Fabry Exercise Intolerance STudy

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Primary Objective(s):1. To study the presence and extend of exercise intolerance in male, female FD patients with classical FD and men with non-classical FD, in different stages of the disease.2. To determine the aetiology of exercise intolerance in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Observational invasive

Summary

ID

NL-OMON55038

Source
ToetsingOnline

Brief title
FEISTY

Condition

- Cardiac disorders, signs and symptoms NEC
- Congenital and hereditary disorders NEC

Synonym
angiokeratoma corporis diffusum, Fabry disease

Research involving
Human

Sponsors and support

Primary sponsor: Interne Geneeskunde- Endocrinologie en Metabolisme
Source(s) of monetary or material Support: Eigen afdelingsgeld;stichting SPHINX Amsterdam en United for Metabolic Diseases (collectebusfonds) en FSIGN (Fabry patientenvereniging)

Intervention

Keyword: Cardiopulmonary tests, Exercise intolerance, Fabry disease

Outcome measures

Primary outcome

1. Differences in V*O2 kinetics between FD patients and healthy control subjects as a readout of exercise capacity.

2. To assess the aetiology of exercise intolerance study parameters and clinical follow-up data (Amsterdam UMC clinical Fabry database) will be used. The following parameters will be taken into account and compared with the healthy control group (NB cardiac imaging will not be performed the control group):

- Pulmonary involvement/ bronchial obstruction:

Pulmonary function test: abnormal FEV1/VC (Tiffeneau-index) at rest. During maximum CPX test: low V*O2 max, anaerobic threshold, low ventilation (VE) reserve, high heart rate (HR) reserve, high CO2 ventilation equivalent (EqCO2) and low O2 saturation O2 (pulse oximetry, SpO2).

- Cardiac dysfunction:

Cardiac imaging (part of routine clinical follow-up in FD patients): signs on echocardiogram of Heart failure with preserved ejection fraction (HFpEF): low early diastolic mitral annular velocity e* (septal < 7 cm/s and lateral < 10 cm/s), the ratio of transmitral Doppler early filling velocity to tissue

Doppler early diastolic mitral annular velocity (E/e*) >= 9 or tricuspid regurgitation (TR) velocity > 2.8 m/s, global longitudinal strain (GLS) < 16%, left atrial volume index (LAVI) >= 29 ml/m2, left ventricular mass index (LVMi) of 115 g/m2 and 95 g/m2 for men and women, respectively, relative wall thickness > 0.42, left ventricular wall thickness >= 12 mm), biochemical: NT-proBNP >= 125 pg/ml (sinus rhythm) and NT-proBNP >= 365 pg/ml (atrial fibrillation).
During maximum CPX: low V*O2 max, low HR reserve, low Cardiac output (CO) and low anaerobic threshold. High EqCO2 and a O2 pulse plateau.

- Skeletal muscle alterations:
During maximum CPX: Low V*O2 max, low HR reserve, low maximum O2 pulse, low AT. High VE reserve. Muscle biopsy with typical signs of sphingolipid accumulation (electron microscopy) and mitochondrial dysfunction. Signs of muscle atrophy and strength in comparison to the healthy control subjects.

Secondary outcome

To determine whether the proposed intermittent exercise test protocol can be used to measure treatment outcome in future studies and to validate if the intermittent exercise test can be useful for clinically meaningful outcomes, one can correlate the V*O2 kinetics during intermittent exercise to:

1. V*O2 max on the incremental maximum CPX;
2. The activity score on the SQUASH Questionnaire.

Study description

Background summary

Fabry disease (FD) is an inherited, highly variable and slowly progressive X linked disorder, which predominantly affects vascular endothelium, the heart, kidneys and the brain. Exercise intolerance is a complaint expressed by the majority of patients, at all stages of the disease. The exact cause, extent and development over time of exercise intolerance in FD is insufficiently understood. This limits preventive measures and adequate treatment.

Study objective

Primary Objective(s):
1. To study the presence and extend of exercise intolerance in male, female FD patients with classical FD and men with non-classical FD, in different stages of the disease.
2. To determine the aetiology of exercise intolerance in Fabry disease.

Secondary Objective(s):
1. To determine whether the exercise test protocol used in this study can be used as a clinical outcome measure in future intervention studies.
2. To investigate difference in the time-relation between V*O2 and circulatory, ventilatory and metabolic variables during intermittent exercise between FD patient groups. These time-relations can provide an indication of the source of possibly slowed V*O2 kinetics.

Study design

Monocenter cross-sectional prospective cohort study.

Study burden and risks

1. The number of site visits: two phone visits and one study visit (One extra study visit in case of optional percutaneous muscle biopsy). Total hours for physical visits: 5 hours. In case of an extra visit: 6 hours.

2. Questionnaires: two questionnaires SQUASH, and (Modified medical research council (mMRC) dyspnea scale) questionnaire. The estimated time to fill in these two questionnaires is 20 minutes.

3. Study procedures: muscle strength test, echo of the leg, rest spirometry, maximum incremental and intermittent CPX test. The estimated time for all this procedures is five to six hours.

4. Blood and other tests: intravenous blood will be taken at two points. The total blood volume that will be drawn is 13.5 ml (3 ml extra in case of optional percutaneous muscle biopsy) . The risk of drawing blood may include some dizziness, discomfort around the bruise and a very low risk of infection.

5. Optional test will be a muscle needle biopsy of m. vastus lateralis, associated with pain and muscle bleeding/ hematomas.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

For FD patients:
- Men and women with a definite known diagnosis of FD.

For Healthy controls:

- Healthy control subjects (men and women) with an age of 18 years or older.

Exclusion criteria

For FD patients:
- Pregnancy;
- Recent acute myocardial infarction (<6 months);
- Uncontrolled arrhythmia/severe conduction disorder (atrial fibrillation or second/third-degree AV block) causing hemodynamic compromise;
- Implantable pacemaker or other cardiac device with complete ventricular pacing;
- Uncontrolled heart failure with hemodynamic compromise;
- Uncontrolled hypertension (Systolic Blood Pressure >150 mmHg and Diastolic Blood Pressure > 100 mmHg on repeated measurements);
- Using medication mimicking chronotropic incompetence (e.g. beta-blockers) that cannot be ceaed 24h in advance of testing.
- Active infection, anaemia, severe renal dysfunction (estimated Glomerular filtration rate <30 ml/min/1,73m2) likely to significantly impact on exercise performance;
- In case of visit 2: use of direct or indirect anticoagulants therapy (DOAC or vitamin K antagonists)

For healthy controls:
- All above mentioned exclusion criteria for FD patients;
- History of reduced lung capacity caused by smoking
- History of active drug use which can affect exercise intolerance;
- History of asthma, chronic obstructive pulmonary disease, heart failure, heart surgery, heart rhythm disorders or congenital heart diseases;
- Use of chronic medication likely to affect exercise tolerance;
- Chronic illness (including orthopaedic, endocrinological, haematological, malignant, gastrointestinal, neurological, muscle or inflammatory disorders) likely to significantly impact on exercise performance;
- > 6 alcohol units per day or >14 alcohol units per week.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-10-2021
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	08-04-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT05413876
CCMO	NL73534.018.21