REPOLARIZATION CHANGES ASSOCIATED WITH AMIODARONE

By Peter Kukla M.D. Ph.D. From Poland

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Dear Professor Andrés Pérez-Riera

I would like to kindly ask you what do you think as a world-wide expert about the repolarization changes associated with amiodarone

Patient data, man- 63 yo, after old myocardial infarction, dilated ischemic cardiomyopathy, LVEDD - 64 mm, LVEF % -26 %. diabetes mellitus, renal insufficiency - eGFR- 35 ml/min, paroxysmal atrial fibrillation – treated with amiodarone for SR conversion (amiodarone 2 x 450 mg iv. within 2 days and stop after SR conversion with long QT on 3rd day.) heart failure NYHA III.

- **Normal kalemia**
- **Medication in use:**
- **Furosemide IV with potassium supplementation**
- **No spironolactone - acute renal failure, CreatIniNa - max 290 umol/l. !**
- **Bisoprolol 2.5 mg/d**
- **Ramipril 2.5 mg/d**
- **Rosuvastatin 10 mg/d**

Questions

What do you think - It is T1+T2 complex or TU complex or T1T2 + U complex.

I wonder of your opinion.

I would like to know what your friends think about it ?

How to proper assess QT interval in this patient to properly avoid SCD and TdP risk.

I am sending ECGs at 25 mm/s and 50 mm/s and 10 mm/mV, and 20 mm/mV

All the best from Poland

Peter Kukla M.D. Ph.D.

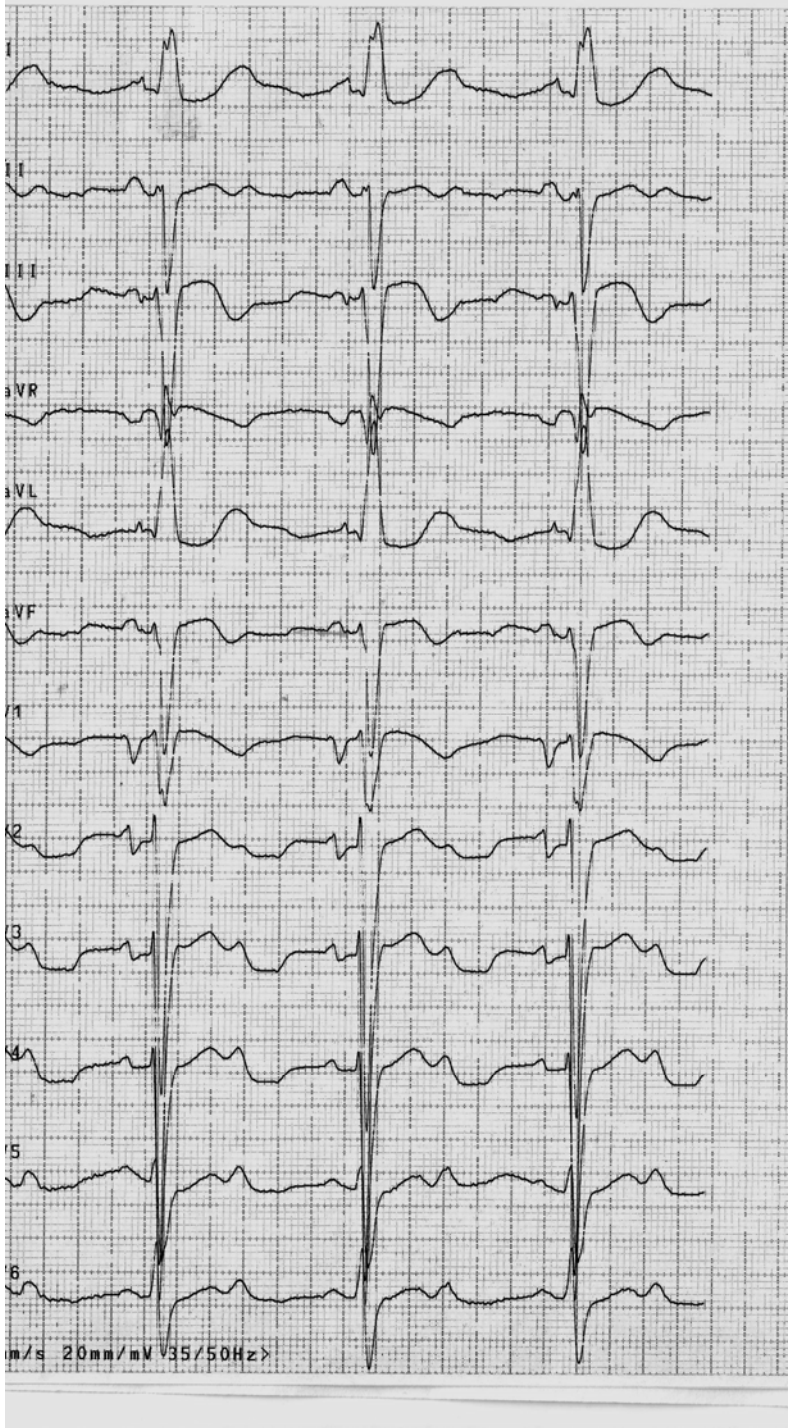
Me gustaría preguntarle qué piensa usted como uno de los expertos mundiales acerca de los cambios en la repolarización asociados con amiodarona.
Paciente del sexo masculino, 53 anos, passado de infarto de miocardio, cardiomiopatia isquemica, diámetro diastólico del VI 64mm, FE 26% diabetes, insuficiencia renal cronica eGFR- 35 ml/min,
Fue administrado amiodarona endovenosa por haver presentado una FA proxísitoca para conversión a RS. (amiodarona 2 x 450 mg EV. en 2 dias y suspendida por reversión al ritmo sinusal y aparición de intervalo QT prolongado al tercer dia.)
Está en tipo funcional NYHA III. El potasio sérico está normal.
Medicación en uso: fursemida EV con suplemento de potasio, bisoprolol 2,5mg/d, ramipril 2,5mg/d, rosuvastatina 10mg/d. No está usando espironolactona por el fallo renal agudo con creatinina - max 290 umol/l. !
¿Qué piensa usted - Es T1 + T2 o complejo de TU o T1T2 + U compleja?.

Me gustaria saber su opinión y la de sus amigos a este respecto

Como evaluar intervalo QT en este paciente para evitar la aparición de TdP y el riesgo de MSC.
Estoy enviando los ECGs a velocidades de 25 mm / s, y 50 mm / s y con voltajes de 10 mm mV /, y 20 mm / mV

Le deseo todo lo mejor desde Polonia

Peter Kukla M.D.Ph.D.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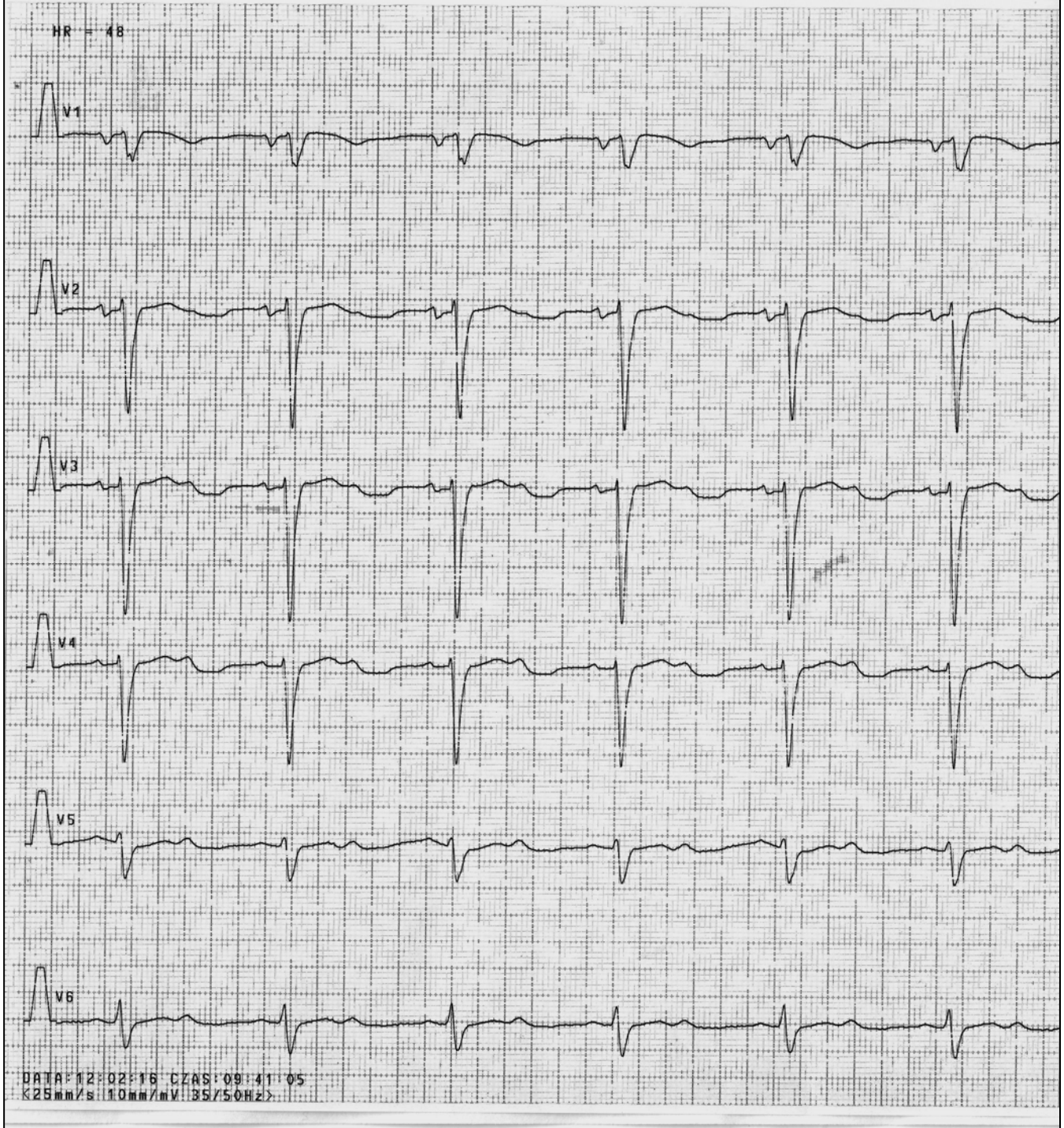
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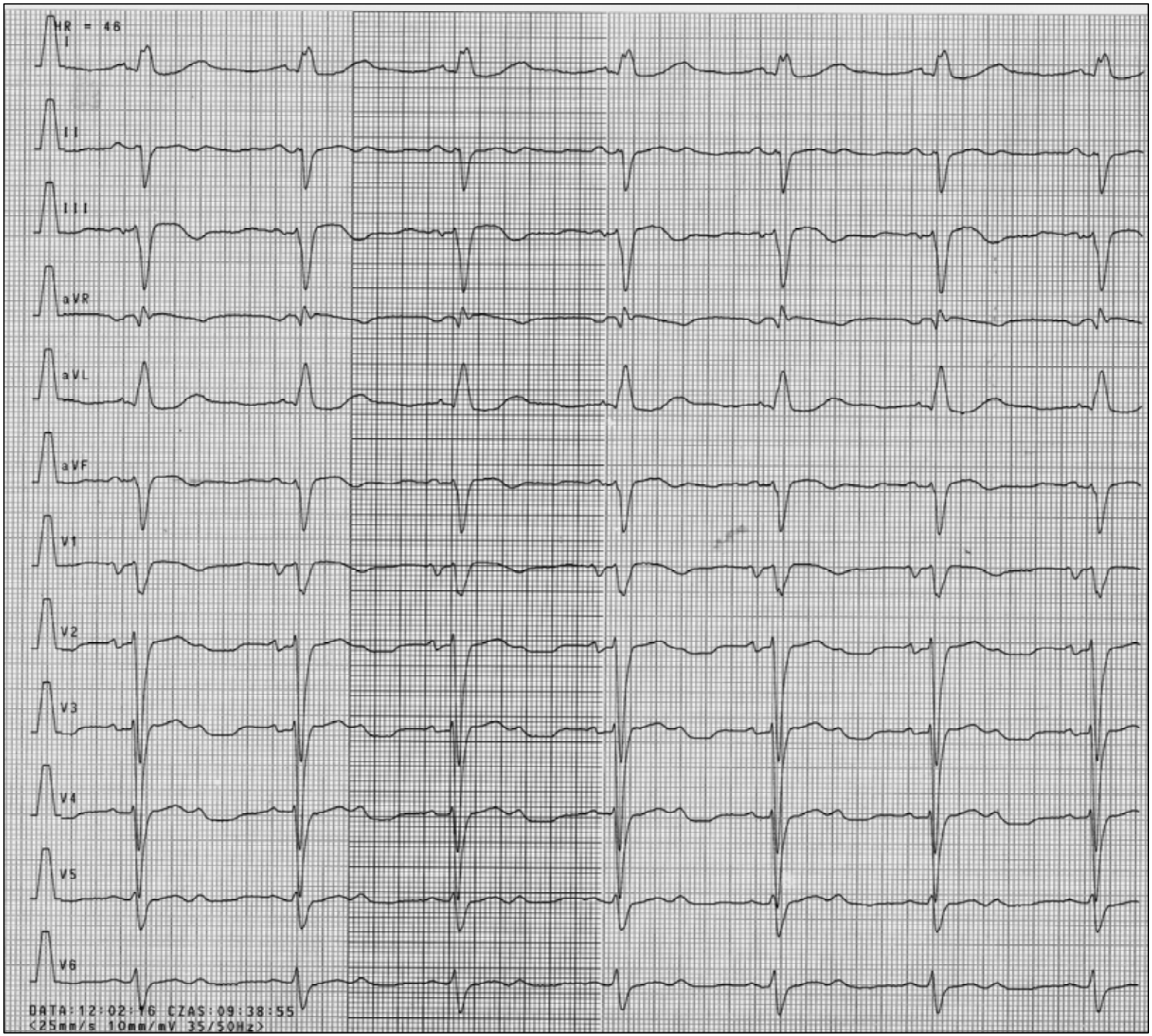
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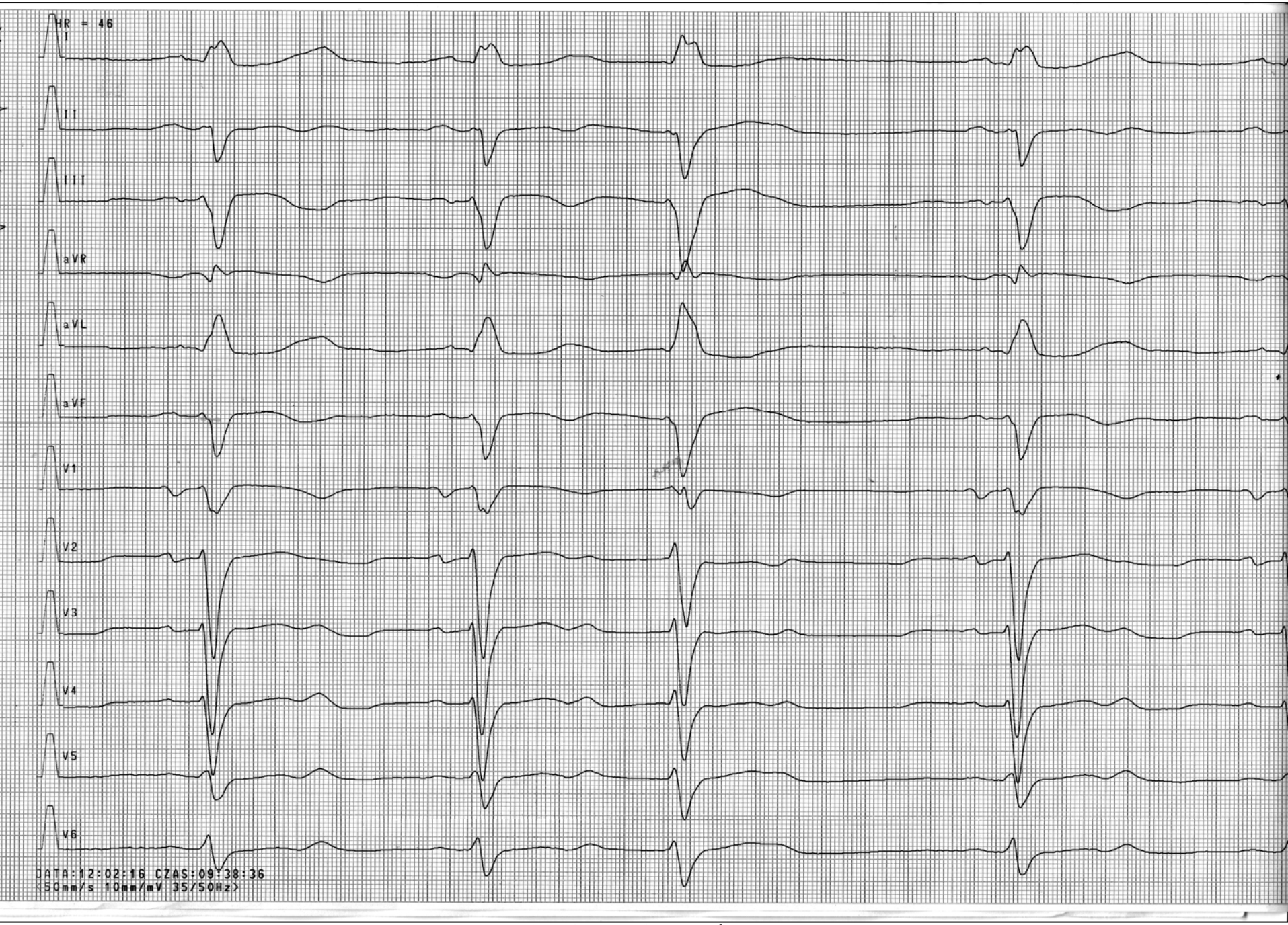
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<50mm/s 10mm/mV 35/50Hz>

2N 50mm/s

COLLEAGES OPINIONS

Amiodarone blocks many ion channels, including sodium, calcium and potassium channels. However, amiodarone does not necessarily block all channels at all times in all patients. Based on the electrocardiogram shown here, it is fairly obvious that in this particular patient and at this particular time, amiodarone is blocking the IKr channel more than other channels. Therefore, instead of seeing the broad wide T-waves commonly seen during amiodarone therapy you see the LQT2-like changes representing IKr blockade.

If you do a Holter monitoring, you are likely to see that if the patient has atrial extrasystoles, following the post-extrasystolic pauses the terminal repolarization wave will increase in amplitude and you are likely to see the atrial extrasystoles trigger pauses that are followed by ventricular extrasystoles in the typical short-long-short sequences. The question is what are the chances that this patient will develop torsade de pontes and the answer is that we do not know.

Many review articles state that amiodarone is a good example of a drug that prolongs the QT interval without leading to torsade de pointes and credit this to its calcium channels blocking actions. However, I have seen amiodarone-induced torsade numerous times.

For this particular patient I would do Holter recordings to look for the long-QT behavior mentioned above an based on that I would reconsider its use.

I hope this helps

Sami Viskin M.D. (Tel Aviv).

Spanish

La amiodarona bloquea muchos canales iónicos, incluyendo los canales de sodio, calcio y potasio. Sin embargo, no necesariamente bloquea todos los canales en todo momento en todos los pacientes. Basado en el electrocardiograma que se muestra aquí, es bastante evidente que en este paciente en particular y en este momento, la amiodarona está bloqueando el canal de I_{Kr} en mayor medida que los otros canales. Por lo tanto, en lugar de ver las ondas T de base anchas comúnmente observadas durante el tratamiento con amiodarona se observan cambios semejantes a la variante LQT2 (onda T bífida) que representan bloqueo IKr.

Si usted hace un Holter, es probable que veamos que el paciente tiene extrasístoles auriculares, seguidas de pausas postextrasistólicas con la repolarización terminal mostrando un incremento en la amplitud, lo cual constituye el gatillo de extrasístoles ventriculares con las típicas secuencias corto-largo-corto.

La pregunta es: ¿cuáles son las posibilidades de que este paciente va a desarrollar torsade Pontes? y la respuesta es que no sabemos.

Muchos artículos de revisión comentan que la amiodarona es un buen ejemplo de medicamento que prolonga el intervalo QT, sin producir torsade de pointes y atribuyen esto al bloqueo concomitante de los canales de calcio. Sin embargo, yo he visto a droga inducir torsades en numerosas ocasiones.

Para este paciente en particular yo haría un Holter, con el objetivo de buscar el comportamiento de QT largo que se mencionó anteriormente y basado en esto iria a reconsiderar su uso.

Espero que esto ayude.

Sami Viskin M.D. (Tel Aviv).

Spanish

Queridos amigos del forum: Analizare el caso del Dr Kukla de Gorlice Polonia
Alargamiento de la auricula izquierda sugeriendo una severa insuficiencia diastólica del VI.
Conducción lenta de la depolarizacion en la AI sugeriendo una severa fibrosis de esta
Desvio del eje del QRS a la izquierda, con S profundas en DIII sugeriendo una hipertrofia de la base cardiaca.
Segmento ST elevado y onda T negativa sugeriendo disquinesia por infarto antiguo de cara inferoposterior.
El desdoblamiento del primer vector en DII indica fibrosis inferior, debido a un infarto antiguo; Ondas r /S profundas precordiales y anchas sugeriere que este paciente desarrolló dilatación ventricular a partir de HVI por enfermedad isquémica crónica.
La rampa inicial de la onda T (controlada por los canales lentos de potasio IKs) no está afectada. La segunda parte de la onda T (desde el ápice hasta el final) controlada por los canales rápidos de potasio está muy alargada 280 ms y una onda tardia se ve en ella. Las drogas que alargan la segunda parte de las ondas T como amiadarona, sotalol, quinidinina , etc deprimen el receptor rápido del potasio Ikr. Este caso es extremo, debido a la alteracion severa de la arquitectura del VI.
Otro factor importante es la bradicardia significativa (56 lpm) debido efecto betabloqueante del fármaco.
Bradicardia + intervalo QT prolongado + onda T desdoblada + enfermedad estructural del VI es un escenario propicio para la aparición de torsades.
Por supuesto que existen varios diagnósticos diferenciales de hipertofia con dilatación del VI como la amiloidosis, sarcoidosis, enfermedad de Aderson, cardiopatia hipertensiva
Un fraternal abrazo
Samuel Sclarovsky

Dear friends of the forum: will analyze the case of Dr Kukla of Poland Gorlice
Elongation of the left atrium suggesting a severe diastolic LV failure.
Slow conduction depolarization in the left atrium suggesting severe fibrosis of this chamber.
Extreme QRS left axis deviation: deep S in III suggesting a hypertrophy of the cardiac base.
ST segment elevation and negative T wave dyskinesia suggesting old inferoposterior myocardial infarction.
The splitting of the first vector in II below indicates fibrosis, due to old infarction;
r /S precordial deep and wide sugeriere that this patient developed ventricular dilatation after chronic ischemic LVH.
Initial ramp of the T wave controlled by slow potassium channels (I_{Ks}) is not affected.
The second part of the T wave (from the apex to the end of the T wave) controlled by rapid potassium channel(I_{Kr}) is very long 280 ms and a late wave is on it. Drugs that prolong the second part of the T waves such as amiadarona, sotalol, quinidinina, etc. quickly depress the potassium IKr receptor. This is an extreme case, due to the severe alteration of the architecture of the LV.
Another important factor is the significant bradycardia (56 bpm) because β-blocker effect of the drug.
Bradycardia + prolonged QT interval + bifid T wave + LV structural disease is a perfect scenario for the occurrence of torsades.
Of course there are several differential diagnoses of dilated LV hipertofia as amyloidosis, sarcoidosis, Aderson disease, hypertensive heart disease.
A fraternal embrace
Samuel Sclarovsky

Dear Andrés: Thanks for sharing the case ECGs. I would like to request a pre-Amiodarone ECGs tracing for QRS-ST-T comparisons. Gracias por compartir este caso con los ECGs. Me gustaria ver los trazados prévios al empleo de la amiodarona

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Dear Professor Andrés Pérez-Riera:: Unfortunately I have no ECG before amiodarone because that patient for the first time was admitted to our hospital. We have no access to earlier ECG tracings.

Peter Kukla.

Querido Profesor Andrés Pérez-Riera infelizmente no tengo los ECGs antes de la administración de la amiodarona porque fue la primera vez que fue admitido en nuestro hospital. No tenemos aceso a trazados iniciales

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Beautiful mind Sami. In most cases amiodarone does NOT cause LQT2-like notched/bifid T waves because it prolongs repolarization homogeneously. Otherwise it could have been pulled off the market long time ago. I wonder some of those patients with bad luck TdP may have a genetic predisposition or on other QT prolonging drugs the same time.

Thus comparing the QRS-ST-T morphology pre- and after-drug is essential in this case. Sincerely yours,Li

Hermoso raciocinio Sami. En la mayoría de los casos, amiodarona no causa el patrón LQT2 simil (ondas T con muescas/bífidas) ya que prolonga la repolarización en forma homogénea. De lo contrario, hubiera sido retirada del mercado hace mucho tiempo. Me pregunto si algunos de esos pacientes pueden tener una predisposición genética o otros medicamentos prolongan el intervalo QT al mismo tiempo.

Por lo tanto la comparación de la morfología del QRS-ST-T pre- y después de las drogas es esencial en este caso. Atentamente, Li

Estimado Peter Kukla M.D.Ph.D.
En el paciente que ha referido presenta signos de crecimiento auricular izquierdo, BCRI con una duracion del QRS de 0,16 seg y eje desviado a la izquierda. Probale secuela inferior y anterior extensa. No evidencia de isquemia miocardica aguda. Si no posee territorios revascularizables, estoy seguro estoy ya fue evaluado previamente. Si presenta territorios revascularizacion. Por la FEY de eyeccion referida y los transtornos de la conduccion es un candiadato a terapia de resincronizacion cardiaca y CDI.
Presenta prolongacion del intervalo QT, en esto creo la amiodarona solo evidencio el aumento de este por las interacciones de los medicamentos y cardiopatia de base que presentaba previamente. Ademas de las interacciones medicamentosas de la medicacion referida, lo refirio diabetico, seria interesante conocer los medicamentos no cardiológicos que recibe ya que en un paciente con clearence renal disminuido es mas frecuente la aparicion de efectos adversos por los medicamentos administrados. La disminucion de la eliminacion renal de un farmaco que posee union a proteinas plasmaticas y/o metabolismo hepatico se vera influenciado por otro farmaco de eliminacion renal, a pesar de que el medicamento administrado no sea de eliminiacion renal. El paciente referido recibe suplementos de potasio, no se ha tenido en cuenta la hipomagnesemia como factor asociado, o el hipotiroidismo.
Un cordial saludo y mis disculpas por lo extenso del mensaje.
Martin Ibarrola

La amiodarona bloquea inactivando los canales del sodio y actua por inhibición no competitiva de los diversos receptores alfa y beta el corazón, Sus efectos más importantes son: prolongación del potencial de acción, consecuentes con la actividad antiarrítmica clase III. Aumenta en la duración del potencial de acción en las aurículas, ventrículos y nódulo AV. La repolarización se atrasa teniendo la amiodarona una fuerte acción antifibrilatortoria. Posee efectos clase I "Lidocaina": deprime la Vmax y la velocidad de conducción. Prolonga el periodo refractario efectivo de la aurícula, ventrículos, nódulo AV, y sistema His-Purkinje.

Raramente, puede provocar TdP. De los fármacos de clase III, la amiodarona y la azimilida se asocian con un riesgo menor de TdP (< 1%) La dofetilida y el sotalol (3% y 2.5% respectivamente). Son factores de riesgo para la aparición de TdP el sexo femenino, un intervalo QT prolongado de base, la administración simultánea de otros fármacos que provocan la prolongación de este intervalo, la hipopotasemia, la hipomagnesemia, la bradicardia y la enfermedad cardíaca estructural.

La amiodarona se metaboliza en el hígado. Las reacciones enzimáticas del sistema citocromo P450 producen un metabolito activo, la desetilamiodarona, que tiene efectos electrofisiológicos similares al compuesto original. depuración renal es mínima, por lo que no se debe corregir la dosis en los pacientes con insuficiencia renal. Finalmente, se produce la glucuronidación del fármaco y se excreta por vía biliar.

El efecto Wolff-Chaikoff. zonas con alto contenido de iodo en el medio ambiente (con una incidenciadel 13%), a la inversa de lo que sucede en zonas con bajo contenido en iodo (incidencia del 6,4%). pacientes con trastornos subyacentes en la glándula tiroides. diagnóstico es presumido cuando hay aumento en los niveles de TSH y disminución en los de T4 y T3. el aumento de la TSH durante los primeros tres meses de comenzado el tratamiento con amiodarona no es en sí diagnóstico ya que puede ser un fenómeno transitorio. compromiso hepático por la utilización de amiodarona varía según los autores entre 4% y 25%.

El bisoprolol se elimina por igual por vía renal y extrarrenal con 50% de la dosis que aparece sin alterar en la orina mientras que el resto aparece como metabolitos inactivos. Menos del 2% de la dosis se excreta en las heces. La semi-vida de eliminación del bisoprolol es de 9-12 horas y es algo mayor en los pacientes ancianos. En los sujetos con una CrCl < 40 ml/min, la semi-vida de eliminación es unas tres veces mayor que en los sujetos sanos. En los pacientes con cirrosis, la semi-vida de eliminación oscila entre 8.3-21.7 horas.

La administración concomitante de amiodarona y bisoprolol ha demostrado en algún caso aumentar la bradicardia

Síndrome de QT Largo Adquirido."Torsade de Pointes"Marcelo E. Lanzotti, Norberto Citta

Not sure are significance of these changes but amiodarone is associated with marked lenghthening of the QT-QU intervals but seldom produces torsade.
Antzelevitch's studies suggest that althoughh repolarization is prolonged there is less dispersion of refractoriness in wedge preparations.
If the effects are effective in rhythm control would continue.
I know of Rodin and Viskin's observations that a T1/T2 is associated with increased risk of torsade.

No estoy seguro del significado de estos cambios, pero la amiodarona se asocia con marcada prolongación de los intervalos QT-QU, no obstante rara vez produce torsade.
Los estudios de Antzelevitch realizados en preparados de cuña "wedge preparations" sugieren que repolarización se prolonga, no obstante hay menor dispersión de la refractariedad.
Si los efectos son eficaces en relación al control del ritmo continuaria.
Las observaciones de Rodin y Viskin en casos de T1/T2 se asocian con un mayor riesgo de torsade.

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FINAL COMMENTS

By Andrés Ricardo Pérez-Riera M.D. Ph.D.
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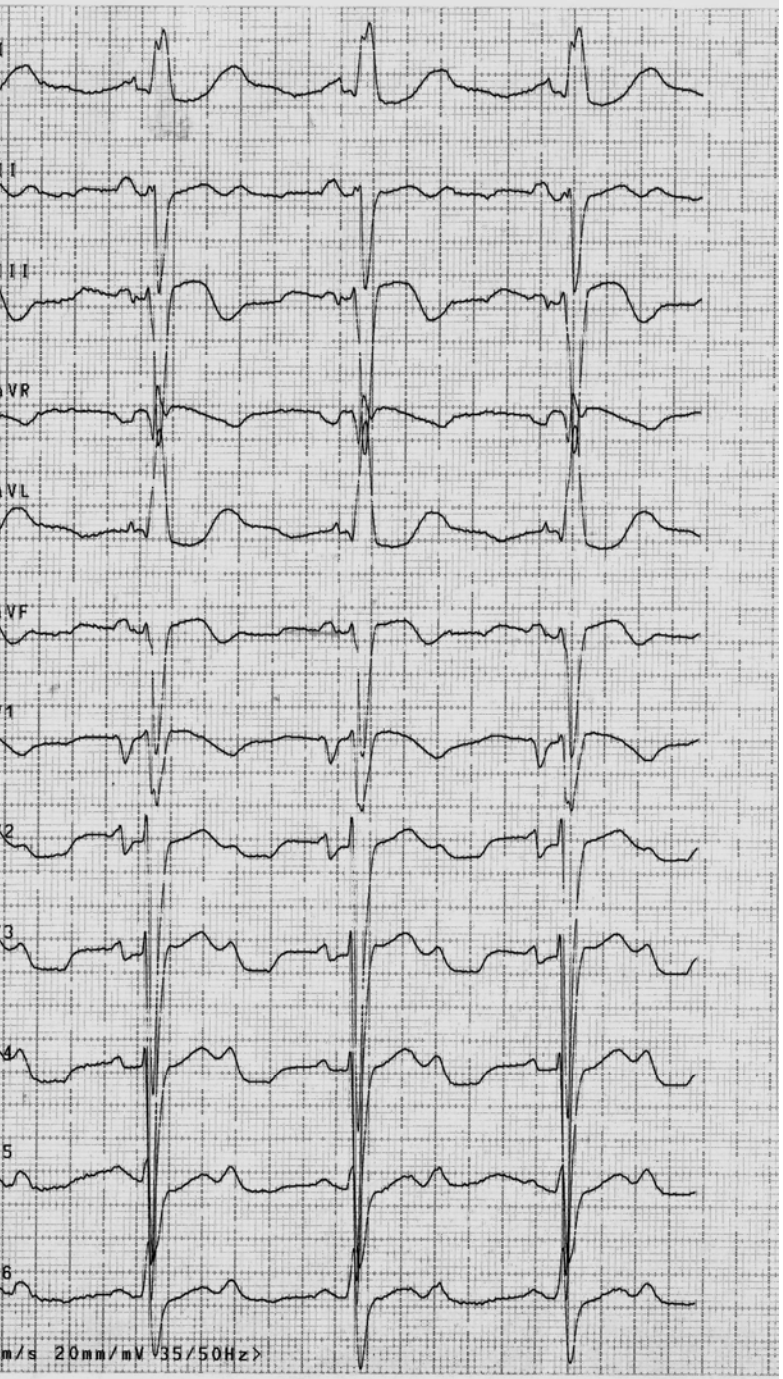
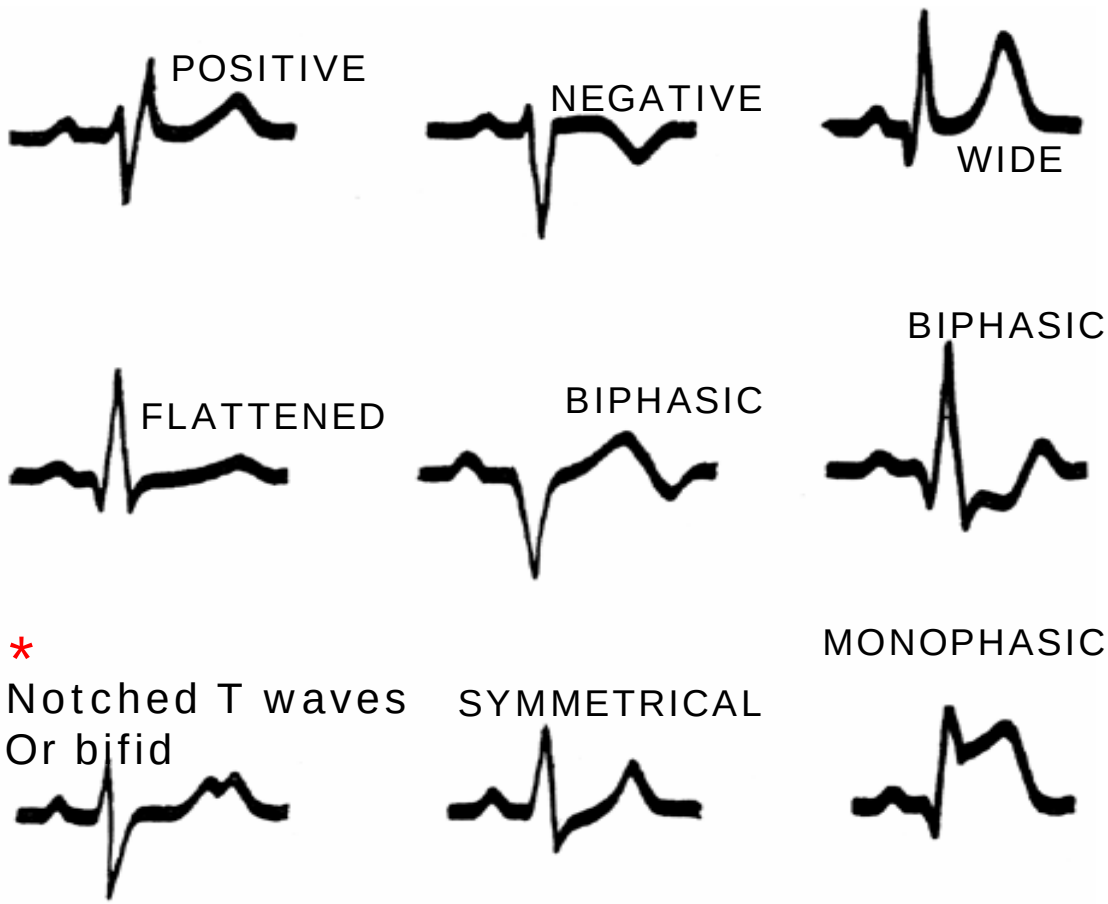
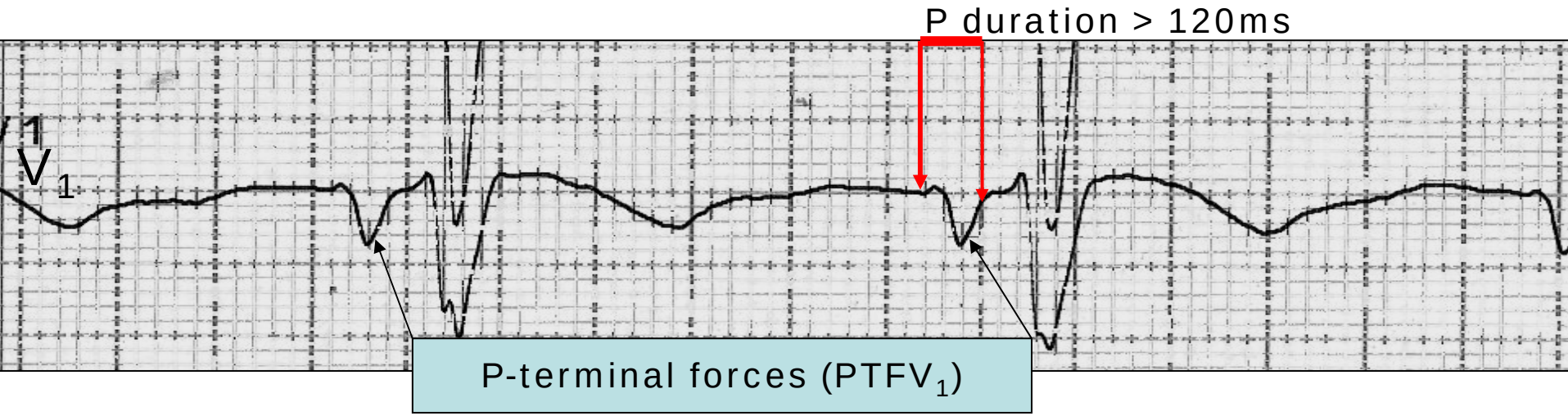


Heart rate 50bpm: sinus bradychardia, extreme left axis deviation, (QRS axis -60º), Left atrial enlargement, advanced inter-atrial block, Left ventricular hypertrophy /enlargement, QRS electrical alternans, Complete Left Bundle branch Block, Left Anterior Fascicular Block and very prolonged QT interval 800ms with bimodal or bifid T wave T1-T2 (LQT2-Like pattern*)

Different morphologies of T wave: positive, negative, wide, flattened, biphasic, bifid, symmetric and monophasic.



LEFT ATRIAL ENLARGEMENT



P wave with increased duration: ≥ 110 ms in adults

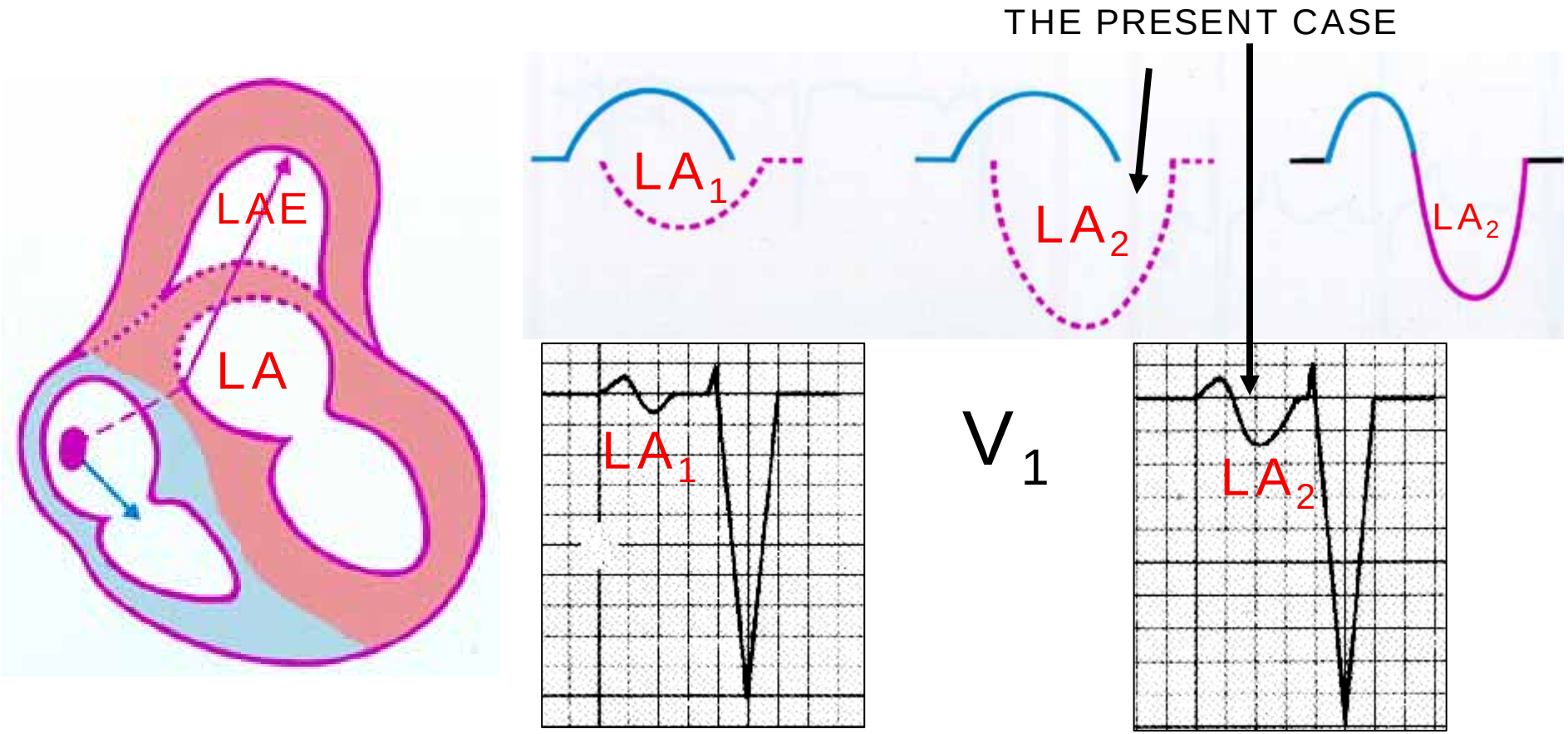
Increase in depth and duration of final negative component of the wave in V_1 (left atrial enlargement: positive Morris' index(1): slow and deep P final component in V_1. $PTFV_1$.

P terminal forces in lead V_1 equal or more negative than 0,04mm/seg.: product of the duration of the final P negative component (duration expressed in seconds); while depth is expressed in mm. Values above 0.03 mm per second constitute a highly sensitive criterion for diagnosis of LAE. The normal PTF-V1 does not exceed 0,04s wide and 1mm deep, i.e., 0,04mm/s

Indirect criteria of LVH: left ventricular failure by increase of Pd2 of LV. E.g.: extensive infarctions, dilated cardiomyopathy.

1. **Morris JJ Jr, Estes EH Jr, Whalen RE, Thompson HK Jr, Mcintosh HD. P-WAVE ANALYSIS IN VALVULAR HEART DISEASE. Circulation. 1964 Feb;29:242-252.**

LEFT ATRIAL ENLARGEMENT HORIZONTAL PLANE



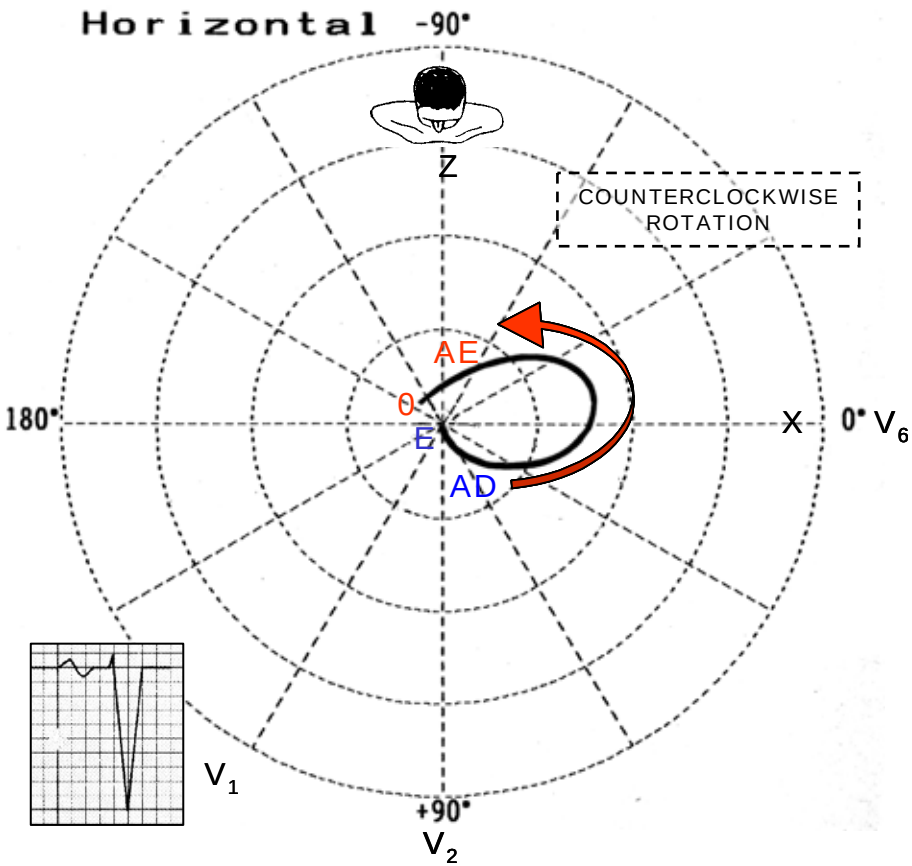
$LA_{2/}$: **final deep and slow component:** LAE

≥ the area of one small square the final minus portion indicates left atrial enlargement, abnormality or advanced interatrial block

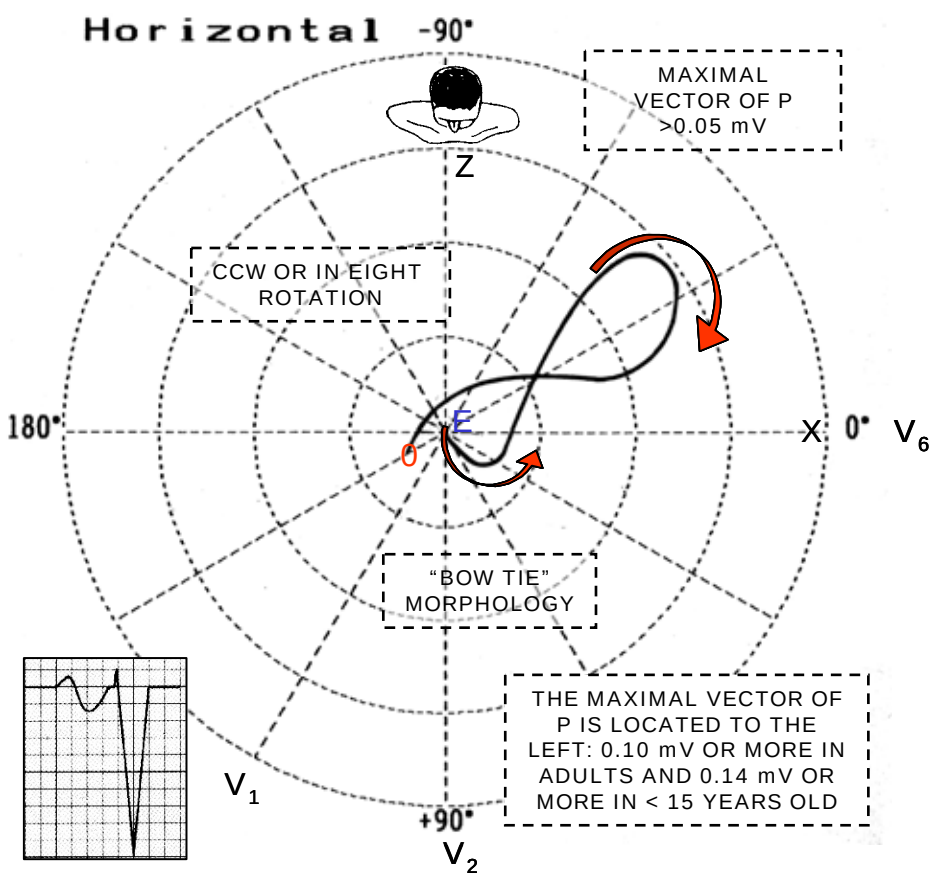
P LOOP IN LEFT ATRIAL ENLARGEMENT
HORIZONTAL PLANE

NOTE: THE FINDINGS IN THE SAGITTAL AND FRONTAL PLANES USUALLY ARE NOT RELEVANT IN DIAGNOSIS

NORMAL P LOOP

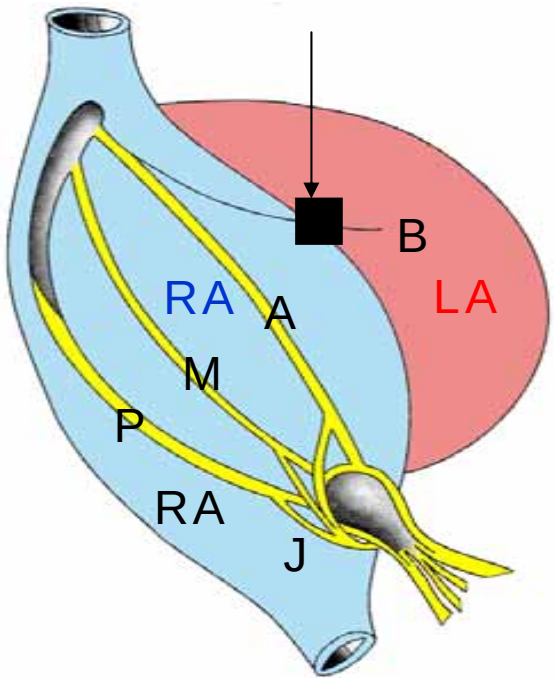


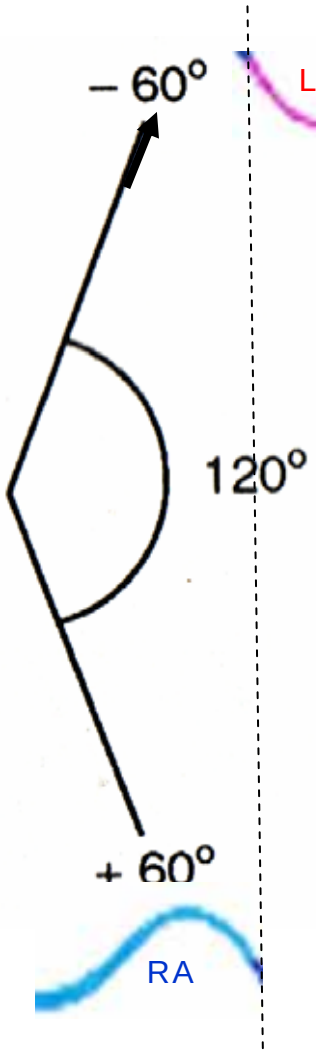
P LOOP IN LEFT ATRIAL ENLARGEMENT



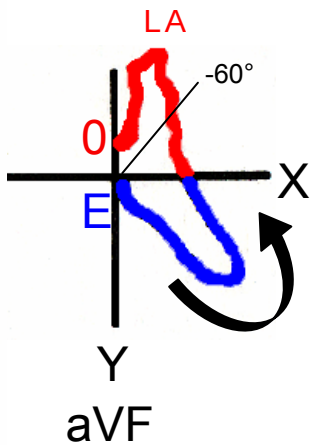
ADVANCED INTERATRIAL BLOCK

Complete block in
Bachmann's bundle

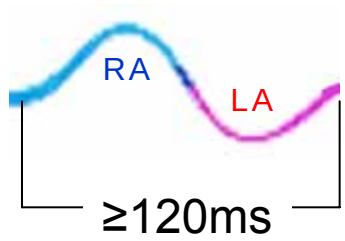




P loop in FP



P wave in lead "y"
aVF



Leads III and or aVF
Plus-minus P wave pattern

Biphasic P waves, in some inferior leads.

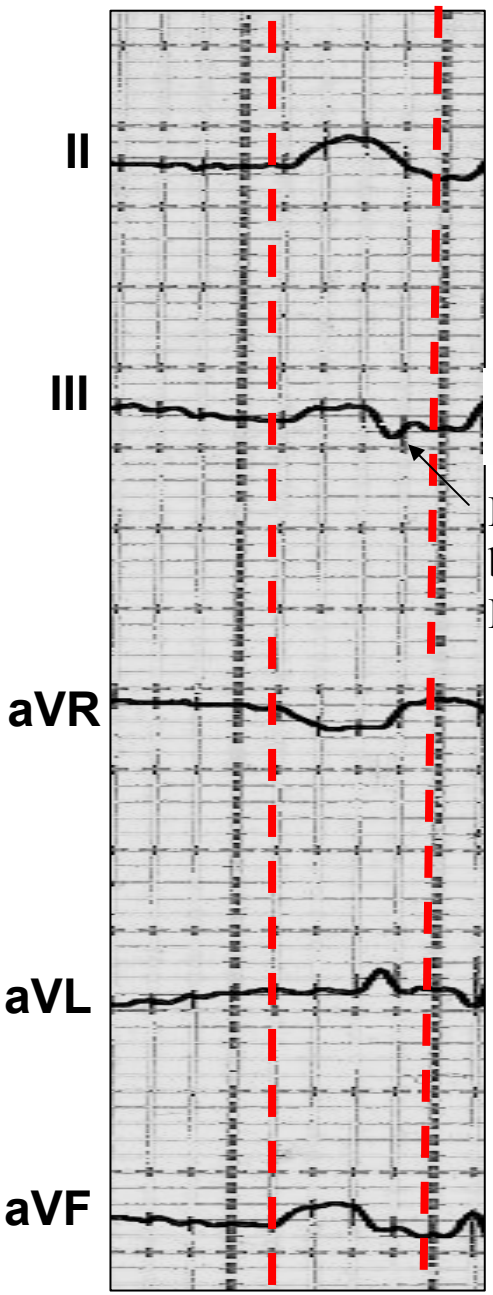
Third Degree (Advanced)

Electrical impulse is blocked in Bachmann's bundle, but retrograde left atrial activation usually occurs.

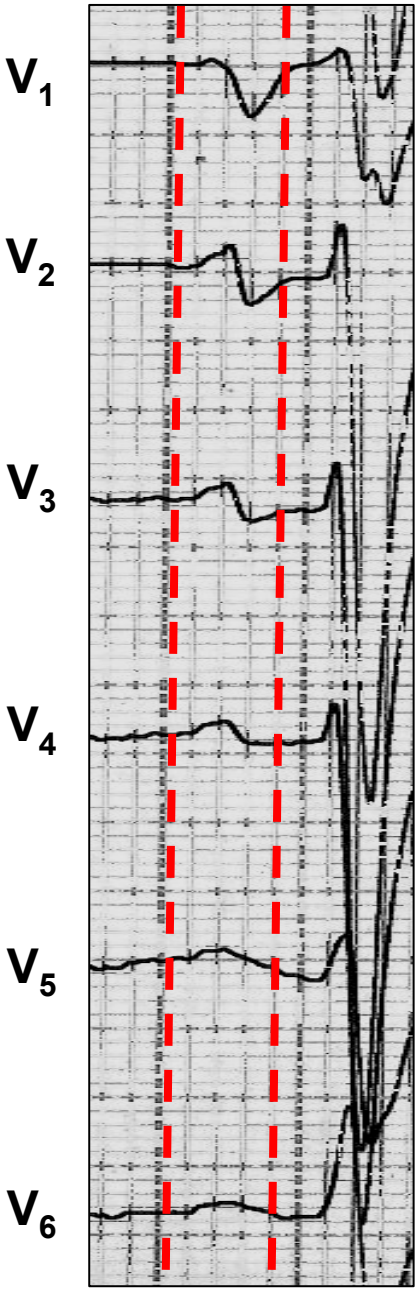
1. **Ariyarajah V, Spodick DH. Advanced interatrial block: a classic electrocardiogram. Cardiology. 2005;104:33-34.**

P duration near 160ms,

The lead where P wave starts before (aVR) should be considered the true onset of the P wave; and the lead that P wave ends latter (II) should be considered the true end of the P wave.

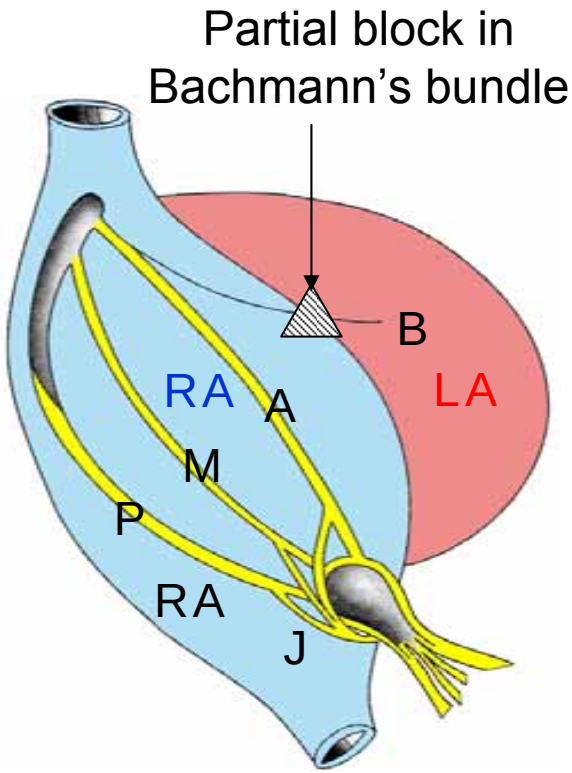


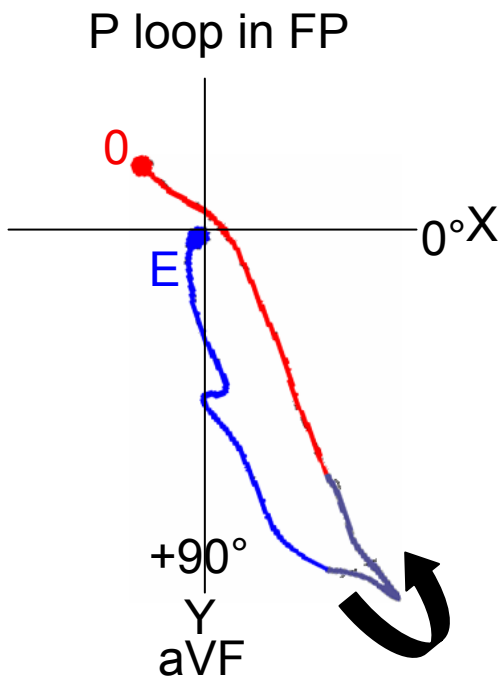
Plus-minus biphasic (+/-) P waves

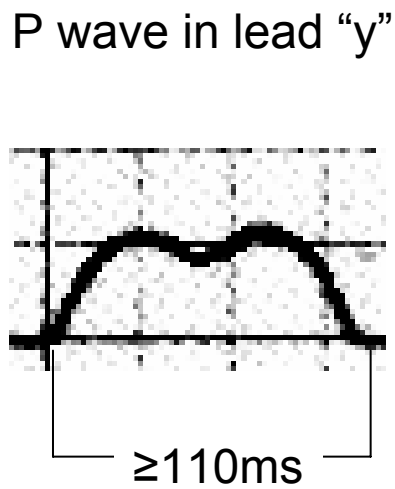


P duration ≥ 120ms, and plus-minus biphasic (+/-) P waves in inferior leads II, III, and/or aVF

PARTIAL INTERATRIAL BLOCK (IAB)







First-degree (Partial IAB)

The electrical impulse is conducted from the right atrium (RA) to the left atrium (LA) trough Bachmann's bundle, but conduction is delayed. The ECG shows a P wave of ≥ 110ms in several leads with a variable negative wave in V_1. The P-wave morphology is similar to that in left atrial enlargement, but usually a negative P wave in V_1 is less evident. It is not the present case.

Prevalence

High. Several studies have reported that the prevalence of IAB is more than 40% in hospital inpatients. Despite this, IAB remains largely underdiagnosed and commonly ignored. Advanced form is much less common that partial form. The condition remains largely underdiagnosed and commonly ignored[1]. Spodic consider this ECG abnormality is present in pandemic proportions especially at ages 60 and over and in unselected hospital patients. Because of its pathologic implications it requires widespread attention as a "pandemy"[2].

Associated conditions

1. Coronary Artery Disease
2. Hypertension
3. Diabetes Mellitus
4. Atrial fibrillation (strong associations)
5. Potential risk for embolism
6. Left Atrial Enlargement(LAE).
7. Left atrial electromechanical dysfunction[3].

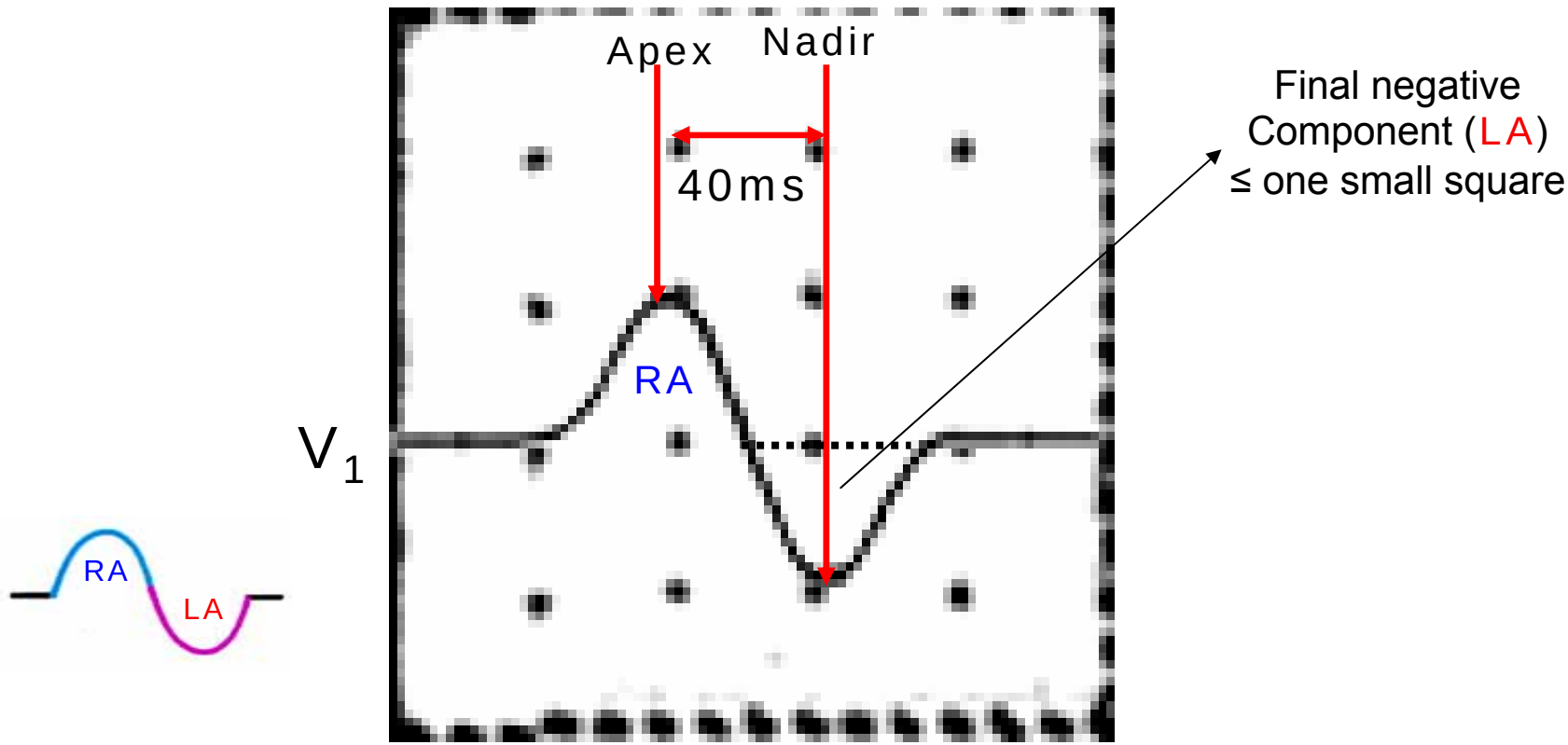
Electrocardiographic characterization

1)P-wave duration ≥120ms[3]. P-wave duration is generally accepted as the most reliable non-invasive marker of atrial conduction and its prolongation is stronger associated with AF. However, patients with paroxysmal AF without structural heart disease may not have P-wave prolongation thus suggesting that the global conduction slowing is not an obligatory requirement for development of AF[4].

1. **Kitkungvan D, Spodick DH. Interatrial block: is it time for more attention? J Electrocardiol. 2009 Nov-Dec;42:687-692.**
2. **Spodick DH, Ariyarajah V.Interatrial block: the pandemic remains poorly perceived. Pacing Clin Electrophysiol. 2009 May;32:667-672.**
3. **Ariyarajah V, Spodick DH. The Bachmann Bundle and interatrial conduction. Cardiol Rev. 2006 Jul-Aug;14:194-199.**
4. **Platonov PG. Atrial conduction and atrial fibrillation: what can we learn from surface ECG? Cardiol J. 2008;15:402-407.**

2. P terminal force (Ptf) plus-minus P wave (biphasic configuration) in lead V1≥ the area of one small square the final minus portion indicates left atrial abnormality, particularly LAE, which is a strong correlate of IAB.
3. Prolonged intrinsecoid P-wave deflection (from the apex to nadir) of the biphasic P wave in lead V1 >40ms

Representation of normal P wave in V_1



4. Often bifid ("notched") P waves
5. “Dome-and-spike" P-waves. 4 and 5 predominatly on leads II and from V_3 to V_6[1].

1. **Ariyarajah V, Apiyasawat S, Puri P, Spodick DH. Specific electrocardiographic markers of P-wave morphology in interatrial block. J Electrocardiol. 2006 Oct;39:380-384.**

Bayés de Luna A et al[1]. studied 16 patients with ECG evidence of advanced interatrial block and retrograde activation of the left atrium (LA): P duration ≥ 120ms, and plus-minus biphasic (+/-) P waves in some inferior leads II, III, and/or VF.

Eight patients had valvular heart disease, four had dilated cardiomyopathy and four had other forms of heart disease.

Patients with valvular heart disease and cardiomyopathy were compared with a control group of 22 patients with similar clinical and echocardiographic characteristics, but without this type of interatrial block.

Patients with advanced interatrial block and retrograde activation of the LA had a much higher incidence of paroxysmal supraventricular tachyarrhythmias (93.7%) during follow-up than did the control group. Eleven of 16 patients (68.7%) with advanced interatrial block and retrograde activation of LA had atrial flutter (atypical in seven cases, typical in two cases, and with two or more morphologies in two cases). Six patients from the control group (27.7%) had sustained atrial tachyarrhythmias (five atrial fibrillation and one typical atrial flutter). The atrial tachyarrhythmias were due more to advanced interatrial block and retrograde activation of LA and frequent PACs than to LAE, because the control group with a LA of the same size, but without advanced interatrial block and retrograde activation of LA and with less incidence of PACs, had a much lower incidence of paroxysmal tachycardia.

Bayés de Luna et al[2]. demostrated the value of preventive antiarrhythmic treatment in patients with advanced interatrial block

1. **Bayés de Luna A, Cladellas M, Oter R, Torner P, Guindo J, Martí V, Rivera I, Iturralde P.Interatrial conduction block and retrograde activation of the left atrium and paroxysmal supraventricular tachyarrhythmia. Eur Heart J. 1988 Oct; 9:1112-1118.**
2. **Bayés de Luna A, Oter MC, Guindo J. Interatrial conduction block with retrograde activation of the left atrium and paroxysmal supraventricular tachyarrhythmias: influence of preventive antiarrhythmic treatment. Int J Cardiol. 1989 Feb;22:147-150.**

DIAGNOSIS CRITERIA OF ADVANCED INTERATRIAL BLOCK AND RETROGRADE ACTIVATION OF THE LEFT ATRIUM(LA)

1. **Biphasic P waves, in some or all inferior leads.**
2. **P duration ≥120ms**
3. **Angle between the first portion (RA) and end portion (LA) >90º**
4. **Orthogonal Y lead plus-minus with the final negative portion ≥ 40ms**
5. **≥ 40ms final portion of P loop upstart orthogonal X and Z leads.**
6. **Final portion of P loop delayed, notches and slurring in the last part of the P loop**
7. **High Esophageal lead with positive P wave polarity and delayed**
8. **Low Esophageal lead with plus-minus P wave polarity and delayed**
9. **Intracavitary ECG with P wave activation craniocaudal inside the RA.**
10. **Intracavitary ECG with P wave activation caudal-cranial inside LA.**

1. **Bayés de Luna A. TRATADO DE ELECTROCARDIOGRAFIA CLÍNICA. Capítulo IV. Pagina 153. Editorial Cientiífico-médica. Barcelona. 1988.**
2. **Bayés de Luna A, Gusí Gené C, Soler Soler J, Fort de Ribot R, Llamas Lombardia A, Roman Castillo M, TrillaSanchez E. Electrocardiologia clínica (2 volúmenes). Cinetiífico-Médica, Barcelona 1977.**

From 81,000 ECGs Bayes de Luna et al[1] collected 83 cases that fulfilled the criteria of Interatrial Conduction Disturbances with Left Atrial Retrograde Activation (IACD-LARA) (P +/- in II, III and/or VF with P width ≥ 120 msec.).
The authors present the detailed study of 35 cases with surface ECG and VCG and 29 cases with orthogonal ECG leads.
The results are then compared against two control groups: with structural heart disease (30 cases) and without structural heart disease (25 cases).
The prevalence of IACD-LARA was nearly 1% globally, and 2% among patients with valvular heart disease.

The diagnostic criteria for Interatrial Conduction Disturbances with Left Atrial Retrograde Activation (IACD-LARA) are:
1) ECG: P +/- in II, III and/or VF with P ≥ 120 ms.
2) Open angle > 90 º between the first and the second part of the P loop.
3) Orthogonal ECG: P +/- in Y lead with a negative mode greater than 40 m.
4) VCG: More than 50 msec. above the X or Z axis
5) Duration of the P loop ≥ 110 ms
6) Open angle between the two parts of the P loop in both frontal and right sagittal planes
7) Presence of notches and slurring in the last part of the P loop.

1. Bayes de Luna A, Fort de Ribot R, Trilla E, Julia J, Garcia J, Sadurni J, Riba J, Sagues F. Electrocardiographic and vectorcardiographic study of interatrial conduction disturbances with left atrial retrograde activation.J Electrocardiol. 1985 Jan;18:1-13.

Why LVH?
Electrocardiographic diagnosis of LVH in the presence of LBBB

The presence of LBBB on 12-lead ECG may obscure the diagnosis of LVH.
The criterion of SV2 + RV6 greater than 4.5 mV demonstrated a sensitivity of 86% and a specificity of 100% for LVH diagnosis in presence of LBBB.
QRS duration of greater than 160 msec plus left atrial enlargement strongly supports the diagnosis of LVH in presence of LBBB.(1)
There are not difference in limb lead voltage, intrinsicoid deflection, or mean frontal plane QRS axis.
The following criteria can be helpful in left bundle branch block: QRS voltage increase, left atrial enlargement, QRS duration > 155 ms.(2)
LVH can be diagnosed in the presence of LBBB with an accuracy at least similar to that observed in patients without this conduction defect. Computer-assisted interpretation of the ECG may be useful in the diagnosis of LVH as it enables the implementation of more accurate algorithms. Diagnostic algorithms, voltage-duration products, and certain compound criteria had the best sensitivities.(3)
LA abnormality is a significantly diagnostic of LVH in the presence of LBBB. Age, body mass index, body surface area, frontal axis, and QRS duration are also significant predictors of LV mass.(4)

1. **Klein RC, Vera Z, DeMaria AN, Mason DT. Electrocardiographic diagnosis of left ventricular hypertrophy in the presence of left bundle branch block. Am Heart J. 1984 Sep;108:502-506.**
2. **Oreto G, Saporito F, Messina F, Lanteri S, Luzza F. Electrocardiographic diagnosis of left ventricular hypertrophy in the presence of intraventricular conduction disturbances]. G Ital Cardiol (Rome). 2007 Mar;8:161-167**
3. **Rodríguez-Padial L, Rodríguez-Picón B, Jerez-Valero M, et al.Diagnostic accuracy of computer-assisted electrocardiography in the diagnosis of left ventricular hypertrophy in left bundle branch block. Rev Esp Cardiol. 2012 Jan;65:38-46.**
4. **Mehta A, Jain AC, Mehta MC, Billie M.Usefulness of left atrial abnormality for predicting left ventricular hypertrophy in the presence of left bundle branch block. Am J Cardiol. 2000 Feb 1;85:354-359.**

1.

Kafka parameters for the diagnosis of LVH in presence of LBBB

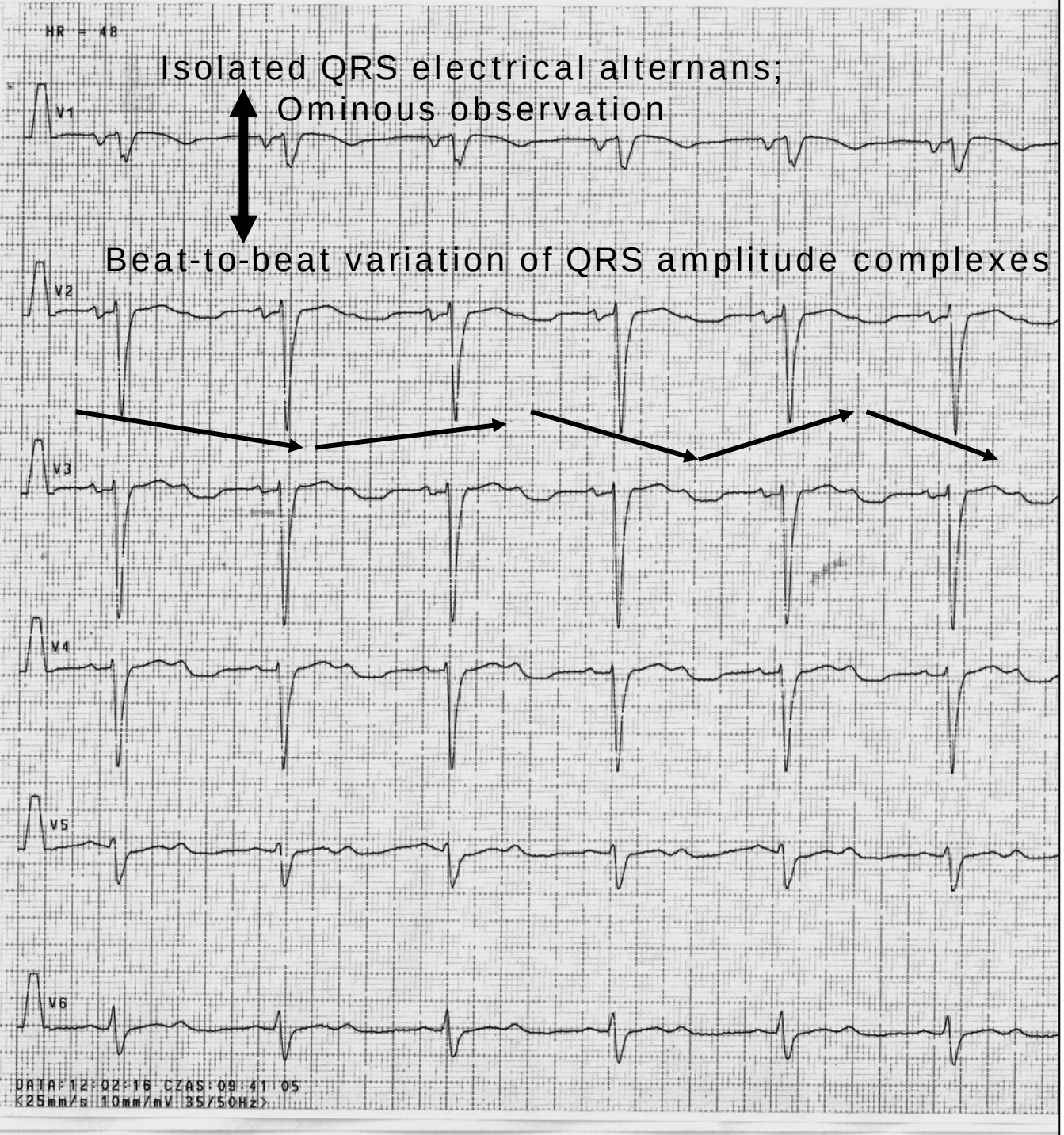
Kafka et al selected and used 5 electrocardiographic parameters in cumulative fashion for the diagnosis of LVH in presence of LBBB:

1. RaVL ≥11mm;
2. QRS axis ≤40º or SII greater than RII;
3. SV1 + RV5 to RV6 ≥ 40mm;
4. SV2 ≥30mm
5. SV3 ≥ 25mm

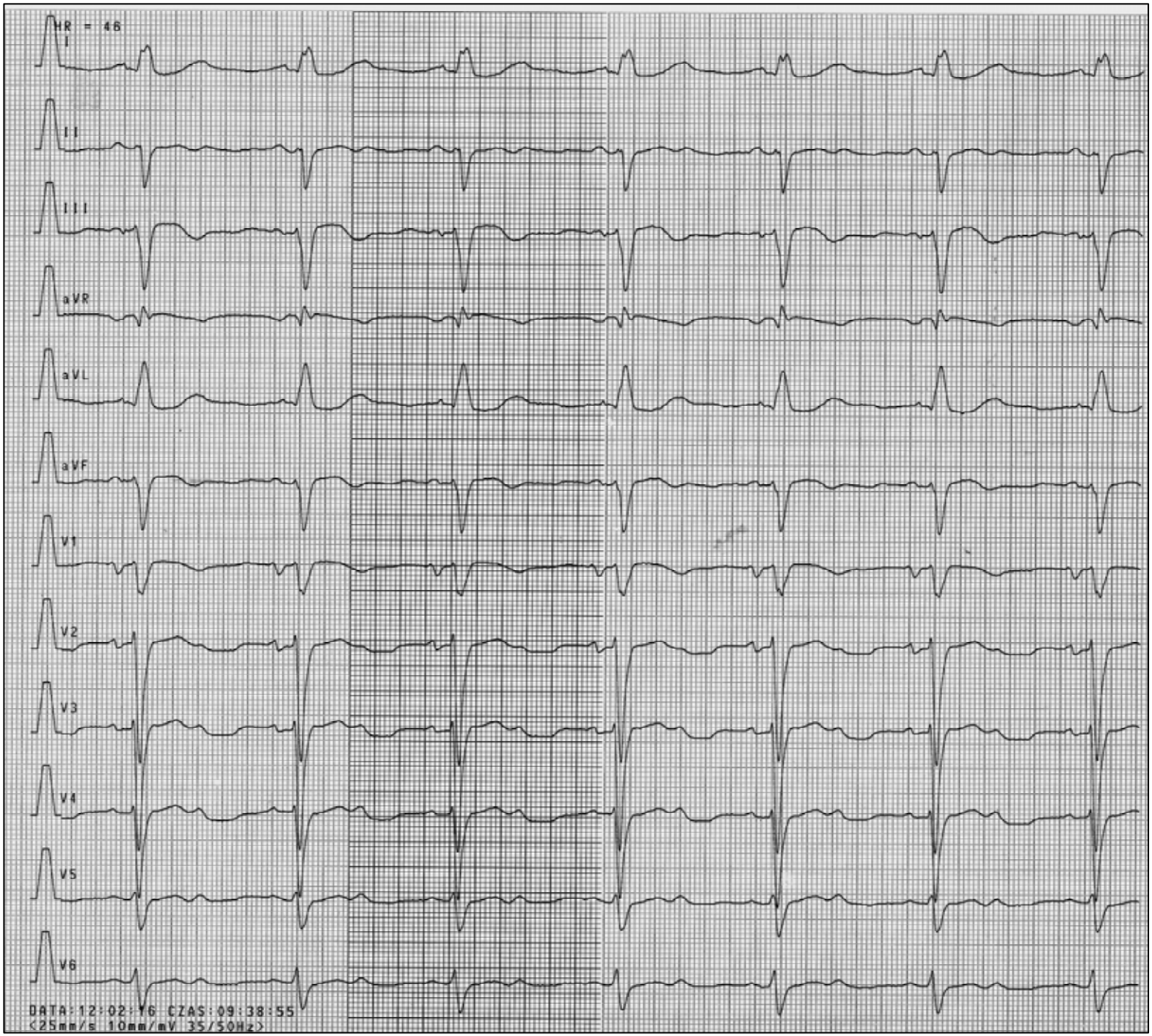
This cumulative approach was superior to using single conventional criterion such as the SV1 + RV5 or RV6. When LVH was defined as an M-mode index of at least 115 g/m2, the sensitivity was 75% and specificity 90%. Using an M-mode mass of at least 215 g as the standard, the sensitivity was 73% and the specificity 66%.

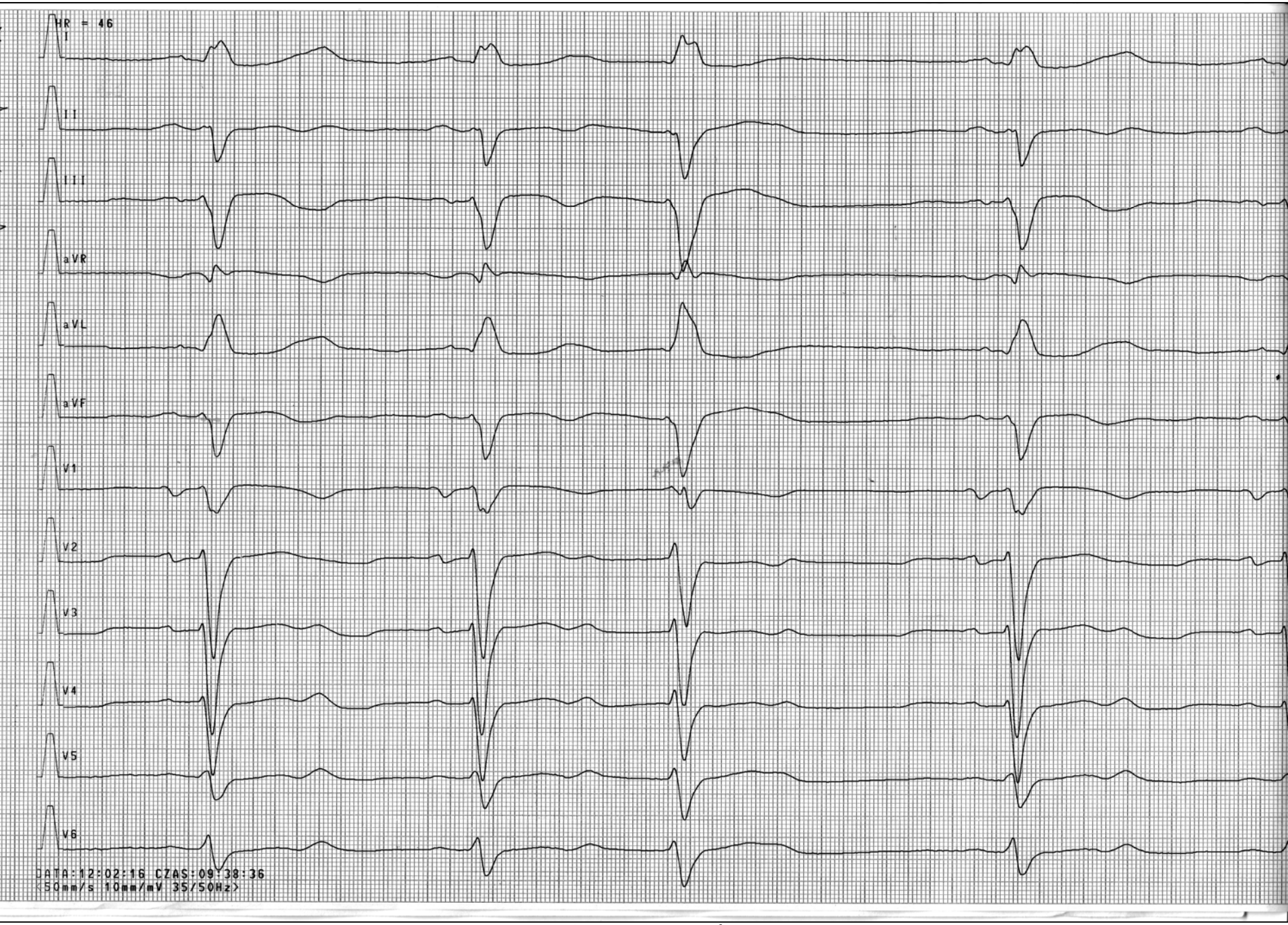
LVH can be diagnosed by ECG criteria in the presence of LBBB at least as reliably as in normal conduction.(1)

1. **Kafka H, Burggraf GW, Milliken JA. Electrocardiographic diagnosis of left ventricular hypertrophy in the presence of left bundle branch block: an echocardiographic study. Am J Cardiol. 1985 Jan 1;55:103-106.**



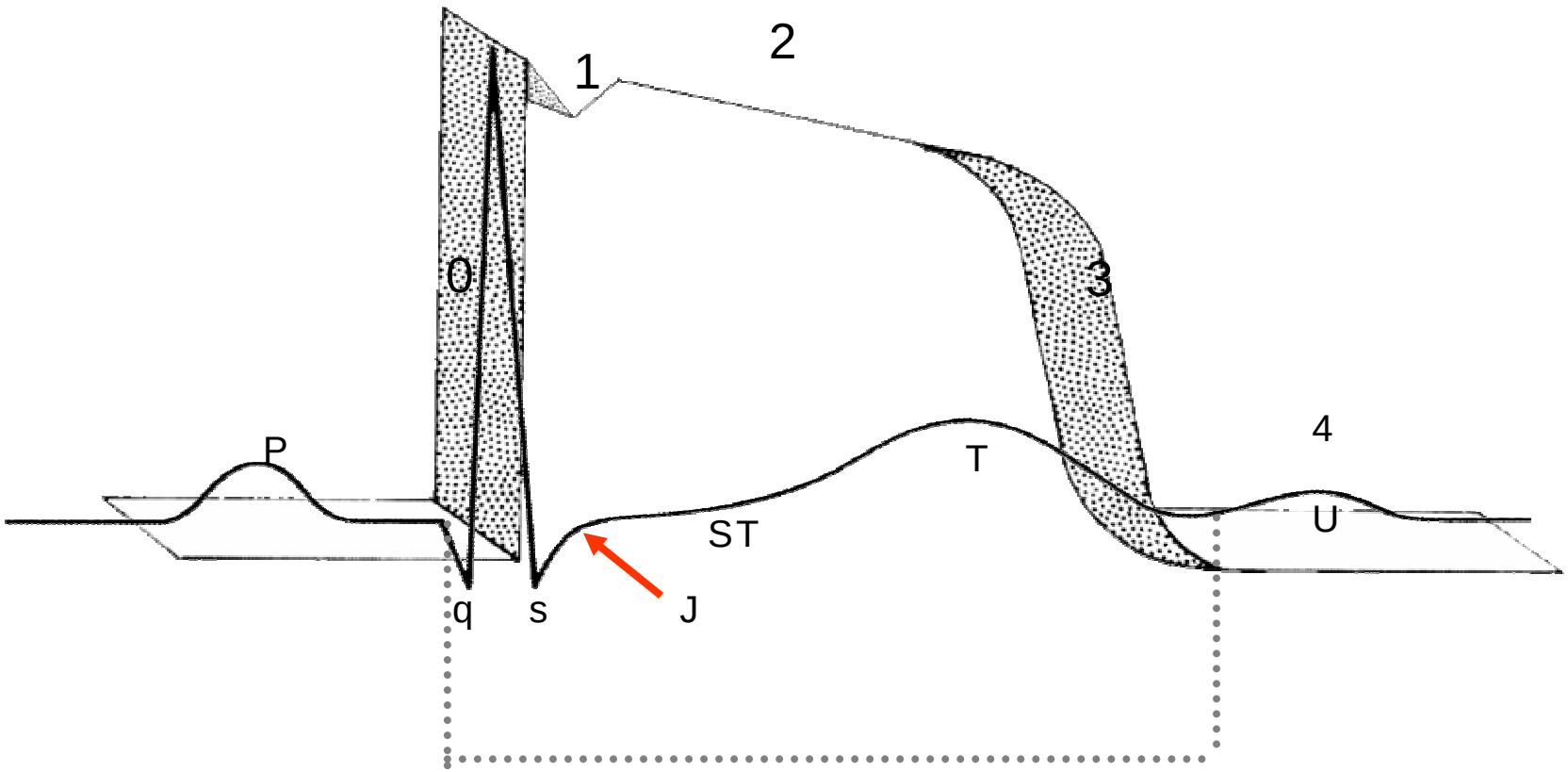
Electrical alternans is a phenomenon seen on the ECG with alternation in the amplitude of QRS complexes. The term electrical alternans totalis is used when the amplitudes of all the waves (P, QRS and T) show alternating amplitude. Electrical alternans totalis is seen in cardiac tamponade and is thought to be due to the heart swinging movement of the heart within the pericardial cavity. Electrical alternans may sometimes be associated with its mechanical counter part: pulsus alternans or alternating pulse Pulsus alternans is a physical finding with arterial pulse waveform showing alternating strong and weak beats. It is almost always indicative of left ventricular systolic impairment, and carries a poor prognosis. In left ventricular dysfunction, the EF will decrease significantly, causing reduction in stroke volume, hence causing an increase in end-diastolic volume. There may initially be a tachycardia as a compensatory mechanism to try to keep the cardiac output constant. As a result, during the next cycle of systolic phase, the myocardial muscle will be stretched more than usual and as a result there will be an increase in myocardial contraction, related to the Frank–Starling physiology of the heart. This results, in turn, in a stronger systolic pulse.


HR = 46
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
DATA:12:02:16 CZAS:09:38:55
<25mm/s 10mm/mV 35/50Hz>
I


HR = 46
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
DATA:12:02:16 CZAS:09:38:36
<50mm/s 10mm/mV 35/50Hz>

2N 50mm/s

CORRELATION BETWEEN NORMAL ACTION POTENTIAL AND ECG WITH NORMAL QT INTERVAL



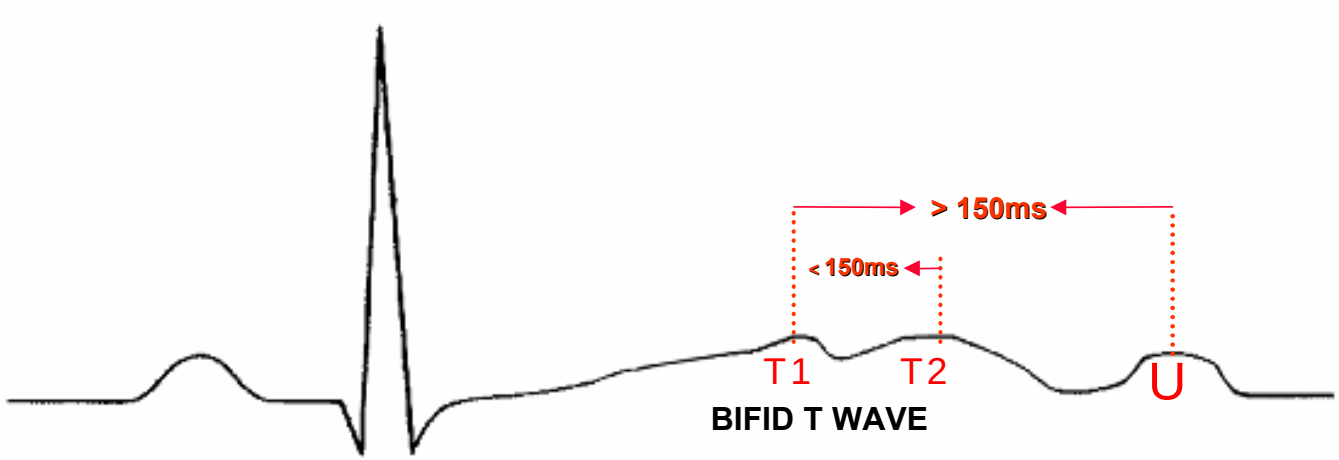
QT interval or electric systole

Normal value: 350 to 440 ms or 446 ± 15%

Correlation between normal action potential and ECG with normal QT interval.

DIFFERENTIATION OF BIMODAL OR NOTCHED T WAVES WITH T-U INTERVAL

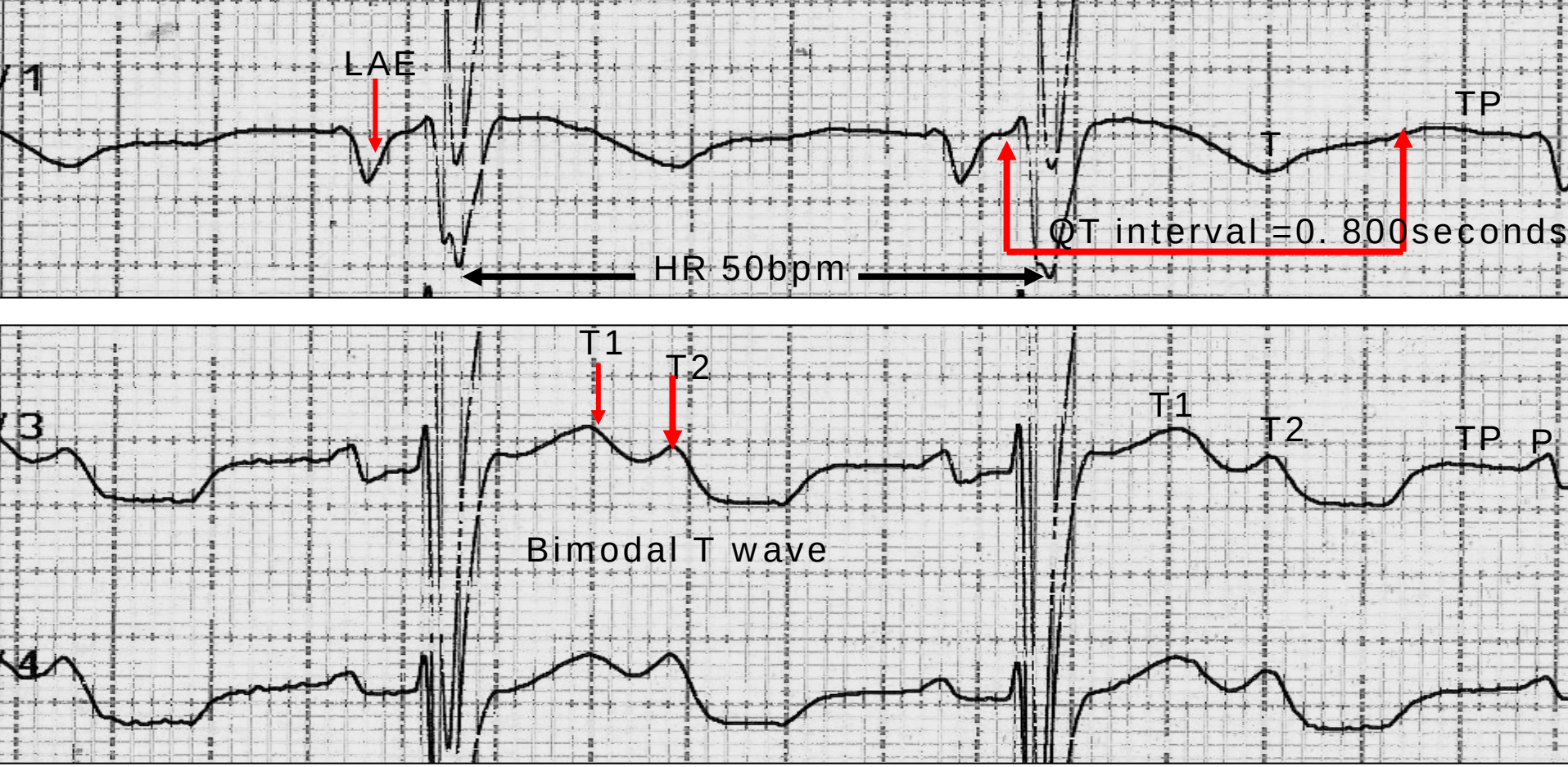
Bimodal, bifid or notched T waves may be distinguished from the T-U interval: the second apex of bimodal T wave (T2) is at a distance from the first one (T1) < 150 ms; the T1-U interval is > 150 ms ([1-2]).



The second apex of bimodal T wave (T2) is at a distance < 150 ms from the first module (T1): The T1-U interval is always > 150 ms.

1. **Lepeschkin E.: Physiologic basic of the U wave. In Advances in Electrocardiography. Edited by Schlant RC, and Hurst JW. New York, Grune & Stratton 1972;pp 431-447.**
2. **Lepeschkin, E.:The U wave of the electrocardiogram. Mod Concepts Cardiovasc Dis 1969;38:39.**

Differentiation between bimodal or notched T waves in T-U interval.



T1-T2 distance: 150ms. The second apex of bimodal T wave (T2) is at a distance < ≤150 ms from the first module (T1): The T1-U interval is always > 150 ms.

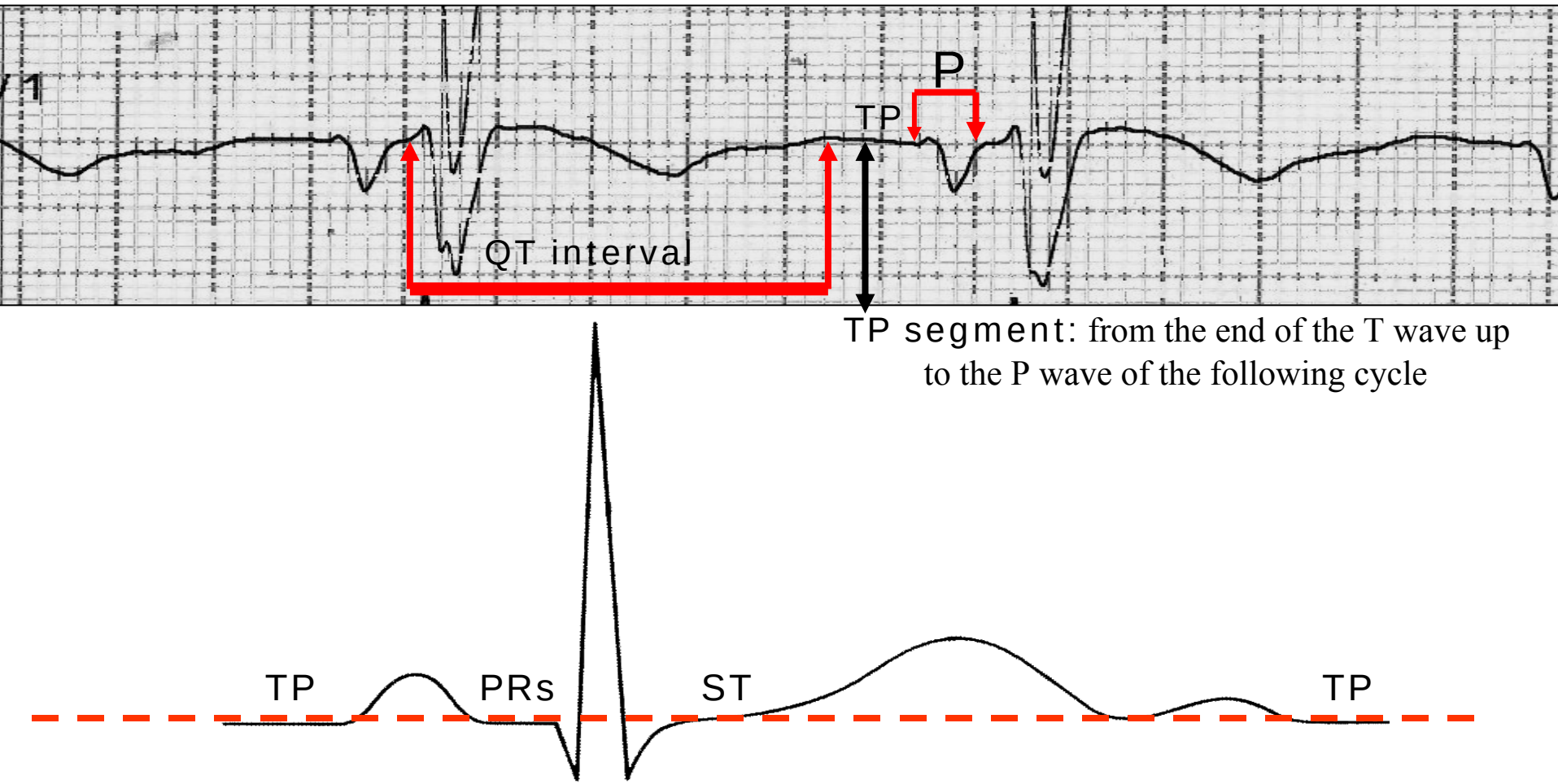
MEAN PREDICTED QT VALUES AT VARIOUS RR CYCLE LENGTHS

RR seconds 1.20, Heart rate = 50beats/min,

QT for Men: Mean value: 0.407, Lower limit; 0.363. Upper limit 0.451 seconds.

1. **Sagie A, Larson MG, Goldberg RJ, Bengtson JR, Levy D. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study) Am J Cardiol. 1992 Sep 15;70:797-801.**

PRs, ST & TP segments



The PR segment is leveled when it is at the same level of the PR segment of the beat being studied.

Usually, PR segment (end of P wave up to QRS complex onset), ST segment (from J point or the end of QRS up to the beginning of the T wave) and TP segment (from the end of the T wave up to the P wave of the following cycle) segments are at the same level. The figure shows a normal ECG and a line of dots pointing out the level of the three segments: **PR**, **ST** and **TP**.

ELECTROCARDIOGRAPHIC MODIFICATIONS WITH ANTIARRHYTHMIC DRUGS

- **Effects of antiarrhythmic drugs in ECG**
  - It suggest the following modifications:
    - QT interval prolongation.
    - Prominent U wave or byphid T waves T1-T2.
    - Nonspecific modifications of ST segment and T wave.
    - Decrease of atrial flutter rate.

- **Toxicity of antiarrhythmic drugs**
  - It suggests the following modifications:
    - Prolongation of QT interval.
    - Torsade de Pointes.
    - QRS complexes broadening.
    - Different degrees of AV block.
    - Significant sinus bradycardia, sinus arrest or sinoatrial block.

Electrocardiographic modifications that suggest effect of drugs.

PHARMACOLOGICAL CAUSES OF QT INTERVAL PROLONGATION

CARDIOVASCULAR DRUGS WITH THE POTENTIAL OF PROLONGING THE QT INTERVAL

LQTS is characterized by inherited or acquired prolonged QT interval on the surface ECG. This can lead to torsade de pointes (TdP) and ventricular fibrillation. In the acquired form of the disease, medications from several classes can cause TdP VT or potentiate the ECG findings. These include class IA and III antiarrhythmics, antibiotics (macrolides and quinolones), antidepressants (tricyclics and selective serotonin reuptake inhibitors), antipsychotics (haloperidol and phenothiazines), and antiemetics (ondansetron and prochlorperazine).

ANTIARRHYTHMIC AGENTS:

1. Class IA antiarrhythmics**:** quinidine, procainamide, disopyramide and ajmaline.
2. Class IC antiarrhythmics**:** propafenone, flecainide, encainide, N-acetyl-procainamide or NAPA.
3. Class III antiarrhythmics**:** rarely with sotalol and exceptionally with amiodarone <1%;
4. ADENOSINE.

Antiarrhythmic drugs with the capacity of prolonging QT interval.

AMIODARONE

Amiodarone remains one of the most commonly prescribed antiarrhythmics effectively treating atrial fibrillation and ventricular arrhythmias. Amiodarone has class I, II, and IV effects

Class I effect: It decreases conduction velocity (negative dromotropism) by blocking rapid Na^+ channels

Class II effect: produced non competitive β-adrenergic blockade that can cause singnificative bradychardia within several days

Class IV effect: reduces inward L-type calcium channel activity in a use-dependent manner

Amiodarone, a complex compound that was synthesized as an antianginal agent, has been an exception in this regard. Its therapeutic use is associated with a negligibly low incidence of TdP, even though the drug produces significant bradycardia and QT lengthening to 500 to 700 ms. Electrophysiologic studies suggest that this paradox is likely due to the differential block of ion channels in endocardium, epicardium, midmyocardial (M) cells, and Purkinje fibers in the ventricular myocardium. There is also clinical evidence suggesting that amiodarone reduces the "torsadogenic" effects of pure class III agents.

Amiodarone prolongs the QT interval by prolongs myocardial repolarization homogeneously reducing dispersion of refractoriness, reentry, and proarrhythmic via potassium channel blockade I_{ks} and I_{kr}. Incidence of TdP is <1%(1), Diligent monitoring for potentially serious side effects especially in the elderly is paramount.(2)

Produces inhibitions of thyroxin (T4) deiodination to triiodothyronine (T3) can contribute to anti arrhythmic efficacy.

1. **Vorperian VR, Havighurst TC, Miller S, January CT. Adverse effects of low dose amiodarone: a meta-analysis.J Am Coll Cardiol. 1997 Sep;30:791-798.**
2. **Morris D, Cameron N.Did you know? Why** amiodarone **requires diligent monitoring? Can J Cardiovasc Nurs. 2011;21:3-6.**

In patients with scant bodily mass and CHF with history of TdP or renal problems (not metabolized, and 100% is eliminated by the unaltered kidney). The drug should be started in a hospital environment. The drug causes significant increase of QT and QTc or JT intervals, especially with lower rates. Generally, it causes increase of 40 ms to 100 ms. By EV via, it also prolongs the QT interval. The increase of the QT interval is due to its class III antiarrhythmic action by prolonging phase 3 of AP, by blocking the potassium Ikr channels and causing a greater AP prolongation of M cells in comparison to endocardial and epicardial cells, causing T waves of low amplitude similar to the LQT2 variant of congenital LQTS, which may foster the appearance of proarrhythmic effects such TdP; however, even increasing QT, its dispersion decreases, thus minimizing vulnerability to fatal TdP. Interestingly, drugs with documented clinical QT interval prolongation, but with low risk for TdP (amiodarone, moxifloxacin and ciprofloxacin) did not decrease the negative electro-mechanical (E-M) window has recently been proposed as an alternative risk marker for TdP in a canine LQT1 model. Furthermore, the E-M window was minimally affected by changes in HR or body temperature. Chronic amiodarone results in a rapid phase-3-repolarization and does not increase dispersion of repolarization. These findings are present in healthy hearts and are preserved in HF. This contributes to the low proarrhythmic potential of amiodarone in HF. On the other hand, Sotalol led to a triangular action potential configuration in sham and failing hearts, whereas amiodarone did not cause triangularization but caused a rapid phase-3 repolarization.(2)

1. **Guns PJ, Johnson DM, Van Op den Bosch J, Weltens E, Lissens J. The electro-mechanical window in anaesthetized guinea-pigs: a new marker for Torsade de Pointes risk screening. Br J Pharmacol. 2011 Nov 29. doi: 10.1111/j.1476-5381.2011.01795.x. Frommeyer G,**
2. **Milberg P, Witte PA new mechanism preventing proarrhythmia in chronic heart failure: rapid phase-III repolarization explains the low proarrhythmic potential of amiodarone in contrast to sotalol in a model of pacing-induced heart failure. Eur J Heart Fail. 2011 Oct;13:1060-1069.**

Hepatotoxicity due to intravenous amiodarone is a rare side effect with a distinct pattern of enzyme disturbances compared to liver damage from oral amiodarone. Intravenous amiodarone is administered for acute arrhythmias often causing heart failure. The enzyme abnormalities and clinical setting are very similar to that of ischemic hepatitis, a far more common condition.

There were no significant differences in the clinical characteristics, laboratory results or histological findings between Hepatotoxicity due to intravenous amiodarone and ischemic hepatitis patients.(1)

The nature of the proarrhythmic reactions induced by antiarrhythmic drugs is linked to the electrophysiologic effects of these agents. Torsades de pointes is the classic form of proarrhythmia observed during therapy with any drug that prolongs repolarization, for example, the class III agents. Its precise electrophysiologic mechanism is not fully elucidated, although the arrhythmia is generally considered to be due either to early afterdepolarization in the context of prolonged cardiac repolarization or to an increase in spatial or temporal dispersion of repolarization. Among the class III drugs the proarrhythmic risk appears to be lowest for amiodarone, probably due to its complex electrophysiologic profile that may create significant myocardial electrical homogeneity.

When class III antiarrhythmic drug-induced proarrhythmia occurs, immediate cessation of therapy with the responsible agent and correction of predisposing factors, such as electrolyte disorders or bradycardia, is mandatory. Intravenous administration of high-dose magnesium sulfate has been demonstrated to be effective in terminating and preventing new episodes of torsades de pointes. Temporary pacing may be necessary.

1. **Gluck N, Fried M, Porat R. Acute amiodarone liver toxicity likely due to ischemic hepatitis.Isr Med Assoc J. 2011 Dec;13:748-752.**

Dofetilide, a class III antiarrhythmic, is one of the few alternatives to amiodarone in patients with AF and HF or CAD.

Manocha et al(1) sought to identify clinical parameters associated with dofetilide success in a large cohort of patients with AF.

A total of 287 patients with AF started on dofetilide were included. Dofetilide was deemed "completely effective" if the patient remained on dofetilide at follow-up and had no recurrences of AF clinically or by ECG. Dofetilide efficacy was analyzed in relation to clinical variables relevant to AF and AF recurrence. After a follow-up of 10.2 ± 7.7 months, 54.7% of the patients remained on dofetilide and it was completely effective in 26.8%. The discontinuation rate during initial hospitalization was 13.3% from excessive QT prolongation and one patient with TdP (successfully treated). A history of CAD was the only univariate predictor of efficacy. CAD remained the only significant factor associated with efficacy of dofetilide in a multivariate regression model. The overall efficacy of dofetilide in patients with CAD was 41.1%, compared to 23.5% in those without CAD. The authors concluded that patients with AF, underlying CAD was significantly associated with dofetilide success(1)

The risks of polypharmacy in the development of LQT and TdP. Early detection of LQT in patients with multiple risk factors in ensuring appropriate treatment.(2)

1. **Manocha P, Bavikati V, Langberg J, Lloyd MS. Coronary artery disease potentiates response to dofetilide for rhythm control of atrial fibrillation. Pacing Clin Electrophysiol. 2012 Feb;35:170-173.**
2. **Digby GC, Pérez Riera AR, Barbosa Barros R, Simpson CS, Redfearn DP, MethotM, Femenía F, Baranchuk A. Acquired long** QT interval**: a case series of multifactorial** QT **prolongation. Clin Cardiol. 2011 Sep;34:577-582.**