Angry Purkinje syndrome. Síndrome del "Purkinje enojado",

Buenas tardes, estimado Doctor. Lo sigo en el foro de arritmias y sus publicaciones y revisiones son excelentes, de hecho son las que siempre me detengo a lero. Felicitaciones.

Dr. Pérez Riera, tengo que revisar un tema para mi formación u enseñanza y no encuentro mucho de este tema en libros y publicaciones.

Me pregunto, y por tal motivo me atreví a escribirle, si usted tendria algo sobre el tema de:

Angry Purkinje syndrome.

Agradeciendo de antemano, su ayuda, y reitero disculpas por el atrevimiento de escribirle, le saluda.

Dr. Luis Manuel Álvarez, .

Medico Cardiólogo

Cubano-Venezolano

Angry Purkinje syndrome. “El síndrome del Purkinje enojado”

Estimado colega Dr. Luis Manuel Álvarez, esta entidad fue recientemente abordada por destacados colegas siendo el principal autor perteneciente a nuestro foro: el Dr **Sami Viskin**.(1) Sami trabaja en el Tel Aviv Sourasky Medical Center y Sackler School of Medicine, en la Universidad de Tel Aviv en Israel.

Los autores presentaron un reciente reporte de caso con las características de este síndrome (**“El síndrome del Purkinje enojado”**) caracterizado por la rara ocurrencia de arritmias ventriculares malignas después de una ablación bien tolerada de TV fascicular relativamente benigna atribuido a **lesión de las fibras de Purkinje o del tejido miocárdico circundante** lo que desencadena extrasístoles ventriculares malignasde acoplamiento corto con capacidad para conducir a una una fibrilación ventricular. Los autores sostienen que por este motivo, se justifica la monitorización electrocardiográfica continua después de la ablación de arritmias ventriculares.

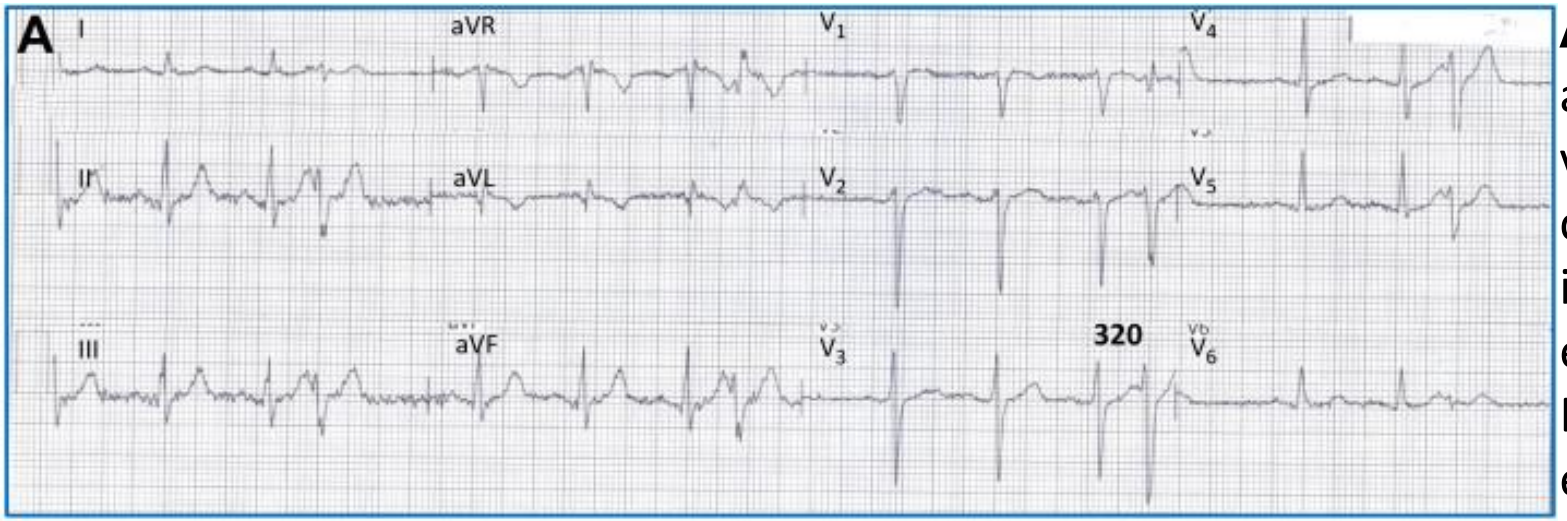
1. **Sami Viskin, MD,* Arie Lorin Schwartz, MD, Yuval Levi, PE, Aviram Hochstadt, MD, and Raphael Rosso, MD. Ventricular fibrillation after ablation of a benign arrhythmia. Angry Purkinje syndrome?. HeartRhythm Case Rep. 2020 Dec; 6(12): 937–941.**

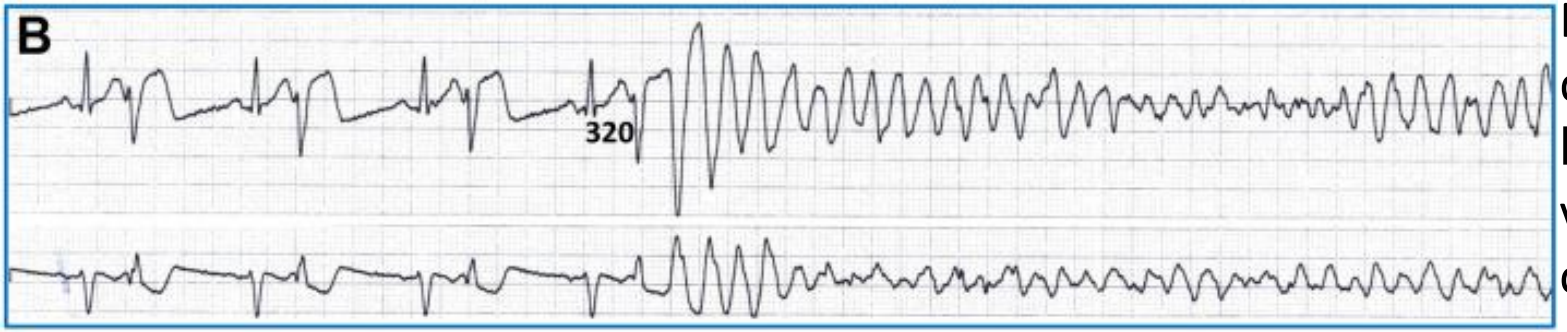
El paciente ablacionado presentó una TV fascicular bien tolerada permaneciendo asintomático por 21 días, y desarrollando a seguir 2 paros cardíacos recurrentes después de esta ablación con radiofrecuencia exitosa.

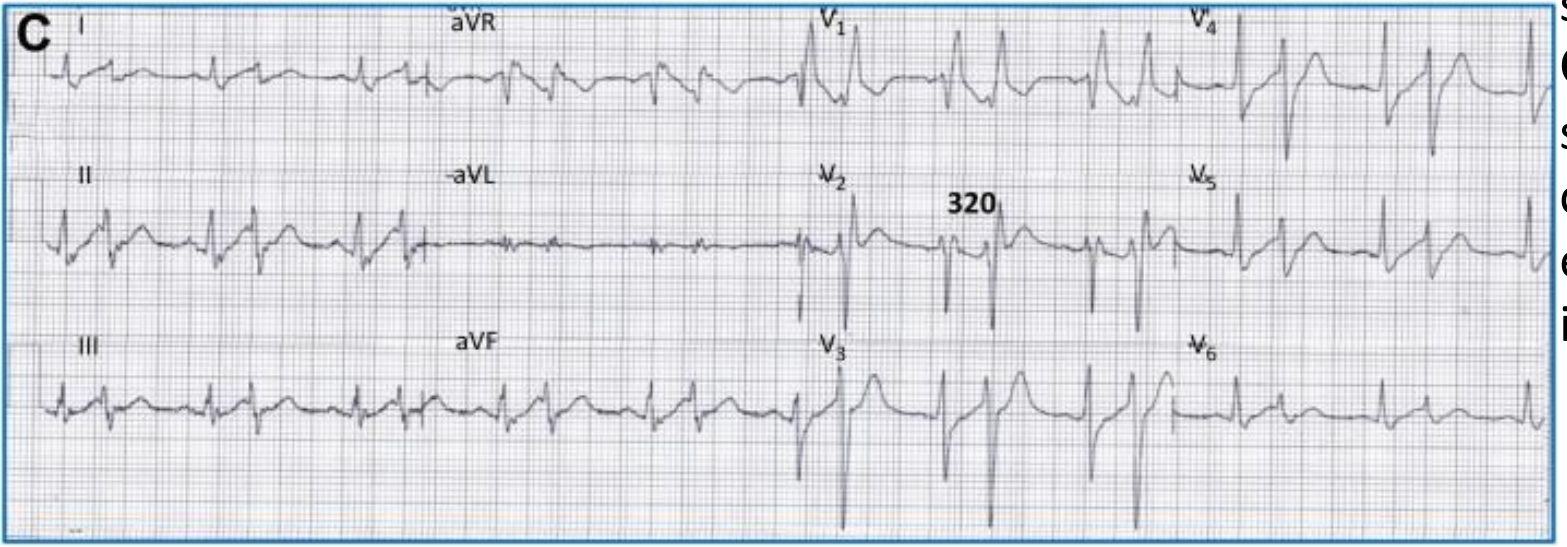
Esta secuencia de eventos de paro cardíaco intrahospitalario fueron iatrogénicos. Específicamente, el evento de FV probablemente se debió a los efectos proarrítmicos de la ablación con RF, mientras que un segundo paro bradiasistólico probablemente fue causado por un efecto colateral de la quinidina. La TV polimórfica causada por extrasístoles ventriculares de acoplamiento corto, en pacientes con enfermedad coronaria sin isquemia miocárdica evidente, habitualmente se origina en fibras de Purkinje ubicadas dentro de áreas de lesión miocárdica reciente. El procedimiento ablativo lesionando algunas fibras de Purkinje, desencadena las extrasístoles ventriculares de acoplamiento corto ocurridas dentro del **período refractario ventricular relativo**, desencadenando así una FV. Las lesiones causadas por la RF pueden haber dado lugar a pequeñas áreas de necrosis miocárdica entre las cuales algunas fibras de Purkinje permanecieron vivas en forma semejante a las fibras de Purkinje sobrevivientes dentro

El mecanismo del paro cardíaco bradiasistólico es especulativo. En ausencia de reacumulación de líquido pericárdico o estenosis coronaria nueva en la angiografía repetida, la causa más probable sería la toxicidad quinidínica. Además, la reversión inmediata del bloqueo AV con QRS ancho mediante inyección intravenosa de bicarbonato de sodio sugiere intoxicación por quinidina por bloqueo del canal de sodio como causa de la parada bradiasistólica. Sin embargo, no se registró un ensanchamiento gradual del QRS antes del evento asistólico. El paciente estaba asintomático y hemodinámicamente estable cuando desarrolló un síncope vagal típico que progresó a asistolia, lo que requirió reanimación prolongada. Los autores especulan que el episodio vagal produjo una fuerte reducción de la actividad simpática que aumentó la corriente de los canales de sodio y calcio, aumentando el cGMP mediado por vago reduciendo la corriente de Na+ y la de Ca++, lo que en presencia de un alto nivel de quinidina podría causar asistolia y deterioro de la conducción. Los efectos de la quinidina en el "canal de I_f funny" no se conocen. Sin embargo, la hidroxicloroquina similar a la quinidina) reduce la frecuencia sinusal al modular la corriente I_f

activada por hiperpolarización y por lo tanto, es posible que la quinidina tenga propiedades de bloqueo de I_f que podrían haber contribuido al paro sinusal. Una vez sobrevenida la bradicardia de origen vagal, la quinidina podría haber afectado la despolarización de fase 4 de las fibras de Purkinje, impidiendo ritmos de escape, perpetuando así la asistolia.La FV después de la ablación de arritmias benignas es raro. Habría apenas 1 reporte,, describiendo TV y FV polimórficas recurrentes que comenzaron 6 horas después de la ablación de una TV idiopática benigna del TSVD. Según el registro de una sola derivación presentado, la TV polimórfica parecía originarse en la zona de ablación y tenía un intervalo de acoplamiento inferior a 400 ms.(**Lacroix D., Kacet S., Lekieffre J. Ventricular fibrillation after successful radiofrequency catheter ablation of idiopathic right ventricular tachycardia. *Am Heart J.* 1994;128:1044–1045**). Es posible que las lesiones por ablación arritmogénica también estén subnotificadas. Hasta que se defina mejor la rareza del **síndrome del "Purkinje enojado",** es necesario vigilancia estrecha del monitor de ECG en busca de extrasístoles de acoplamiento corto durante 24 horas



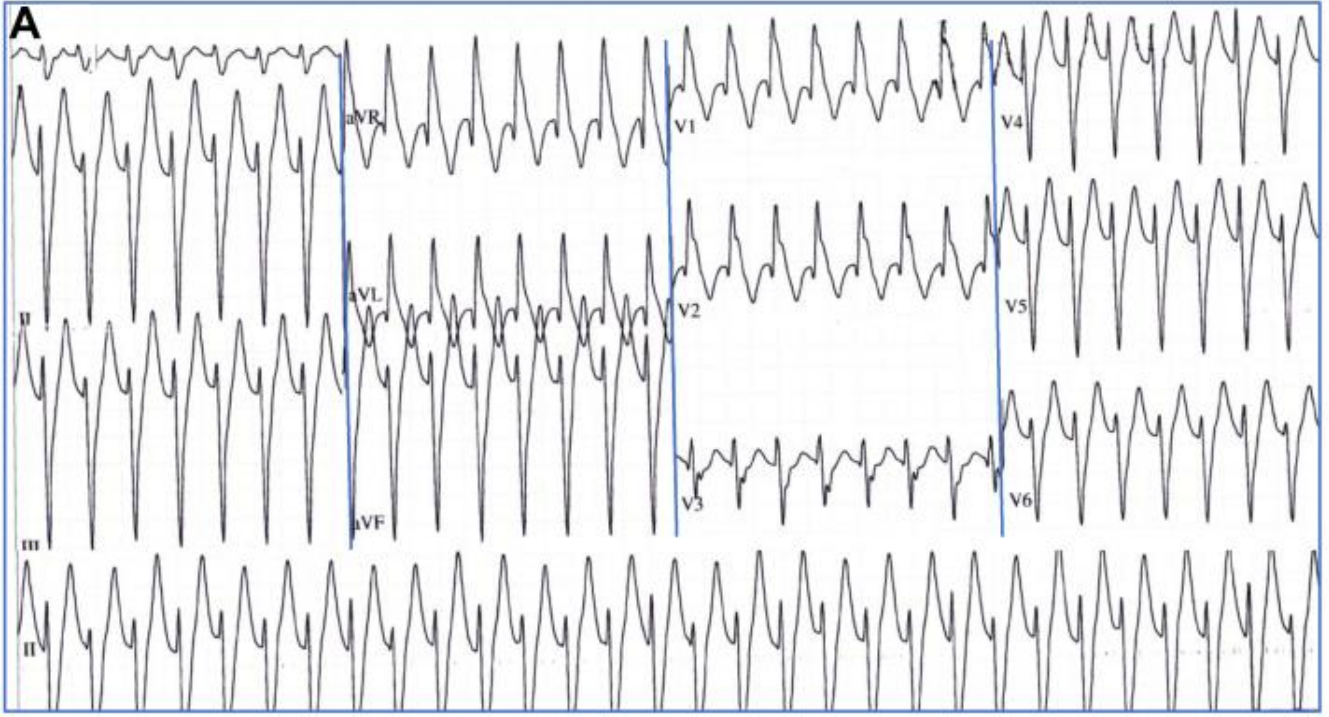




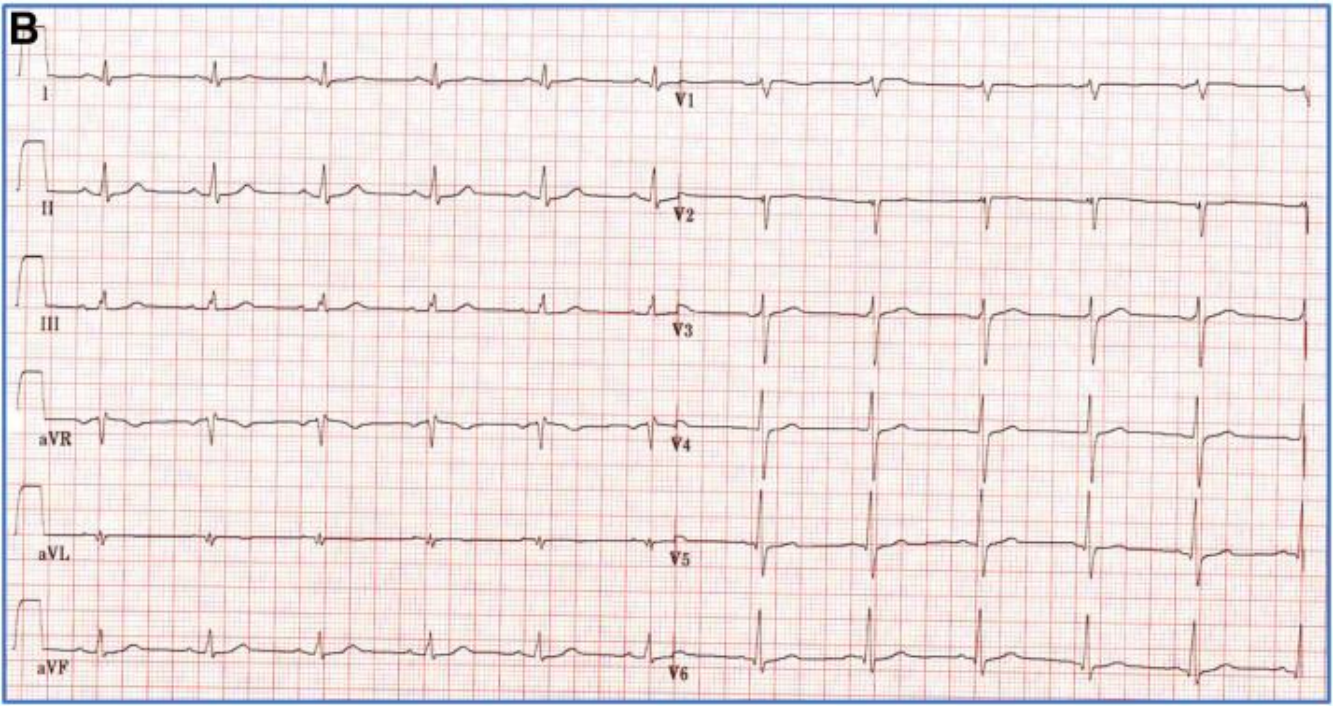
A: ECG registrado 2 horas después de la ablación (asintomático). Extrasístoles ventriculares de acoplamiento muy corto(320ms), patrón de BCRD, eje hacia la izquierda, pero complejos QRS bastante estrechos (mejor observados en V1-V2). Estas características indican que las extrasístoles se originan en las fibras de Purkinje ubicadas en el área de ablación dentro del **fascículo posterior izquierdo**.

B: una hora más tarde, una extrasístole ventricular con intervalo de acoplamiento corto desencadena una TV polimórfica que se deteriora hasta FV.

C: ECG después de la desfibrilación: ritmo sinusal con BCRD y bigeminismo ventricular con intervalo de acoplamiento de 320 ms. En este momento se inició quinidina intravenosa.



A: taquicardia ventricular sostenida (TV), FC: 190 latidos/min, detectada incidentalmente antes de una prueba de ejercicio programada. La TV disminuyó con amiodarona IV. El patrón QRS (morfología de rama derecha con eje superior) y los complejos relativamente estrechos sugirieron el diagnóstico de TV fascicular sensible al verapamilo de Belhansen



B: El verapamilo IV revertió el evento el ritmo sinusal con morfología QRS normal.

Quinidine: mechanisms of action

Antiarrhythmic agent of group 1 – Alkaloid of cinchona, d-isomer of quinine, both extracted from the tree of cinchona. Chemically, the drug is made up by two rings: quinoline and quinuclidine, joined by an alcoholic connection.

Mechanism of action – pharmacokinetics

A. The main mechanism of action is moderate block of inflow of Na^+ in rapid cells (prototype of membrane depressor drug or local anesthetic effect), a fact that decreases AP amplitude (amplitude of phase 0), DV/DT (rate of AP ascension or velocity of ascension of phase 0) and conduction velocity. This union is greater in the activate state. The effect is greater in the presence of acidosis and ischemia.

B. It blocks the multiple K^+ outflow currents in phases 1 and 3, so that AP duration is increased, and consequently, the effective refractory period: JT and QTc interval increase, it favors the appearance of early post-potentials, and these in turn, triggered activity that would lead to a higher tendency to appear “Torsade de Pointes”.

The channels blocked by the drug are:

I_{to}: quinidine acts in phase 1, allowing the slow outflow of K+ “in crescendo”. In normal conditions, this channel is found in a high concentration only in the epicardium and in M cells of the mid myocardium, but not in the endocardium. The characteristics of the I_{to} channel are considered significant in the genesis of ventricular tachycardias in Brugada syndrome. In this syndrome, quinidine causes homogenization of ventricular repolarization, decreasing ST segment elevation in right precordial leads, thus preventing the electrophysiological substrate from reentry in phase 2. Other class I drugs present the opposite effect in Brugada syndrome, increasing J point and ST segment elevation, due to their capacity to block the I_{to} channel (Imaizumi and Giles 1987) (Alings, Dekker et al. 2001), leading to a higher tendency to arrhythmic events.

Delayed rectifier outward K+ channels: these channels enable outflow of K+ in phases 3 and 4 of the SA node. They are channels considered as essential in normal automatism. They have there subtypes: 1) of slow kinetics (Iks); 2) rapid (Ikr); and 3) ultrarapid (Ikur), i.e. with activation and inactivation in variable velocities.

IK1 or “Inward rectifier”: this channel enables outflow of K+ in phase 3. This is a channel of K+ responsible for the state of balance of diastolic transmembrane potential (DTP) or E1.

ICa-L or L type (“long-lasting” or “L-type”): this channel acts in phase 0 of slow cells of SA node and AV node and in phase 2 or “plateau” of rapid fibers. In phase 3, inactivation of this channel occurs.

IKATP: this channel activates when intracellular concentration of ATP decreases. It enables the outflow of K+ in phase 3. It inactivates when cellular ATP concentration increases. Pathologically, it activates in case of ischemia.

IKACh: this channel enables outflow of K+ in phase 3 in the atria, causing shortening of refractory period. This channel of K+ is activated by the muscarinic receptor M2, being significant in the SA and AV nodes, and the atria. In the two former, it may produce hyperpolarization, and in the atria it shortens the refractory period.

IKACh – It seems to be the same as the adenosine receptor or IK(Ado).

Other electrophysiological actions of quinidine

- It decreases ascension velocity in phase 4: **negative dromotropism**;
- Vagolytic effect by block of muscarinic receptor M_2: **sinus tachycardia**;
- Anti α adrenergic action: by block of α_1 and α_2 receptors: **bradycardia;**
- It increases excitability and **ventricular fibrillation threshold**.
- It may originate or **exacerbate early post-potentials** (Roden and Hoffman 1985).
- It may **suppress delayed post-depolarizations**, while it may increase them too.

Action of quinidine on functional properties of cardiac cells

I. **Automatism, rhythmicity or diastolic depolarization:** negative by decreasing the degree of slant of the ascension ramp in phase 4, the threshold potential is shifted to more positive levels, and increases AP duration.

II. **Dromotropism (conduction velocity):** negative by decrease of amplitude in phase 0 of AP and Vmax.

III. **Inotropism (contractility):** mildly negative by discrete negative effect on contractility, leading to increase in LVEDP, and possible exacerbation of CHF; however, most times, the effect is offset by vasodilating action (Rodem 1996). This double negative inotropic effect and peripheral vasodilator, is due to α adrenergic block.

IV. **Batmotropism (excitability):** it increases refractoriness in the atrial and ventricular and His-Purkinje contractile muscle, by prolonging action potential by block of K+ channels in phase 3, virtually not altering the "plateau" in phase 2. Excitability and ventricular fibrillation threshold increases. By blocking rapid Na^+ channels, it decreases the amplitude of action potential of the rapid fiber, Vmax and ascension velocity in phase 0 of atrial, the ventricular and His-Purkinje system myocardial cells (rapid fibers depending on Na^+).

Electrocardiogram with quinidine

- Heart rate:
- SA node:
- Direct effect – it mildly depresses automaticity (bradycardia).
- Indirect effect - vagolytic M2 and block of □1 and □2 receptors of the drug increase HR. For this reason, SA node automaticity is considered not to be affected in therapeutic doses. In toxic doses, it may cause both bradycardia and sinus tachycardia or sinus arrest.
- AV node: It shortens junctional conduction time (A-H interval) and effective refractory period of the AV node (PRE-AV), by anticholinergic indirect effect (vagolytic) and by the direct effect, it increases these periods. Predominance of the first effect is observed when used in therapeutic doses and with medium plasmatic levels of 4.6 mg/L (Josephson, Seides et al. 1974). In toxic doses (levels >10 mg/L), it may cause AV block.
- In patients carriers of 2:1 flutter by anticholinergic effect, it may transform it into 1:1 with the subsequent hemodynamic worsening by increase in ventricular rate.

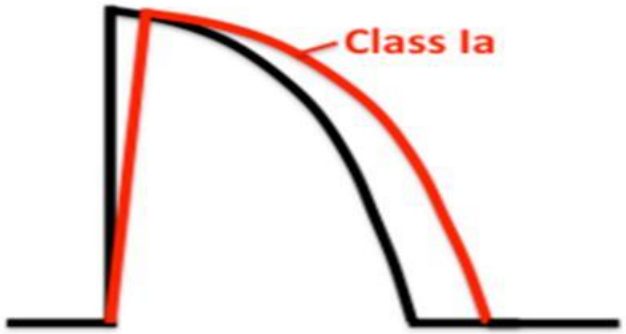
- It prolongs effective refractory periods of the atria, AV node, His-Purkinje system (it prolongs HV); 1 and of the ventricles at ventricular level, as well as accessory bundles. It may cause block in the His-Purkinje system (Hoffman, Rosen et al. 1975, Hoffman, Rosen et al. 1975). It prolongs HV interval. It increases refractory periods throughout the heart: atria, AV node, His-Purkinje system, ventricular contractile myocardium and accessory bundles.
- QRS complex duration: in therapeutic doses, it causes discrete prolongation in QRSd (10-20%). The QRS complex prolongation may be diffuse or only in the final part. QRSd >140 ms or >35% of the baseline tracing, constitutes absolute indication of interruption of the drug. The increase in QRS complex duration is directly related to the plasmatic concentration of the drug. On the contrary, QTc interval prolongation is not related with such concentration (Heissenbuttel and Bigger 1970).
- T wave modifications: as a consequence of the effect on rectifier delayed outward potassium channels in phase 3 of action potential: it increases duration and it affects T wave polarity of ECG:
- In leads where the T wave has positive polarity: it initially decreases voltage and finally causes notches or discrete inversion.

- **In leads where T wave has negative polarity:** T waves decrease their depth. In general, the T vector has an orientation opposite to the final vector of the QRS complex.
- **On the JT interval:** this interval is the distance existing between the J point and the onset of T wave. Quinidine causes prolongation in a degree somewhat greater than the QRS complex.
- **On the QTc interval:** it causes prolongation of this parameter. If the QTc interval reaches 440 ms and the QT interval 600 ms, we consider that the drug caused acquired LQTS. QT interval prolongation is mainly due to the block of different delayed outward K+ rectifier channels in phase 3. When the QTc interval is significantly prolonged, there is a greater possibility for early post-potentials to appear, capable of causing triggered activity, and in turn, polymorphic ventricular tachycardia of the “Torsades de pointes” type, which may degenerate into ventricular fibrillation and quinidine syncope (DiMarco, Garan et al. 1983).

- **QTc interval prolongation:** This severe form of VT appears almost always after a pause, and it is known as “pause-dependent” VT, to distinguish it from adrenergic-dependent torsades. QT interval syndrome may be the consequence of intoxication with other antiarrhythmic agents of the IA group, sotalol, or the calcium antagonist bepridil, neuroleptic agents of the phenothiazine type, tricyclic and tetracyclic antidepressants, cisapride, hypopotassemia, hypomagnesemia, intoxication by organophosphorate insecticides, mitral valve prolapse, intracraneal hemorrhage, subarachnoid hemorrhage, carotid dissection over the course of endarterectomy, nutritional state alterations (parenteral liquid-protein diets), severe bradyarrhythmias, SA node disease, total AV block, and two congenital syndromes: Jervell-Lange-Nielsen with deafness (autonomic recessive) and Romano-Ward (dominant autosomal) (DiMarco, Garan et al. 1983).

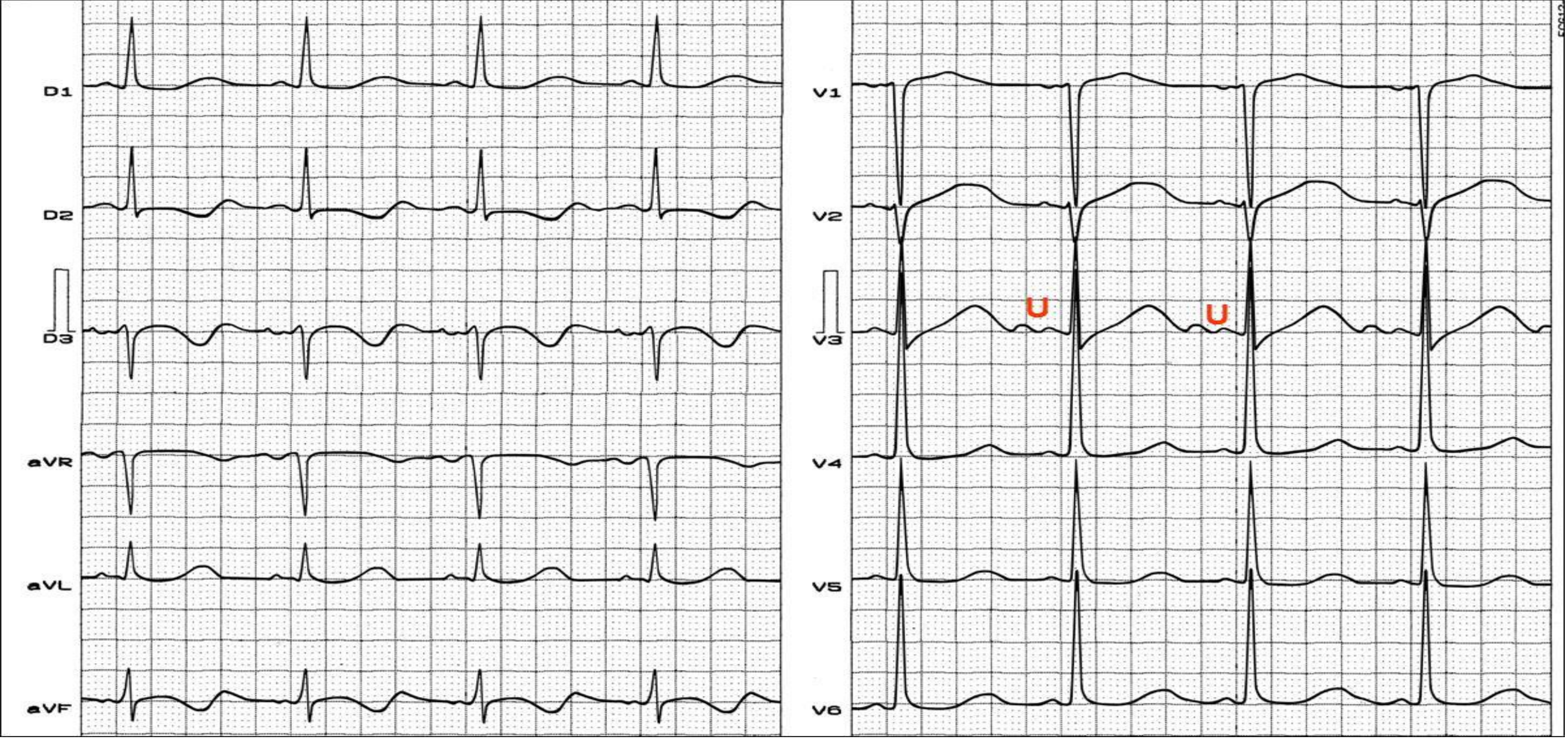
Therapeutic and toxic ECG features with quinidine

Therapeutic effects of quinidine	Toxic effects of quinidine
Decrease of T wave voltage	Broader QRS: if it reaches 140 ms or with 25% increase in initial duration, the drug must be suspended.
T wave polarity inversion	A-V block in different degrees and with origin in the His-Purkinje system.
Prominent U wave: >1.5 mm	Important sinus bradycardia, sinus arrest, or SA block.
P wave notches or modifications	PR interval prolongation: it constitutes a late sign and it occurs with levels above 10 mg/L.
In 2 to 8% of the cases, polymorphic VT, even in therapeutic or subtherapeutic doses.	

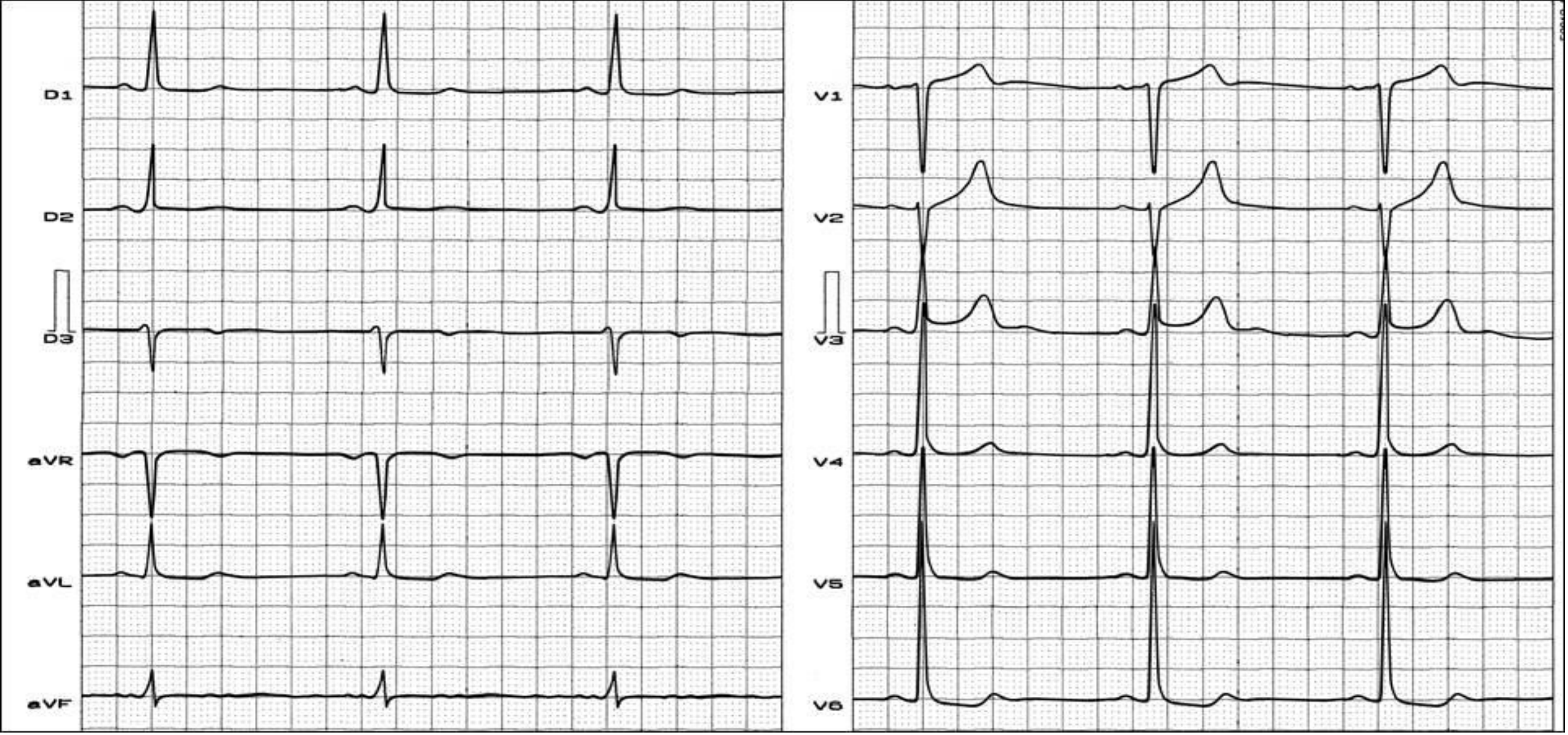


On the ECG:

↑QRS & ↑QT



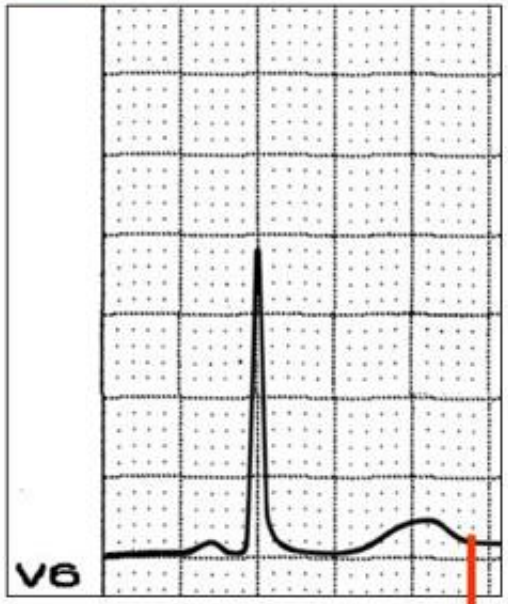
T wave alterations: inverted T wave in inferior leads (consequence of the effect on phase 3 of action potential), long QT and JT intervals and visible U wave in V3 (1.0 mm). Doubtful LVH. Note: level of serum quinidine of 3.6 mg/L



Typical ECG of action of quinidine: The same patient after suspending the drug.

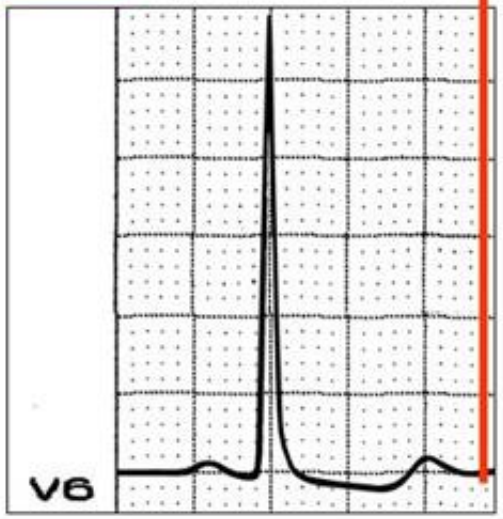
ECG comparison during and after interrupting the drug

With high level of quinidine



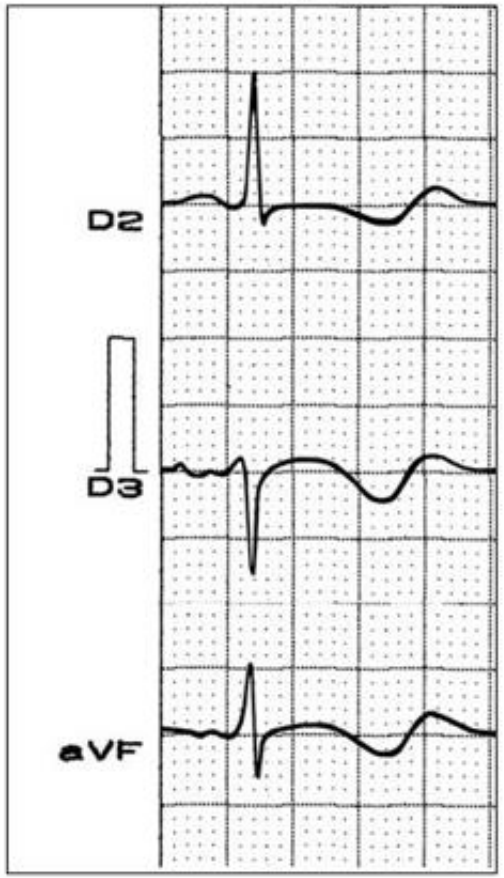
Long QT interval

Without high level of quinidine



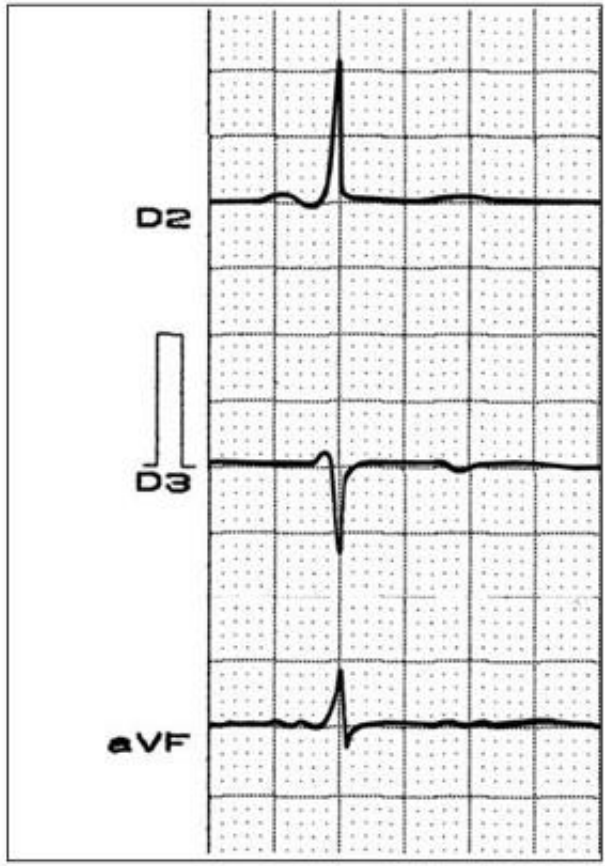
Normal QT interval. The LVH pattern is more evident.

Without high level of quinidine



Biphasic inverted T wave "minus plus"

With high level of quinidine



Isoelectric T wave