Focus on Energy Metabolism in Arrhythmogenic Cardiomyopathy

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To determine whether a standardized exercise workload elicits a different response on 1) metabolites/cardiac biomarkers in the general circulation (measured by blood values), and 2) contraction patterns in local myocardium (measured by...

Ethical review	Approved WMO
Status	Completed
Health condition type	Myocardial disorders
Study type	Observational invasive

Summary

ID

NL-OMON56014

Source
ToetsingOnline

Brief title
FUEL-cardiomyopathy

Condition

- Myocardial disorders
- Chromosomal abnormalities, gene alterations and gene variants

Synonym
arrhythmogenic right ventricular cardiomyopathy; heart muscle disorder in which the heart muscle is replaced by fat and fibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ZonMW Off Road financierinsinstrument

Intervention

Keyword: Arrhythmogenic cardiomyopathy, Exercise, Metabolism

Outcome measures

Primary outcome

There will be two main study parameters: 1) blood metabolite/biomarker levels (e.g. fatty acids, ketones, troponin and nt-proBNP); and 2) echocardiographic parameters (e.g. right ventricular dimension/function and systolic right ventricular pressure, as well as deformation patterns).

As a primary analysis, the main study parameters will be univariably compared between affected ACM patients and controls.

Secondary outcome

Secondary study parameters include the occurrence of VA during the exercise test (defined as (non-) sustained ventricular tachycardia, ventricular fibrillation, or appropriate intervention from an implantable cardioverter-defibrillator).

As a secondary analysis, the main study parameters will be compared between preclinical ACM mutation carriers and controls, and the main study parameters will be associated with the occurrence of VAs.

Study description

Background summary

Arrhythmogenic cardiomyopathy (ACM) is an inherited heart muscle disease that is associated with a risk of potentially life-threatening ventricular arrhythmias (VAs). The disease is caused by pathogenic DNA variants (*mutations*). Remarkably, the majority of VAs in ACM patients occur during exercise, and exercise increases penetrance among ACM-associated pathogenic mutation carriers. While this suggests that exercise is an environmental modifier of ACM, evidence that explains the interaction between exercise and ACM expression is lacking. We hypothesize that patients with ACM have impaired metabolic function, which makes them susceptible to disease development upon exercise.

Study objective

To determine whether a standardized exercise workload elicits a different response on 1) metabolites/cardiac biomarkers in the general circulation (measured by blood values), and 2) contraction patterns in local myocardium (measured by echocardiography) between affected ACM patients and healthy controls. As a secondary objective, we aim to determine whether similar differences can be observed in unaffected ACM mutation carriers versus controls, and whether these metabolic changes are related to VA occurrence.

Study design

Cross-sectional single-center observational case-control study.

Study burden and risks

Affected and preclinical ACM mutation carriers routinely undergo exercise testing and echocardiography as part of their annual ACM workup. This study adds non-invasive breath-gas analysis, two blood draws and an overnight fast. These procedures are thought to have a negligible risk to the patient, while the potential benefit of understanding the role of exercise in ACM pathogenesis is large.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

Affected ACM patients:
- Carrier of a (likely) pathogenic PKP2 variant (i.e. class 4 or 5 variant as per American College of Medical Genetics guidelines).
- Fulfillment of definite ACM diagnosis as per 2010 Task Force Criteria.
- Written informed consent.

Preclinical ACM mutation carriers:
- Carrier of a (likely) pathogenic PKP2 variant (i.e. class 4 or 5 variant as per American College of Medical Genetics guidelines).
- No fulfillment of definite ACM diagnosis as per 2010 Task Force Criteria.
- Written informed consent.

Healthy controls:
- No prior history of cardiac complaints.
- Normal echocardiogram.
- Normal ECG.
- Written informed consent.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded

from participation in this study:

Affected and preclinical ACM mutation carriers:
- Not carrying a (likely) pathogenic PKP2 variant (i.e. class 4 or 5 variant as per American College of Medical Genetics guidelines).
- Prior life-threatening arrhythmia during exercise (including sudden cardiac arrest, ventricular fibrillation, sustained ventricular tachycardia, appropriate implantable cardioverter-defibrillator intervention)
- Unwilling or unable to provide written informed consent

Healthy controls:
- Prior history of cardiac complaints
- Abnormal echocardiogram
- Abnormal ECG
- Unwilling or unable to provide written informed consent

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:	Completed
Start date (anticipated):	05-04-2024
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	30-08-2023
Application type:	First submission
Review commission:	METC NedMec

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
CCMO	NL84335.041.23