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BRIEF COMMUNICATION

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Prevalence and predictors of bradyarrhythmias requiring permanent pacing in patients with Anderson–Fabry disease

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Abstract

Introduction: Bradyarrhythmias are an established red flag for storage cardiac conditions including Anderson–Fabry disease (AFD). The prevalence of bradyarrhythmias requiring a pacemaker (PM) and their timing in AFD is unresolved.

Methods: We evaluated the prevalence and predictors of PM requirement in a large AFD cohort, investigating the occurrence of bradyarrhythmias as initial versus late manifestation. We retrospectively evaluated 82 consecutive AFD patients referred to our multidisciplinary referral center from 1994 to 2020 with a median follow-up of 6.9 years, identifying those requiring pacing. Univariable analysis was performed to identify cardiac features associated with PM implantation.

Results: Five of 82 (6%) AFD patients required PM implantation (5/39, i.e., 13% of those with cardiac involvement), always in the context of advanced cardiomyopathy. In none, bradyarrhythmias were the presenting feature. Indications included sick sinus syndrome in three patients, advanced atrioventricular block in two patients. QRS prolongation during follow-up strongly correlated with the onset of bradyarrhythmias.

Conclusion: Severe bradyarrhythmias are relatively frequent in patients with AFD cardiomyopathy, but do not represent a mode of presentation, occurring late in the disease course and always in the context of advanced cardiac involvement. Monitoring QRS variations over time may help to identify patients requiring pacing.

KEYWORDS
Anderson–Fabry disease, bradyarrhythmias, pacemaker

1 | INTRODUCTION

Bradyarrhythmias are an established red flag for storage disorders, including Anderson–Fabry disease (AFD).[1] The prevalence of bradyarrhythmias requiring a pacemaker (PM) and their occurrence as the initial manifestation in undiagnosed AFD has been scarcely described in the literature.[2] The quest for red flags leading to early AFD diagnosis identification is considered clinically relevant, allowing implementation of pharmacological treatments when they can exert the greatest efficacy.[3] Furthermore, in individuals with known AFD cardiomyopathy, easy and cost-effective markers of risk for PM requirement may help

Abbreviations: AFD, Anderson–Fabry disease; AV, atrioventricular; ECG, electrocardiography; ERT, enzyme replacement therapy; FU, follow-up; HC, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LVH, left ventricular hypertrophy; LVMWT, left ventricular maximal wall thickness; PM, pacemaker.

prevent clinical complications including syncope and sudden death.

In the present study, we therefore assessed a consecutive AFD cohort, investigating the presence of bradyarrhythmias requiring pacing as an onset symptom of a disease and identifying the most significant predictors of PM requirement during the course of the disease.

2 | PATIENTS AND METHODS

2.1 | Study design

A retrospective longitudinal observational design was used. All AFD patients consecutively followed at Cardiomyopathy Unit, Careggi University Hospital, Florence (Italy), from 1994 to 2020, were included. The following information and inclusion criteria were respectively collected and used:

- Baseline and follow-up (FU) clinical features, including signs of multisystemic involvement, enzyme replacement therapy (ERT) requirement, renal, cerebrovascular, and cardiac events.
- Cardiac instrumental evaluation at baseline and FU, including main electrocardiography (ECG) and echocardiographic features. We defined cardiac involvement as an echocardiographic demonstration of left ventricular hypertrophy (LVH) with a maximum wall thickness ≥13 mm, according to previous studies.[4,5]
- Only patients with ≥1 year FU were included.

We identified the overall prevalence of PM implantation in this cohort and investigated which variables were significantly related to PM requirement. We investigated whether pacing occurred before AFD diagnosis and/or was the main reason for diagnosis.

The study was approved by the local ethics committee.

2.2 | Statistical analysis

IBM SPSS 23 was used for all statistical analyses. We used the χ^2 test to determine independence in distribution among categorical variables; in the case of 2 × 2 tables with an expected cell count of <5, we used Fisher's exact test. We used the Mann–Whitney test to verify the correlation between quantitative variables. A two-sided p value <.05 was considered significant. The survival curve was used to describe the relationship between PM implantation and QRS width.

3 | RESULTS

From 1994 to 2020, 82 patients with genetically confirmed AFD have been evaluated at our center with a median FU of 6.9 [3.5–12] years (Table 1). Overall, there was a prevalence of women [52/82 (63%)], the most part of them being diagnosed after familiar or newborn genetic screening [43/52 (83%)]. Instead, most part of men was diagnosed as proband [22/31 (71%)]. Men were more symptomatic (56.7% male vs. 26.9% female in NYHA II at FU; $p = .008$), more treated with ERT (73.3% of male vs. 30.7% of female were on ERT during the course of disease; $p = .001$), and prone to all-cause mortality (7/30 male vs. 1/52 women; $p = .003$).

Grade I atrioventricular (AV) block was present at diagnosis in four men (13%) and one woman (2%), and developed in four additional men during FU [overall 8/30 (27%); $p = .001$ compared to women]. QRS duration was longer in male patients, especially at final evaluation ($p = .003$). At echocardiography, 27 (33%) patients had evidence of AFD cardiomyopathy (i.e., LVH) at baseline, while the global prevalence reached 47% (39/82) over FU. During FU, three patients (4%) underwent ICD implantation, all in primary prevention.

Overall, five patients (6%; 2/30 males and 3/52 females) required a PM: two due to advanced AV block and three due to sick sinus syndrome (SSS) (Table 1). All PM implanted were dual chamber, programmed in DDD mode, with Automatic Mode Change to AAI in patients with SSS; at FU device interrogation showed a medium pacing rate of 62% [standard deviation (SD) ± 7%] and a medium ventricular pacing rate of 43% (SD ± 19%).

The median age at PM implantation was 59 [interquartile range (IQR) 55–66] years. Only in one patient implantation anticipated AFD diagnosis. However, this 54-year-old woman had a history of gradual onset of LVH, angina, and exertional dyspnea dating back >10 years and was previously labeled as sarcomeric hypertrophic cardiomyopathy (HCM). The prevalence of PM implantation was 5/39 (13%) among patients with cardiac involvement [2/20 (10%) in men and 3/19 (15%) in women ($p = .083$), all on ERT at the time of implant except the aforementioned undiagnosed woman] and zero among those without.

At univariable analysis, baseline PR interval >200 ms, baseline QRS > 120 ms, entity of QRS variation during FU and LV maximal wall thickness (LVMWT) at baseline echocardiography evaluation were associated with PM requirement (Table 2). Conversely, QRS stability during FU ruled out the need for pacing (Figure 1A). At Kaplan–Meier survival analysis, a baseline QRS duration ≥120 ms significantly stratified risk of PM requirement ($p = .012$) (Figure 1B).

4 | DISCUSSION

In our cohort of 82 AFD patients followed for almost 7 years, we found a prevalence of PM implantation of 6% (i.e., <1% per year). The median age at implant was 59 years, ranging from 54 years in a patient followed for over a decade with a generic diagnosis of HCM. Bradyarrhythmias were never the presenting symptom and always occurred in patients with full-fledged HCM phenotype, generally with a long-standing history of dyspnea or angina. Consistently, bradyarrhythmias requiring PM implantation as the first manifestation of AFD are virtually absent in the literature, even in older patients. Our findings are in line with the limited literature available, based mainly on cross-sectional evaluations.[6,7] In a cohort of 188 individuals

TABLE 1 Baseline and follow-up clinical and instrumental features of 82 patients with Anderson–Fabry disease

	Total = 82	Males (*N* = 30) (36.6%)	Females (*N* = 52) (63.4%)	*p* value
Baseline				
Age at diagnosis	41 [29.3–52.8]	44 [29.5–50]	40 [30–53]	.749
Proband	31 (37.8%)	22 (73.3%)	9 (17.3%)	**.001**
Smoker	7 (8.5%)	3 (10%)	4 (7.7%)	.703
Hypertension	29 (35.4%)	12 (40%)	17 (32.7%)	.505
Dyslipidemia	41 (50%)	20 (66.7%)	21 (40.4%)	**.022**
eGFR EPI-CKD (ml/min/1.73 m^2)	100 [77.2–119.2]	100 [58–130]	101.5 [83.5–116.7]	.967
Moderate proteinuria (>500 mg/day)	22 (26.8%)	16 (53.3%)	6 (11.5%)	**.001**
LysoGB3 (ng/ml)	3.8 [1.7–9.4]	6.4 [3.9–13.9]	2.7 [1.5–5.2]	**.016**
Baseline NYHA class				.072
I	62 (75.6%)	19 (63.3%)	43 (82.7%)	
II	19 (23.2%)	11 (36.7%)	8 (15.4%)	
III–IV	1 (1.2%)	0	1 (1.9%)	
Peripheral neuropathy	44 (53.7%)	17 (56.7%)	27 (51.9%)	.068
Vortex keratopathy	29 (35.4%)	12 (40%)	17 (32.7%)	.461
Angiokeratoma	28 (34.1%)	15 (50%)	13 (25%)	.060
Audiovestibular involvement	46 (56.1%)	23 (76.7%)	23 (44.2%)	**.013**
Peripheral neuropathy	44 (53.7%)	17 (56.7%)	27 (51.9%)	.068
ECG				
PR duration (ms)	140 [125–160]	149 [128–168]	140 [125–153]	.153
QRS duration (ms)	94 [84–105.25]	97 [90–110]	90 [82–103]	**.037**
QRS > 120 ms	8 (9.7%)	4 (13.3%)	4 (7.7%)	.455
PR < 120 ms	11 (13.4%)	3 (10%)	8 (15.4%)	.738
PR > 200 ms	5 (6.1%)	4 (13.3%)	1 (1.9%)	.060
LVH	26 (31.7%)	12 (40%)	14 (26.9%)	.189
Echocardiography				
EF (%)	63.5 [60–68]	63 [59–67]	64.5 [60.5–70]	.153
LVMWT (mm)	11 [9–15.3]	11 [10–20]	9.5 [8–13.5]	**.006**
LVH	27 (32.9%)	12 (40%)	15 (28.8%)	.301
Follow-up				
Total follow-up (years)	6.9 [3.5–12]	7.3 [3.8–12.6]	6.9 [3.1–11.1]	.560
On ERT	38 (46.3%)	22 (73.3%)	16 (30.7%)	**.001**
On Migalastat	30 (36.6%)	15 (50%)	15 (28.8%)	.055
On ACE-i/ARB	31 (37.8%)	20 (66.7%)	11 (21.2%)	**.001**
On beta-blockers	26 (31.7%)	11 (36.7%)	15 (28.8%)	.492
On antiplatelets	9 (10.9%)	3 (10%)	6 (11.5%)	.807
On anticoagulants	21 (25.6%)	10 (33.3%)	11 (21.2%)	.173
Kidney transplantation	14 (17.1%)	7 (23.3%)	7(13.5%)	.252

TABLE 1 (Continued)

	Total = 82	Males (N = 30) (36.6%)	Females (N = 52) (63.4%)	p value
TIA or stroke	14 (17.1%)	6 (20%)	8 (15.4%)	.593
Angina	18 (21.9%)	10 (33.3%)	8 (15.4%)	.059
Syncope	7 (8.5%)	1 (3.3%)	6 (11.5%)	.200
NSVT	8 (9.8%)	6 (20%)	2 (3.8%)	**.046**
AF	4 (4.8%)	1 (3.3%)	3 (5.8%)	.999
PM implantation	5 (6.1%)	2 (6.7%)	3 (5.8%)	.662
SSS	3 (3.7%)	1 (3.3%)	2 (3.9%)	.732
AV block	2 (2.4%)	1 (3.3%)	1 (1.9%)	.235
ICD implantation	3 (3.7%)	2 (6.7%)	1 (1.9%)	.296
Final NYHA class				**.008**
I	47 (57.3%)	11 (36.7%)	36 (69.2%)	
II	31 (37.8%)	17 (56.7%)	14 (26.9%)	
III–IV	4 (4.8%)	2 (6.7%)	2 (3.8%)	
Cardiac death	5 (6.1%)	4 (13.3%)	1 (1.9%)	.057
All-cause mortality	8 (9.8%)	7 (23.3%)	1 (1.9%)	**.003**
ECG				
PR duration (ms)	150 [134–165]	160 [150–200]	147 [129–158]	**.002**
QRS duration (ms)	100 [89–115]	110 [99–135]	96 [86–110]	**.003**
QRS > 120 (ms)	15 (18.3%)	9 (30%)	6 (11.5%)	**.037**
PR < 120 ms	7 (8.5%)	3 (10%)	4 (7.7%)	.998
PR > 200 ms	9 (10.9%)	8 (26.7%)	1 (1.9%)	**.001**
LVH	30 (36.6%)	14 (46.7%)	16 (30.8%)	.150
Echocardiography				
EF (%)	63 [60–65]	63 [55.8–66]	63 [60–65]	.549
LVMWT (mm)	12 [9–16]	15 [12–19]	10.5 [8–14]	**.002**
LVH	39 (47.6%)	20 (66.7%)	19 (36.5%)	**.009**
Region of LVH				.054
Concentric	17 (20.7%)	10 (33.3%)	7 (13.5%)	
Septum	20 (24.4%)	8 (26.7%)	12 (23.1%)	
Inferior/lateral	1 (1.2%)	1 (3.3%)	0	
Apex	1 (1.2%)	1 (3.3%)	0	
LVOTO	4 (4.8%)	2 (6.7%)	2 (3.8%)	.603

Note: Continuous variable expressed as a median and QR. eGFR was estimated according to CKD-EPI. LVH at ECG was defined according to Sokolow–Lyon criteria. LVH at echocardiography was defined as maximal wall thickness ≥13 mm. *P* values with statistical significance are indicated as bold values.

Abbreviations: ACE-i, ACE inhibitors; AF, Anderson–Fabry; ARB, angiotensin receptor blockers; AV, atrioventricular; CKD-EP, Chronic Kidney Disease Epidemiology Collaboration; ECG, electrocardiography; EF, ejection fraction; ERT, enzyme replacement therapy; eGFR, estimated glomerular filtration rate; EPI-CKD, Epidemiology Collaboration-Chronic Kidney Disease; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LVH, left ventricular hypertrophy; LVMWT, left ventricular maximal wall thickness; LVOTO, left ventricular outflow tract obstruction; NSVT, nonsustained ventricular tachycardias; NYHA, New York Heart Association; PM, pacemaker; SSS, sick sinus syndrome; TIA, transient ischemic attack.

TABLE 2 Predictors of permanent pacing requirement in 82 patients with Anderson–Fabry disease

	PM requirement (*N* = 5)	No PM requirement (*N* = 77)	*p* value
ECG			
Baseline PR duration (ms)	160 [130–199]	140 [126–160]	.357
Baseline QRS duration (ms)	125 [120–135]	92 [84–102]	**.030**
Baseline PR < 120 ms	1 (20%)	10 (13%)	.449
Baseline PR > 200 ms	2 (40%)	3 (3.9%)	**.018**
Baseline QRS > 120 ms	4 (80%)	5 (6.5%)	**.003**
Baseline LVH	3 (60%)	22 (28.5%)	.163
Final PR duration (ms)	218 [189–221]	150 [132–164]	**.024**
Final QRS duration (ms)	160 [166–180]	100 [88–111]	**.004**
Final PR < 120 ms	0	7 (9.1%)	.576
Final PR > 200 ms	2 (40%)	7 (9.1%)	**.035**
Final QRS > 120 ms	4 (80%)	11 (14.3%)	**.003**
Final LVH	3 (60%)	27 (35.1%)	.350
ΔPR (base-FU, ms)	20 [10–32]	4 [0–17]	.314
ΔQRS (base-FU, ms)	31 [21–36]	4 [1–8]	**.001**
Echocardiography			
Baseline EF (%)	62 [59–65]	64 [60–68]	.585
Baseline LVMWT (mm)	17 [11–21]	10 [9–15]	**.041**
Baseline LVH	3 (60%)	24 (31.2%)	.325
Final EF (%)	52 [50–60]	63.5 [60–65.5]	**.009**
Final LVMWT (mm)	21 [16–23]	12 [9–15]	**.002**
Final LVH	5 (100%)	34 (44.2%)	**.021**
ΔLVMWT (base-FU, ms)	4 [0–5]	0 [0–3]	.324

Note: Continuous variable expressed as a median and IQR. LVH at ECG was defined according to Sokolow–Lyon criteria. LVH at echocardiography was defined as maximal wall thickness ≥13 mm. *P* values with statistical significance are indicated as bold values.

Abbreviations: ECG, electrocardiography; EF, ejection fraction; FU, follow-up; IQR, interquartile range; LVH, left ventricular hypertrophy; LVMWT, left ventricular maximal wall thickness; LVOTO, left ventricular outflow tract obstruction; PM, pacemaker.

<70 years with conduction abnormalities requiring PM implantation, none were found to have AFD with genetic screening.[8] In another study, 531 male patients implanted with a PM or ICD in the age range 30–76 years were screened for AFD and only in three unrelated patients (0.56%) a GLA mutation was identified. However, at the time of implant (mean age 62 ± 5 years), cardiac and systemic signs of AFD were already overt.[9] Remarkably, only a single case report described a bradyarrhythmic clinical onset in a 34-year-old Japanese man.[2]

These observations suggest that, in patients with AFD, severe bradyarrhythmias occur late in the disease course and generally in the presence of established cardiomyopathy features. This suggests a sufficient degree of predictability in patients without overt cardiac involvement, allowing adequate surveillance and prevention during FU. Furthermore, our data discourage systematic initiatives aimed at screening populations with juvenile bradyarrhythmias for the early identification of AFD.

In our AFD cohort, we could identify several features associated with PM implantation including long PR, QRS duration, and LVMWT. Of these, QRS at baseline and QRS delta during FU were the most specific, in agreement with the study of O'Mahony et al.,[10] where 12/189 (6%) AFD patients received a PM during 4.8 years and QRS prolongation was the most relevant risk marker.

The absence of patients requiring PM among those with QRS stability during FU underlines the importance of ECG for the selection of patients worthy of closer monitoring.

4.1 | Limitations

The major limitation of this study is the small number of patients reaching the end-point (PM requirement), thus limiting the

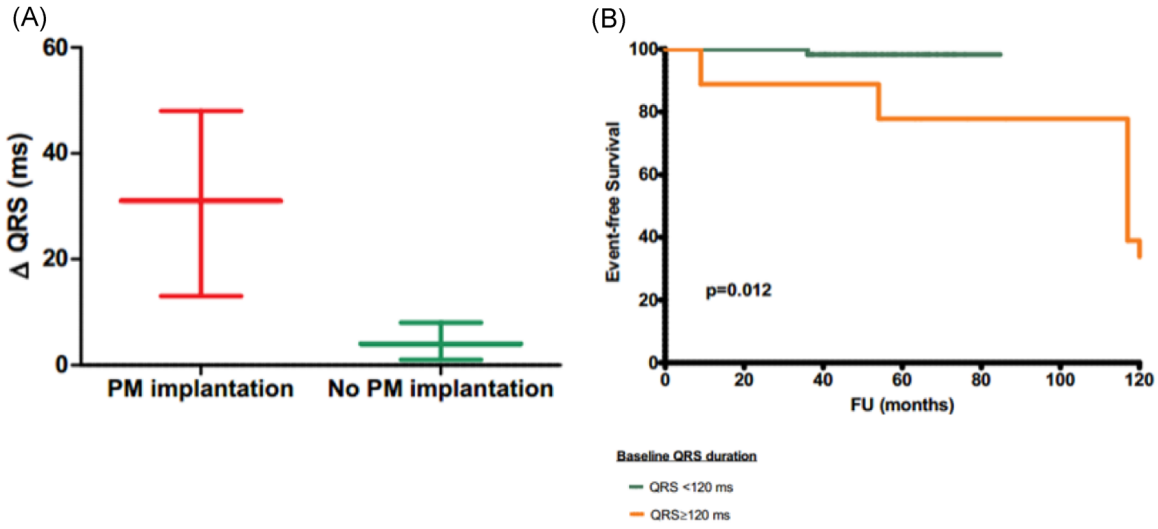

FIGURE 1 (A) Distribution of QRS increase (expressed as median and IQR) in AFD patients with and without PM requirement. QRS duration stability during the course of disease predicts the absence of bradyarrhythmias in our AFD cohort. (B) Survival free from pacemaker implantation based on QRS duration at baseline evaluation in 82 patients with Anderson–Fabry disease. Kaplan–Meier analysis shows an increased likelihood of pacing requirement in patients with baseline QRS duration >120 ms, independent of ECG morphology or rhythm. AFD, Anderson–Fabry disease; IQR, interquartile range; PM, pacemaker

power of the statistical model. Furthermore, clinical and genetic screening in the families of AFD patients was not systematic; therefore, we cannot exclude that affected relatives with mild phenotypes may have developed bradyarrhythmias at an early stage. However, no patients had a known history of juvenile PM implantation in their pedigree.

5 | CONCLUSIONS

Severe bradyarrhythmias were never the onset manifestation of AFD in our cohort, occurring relatively late during the clinical course of the disease and in the context of advanced cardiomyopathy. QRS variation at serial ECG evaluation is a useful marker to identify patients at risk of PM requirement.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Shah JS, Hughes DA, Sachdev B, et al. Prevalence and clinical significance of cardiac arrhythmia in Anderson–Fabry disease. *Am J Cardiol*. 2005;96(6):842-846. doi:10.1016/j.amjcard.2005.05.033
2. Kato Y, Ishikawa A, Aoki S, et al. Fabry disease with pacemaker implantation as the initial event. *Intern Med*. 2019;58(20):2993-3000. doi:10.2169/internalmedicine.2468-18
3. El Dib R, Gomaa H, Ortiz A, Politei J, Kapoor A, Barreto F. Enzyme replacement therapy for Anderson-Fabry disease: a complementary overview of a Cochrane publication through a linear regression and a pooled analysis of proportions from cohort studies. *PLoS ONE*. 2017;12(3):e0173358. doi:10.1371/journal.pone.0173358
4. Sachdev B, Takenaka T, Teraguchi H, et al. Prevalence of Anderson–Fabry disease in male patients with late onset hypertrophic cardiomyopathy. *Circulation*. 2002;105:1307-1411. doi:10.1161/01.CIR.0000012626.81324.38
5. Chimenti C, Pieroni M, Morgante E, et al. Prevalence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy. *Circulation*. 2004;110(9):1047-1053. doi:10.1161/01.CIR.0000139847.74101.03
6. Linhart A, Kampmann C, Zamorano JL, et al. Cardiac manifestations of Anderson–Fabry disease: results from the international Fabry outcome survey. *Eur Heart J*. 2007;28(10):1228-1235. doi:10.1093/eurheartj/ehm153
7. Lobo T, Morgan J, Bjorksten A, et al. Cardiovascular testing in Fabry disease: exercise capacity reduction, chronotropic incompetence and improved anaerobic threshold after enzyme replacement. *Intern Med J*. 2008;38(6):407-414. doi:10.1111/j.1445-5994.2008.01669.x

8. López-Sainz Á, Climent V, Ripoll-Vera T, et al. Negative screening of Fabry disease in patients with conduction disorders requiring a pacemaker. *Orphanet J Rare Dis*. 2019;14:170. doi:10.1186/s13023-019-1140-3
9. Hemelsoet D, De Keyser J, Van Heuverswyn F, et al. Screening for Fabry disease in male patients with arrhythmia requiring a pacemaker or an implantable cardioverter–defibrillator. *Circulation*. 2021;143(8):872-874. doi:10.1161/CIRCULATIONAHA.120.051400
10. O'Mahony C, Coats C, Cardona M, et al. Incidence and predictors of anti-bradycardia pacing in patients with Anderson–Fabry disease. *Europace*. 2011;13(12):1781-1788. doi:10.1093/europace/eur267

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