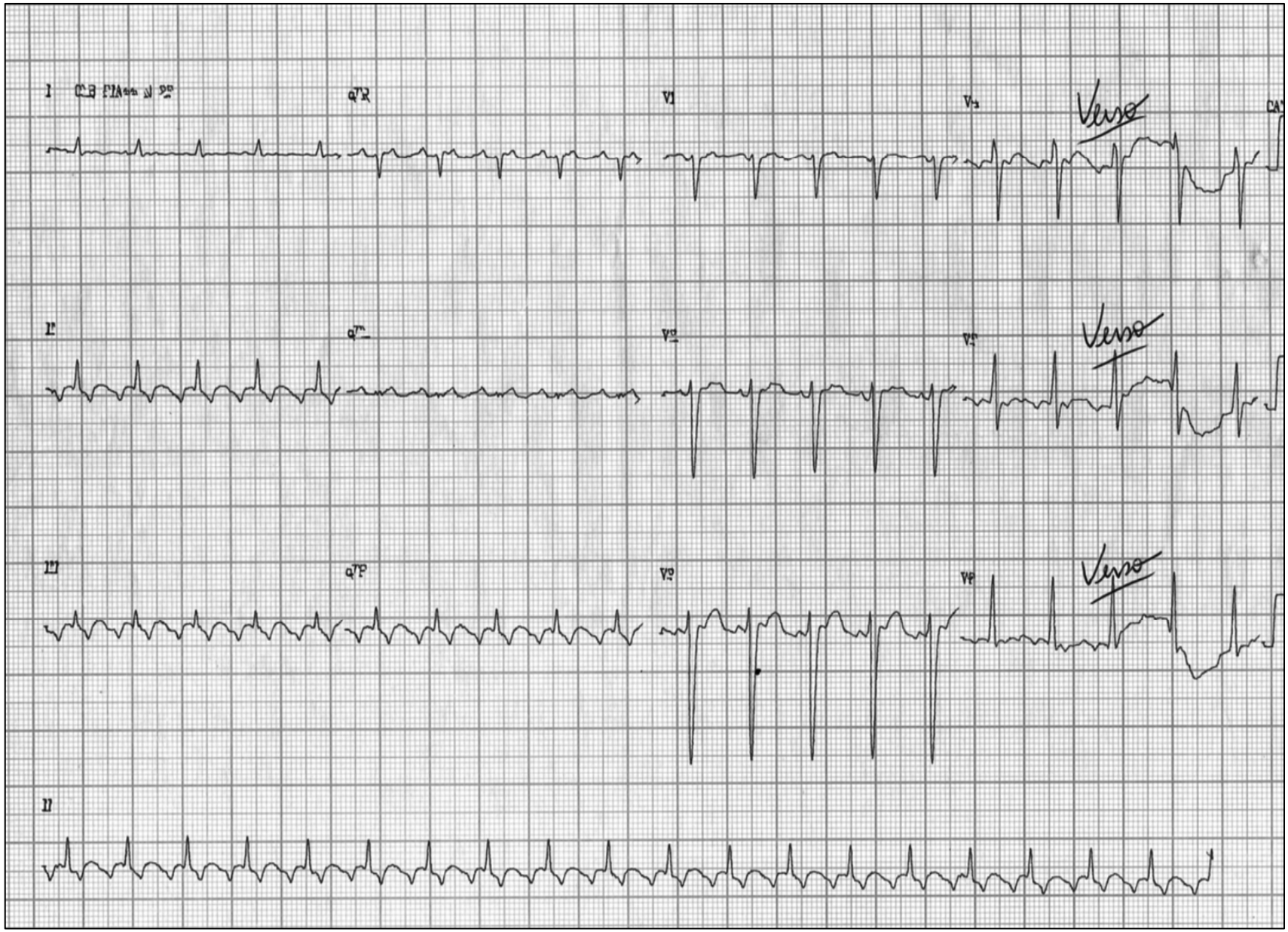
CASE REPORT

- Following we will show a series of 5 tracings of a patient that was admitted with atrial flutter, AV conduction 2:1 (ECG 1), and signs and symptoms of congestive heart failure. In spite of the contraindication, he was submitted to therapy with oral propafenone to attempt chemical reversion (electric cardioversion would have been ideal).
- After administering oral propafenone (2 tablets with 300mg each in 2-hour interval), the patient developed hemodynamic instability, secondary to broad QRS tachycardia (ECG 2):
  - Broad Supraventricular tachycardia: Flutter 1:1 with QRS widening? or
  - Monomorphic Ventricular Tachycardia ?

- Even after reversion, the ECG shows wide QRS complex with Complete LBBB pattern (ECG 3).
- Finally, the fifth tracing recorder 48h after stop propafenone shows sinus rhythm with narrow QRS complex.

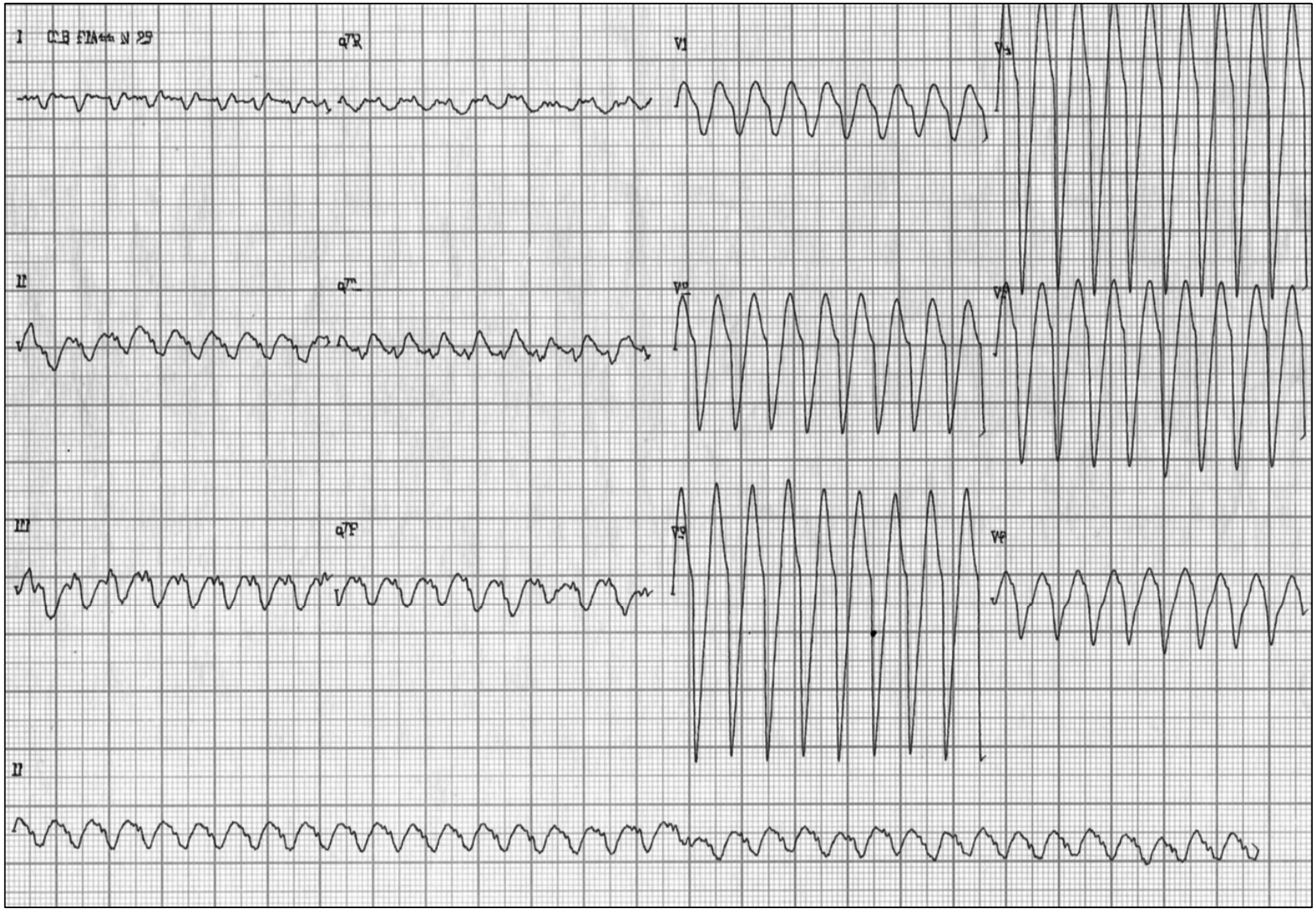
- I would like to hear your commentaries about this case of proarrhythmia induced by propafenone.

ECG1



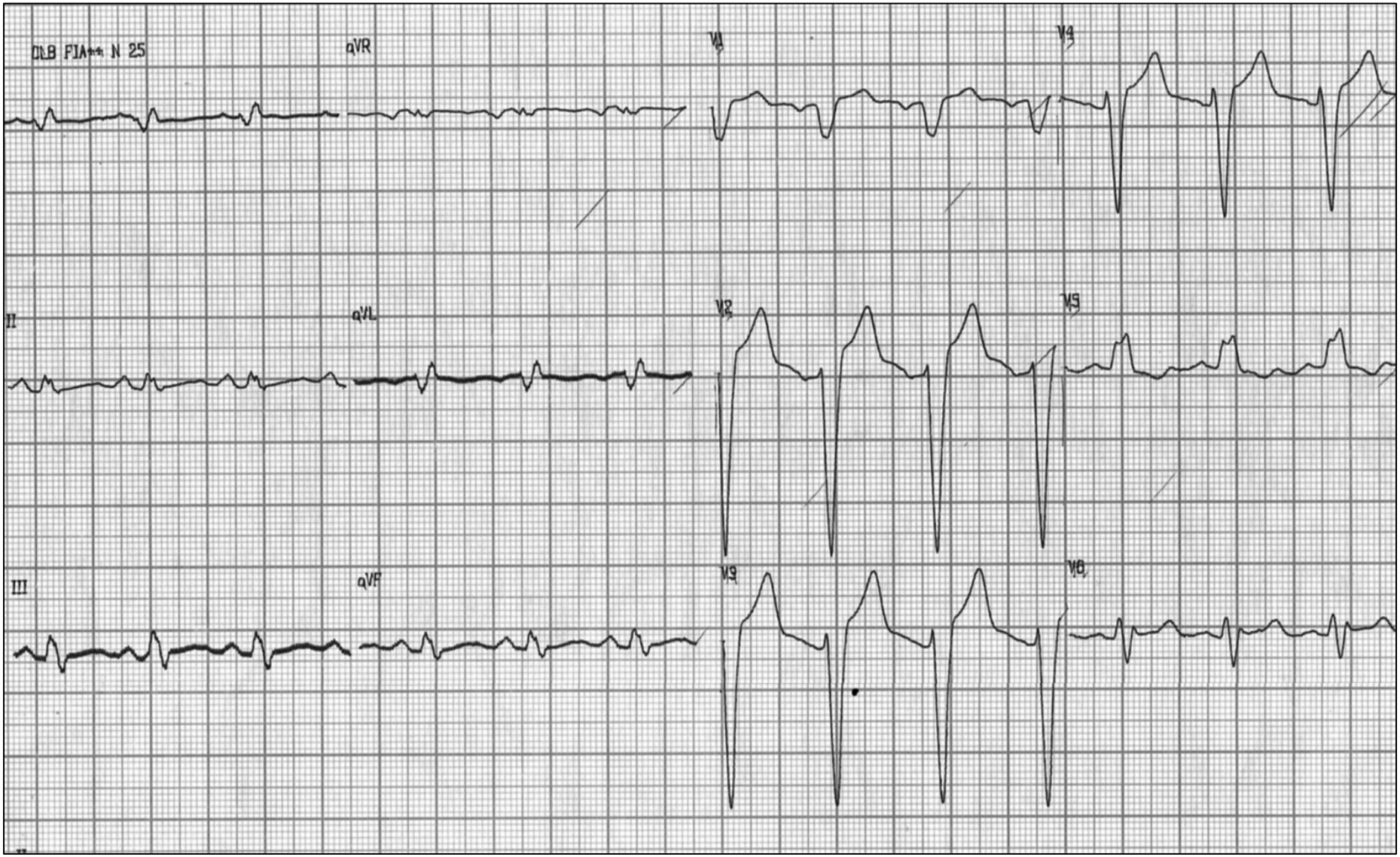
Patient with clinical picture of congestive heart failure:

ECG2



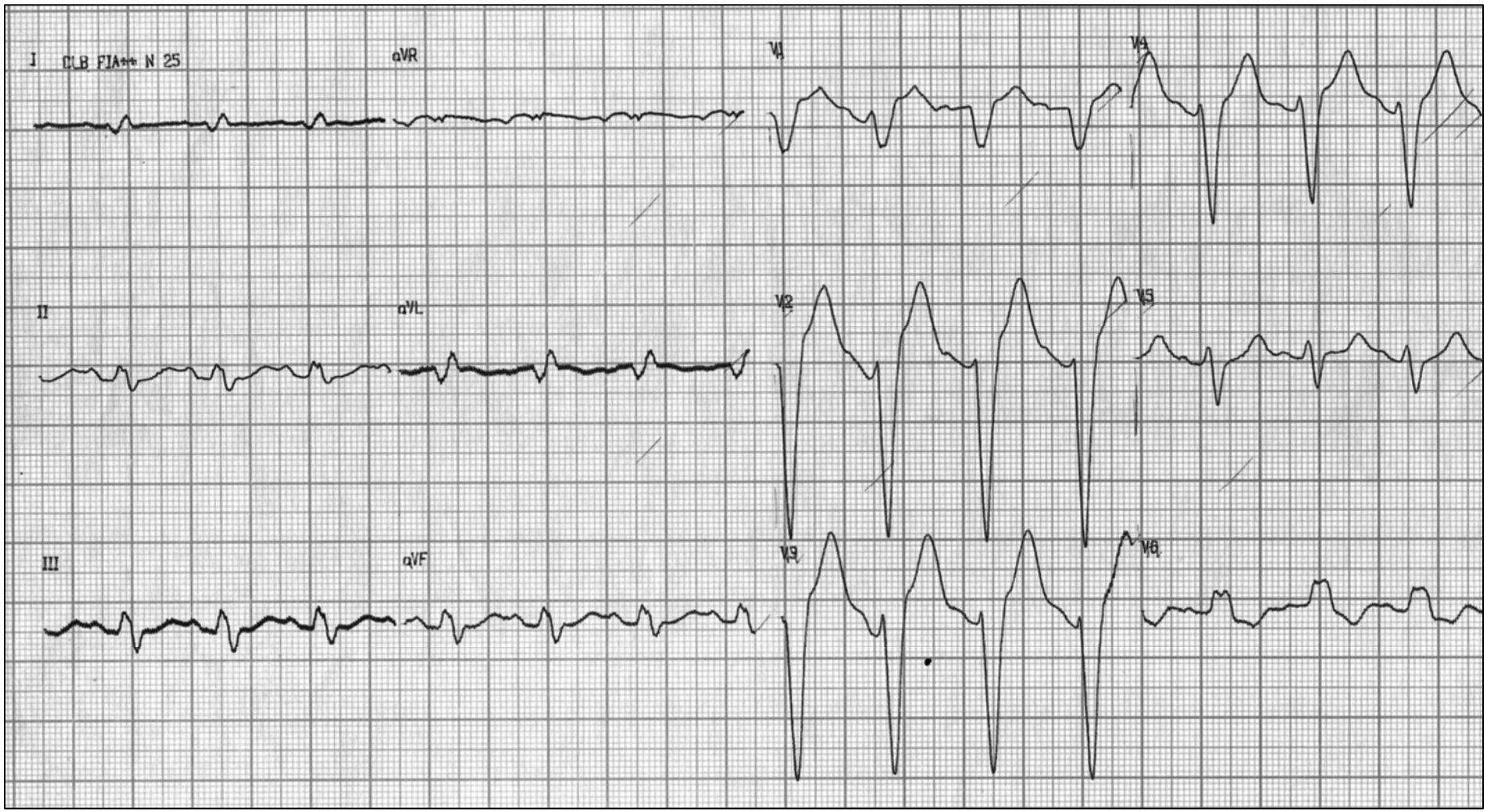
1:40 after oral administration of propafenone (2 tablets with 300mg each).

ECG3

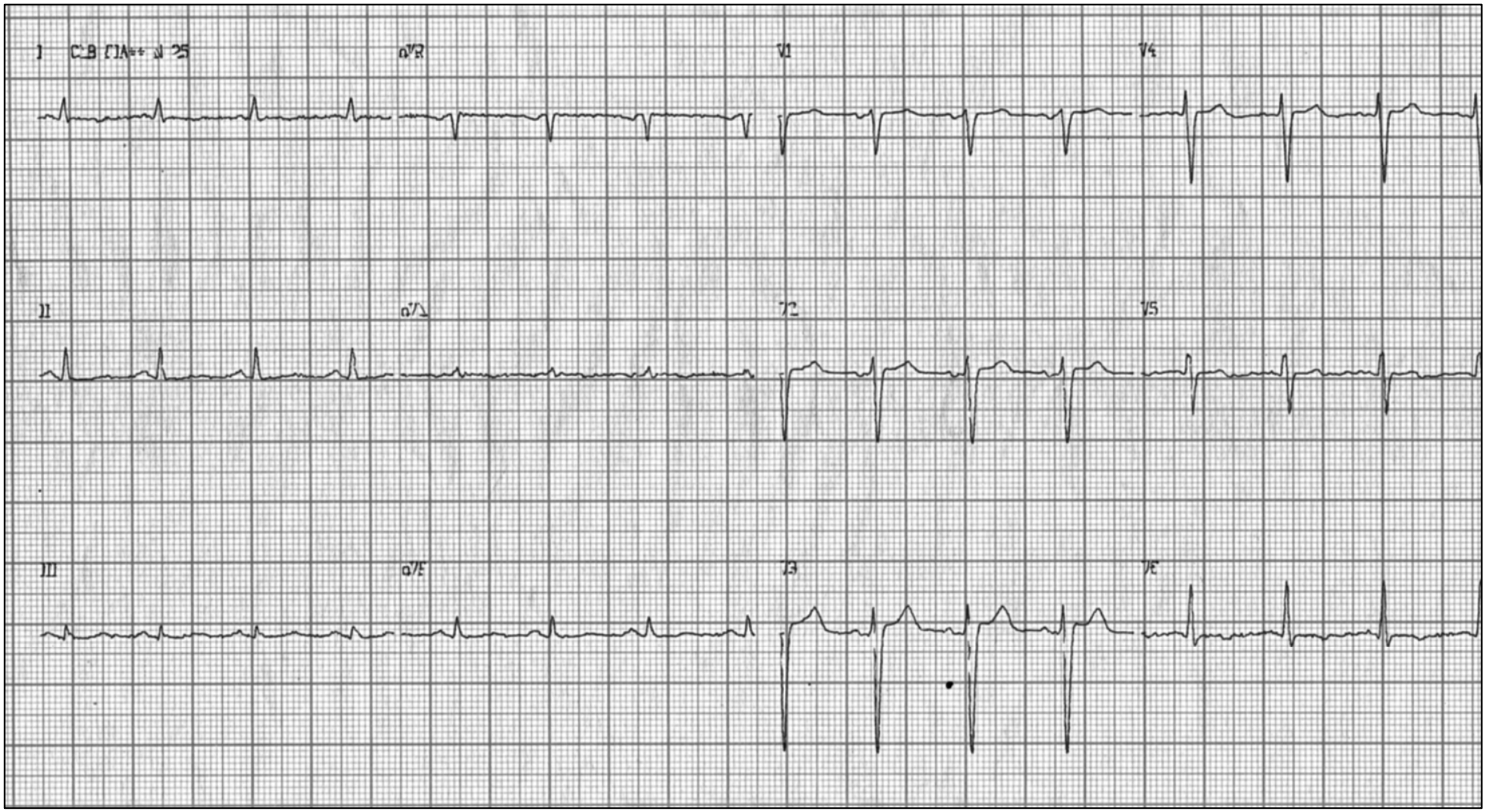


Immediately after cardioversion

ECG4



ECG5



48 hours after stop propafenone administration

COMMENTARIES

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St. Jude Medical CRMD

This is not seen very frequently which makes it an even better teaching case. We know that any of the Class 1 antiarrhythmic agents may be pro-rhythmic and there would be a tendency for physicians to label the rhythm (ECG 2) as a double tachycardia (VT and Aflutter). However, if that were the case, I would expect the "VT" to not be exactly the same rate as the flutter rate in the atrium. If one used calipers to encompass multiple consecutive flutter intervals as taken from the rhythm strip on Lead II at the bottom of the page on ECG 1 and then move to ECG 2 with the wide QRS tachycardia, the wide QRS tachycardia rate is exactly the same as the flutter rate.

The wide-QRS complex in ECG 2 could be either rate-dependent aberration or associated with the propafenone itself to slow sodium conduction and widen the QRS or a combination of the two. Following cardioversion and restoration of sinus rhythm, ECG 3, the QRS remains wide. While it may take some time for rate dependent bundle branch block to resolve following termination of the rapid rate, if that was the explanation, it should have resolved by ECG 4 presuming that ECG 3 was recorded immediately following cardioversion. Hence, in addition to facilitating conduction via the AV node, the propafenone also impacted the QRS duration and this took a couple of days to fully resolve.

COMMENTARIES

Dr Adrian Baranchuk, MD FACC- Assistant Professor of Medicine
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Kingston General Hospital

1. Why the LBBB aberrancy during tachycardia (rate-dependent) has a different morphology than the LBBB in sinus rhythm? (Leads I and V5-V6 are totally different; could this be explained on a basis of heart rate?)

2. Why the shift in the axis?

3. Why there is an initial q wave in Leads I / AVL during LBBB during sinus rhythm in the absence of lateral MI? (Is this something specific of Propafenone intox?)

I know it sounds rare (even stupid?) but double tachycardia with isochronous dissociation remains a possibility.

COMMENTARIES

Prof. Dr. Andrés Ricardo Pérez Riera Chief of the Sector of Electro-Vectocardiography of the Discipline of Cardiology, School of Medicine, ABC Foundation – Santo André – São Paulo – Brazil

ECG1:
Classical or common flutter by presenting F wave rates between 240 and 330 bpm (in this case less than 300) and negative polarity in DII, DIII, and aVF without baseline. Waves with sawtooth or picket-fence appearance, called F waves with rates between 250 and 350 bpm, are better observed in the inferior wall and V1, with slow descending and fast ascending slope. These waves are similar to inverted P followed by an ascending slope: Tp waves.

ECG2: Tachycardia with monomorphic wide QRS. Is it supraventricular tachycardia/is it VT?
Answer:
In favor of the first hypothesis:
- Very high HR: 214 bpm.
- Absence of capture beats.
- Absence of fusion beats. Possible and characteristic presence of fusion beats (Dressler beats). They are beats with morphology of QRS intermediary between pure sinus beat and pure ectopic beat, because the ventricular complex results from the activation of the biventricular chamber by two wave fronts: one coming from the VT and the sinus one: the resulting beat is an incomplete capture (fusion beat).
- QRSd: 120 ms.
- S nadir in V1 and V2<60 ms (TV>60 ms).

COMMENTARIES

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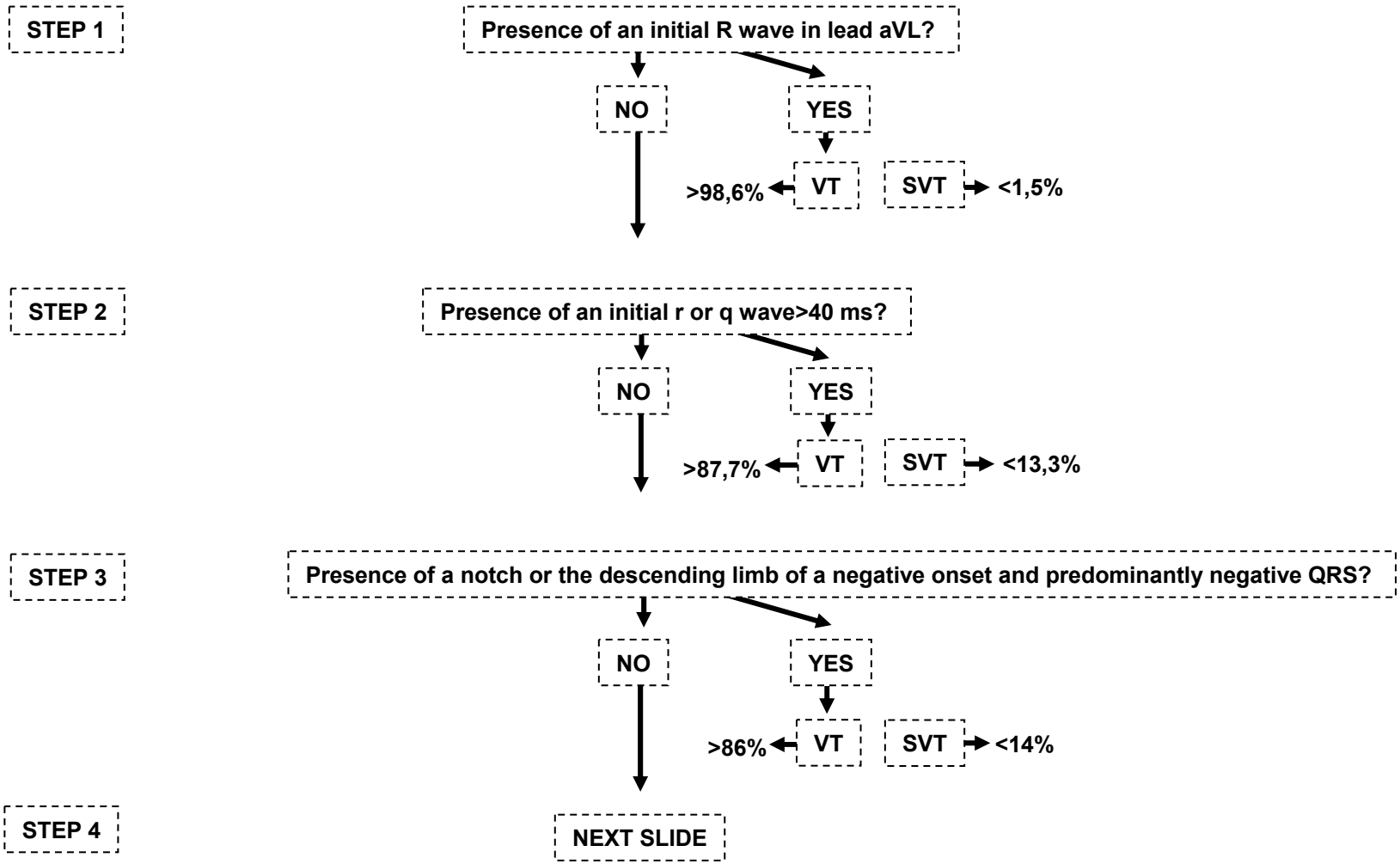
ECG2:

In favor of a ventricular source we have:

- Absence of RS complex from V1 through V6.
- Matching pattern: Precordial leads consist of complexes that are completely negative.
- Criteria that indicate VT: presence of negative QRS complexes from V4 through V6.
- New Vereckei algorithm[1] (next slide), using only the aVR lead to differentiate VT with wide QRS. Presence of initial R wave in aVR? In this case, there is small initial r in aVR; consequently, it is VT. Presence of a notch in descending slope of predominantly negative QRS complex? Answer, yes: VT.
- QS in V1 and V2 leads (specificity: 96%; sensitivity: 96%; predictive accuracy: 97%).
- Initial r wave in aVR lead: specificity >98.6%.
- Conclusion: VT.

1) Vereckei A, et al. Heart Rhythm. 2008; 5: 89.

NEW ALGORITHM USING ONLY LEAD AVR FOR DIFFERENTIAL DIAGNOSIS OF WIDE QRS COMPLEX TACHYCARDIA

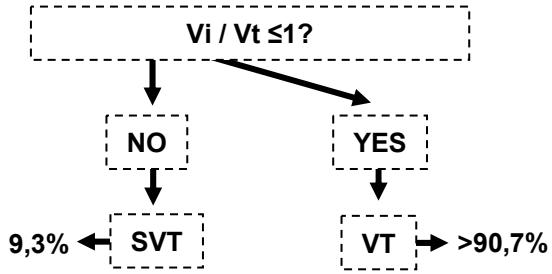


Vereckei A, Duray G, Szénási G, Altemose GT, Miller JM. New algorithm using only lead aVR for differential diagnosis of wide QRS complex tachycardia. Heart Rhythm. 2008; 5: 89

NEW ALGORITHM USING ONLY LEAD AVR FOR DIFFERENTIAL DIAGNOSIS OF WIDE QRS COMPLEX TACHYCARDIA

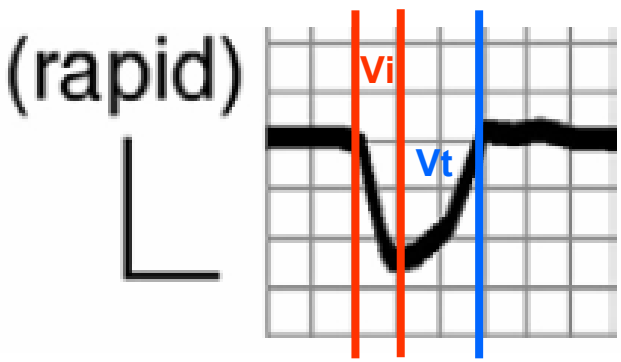
STEP 4

Vi: initial excursion velocity of QRS complex.
Vt: terminal excursion velocity of QRS complex



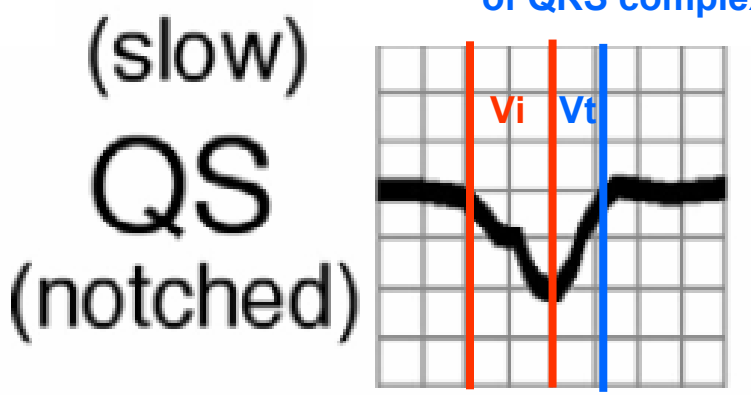
Ventricular activation-velocity ratio The vertical excursion (in millivolts) recorded during the initial (Vi) and terminal (Vt) 40 ms of the QRS complex.
If ≤1= VT
or >1=SVT.

Vt: terminal excursion of QRS complex.



Vi: initial excursion of QRS complex.
≤1 = TV

Vt: terminal excursion of QRS complex.



Vi: initial excursion of QRS complex.
>1 = TVS

Vereckei A, Duray G, Szénási G, Altemose GT, Miller JM. New algorithm using only lead aVR for differential diagnosis of wide QRS complex tachycardia. Heart Rhythm. 2008; 5: 89

COMMENTARIES

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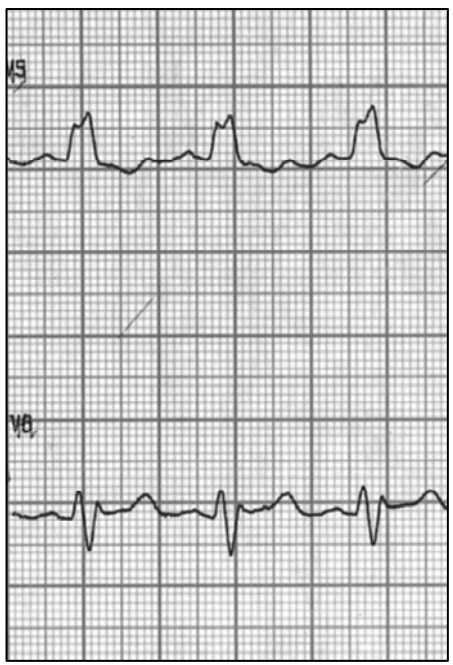
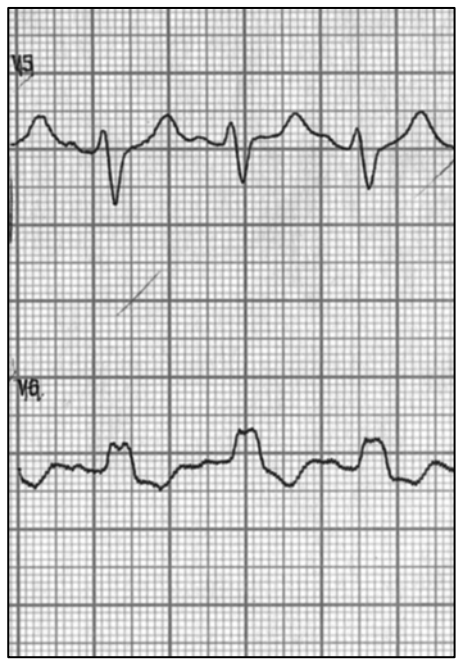
ECG3: LAE + Complete LBBB, high lateral inactive area ?
Low voltage in frontal plane.
ECG4: LAE + Complete LBBB, high lateral inactive area ?
Why differences between V5 and V6?
Answer: I think that is a technical problem (different position of electrodes in left precordial leads)

ECG3



ECG4



COMMENTARIES

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- Propafenone is an antiarrhythmic agent, class 1C, with weak additional β-blocking properties and minimal calcium-antagonist properties. Its absorption orally is reduced by having an extensive and dose-dependent hepatic metabolism of first passage (pre-systemic clearance). Plasma propafenone concentrations is markedly influenced by CYP2D6 genotype-derived phenotype. The drug is absorbed by this pathway a 95%; however, its bioavailability is just 12% and the maximal plasmatic concentration when administered orally is 2 hours.

- Hepatic impairment decreases the elimination of many antiarrhythmics to such an extent that dosage reductions are highly recommended in such populations, especially in patients with cirrhosis.

COMMENTARIES

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Mechanisms of action

- Na+ rapid channels block, Vmax, phase 0 amplitude, in a closed or tonic (inactive) state, while predominantly open (phasic). The block of the mentioned channels is dose and voltage-dependent, manifesting in a more intense way in fast rates. The phenomenon occurs predominantly in the His-Purkinje system and in the ventricular contractile muscle.
- It increases the refractory periods of the atria, inconstantly of the AV node, and ventricles.
- Additionally, propafenone blocks Kvl.4deltaN channel through intracellular bindings and that binding of propafenone with Kvl.4deltaN channel leads to a conformational change on the extracellular site which accelerates C-type inactivation, suggesting that propafenone, as an open channel blocker, may affect the mechanism of C-type inactivation[1].

1) **Tian L. et al. J Physiol Biochem. 2006; 62:263-270.**

COMMENTARIES

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- Channels are water-filled membrane-spanning proteins, which undergo conformational changes as they gate, i.e. open or close. These conformational changes affect both the shape of the channel and the volume of the water-filled pore. The intracellular side of the pore closes during C-type inactivation and the volume change is similar to that associated with activation or deactivation. This is also similar to the pore volume estimated from the crystal structure of KcsA and MthK K+ channels. Intracellular osmotic pressure also strongly inhibited re-opening currents associated with recovery from inactivation, which is consistent with a physical similarity between the C-type inactivated and resting closed state.
- Mild noncardioselective β-blocking effect.
- Minimal calcium-antagonist effect (a hundred times lower than verapamil).

COMMENTARIES

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Effect on the functional properties of the heart

- **Automatism:** Negative. In Purkinje fibers, it decreases the velocity of ascension of phase 4 (potassium channel block). Only in a high dose it may depress it by antagonist effect of the calcium channel in the action potential of slow fibers in the SA node.
- **Dromotropism:** Significantly negative throughout all cardiac structures. It explains the CLBBB pattern observed
- **Excitability:** Batmotropic negative. It increases refractoriness and the refractory period in the atria and ventricles by increasing the diastolic threshold of excitability and prolonging action potential duration
- **Contractility:** Negative inotropic that manifests only in patients with compromised ventricular function.

COMMENTARIES

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Hemodynamic effects:

1)Decrease of systolic atrial pressure.

2)Reflexive increase of HF.

3)Fall of LVEDP.

4)In 10% of the cases there is decrease in pulmonary artery pressure.

- **Effects on His electogram:** It increases the recovery time of the SA node and sinoatrial conduction; **P-A** (in a significant way); and **A-H** and **H-V** to a less extent.

Anomalous bundles: It increases the effective anterograde refractory period, and the retrograde one to a less extent.

COMMENTARIES

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Modifications on the ECG

- **Rhythm:** Ventricular fibrillation and Brugada-like ECG pattern was described during propafenone treatment[1]

- **HR:** It may cause a discrete reflexive increase by systolic BP decrease. In a high dose it may affect sinus automatism. In patients with sinus dysfunction, it may cause bradycardia

- **P wave:** As a consequence of the potential increase of **P-A** (intra-atrial) and interatrial (LA/RA) time, it may increase P wave duration.

- **PR interval:** It may cause an important increase as a consequence of **A-H** and **H-V** prolongation. The administration should be interrupted if the parameter reaches 30 ms.

1) Jastrzebski M. Kardiol Pol. 2008;66:207-2099.

COMMENTARIES

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- **QRS duration:** It may increase significantly. The administration should be interrupted when QRS reaches a duration equal or higher than 180 ms. It explains the pattern of CLBBB observed.
- **J-T:** It does not change with any 1C class drug. Rarely, propafenone-induced Brugada-like ECG changes mistaken as acute myocardial infarction[1].
- **T wave alterations:** Abnormal ventricular activation due to propafenone toxicity can result in persistent T-wave changes known as "cardiac memory"(CM).Propafenone toxicity can cause significant QRS widening and markedly abnormal ventricular activation pattern. Aberrant ventricular activation upon its resolution is known to produce persistent T-wave changes known as "CM[2].
- **QTc:** There is controversy as to the effect on this parameter; however, the prevailing opinion is that it is extended not so expressively as a consequence of QRS increase. In brief, the most expressive effects of the drug on the ECG are: increases in PR and QRS duration.

1) **Chutani S, et. al. Emerg Med J. 2008; 25: 117-118.**
2) **Wylie JV Jr, et.al. Pacing Clin Electrophysiol. 2007 ;30:1161-1164.**

COMMENTARIES

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Indication: It may be used for:

Preventive management of reentrant supraventricular tachycardias at the AV node and accessory pathways, by depressing conduction in both levels[1]. Very efficient in supraventricular tachyarrhythmic events in WPW syndrome.

Supraventricular and ventricular tachycardia in children. The endovenous pathway is used, applying it in five minutes, 1 mg/Kg[2]. In adults, the dose will be 2 mg/Kg in slow bolus, with an estimated efficacy of 60 to 100% of cases[3]. We should remember that the first choice in these cases is vagal maneuvers, and if they fail, pharmacological therapy is chosen, with adenosine and verapamil being the first-line choices.

1) **Ludmer PL, et al. J. Am. Coll. Cardiol. 1987; 9:1357-63.**
2) **Camargo, P. R. e col.; Arritmias em crianças. Rev Soc. Cardiol. Estado de São Paulo. 1998 1:105-16.**
3) **Bertni, G. e col.; J. Emerg. Med. 1990; 8:15-2.**

COMMENTARIES

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Propafenone is used for the prevention of atrial tachyarrhythmias after cardiac surgery The drug is administred 1 mg/kg infused in 1 h, followed by a continuous infusion at a rate of 4 mg/kg/24 h until the following morning, and subsequently 450 mg/day orally until the sixth postoperative day. The frequency of occurrence of atrial tachyarrhythmia is lower in the propafenone group than in the placebo group (29.7% vs. 53.3%, $P < 0.05$; relative risk, 0.56). Plasma propafenone concentrations is markedly influenced by CYP2D6 genotype-derived phenotype[1].

Atrioventricular reentrant tachycardia (AVRT) is the most common cause of supraventricular tachycardia in young children. In nearly 70% of cases, there is manifest preexcitation on ECG. In the rest, the accessory pathway is concealed. Drugs control AVRT by affecting conduction through the atrioventricular node (beta-blockers, digoxin, verapamil) or accessory pathway (flecainide, propafenone) or both (sotalol, amiodarone).

1) Mörike K, Clin Pharmacol Ther. 2008; 84:104-110.

COMMENTARIES

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Adenosine is the drug of choice in acute management of AVRT in hemodynamically stable children. In adenosine-resistant cases, intravenous flecainide, procainamide, esmolol, propafenone and amiodarone are other treatment options. Hypotension and bradycardia can occur during administration of these drugs[1].

Prevention of recurrence of atrial fibrillation and flutter, both refractory and symptomatic[2] as long as ventricular function is good and the etiology is not coronary[3].

1) **Ratnasamy C, et.al. Curr Pharm Des. 2008; 14:753-761.**
2) **Antman, E. M. e col.; J. Am. Coll. Cardiol. 1001-11, 1988.**
3) **de Paola, A. A. V. e col.; Fibrilação atrial. Rev. Soc. Cardiol. Estado de São Paulo 1:46-56, 1998**

COMMENTARIES

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The PITAGORA trial: is a multicentre, prospective, randomized, single blind design to compare amiodarone with Class IC Anti-arrhythmic drugs (AADs) in patients who have an AF history and are paced for sinus node disease (SND). One hundred seventy-six patients (46% men, 72 +/- 8 years) were enrolled received a Medtronic AT500 pacemaker. AADs were randomly assigned with a 3: 2 ratio between Class III and Class IC (propafenone or flecainida.)

Randomization was stratified in order to assign two patients to amiodarone and one patient to sotalol every three Class III AAD patients. After a 5-month observational period, Kaplan-Meier 1-year freedom from atrial tachyarrhtymias episodes >10 minutes, 1 day, and 7 days was 40%, 73%, and 91% for amiodarone and 28%, 78%, and 86% for class IC AADs (P = nonsignificant).

The authors conclude that in patients paced for SND and suffering from atrial tachyarrhtymias, class IC AADs proved not to be inferior to amiodarone in terms of the primary composite end point described or end points which were differently composed of mortality, efficacy, or AAD side effects. The AADs studied also showed similar results in terms of symptoms, quality of life, and freedom from atrial tachyarrhythmias recurrences.
Acute term or suppression of recurrent ventricular tachycardia[1].

1) Gulizia M, et al. Am Heart J. 2008; 155: 100-107.

COMMENTARIES

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Equivalent to quinidine for the suppression of premature ventricular contractions. Atrial fibrillation (AF) is the most frequent sustained arrhythmia. After restoration of normal sinus rhythm, the recurrence rate of AF is high. Antiarrhythmic drugs have been widely used to prevent recurrence, but the effect of these drugs on mortality and other clinical outcomes is unclear.

Several class IA, IC and III drugs are effective in maintaining sinus rhythm but increase adverse events, including pro-arrhythmia, and disopyramide and quinidine are associated with increased mortality. Any benefit on clinically relevant outcomes (embolisms, heart failure, mortality) remains to be established[1].

1) Lafuente-Lafuente C, et al. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD005049

COMMENTARIES

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Contraindications

1)Manifest CHF.

2)Cardiogenic shock, except for tachyarrhythmias.

3)Bradycardia lower than 50 bpm.

4)Sinus node disease.

5)Pre-existing disorders of sinoatrial, atrioventricular and intraventricular conduction of a high degree.

6)Asthmatic or COPD patients.

Side effects

Although it is generally well tolerated, 30 to 45% of patients may experience adverse cardiac effects. In 15 to 20% of patients, adverse effects may involve other organ systems.

COMMENTARIES

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Neurological: A wide variety of adverse central nervous system effects have been reported in association with propafenone; dizziness is the most common. shudders, blurry vision, paresthesia. These symptoms are observed with levels above 1100 ng/ml.
Ataxia caused by propafenone has been reported[1].
Psychiatric: Psychotic episodes.
Gastrointestinal: Nausea, metallic taste, vomits, loss of appetite, constipation, alterations in liver function test, transient choleostasic diarrhea hepatitis,upset stomach.
Cutaneous: Rash, psoriasis[2]**.**
Hematological: Reversible neutropenia, agranulocytosis, hyponatremia, and lupus-like syndrome.
Respiratory: Bronchospasm by the β-blocking effect and acute pleuritis.

1) **Odeh M**, **Am J Med Sci. 2000;320:151-153.**
2) **Palleschi GM, et al. Clin Exp Dermatol. 2008; 33:209-210.**

COMMENTARIES

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Cardiovascular: Present in 15% of the cases. Worsening of pre-existing arrhythmia has been reported in 10% of cases.
It may cause SA Node dysfunction in patients with normal sinus function, as well as it may worsen sinus function in patients with abnormal intrinsic sinus function.
It may cause AV conduction disorders.
It may trigger or worsen symptoms of congestive heart failure, leading to acute pulmonary edema and cardiogenic shock. Symptoms of CHF are observed in 5 to 10% of the cases.

A previously healthy 73-year-old woman presented to hospital with acute atrial fibrillation. After intravenous procainamide failed to restore sinus rhythm, she was treated with 300 mg of oral propafenone and discharged with a prescription for propafenone and propranolol. Six hours later she took 150 mg of propafenone as prescribed. Within 1 hour she became dyspneic and collapsed. On arrival in hospital she was unconscious, with a wide complex tachycardia and no obtainable blood pressure.

COMMENTARIES

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After defibrillation and lidocaine, she converted to a wide complex sinus rhythm, but remained profoundly hypotensive despite intravenous epinephrine and dopamine. Hypertonic sodium bicarbonate (HCO3) was administered and, shortly thereafter, her blood pressure increased, her QRS duration normalized and her clinical status improved dramatically. In this case of severe refractory propafenone-related cardiac toxicity, intravenous HCO3 led to a profound clinical improvement. Emergency physicians should be familiar with the syndrome of sodium-channel blocker poisoning and recognize the potentially important role of bicarbonate in its treatment[1].

1) Brubacher J. CJEM. 2004;6:349-356.

COMMENTARIES

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Others:

Side effects in pregnancy for the mother/fetus couple

Risk category

FDA classification: C. Probably safe. Insufficient data. Adverse effects were not proven for the fetus in clinical use or in a lab test[1]; even so, it is not advised during pregnancy. In few reports it was well tolerated by the fetus (without teratogenesis) and the mother.

Mother/fetus ratio

0.14 to 0.20.

Milk/plasma ratio

0.14 to 0.20. Propafenone and its active metabolite pass on to maternal milk.

1) Cox JL et al. Prog, Cardiovasc. Dis. 1993;36:133-78

COMMENTARIES

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Pharmacological interactions

Digoxin: It increases the plasmatic concentration of this drug in 83% in average[1].

Propranolol: Idem.

Warfarin: It increases the levels of coumarinic agents due to its high rate of union with plasmatic proteins.

Quinidine: Small doses inhibit the metabolism of propafenone.

Cimetidine: It increases the levels of propafenone.

Amiodarone: Both drugs enhance mutually in refractory ventricular arrhythmias[2].

Venlafaxine: Venlafaxine is metabolized primarily by CYP2D6 and is a substrate of P-glycoprotein. Propafenone, a known substrate and inhibitor of both CYP2D6 and P-glycoprotein, could therefore be involved in venlafaxine-induced hallucinations through the increase of venlafaxine plasma concentrations. To prevent the onset of clinical disturbances during venlafaxine treatment, Garery et al. suggest careful evaluation of concomitant treatment with CYP2D6 or P-glycoprotein inhibitors (eg, propafenone) and, when possible, venlafaxine serum concentration monitoring[3].

1) Salerno, D. M. e col.; Am. J. Cardiol. 1984;53: 77-83.
2) Coumel P. et al. Am. J. Cardiol. 1984; 54:20D-22D.
3) Garery P, et al. Ann Pharmacother. 2008; 42:434-438.