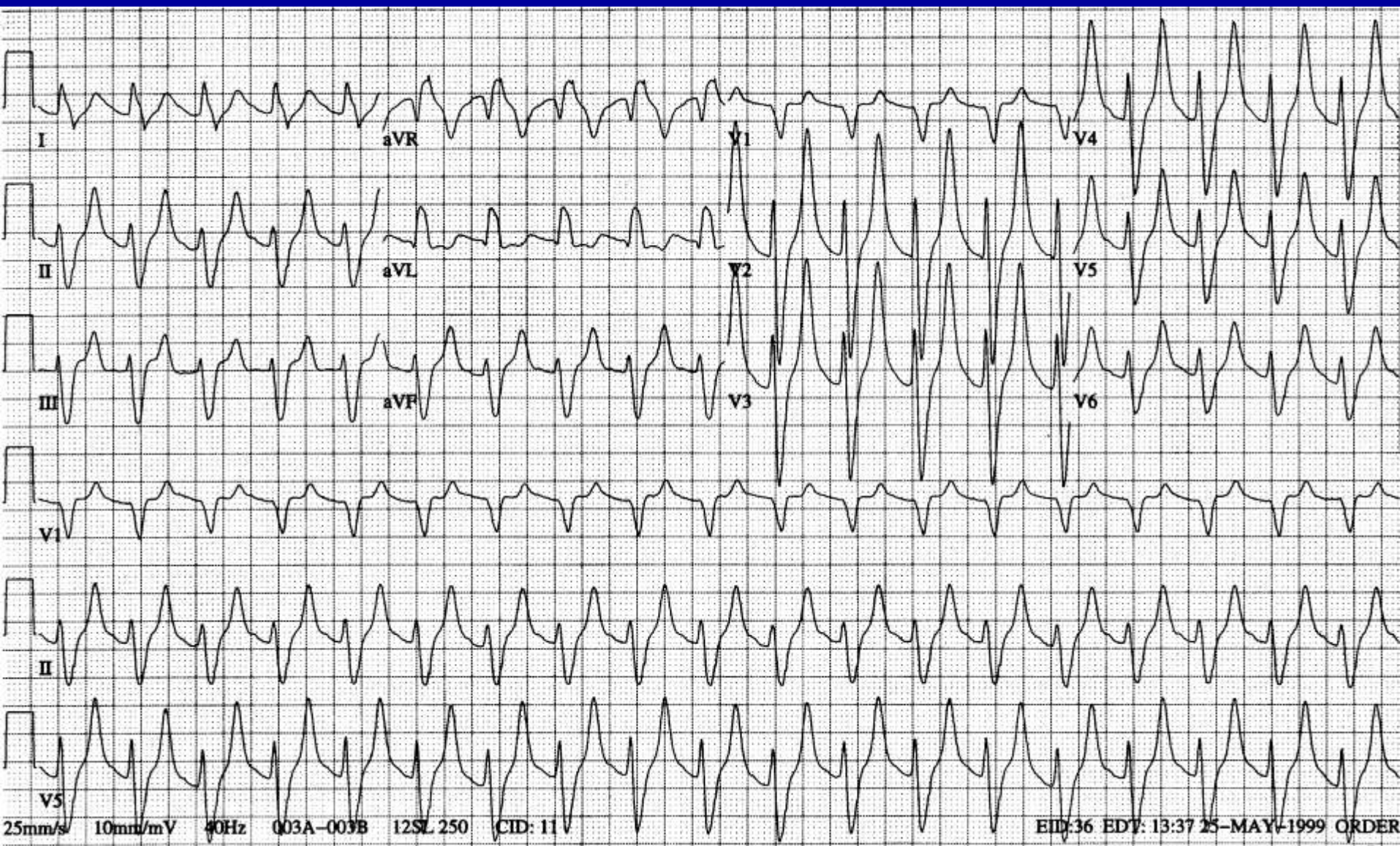
1999

# Hyperkalemia case 3



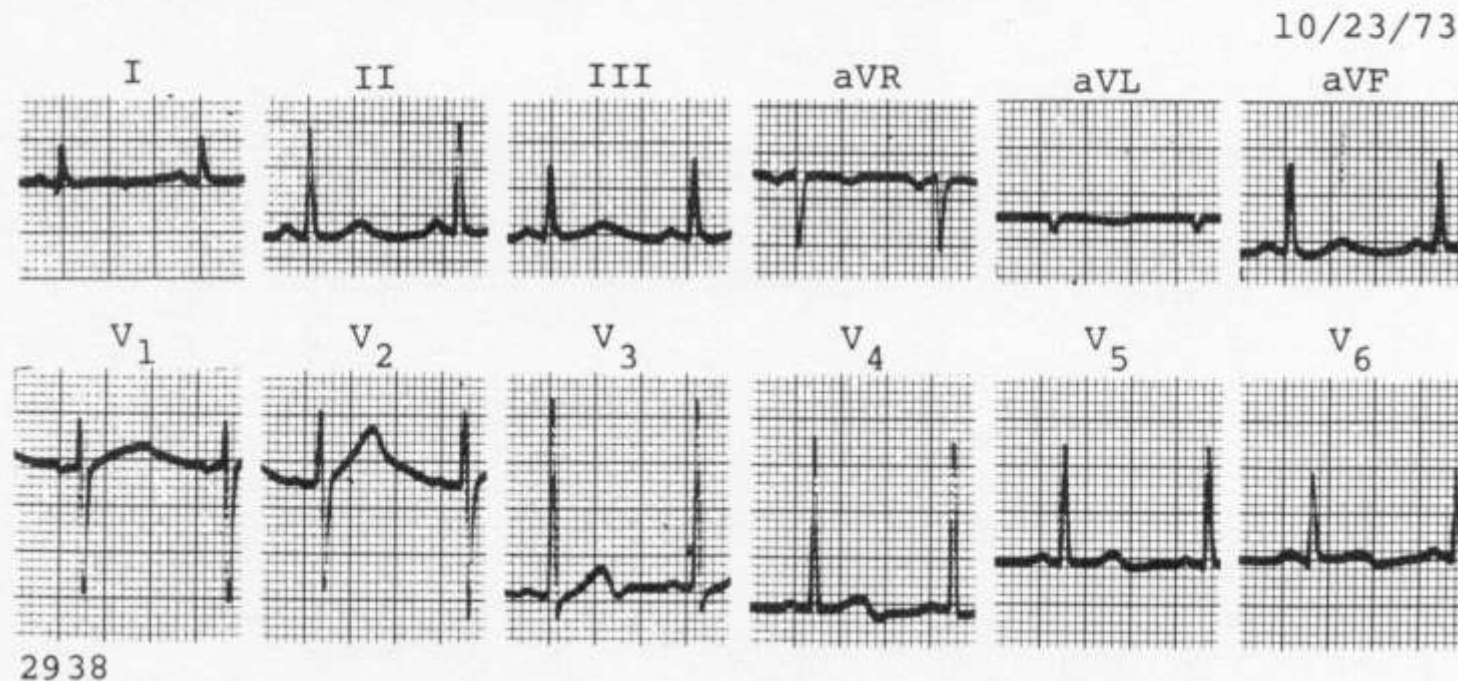
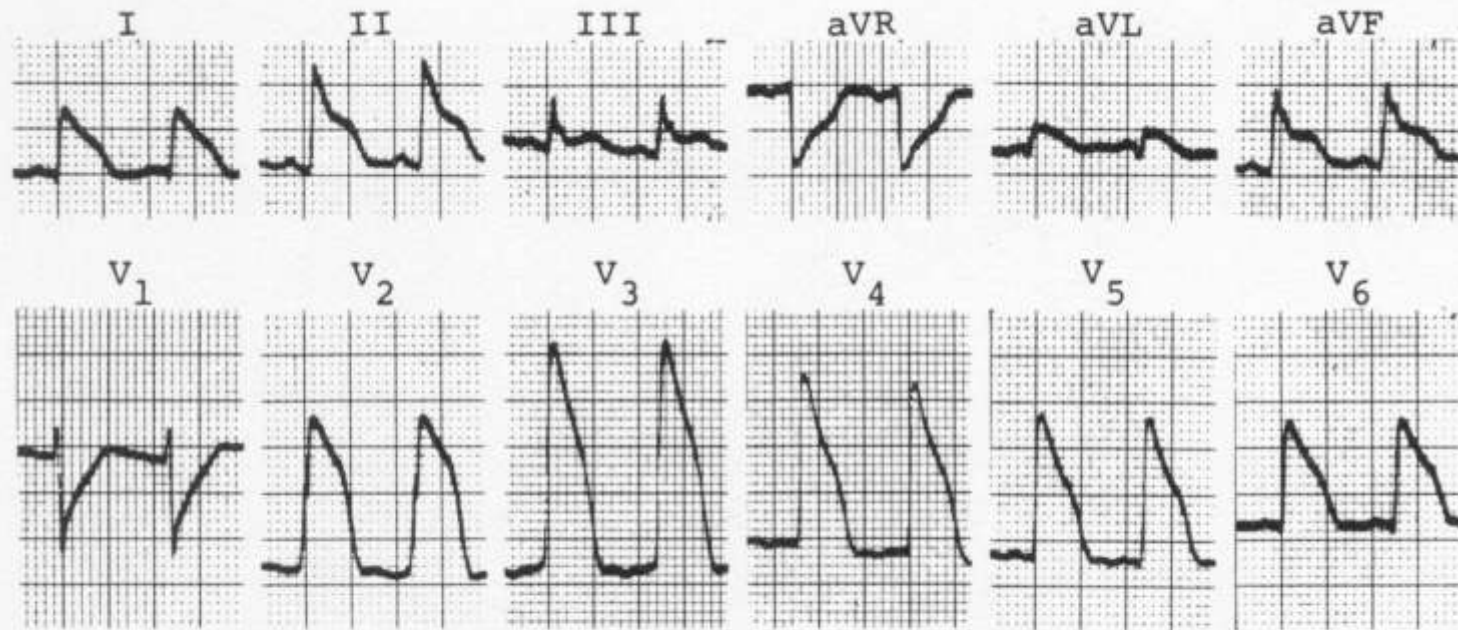


# 1999 plus 2 hours Hyperkalemia case 3





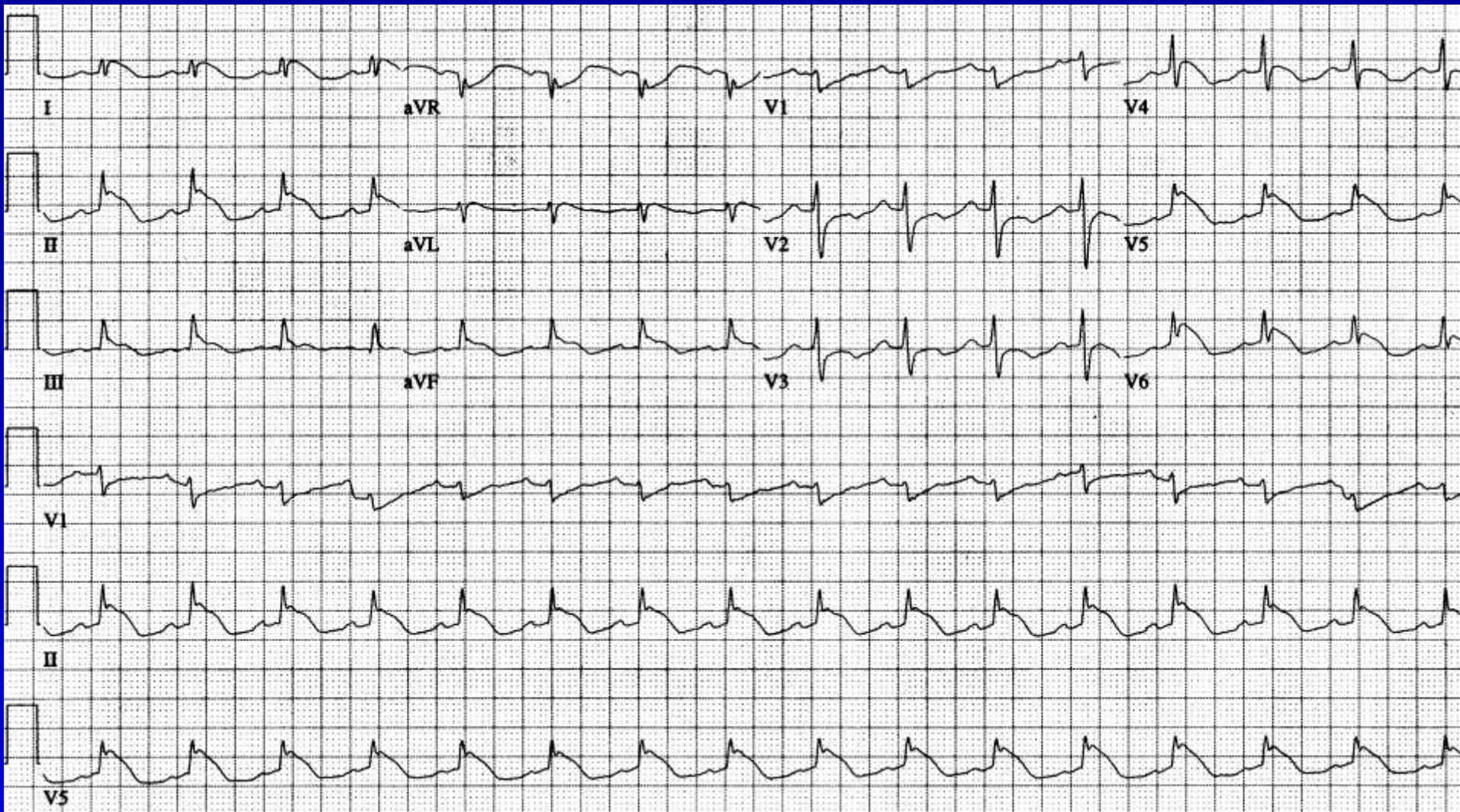
# Hyperkalemia with ST elevation





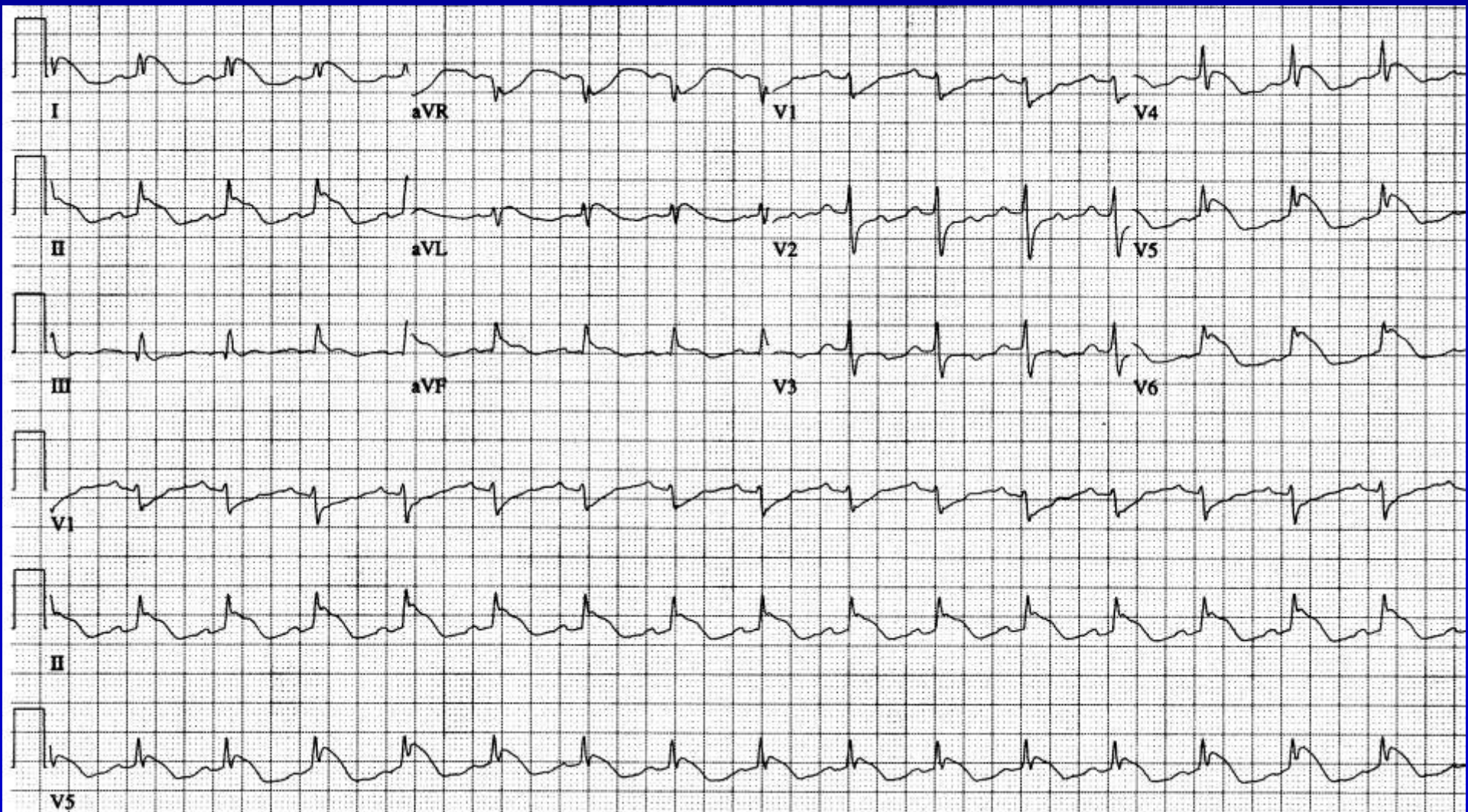
Initial

# Hyperkalemia case 4



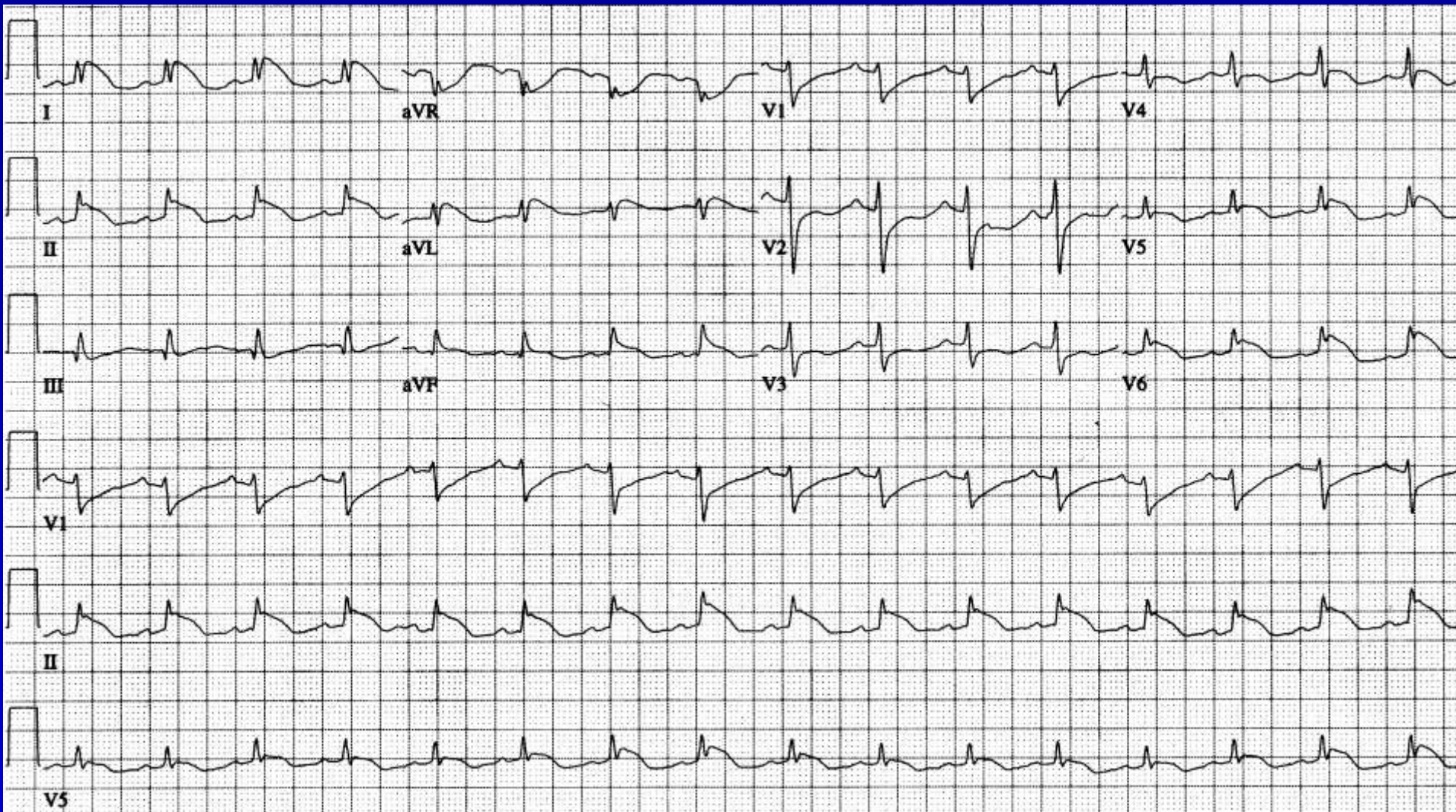


# Plus 18 minutes Hyperkalemia case 4



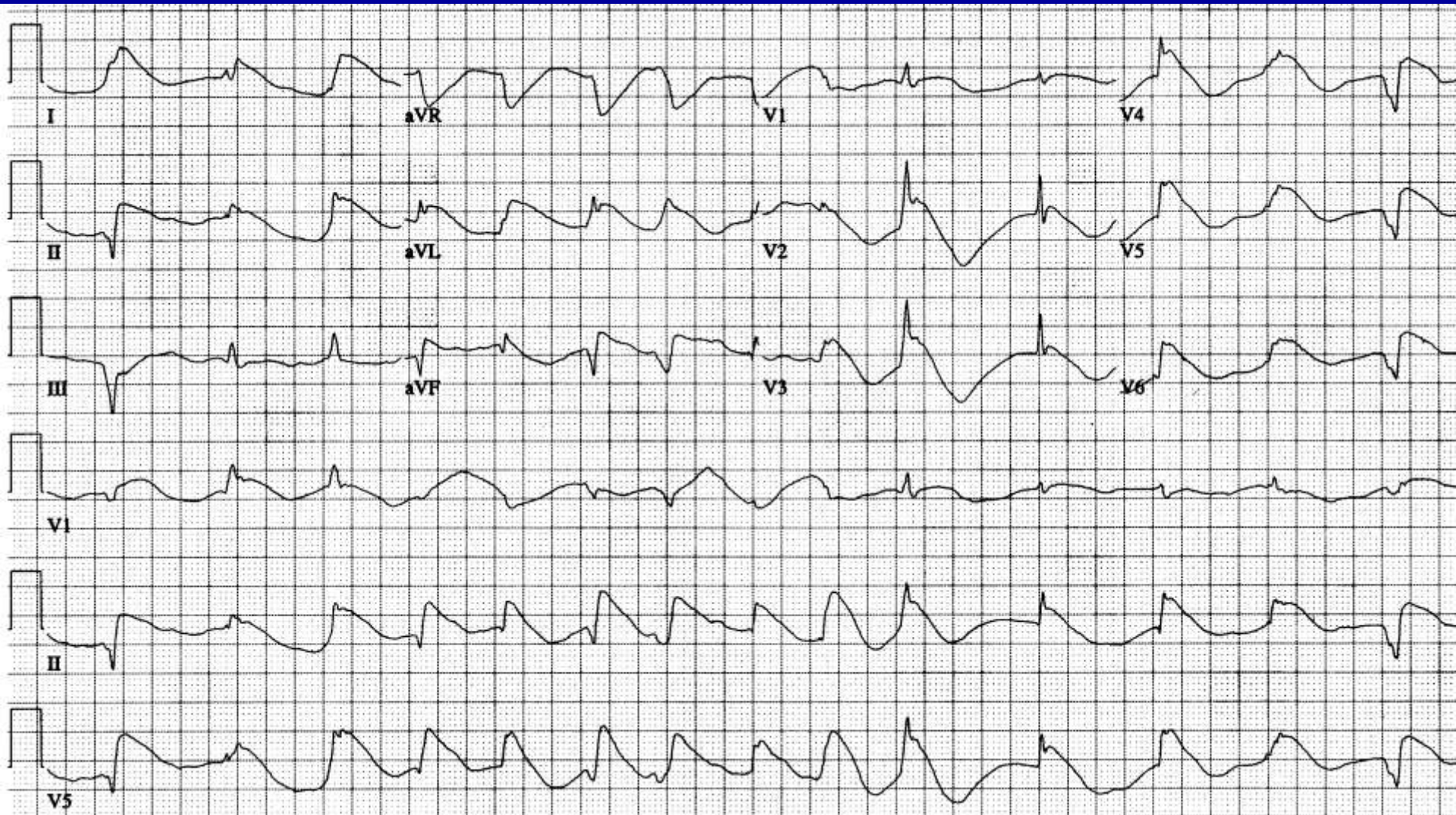


# Plus 36 minutes Hyperkalemia case 4





# Hyperkalemia case 4



Plus 3 hours; died 6 hours later

# Hypokalemia case 1



Limb leads –  $K = 2.8$



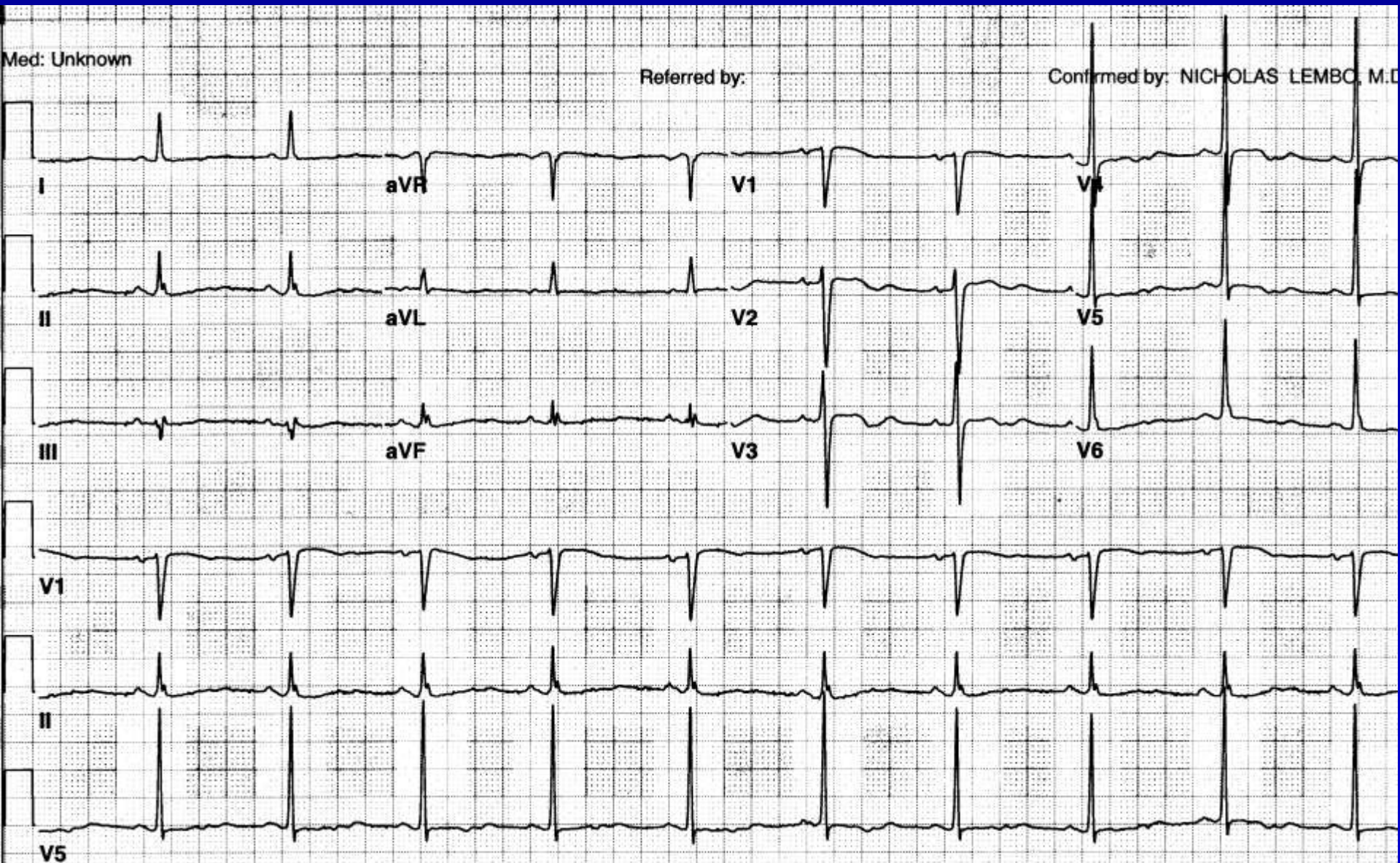
# Hypokalemia case 1



Chest leads

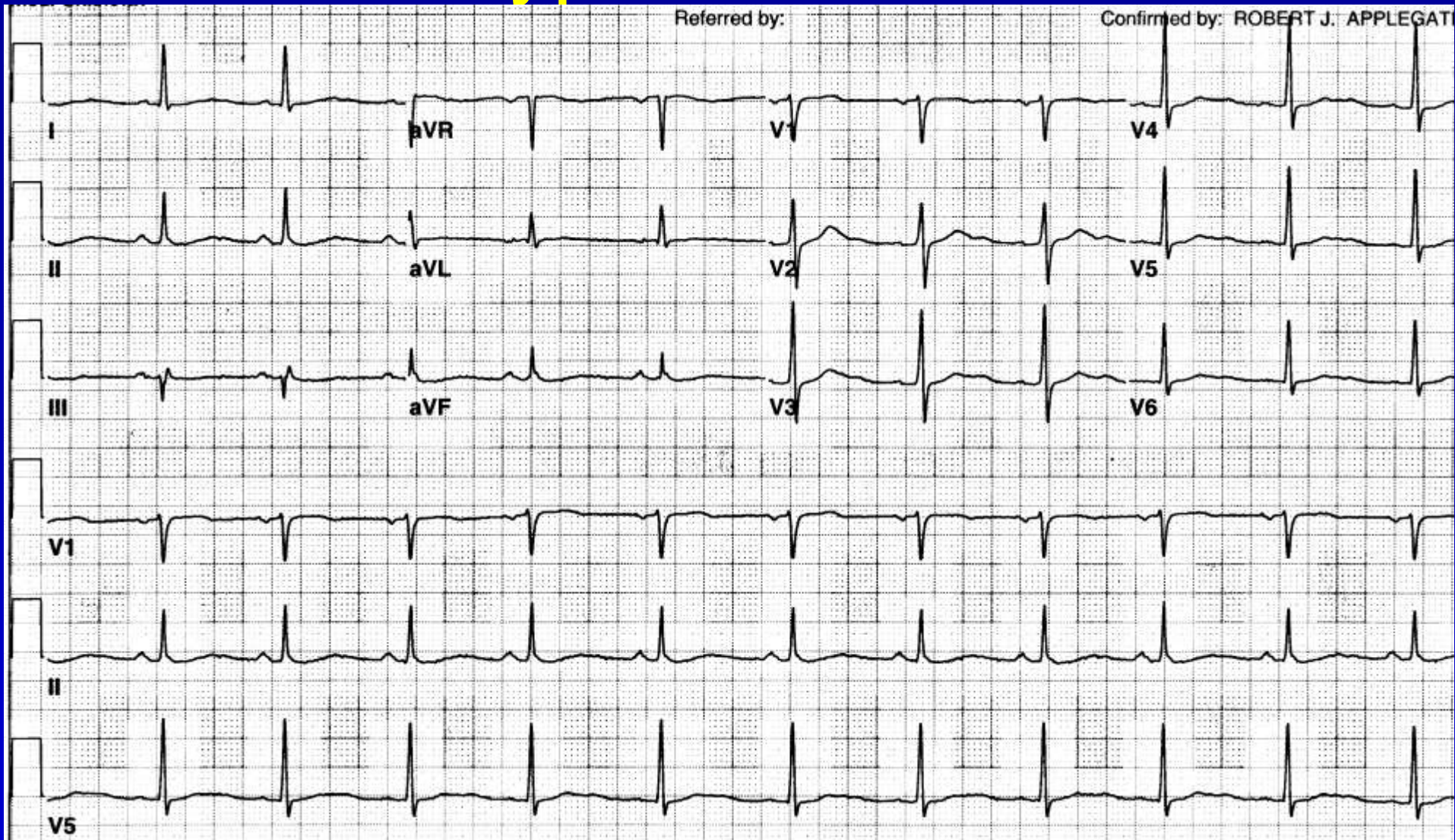
K unknown

# Hypokalemia case 2



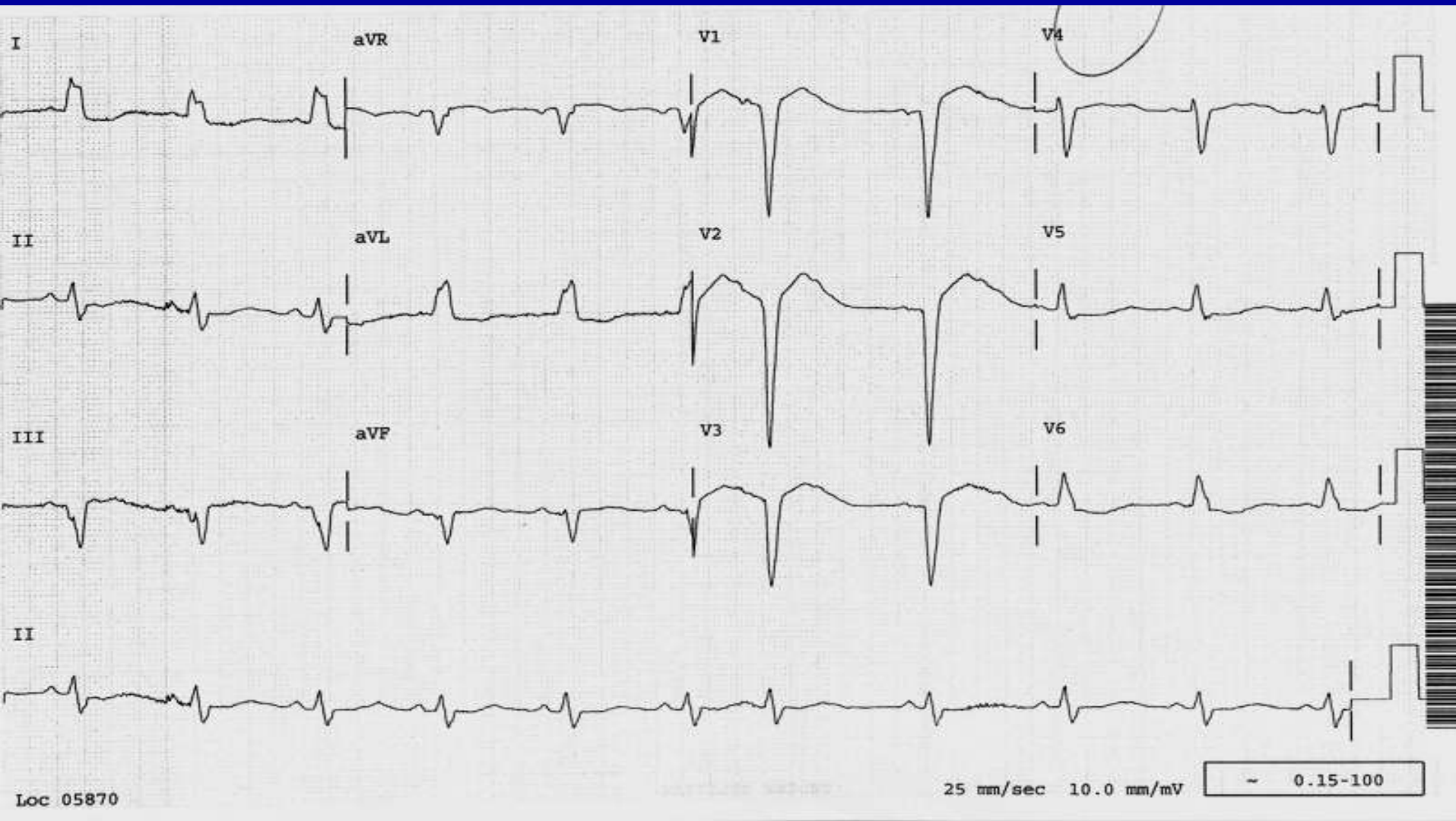


# Hypokalemia case 3



K unknown

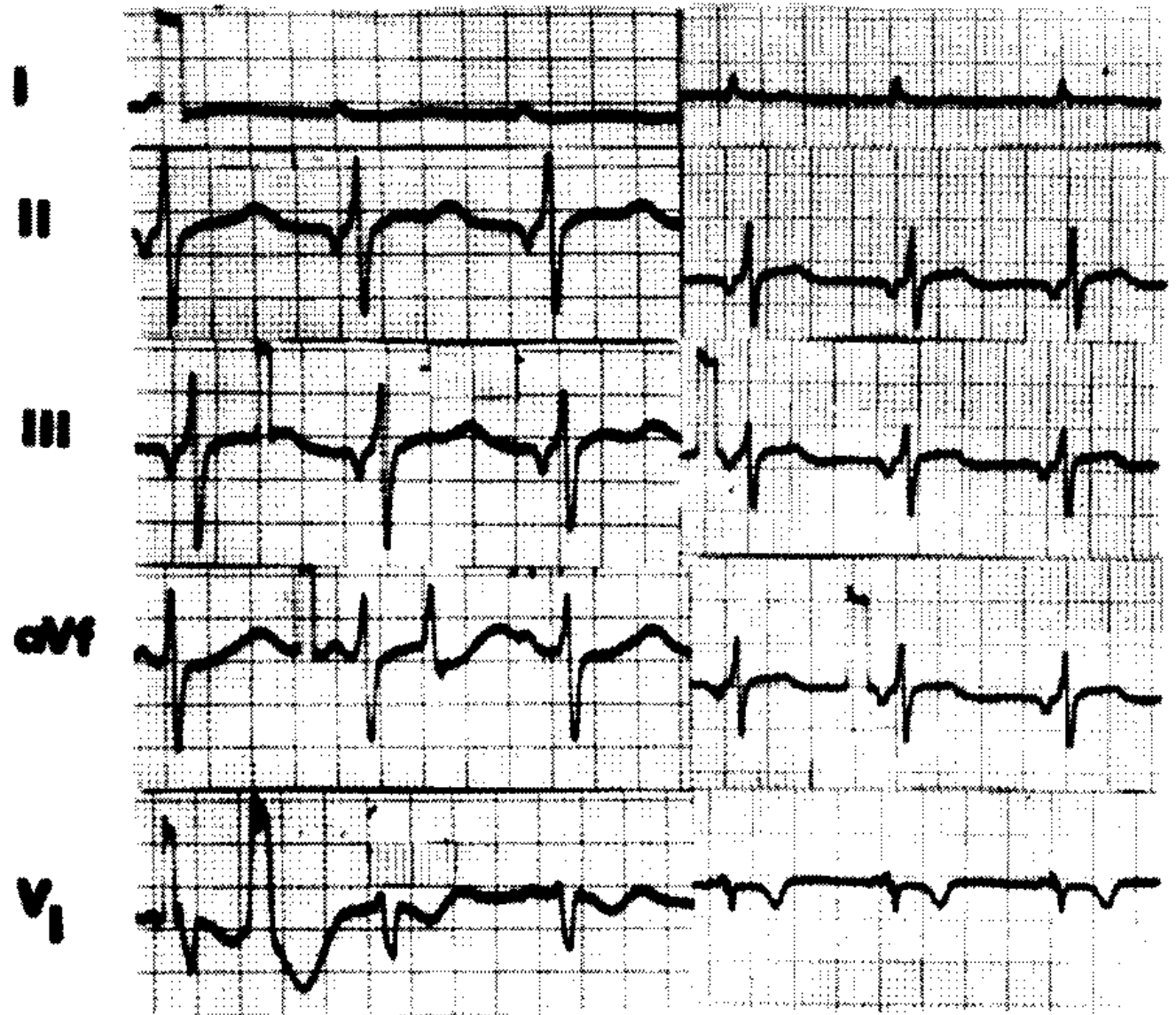
# Hypokalemia case 4



K 2.0



# Hypo- kalemia



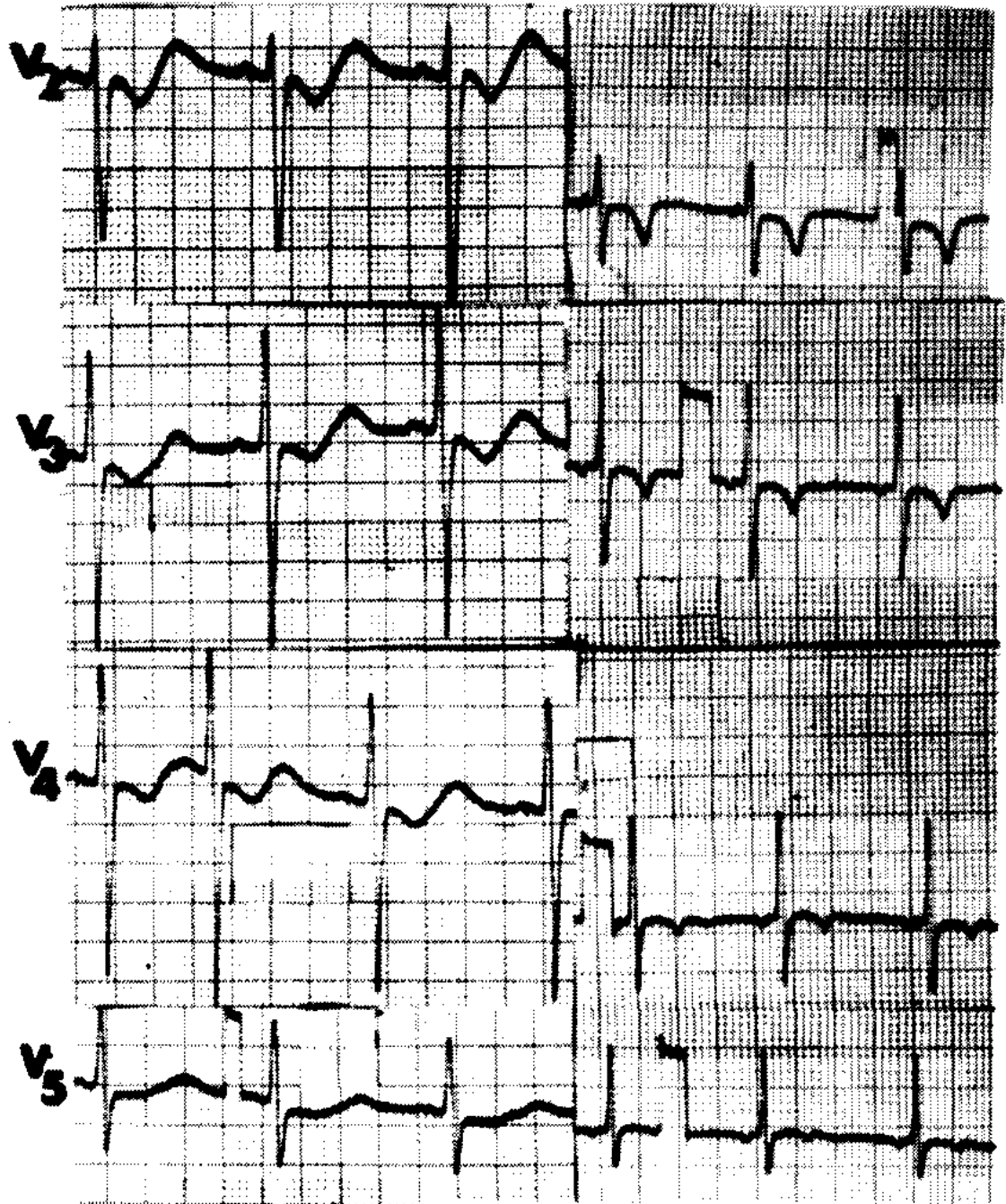
Surawicz,  
p. 526

**7-13-66 K=1.1**

**7-21-66 K=5.7**

# Hypo- kalemia

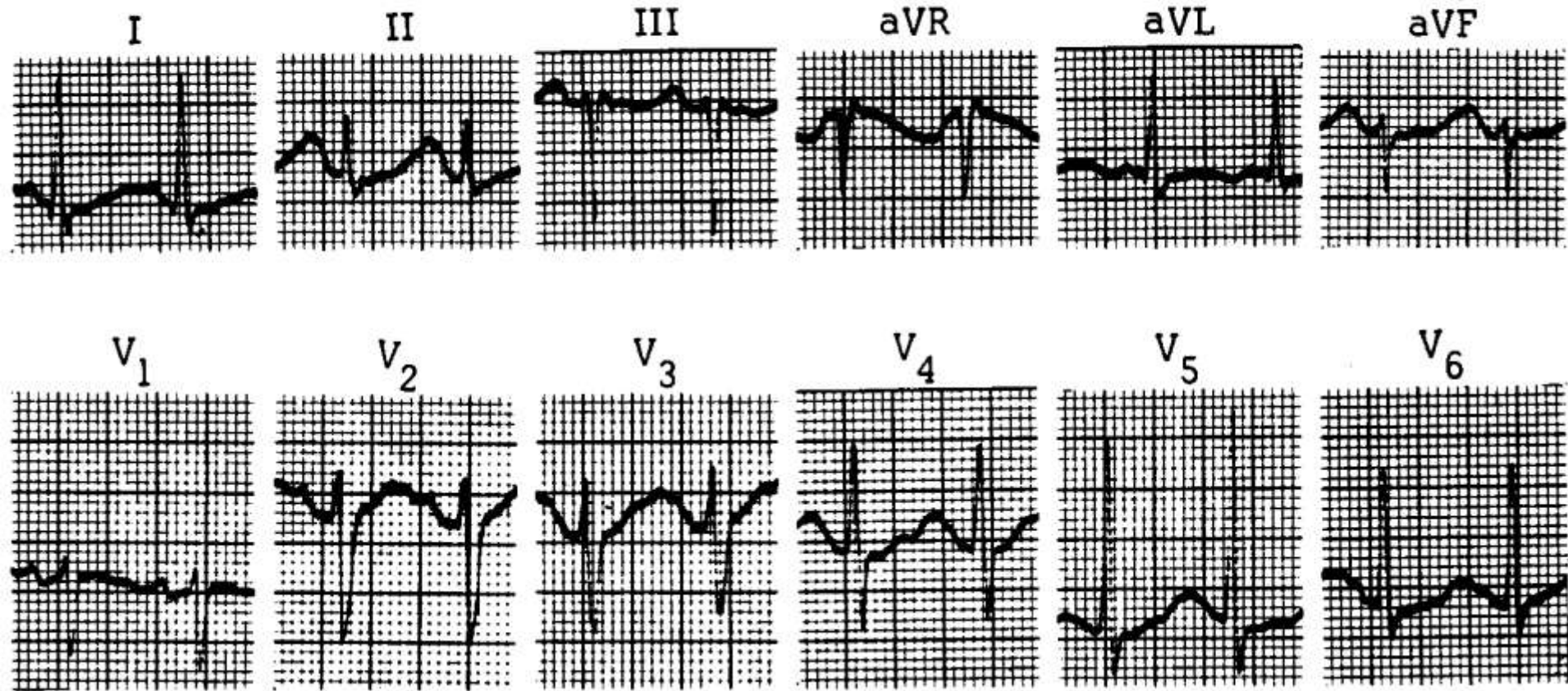
Surawicz,  
p. 526





# Hypokalemia

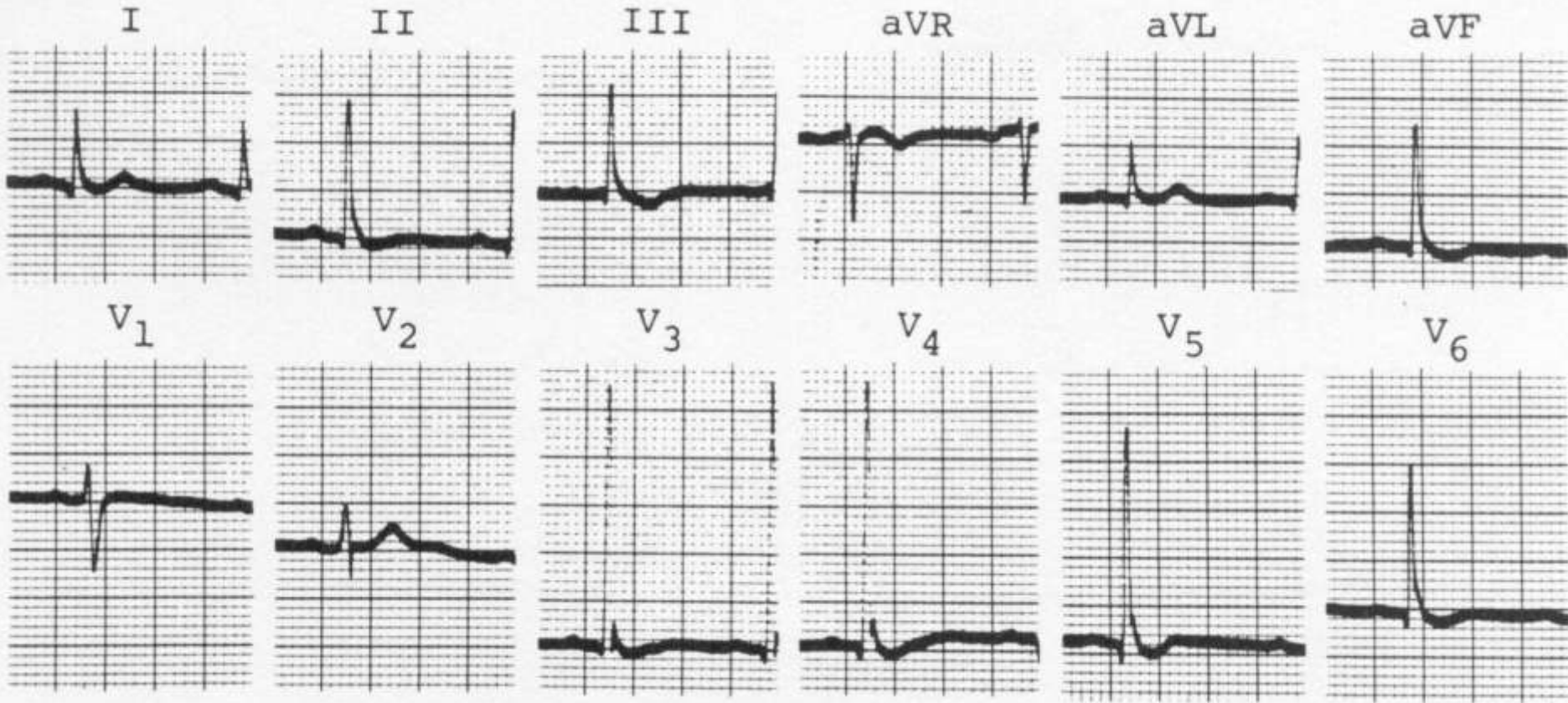
2-23-74



K = 2.4

Surawicz,  
p. 525

# Hypercalcemia



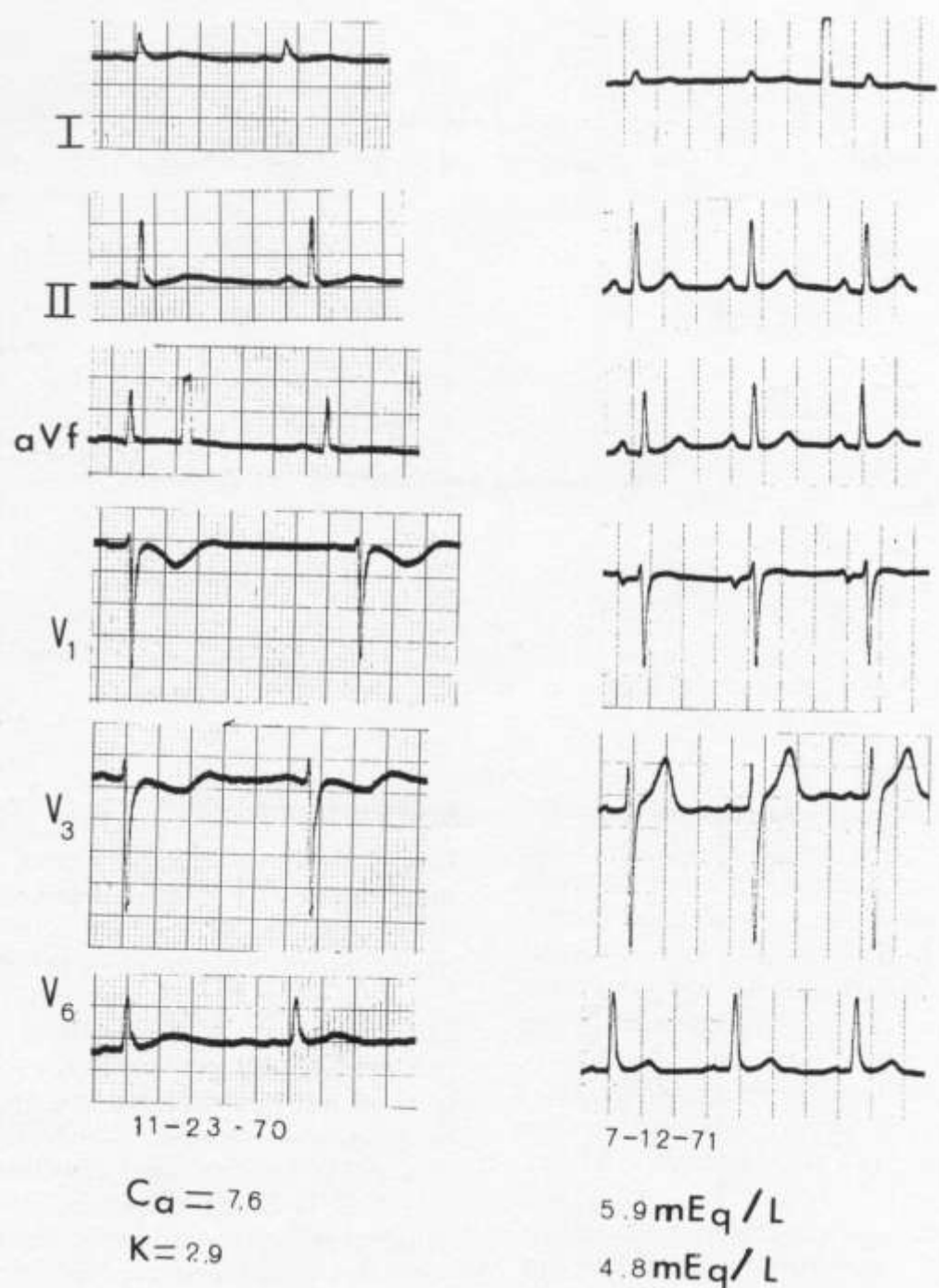
29-year old woman with lymphoma and  
bone involvement with Calcium 17.4

Surawicz,  
p. 529

# Hypercalcemia and Hypokalemia

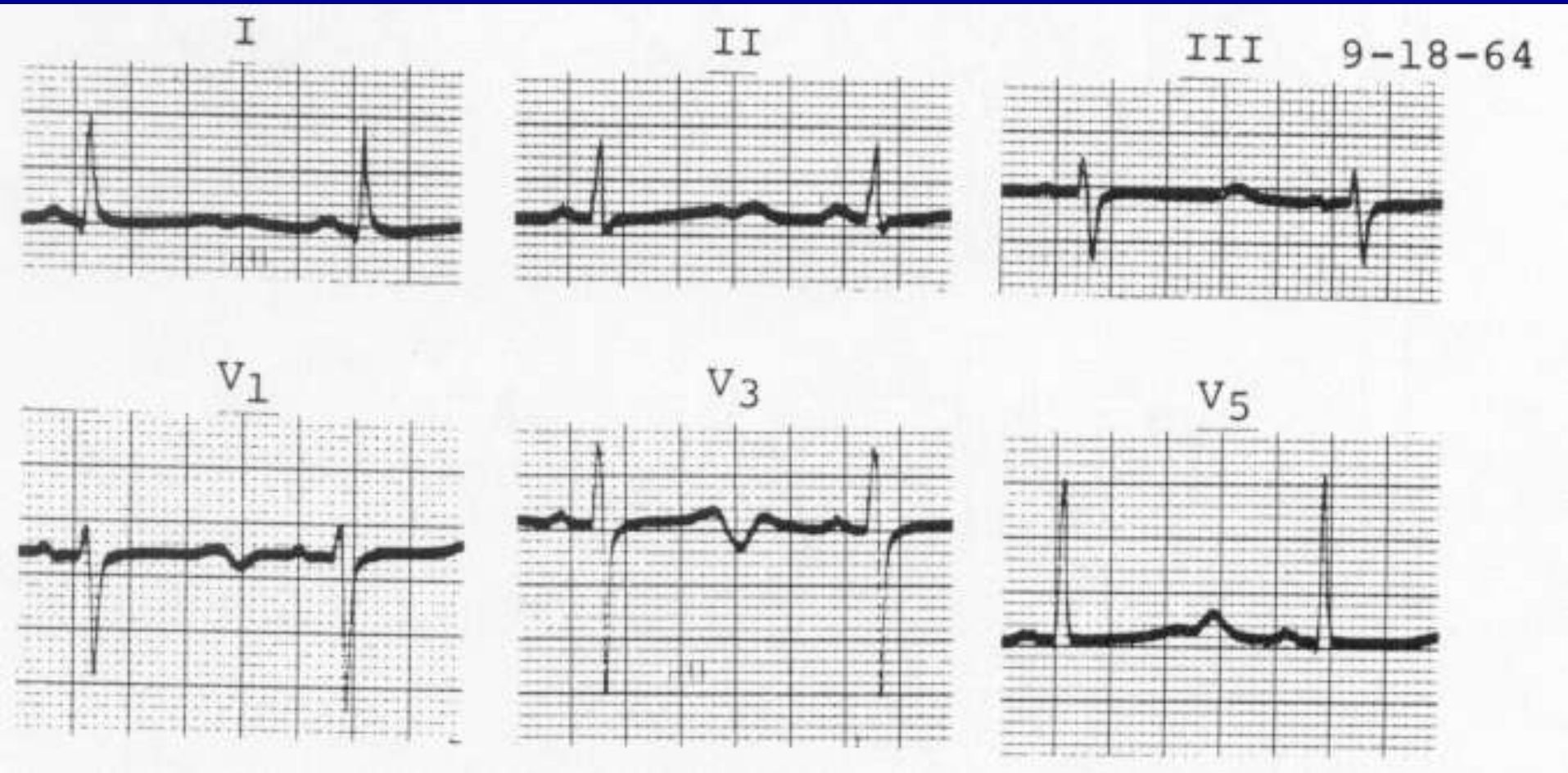
41-year old man with  
multiple myeloma , later  
normalized

Surawicz,  
p. 530





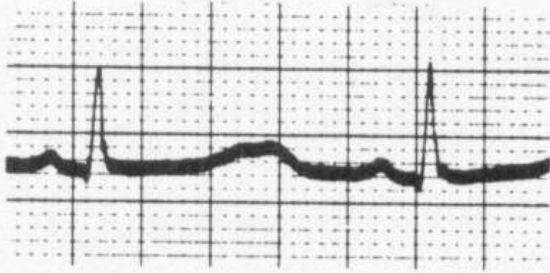
# Hypocalcemia



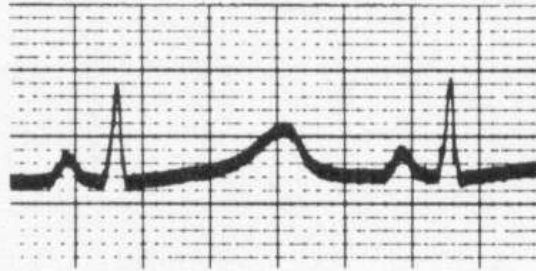
31-year old man with chronic renal failure Surawicz,  
Calcium 5.8 and K 3.3 p. 528

# Hypocalcemia

I

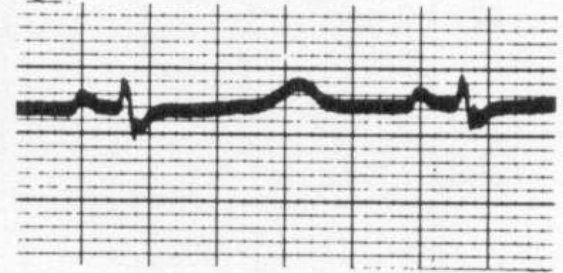


II

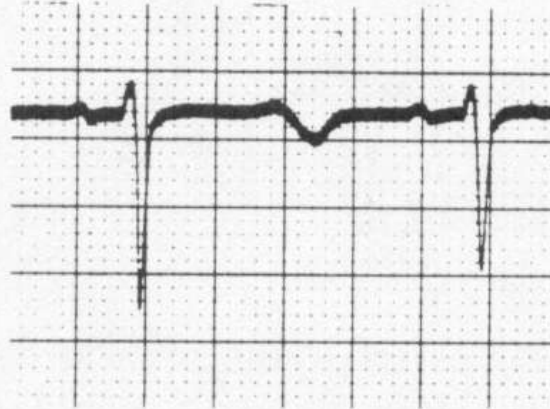


III

9-23-64



V<sub>1</sub>



V<sub>4</sub>

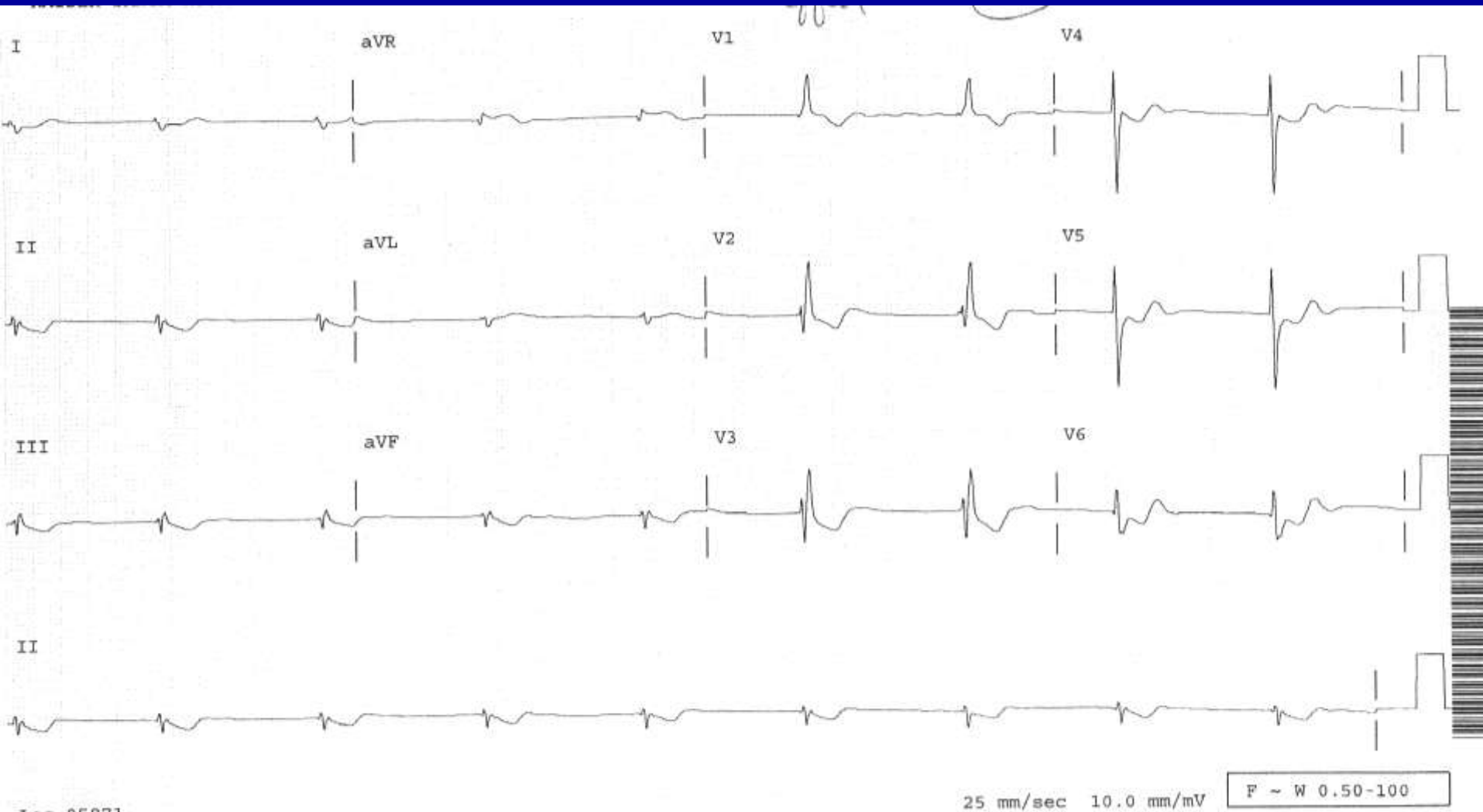


V<sub>6</sub>



31-year old man with chronic renal failure Surawicz,  
K now down to 2.8 p. 528

# Digitalis Intoxication



Short QT; Increase in automaticity; decrease in AV conduction