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(CASE REPORT)

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Cardiovascular disorders in a patient with Fabry disease: A serious prognostic factor

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Abstract

Fabry disease (FD) is an inherited rare metabolic disease caused by a mutation in the GLA gene, encoding the lysosomal enzyme alpha-galactosidase A. The disorder is a systemic disease that manifests as cerebrovascular and cardiac disease, chronic renal failure, skin lesions, peripheral neuropathy, and other abnormalities. Arrhythmias, cardiac conduction disorders, and sudden deaths in Fabry diseases represent the main prognostic factors and are usually hard to manage. We describe here the case of a 56-year-old woman followed for Fabry disease with conductive and rhythmic cardiac involvement. Our case illustrates the pivotal role of critical clinical thinking in the management of rare but treatable hereditary cardiomyopathy like Fabry disease.

Keywords: Fabry Disease; Arrhythmias; Conduction Disorders; Cardiovascular Implantable Electronic Devices; Anticoagulation.

1. Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by a deficiency in the enzyme α-galactosidase A (AGAL-A), secondary to mutations in the GLA gene. These mutations lead to the progressive accumulation of globotriaosylceramide (Gb3) in lysosomes of different types of cells, including those of the heart, and may lead to different clinical scenarios (1). This condition is earlier and more severe in men, and due to the intense targeted screening, the prevalence in the Western world has dramatically increased (1 in 2500) (2). Cardiac damage starts early in life, progresses sub-clinically before significant symptoms occur, and usually manifests as left ventricular hypertrophy (LVH) (3). Arrhythmias, cardiac conduction abnormalities, and sudden death represent the most common cardiovascular causes of death in Fabry disease and represent a real therapeutic challenge (3).

2. Observation

We report in our article the case of a 56-year-old woman followed for Fabry disease. In addition, our patient is the mother of two children that have been diagnosed and treated for the same condition from a young age; she has also been followed for arterial hypertension for seven years and has been treated with a combination of Amlodipine 5 mg and Diltiazem 60 mg. Our patient self-presented to our cardiac exploration unit with heart palpitations, atypical chest pain, and nausea over a period of 2 months. Her clinical exam was normal, with stable vitals and no sign of right or left heart failure. The 12-lead electrocardiogram showed a RBBB and a LAFB (bifascicular block) with premature bigiminy ventricuclar contractions; the PR duration was normal at 170 msec as well as that of the QT at 430 msec (Figure 1). The transthoracic echocardiography revealed restrective cardiomiopathy with normal left ventricular ejection at 71% (Figure 2; a, b, c).

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The coronary angiography revealed unobstructed coronary arteries apart from a fortuitous discovery of an incipient coronaro-cameral fistula of the proximal circumflex artery, which does not explain the symptomatology of our patient (Figure 3; a, b).

The 48-hour Holter ECG detected paroxysmal atrial fibrillation with no other significant arythmias or cardiac conduction disorders. Otherwise, an electrophysiological exploration was performed and revealed a moderate lengthening of infra-hissal conduction, not aggravated by increasing atrial pacing, with an AH interval of 57 msec and an HV interval of 62 msec, with no indication for immediate pacemaker implantation (Figure 4; a, b, c). It should be noted that the biological analyses were without anomalies.

In terms of treatment, and given the presence of paroxysmal atrial fibrillation, our patient was put on Rivaroxaban 20 mg per day. Concerning conduction and rhythm disorders, neither immediate pacing nor implantable cardioverter-defibrillators (ICD) were indicated; nevertheless, a Holter ECG and a follow-up electrophysiological exploration are necessary at one year.

3. Discussion

The multisystem nature of FD means that patients can present with a variety of symptoms. Classic FD in males is characterized by the onset of symptoms in childhood, absent or severely reduced (<1% of normal) AGAL-A enzyme activity and microvascular endothelial Gb3 accumulation (4) However, genetic analysis remains the reference diagnosis for Fabry disease (5).

Typical manifestations include angiokeratoma, hypohidrosis, peripheral neuropathy, premature stroke, microalbuminuria and proteinuria, renal insufficiency, and cardiomyopathy (4).

Cardiac involvement is frequent in FD. Patients develop hypertrophic cardiomyopathy (HCM), arrhythmias, conduction abnormalities, and valvular abnormalities. This symptomatology becomes evident in men at 32 years of age and in women at 40 years (5, 6).

Palpitations are reported by 15% to 43% of adult patients, depending on sex and stage of the disease, and the most frequent cause is probably atrial arrhythmia. Heart failure symptoms are reported in up to a quarter of patients. In the majority of patients, LV ejection fraction is normal, and symptoms are caused by increased LV diastolic pressures (4).

The ECG can contribute to the diagnosis, revealing in particular signs of ventricular hypertrophy and a short PR. In elderly patients, it is especially necessary to look for sinus bradycardia, progressive conduction disease, supraventricular or ventricular arrhythmia, which presents a marker of poor prognosis. For this reason, regular 24-hour ambulatory ECG monitoring is recommended in these patients, or even electrophysiological exploration in some cases (4, 7).

Echocardiography is the most useful method for diagnosing and monitoring FD-related cardiomyopathy. Typical findings include concentric LV remodeling or hypertrophy without resting LV outflow tract obstruction (3, 4).

The most common rhythm and conduction disorders in FD are supraventricular and ventricular arrhythmias. According to cross-sectional studies, AF affects about 5% of men and 3% of women (8).

Maintenance of sinus rhythm rather than rate control is recommended for patients with FD and AF. All patients with AF and atrial flutter should receive anticoagulation with DOACs or VKAs unless contraindicated (4).

Pacing may be considered if there is chronotropic incompetence in the symptomatic patient, associated with resynchronization if there is ventricular dysfunction and/or a wide QRS > 120 msec (4).

An ICD is recommended in patients who have survived a cardiac arrest due to ventricular tachycardia or fibrillation, or who have spontaneous sustained ventricular tachycardia causing syncope or hemodynamic compromise and have a life expectancy of >1 year (4).

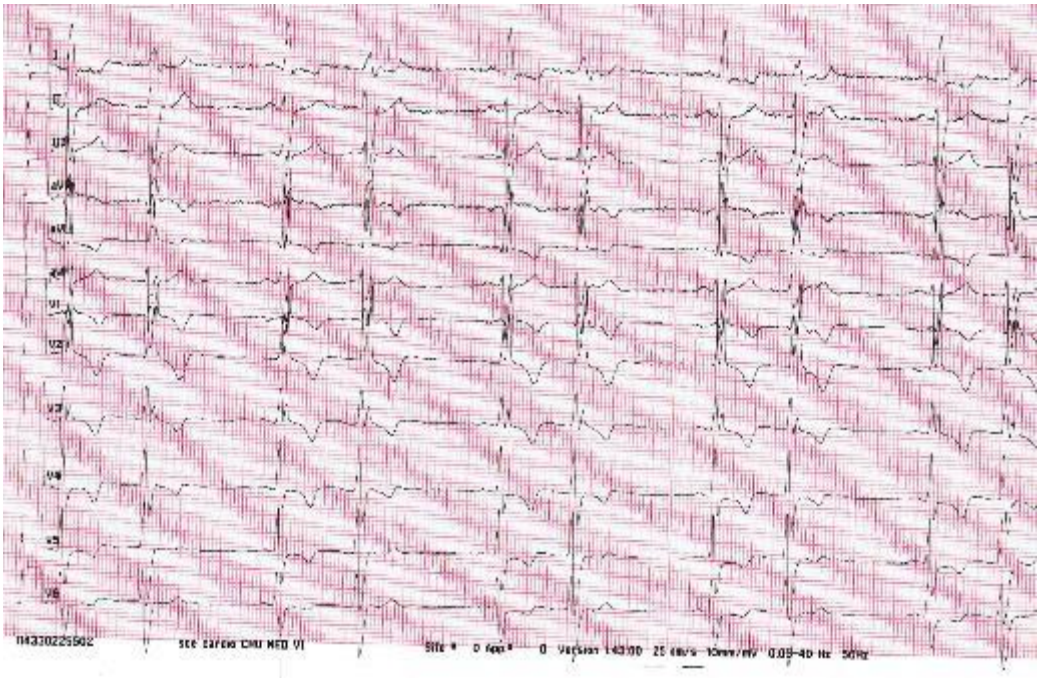

Figure 1 The 12-lead electrocardiogram showed a RBBB and a LAFB (bifascicular block) with premature bigiminy ventricuclar contractions; the PR duration was normal at 170 msec as well as that of the QT at 430 msec.

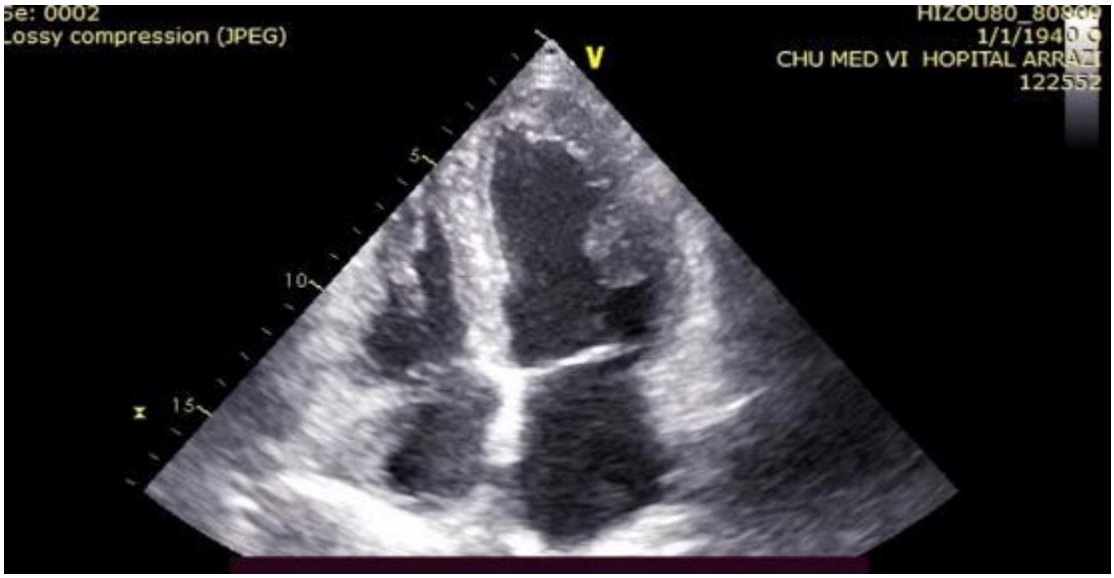

Figure 2a Transthoracic echocardiography, four chamber view : biventricular hypertrophy with dilatation of the left atrium.

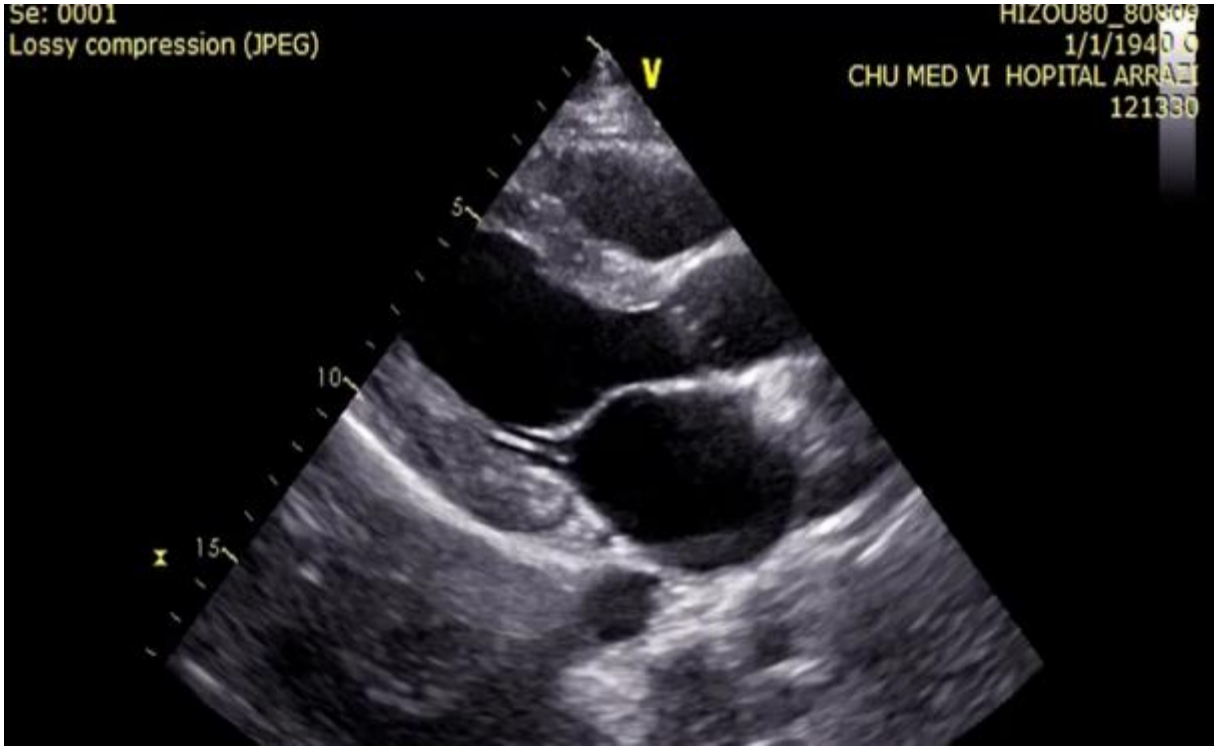

Figure 2b Transthoracic echocardiography, parasternal long axis view : non-dilated hypertrophied left ventricle

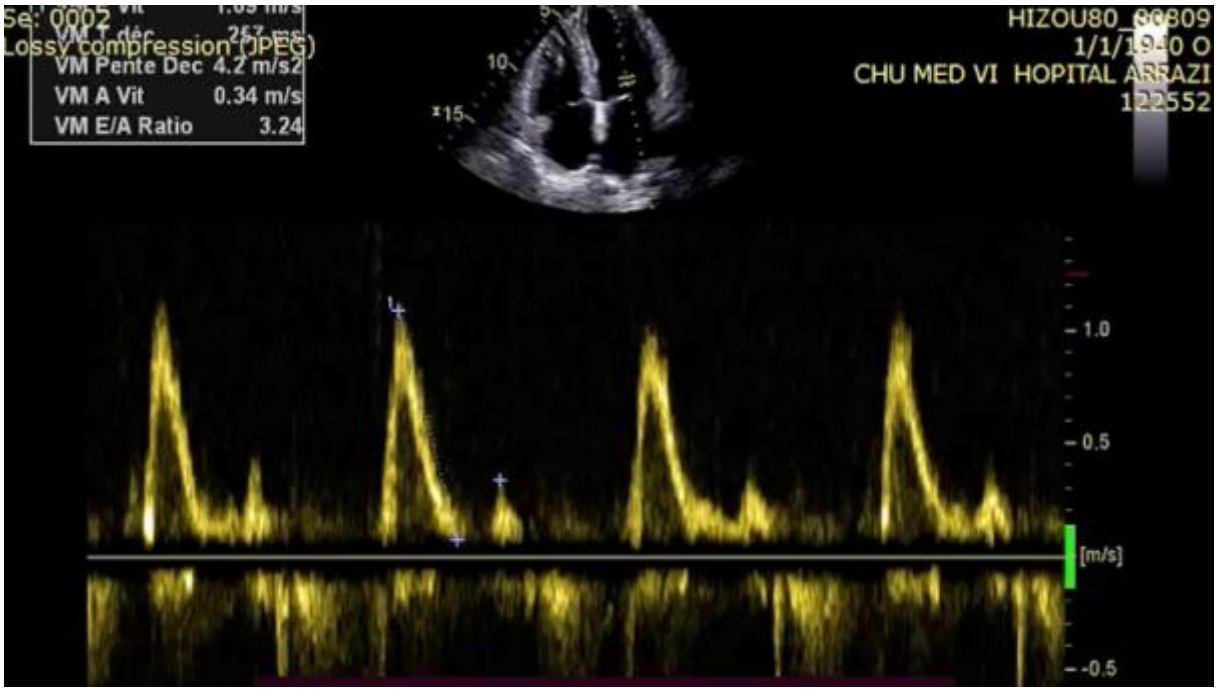

Figure 2c Pulsed-wave Doppler of the Mitral Valve : restrictive mitral inflow.

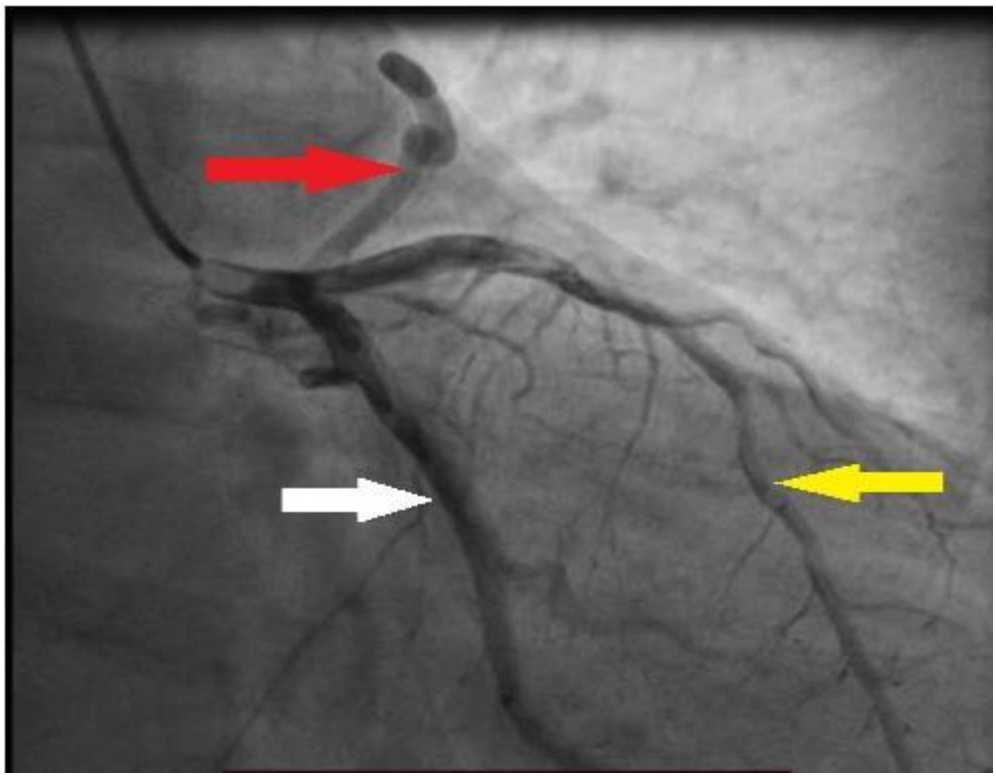

Figure 3a Coronary angiography, RAO caudal projection: circumflex artery (white arrow); anterior descending artery (yellow arrow); coronaro-cameral fistula of the proximal circumflex artery (red arrow)

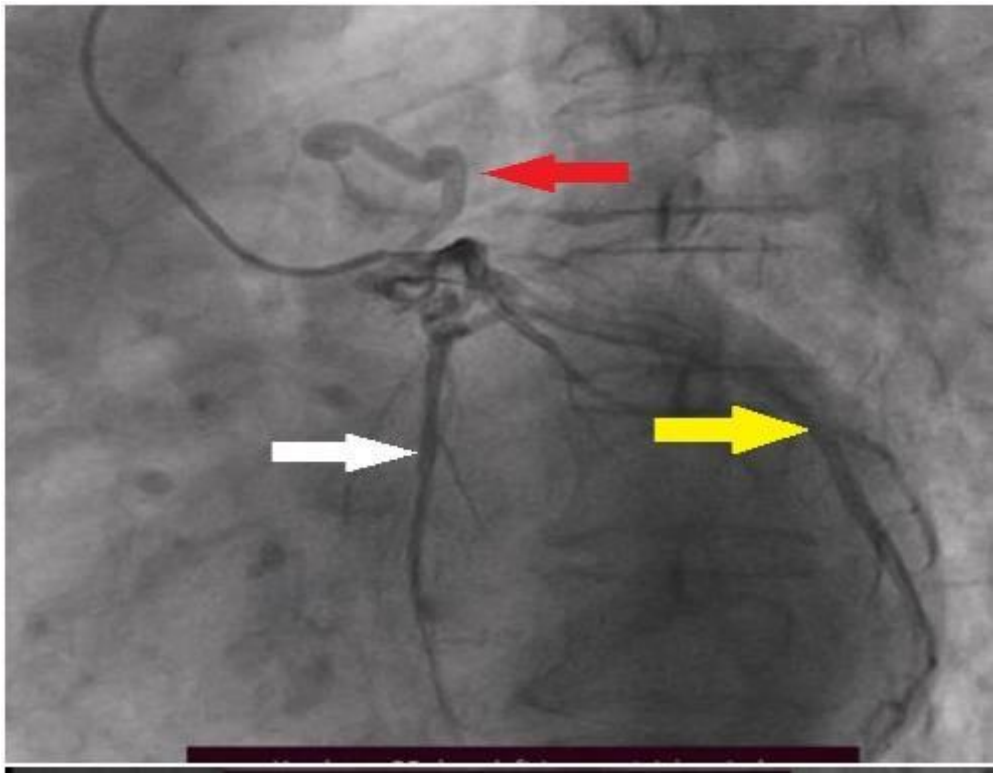

Figure 3 b Coronary angiography, PA caudal projection: circumflex artery (white arrow); anterior descending artery (yellow arrow); coronaro-cameral fistula of the proximal circumflex artery (red arrow)

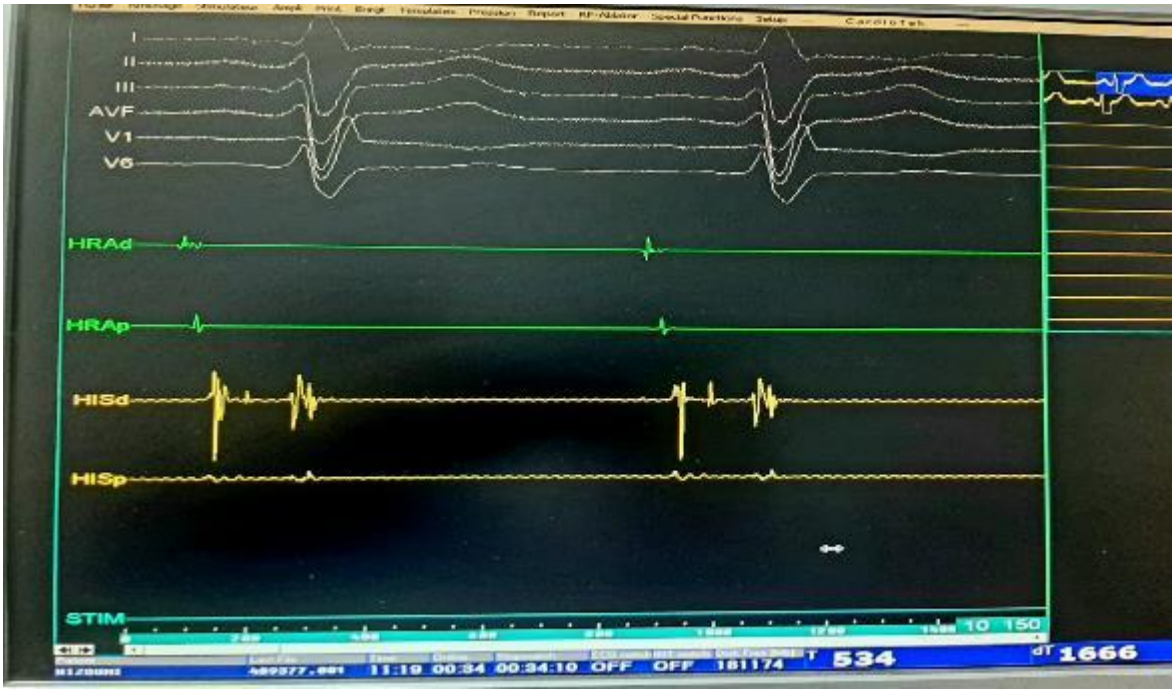

Figure 4 a Endocavitary electrophysiological exploration

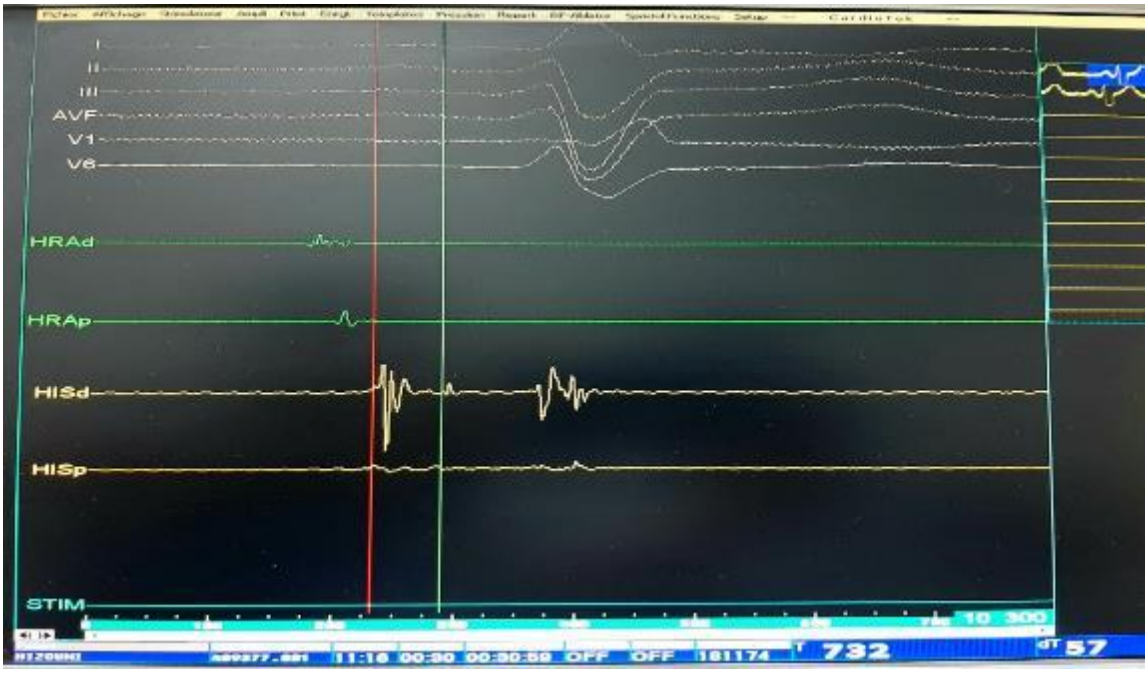

Figure 4 b Endocavitary electrophysiological exploration: an AH interval of 57 msec

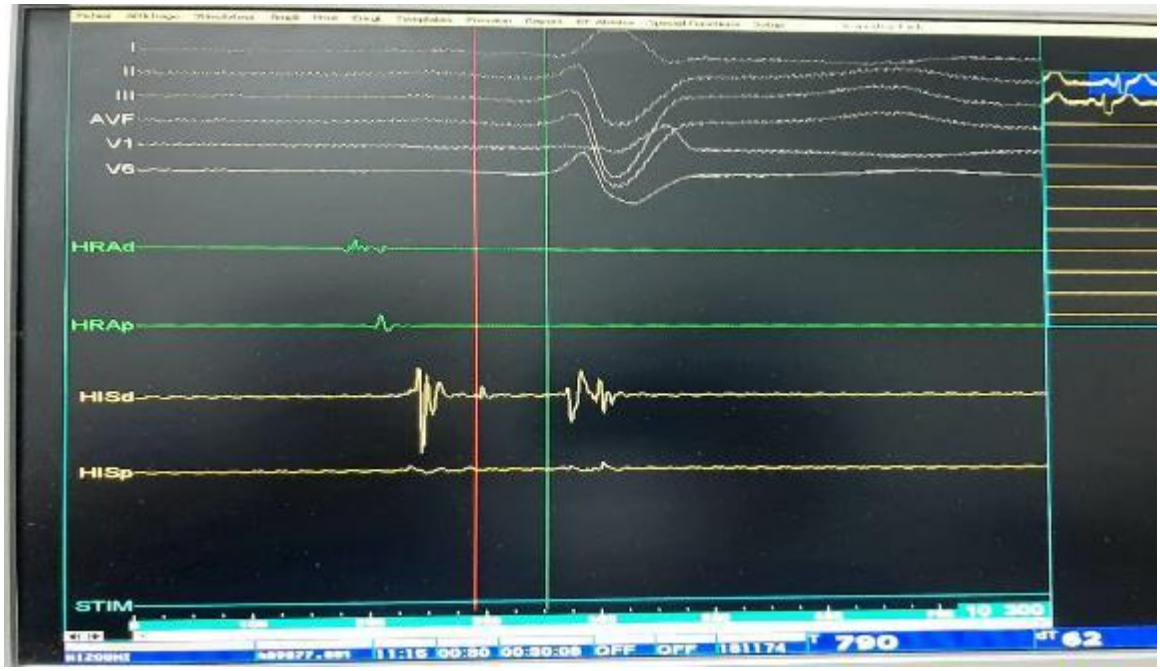

Figure 4c Endocavitary electrophysiological exploration: an HV interval of 62 msec

4. Conclusion

Patients with FD require a multidisciplinary approach, including a systematic cardiac evaluation. Recent advances in our understanding of the complexity of FD have significantly improved diagnostic and therapeutic approaches, particularly for cardiovascular manifestations where screening and treatment should be personally adapted to each patient.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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