Symptomatic adolescent with non-obstructive asymmetric hypertrophic cardiomyopathy with events of sustained, hemodynamically stable, irregular and fast wide QRS complex tachycardia

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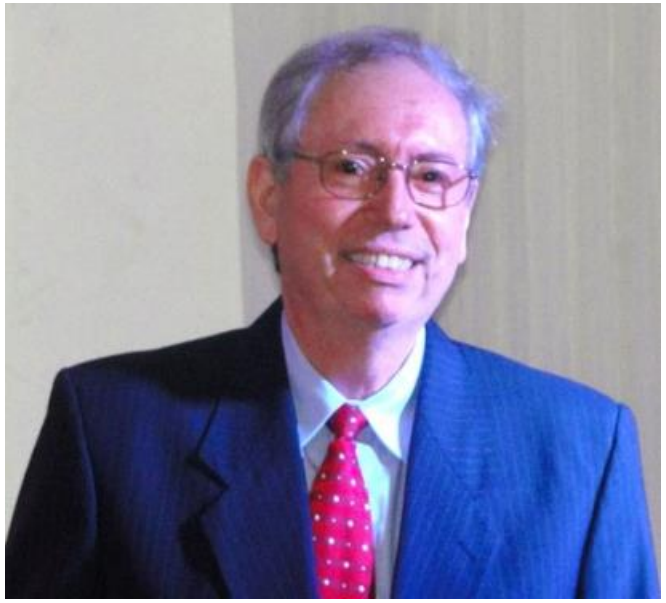

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Portuguese: Relato de caso

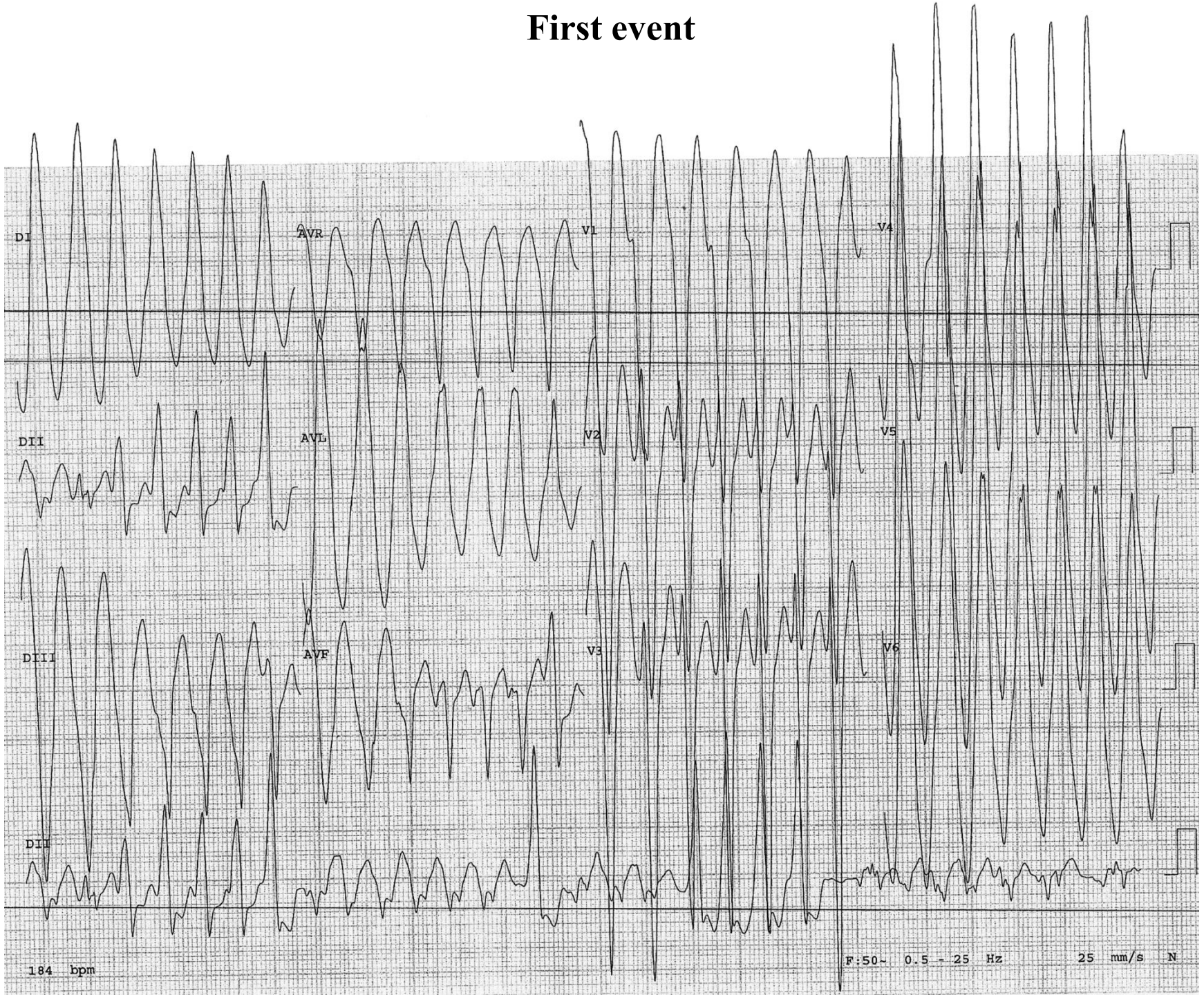
Adolescente do masculino, Caucasiano, 16 anos, com raras queixas de palpitações rápidas e concomitante dor precordial.
O paciente teve por duas vezes eventos de taquicardia irregular rápida (registrados em 20014 e 2017), de complexos largos, e com estabilidade hemodinâmica#, (2014 e 2017). Na primeira ocasião, realizara tratamento ablativo no mesmo ano 2014). Nega síncope ou parada cardíaca recuperada. Em tratamento com amiodarona. Exame físico (fora da crise) sopro sistólico discreto de insuficiência mitral e quarta bulha. Resto nada digno de nota.
O ecocardiograma transtorácico: cardiomiopatia hipertrófica assimétrica não obstrutiva a predomínio da parede posterior
Perguntas:
1)Qual o diagnóstico eletrocardiográficos dos eventos?
2)Qual o diagnóstico do ECG de base?
3)Qual o substrato eletrofisiológico e porque?

English: Case report

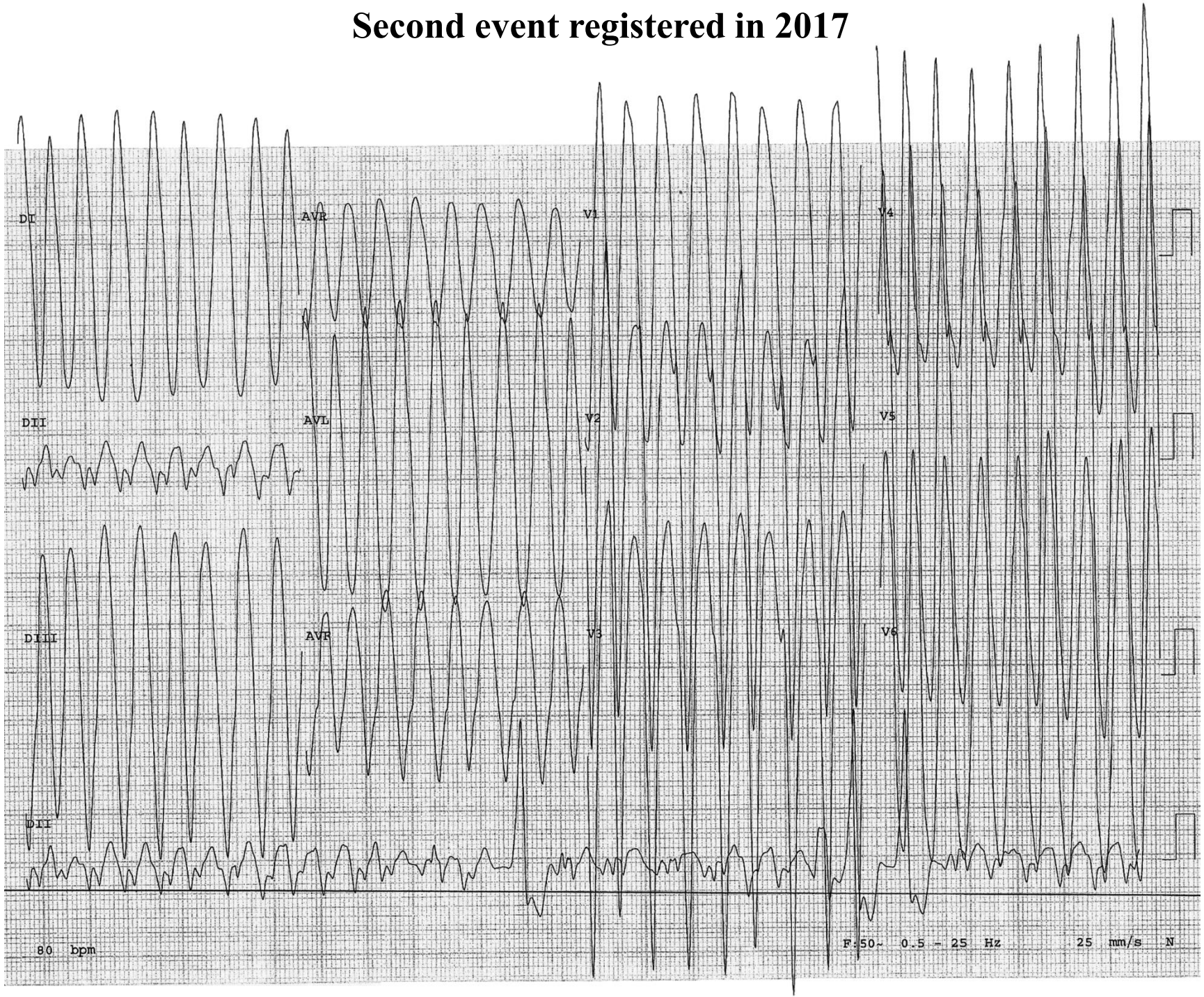
Adolescent, male, Caucasian, 16 years old, with rare complaints of rapid palpitations and concomitant precordial pain.
The patient had, on two occasions, sustained (with hemodynamic stability in 2014) and unstable in 2017. On the first occasion, was performed ablative treatment in the same year 2014. Deny syncope or recovered cardiac arrest. On treatment with amiodarone.
Physical examination (out of the crisis). Weight: 50kg , High: 1.70m,
CV: discrete systolic murmur of mitral insufficiency and fourth sound. Rest nothing worth noting.
Transthoracic echocardiogram: shows non obstructive asymmetric hypertrophic cardiomyopathy, with predominance of the posterior wall.
No genetic study and no nuclear magnetic resonance (MRI) yet.
* **Definition of Stable Tachycardia** For a diagnosis of stable tachycardia, the patient meets the following criteria:
- The patient's heart rate ≥100 bpm.
- The patient does not have any serious signs or symptoms as a result of the increased heart rate.

Questions:
What is the electrocardiographic diagnosis of the events?
What is the baseline ECG diagnosis?
What is the electrophysiological substrate and why?

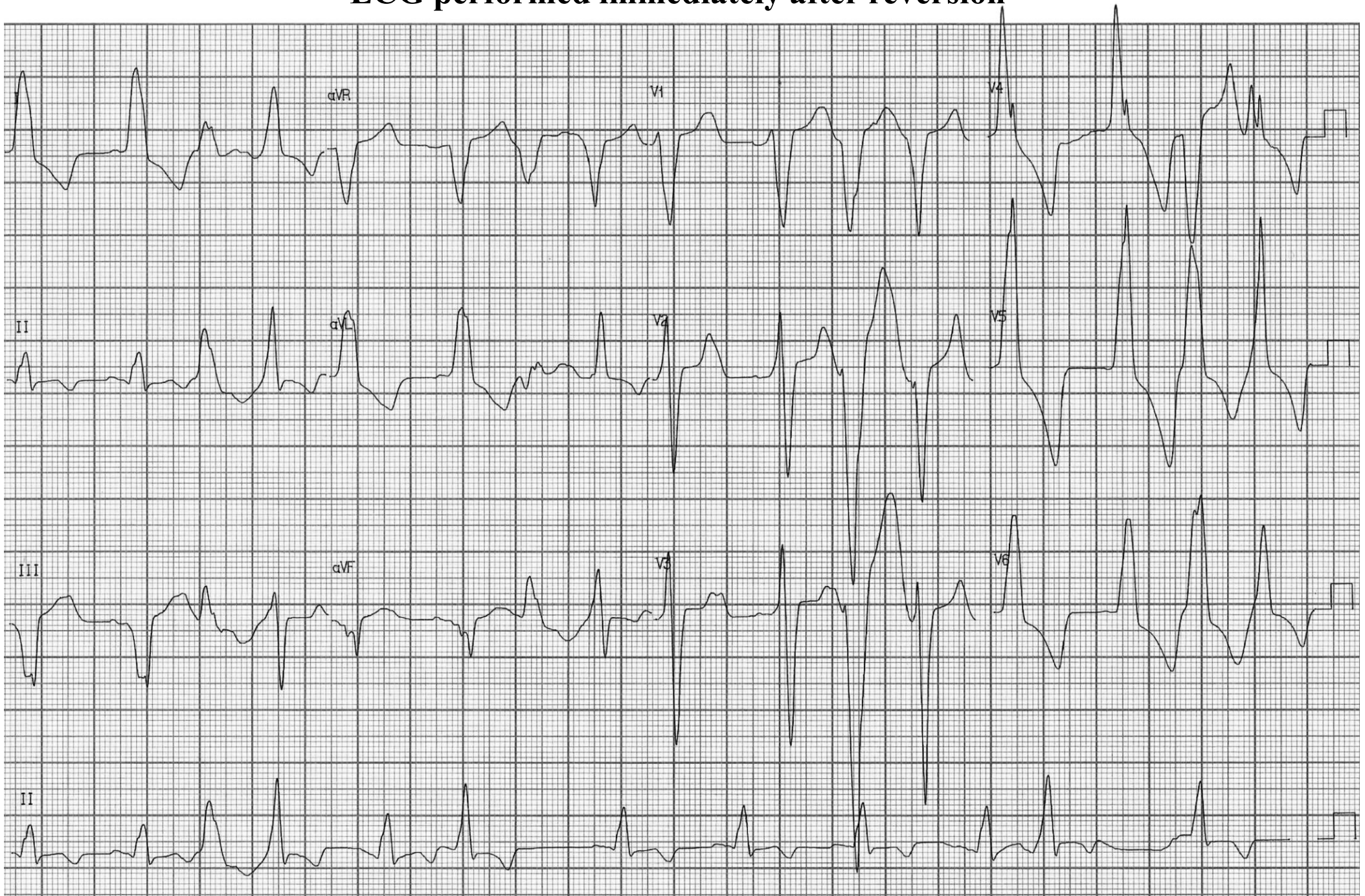
First event


DI
AVR
V1
V4
DII
AVL
V2
V5
DIII
AVF
V3
V6
DIII
184 bpm
F:50~ 0.5 - 25 Hz
25 mm/s N

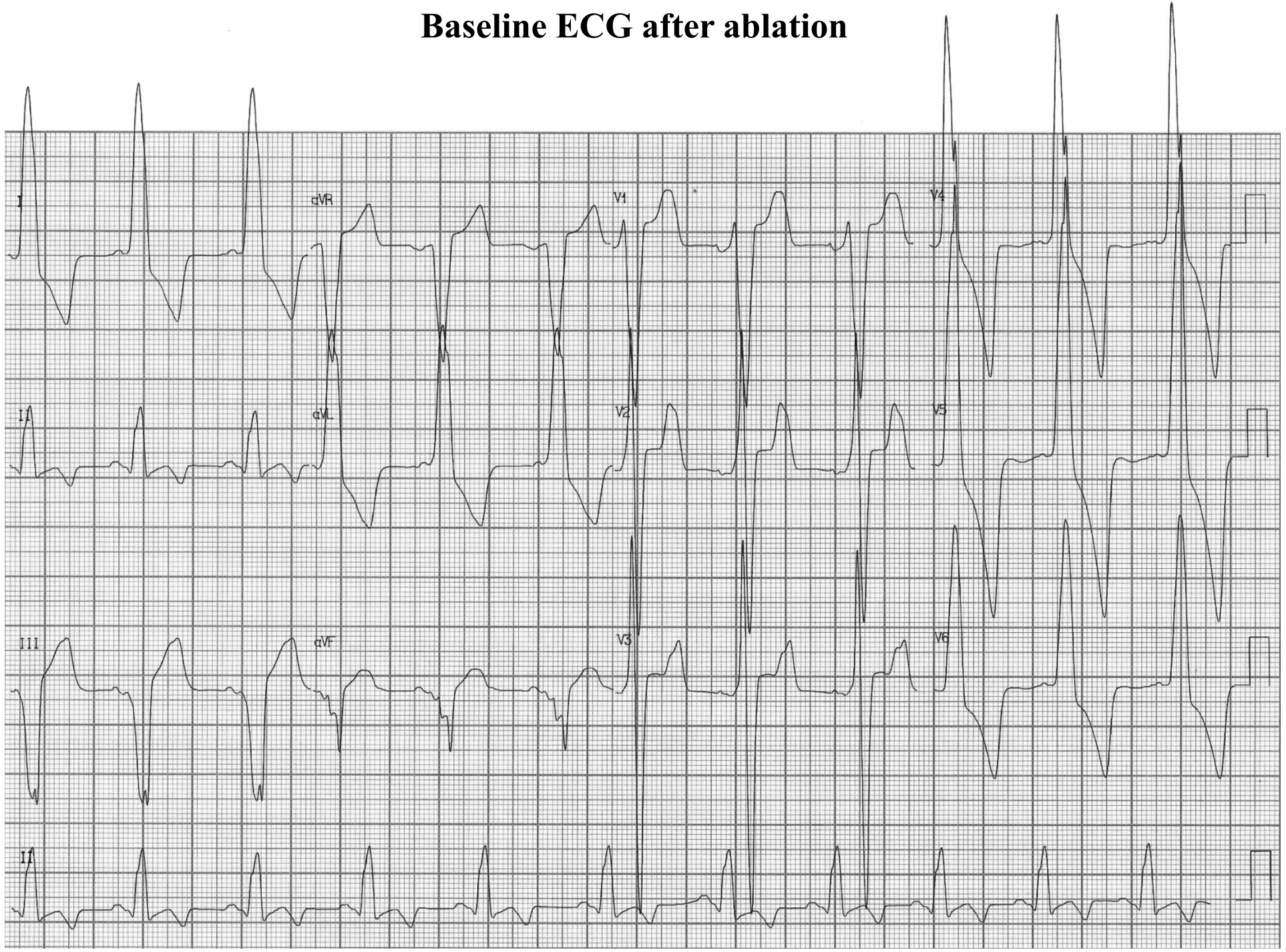
Second event registered in 2017



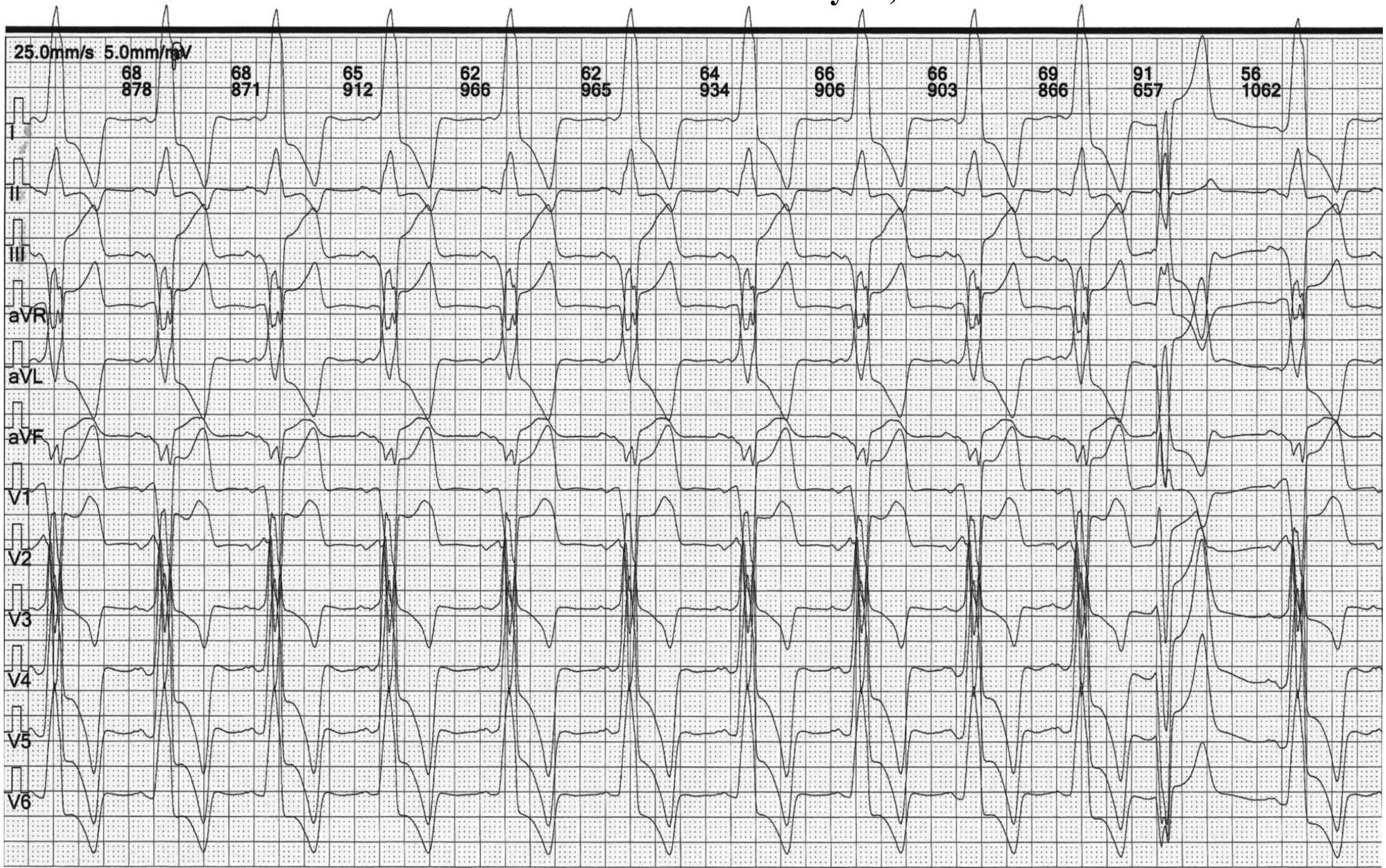
ECG performed immediately after reversion



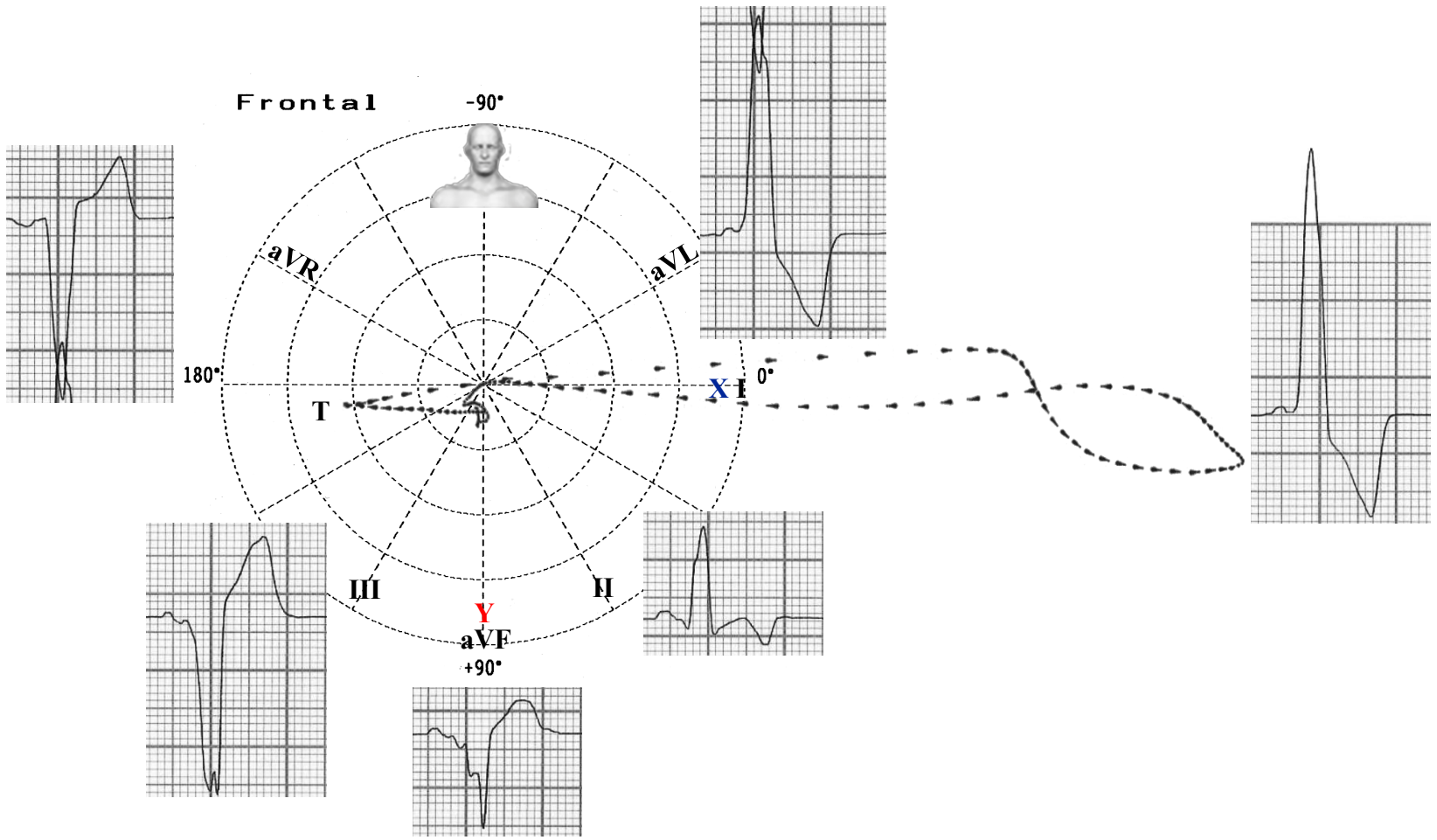
Baseline ECG after ablation



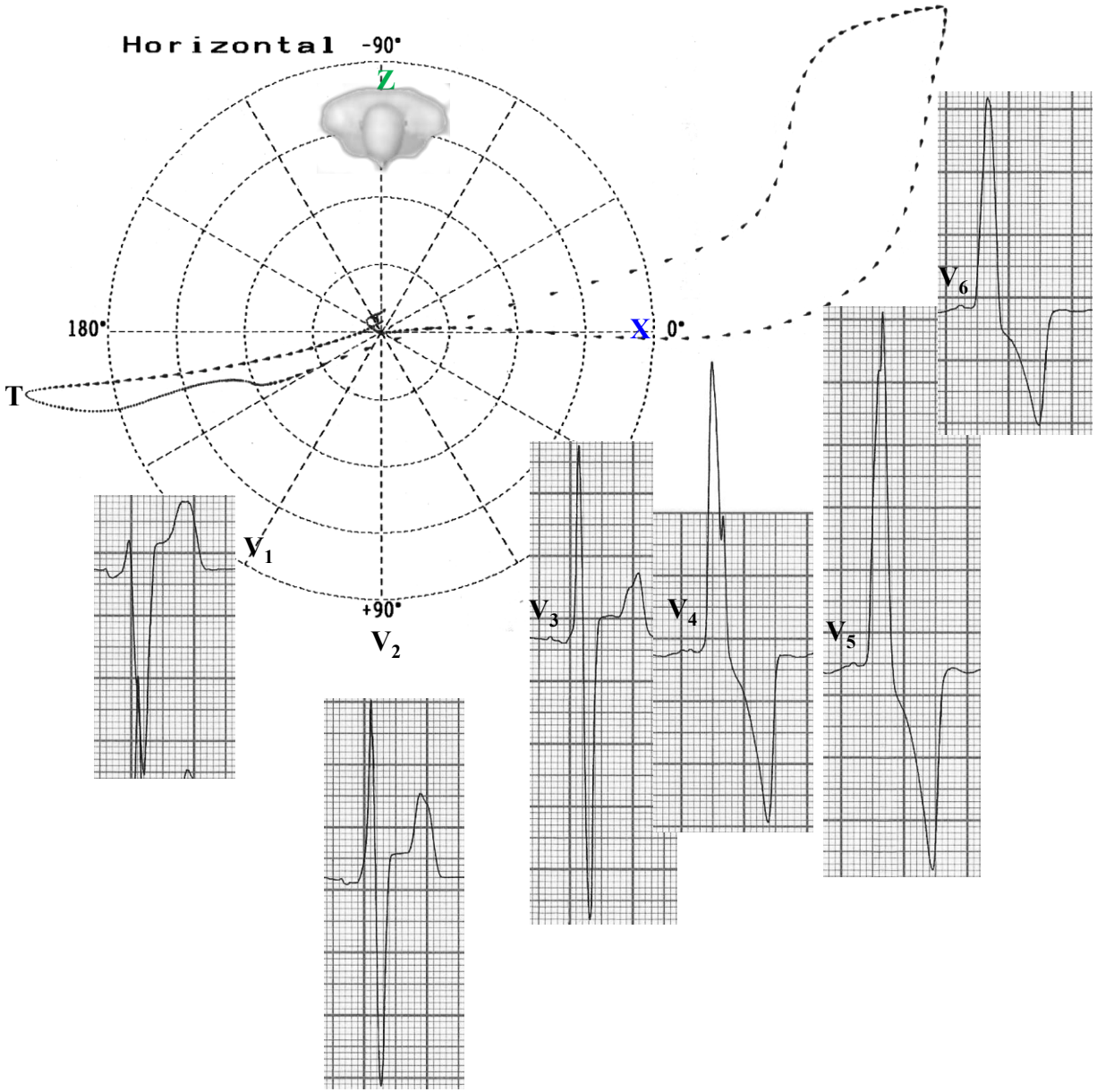
Baseline ECG Date: January 31, 2017



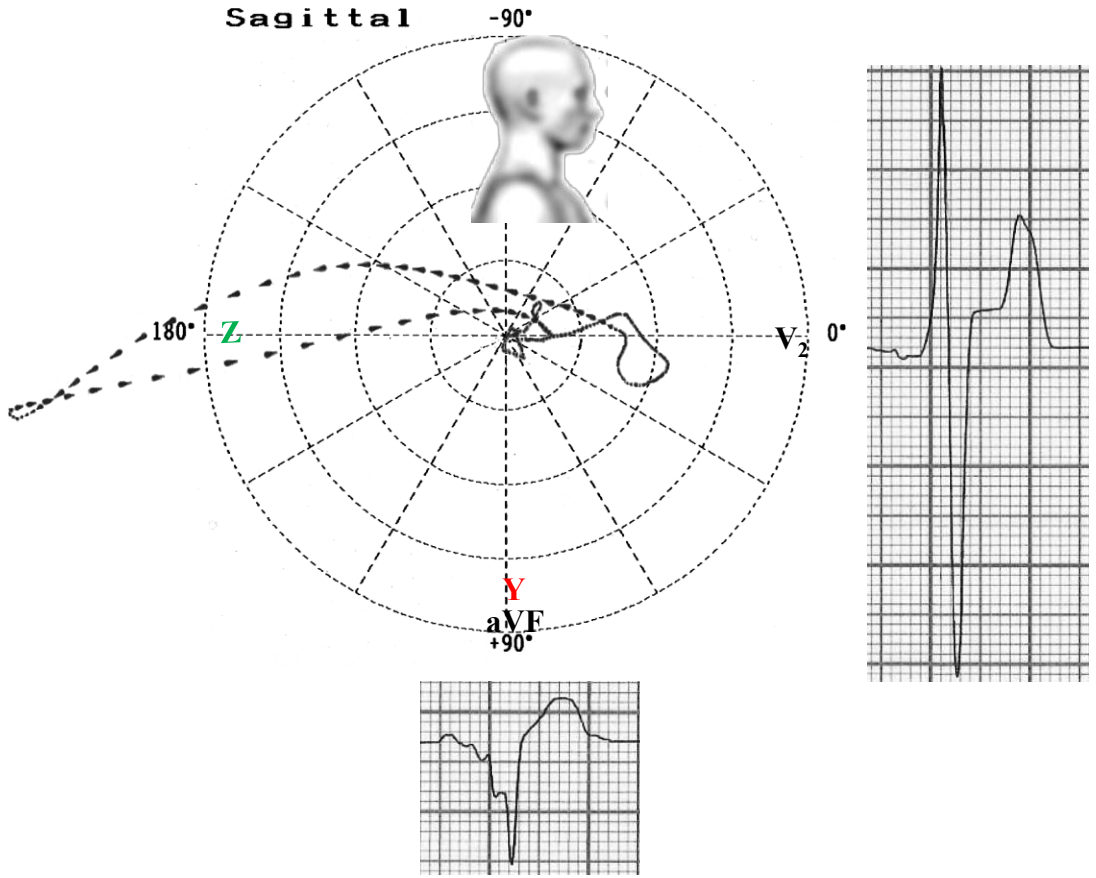
Baseline ECG/VCG correlation in the frontal plane



Baseline ECG/VCG correlation in the horizontal plane

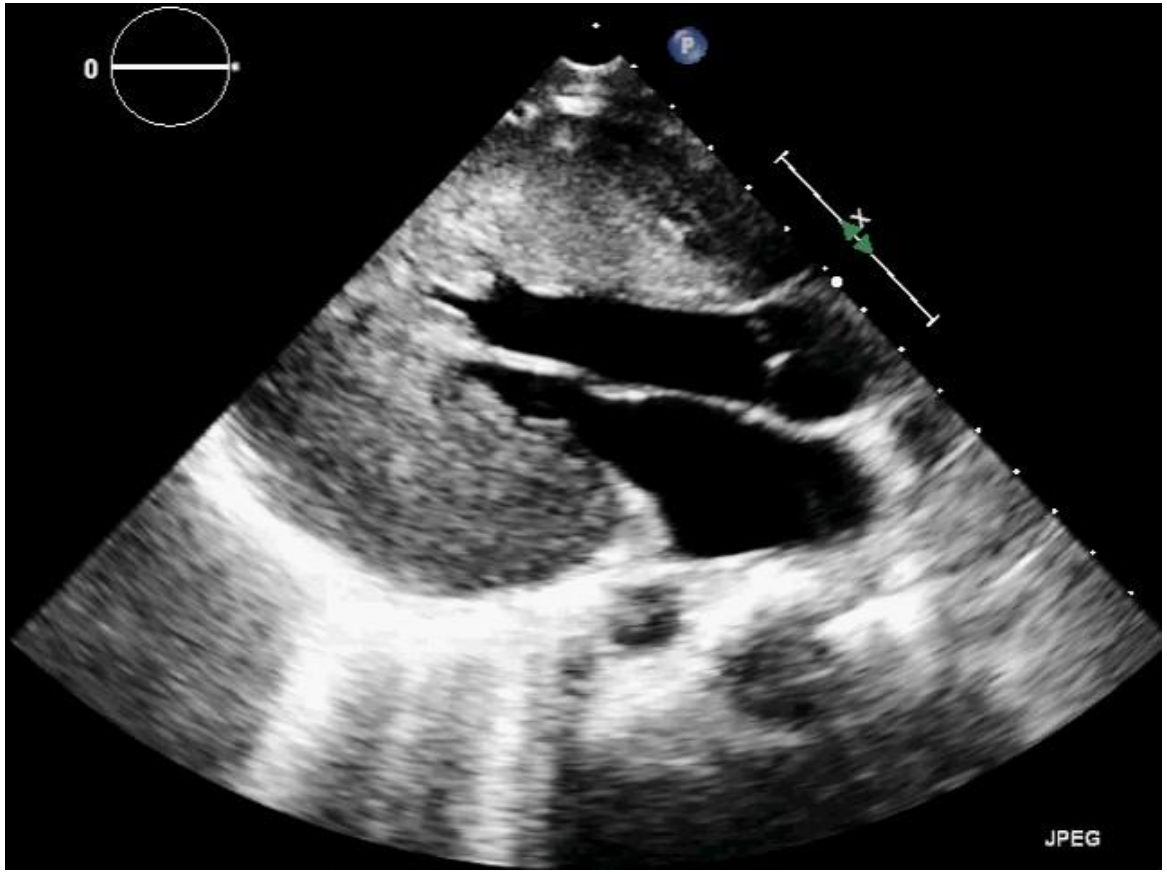


Baseline ECG/VCG correlation in the right sagittal plane

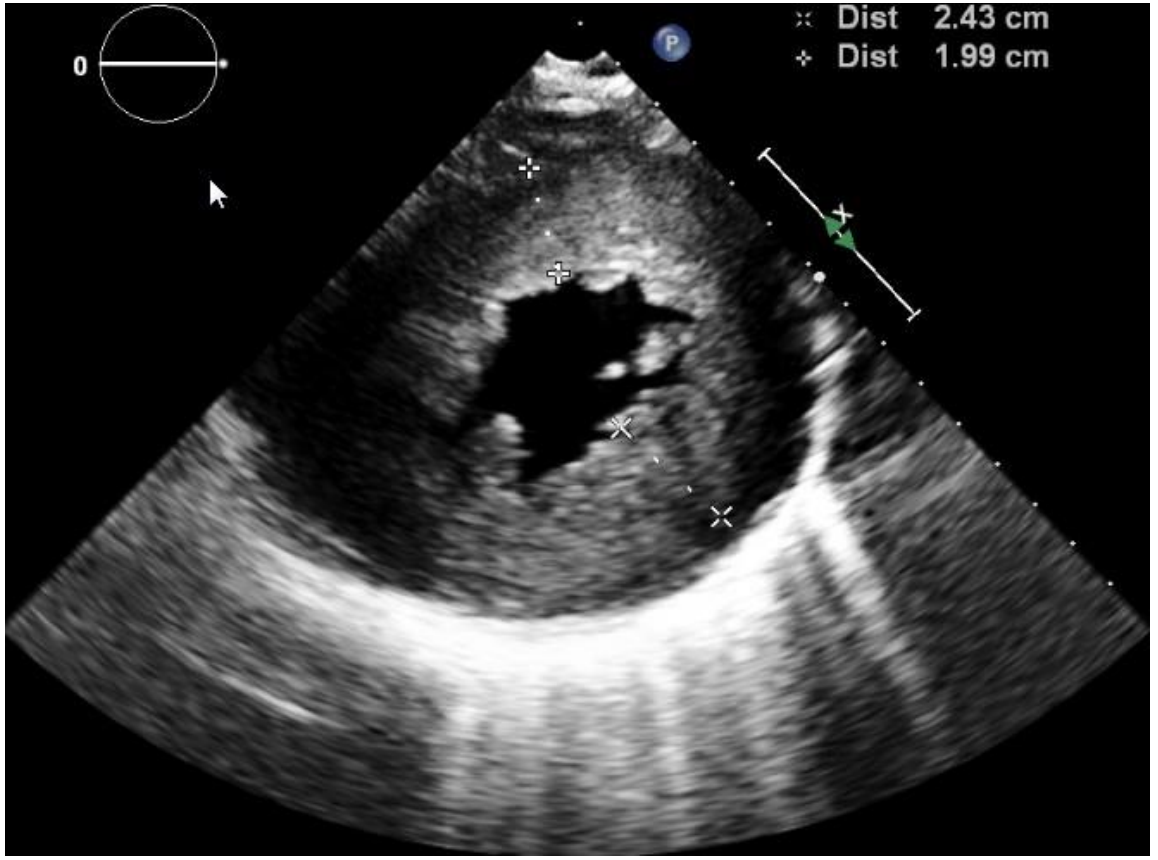


Transthoracic echocardiogram

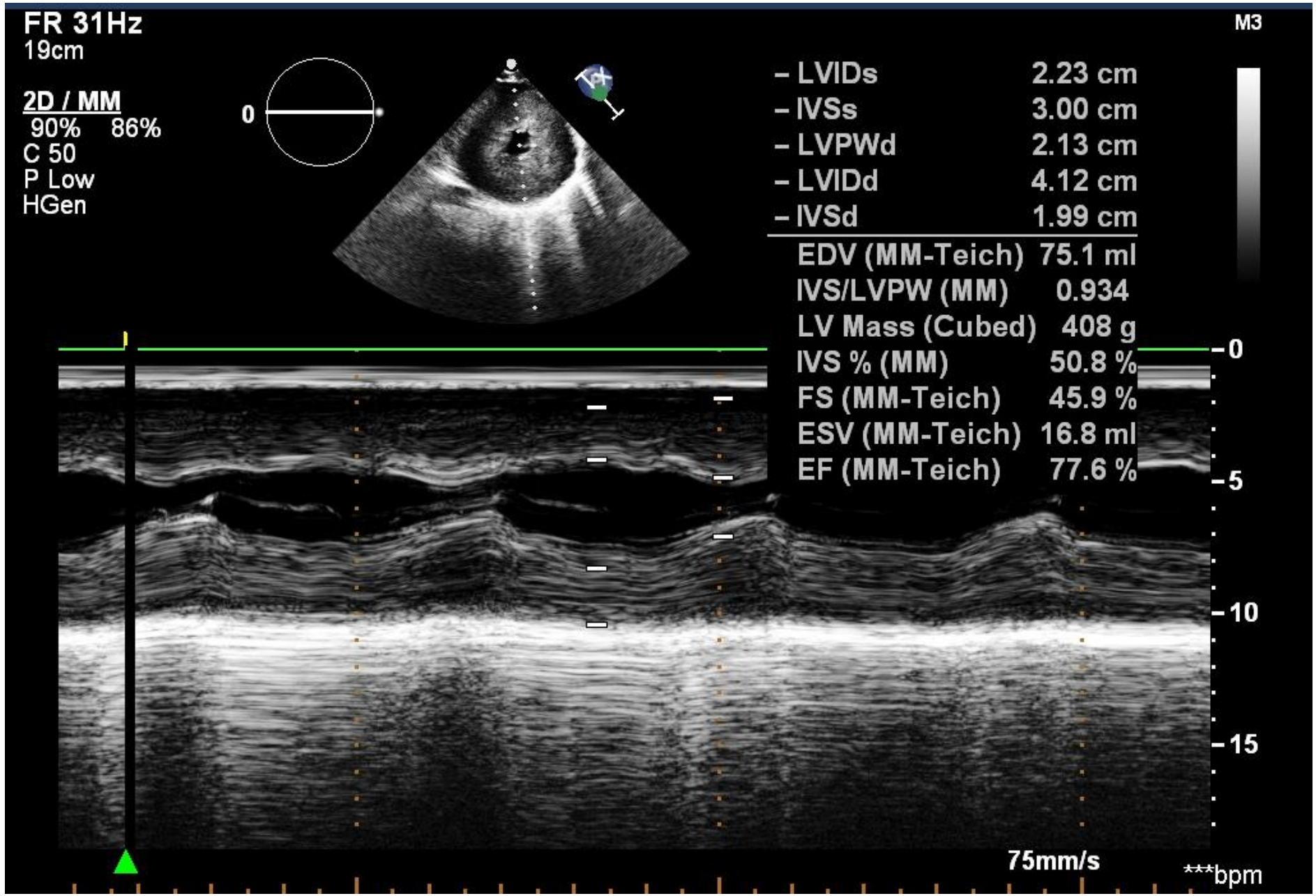
Longitudinal long-axis view



Parasternal short axis view



Transthoracic 2D echocardiographic shows non obstructive asymmetric hypertrophic cardiomyopathy, with predominance of the posterior wall (LV end diastolic posterior wall diameter = 24mm and IVS end diastolic thickness = 20mm), LVEF: 65%, LV mass: 409g (normal value from 94 to 276g), final diastolic volume 55ml (normal value 73 to 155ml), LV ejection volume 35ml (normal value 64 to 99ml), volume / mass ratio 0.13ml / g (normal value 0.49 to 0.90ml / g), minimal mitral regurgitation, LV diastolic dysfunction grade II, LV preserved biventricular function, discreet RV involvement, estimated pulmonary artery systolic pressure of 34 mm Hg and minimal tricuspid regurgitation.


FR 31Hz
19cm
2D / MM
90% 86%
C 50
P Low
HGen
0
M3
– LVIDs 2.23 cm
– IVSs 3.00 cm
– LVPWd 2.13 cm
– LVIDd 4.12 cm
– IVSd 1.99 cm
EDV (MM-Teich) 75.1 ml
IVS/LVPW (MM) 0.934
LV Mass (Cubed) 408 g
IVS % (MM) 50.8 %
FS (MM-Teich) 45.9 %
ESV (MM-Teich) 16.8 ml
EF (MM-Teich) 77.6 %
0
5
10
15
75mm/s
***bpm

Colleagues opinions

Dear Raimundo & Andres,
The patient has 2 or more accessory pathways, located in the right lateral region.
There is one QRS that is not preexcited that shows a right bundle branch block with left posterior fascicular block.
Ventricular preexcitation, conduction system disease, and hypertrophic cardiomyopathy suggest a PRKAG2 gene mutation resulting in glycogen storage disease. This is usually inherited as an autosomal dominant trait, so family history is very important initially to confirm or rule out this disorder. If possible genetic testing should be performed.
It is very important to assess conduction through the normal intraventricular conduction system before performing ablation of the accessory A-V pathway/s. I have had similar cases with associated conduction system disease that progress to A-V block after the ablation, not because the ablation has damaged the bundles, but because of the natural progression of the disease. This needs to be discussed with the patient before proceeding with ablation.

Saludos,
Mario D. Gonzalez, MD, PhD

Dear friends,
I think this is AF with prexcitation with left axis deviation.
Patients with HCM have higher incidence of WPW syndrome. The ECG in Sinus rhythm shows short PR interval and slurred QRS. Is obvious with negative delta (δ) waves in leads III and aVF.
The two wide complex tachycardia's are typical of AF with conduction over accessory pathways.
In these cases verapamil, digoxin and lidocaine should not be used.
Catheter ablation of accessory pathway seems reasonable.
Best regards

Mohammad **Shenasa,** MD, FACC Heart & Rhythm Medical Group
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408-286-2922 (Fax)

Hello, I agree with Mohammad. There are delta waves of pre-excitation and HCM patients have an increased risk for WPW. And I also think that the wide complex irregular tachycardia is AF.

Best regards

Kjell **Nikus** MD, PhD

Tampere University Hospital

Finland

Spanish

Estimado Potro.

Presenta una vía accesoria antero-septal derecha por algoritmo de Milstein (ver próximo slide) y en los trazados previos fibrilación auricular conducida por haz accesorio. EV aisladas luego de recuperarse de la FA. Tanto la FA como la presencia de vías accesorias se suelen presentar en la miocardiopatía hipertrófica.

Conducta: Estudio electrofisiológico y ablación de vía accesoria.

Un cordial saludo

Martín Ibarrola

English

Dear friends Raymond and Andrés

It presents a right anteroseptal accessory pathway (AP) by Milstein algorithm (see next slide) and in the previous ECGs, AF conducted by AP.

Isolated PVC after recovering from AF. Both AF and the presence of AP are usually present in hypertrophic cardiomyopathy.

Management: Electrophysiological study (EPS) and AP ablation.

Kind regards

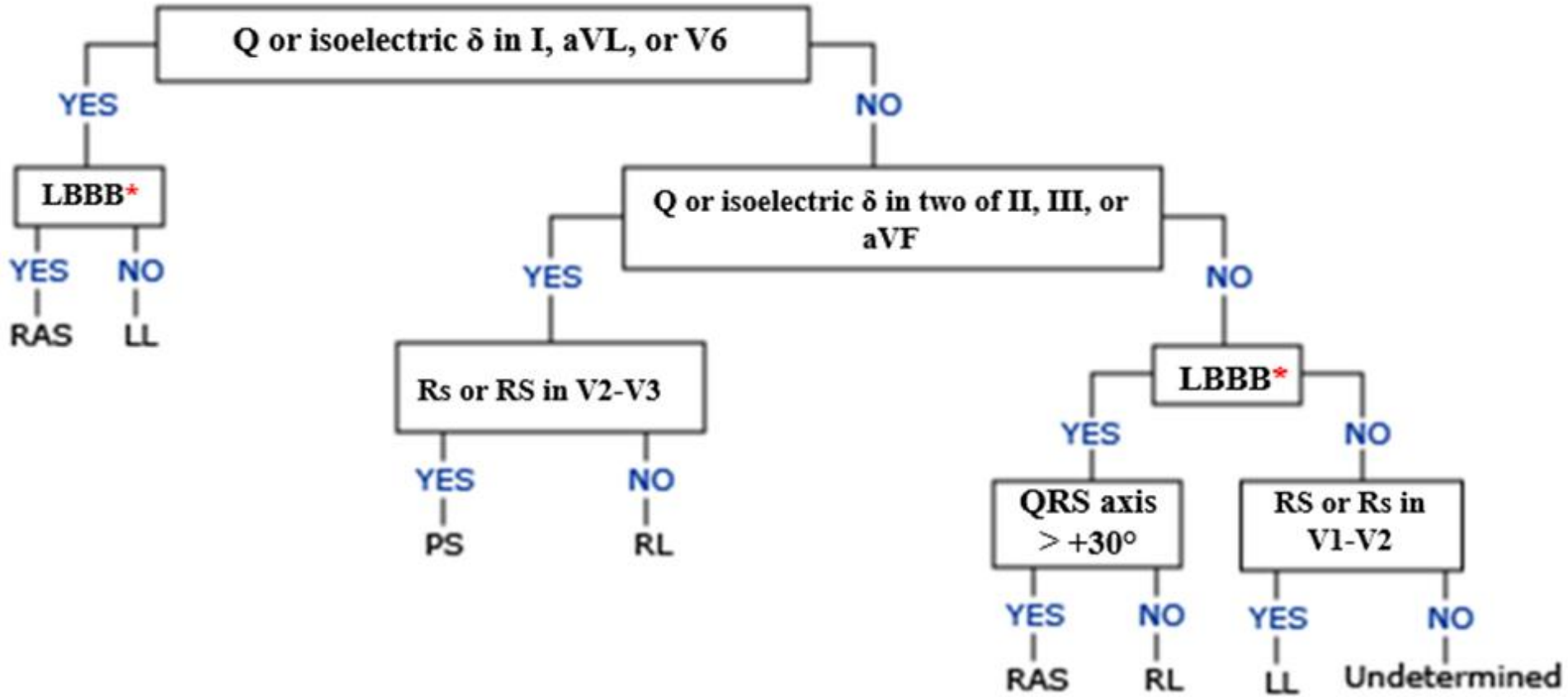
Martin Ibarrola M.D. FAHA_FASE-FESC

Universidad de El Salvador; UBA

Argentina

Algorithm to localize accessory pathway in preexcitation syndrome: Milstein Mapping algorithm

AP location in the WPW syndrome influences the success and morbidity of nonpharmacological therapies, so that an estimate of AP location is relevant to the practicing physician. Milstein et al **(Milstein 1987)** derived an algorithm for AP localization based on the ECG. They tested it in a population of 141 patients with the WPW syndrome in whom AP localization was made by EPS and/or intraoperative mapping. The goal of the algorithm was to localize the AP to one of four anatomic regions, namely, left free wall, posteroseptal, anteroseptal or right free wall by using a simple, easy-to-apply scheme. Each of two observers, blinded to the results of mapping, correctly identified the anatomic location of 91% and 90% of APs, respectively. The authors concluded that a simple algorithm using the ECG can provide a valuable first approximation of AP location in the WPW syndrome.



Mapping algorithm for localization of AP in the preexcitation syndrome using the morphology of the δ wave on the electrocardiogram. δ: delta wave; **RAS: Anteroseptal ;LL: Left free wall; PS: Posteroseptal; RL: Right free wall*** + QRS ≥90 msec in L1 and rS in V1 and V2.

Spanish: Aduendum de Martín Ibarrola

Estimados Raimundo y Andrés, desearía realizar una aclaración. En el año 2014 el paciente presenta una taquicardia rápida irregular aberrante. En II y aVF se observan salvas con complejos QRSs con diferentes ejes eléctricos. En II y aVF comienza con morfología QS y luego aparecen salvas con patrón Rs en estas derivaciones, lo cual se observa claramente en la tira de ritmo de II. Consecuentemente, se trata de una FA que conduce por 2 diferentes vías accesorias con diferentes periodos refractarios. La vía con el patrón Rs se agota en su conducción anterógrada y vuelve a conducir por la otra vía. Esto queda evidente después de la ablación del 2014 donde se ablacionó la vía con patrón Rs en II y aVF. De esta forma, el paciente quedó con 1 vía que es la que se evidencia en la FA por vía accesoria posterior con II y aVF negativas.
Ambas son vías derechas, la actual póstero-septal derecha y la ablacionada en 2014 ántero-septal derecha.
El riesgo de muerte súbita a los 5 años por lo referido de su MCH es de 3,88%. Por lo que la indicación de CDI para prevención primaria generalmente no estaría indicada.
Un cordial saludo
Martín Ibarrola

English: Addendum from Martín Ibarrola

Dear Raimundo and Andrés, I would like to clarify. In 2014, the patient had an irregular rapid tachycardia. In II and aVF we observe salvoes with QRS complexes showing two different QRS electrical axes. In II and aVF start with QS morphology and then change to another Rs pattern that appear in these leads, which is clearly observed in the II rhythm strip. Consequently, it is an AF with 2 different APs with different anterograde refractory periods. The AP with the Rs pattern is exhausted anteriorly and the conduction returns by the other AP. This is evident after the ablation of 2014 where the AP with Rs pattern was ablated in II and aVF. In this way, the patient was left with only one AP that is evidenced in AF by posterior AP with negative II and aVF. Both APs are right-sided, the current one is right-sided posteroseptal and the one ablated in 2014 is right anteroseptal. The risk of sudden death at 5 years for the referred MCH is 3.88%. So the ICD indication for primary prevention would generally not be indicated.
A cordial greeting

Dear Raimundo and Andrés, by my opinion it is:

1. Supraventricular tachycardia in patient with
2. WPW ECG pattern (short PR, delta wave, wide QRS complex) and left ventricular hypertrophy (deep S in right and high R in left precordial leads. and
3. Antidromic reentry via lateral-posterior localization of accessory pathway (negative delta way in II, aVR and aVF leads) of right ventricular .

Best regards

Leonid **Makarov**

Prof. dr. Leonid Makarov M.D., Ph.D. Head of Center for Syncope and Arrhythmias in Children and Adolescents of Federal Medico-Biology Agency of Russia. President of the Russian Society for Holter Monitoring (ROHMINE). Adress: Central Children Clinical Hospital FMBA of Russia. 115409 Moskvorechie str. 20. Tel. +7 (499)324-5756 E-mail: leonidmakarov@yahoo.com

The patient has atrial fibrillation with rapid conduction over a mid or posterior septal accessory pathway. There is very rapid conduction over this pathway which at times mimics a rapid regular rhythm. If he has other risk factors for SCD will need a defibrillator but certainly needs a fresh attempt at ablation of AP.
In addition there are reports linking HCM with WPW in families. Was there a family history of HCM or WPW?

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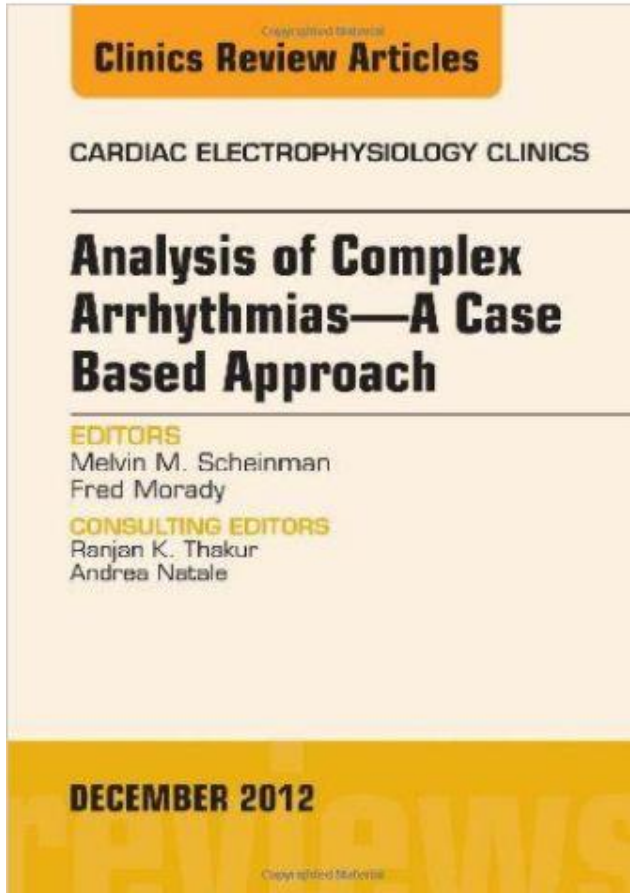

I think it is WPW with atrial fibrillation.

Yochai Birnbaum, MD, FACC, FAHA
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Final comments by
Andres Ricardo Perez Riera & Raimundo Barbosa Barros

In the first place, like a living organism, Truth grows and its gradual evolution may be traced form the tiny germ to the mature product. Never springing, Minerva-like, to full stature at once, Truth may suffer all the hazards incident to generation and gestation. Much of history is a record of the mishaps of truth which have struggled to the birth, only to die or else to wither in premature decay, Or the germ may be dormant for centuries, awaiting the fullness of time -- All scientific truth is conditioned by the state of knowledge at the time of its announcement.

William Osler, MD, FRS.
Harveian Oration,
Royal College of Physicians
18th October 1906

Distinguishing Features of Wide QRS Complex Tachycardia (WCT)

A. Regular

1. *Ventricular Tachycardia (VT):* is the most common cause of WCT: 80% of all cases of WCT.
2. *Supraventricular Tachycardia with Aberrancy.(SVT-A)*: 15 to 30% of all cases.
3. *Supraventricular Tachycardia with ventricular activation occurring over an anomalous atrioventricular connection (Preexited SVT in Wolff-Parkinson White Syndrome)*. It represents only 1 to 5% of all cases.
4. *Supraventricular tachycardia with wide QRS complexes due to abnormal muscle-to-muscle spread of impulse:* In this subset, His-Purkinje conduction may be relatively normal but the baseline rhythm on ECG suggest RBBB, LBBB, or nonspecific intraventricular conduction defect (NSIVCD). Example repair Fallot's tetralogy with appearance of RBBB in patients who have undergone right ventriculotomy with delayed conduction on right ventricular outflow tract (RVOT). Appearance of LBBB is observed in dilated cardiomyopathy in which the left side conduction delay is due to diffuse slowed muscle-muscle rather than His-Purkinje disease.
5. *Supraventricular tachycardia with wide QRS complex due to drugs overdose* such as digitalis (severe digitalis overdose cause bidirectional VT) tricyclic antidepressant, lithium (**Francis 2004**), cocaine (**Lange 2001;Levis 2005**), dehydroamino (**Clark 1992**), sodium channels blockers (**Hollowell 2005**) such as Class IA (procainamide, quinidine and dysopiramide) and IC agents (flecainide, encainide, propafenone), or electrolyte disturbance –induced changes: ex. Hyperkalemia.
6. *Post resuscitation.*
7. *Pacemaker-mediated tachycardia (PMT) or paced ventricular rhythm*. These patients may have SVT or activity-driven AV WCT.
8. *Malingering and/or ECG artifact (pseudo VT):* ex. Parkinson tremor-related artefact mimicking VT.

B. Irregular

1. *Preexcited atrial fibrillation (AF)*: AF can occur in up to 20% of patients with WPW. HR > 200 bpm, irregular rhythm, wide QRS complexes due to abnormal ventricular depolarization via accessory pathway (AP), QRS complexes change in shape and morphology, but the axis remains stable unlike polymorphic VT.
2. *AF with aberrant conduction with preexistent BBB or aberrancy:* HR 100-140bpm.

Summary pearls for Wide Complex Tachycardia's

1. Interpretation of ECGs demonstrating WCTs should be based on clinical circumstances, not the ECG itself.
2. Although many algorithms and diagnostic criteria exist to help clinicians correctly interpret WCTs, these are not foolproof. Therefore, clinicians must be comfortable accepting an interpretation of an ECG representing a WCT as "WCT of uncertain etiology." It is important to consider this when selecting therapies for patients presenting with WCTs, as some therapies can cause hemodynamic compromise or cardiovascular collapse.
3. Clues may be found in a patient's previous ECG, or from capture and/or fusion beats identified in the ECG or rhythm strip. AV dissociation (if identified) makes the diagnosis of VT much more likely. But pre-excited AF is possible.
4. In patients with structural heart disease, especially older patients with previous MIs or previous episodes of VT, the diagnosis of VT is far more likely and should be considered until proven otherwise.

Overview In 2014, the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) released updated guidelines for the management of patients with atrial fibrillation (AF). These guidelines supersede the AF guideline published in 2006 and updated in 2011. The guidelines provide the following revised classification schema, based on duration of episodes (**January 2014**) or AF patterns.

- **First diagnosis AF:** AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF related symptoms.
- **Paroxysmal AF:** Most common sub-type (50% of cases). Episodes of AF that terminate spontaneously or with intervention within 7 days of onset (mostly within 24 hours). Paroxysmal AF may recur with variable frequency.
- **Persistent AF:** Episodes of continuous AF that last more than 7 days and do not self-terminate. Including episodes that are terminated by cardioversion, either with drug or by direct current cardioversion, after 7 days or more.
- **Long-standing persistent AF:** Longstanding AF, episodes of continuous AF that usually last more than 12 months despite treatment when it is decided to adopt a rhythm control strategy.
- **Permanent AF:** Applies when a joint physician/patient decision has been made to accept the presence of AF and stop further attempts to restore and/or maintain sinus rhythm (as this represents clinical acceptance rather than an inherent pathophysiological attribute of AF, it is understood that acceptance of AF may change as symptoms, efficacy of interventions, and patient/physician preferences evolve). Consequently, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be reclassified as long standing persistent AF.

- **Lone AF:** AF arising in structurally normal heart without a external precipitant. Increasing evidence suggests a number of often subtle cardiac alterations associated with apparently 'lone' AF, which may have relevant prognostic implications (**Potpara 2011**). 60 years following the first description, current guidelines define 'lone' AF as any AF in patients ≤ 60-year old without clinical or echocardiographic evidence of any cardiopulmonary disease including hypertension (**Camm 2010; Fuster 2011**) or AF in younger patients without any identifiable comorbidities (**Gillis 2011**). 'Lone' AF should be distinguished from idiopathic AF, the term which is often used to describe AF of unidentifiable cause in patients older than 60 years (**Fuster 2011; Kopecky 1999a**). Such a distinction is clinically justified, as the lifetime incidence of stroke rises sharply starting from age of 55 (for a decade, the risk increases from 5.9% to 11.0% in men and from 3.0% to 7.2% in women AF patients), reaching the threshold for oral anticoagulation therapy at age of 65 or above even in the absence of other stroke risk factors (**Wolf 1991; Camm 2012; Marinigh 2010**). Indeed, an observational study of 55 AF patients who would have been diagnosed with 'lone' AF if they had not been older than 60 years at the time of diagnosis (their mean age was 74 years) found that survival of these patients was similar to age- and sex-matched controls during the median 9.6-year follow-up, but the cardiovascular event rate [a composite of stroke, transient ischemic attack (TIA) or myocardial infarction] was significantly higher, and the survival rates free of stroke or TIA were significantly lower in the AF group (5.0% vs. 1.3% per person-year and 80% vs. 98%, respectively, both $p < 0.01$) (**Kopecky 1999b**). Similar to AF with an underlying disease, 'lone' AF is more frequent in males (male-to-female ratio of 3–4:1) (**Miyasaka 2006; Brand 1985; Kopecky 1987; Scardi 1999; Potpara 2012a; Potpara 2012b**).Male preponderance is more striking in sporadic 'lone' AF compared with familial AF, possibly because of a concealed X-linked recessive AF in males with negative family history and apparently sporadic AF, whose mothers and sisters might be the healthy carriers (**Chen 2008**). However, familial and sporadic 'lone' AF are clinically indistinguishable. Aging is closely related with the risk of incident AF. Overall, the prevalence of AF in individuals younger than 60 years is < 1%, whilst ~10% of those ≥ 80 have AF (**Go 2001; Miyasaka 2006**). However, the true prevalence of 'lone' AF is unknown, ranging between 1.6% and 30% of all AF cases in the published reports which used variable definitions of 'lone' AF with respect to the age limit, left atrial size and associated hypertension (**Evans 1954; Brand 1985; Kopecky 1987; Davidson 1989; Rostagno 1995; Scardi 1999; Jouven 1999; Jahangir 2007; Potpara 2010,2012a**). In general, data on the natural history and prognosis of 'lone' AF are sparse. The clinical perception of 'lone' AF mostly stems from the results of a relatively small number of observational studies (**Evans 1954; Brand 1985; Kopecky 1987; Davidson 1989; Rostagno 1995; Scardi 1999; Jouven 1999; Jahangir 2007; Potpara 2010,2012a; Weijs 2012,2013**) and a post hoc analysis from one randomised trial, which compared rate vs. rhythm control in patients with non-valvular AF (**Rienstra 2004**). These studies have certain limitations, including the small cohorts wherein some patients even were not truly 'lone' AF because of older age (**Evans 1954; Brand 1985; Rostagno 1995; Potpara 2010; Rienstra 2004; Weijs 2012,2013**) or hypertension (**Rienstra 2004**). The studies yielded conflicting results, but most of them suggested that 'lone' AF is a benign disorder with outcomes comparable to the general adult population. The largest of the 'lone' AF studies, with 346 carefully characterized newly

diagnosed 'lone' AF patients and a 12-year follow-up (**Potpara 2012a**) demonstrated that these patients do have a favorable prognosis as long as they have truly 'lone' arrhythmia. However, with aging and/or the occurrence of cardiovascular comorbidities in such patients, the risk of development of AF-related complications (e.g., thromboembolic events or HF) increases (**Potpara 2012a**). A study suggested that 'lone' AF patients develop cardiovascular disease more often, at younger age and with a more severe disease profile compared with healthy controls in sinus rhythm (**Weijs 2013**). However, the study was rather small (only 41 'lone' AF patients) and the findings could be just a play of chance. Another study observed that as many as 44% of patients originally thought to have 'lone' AF may actually have occult hypertension (**Katritsis 2005**). Taken together, these data suggest that 'lone' AF patients should have a regular clinical follow-up dedicated to the primary and secondary prevention of cardiovascular disease and AF-related complications. Paroxysmal (i.e., self-terminating) 'lone' AF has been suggested to implicate a better prognosis in terms of thromboembolic events and mortality, as compared to chronic 'lone' arrhythmia (**Scardi 1999**). Indeed, majority of 'lone' AF patients present with paroxysmal arrhythmia and have a relatively low rate of progression to permanent AF over a long-term follow-up. In the Belgrade AF study, for example, < 10% of patients initially had a permanent arrhythmia. However, the progression from paroxysmal to chronic AF subsequently occurred in 27% of patients (at 11.9 ± 7.5 years following the AF diagnosis) and was an independent marker for adverse cardiovascular events (**Potpara 2012a**). In the original description of 'lone' AF, the authors had emphasized that there was no increase in the left atrial size during follow-up (at least as assessed using chest radiography). More recently, it has been shown that 'lone' AF patients with increased left atrial volume (>32 ml/m^2), either at diagnosis or during the follow-up, subsequently experienced adverse cardiovascular events including stroke (**Osranek 2005**). It is further noted that episodes often increase in frequency and duration over time. In addition, the term **"lone AF"** to identify AF in typically younger patients without structural heart disease, hypertension, or diabetes mellitus, or external causes such as hyperthyroidism, is deemed potentially confusing and should not be used to guide treatment decisions. The European Society of Cardiology (ESC) utilizes a similar classification schema published in its 2010 guidelines. The ESC included one additional characterization, **silent AF (asymptomatic),** which can manifest as AF-related complications such as ischemic stroke or tachycardiomyopathy, or is diagnosed incidentally on ECG. Any form of AF may be silent or asymptomatic (**Camm 2010**). Patients with AF, the class I recommendation regarding management of patients with pre-excited AF with rapid ventricular response includes IV infusion of procainamide (10mg/kg body weight over 5 minutes) if patient is hemodynamically stable, immediate synchronized cardioversion if the patient is unstable, and subsequent radiofrequency catheter ablation (RFCA) of the AP (**January 2014;Blomstrom-Lundqvist 2003**). This procedure involves the use of unmodulated, high-frequency alternating current flow through tissue to cause heat, cell desiccation, and coagulation necrosis for the purpose of destroying troublesome areas and APs in the heart. The closed electrical circuit required for cadiac ablation is achieved by radiofrequency generator, connecting leads, and unipolar or bipolar electrodes. Administration of amiodarone, adenosine,

β-blockers, and calcium channel blockers should be avoided as these will isolate the accessory pathway and thus predispose to fatal arrhythmias such as ventricular fibrillation by increasing the ventricular rate (**January 2014; Blomstrom-Lundqvist 2003; Simonian 20010; McGovern 1986**). When AF occurs in a patient with more than one AP, AV conduction via the extra connections plus the AV node results in an irregular fast rhythm, fusion beats, and polymorphous broad QRS tachycardia.
Rapid anterograde conduction in the setting of ventricular preexcitation is associated with an increased risk of SCD. The effect of isoproterenol in children anesthetized with ventricular preexcitation, APs display shorter conduction properties at younger ages and important adrenergic sensitivity at all ages. Use of low-dose isoproterenol resulted in a substantial increase in the number of patients who would otherwise meet typical criteria for ablation (**More 2011**).

- **Acute AF:** Any subtype of AF within the first 24 hours of onset, be it persistent, permanent or paroxysmal.

Genetic predisposition

AF, especially early-onset AF, has a strong heritable component that is independent of concomitant cardiovascular conditions (**Fox 2004; Oyen 2012**). A few young AF patients suffer from inherited cardiomyopathies or channelopathies mediated by disease-causing mutations. These monogenic diseases also convey a risk for sudden death. Up to one-third of AF patients carry common genetic variants that predispose to AF, albeit with a relatively low added risk. At least 14 of these common variants, often single nucleotide polymorphisms, are known to increase the risk of prevalent AF in populations (**Ellinor 2012; Olensen 2014; Sinner 2014**). The most important variants are located close to the *paired-like homeodomain transcription factor 2* (Pitx2) gene on chromosome 4q25 (**Gudbjartsson 2007; Lubitz 2014**). These variants modify the risk of AF up to seven-fold. Several of the AF risk variants are also associated with cardioembolic or ischemic stroke, possibly due to silent AF (**Tada 20014**). Changes in atrial action potential characteristics, atrial remodelling, and modified penetration of rare gene defects have been suggested as potential mechanisms mediating increased AF risk in carriers of common gene variants. Genetic variants could, in the future, become useful for patient selection of rhythm or rate control (**Parvez 2013**). While genomic analysis may provide an opportunity to improve the diagnosis and management of AF in the future (**Kirchhof 2013**), routine genetic testing for common gene variants associated with AF cannot be recommended at present (**Ackerman 2011**).

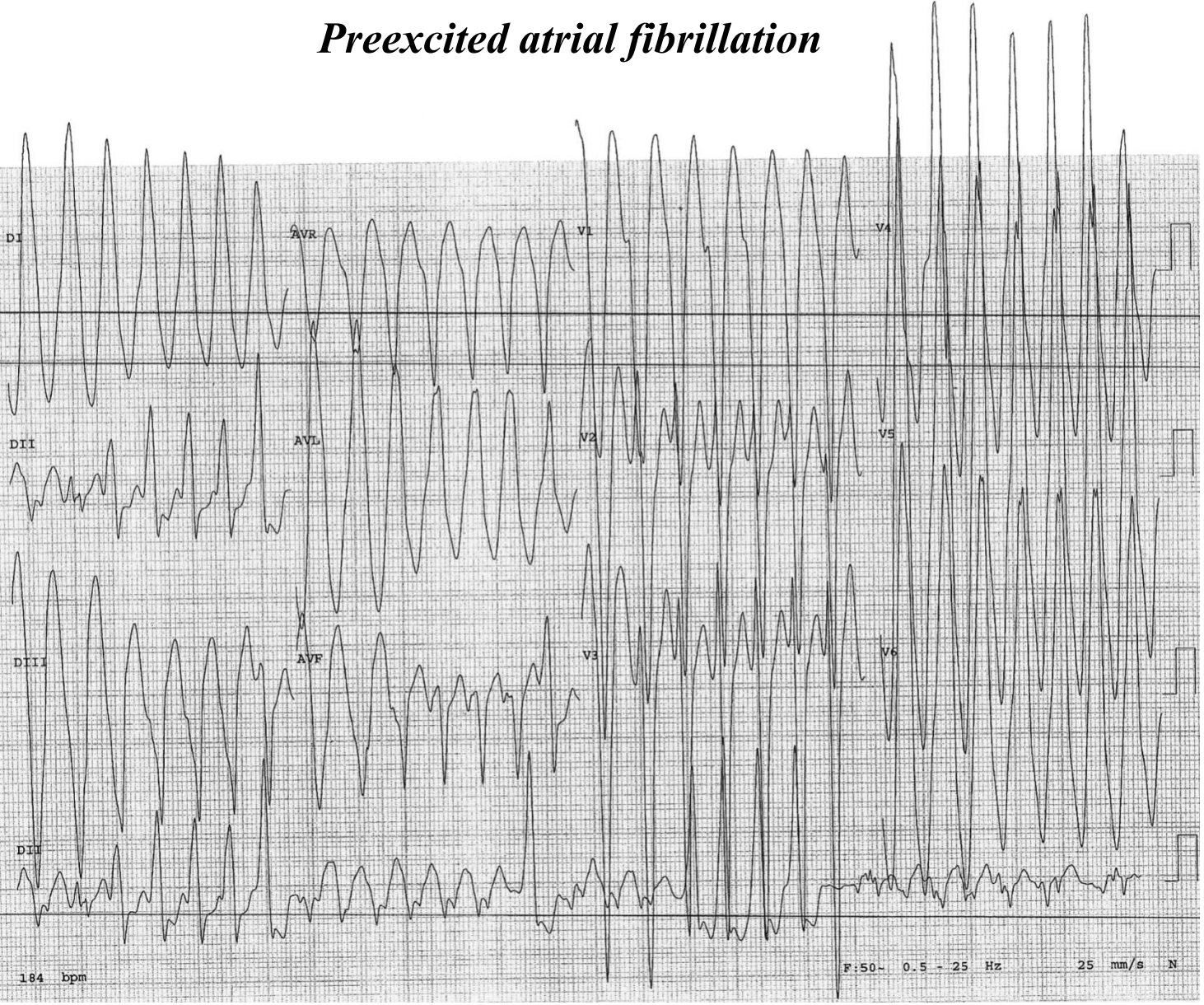
Cardiovascular morbidity and mortality associated with atrial fibrillation

Event	Association with AF
Death	Increased mortality, especially cardiovascular mortality due to sudden death, heart failure or stroke.
Stroke	20-30% of all strokes are due to AF. A growing number of patients with stroke are diagnosed with "silent", paroxysmal AF.
Hospitalizations	10-40% of AF patients are hospitalized every year.
Quality of life	Quality of life is impaired in AF patients independent of other cardiovascular conditions.
Left ventricular dysfunction and heart failure	Left ventricular dysfunction is found in 20-30% of all AF patients. AF causes or aggravates LV dysfunction in many AF patients, while others have completely preserved LV function despite long-standing AF.
Cognitive decline and vascular dementia	Cognitive decline and vascular dementia can develop even in anticoagulated AF patients. Brain white matter lesions are more common in AF patients than in patients without AF.

Electrophysiological studies (EPSs) can be used in patients with WPW syndrome to determine the following:

- The mechanism of the clinical tachycardia
- The electrophysiological properties (eg, conduction capability, refractory periods) of the AP and the normal atrioventricular (AV) nodal and His Purkinje conduction system
- The number and locations of APs (necessary for catheter ablation)
- The response to pharmacologic or ablation therapy

Preexcited atrial fibrillation

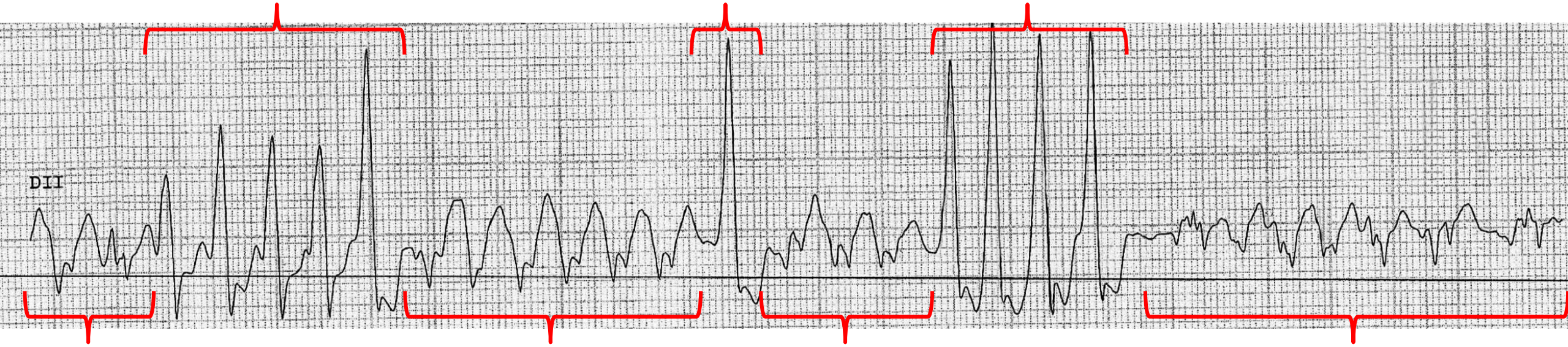


ECG diagnosis: Sustained wide or broad QRS complexes, irregularly irregular ventricular rhythm (significant variations in both the RR intervals and QRS complexes.), stable, fast ventricular response (heart rate (HR) > 180bpm. (in the present case the HR is between 214 and 250bpm), QRS complexes change in shape and morphology but axis remains stable unlike polymorphic VT, beat-to-beat variations in the QRS complex morphology, presence of capture and fusion beats. Fusion, Dressler or hybrid beats and capture beats is strong evidence of VT but is not diagnostic. Fusion beats and capture beats are also seen in AF with conduction over an accessory pathways (APs) (a broad QRS tachycardia that is morphologically identically to VT). Capture beats are common when procainamide is given, in which case the AP is blocked or at least compromised. Fusion beats may also occur when an end diastolic ventricular beat fires during sinus tachycardia with BBB. This phenomenon is probably a rare occurrence, but with its two fusion beats demonstrates that it is a possibility. Patients with WPW syndrome, concealed APs, or Mahaim fibers who develop SVT have a QRS pattern identical to that of VT. Conversely, certain types of VT have exactly the same QRS pattern as SVT with aberration.
Finally, the lower II long strip shows two well defined QRS

Polarity: positive and negative. What does it mean? Answer: when AF occurs in a patient with more than one AP, AV conduction via the extra connection plus the AV node results in a irregular rapid rhythm with polymorphous broad QRS tachycardia.

Conclusion: this is an AF with multiple APs (at least two). Please, see in the next slides a long II strip that shows sudden changes of QRS polarity.

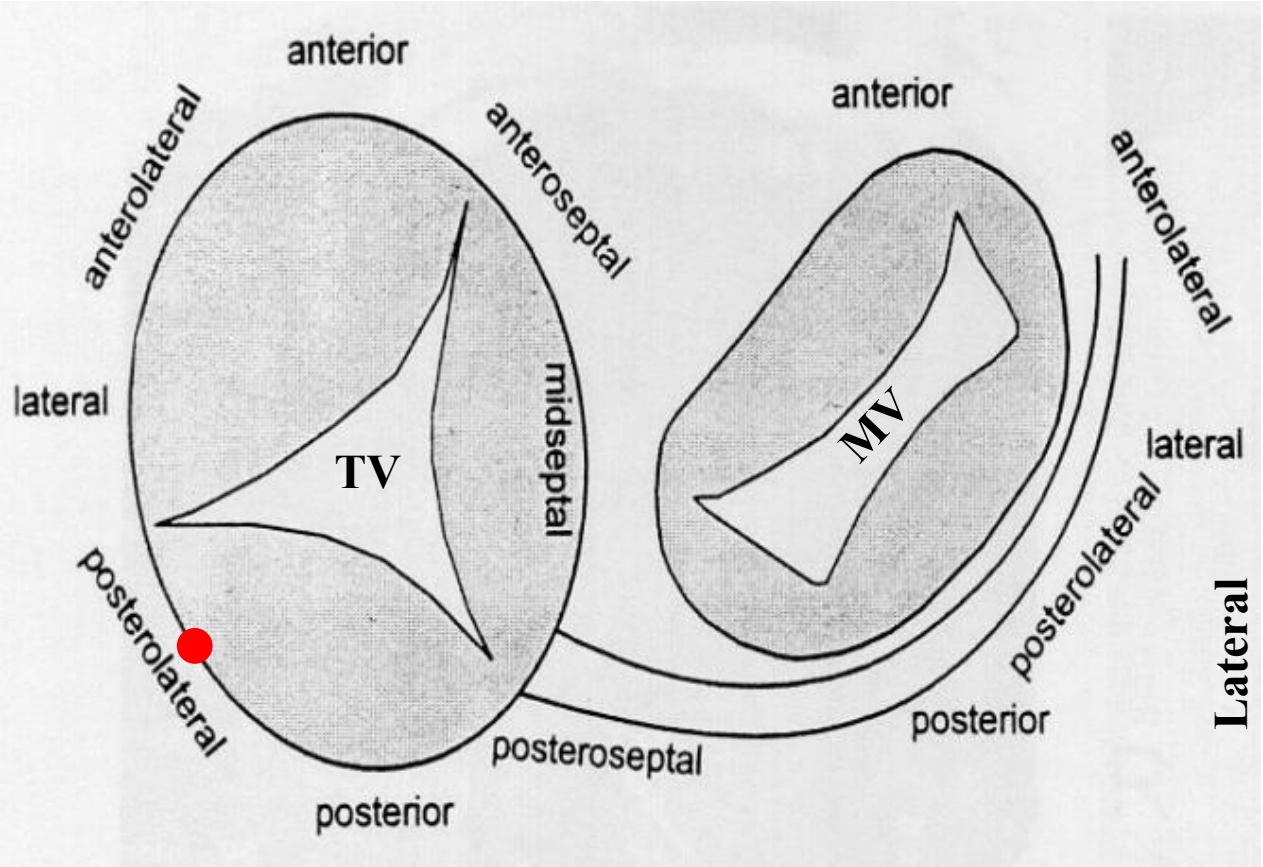
Long II strip



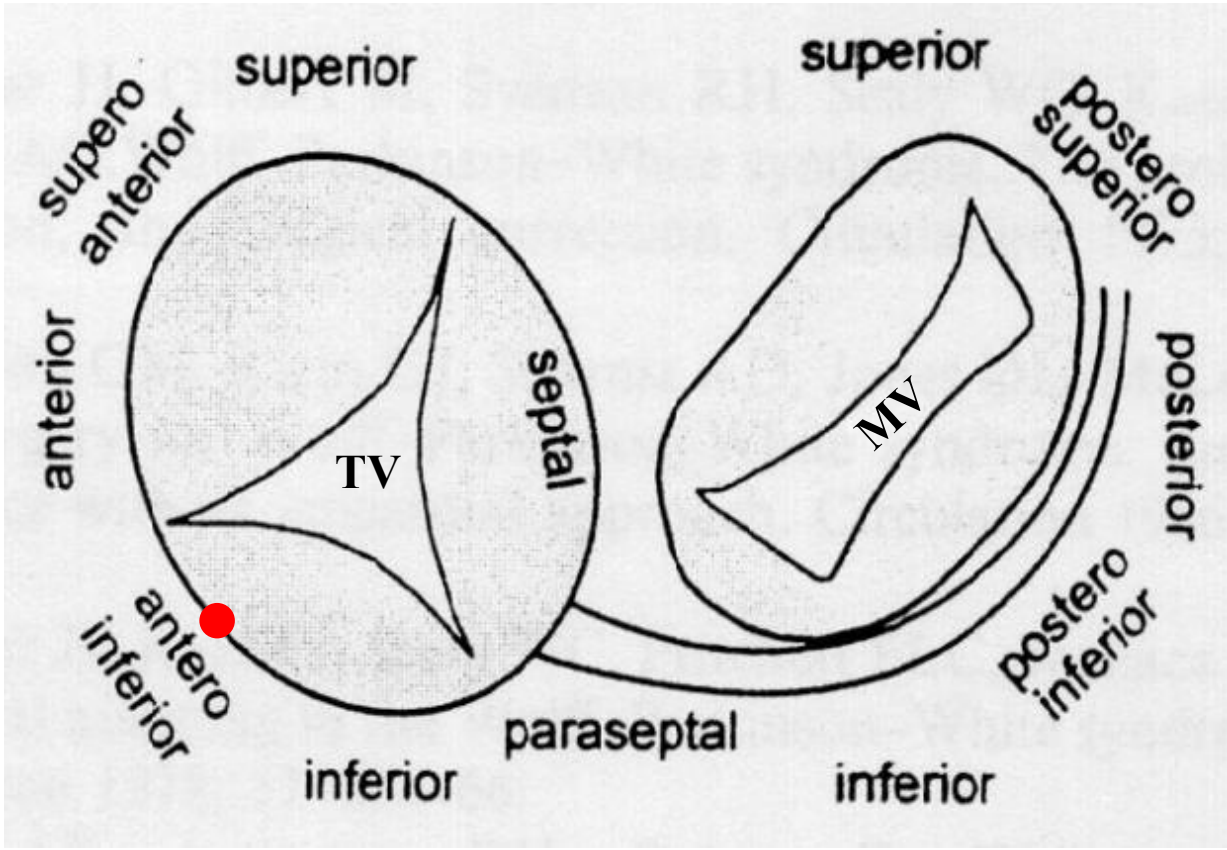
Conclusion: AF with multiple APs. In the present case, two APs are operatives: posteroseptal AP (predominantly positive QRS complexes) and anteroseptal AP (negative QRS complexes). It is alternating AP conduction down. The existence of these two APs leading downward anterogradely explain the failure of the first ablation procedure performed in 2014.

Comments: Multiple APs in patients with the WPW syndrome are rare and associated with a higher risk of VF. In the present case, the patient has two APs with anterograde conduction and a fasciculoventricular fiber. The ECG showed AF with wide QRS complex suggestive of preexcitation. The EPS demonstrated the presence of two atrioventricular APs with antegrade conduction (right posteroseptal and right anteroseptal). After the first ablation of the two APs, the ECG showed a persistent delta wave with a short HV interval. Atrial stimulation demonstrated decremental conduction, progressive lengthening of the AH interval and no modification in the HV interval nor in the preexcitation pattern, suggestive of the presence of a fasciculoventricular fiber. This exceptional case report is demonstrative of the complexity of the WPW syndrome, and the feasibility and efficacy of RFCA in a single procedure. Unfortunately, in the present case the RFCA was incomplete, which explains the failure of the procedure. On February 7th, 2017 was performed a new ablation of AP located in the anteroinferior AP (old nomenclature right posterolateral).

The old nomenclature (Cosio 1999)

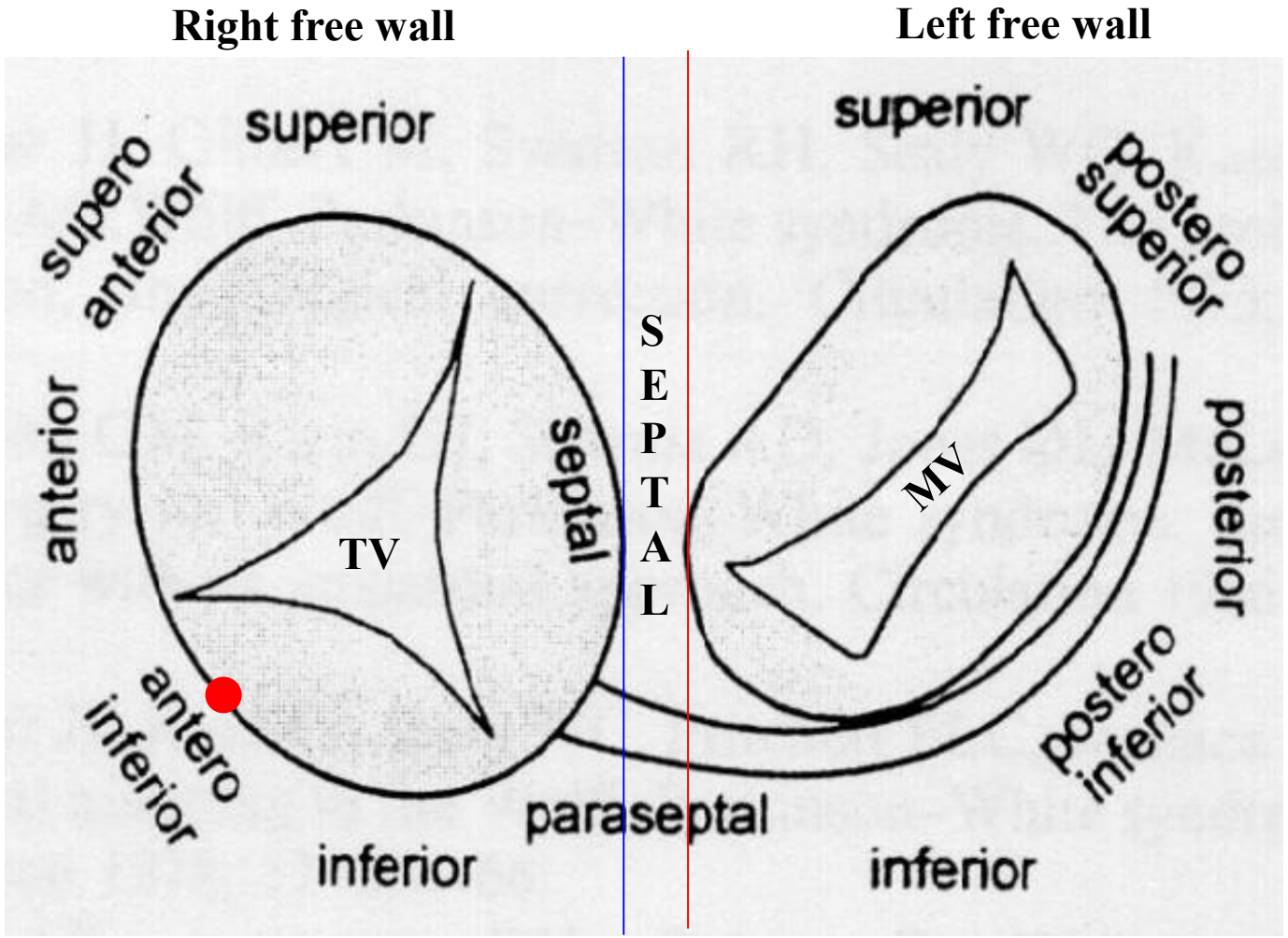


The new nomenclature

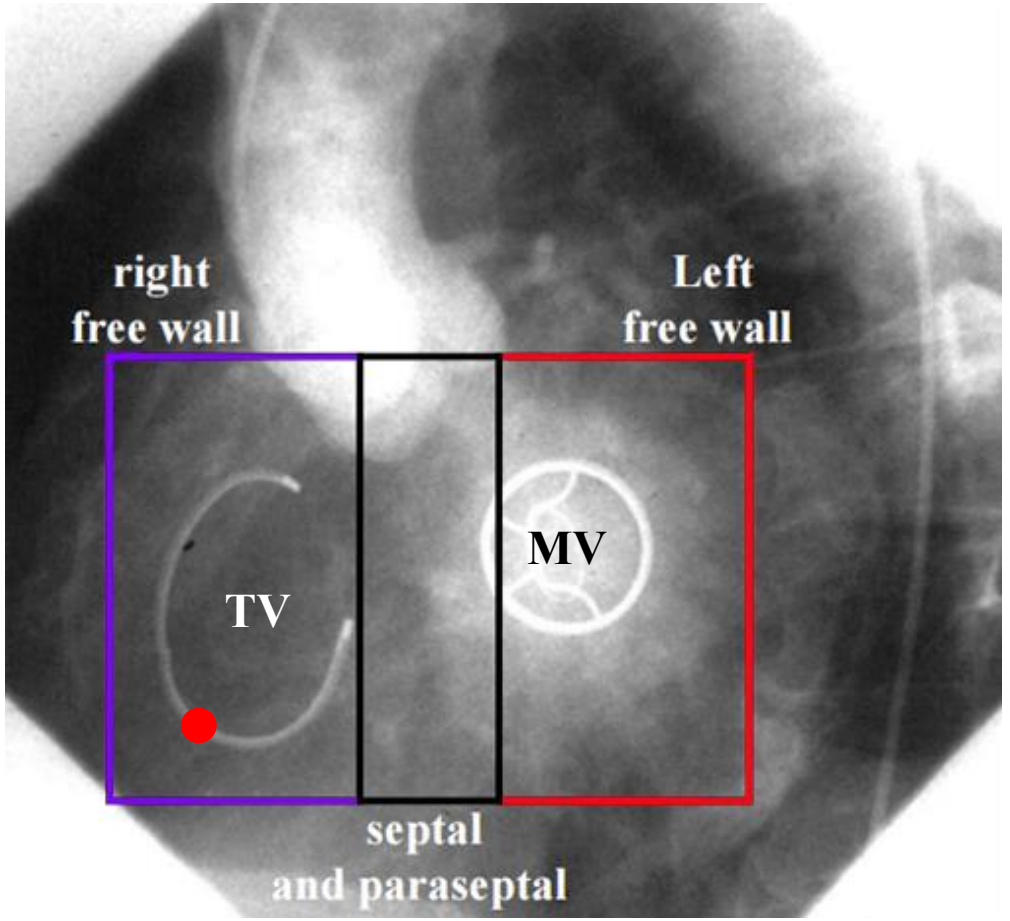


On February 7th, 2017 was performed a new ablation in the anteroinferior location (old nomenclature: right posterolateral ●).

The new nomenclature

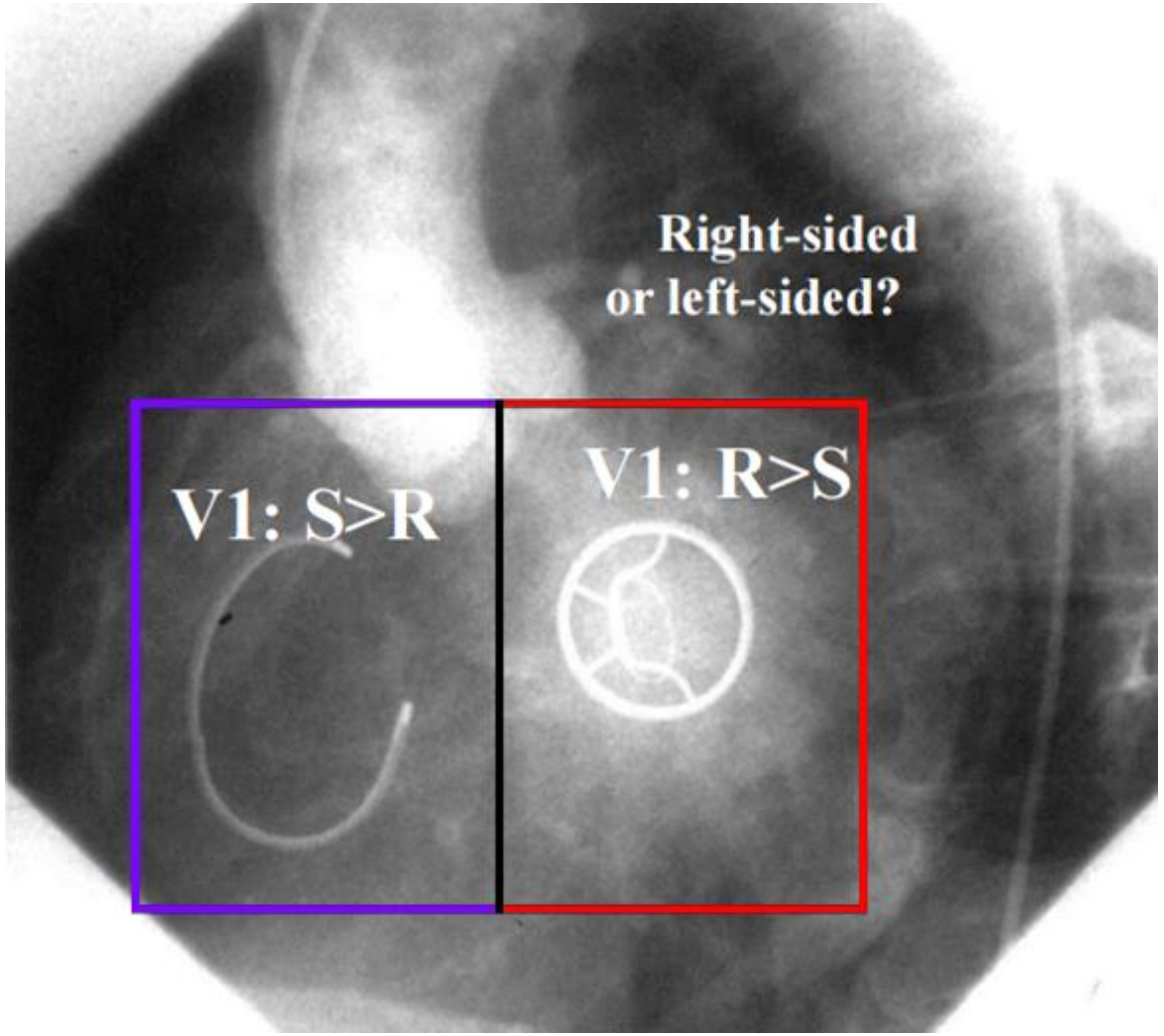


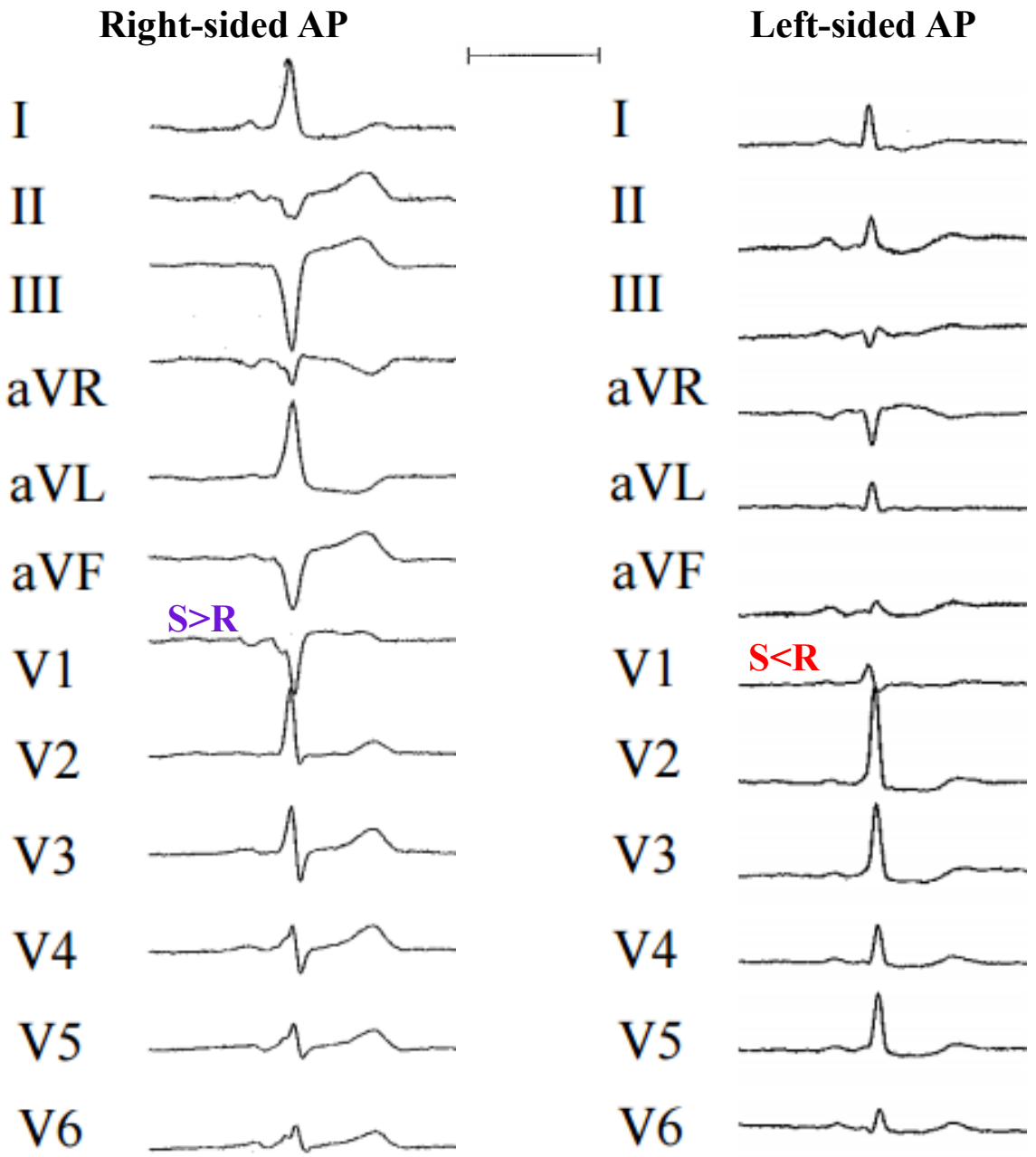
AP location in fluoroscopic anatomy



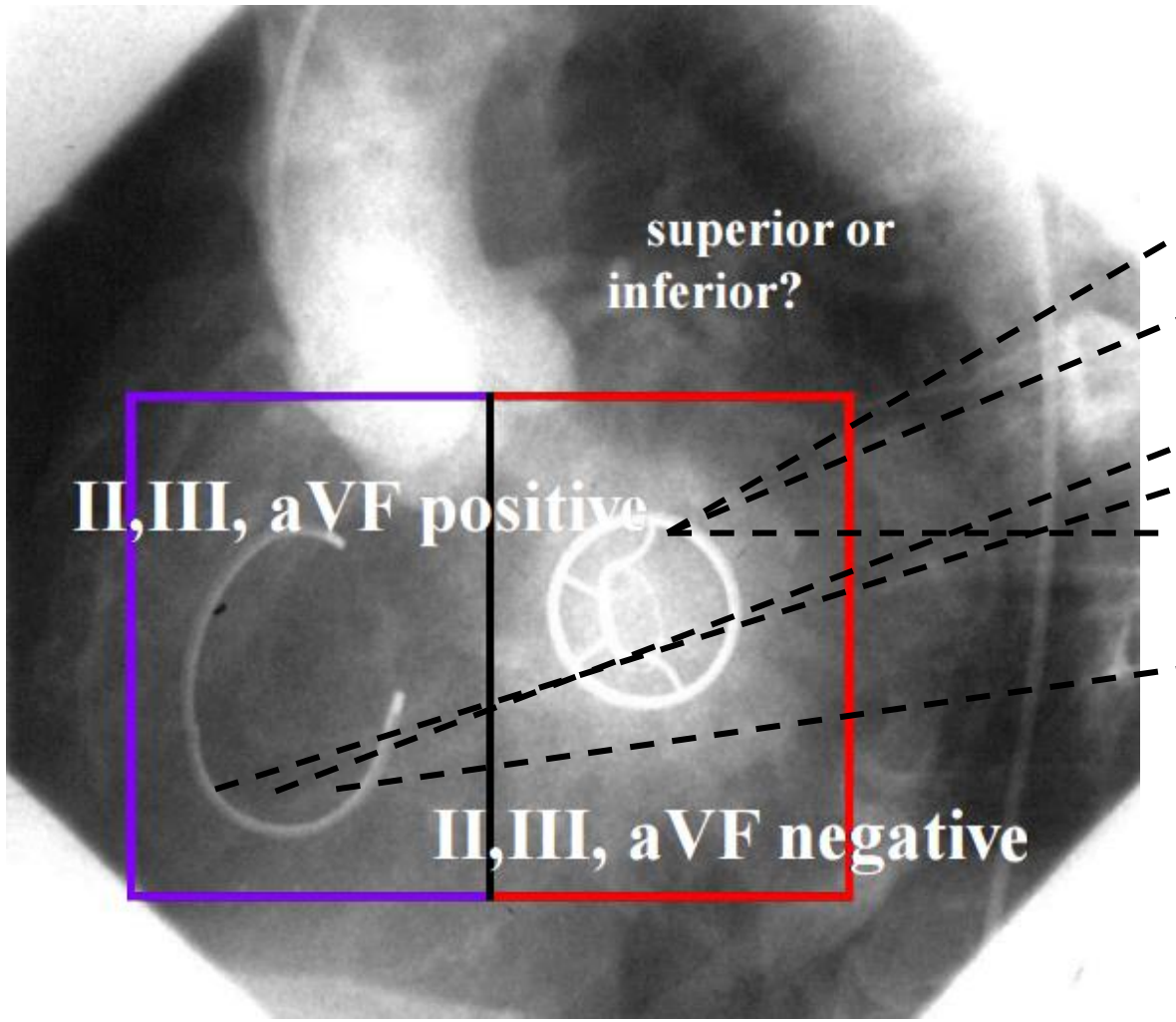
TV: tricuspid valve; MV: mitral valve; ● : anteroinferior location ablated in 2017

How to localize the accessory pathway? ECG criteria

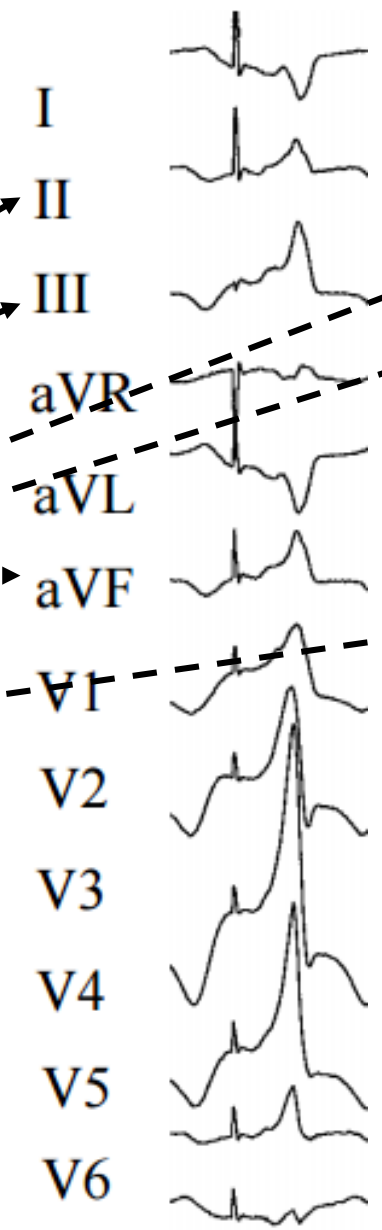




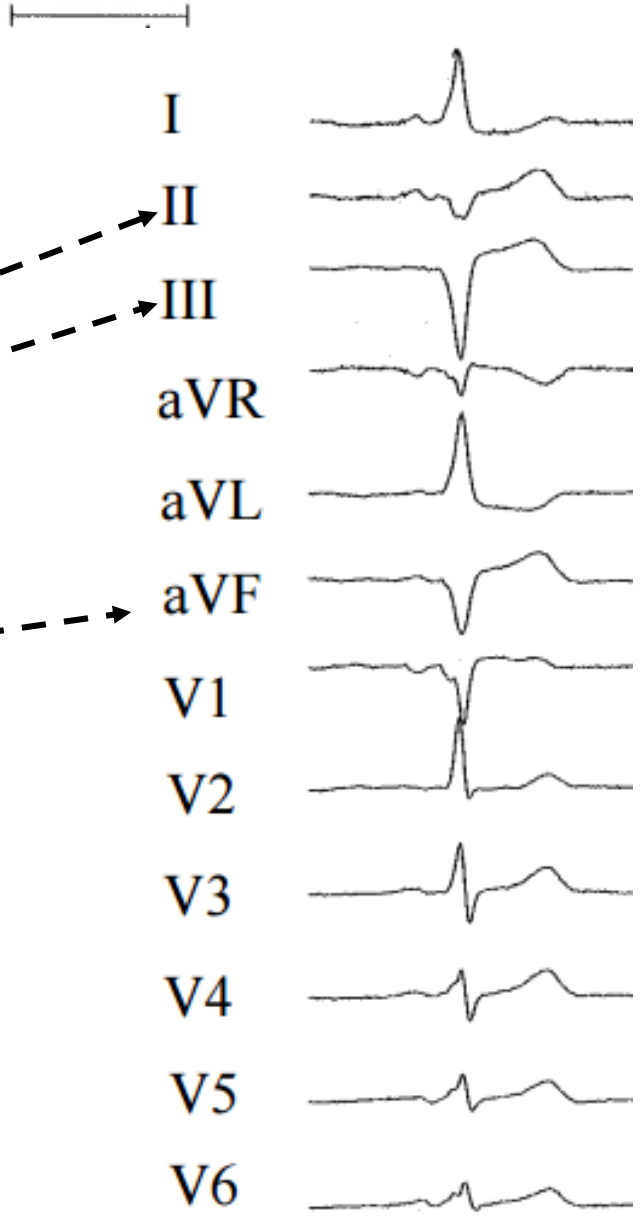
Superior or inferior localizations of Accessory Pathway?

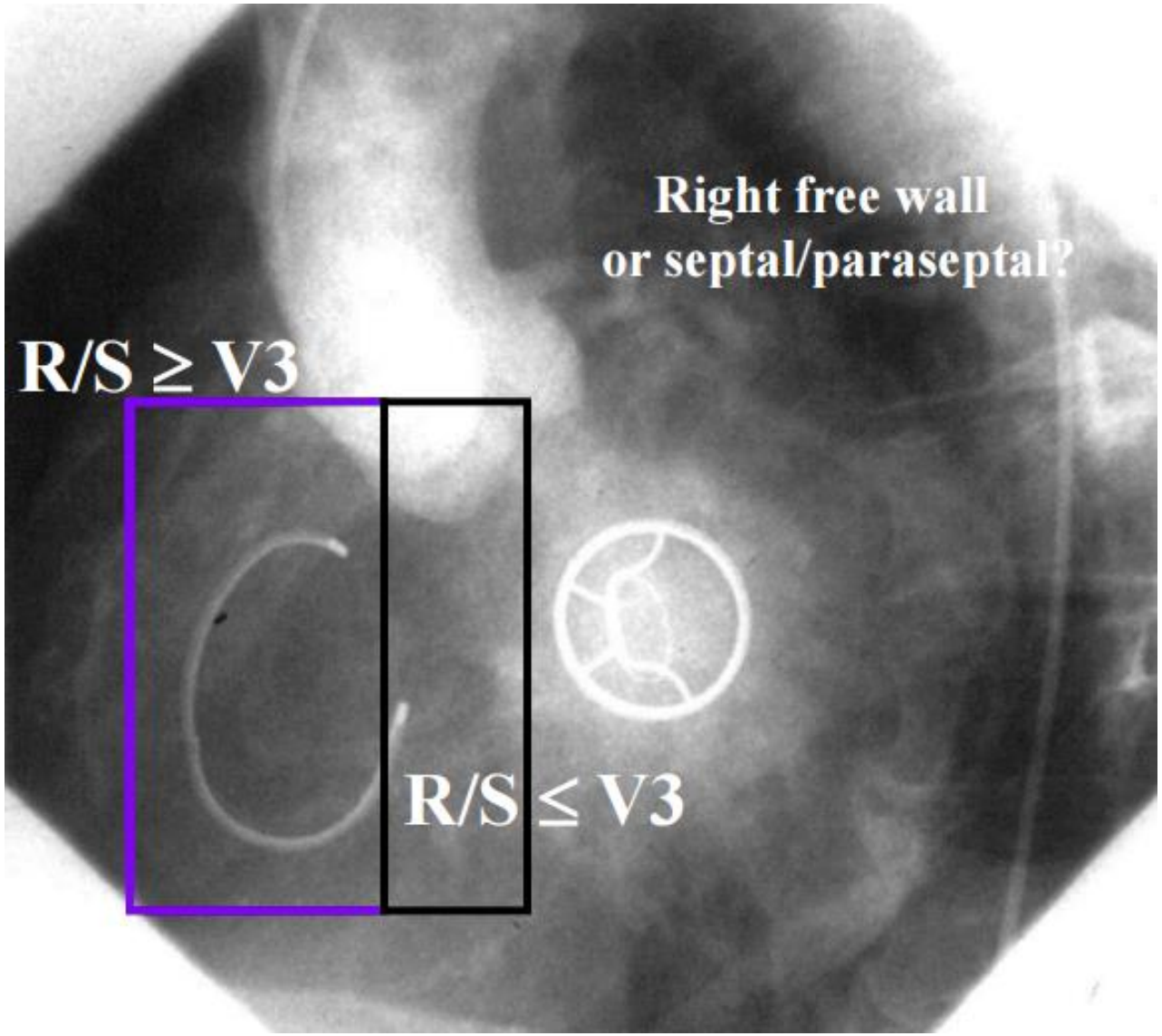


Left-sided superior AP

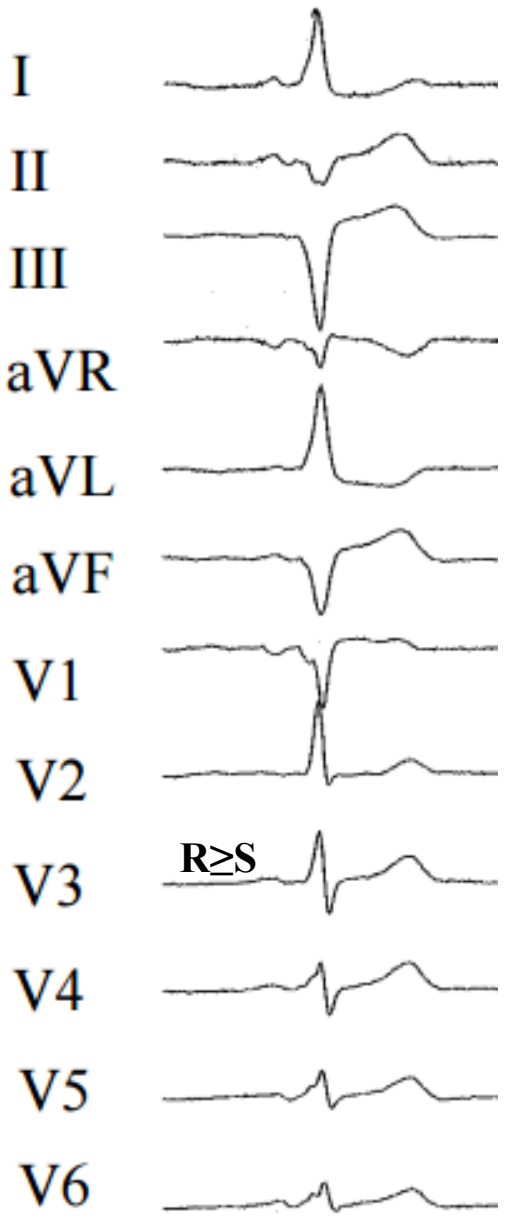


Right-sided inferior AP

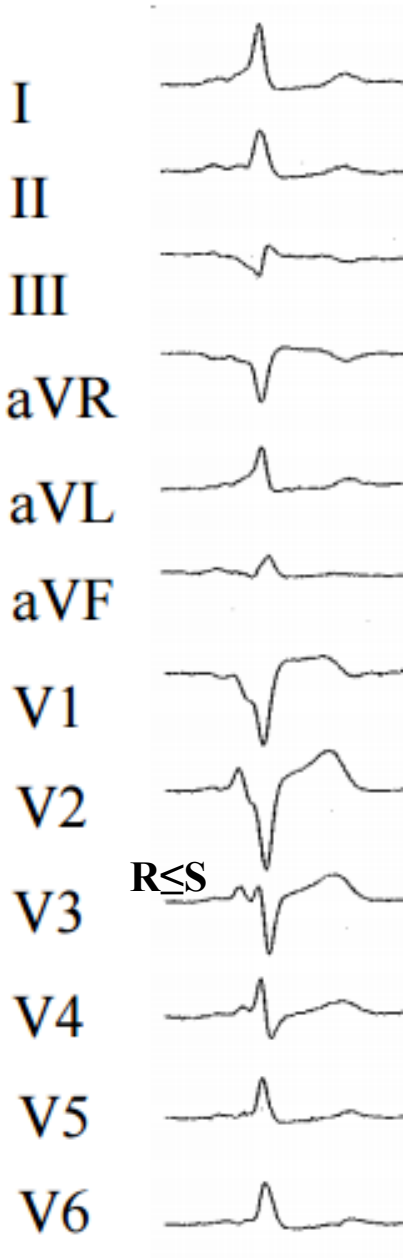




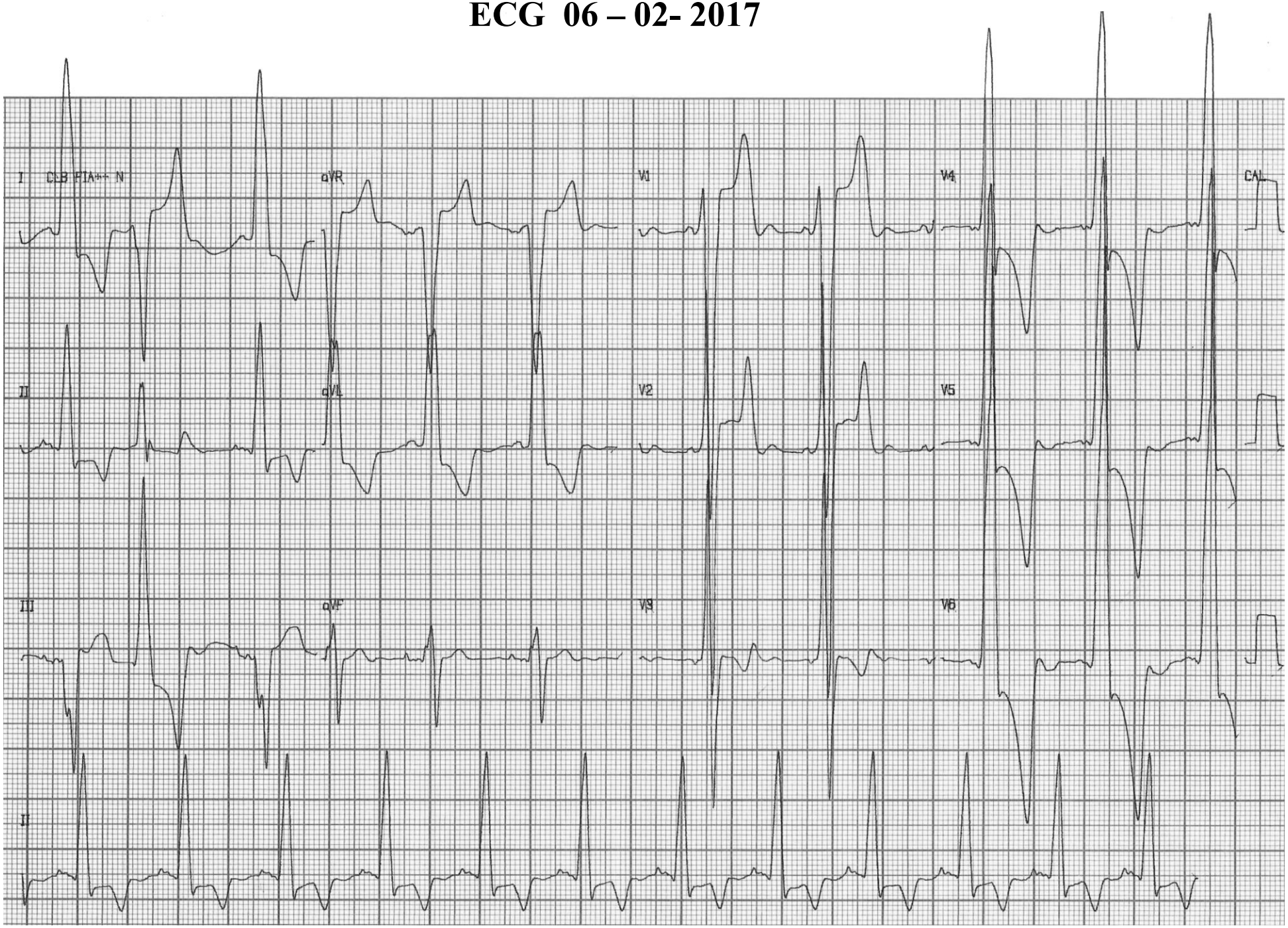
Right-sided free wall AP



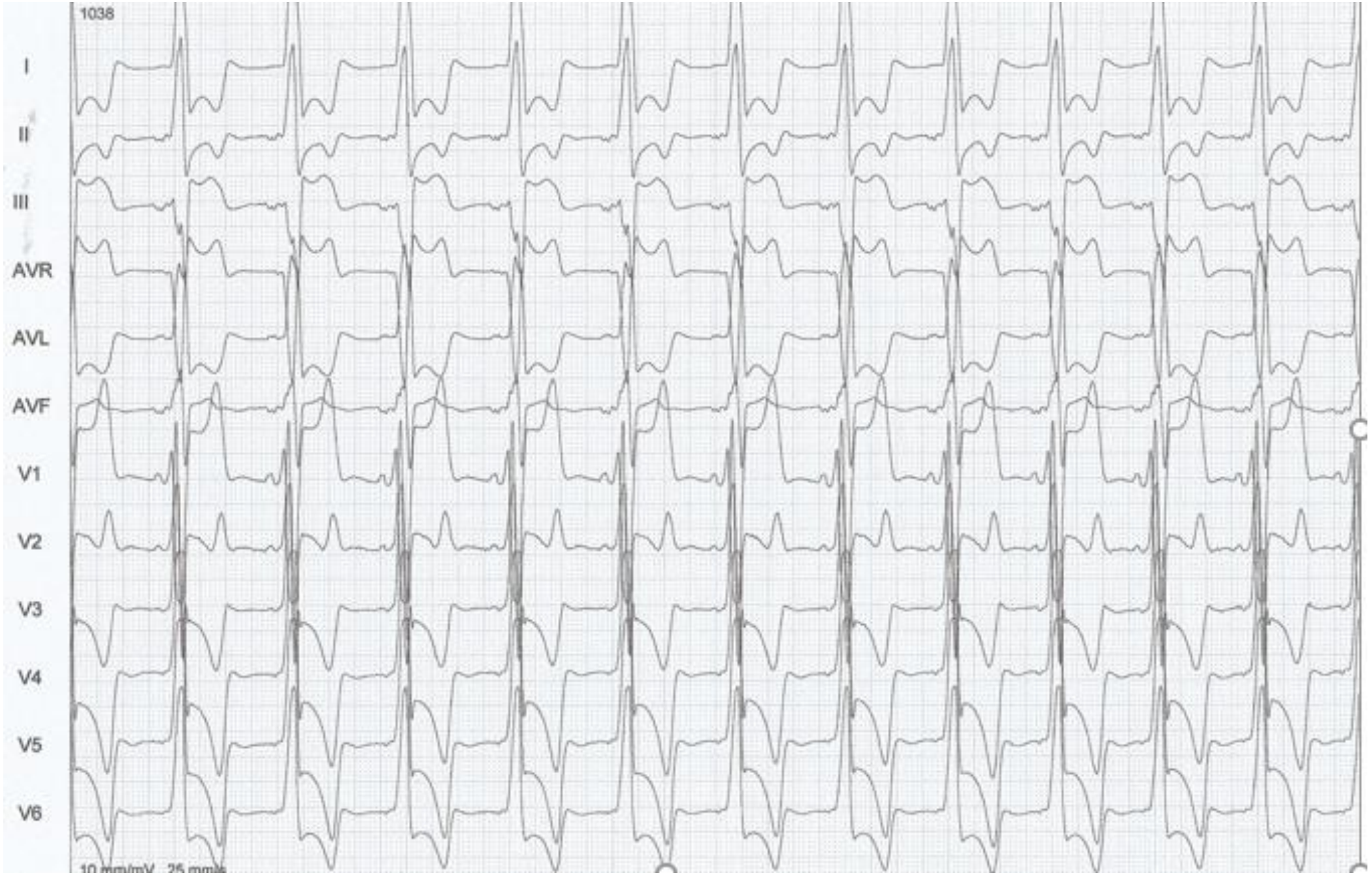
Right-sided free wall AP



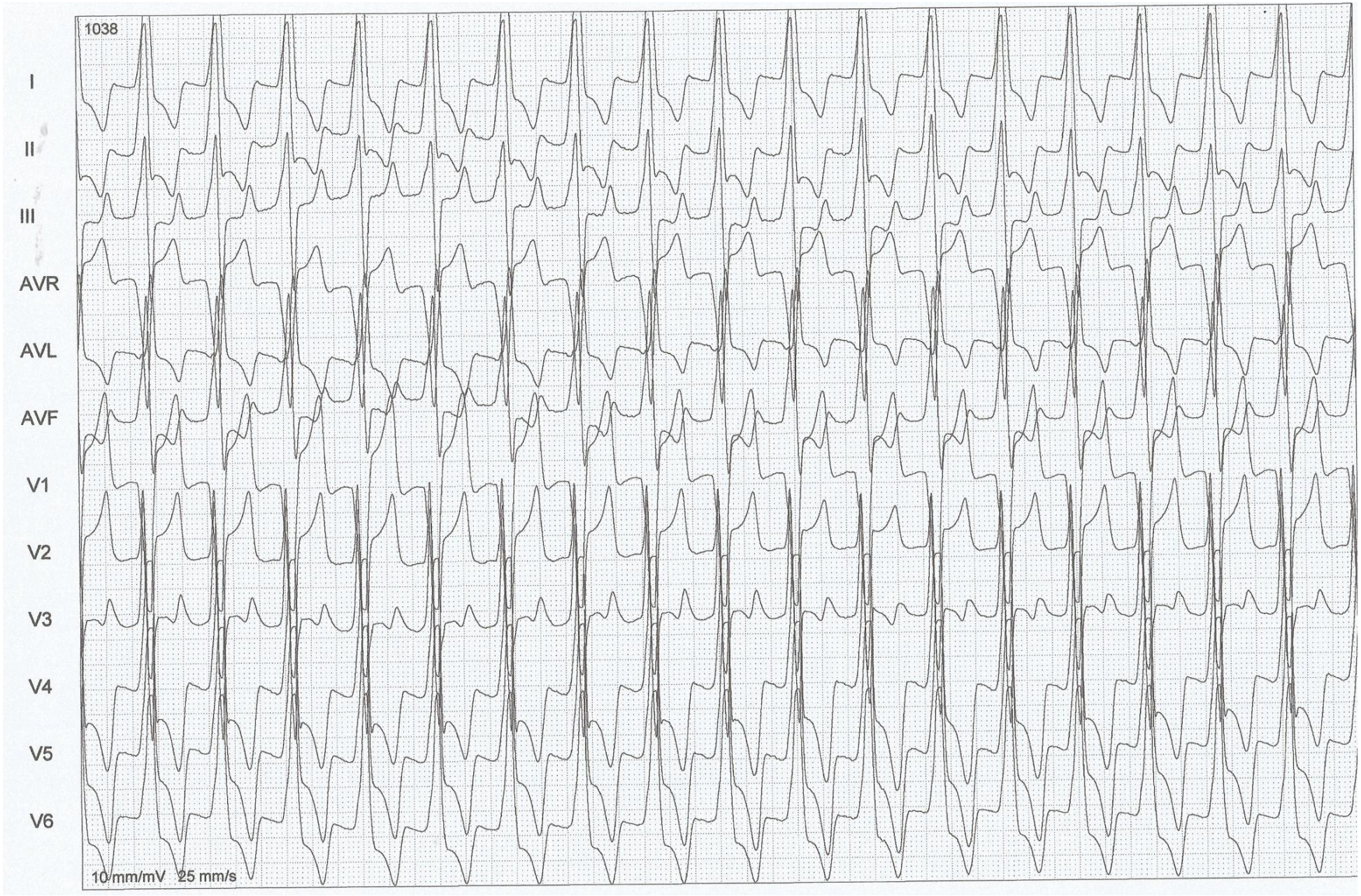
ECG 06 – 02- 2017



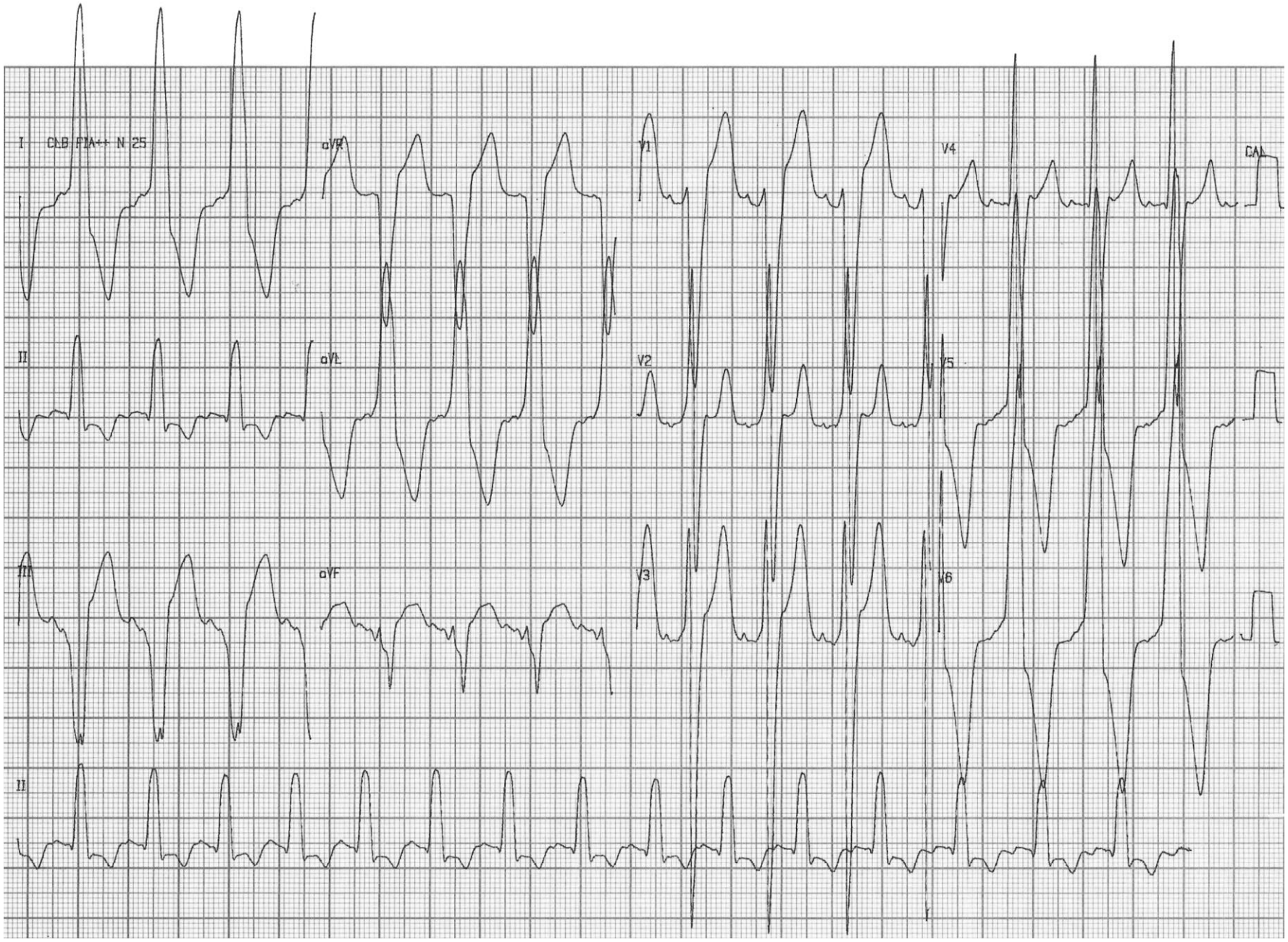
ECG pre- EPS in the laboratory



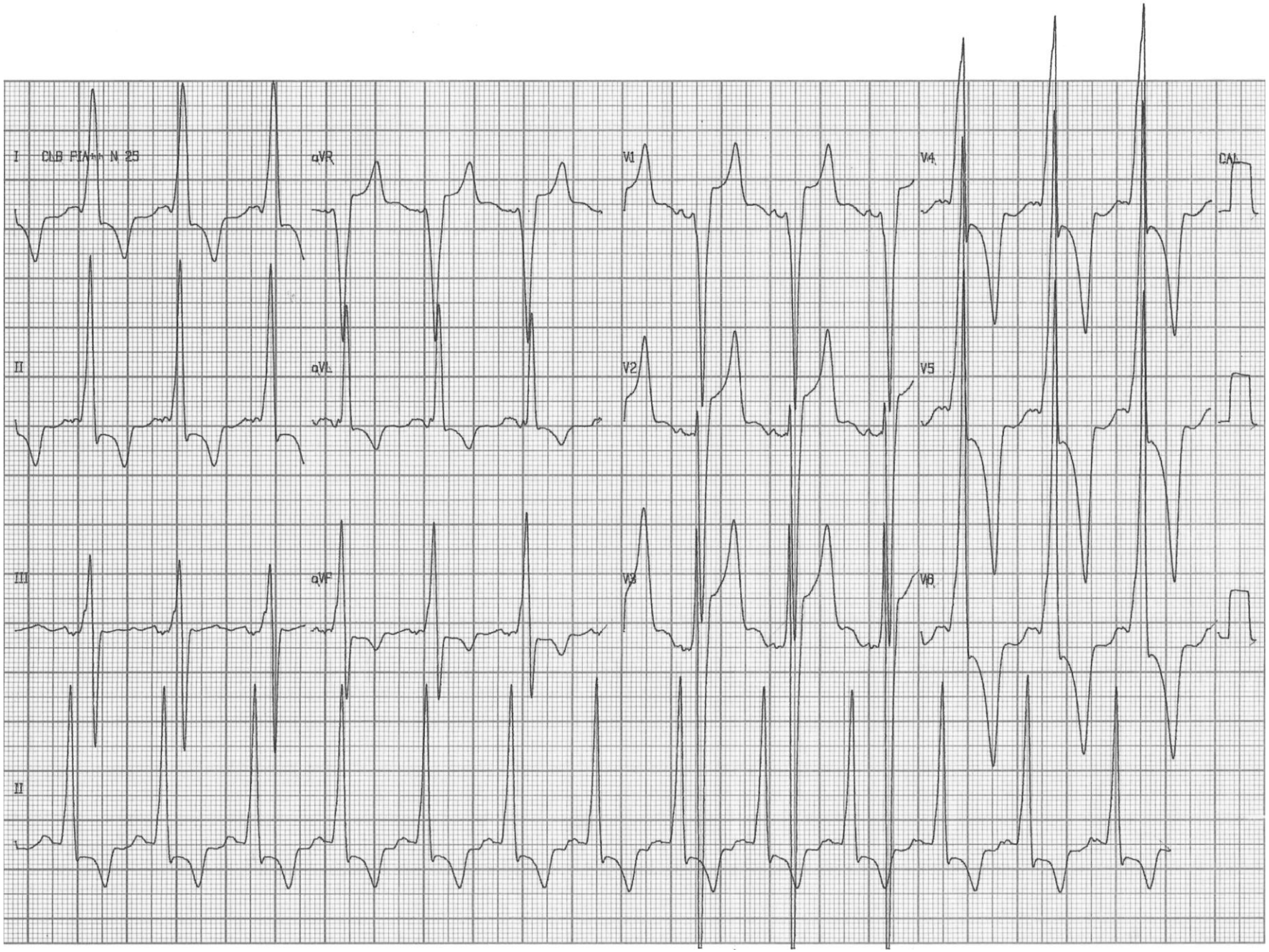
ECG February 07, 2017 - immediately after ablation



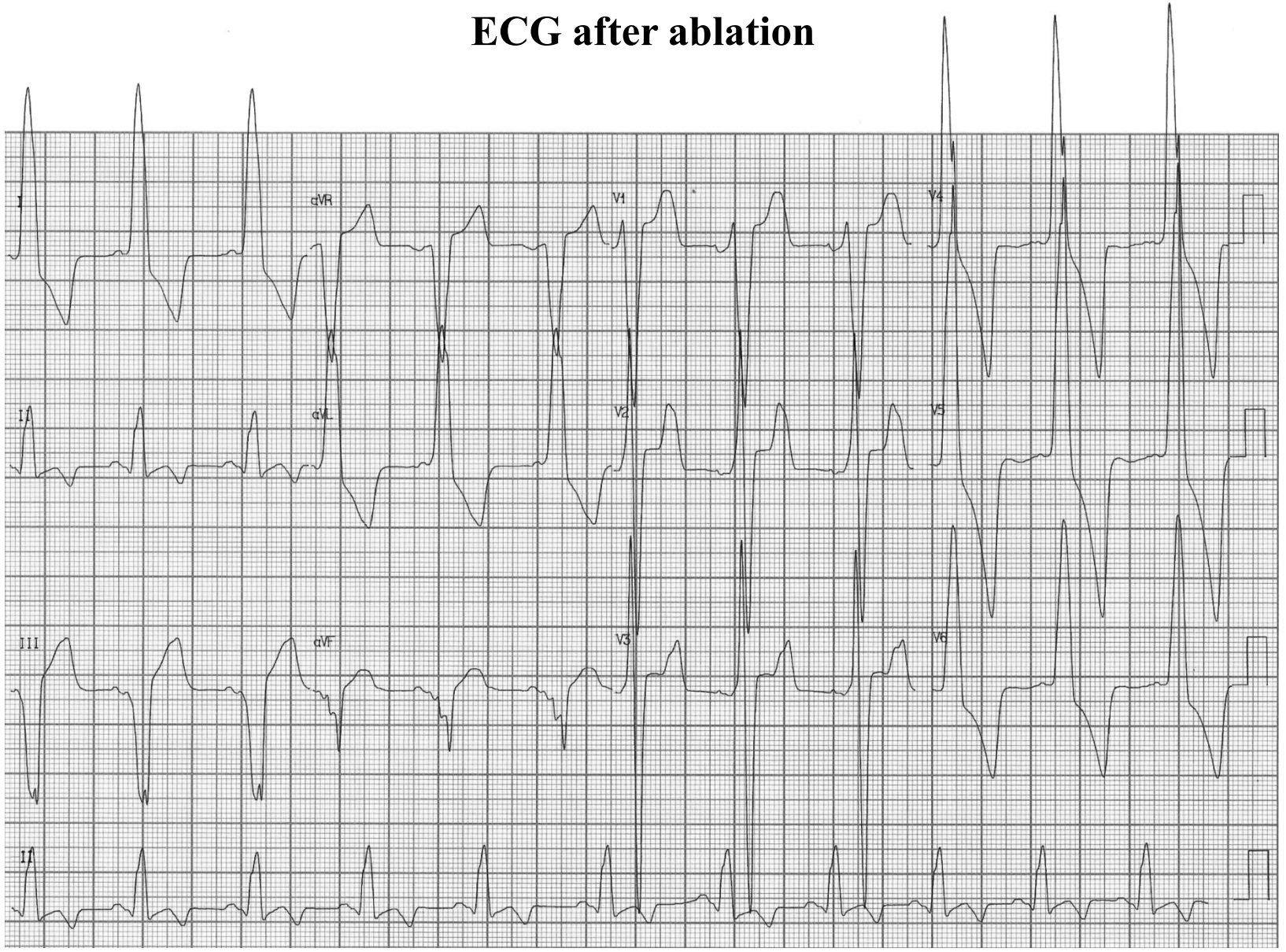
ECG February 08, 2017 - 24hours after ablation



ECG February 14, 2017 - one week after ablation

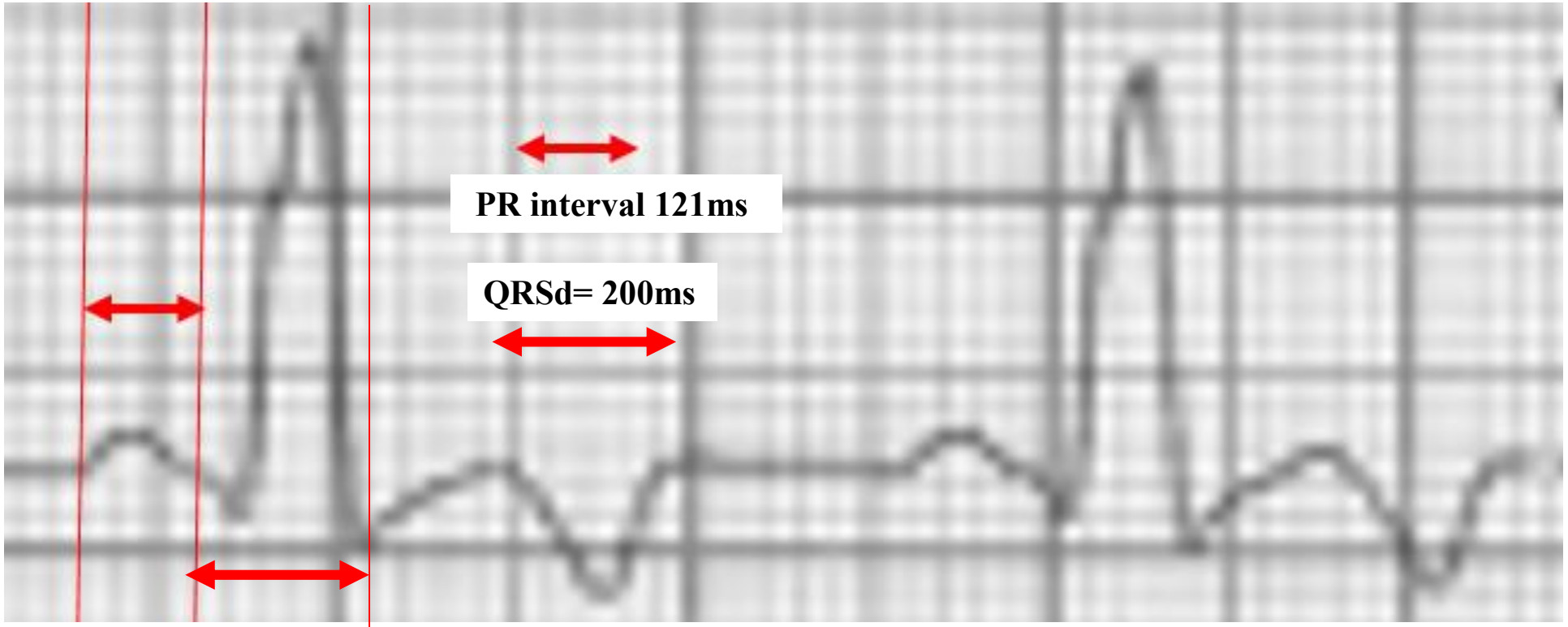


ECG after ablation



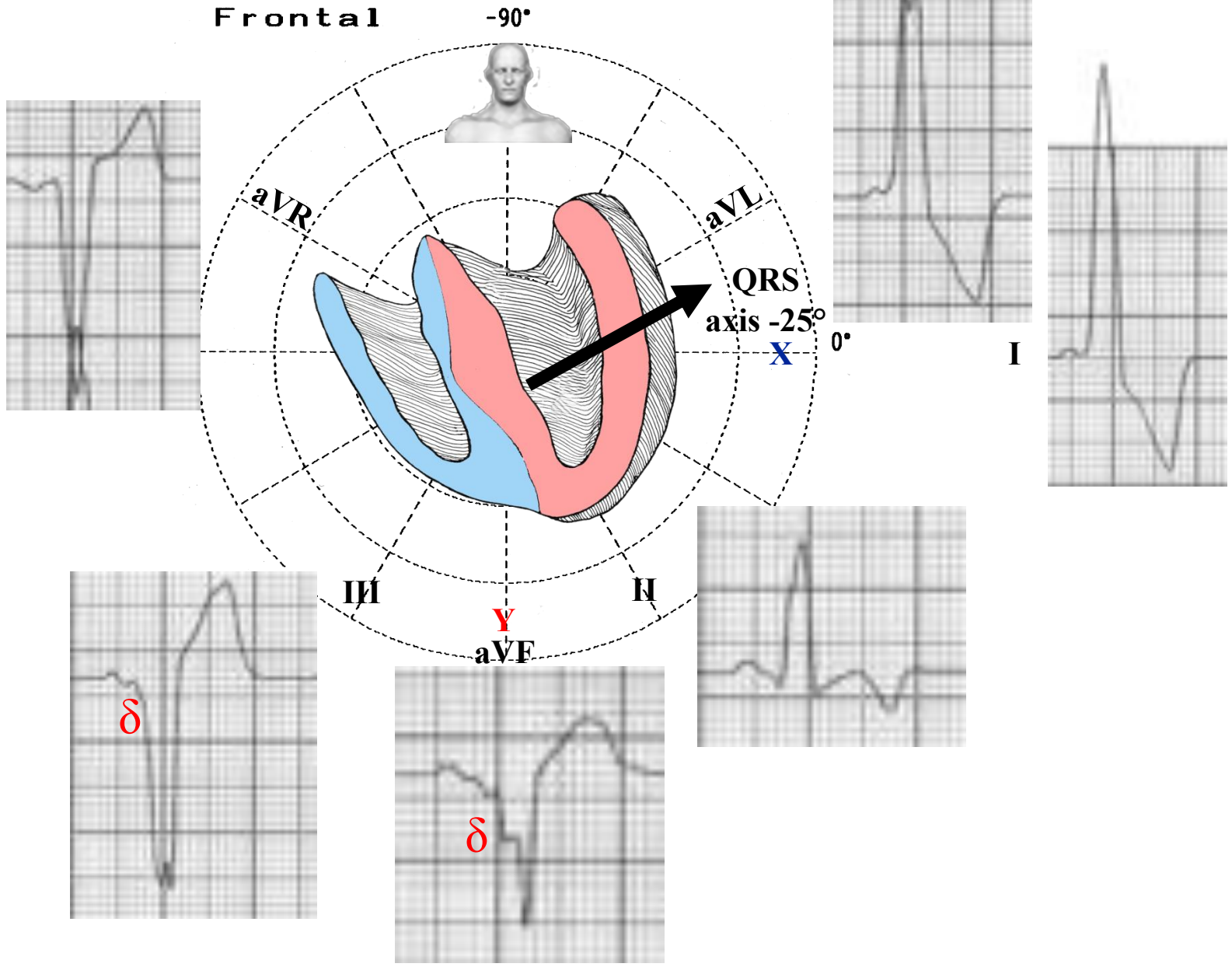
ECG diagnosis: converted back to normal sinus rhythm, classic delta wave, **normal** PR interval (121ms), wide QRS complexes (200ms) with LBBB-like pattern, and pseudo inferior myocardial infarction and S>R in V1suggesting right-sided AP.

Conclusion: atriofascicular pathway. Why? Answer in the next slide…..

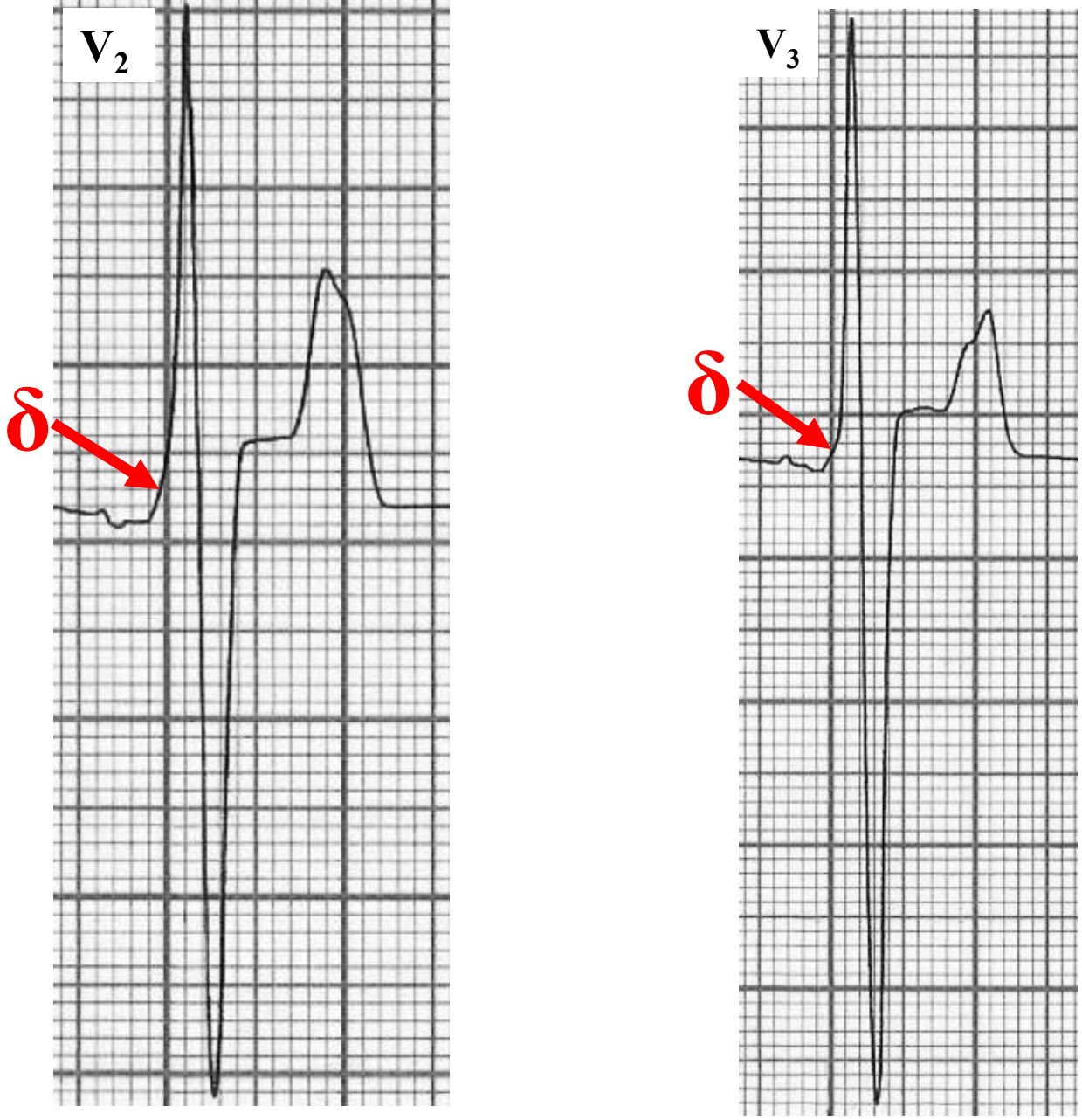


ECGs of patients with atriofascicular or atrioventricular pathways (pseudo-Mahaim) have minimal or no preexcitation and absence of septal Q wave in leads V5 or V6 (**Haissaguerre 1995**). Some patients show normal PR interval and typical LBBB-like pattern such as the present case. A preexcited ECG is more likely to occur in an atrioventricular decremental pathway (**Heal 1995**). Precordial transition (R/S =1) usually occurs at V4 to V6 such as the present case. Latent preexcitation has been reported, in patients with spontaneous LBBB-like antidromic tachycardia, without preexcitation at rest and during atrial pacing (**Davidson 2002**). A "concertina" effect is observed spontaneously in many patients. Anterograde conduction (**Gillete 1982**) over atriofascicular fibers yields a typical LBBB pattern with variable axis, superior frontal plane axis being the most commom one (ranging from -25° to -60° such as the present case), but it is of no help in differentiating it from the atrioventricular pathways. QRS complex is usually larger(the present case has 200ms) with anterograde conduction over an AP, with a slurred on QRS onset (**Bardy 1984**) due to distal muscular insertion, which can be better appreciated in the r wave of V2 to V4 (>40 ms in atrioventricular pathways) (**Haissaguerre 1995**).

ECG/VCG correlation in the frontal plane



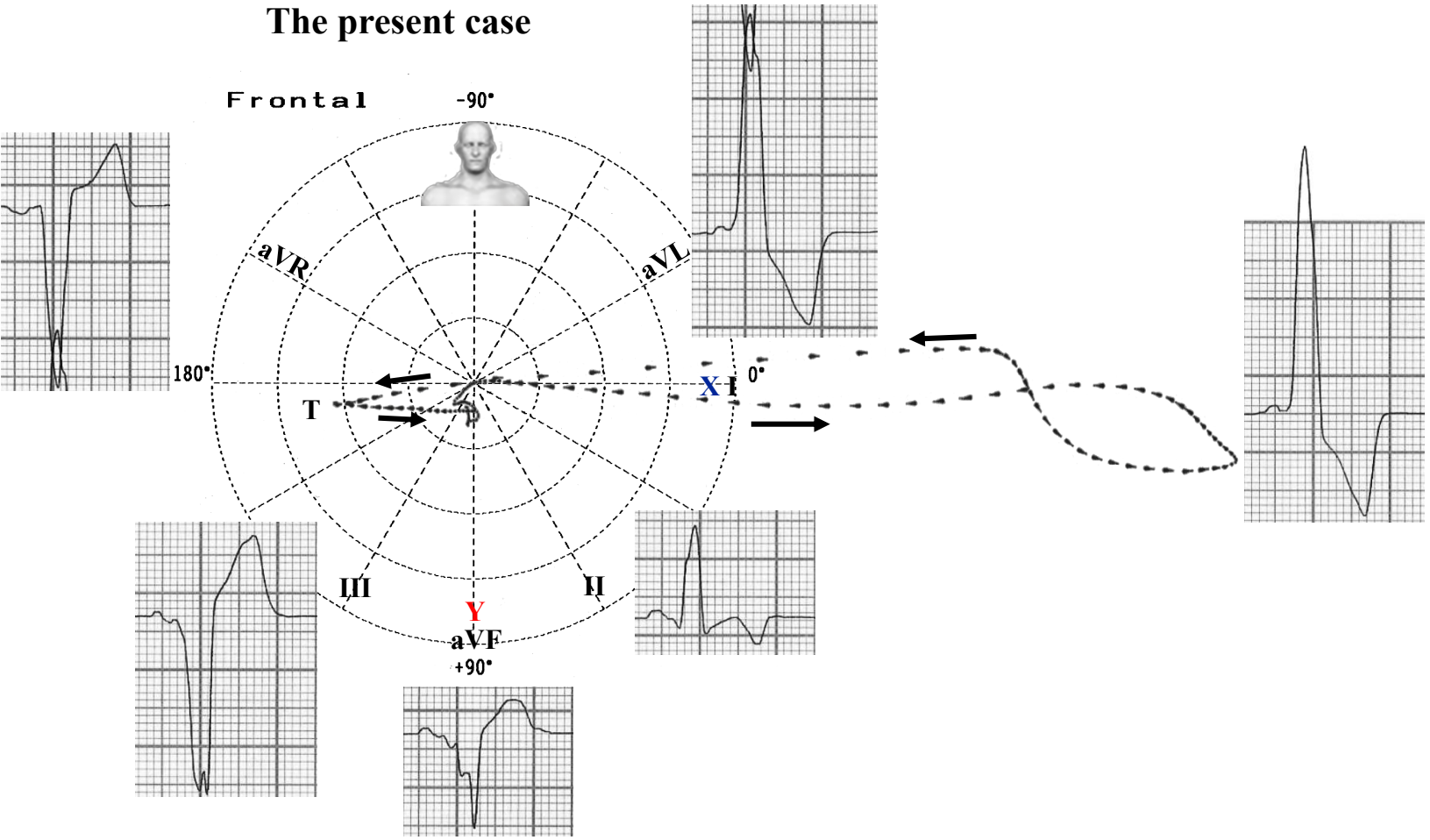
Left superior QRS axis is the most common in patients with atriofascicular or atrioventricular pathways ranging from -25° to -60° such as the present case. Pseudo inferior myocardial infarction in inferior leads III a aVF.



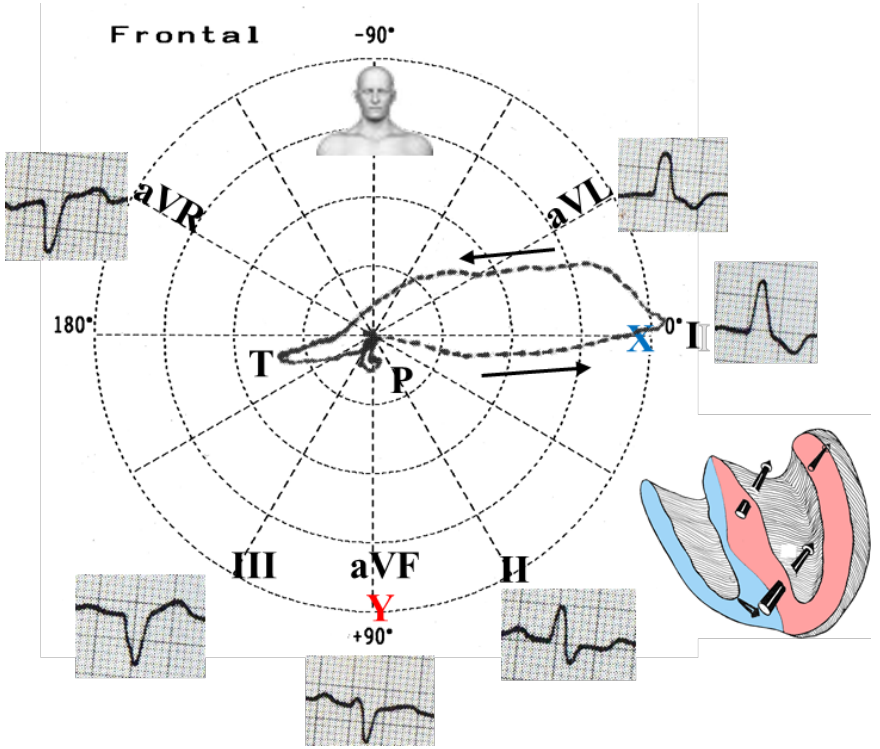
A slurred on QRS onset upstroke (δ) of the R-waves (red arrows) due to distal muscular insertion, which can be better appreciated in the R wave of V2 to V4 (>40 ms in atrioventricular pathways). Wide QRS interval with an initial slow deflection (delta wave). Wide QRSd = 200ms!!!

ECG/VCG correlation in the frontal plane

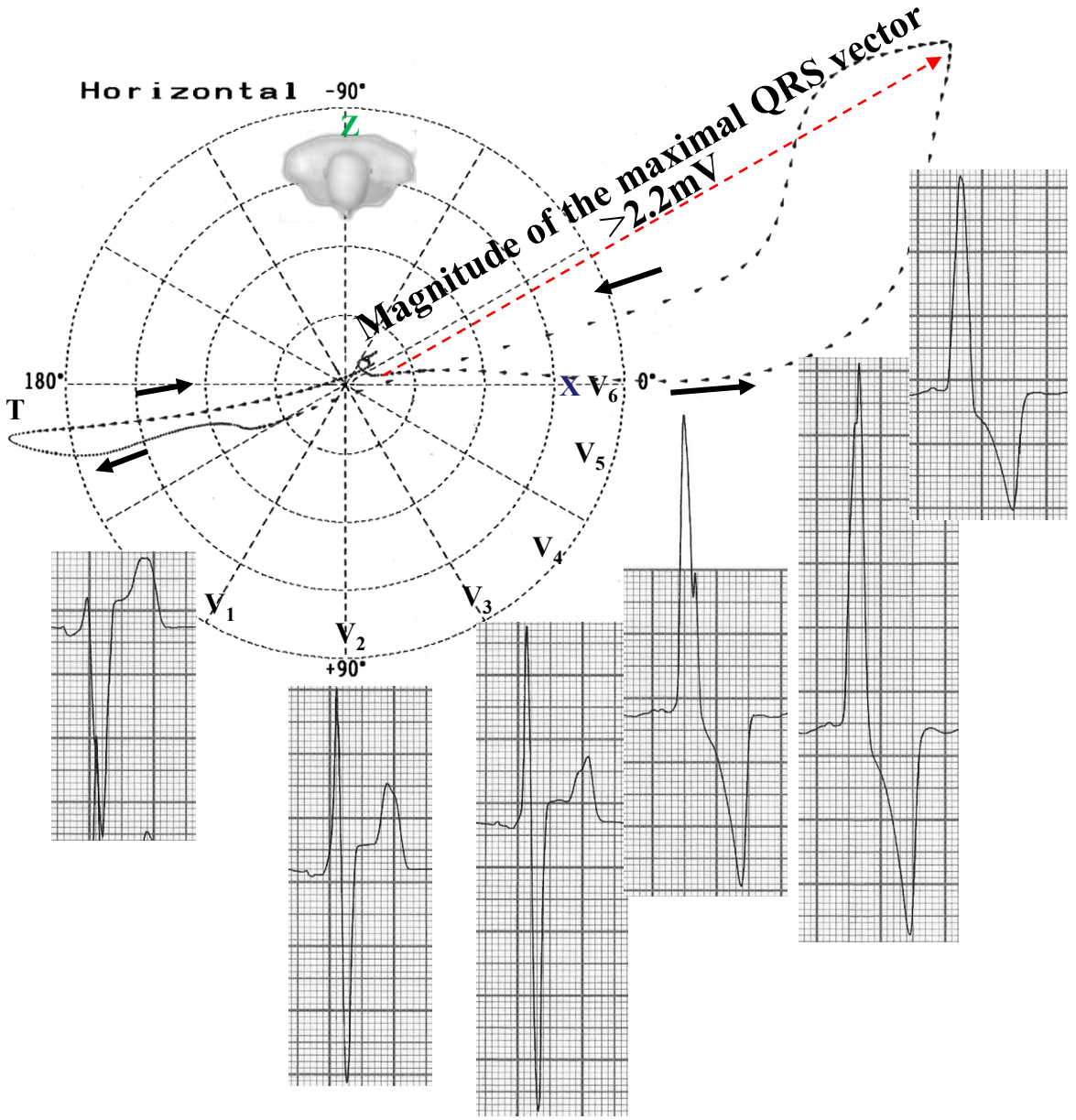
The present case



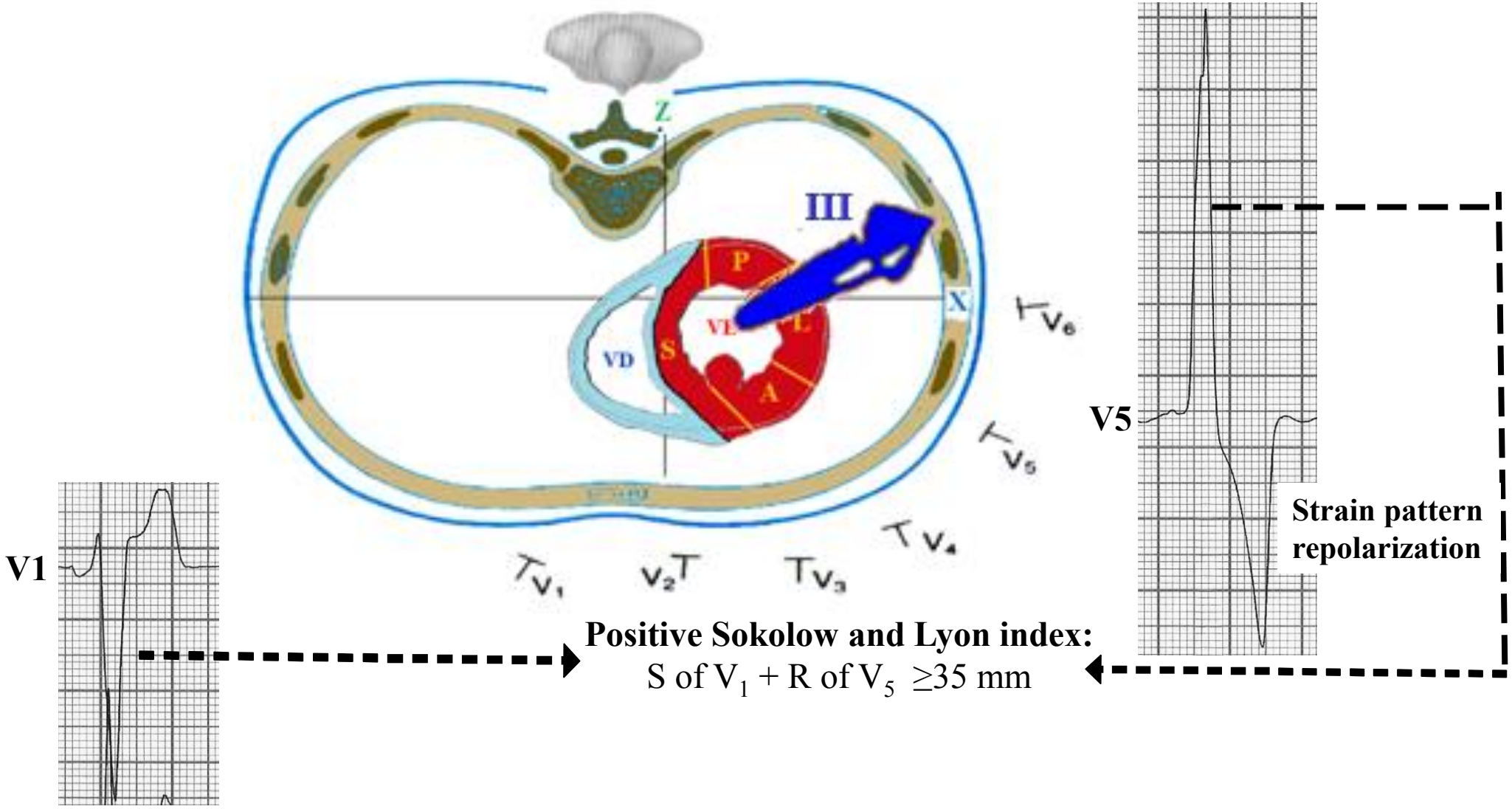
“true” LBBB



ECG/VCG correlation in the horizontal plane



Magnitude of the maximal QRS vector and T vectors are very augmented: The magnitude of maximal QRS vector e T vector is obtained from the 0 point up to the farthest point of the QRS loop and the magnitude of maximal T loop (normal values 2.2mV, 0.75mV respectively = LVH).

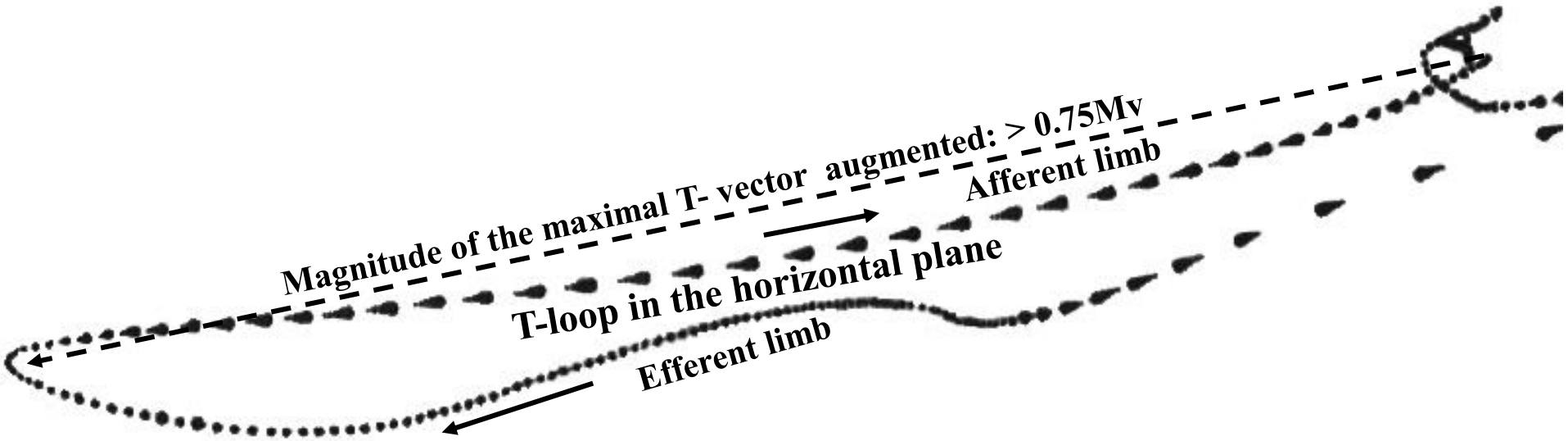


Positive Sokolow and Lyon index: S of V1 + R of V5 ≥35 mm or 3.5 mV in adults older than 30 years; ≥40 mm between 20 and 30 years; and >60 mm between 16 and 20 years old; and >65 mm between 11 and 16 years old.

In the present case SV1= 31mm + RV5= 56 mm = 87mm = LVH.

Strain pattern in the left precordial leads, ST segment depression of upper convexity is observed, followed by negative asymmetrical T wave with the downsloping part slower than the upsloping one. Note: in the Romhilt-Estes score system for LVH (**Romhilt-Estes 1968**), the presence of strain pattern yields a score of 3, and if in use of digitalis only 1.III-

T-loop in the horizontal plane

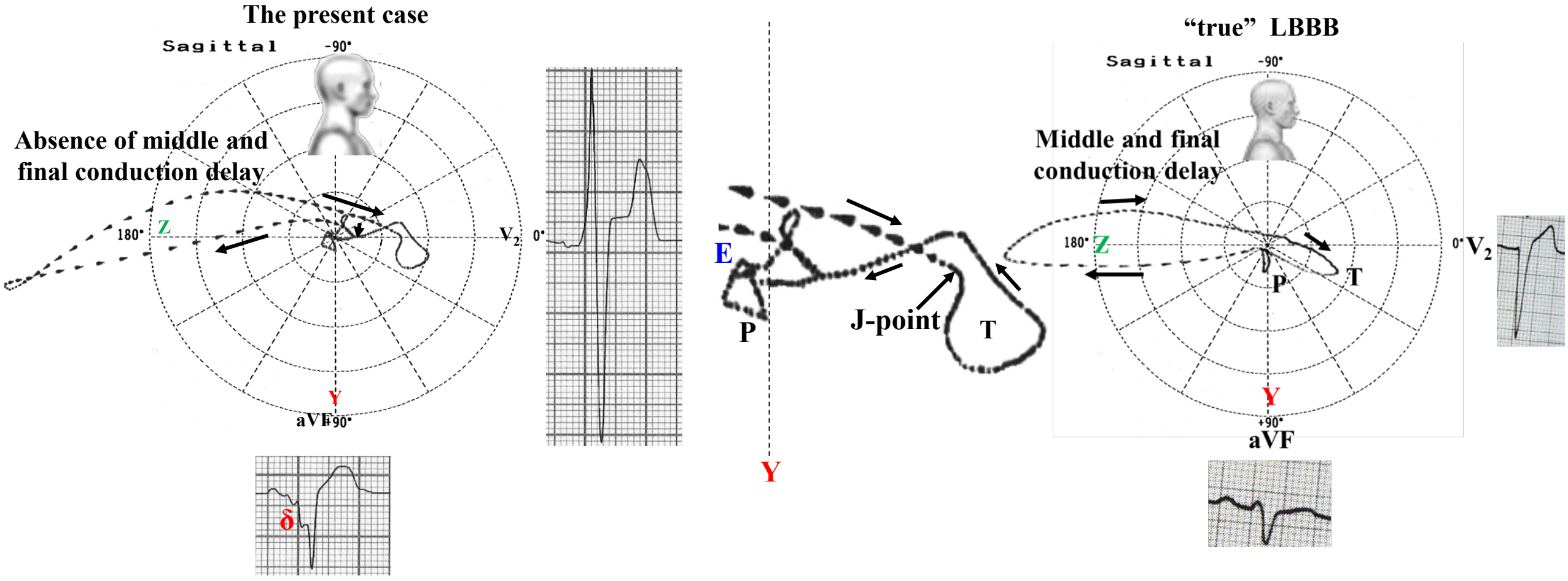


1) Elongated morphology
2) Efferent limb: with slow inscription(Corresponding to the ascending slope of the T): Comets more closely together.
3) Afferent limb with fast inscription. Comets separated from each other. Corresponding to the descending ramp of the T-loop
4) Secondary repolarization disturbance: Efferent limb with it comets more separates and afferent limb with comets more close one to another

Differential diagnosis between atriofascicular or atrioventricular pathways and LBBB (original observations)

	The present case	"true" LBBB
The QRS duration	Very broad: 200 ms	Always ≥120 msin adults, ≥100ms between 4 to 16years of age and ≥ 90ms in children less than 4 years of age. In "true" Strauss stricted criteria LBBB requires a QRS width of ≥130 ms (in woman) and ≥140 ms (in man) with mid-QRS notching or slurring in ≥ 2 contiguous leads (**Strauss 2011**).
QRS complexes after the 40 ms	Slowly and continuously widened "left bundle branch block like" QRS patterns are mostly occur in left ventricular hypertrophy or in a metabolic/infiltrative disease (**Préda 2013**).	After the 40th ms of the QRS notched/slurred R waves are characteristic in minimum two of I, aVL, V1, V2, V5 and V6 leads, in addition to a ≥40 ms increase of the QRS complex, as compared to the original. QRS complex. mid-QRS notching or slurring (**Tian 2013**).
The QRS loop shape	Elongated and narrow	Elongated and narrow
Initial 10 to 20 ms vector	Directed to the left and with initial delay (δ)	Directed to the left and anteriorly
QRS loop conduction delay	Initial conduction delay (δ)	Middle and final conduction delay
Main body of the QRS loop location in the HP	≈ -10° to -20°	≈ -60° to -90°
Main body QRS loop rotation	Counterclockwise	Clockwise
Magnitude of the max QRS vector	Very augmented >2.2 mV	Increased above normal exceeding 2 mV

ECG/VCG correlation in the right sagittal plane



E point: it indicates the onset of heart activation in the superior area of the right atrium(sinoatrial node (SAN; or sinus node)) In this point, the intersection of three orthogonal leads occurs (X, Z and Y).

0 point: it corresponds to the end of biatrial chamber activation, QRS loop onset (because PR segment does not exist, it is only a point) and the end of ventricular repolarization (T loop).

J point: in vectorcardiography, it corresponds to 3 elements: end of ventricular depolarization (QRS complex); beginning of repolarization (ST segment) when it does not present depression or elevation, and T wave onset.

Determinant condition of ventricular heart rate during AF in WPW syndrome

The following factors determine ventricular rate during AF

1) ***Refractory period duration of the AP in the anterograde direction***
2) ***Refractory period of the AV node***
3) ***Refractory period of the ventricle***
4) ***Concealed anterograde and retrograde penetration into the AP***
5) ***Sympathetic stimulation*** shortness the refractory period of the AP and accelerates the rate. It is important to terminate this tachycardia promptly and to reassure the patient in the meantime. A reflex sympathetic response to the ventricular rate: anxiety adds to this response. If the refractory period of the AP is short, the heart rate can exceed 300 bpm. This life-threating arrhythmia may deteriorate into VF.
6) APs highly sensitive to catecholamines may show intermittent preexcitation at baseline with potential for rapid conduction during AF and sudden death (**Gemma 2013**).

The overall risk of SCD in WPW syndrome is low, with reports ranging from 0.02% to 0.39% per year follow-up (**Fitzsimmons 2001; Blomstrom-Lundqvist 2003; Timmermans1995**). In patients at risk for SCD, AF may degenerate into ventricular fibrillation due to rapid AV conduction over the AP. Thus, **the risk of SCD is determined by the anterograde conduction properties** of the AP. The finding of intermittent preexcitation during sinus rhythm suggests the presence of an AP with long anterograde refractory periods and is thought to identify a group of patients at very low risk of SCD. Further risk stratification is not recommended for this subgroup of WPW syndrome patients (**Blomstrom-Lundqvist 2003; Klein 1983**). Distinguishing WPW AF from other wide-complex tachycardias is paramount such that proper treatment can be initiated. The ECG differential diagnosis for a patient presenting with an irregular, wide-complex tachycardia consists of AF with aberrant conduction, WPW AF, and polymorphic VT -TdP. Differentiation of these rhythms represents a challenge for even the most experienced physician., improper classification of a patient's rhythm can lead to therapeutic misadventures and potentially poor outcomes. Discriminating WPW AF from TdP and AF with aberrant conduction is challenging. Age and past medical history can certainly add to the clinician's

consideration of the patient presentation, with young healthy individuals being more likely to have WPW AF, whereas older individuals with a past cardiac history experience VT more often. TdP has very similar ECG characteristics as WPW AF: a widened QRS complex, changing R-R intervals with a HR of 150 to 300 beats/min, and a QRS complex that changes frequently. Certain subtypes of polymorphic VT, such as TdP, presents with an indulating baseline; in contrast, WPW AF usually has a stable ECG baseline with no alteration in the polarity of the QRS complexes. AF with aberrant conduction occurs when a patient with a preexisting BBB or a rate responsive BBB has a rapid ventricular response to AF. The ECG will show a wide complex tachycardia of irregular rate with stable beat-to-beat QRS configuration, contrasting the variable beat-to-beat QRS configuration in WPW AF. Treatment of patients with AF in WPW who are unstable (eg, hypotension, pulmonary edema, ischemic chest pain, and altered mentation) requires consideration for immediate electrical cardioversion. If the patient is stable, chemical cardioversion may be attempted with the patient being continuously monitored and with ready access to electrical cardioversion. Procainamide (30 mg/min, maximal dose 17 mg/kg) has traditionally been the treatment of choice for patients who are stable with WPW AF (**Cummins 2000**). By blocking fast inward Na current and outward K current, procainamide has been shown to prolong the effective refractory period of atrial, ventricular, and AP tissue as well as slow antegrade and retrograde conduction in the AP. Because of the potential for severe hypotension with rapid IV administration, procainamide requires a somewhat slow rate of infusion and also has a relatively slow onset of action, not reaching therapeutic blood levels for 40 to 60 minutes. Amiodarone (150 mg I Vover 10 minutes) is another agent used by practitioners for chemical conversion of patient's with a wide complex tachycardia and is quoted in the 2005 American Heart Association Advanced Cardiac Life Support guidelines as the bantiarrhythmic to consider in WPW AF (**Cummins 2000**). Q Although amiodarone, given orally, has been shown to be successful in treating recurrent atrial arrythmias, the consequences of rapid IV amiodarone administration are quite different because of its pattern of acute electrophysiologic effects. Short-term IV amiodarone administration modifies sinus and AV node properties with little, if any, effect on fast-channel tissues (ie, APs). This observation may be explained by the pharmacokinetic fact that accumulation of amiodarone's desethyl metabolite is responsible for much of the long-term effects on fast-channel tissues. Administration of IV amiodarone to patients in AF has been shown to cause acceleration of the ventricular rate and degeneration into VF. Taking these factors into consideration, the use of IV amiodarone for the treatment of patients identified as having WPW AF should be made with caution.

Ibutilide is a reasonable agent for management of AF in patients with WPW. As a class III antiarrhythmic agent, ibutilide prolongs the action potential duration and refractoriness by enhancing the slow inward sodium current and blocking delayed-rectifier outward K current, resulting in QT interval prolongation. It is given at a dosage of 1 mg (0.01 mg/kg for patients b60 kg) over 10 minutes and can be repeated once after a 10-minute period. It has a very short half-life of 4 hours; it does not interact with most of the medications that are used for rate control (β-blockers, diltiazem, verapamil, digoxin); its dosing requires no concern for hepatic or renal function; it is safe in elderly patients; and it is very rapid in

action, with a mean conversion time of approximately 20 minutes. In the non-WPW AF patient, the superiority of ibutilide over procainamide (**Vereckei 2001**) in the conversion of AF/flutter has been documented in numerous studies, with rates of conversion with ibutilide of 32% to 51% in patients with AF and 64% to 76% in patients with atrial flutter, compared with 0% to 21% in AF and 5% to 14% in atrial flutter with procainamide. Ibutilide had minimal effect on blood pressure, whereas procainamide reduced blood pressure significantly, with decreases in diastolic blood pressure up to 67 mm Hg. The safety and success of ibutilide in the conversion of AF to sinus rhythm in the ED were reiterated by Viktorsdottir et al (**Viktorsdottir 2006**) when they found ibutilide converted 64% of patients presenting with AF to sinus rhythm compared with 29% conversion with rate controlling drugs. Regarding patients with WPW, Glatter et al (**Glater 2001**) showed that ibutilide significantly prolongs the refractory period of APs and promptly decreases the HR response in patients with WPW AF. By prolonging the AP refractory period, ibutilide decreases the likelihood of a potential fatal ventricular arrhythmia, an essential characteristic for any drug given for treatment of WPW AF. Several case reports have had excellent results with ibutilide in treating wide complex AF and WPW AF. With a faster onset of action, a better conversion rate in patient's with AF/flutter, prolongation of the AP refractory period, and stable blood pressure profile, ibutilide may be superior to procainamide for chemical conversion of WPW AF. The primary concern with ibutilide use is the development of TdP due to prolongation of the QT interval. Patients who present with WPW AF, however, usually are young and have normal ventricular function, therefore placing them at a lower risk for ibutilide-induced arrhythmias. Patients identified as having WPW AF should not be treated with medications that prolong conduction through the AV node, such as digitalis compounds and calcium channel. The use of ibutilide in patients receiving class IC agents is as successful in restoring sinus rhythm and has a similar incidence of adverse effects as the use of ibutilide alone (**Hongo 2004**). FCA of anomalous APs is a strong therapeutic option for all patients, independent of the risk of SCD. However, RFCA is associated with serious complications, but many studies confirm an overall good prognosis for most of the patients with ECG pattern of ventricular preexcitation. Treatment with adenosine, which is the standard medical therapy of atrioventricular reentry tachycardia, led to the development of an irregular wide complex tachycardia, caused by fast ventricular response to AF. Adenosine may cause VF when administered during preexcited AF. This phenomenon is seen in patients having APs with short anterograde refractory periods ($\leq$ 250ms) and shortest R-R interval during AF (246 +/- 51 ms) (**Gupta 2002**). The antiarrhythmic properties of adenosine, its ultra-short half-life and the absence of frequent serious side effects make it a front-line agent in arrhythmia management, especially in the treatment of atrioventricular nodal reentrant tachycardia. Due to a shortening of atrial refractoriness, adenosine can facilitate the induction of AF mainly in patients with short AP antegrade refractory period. A patient history of AF is a contraindication for cardioversion with adenosine and needs to be assessed in children with reentry tachycardia. High-risk patients may potentially profit from prophylactic comedication with antiarrhythmic agents, such as flecainide, ibutilide, or vernakalant, before adenosine administration (**Hien 2016**). Both right- and left-sided APs can be mapped and ablated safely during pre-excited AF without delay, and acute success and recurrence rates and long-term follow-up results are similar to those of APs ablated during sinus rhythm (**Kose 2005**).

In young with WPW syndrome, occurrence of AF with a rapid ventricular response during EPS correlated well with a history of syncope and may be the cause of syncope in most patients. EPS may be helpful in identification of young patients with WPW at risk for syncope because all .patients with syncope and AF have a short RR interval between 2 consecutive preexcited QRS complexes during AF ≤220 ms. In contrast of patients without syncope (**Paul 1990**).

Spontaneous degeneration of atrioventricular reentrant tachycardia has been reported to represent the most frequent mode of initiation of AF during EPS.

Hemodynamic changes during tachycardia may lead to increased sympathetic tone, hypoxemia or increased tension of the atrial wall, thus, triggering AF. Induction of reentrant tachycardia during EPS has shown to be strongly correlated to its clinical prevalence and is inducible in up to 77% of patients with AF.

The pathogenesis and high incidence of AF in patients with WPW syndrome is related to presence and functional anterograde properties of the AP.

Atrial flutter/AF or wide-complex tachycardia is treated as follows: IV procainamide or amiodarone if wide-complex tachycardia is present, VT cannot be excluded, and the patient is stable hemodynamically Ibutilide. The initial treatment of choice for hemodynamically unstable tachycardia is direct-current synchronized electrical cardioversion, biphasic, as follows:

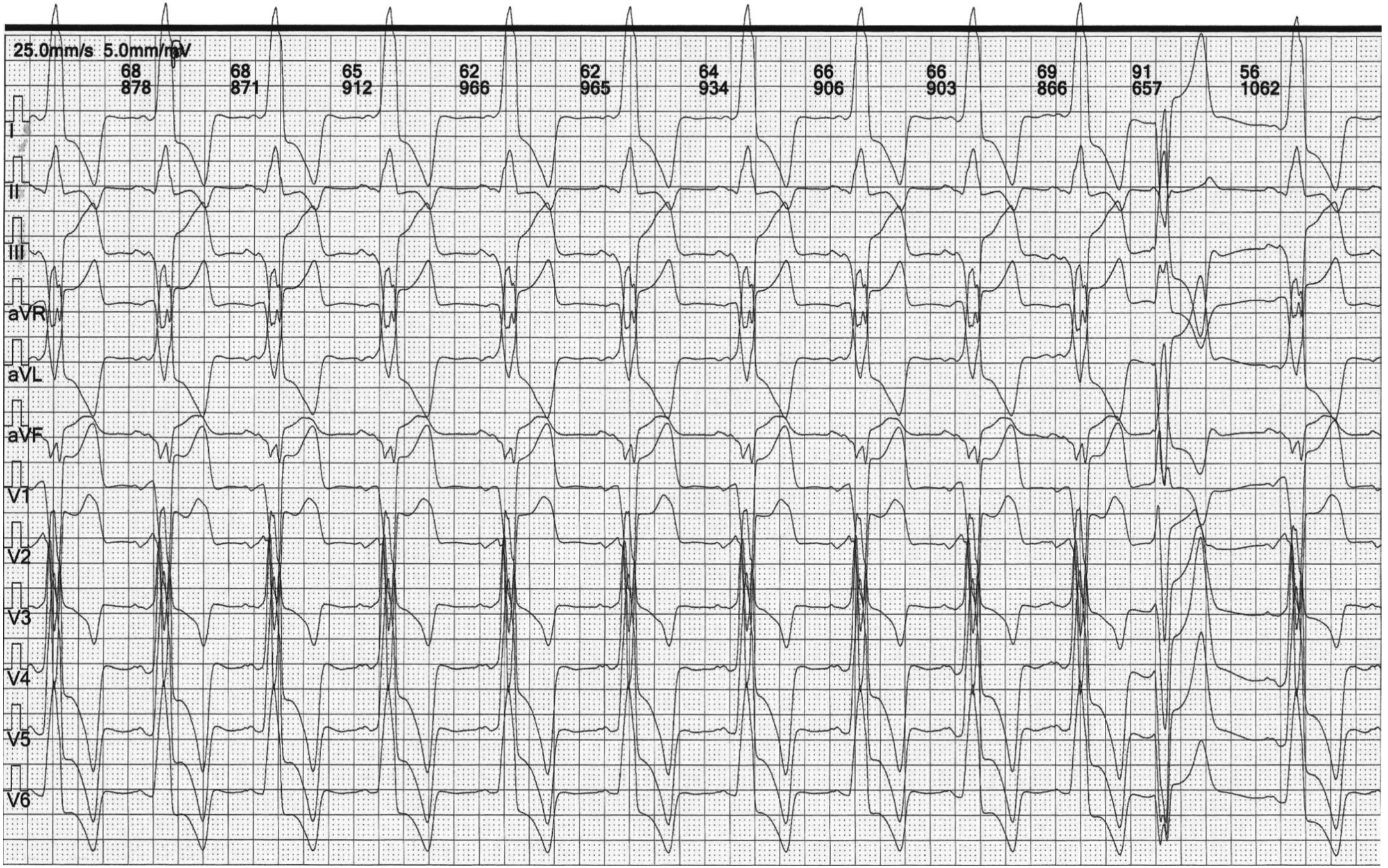
A. Level of 100 J (monophasic or lower biphasic) initially.
B. If necessary, a second shock with higher energy (200 J or 360 J).

Observation: Stable sustained wide QRS tachycardia, is associated with a high mortality rate and may be a marker for a substrate capable of producing a more malignant arrhythmia. ICD therapy may be indicated in patients presenting with stable VT (**Raitt 2001**).

Radiofrequency Catheter ablation (*RFCA*): RFCA is indicated in the following patients: 1. symptomatic AVRT; 2. AF or other atrial tachyarrhythmias that have rapid ventricular response via an AP (preexcited AF); 3. Patients with AVRT or AF with rapid ventricular rates found incidentally during EPS for unrelated dysrhythmia, if the shortest preexcited RR interval during AF is 250 ms (**Calkins1991**). 4. Asymptomatic patients with ventricular preexcitation whose livelihood, profession, insurability, or mental well-being may be influenced by unpredictable tachyarrhythmias or in whom such tachyarrhythmias would endanger the public safety (**Calkins 2012**). 5. Patients with WPW and a family history of SCD.

Surgical treatment RFCA has virtually eliminated surgical open heart treatments in the vast majority of WPW patients, with the following exceptions: I. Patients in whom RFCA (with repeated attempts) fails; II. Patients undergoing concomitant cardiac surgery (possible exception); III. Patients with other tachycardias with multiple foci who require surgical intervention (very rare).

Date: January 31, 2017



Preexcitation by tracts and connections (old Mahaim-type preexcitation)

The term *Mahaim-type preexcitation* is not recommended because the diagnosis cannot be made with certainty on the basis of the surface ECG (**Surawitcz 2009**). During pathologic examination of the heart, Mahaim and Benatt (**Mahaim 1937**) identified islands of conducting tissue extending from the His bundle tissue into the ventricular myocardium. These fibers were termed fasciculoventricular fibers (Mahaim fibers). This description was subsequently expanded to include connections between the atrioventricular node(AV-Node) and the ventricular myocardium (nodoventricular fibers). These findings have been confirmed by other investigators, but true continuity of these pathways is less common than was initially suspected (**Anderson 1975 Lev 1955; James 1961**).

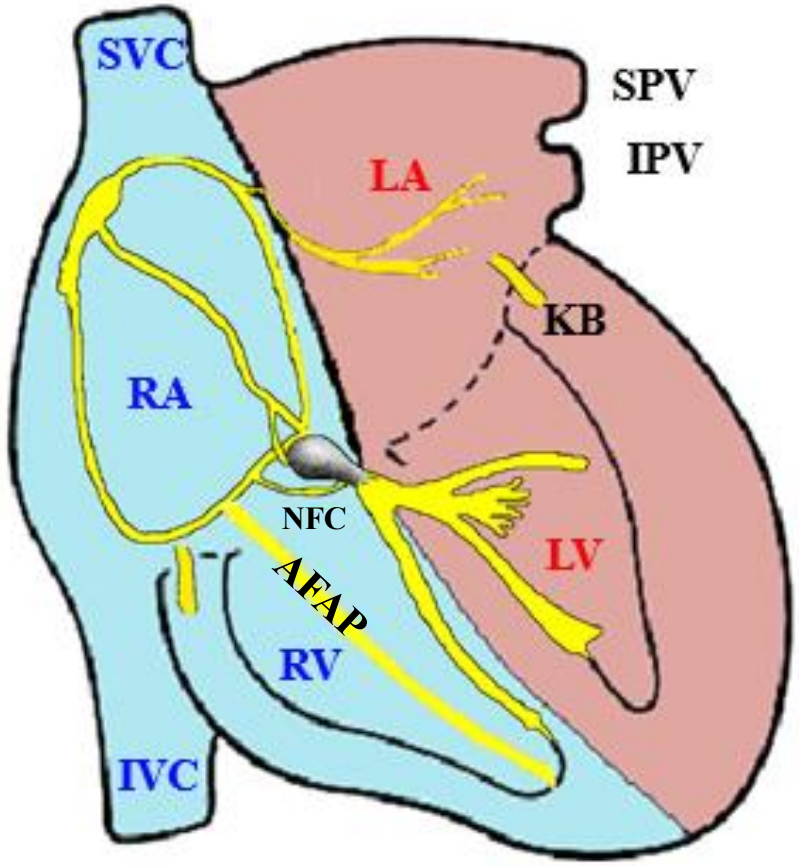
A) Tracts: Nodofascicular, atriofascicular fibers or atrioventricular pathway (pseudo-Mahaim)

B) Connections: Nodoventricular fibers, fasciculoventricular and atrioventricular.

Definition: A form of ventricular pre-excitation characterized by a **normal** PR interval and wide QRS interval with an initial slow deflection (δ wave) (**Wellens 1971; Sternik 2003; Hanon 2005**). In this syndrome, the atrial impulse travel to the ventricle via the Mahaim fibers which connect atrioventricular node directly to the right ventricle wall apex (nodoventricular accessory pathway) or to the right bundle branch of His (nodofascicular accessory pathway). There are anomalous accessory pathways that starting from the AV node, or the His bundle, or its branches, or even from the atrial muscles, end in the right ventricular contractile myocardium (**connections**) or insert into the conduction-specific tissue fibers (**tracts**), frequently in the right bundle branch of the His bundle. The fibers that originate in the conduction system after the AV node, present normal-duration PR interval in ECG, and if they end in the right septal contractile muscle (nodoventricular connections and fasciculo-ventricular), by slowly activating initially the RV (δ wave), the QRS pattern becomes similar to complete LBBB (Mahaim type pre-excitation). Reentry tachycardia typically has LBBB morphology.

Summary: Right sided accessory pathways connecting either AV node to ventricles, fascicles to ventricles, or atria to fascicles ECG features: Sinus rhythm ECG may be normal. May result in variation in ventricular morphology.

Atrioventricular pathways



Atriofascicular accessory pathway (AFAP): Its proximal insertion is located on tricuspid annulus and its distal insertion in the RV ápex Purkinje network. These fibers have decremental conduction properties but lesser than the AV node one. **NFC** – Nodofascicular Connection.

This is the explanation for LBBB like pattern. Sterninck et al showed electrophysiological evidence suggesting a long AV AP inserting close to the distal RBB rather than an atriofascicular connection in this patient with a Mahaim fiber (**Sternick 2004**).

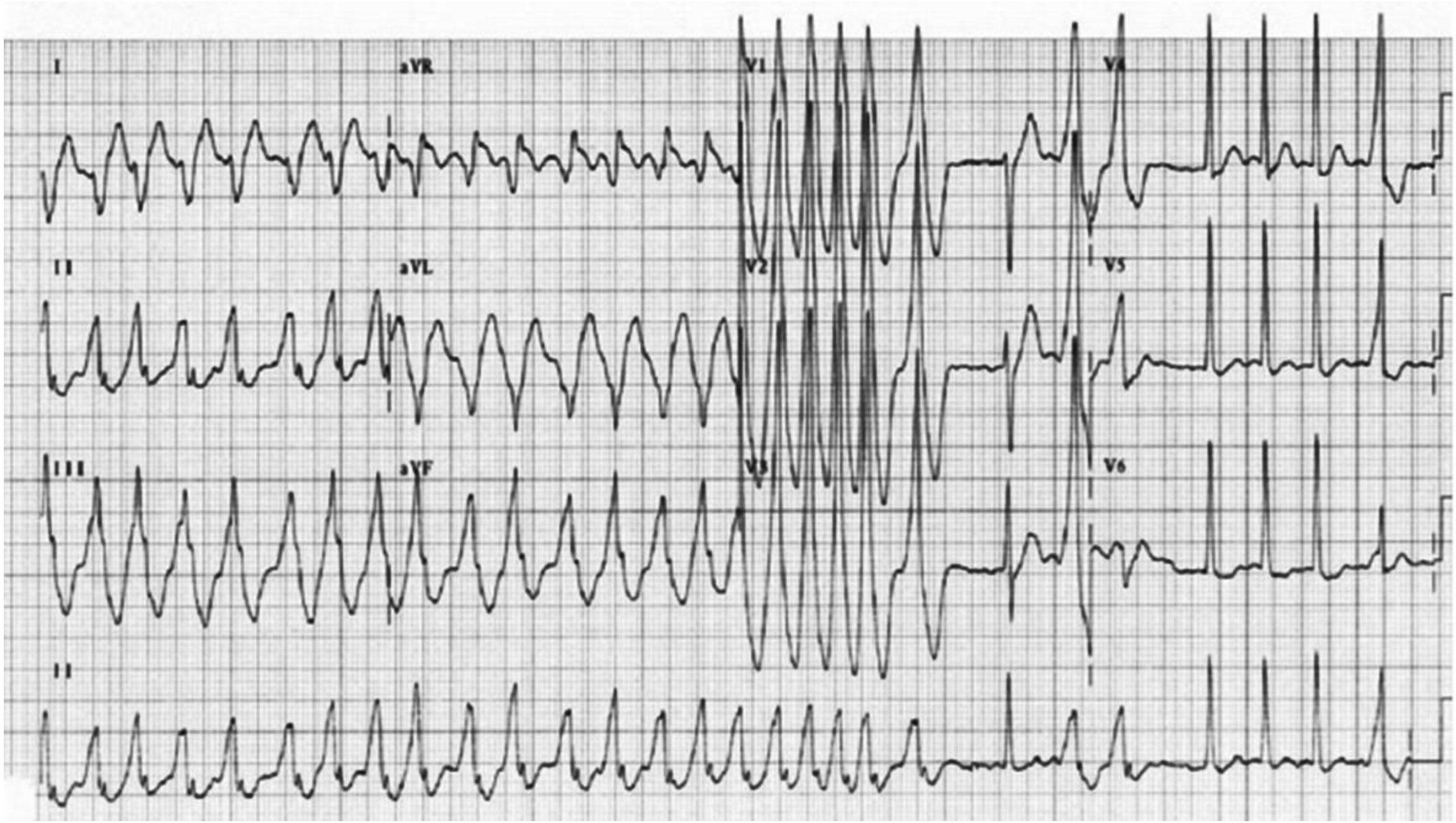
Electrocardiogram and electrophysiological features of patients with atriofascicular or atrioventricular pathways (pseudo-Mahaim).

A. During sinus rhythm

1. Minimal, latent or no pre-excitation, without pre-excitation at rest and during atrial pacing **(Davidson 2002)**.
2. Eventual absence of septal Q wave in left precordial leads V5 or V6 (**Haissaguerre 1995**).
3. Frequent rS pattern in III lead. This pattern disappears after ablation. A narrow QRS with an rS pattern in lead III during sinus rhythm in a patient with a history of palpitations should alert the physician to the possibility of a Mahaim fiber (**Sternick 2004**).
4. Normal AH interval and short HV interval (between 10-20 ms).
5. Decremental conduction across AFAP.

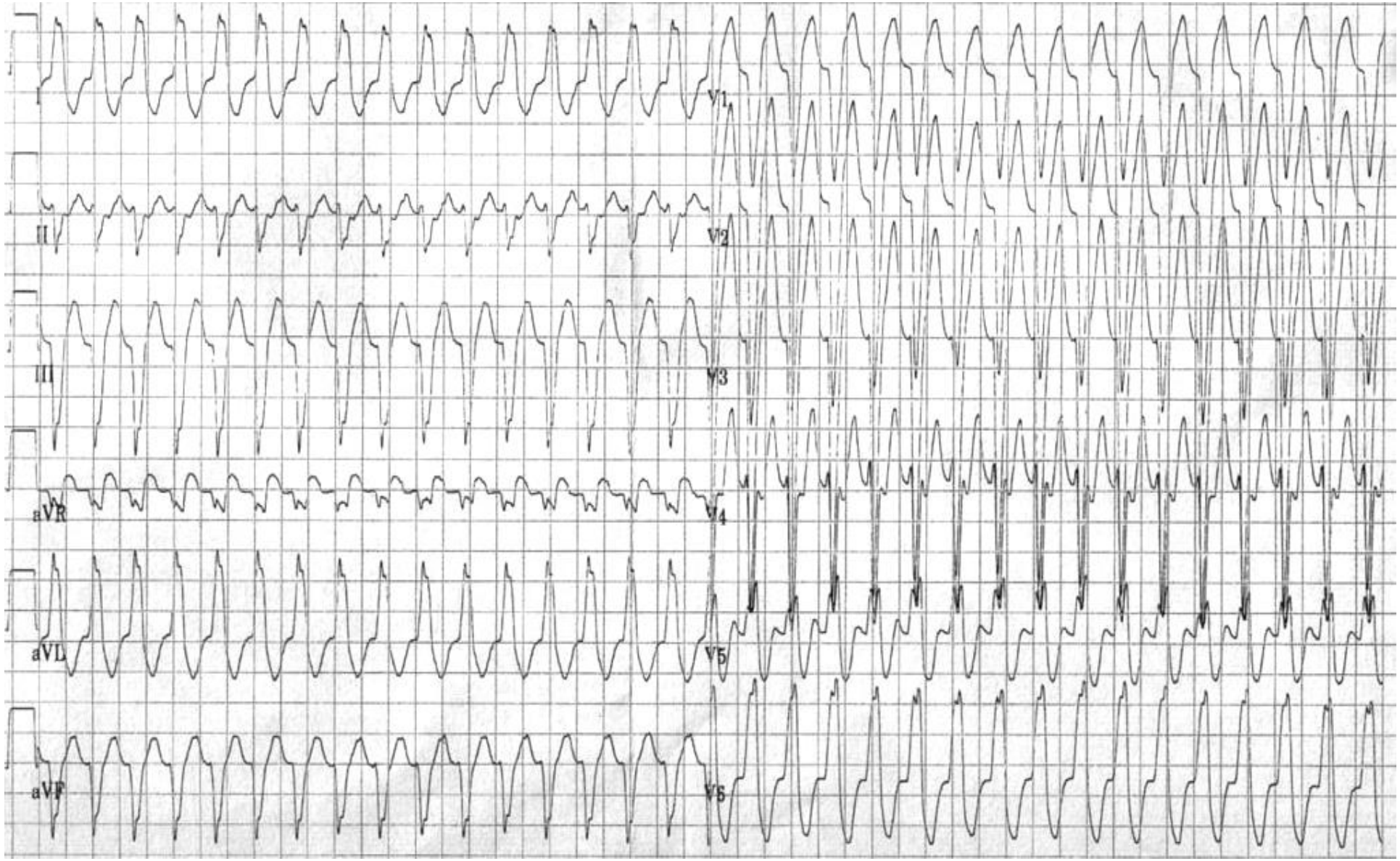
B. During the events (LBBB-like antidromic tachycardia):

1. Typically left bundle branch block-like QRS complex with left axis deviation from -25° to -60° or intermediate.
2. QRS duration <150 ms (always < 180 ms).
3. Precordial transition predominantly at V4-V5 or V6 (**Heal 1995**).
4. Eventually QS pattern from V1 to V6 with transition in V7-V8 in cases of clockwise rotation of the heart around longitudinal axis (**Volders 2003**).
5. Anterograde conduction over atriofascicular fibers: Broad QRS, slurred QRS onset (**Bardy 1984**) due to distal insertion, which can be better appreciated in the r wave of V2 to V4 (>40 msc) (**Haissaguerre 1995**).
6. Absence of dissociation AV because atrium is integrant of the circuit.
7. Always 1:1 AV conduction (absence of AV dissociation) with V-A interval > 70 ms.



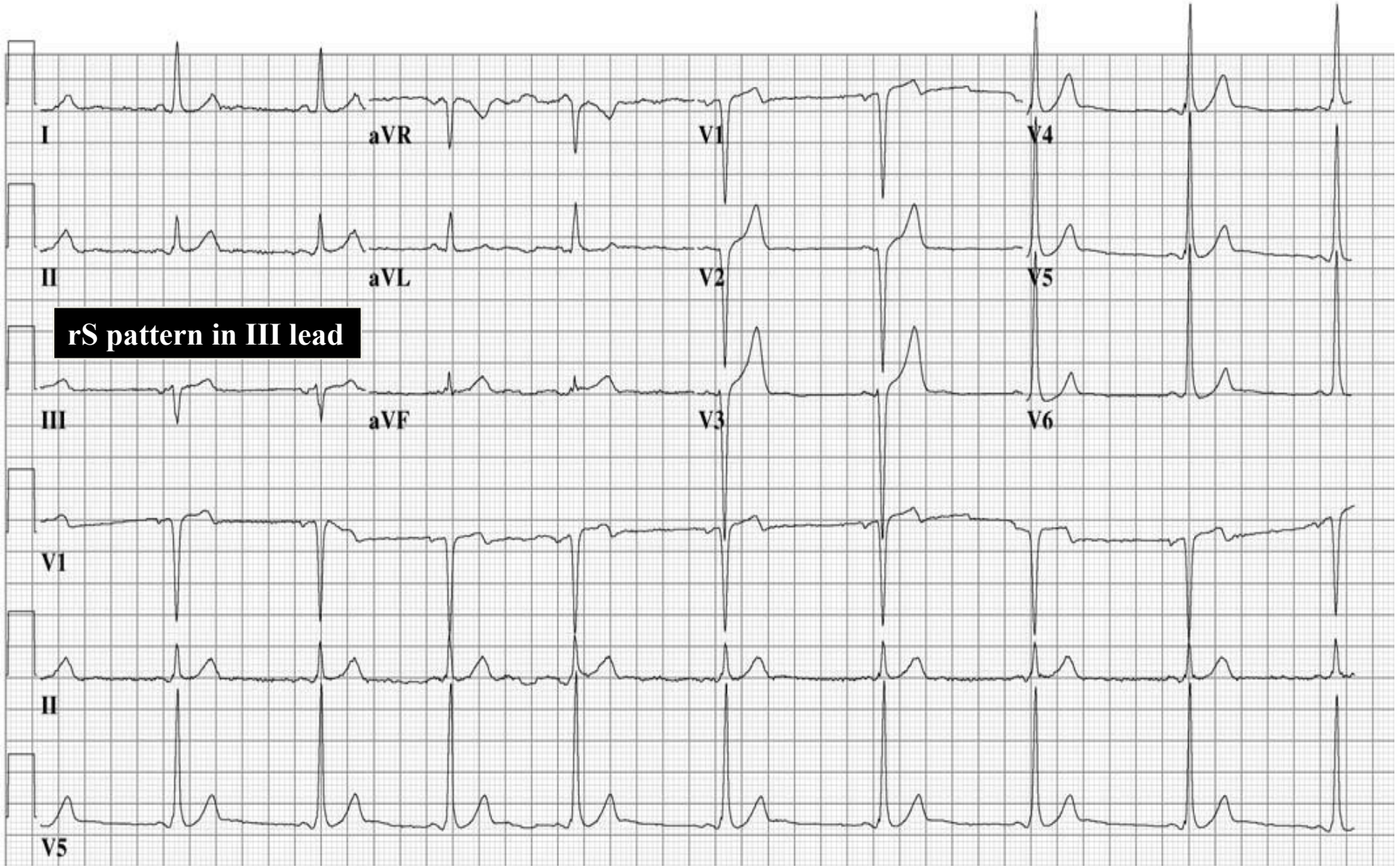
ECG diagnosis: AF with fast preexcited ventricular response. The shortest preexcited R–R interval measured 230 ms. δ wave morphology negative in leads I and aVL and positive in V1 suggests a left lateral AP. Numerous fusion and capture beats.

Example of antidromic tachycardia over atriofascicular pathway



ECG performed during event of antidromic tachycardia over atriofascicular pathway. QRS complexes show LBBB pattern with transition zone in V5, which suggests that the distal insertion of the portion of the pathway attached on RV apex. There is no AV dissociation because the atrium is integrant of the circuit.

Typical rest ECG in a patient with atriofascicular accessory pathway



Atriofascicular accessory pathway (AFAP): Minimal pre-excitation, PR interval 110 ms with minimal delta wave insinuation. Absence of initial q wave in left leads (I, aVL, V5 and V6), and rS pattern in III.

Fasciculoventricular pathway

These are uncommon accessory pathways that connect the bundle of His or its branches with the ventricular septal myocardium. Once these accessory pathways have been identified, they do not need to be eliminated because they are not associated with sustained tachycardia (**Arias 2014**).

ECG and EFS of fasciculoventricular pathway:

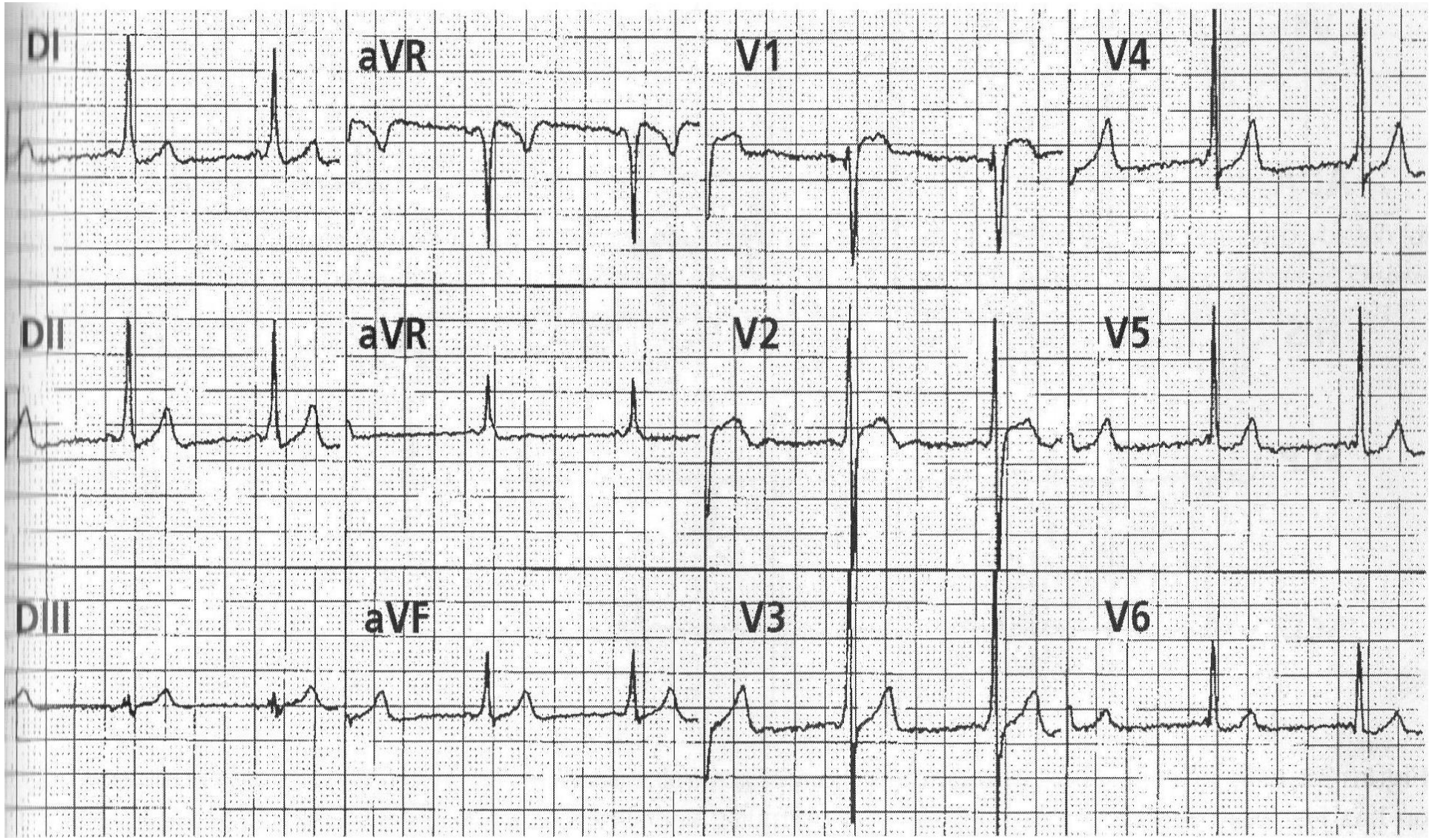
- Normal QRS axis (0° to +75°).
- Normal or minimal short PR interval by enhanced A-V nodal conduction.
- Precordial transition at V2 or V3 indicative of an anteroseptal or midseptal pathway.
- Eventual initial q wave in V1 lead (indicative of right side initial depolarization).
- Atrial pacing do not change the degree of preexcitation.
- Junctional beats are preexcited.
- Intravenous adenosine yields blocked P waves (very important for differential diagnosis with genuine WPW.
- Short HV interval of 10 ms (15 to 25 ms).

Differential diagnosis

	Fasciculoventricular pathway	Genuine WPW
PR interval	Normal or short	Short
IV adenosine or verapamil	Pre-excitation does not change PR interval prolongation and posible blocked P wave	Increasing the degree of pre-excitation Absence of blocked P wave
Symptomatology	Assymptomatic without clinical importance easy no invasive diagnosis	Frequent tachyarrhythmias

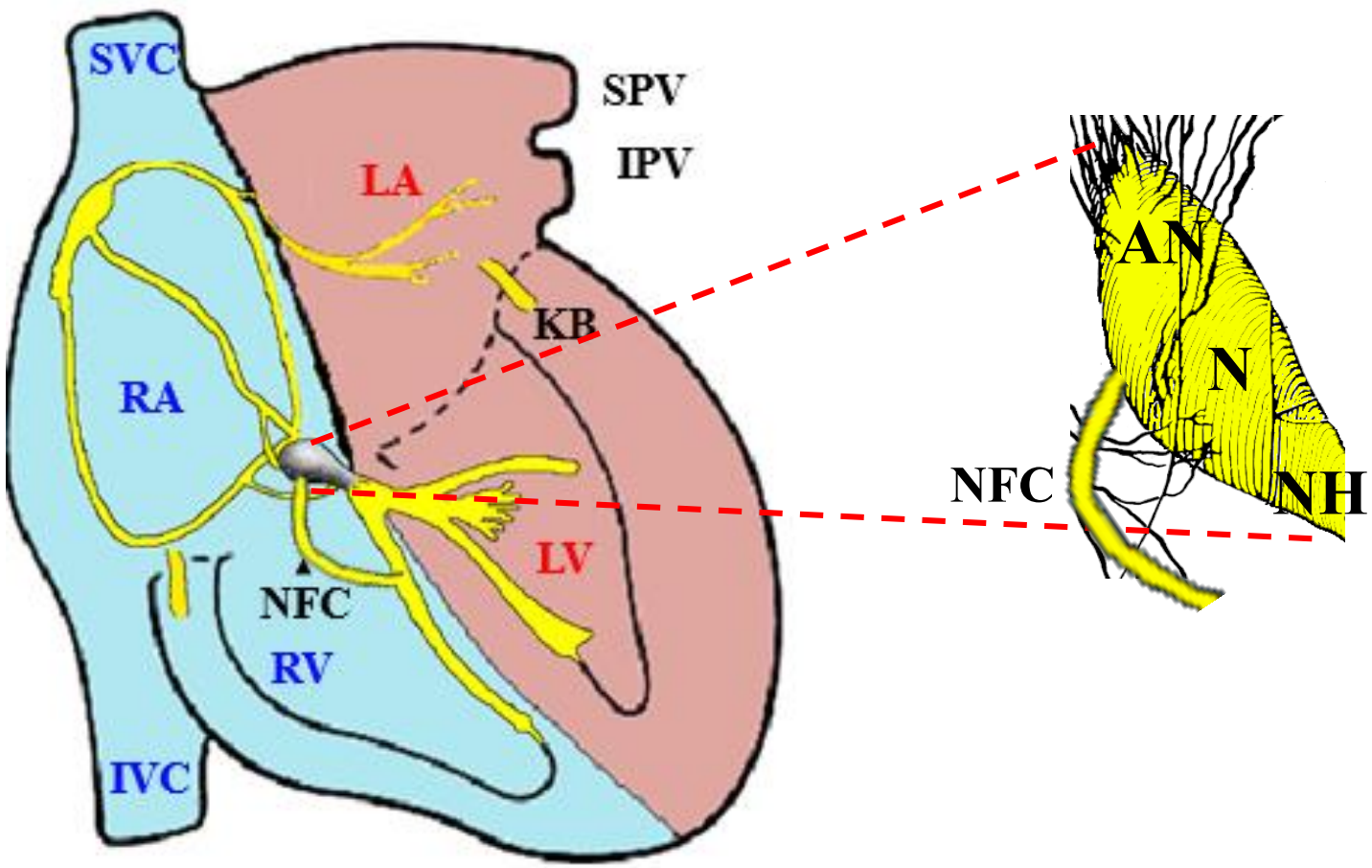
ECG of a patient with fasciculoventricular pathway

Courtesy Dr. Daniel Dasso



ECG diagnosis: initial q wave in V1 indicative that the beginning of ventricular activation occurs on the right side.

Nodofascicular connection (NFC) or nodoventricular pathways



Concept of NFC: They are bundles that connect any AV nodal area (usually N region) with right bundle branch.

SVC – Superior Vena Cava; **IVC** – Inferior Vena Cava; **RA** – Right Atrium; **LA** – Left Atrium; **SPV** – Superior Pulmonary Vein; **IPV** – Inferior Pulmonary Vein; **KB** – Kent Bundle; **NFC** – Nodofascicular Connection; **AN** – Atrionodal portion of AV node; **N** – Nodal portion of AV node; **NH** – Node AV Hisian portion

ECG and EPS of nodofascicular connection (NFC) or nodoventricular pathways

1. Absence or minimal pre-excitation (observation: His bundle stimulation normalizes QRS complex).
2. During the events prolonged QRs duration with LBBB-like pattern with or without AV dissociation (**Mantovan 2000**). The presence of AV dissociation is an important factor of differential diagnosis atriofascicular accessory pathway (AFAP).
3. Eventual dual AV nodal conduction. Evans and et al presented a case of a patient with a nodoventricular tract, associated with dual AV nodal conduction and AV nodal reentrant tachycardia, and an anteroseptal location of the slow AV nodal pathway. The remarkable feature of this case was the site of successful ablation, in the anteroseptum just anterior and superior to the His bundle, where both preexcitation and dual AV nodal physiology were abolished (**Evans 1999**).
4. It is possible orthodomic tachycardias when existing retrograde conduction.
5. Absence of Mahaim potential on tricuspid ring.

Hypertrophic cardiomyopathy and ventricular preexcitation relationship

Clinicians have long recognized the association of WPW syndrome with autosomal dominant familial hypertrophic cardiomyopathy. However, only comparatively recently was a genetic substrate linking hypertrophic cardiomyopathy to WPW syndrome and skeletal myopathy described (**Gollob 2001**). Patients with mutations in the gamma 2 subunit of adenosine monophosphate (AMP)-activated protein kinase (PRKAG2) develop cardiomyopathy characterized by ventricular hypertrophy, WPW syndrome, AV block, and progressive degenerative conduction system disease. MutationPRKAG2-gene is a rare cause of hypertrophic cardiomyopathy (HCM) and characteristicaly shows phenotypic heterogeneity. Müllertz et al. studied in a same family presenting with paroxismal AF, pre-excitation with short PR interval and EPS with or without APs, and AV block with syncopes and atrioventricular (AV) block requiring a DDD pacemaker implantation (**Müllertz 2016**).

Another mutation is believed to produce disruption of the annulus fibrosus by accumulation of glycogen within myocytes, which causes preexcitation. This is thought to be the case in Pompe disease, Danon disease (DD). Several features may contribute to the early and severe cardiac phenotype in female DD patients. The type of mutation may account for the early disease onset, while both the inhomogeneous distribution of LAMP2 loss and the presence of microvascular remodeling may be determinant in the rapid progression to heart failure (**Botillo 2016**). Infantile Pompe disease or glycogen-storage disease type II is a fatal genetic muscle disorder that is caused by deficiency of acid alpha-glucosidase (GAA). These patients have a shortened PR interval, large left ventricular (LV) voltages, and an increased QT dispersion (QTd).

Bowles et al have identified a novel locus in a family with WPW, *MYH6* p.E1885K. All of the family members with WPW but none of the unaffected relatives demonstrated this variant. *MYH6* variants have been associated with atrial septal defects, cardiomyopathies, and sick sinus syndrome (**Bowles 2015**). Mutations in the lysosome-associated membrane protein 2 (LAMP2), which cause accumulation of cardiac glycogen, are thought to be the etiology of a significant number of hypertrophic cardiomyopathies in children, especially when skeletal myopathy, WPW syndrome, or both are present. APs are considered congenital phenomena that are related to a failure of insulating tissue maturation within the AV ring—even though their manifestations are often detected in later years, making them appear to be "acquired“. On rare occasions, acquired WPW syndrome has occurred in patients who have undergone congenital heart surgery, which may be owing to an acquired functional epicardial AV connection (**Khairy 2014**). Family studies, as well as molecular genetic investigations, indicate that WPW syndrome, along with associated preexcitation disorders, may have a genetic component. It may be inherited as a familial trait, with or without associated congenital heart defects (CHDs) (**Ehtisham 2005**); 3.4% of those with WPW syndrome have first-degree relatives with preexcitation. The familial form is usually inherited as a mendelian autosomal dominant trait. Although rare, mitochondrial inheritance has also been described. The syndrome may also be inherited. with other cardiac and noncardiac disorders, such as familial atrial septal defects, familial hypokalemic periodic paralysis, and tuberous sclerosis.

Cardiac manifestations in Fabry disease (FD) are mainly characterized by left ventricular hypertrophy (LVH), such as hypertrophic cardiomyopathy. Additionally, conduction defects, valvular deficiencies, and myocardial infarctions are cardiac manifestations of FD in some patients.

In FD, two-dimensional speckle strain imaging shows a loss of base-to-apex in global and segmental longitudinal and circumferential strain CS gradient may be a specific LV deformation pattern of Fabry cardiomyopathy in patients with and without LVH (**Labombarda 2017**). The following table shows clues for differential diagnosis of FD and HCM.

Summary of the nine criteria that were pre-selected based on the systematic review. with sensitivity and specificity calculation (Smid 2014)

Fabry diagnosis	Entry criteria	Sen.%	Spec.%	Exit criteria	Prev.
ECG	PQ interval minus P wave duration > 40 ms (**Namdar 2012**) Corrected PQ interval b 144 ms (**Namdar 2012**)	82 82	99 90	Low voltages: Sokolow–Lyon index of ≤1.5 mV total QRS amplitude in I, II, III b 1.5 mV (**Hoigne 2006, Namdar 2012**)	0
Echo	• Increased papillary muscle • LV wall ≥ 12 mm • When LV wall is > 13 mm (39)	75 100	86 ND		
CMR				▪ LVOTO ((**Kounas 2008; Pieroni 2006**) ▪ Pericardial effusion (**Hoigne 2006**) ▪ CMR Late enhancement in papillary muscles (**Pieroni 2006;-Niemann 2011**)	0 0 0

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Journal of Electrocardiology

January 15, 2017

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