Quinidine: mechanisms of action

Antiarrhythmic agent of group 1A – 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 1987; Alings 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 (I_{ks}); 2) rapid (I_{kr}); and 3) ultrarapid (I_{kur}), i.e. with activation and inactivation in variable velocities.
- **I_{K1}** 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.

- **I_{Ca-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.
- **I_{KATP}:** 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.
- **I_{KACh}:** 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 M^2, 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.
- **I_{KACh}** – It seems to be the same as the adenosine receptor or I_K(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 (Rodem 1985).
- It may suppress delayed post-depolarizations, while it may increase them too.

Action of quinidine on functional properties of cardiac cells

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

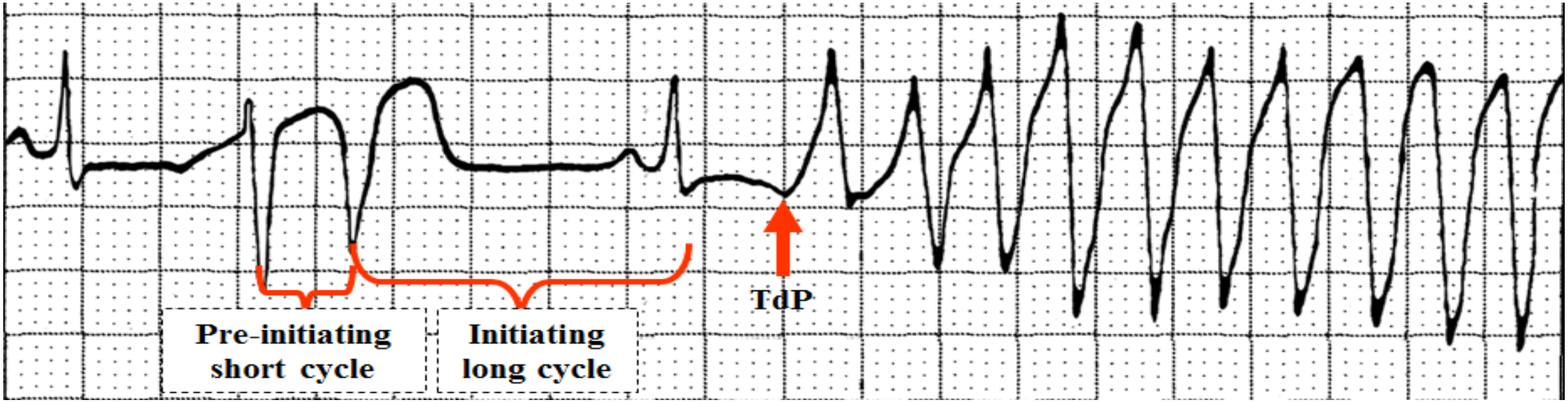
ELECTROCARDIOGRAM MODIFICATIONS WITH QUINIDINE

- **Heart rate:**
  - ➢ **SA node:**
    - ✓ **Direct effect –** it mildly depresses automaticity (bradycardia).
    - ✓ **Indirect effect -** vagolytic M_2 and block of α_1 and α_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 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 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 (Macfarlane 1989). 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 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 (Di Marco 1983).

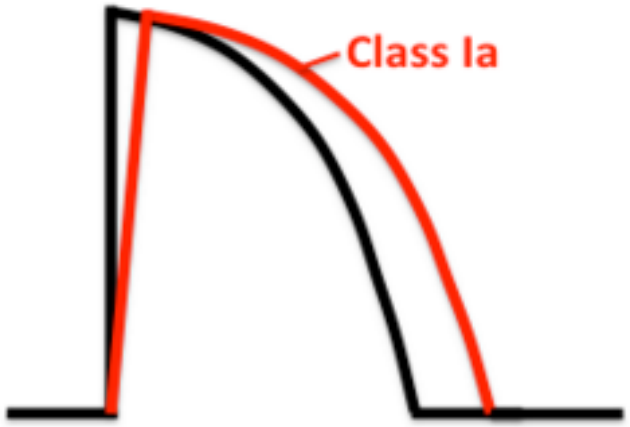
- **QTc interval prolongation:** This severe form of VT appears almost always after a pause, and it is known as "pause-dependent" VT, to distinguish it from adrenergic-dependent torsades. QT interval syndrome may be the consequence of intoxication with other antiarrhythmic agents of the IA group, sotalol, 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) (Di Marco 1983).



After pauses by "long-short" sequence or in bradyarrhythmias, complete AV block and sudden PR interval prolongation. TdP that started by intoxication with quinidine. The cycle interrupted by TdP is longer than the prior cycle.

Therapeutic and toxic ECG features with quinidine (Chou 1996)

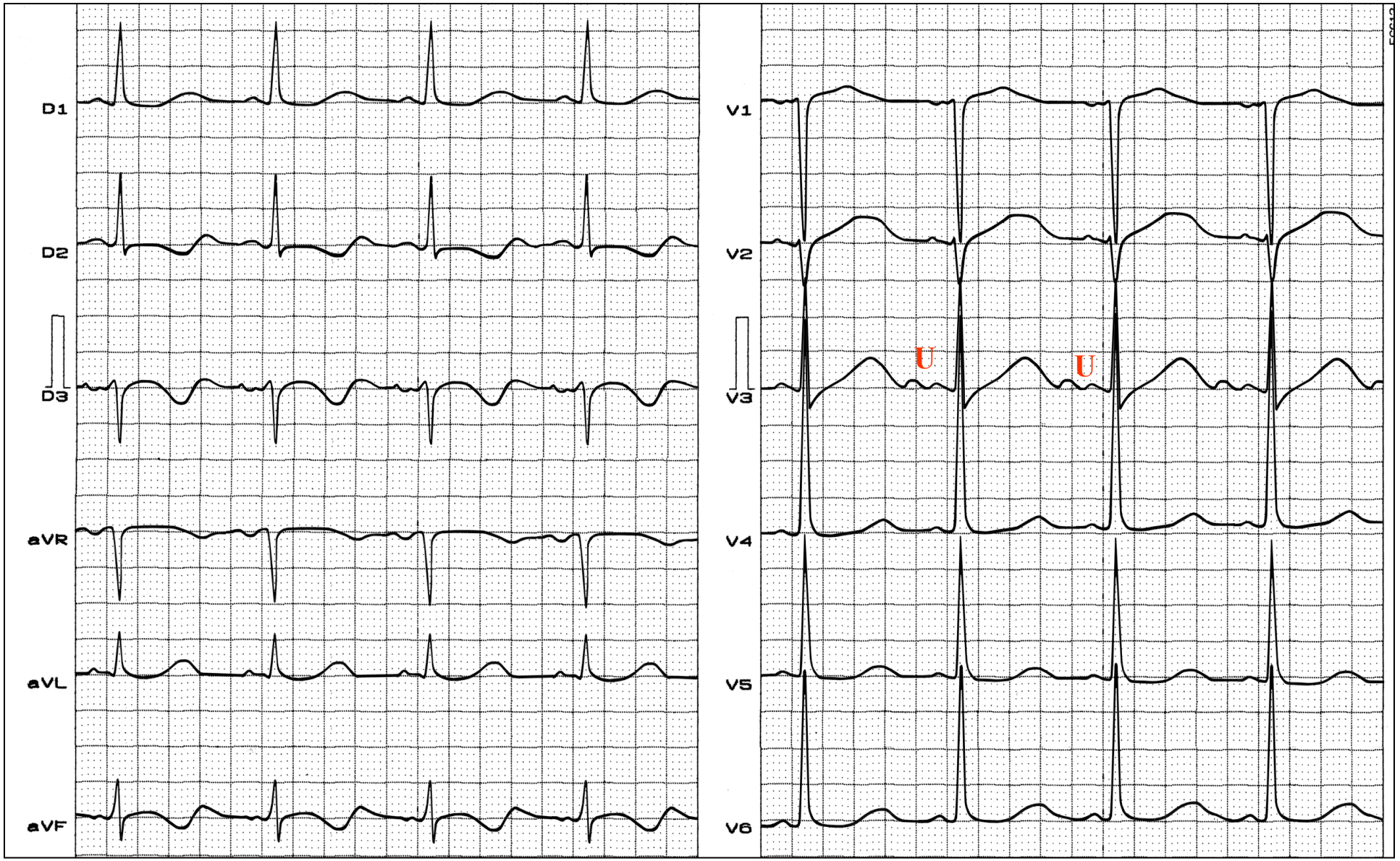
Therapeutic effects of quinidine	Toxic effects of quinidine
Decrease of T wave voltage	Broader QRS: if it reaches 140 ms or with 25% increase in initial duration, the drug must be suspended.
T wave polarity inversion	A-V block in different degrees and with origin in the His-Purkinje system.
Prominent 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

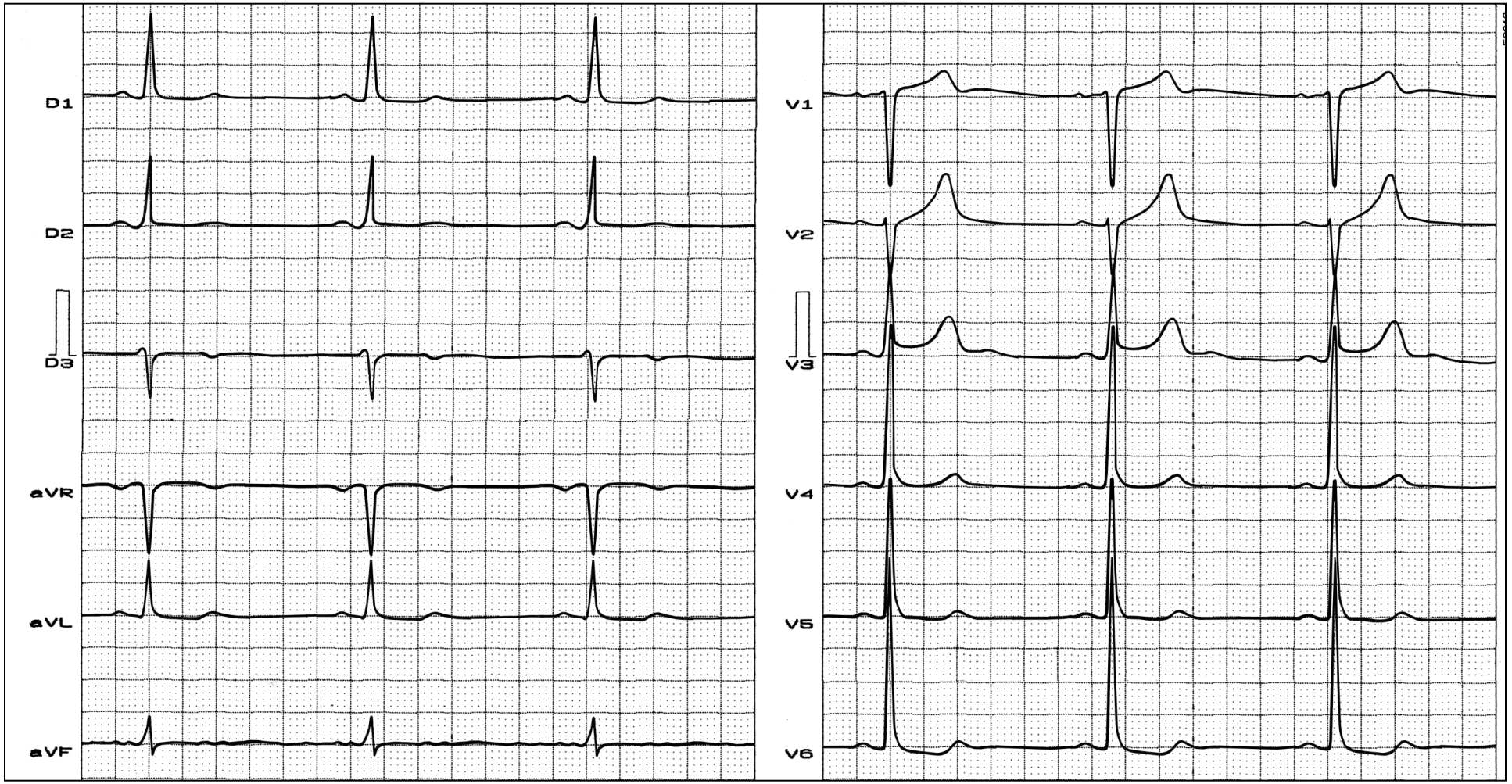
Typical ECG of action of quinidine



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 LVE.

Note: level of serum quinidine of 3.6 mg/L

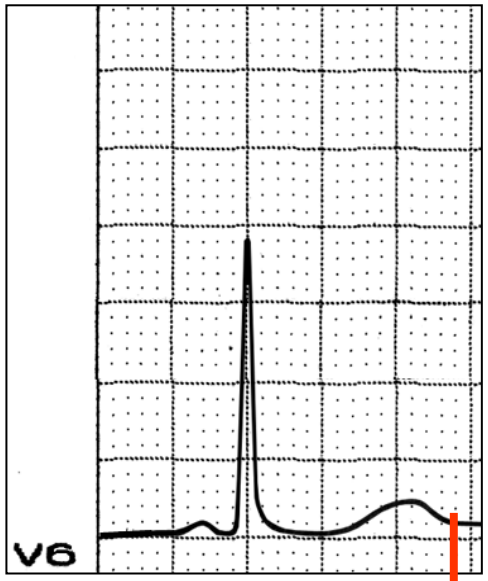
Typical ECG of action of quinidine



The same patient after suspending the drug.

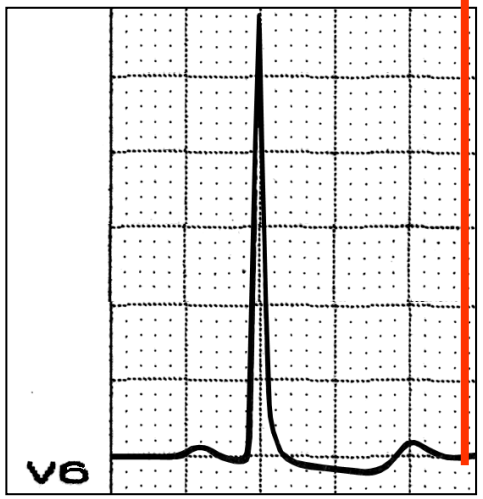
ECG comparison during and after interrupting the drug

With high level of quinidine



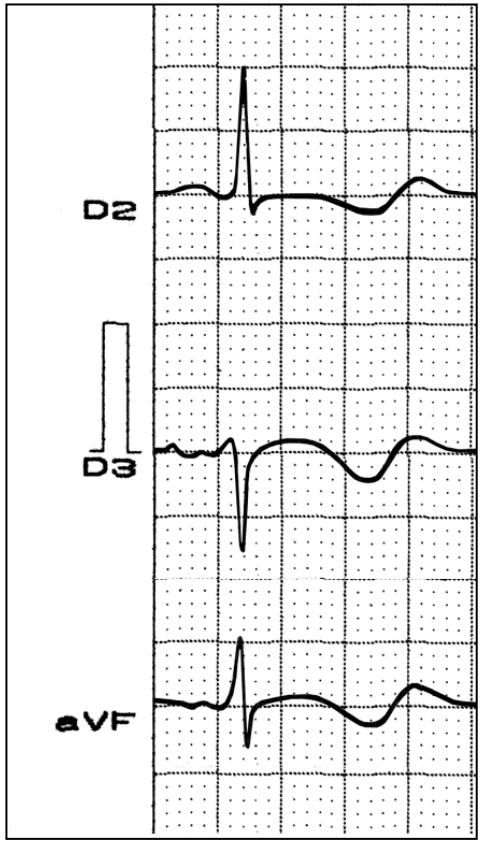
Long QT interval

Without high level of quinidine



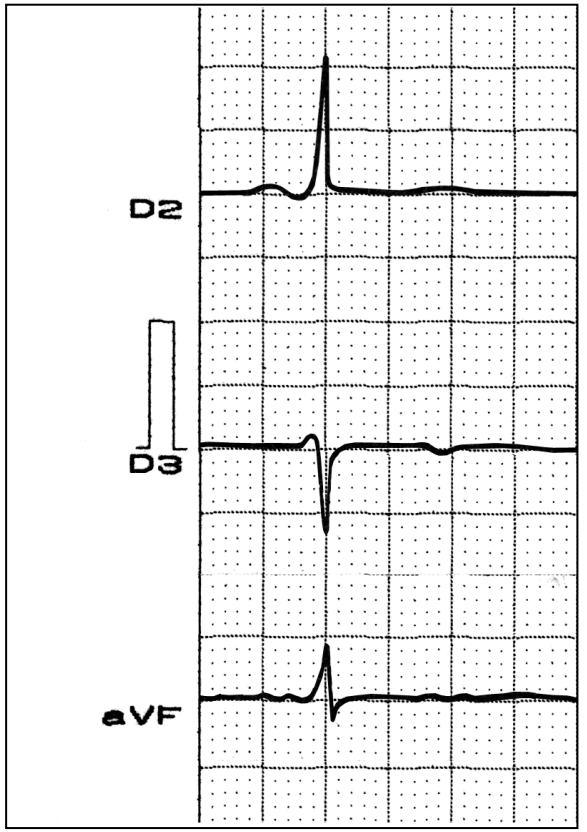
Normal QT interval. The LVE pattern is more evident.

Without high level of quinidine



Biphasic inverted T wave "minus plus"

With high level of quinidine



Isoelectric T wave