Exercise Capacity in Congenital Heart Disease: The Role of Muscle Metabolism

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To investigate whether patients with pulmonary arterial hypertension, Fontan circulation and tetralogy of Fallot have an impaired skeletal muscle energy metabolism compared to healthy controls.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital cardiac disorders
Study type	Observational non invasive

Summary

ID

NL-OMON45601

Source
ToetsingOnline

Brief title
Exercise Capacity in Congenital Heart Disease

Condition

- Congenital cardiac disorders

Synonym
congenital heart disease, decreased exercise tolerance

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: 31 P MRS, congenital heartdisease, exercise capacity, muscle metabolism

Outcome measures

Primary outcome

o Quadriceps phosphocreatine concentration (PCr) at rest and during progressive exercise (exercise intensities 0-100% of workload corresponding to VO2max)

o Quadriceps inorganic phosphorus concentration (Pi) at rest and during exercise (exercise intensities 0-100% of workload corresponding to VO2max)

o Quadriceps pH at rest and during exercise (exercise intensities 0-100% of workload corresponding to VO2max)

o Post-exercise recovery rate of quadriceps PCr concentration

o Post-exercise recovery rate of quadriceps Pi concentration

o Post-exercise recovery rate of quadriceps pH

Secondary outcome

n.a.

Study description

Background summary

A decrease in exercise capacity is widely seen in patients suffering from various congenital heart diseases, including pulmonary arterial hypertension (PAH), Fontan circulation or tetralogy of Fallot (TOF). Several studies have shown lower maximal oxygen consumption compared to healthy controls.The lower exercise capacity seen in these patients has typically been attributed to a diminished cardiorespiratory function. As a result, scientific research into exercise intolerance in these patients has focused mainly on the hemodynamic and cardiorespiratory function * e.g., reduced ventricular function and cardiac output. Patients with pulmonary arterial hypertension, tetralogy of Fallot or a Fontan circulation are at risk of developing progressive heart failure over

time, with consequential reduction of cardiac output and peripheral circulation. Results of recent research has shown that in addition to cardiac output, peripheral hemodynamic and muscular changes such as atrophy, morphological, vascular or metabolic changes may contribute to exercise intolerance in these patients. It is, however, unclear whether these muscular changes are an adaptation to inactivity, reduced peripheral circulation or whether these are intrinsic abnormalities associated with the cardiac disease. Insight in this will help assessing if and which interventions (training, metabolic suppletion) might be beneficial in optimizing exercise tolerance, and thus quality of life for these patients. In the proposed study, the focus will be set at the peripheral factor thought to play an important role in the reduced exercise tolerance in these groups of patients.
This study will, for the first time, acquire measurements of skeletal muscle metabolic function in these groups of patients aiming to find significant differences with healthy controls. Since no such data exist for these groups of patients this study will be performed using sample sizes of 15 subjects for each group.

Study objective

To investigate whether patients with pulmonary arterial hypertension, Fontan circulation and tetralogy of Fallot have an impaired skeletal muscle energy metabolism compared to healthy controls.

Study design

A cross-sectional case-controlled study using in vivo 31P Magnetic Resonance Spectroscopy measurements in skeletal muscle during a standardized in-magnet whole body exercise test.

Study burden and risks

Risk assessment for all groups:
31P MRS is a save and reliable technique for patients without contra-indications for undergoing MRI and is widely used in clinical examination and scientific research to non-invasively obtain in-vivo measurements of phosphorus concentrations in the human body. The combination of in-magnet exercise testing and 31P MRS is used successfully in a previously conducted study by van Brussel et al (2015) using adolescent subjects suffering from an idiopathic inflammatory myopathy. A study conducted by Werkman et al (2016) used a similar combination of in-magnet exercise and 31P MRS using adolescent subjects with cystic fibrosis.
Patients included in the proposed study will have no contra-indications for performing an exercise test at maximum intensity. During regular follow-up these patients undergo a cardiopulmonary exercise test (CPET) once every two years. Nevertheless, these patients are at higher risk when performing a

maximal exercise test compared to healthy subjects. Therefore, patients will only perform the second exercise test, which is a maximal intra-MRI exercise test. Also subjects will be screened for any contra-indications before undergoing a MRI examination.

Burden for patients and controls:
Patients with pulmonary arterial hypertension, Fontan circulation and tetralogy of Fallot undergo a CPET on a regular basis during their follow-up. Therefore, this data already exists and a CPET does not have to be repeated for this study. This is both patient-friendly as well as reducing the risk for participating patients, since they don*t have to perform a maximal exercise test. Participating patients need to visit the Neuro Imaging Center just once for approximately 1 hour. During this visit participants have to perform an exercise test inside a 3T MRI scanner using a MR-compatible ergometer. Personal data acquired from the subject*s CPET will be used to recreate work load increments on the MR-compatible ergometer resulting in exercise intensity at 0 - 100% of VO2max.
Patients with pulmonary arterial hypertension, Fontan circulation and tetralogy of Fallot are expected to have decreased exercise capacity. According to our hypothesis, assuming these subjects are expected to have an altered muscular metabolism, chances are to induce muscle pain temporarily as in untrained subjects. Since subjects undergo a short maximal exercise test, we expect muscle pain to be minimised and therefore classify the burden for patients as minimal. We will monitor these patients accordingly during the study period.

Since healthy subjects have no contra-indications to perform exercise at maximal intensity we classify the burden for healthy subjects as minimal and will not monitor these subjects during the study period.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Patients with pulmonary arterial hypertension:
- Between 8 and 18 years of age
- Diagnosis confirmed at the UMC Groningen
Patients with a Fontan circulation:
- Between 8 and 18 years of age
- Diagnosis confirmed by the UMC Groningen
- Successfully undergone a Fontan procedure
- Stable haemodynamic condition
Patients with tetralogy of Fallot:
- Between 8 and 18 years of age
- Diagnosis confirmed by the UMC Groningen
- Successfully undergone procedure to repair the abnormalities;Healthy subjects between 8 and 18 years of age, without significant cardiac defect or known comorbidity affecting exercise tolerance.;All parents and subjects from 12 y.a.o.:
Written informed consent

Exclusion criteria

Patients and controls:
- age <8 and >18
- not familiar with the Dutch language
- ineligible to perform an exercise test
- with contra-indications for 31P/1H MRS examination
- (suspected) pregnancy
- mental retardation
- with comorbidity affecting exercise tolerance (Anaemia, musculoskeletal injury)

- being under examination for non-diagnosed disease at the time of investigation
Patients:
- with severe complications due to cardiomyopathy/arrhythmia
- with exacerbation of disease at time of investigation
- with a pacemaker implanted
- with severe complications due to epilepsy
- with musculoskeletal disease (i.e. muscular dystrophy)

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-09-2017
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	08-06-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL60210.042.16