Texas Heart Institute Journal

*Clinical Investigation*

# Arrhythmia Burden and Heart Rate Response During Exercise in Anderson-Fabry Disease

Adam W. Powell, MD[1,2]; Samuel G. Wittekind, MD[1,2]; Wayne A. Mays, MS[1,2]; Sean M. Lang, MD[1,2]; Timothy K. Knilans, MD[1,2]; Carlos E. Prada, MD[1,3]; Robert J. Hopkin, MD[1,3]; Clifford Chin, MD[1,2]

[1]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio
[2]The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
[3]Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

*Patients with Anderson-Fabry disease (AFD) have an elevated incidence of resting arrhythmias and ischemic heart disease, but their exercise arrhythmia burden and ischemic changes are not well understood. In addition, little research has been done on heart rate recovery in these patients.*

*We retrospectively reviewed charts of patients with AFD who underwent maximal effort cardiopulmonary exercise testing (CPET) (n=44; 38.2 ± 13.8 yr; 23 men) from 2012 through 2018. Electrocardiographic, Holter monitoring, echocardiographic, cardiac magnetic resonance imaging, and patient demographic data were collected.*

*No patient had adverse events that necessitated CPET termination, whereas 25 (57%) had ectopy during CPET, including 3 (7%) with frequent premature atrial contractions and 5 (11%) with frequent premature ventricular contractions. The ectopic burden was higher during resting electrocardiographic monitoring before exercise. In addition, 7 patients (16%) had pathologic ST-segment or T-wave changes on CPET, defined as ST-segment changes ≥2 mm. Among the patients who had concurrent cardiac magnetic resonance findings with their CPET (n=27), ST-segment or T-wave changes were associated with left ventricular myocardial mass (r=0.43, P=0.02). Chronotropic incompetence was seen during CPET in 28 patients (64%); however, only 2 patients (4%) had abnormal heart rate recovery at 1 minute.*

*This study shows that patients with AFD can safely undergo exercise testing but have a high incidence of exercise-induced arrhythmias and ischemic changes. Ischemic electrocardiographic changes during exercise testing are associated with myocardial mass. Despite the chronotropic incompetence associated with AFD, heart rate recovery appears to be generally preserved in these patients.* ***(Tex Heart Inst J 2022;49(5):e207363)***

**Citation:**
Powell AW, Wittekind SG, Mays WA, Lang SM, Knilans TK, Prada CE, Hopkin RJ, Chin C. Arrhythmia burden and heart rate response during exercise in Anderson-Fabry disease. Tex Heart Inst J 2022;49(5):e207363. doi: 10.14503/THIJ-20-7363

**Key words:**
Arrhythmia; Anderson-Fabry disease/complications; cardiopulmonary exercise test; echocardiography; electrocardiography; exercise tolerance; heart rate recovery; heart rate response

**Corresponding author:**
Adam W. Powell, MD, 3333 Burnett Ave., MLC 2003, Cincinnati, OH 45229-3026

**E-mail:**
Adam.Powell@cchmc.org



Anderson-Fabry disease (AFD) is a rare X-linked lysosomal storage disease that is caused by a mutation in the α-galactosidase A gene that results in impaired degradation and accumulation of globotriaosylceramide, a sphingolipid.[1,2] Accumulation of globotriaosylceramide in the heart, vasculature, and kidneys results in progressive cardiovascular disease, including left ventricular hypertrophy, arrhythmias, diastolic heart failure, and small-vessel disease.[2] Enzyme replacement therapy (ERT), an established treatment for AFD in the United States since the 1990s, relieves left ventricular enlargement and normalizes the PR interval.[3,4] While the incidence of arrhythmia and conduction disturbance on the resting electrocardiogram (ECG) is well established, less is known about the incidence of arrhythmias and ischemic changes during exercise testing.

The cardiopulmonary exercise test (CPET) is a valuable source of information on a patient's overall cardiac function and aerobic fitness and how the heart responds to the stress of exercise.[5] In the laboratory, the CPET is performed for multiple reasons, including to evaluate functional capacity and ECG pathologic conditions, to determine disease severity, and to monitor the effects of treatment regimens such as medication and exercise rehabilitation programs.[6]

In addition to being at increased risk of resting arrhythmias, patients with AFD have chronotropic incompetence and reduced resting heart rates (HR).[7] Little is known about HR recovery after exercise in this population. In patients with similar

phenotypes, such as hypertrophic cardiomyopathy and diastolic heart failure, HR recovery on cessation of maximal exercise is often abnormal, a phenomenon thought to be secondary to autonomic dysfunction.[8,9]

Few published studies have involved the use of CPET to evaluate the exercise arrhythmia burden and HR response in patients with AFD. The aims of this study were 1) to quantify the ischemia and arrhythmia burden in patients with AFD during CPET, 2) to describe the HR response to exercise in these patients, and 3) to use imaging data from our cohort to evaluate the relationship between ECG abnormalities and HR response on CPET with contemporaneous cardiac magnetic resonance (CMR) imaging findings.

## Patients and Methods

We retrospectively reviewed the charts of patients with AFD who underwent screening exercise testing at Cincinnati Children's Hospital from January 2012 through June 2018 as part of the local standard of care. This study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board, and a waiver of consent was granted because the study used existing data and involved no more than minimal risk to the patient.

Data on age, sex, size, and testing date were obtained from chart review. To further categorize the overall arrhythmia burden in this population, resting 12-lead ECG and 24-hour ambulatory Holter monitoring results within 3 months of exercise testing were also collected. Cardiac imaging data, including CMR and echocardiographic results, obtained during that 3-month period were recorded as well. In addition, information was obtained regarding whether the patients were currently receiving ERT.

For patients who had multiple exercise tests, the first maximal effort CPET was included in the analysis. All patients underwent standardized exercise either on the cycle ergometer by the ramp protocol or on the treadmill by the Bruce protocol; the test method was left to the ordering physician's preference. The methodology for exercise testing in the Cincinnati Children's Hospital Medical Center Cardiopulmonary Laboratory has been detailed previously.[10]

Immediately after maximal effort exercise testing, the patient entered a 3-minute unloaded cooldown period. Then, the patient lay supine until the test was completed. Heart rate recovery was recorded at 1, 3, 5, and 10 minutes after exercise and was defined as the difference between the peak HR and the HR recorded at a specific time point as previously described.[11] Exercise ECG findings were evaluated for ectopy and ST-segment or T-wave changes. Ectopy was defined as abnormal if more than one premature beat was observed on the exercise ECG. Abnormalities were further described as follows: rare ectopy was defined as <5 ectopic beats/hour on Holter monitoring (or <5% total QRS complexes on CPET); occasional ectopy, as 5 to 10 ectopic beats/hour on Holter monitoring (or 5-10% total QRS complexes on CPET); and frequent ectopy, as >10 ectopic beats/hour on Holter monitoring (or >10% total QRS complexes on CPET).[12,13] ST-segment or T-wave changes were considered abnormal if a depression ≥2 mm was recorded during exercise testing.

Heart rate reserve on exercise testing was calculated as the difference between the peak and resting HRs. The chronotropic index was computed as the HR reserve divided by the difference between the predicted peak HR and the resting HR. The normal range for chronotropic index was defined as >80%.[14] Abnormal values for HR recovery in patients with AFD have not been adequately described, so we used 2 separate cutoffs for the difference in HR between peak exercise and at 1 minute after exercise: <12 beats/min and <25 beats/min.[11,15] The percentage of predicted peak oxygen consumption ($Vo_2$peak) was calculated with use of the established equations.[16]

All CMR imaging was performed with use of a 1.5-T Philips scanner (Ingenia; Philips Healthcare). Volumetric and functional assessments were made with use of a standard cine steady-state free precession (SSFP) short-axis stack from the mitral valve annulus to the apex. (Vertical and horizontal long-axis acquisitions were used for reference.) Typical parameters for SSFP images were as follows: field of view, 300 × 112 mm; matrix size, 168 × 158 mm; slice thickness, 6 to 7 mm; pixel resolution, 1.8 × 1.8 mm; repetition time/echo time, 2.3/1.17 ms; phases per R-R interval, 30; and parallel imaging factor, 2. Patients whose scans required a gadolinium-based contrast agent received the macrocyclic agent gadoterate meglumine intravenously at a dose of 0.2 mmol/kg. Late gadolinium-enhanced images were acquired with use of a standard inversion recovery gradient-echo pulse sequence in the same geometries as the SSFP acquisitions. The inversion recovery time was chosen to best null the myocardium. Volumetric and functional data were obtained with the QMASS MR (Medis Medical Imaging Systems). To quantify left ventricular mass, endocardial and epicardial volumes were measured during diastole. In accordance with our institution's convention, papillary muscles and trabeculations were excluded. Left ventricular mass was calculated as the myocardial volume multiplied by the specific gravity of myocardium (1.05 g/mL).

### Statistical Analysis

Normally distributed continuous variables were summarized as mean ± SD and were analyzed with use of *t* tests. Logistic regression was used to determine the relationship between the binary presence or absence of ST-segment depressions ≥2 mm and the CMR parameters studied. In addition, logistic regression was used

to determine the relationship between combined more-than-rare atrial and ventricular ectopy and the studied CMR parameters. For all tests, a 2-sided *P* value <0.05 was considered significant. Statistical analyses were performed with use of JMP, version 14 (SAS Institute Inc.).

## Results

Forty-four patients who completed a total of 74 tests were included in this study (Table I). The results of the first maximal effort test for each patient were included in the analysis. Of those 44 tests, 22 (50%) were performed on the treadmill according to the Bruce protocol, and 22 (50%) were performed on the cycle ergometer according to the ramp protocol. Six of the 44 patients (14%) were not prescribed ERT (agalsidase-β) before their CPET for the following reasons: 2 patients had discontinued ERT after experiencing side effects; 1 patient deferred ERT because there was no evidence of renal, cardiac, or corneal involvement; 1 patient previously had self-discontinued ERT for lack of benefit; and 2 patients had no stated reason for not taking ERT. The 38 patients (86%) taking ERT at the time of CPET had a mean total treatment time of 4.3 ± 4.1 years. Forty-one patients (93%) had cardiac imaging done either before or on the day of their exercise testing; 25 (57%) had a CMR image only, 12 (27%) had an echocardiogram only, and 4 (9%) had both (Table I).

Resting ECGs were recorded in 42 patients (95%) within 3 months before undergoing CPET (Table II). Comparing the resting ECG and CMR results revealed significant correlations between the QRS interval and left ventricular myocardial mass ($r$=0.42; $P$=0.02) and between the corrected QT interval and end-diastolic volume in both the left ($r$= −0.43; $P$=0.02) and right ventricles ($r$= −0.46; $P$=0.01).

Of the 44 patients, 37 (84%) wore a Holter monitor within 3 months before undergoing the CPET. Of those 37 patients, only 6 (16%) had no arrhythmia. Most patients with ectopy had single or rare premature atrial and ventricular contractions. Arrhythmias of potential clinical significance included nonsustained atrial tachycardia or occasional to frequent premature atrial contractions in 6 patients (16%) and nonsustained ventricular tachycardia or occasional-to-frequent premature ventricular contractions in 4 patients (11%). Atrial fibrillation was noted in 1 patient. There was no significant relationship between occasional or greater ectopy on Holter monitoring and the left ventricular myocardial mass on CMR imaging.

Overall, none of the 44 patients had to terminate exercise testing prematurely because of ECG abnormalities or safety concerns. On exercise ECGs, 25 of 44 patients (57%) had ectopy, including 3 (7%) with occasional premature atrial contractions, 3 (7%) with frequent premature atrial contractions, 2 (4%) with occasional premature ventricular contractions, and 5 (11%) with frequent premature ventricular contractions. No patient had increased ectopy from baseline during the later stages of exercise. In addition, 7 patients (16%) had pathologic ST-segment or T-wave changes, defined as ST-segment depression ≥2 mm from baseline in the inferior leads (n=2), lateral leads (n=2), or inferolateral leads (n=3). More-than-rare ectopy on CPET was correlated with more-than-rare ectopy on the Holter monitor ($r$=0.66; $P$ <0.0001). The ST-segment depression during CPET correlated with left ventricular myocardial mass ($r$=0.43; $P$=0.02) measured on CMR images. There were no significant associations between ectopy or ST-segment or T-wave changes on CPET and ERT time, percent predicted $Vo_2$peak, or maximal systolic blood pressure. Ectopy on CPET was associated with age ($r$=0.42; $P$=0.008) and weight ($r$=0.35; $P$=0.03), but not with sex. ST-segment changes on CPET were associated with age ($r$=0.43; $P$=0.0001), but not with weight or sex.

**TABLE I. Baseline Demographic, Clinical, and Imaging Data of 44 Patients With Anderson-Fabry Disease**

| Variable | Value |
|---|---|
| Sex | |
| Male | 23 (52) |
| Female | 21 (48) |
| Age (yr) | 38.2 ± 13.8 |
| Height (cm) | 170.7 ± 8.9 |
| Weight (kg) | 77.9 ± 19.8 |
| Body surface area ($m^2$) | 1.9 ± 0.3 |
| Body mass index | 26.8 ± 6.7 |
| ECG results (n=16) | |
| Abnormal systolic function low-normal* | 1 (8) |
| LV hypertrophy | 6 (37) |
| CMR imaging results (n=29) | |
| LV hypertrophy | 9 (33) |
| Late gadolinium enhancement | 8 (29) |
| LV ejection fraction (%) | 61.3 ± 7.3 |
| LV myocardial mass ($g/m^2$) | 64.1 ± 18.7 |
| LV end-diastolic volume ($mL/m^2$) | 85.1 ± 15.8 |
| LV end-systolic volume ($mL/m^2$) | 33.7 ± 11.1 |
| RV ejection fraction (%) | 60 ± 4.6 |
| RV myocardial mass ($g/m^2$) | 16.6 ± 4.6 |
| RV end-diastolic volume ($mL/m^2$) | 84.9 ± 18.3 |
| RV end-systolic volume ($mL/m^2$) | 34.5 ± 10.9 |

CMR = cardiac magnetic resonance; ECG = echocardiographic; LV = left ventricular; RV = right ventricular

* Defined as an ejection fraction of 50% to 55%.

Data are expressed as number and percentage or as mean ± SD.

**TABLE II. Results of Baseline ECG, Holter Monitoring, and Cardiopulmonary Exercise Test Arrhythmia Burden in 44 Patients With Anderson-Fabry Disease**

| Variable | Value |
|---|---|
| Baseline ECG (n=42) | |
| Predominant rhythm | |
| Sinus | 40 (95) |
| Ectopic atrial | 2 (5) |
| PR interval (ms) | 148 ± 26.6 |
| QRS interval (ms) | 95.4 ± 14.5 |
| QTc interval (ms) | 419 ± 27.8 |
| Ectopy | |
| None | 40 (95) |
| Single PAC | 1 (2.5) |
| Single PVC | 1 (2.5) |
| Holter monitor results (n=37) | |
| Sinus as predominant rhythm | 37 (100) |
| Atrial ectopy | |
| None | 6 (16) |
| Rare | 25 (68) |
| Frequent | 2 (5) |
| Frequent with episodes of PAT | 3 (8) |
| Atrial fibrillation | 1 (3) |
| Ventricular ectopy | |
| None | 10 (27) |
| Rare | 23 (62) |
| Occasional | 1 (3) |
| Frequent | 1 (3) |
| Frequent with episodes of NSVT | 2 (5) |
| CPET ECG results (n=44) | |
| Sinus as predominant rhythm | 44 (100) |
| Atrial ectopy | |
| None | 33 (75) |
| Single PAC | 2 (4) |
| Rare | 3 (7) |
| Occasional | 3 (7) |
| Frequent | 3 (7) |
| Ventricular ectopy | |
| None | 21 (48) |
| Single | 6 (14) |
| Rare | 10 (23) |
| Occasional | 2 (4) |
| Frequent | 5 (11) |
| ST-segment or T-wave changes | |
| None | 29 (66) |
| Nonspecific T-wave changes | 6 (14) |
| ST-segment depression <2 mm | 2 (4) |
| ST-segment depression ≥2 mm | 7 (16) |

CPET = cardiopulmonary exercise test; ECG = electrocardiographic; NSVT = nonsustained ventricular tachycardia; PAC = premature atrial contraction; PAT = paroxysmal atrial tachycardia; PVC = premature ventricular contraction

Data are expressed as number and percentage or as mean ± SD.

**TABLE III. Results of Exercise Testing in 44 Patients With Anderson-Fabry Disease**

| Variable | Value | Normal Range |
|---|---|---|
| Predicted $Vo_2$peak (%) | 80.2 ± 20.3 | >80 |
| Maximum SBP (mmHg) | 175.9 ± 21 | Varies |
| Resting heart rate (beats/min) | 66.7 ± 12.5 | Varies |
| Maximum heart rate (beats/min) | 151.2 ± 26.2 | Varies |
| Predicted maximum heart rate (%) | 82.9 ± 11.5 | >85 |
| Heart rate reserve (beats/min) | 84.5 ± 24.3 | Varies |
| Chronotropic index (%) | 73.3 ± 17.8 | >80 |
| Heart rate recovery* (beats/min) | | |
| 1 min | 44.9 ± 20.3 | >12 |
| 3 min | 60.5 ± 16.5 | Varies |
| 5 min | 63.8 ± 16.4 | Varies |
| 10 min | 66.3 ± 17.4 | Varies |

SBP = systolic blood pressure; $Vo_2$peak = peak oxygen consumption

* Defined as the difference between heart rate at peak exercise and heart rate at the designated time point after exercise.

Data are presented as mean ± SD.

The mean percent predicted maximal HR (82.9% ± 11.5%; normal, >85%) and chronotropic index (73.3% ± 17.8%; normal, >80%) were both abnormally low (Table III). Chronotropic incompetence, defined as a chronotropic index <80%, was seen in 28 patients (64%). The chronotropic index correlated with the percent predicted $Vo_2$peak ($r$=0.37; $P$=0.01) and the maximal systolic blood pressure ($r$=0.36; $P$=0.02). When HR recovery was defined as a difference of <12 beats/min between peak exercise and 1 minute after exercise, 2 patients (4%) had abnormal HR recovery; when HR recovery was defined as <25 beats/min, 11 patients (25%) had abnormal HR recovery. The chronotropic index correlated with HR recovery at 1 minute ($r$=0.43; $P$=0.004) and 3 minutes ($r$=0.67; $P$ <0.0001).

When the patients with normal (n=16) and abnormal (n=28) chronotropic indices were compared, they differed significantly in the number of arrhythmias present on the Holter monitor (56% vs 100%; $P$=0.003) and CPET (6% vs 64%; $P$=0.0002), but this difference was not seen in the patients with pathologic ST-segment or T-wave changes (25% vs 7%; $P$=0.11). Unsurprisingly, patients with normal chronotropic indices had a higher percent predicted $Vo_2$peak (89.3 ± 20.8% vs 74.5 ± 18.6%; $P$=0.02) and maximal systolic blood pressure (185.5 ± 4.9 vs 170 ± 3.7 mmHg; $P$=0.006).

## Discussion

Few studies have evaluated exercise testing results in patients with AFD, and even fewer have studied the exercise arrhythmia burden in this population, even though resting ECG abnormalities in patients with AFD are well established. Schiffman and colleagues[17] reported

the incidence of atrial and ventricular arrhythmias in patients with AFD to be as high as 27% to 42%. Our cohort is noteworthy in that 84% of the patients had Holter data that showed either atrial or ventricular ectopy; this rate is significantly higher than the rates found in healthy persons.[18,19] This may simply reflect a difference in how ectopy was defined in previous studies; it is unclear whether Schiffman and colleagues[17] included all ectopy (including a single premature beat) or limited it to more potentially clinically relevant ectopy. Also of note, a relatively large percentage of our patients (25%) had potentially clinically significant arrhythmias (frequent premature atrial or ventricular contractions, atrial fibrillation) recorded on the Holter monitor. Interpretation of the arrhythmia burden from CPET results should take this into account.

We found that 59% of patients in our cohort exhibited either atrial or ventricular ectopy during CPET. Moreover, the 18% rate of frequent premature ventricular contractions in our study cohort is significantly higher than what has been reported in normal healthy adults.[20,21] Yet, despite the high prevalence of ectopy during CPET, none of our patients needed to terminate the testing because of their ECG abnormalities, providing further reassurance that exercise testing in this population is safe. It is also reassuring that, despite their high baseline resting ectopic burden on Holter monitoring and during early exercise, our patients had significantly less ectopy during the later stages of exercise. This implies that the overall ectopic burden was suppressed by the catecholamine surge that occurs during exercise, which is typical observation in patients with structurally normal hearts.[22] Our finding is interesting given that previous research showed an elevated risk of sudden cardiac death (SCD) in patients with AFD, particularly those with a history of left ventricular hypertrophy, late gadolinium enhancement on CMR imaging, or nonsustained ventricular tachycardia.[23] It remains to be seen whether exercise ECG is useful for SCD risk stratification.

An additional finding in this study, previously undescribed, is that 16% of patients had pathologic ST-segment or T-wave changes (defined as ≥2-mm ST-segment depression) during exercise testing, which is a markedly higher rate than that in a healthy adult population.[24] Because our patients were asymptomatic and were undergoing screening tests, this finding is potentially worrisome. This population has a high incidence of premature atherosclerotic coronary artery disease, secondary to lipid accumulation in the small vessels.[25] Even though there were no adverse events in this study, the relatively high incidence of ST-segment or T-wave segment changes in these asymptomatic patients could indicate that aggressive screening for coronary artery disease and microvascular cardiac disease is warranted in these patients. An additional mechanism for these changes could be related to the increased myocardial oxygen demand of the thickened muscle. This possibility is supported by the correlation between pathologic ST-segment or T-wave changes on CPET and left ventricular myocardial mass on CMR imaging, as well as by the fact that patients with AFD and left ventricular hypertrophy are at increased risk of SCD.[23]

Left ventricular hypertrophy is a well-established aspect of AFD and is thought to be secondary to both concentric myocardial hypertrophy and replacement fibrosis.[2] A previous study showed that myocardial fibrosis was a strong predictor of ventricular ectopy in AFD patients not taking ERT.[26] Although our cohort was healthier, with only 25% of patients having late gadolinium enhancement on CMR imaging, both ectopic burden and pathologic ST-segment or T-wave changes were associated with left ventricular myocardial mass on CMR imaging. In addition, the relatively large ectopic burden in these patients despite minimal fibrosis and ERT implies that treatment does not prevent lipid deposition in the conduction system—the previously proposed mechanism for these changes.[7] This implication is somewhat supported by the lack of a significant correlation between ERT time and ectopy on CPET in our study, although this question could be better addressed if CPET results were compared between patients taking and not taking ERT.

The HR response to exercise in AFD has not been well studied . A lower resting HR and blunted maximal HR have been well described[10,27] and were seen in our cohort. No studies to date have evaluated HR recovery in these patients, even though it is a potential marker of autonomic dysfunction in patients with heart failure.[8] Heart rate recovery involves reactivation of the parasympathetic system and is highly sensitive to vagal tone.[28] In our cohort, the prevalence of HR recovery abnormalities depends on which criterion for normal is used. Only 2 patients had abnormal HR recovery when we defined it as <12 beats/min at 1 minute after exercise.[11] In addition, HR recovery correlated with the chronotropic index, which is somewhat expected because the HR response and recovery reflect a healthy balance between the sympathetic and parasympathetic nervous systems. The overall normal HR recovery in our cohort may indicate that autonomic dysfunction has little effect on exercise tolerance in these patients. On the other hand, when we defined abnormal recovery as <25 beats/min at 1 minute after exercise, as Jouven and colleagues[15] have suggested, 11 patients (25%) had an abnormal HR recovery. This suggests that autonomic dysfunction plays a major causal role in one quarter of AFD cases. This cutoff value is potentially important in that otherwise asymptomatic adults who have an HR recovery of <25 beats/min at 1 minute after exercise have a 2.2 relative risk of all-cause mortality when compared with adults with more normal values.[15] Additional research on HR recovery will bring more consensus on normative data

and will also warrant reexamination in the AFD population.

### Limitations

This study had several potential limitations. First, the cohort was relatively small but ranged widely in age, which is not unusual in studies of uncommon diseases. Second, patients in this cohort had to be capable of performing an exercise test, which created a potential selection bias toward healthier patients. This bias may explain why the systolic blood pressure response to exercise in our cohort was normal, which is unusual in the AFD population. The relatively good health of the cohort may also explain its low rates of left ventricular hypertrophy and interstitial fibrosis (Table I), both of which are risk factors for impaired exercise tolerance.[26] Given the known risk factors for arrhythmias and ischemia, it is reasonable to hypothesize that the burden for each should be worse in patients with left ventricular hypertrophy and interstitial fibrosis; however, this should be confirmed by additional study. Third, because this was a descriptive retrospective study with a small cohort, we can draw no conclusions about the future clinical relevance of the ECG findings. Future studies should analyze the long-term impact of the atrial and ectopic burden in patients with AFD. Last, our CPET findings should be interpreted in light of the fact that $Vo_2$peak and peak HR are 5% to 10% higher in exercise testing with a treadmill than in exercise testing with a cycle ergometer.

## Conclusion

Patients with AFD have a high incidence of arrhythmias on both resting and exercise ECG. In addition, approximately 15% of such patients have pathologic ST-segment or T-wave changes on exercise ECG. The exercise-induced pathologic ST-segment or T-wave changes in our cohort were associated with elevated left ventricular myocardial mass, possibly reinforcing the link between left ventricular hypertrophy and cardiac events. However, HR recovery tended to be normal. Future studies should evaluate HR responses in a more wide-ranging AFD phenotype.


## Acknowledgments

We thank the Exercise Physiology Laboratory faculty and staff and the Division of Human Genetics at Cincinnati Children's Hospital Medical Center for their assistance in performing this study.

**Published:** 7 September 2022

**Author Contributions:** Dr. Powell was involved with all facets of the project including planning, data gathering and analysis, and manuscript formation. Dr. Wittekind was involved with data analysis and manuscript draft formation. Dr. Mays was involved with data gathering and critical review of the manuscript. Dr. Lang was involved in critical review of the manuscript and cardiac imaging data analysis. Dr. Knilans was involved in review of the manuscript and analysis of the ECG data. Drs. Prada, Hopkin and Chin were involved in manuscript formation.

**Conflict of Interest Disclosures:** None

**Funding/Support:** None


## References


1. Duro G, Musumeci MB, Colomba P, Zizzo C, Albeggiani G, Mastromarino V, et al Novel α-galactosidase A mutation in patients with severe cardiac manifestations of Fabry disease. Gene 2014;535(2):365-9.
2. Seydelmann N, Wanner C, Störk S, Ertl G, Weidemann F. Fabry disease and the heart. Best Pract Res Clin Endocrinol Metab 2015;29(2):195-204.
3. Spinelli L, Pisani A, Sabbatini M, Petretta M, Andreucci MV, Procaccini D, et al. Enzyme replacement therapy with agalsidase beta improves cardiac involvement in Fabry's disease. Clin Genet 2004;66(2):158-65.
4. Waldek S. PR interval and the response to enzyme-replacement therapy for Fabry's disease. N Engl J Med 2003;348(12):1186-7.
5. Eisenmann JC, Guseman EH, Morrison K, Tucker J, Smith L, Stratbucker W. Graded exercise testing in a pediatric weight management center: the DeVos protocol. Child Obes 2015;11(6):657-63.
6. Washington RL, Bricker JT, Alpert BS, Daniels SR, Deckelbaum RJ, Fisher EA, et al. Guidelines for exercise testing in the pediatric age group: from the Committee on Atherosclerosis and Hypertension in Children, Council on Cardiovascular Disease in the Young, the American Heart Association. Circulation 1994;90(4):2166-79.
7. Lobo T, Morgan J, Bjorksten A, Nicholls K, Grigg L, Centra E, Becker G. Cardiovascular testing in Fabry disease: exercise capacity reduction, chronotropic incompetence and improved anaerobic threshold after enzyme replacement. Intern Med J 2008;38(6):407-14.
8. Gharacholou SM, Scott CG, Borlaug BA, Kane GC, McCully RB, Oh JK, Pellikka PA. Relationship between diastolic function and heart rate recovery after symptom-limited exercise. J Card Fail 2012;18(1):34-40.
9. Patel V, Critoph CH, Finlay MC, Mist B, Lambiase PD, Elliott PM. Heart rate recovery in patients with hypertrophic cardiomyopathy. Am J Cardiol 2014;113(6):1011-7.
10. Powell AW, Jefferies JL, Hopkin RJ, Mays WA, Goa Z, Chin C. Cardiopulmonary fitness assessment on maximal and submaximal exercise testing in patients with Fabry disease. Am J Med Genet A 2018;176(9):1852-7.
11. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. JAMA 2000;284(11):1392-8.

12. Ephrem G, Levine M, Friedmann P, Schweitzer P. The prognostic significance of frequency and morphology of premature ventricular complexes during ambulatory Holter monitoring. Ann Noninvasive Electrocardiol 2013;18(2): 118-25.
13. Lee V, Perera D, Lambiase P. Prognostic significance of exercise-induced premature ventricular complexes: a systematic review and meta-analysis of observational studies. Heart Asia 2017;9(1):14-24.
14. Wilkoff BL, Corey J, Blackburn G. A mathematical model of the cardiac chronotropic response to exercise. J Electrophysiol 1989;3(3):176-80. Available at: https://doi.org/10.1111/j.1540-8167.1989.tb01549.x
15. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005;352(19): 1951-8.
16. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation: including pathophysiology and clinical applications. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 154-180
17. Schiffmann R, Warnock DG, Banikazemi M, Bultas J, Linthorst GE, Packman S, et al. Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. Nephrol Dial Transplant 2009;24(7):2102-11.
18. Messineo FC. Ventricular ectopic activity: prevalence and risk. Am J Cardiol 1989;64(20):53J-56J.
19. Hingorani P, Karnad DR, Rohekar P, Kerkar V, Lokhandwala YY, Kothari S. Arrhythmias seen in baseline 24-hour Holter ECG recordings in healthy normal volunteers during phase 1 clinical trials. J Clin Pharmacol 2016;56(7):885-93.
20. Frolkis JP, Pothier CE, Blackstone EH, Lauer MS. Frequent ventricular ectopy after exercise as a predictor of death [published erratum appears in N Engl J Med 2003;348(15):1508]. N Engl J Med 2003;348(9):781-90.
21. Jouven X, Zureik M, Desnos M, Courbon D, Ducimetière P. Long-term outcome in asymptomatic men with exercise-induced premature ventricular depolarizations. N Engl J Med 2000;343(12):826-33.
22. Robinson B, Xie L, Temple J, Octavio J, Srayyih M, Thacker D, et al. Predicting utility of exercise tests based on history/Holter in patients with premature ventricular contractions. Pediatr Cardiol 2015;36(1):214-8.
23. Baig S, Edward NC, Kotecha D, Liu B, Nordin S, Kozor R, et al. Ventricular arrhythmia and sudden cardiac death in Fabry disease: a systematic review of risk factors in clinical practice. Europace 2018;20(FI2):f153-f161.
24. Doan AE, Peterson DR, Blackmon JR, Bruce RA. Myocardial ischemia after maximal exercise in healthy men: a method for detecting potential coronary heart disease? Am Heart J 1965;69:11-21.
25. Linhart A, Kampmann C, Zamorano JL, Sunder-Plassmann G, Beck M, Mehta A, et al. Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. Eur Heart J 2007;28(10):1228-35.
26. Krämer J, Nordbeck P, Störk S, Ritter C, Ertl G, Wanner C, Weidemann F. Electrical changes in resting, exercise and Holter electrocardiography in Fabry cardiomyopathy. JIMD Rep 2015;28:19-28.
27. Wilson HC, Hopkin RJ, Madueme PC, Czosek RJ, Bailey LA, Taylor MD, Jefferies JL. Arrhythmia and clinical cardiac findings in children with Anderson-Fabry disease. Am J Cardiol 2017;120(2):251-5.
28. Jae SY, Kurl S, Laukkanen JA, Zaccardi F, Choi YH, Fernhall B, et al. Exercise heart rate reserve and recovery as predictors of incident type 2 diabetes. Am J Med 2016;129(5):536.e7-12.