COBRA3 (COngenital heart defects: BRidging the gap between growth, maturation, Regeneration, Adaptation, late Attrition and Ageing)

We want to research the effects of growth, maturation and regeneration on the aging of the heart in patients with a congenital heart defect.

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON29512

Source
Nationaal Trial Register

Brief title
COBRA3

Health condition

Congenital heart disease
Tetralogy of Fallot (TOF)
Atrial septal defect (ASD)
Univentricular heart

Pulmonary arterial hypertension

In het Nederlands: Aangeboren hartafwijkingen, Tetralogie van Fallot, atrium septum defect, pulmonale hypertensie, univentriculair hart.

Sponsors and support

Primary sponsor: Erasmus Medical Centre Rotterdam
Source(s) of monetary or material Support: Dutch Heart Foundation

Intervention

Outcome measures

Primary outcome

- Right and/or left ventricular or single ventricular end-systolic volume indexed to body surface area (ml/m2 BSA) (patients > 7 years of age)

- Maximal oxygen uptake (adjusted for age, gender and weight) (children > 5 years of age, adults) (not in PAH patients)

Secondary outcome

- Maximal work load (in VSD, ASD, Fallot and Fontan patients) / walking distance in 6 min (only PAH patients). (adjusted for age, gender and
weight) (if age permits).
- Right and/or left ventricular or single ventricular ejection fraction.
- Regional right and/or left ventricular or single ventricular strain / strain rate.
- NT-pro-BNP levels in blood.

Study description

Background summary

Congenital Heart Defect (ConHD) is the most common birth defect, affecting 0.8% of live births. After invasive treatment, many ConHD patients survive with relatively few problems for many years, despite abnormal loading conditions of the heart. However, about 50% of patients with ConHD reaching adulthood die from heart failure, arrhythmias or pulmonary hypertension, especially in diseases affecting the right ventricle (RV). This morbidity and mortality in young adulthood has created a new health care problem, affecting over 4 million patients with ConHD in North-America and Europe. Current progress in management, prognosis and therapy is hampered by our lack of: 1) mechanistic insight into the impact of

ConHD on postnatal growth, function and homeostasis of the heart, 2) ability to identify patients at risk in an early stage and 3) specific therapies aimed to prevent or reverse heart failure in the setting of ConHD. The heart of children grows rapidly, proliferates, remodels and has the potential to renew its cells. Our hypothesis is that these properties are important factors in preserving homeostasis in the context of ConHD and abnormal cardiac loading conditions during childhood, keeping attrition at bay. Therefore, the aims of our study are to gain mechanistic insight into the impact of ConHD on growth, renewal and homeostasis of the heart, especially the RV, to improve identification of patients at risk for attrition of heart function in ConHD and to establish the context to develop therapies to prevent or reverse heart failure or arrhythmias in ConHD patients. This study will enroll patients of several academic hospitals in the Netherlands.

Study objective

We think that the postnatal growth period is critical for establishing normal heart function, and that the interaction of growth and effects of ConHD in this period are clinically highly relevant. Because the postnatal growth period precedes the period of development of pathology seen in adult ConHD patients, the pediatric age range is the most suitable target age for establishing predictive parameters and targets for early, preventive, treatment.

To address the issues described above, we hypothesize that:

- in the pediatric age range favorable factors are active that help maintain myocardial homeostasis through identified (e.g. Hippo) and unidentified pathways.

- these pathways may be affected by the genetic and structural differences that were causative for - and result from - congenital heart defects.

- excess demand on these pathways, or their dysfunction, due to repeated and continued abnormal loading, leads to premature exhaustion of (regenerative) capacity to maintain homeostasis in adults with ConHD.

- favorable factors to stimulate maintenance of myocardial homeostasis as well as harmful factors related to pending failure and arrhythmias may be detected in blood of children and adults.

The overall aims of the consortium project are:

1. Assess the impact of ConHD on growth, renewal and premature ageing.

2. Identify mechanisms and factors of growth, renewal and cell death, epigenetic status, and the origin of cardiac cells during postnatal development and homeostasis.

3. Assess characteristics of the clinical state of the patients (including exercise capacity),

(pro-) arrhythmic changes and quantification of ventricular function.

Study design

Timeline study procedures group 1

Before operation:

- Echo

- Bloodsampling

- 24-h Holter monitoring

- MRI (>7 years of age)

- Exercise test (>5 years of age)

During operation/catheter intervention:

- Biopsy

2 weeks after operation/catheter intervention:

- Echo

- Blood sampling

- 24-h Holter monitoring

1 years after operation/catheter intervention:

- Echo

- Blood sampling

- 24-h Holter monitoring

- MRI (>7 years of age)

- Exercise test (>5 years of age)

Timeline study procedures group 2

During long-term follow-up after operation/catheter intervention

- Echo

- Blood sampling

- 24-h Holter monitoring

- MRI (>7 years of age)

- Exercise test (>5 years of age)

Methods/instruments:

ECG: Standard 12-lead and 24-hour ECG’s will be performed in all study participants.

24 hour Holter monitoring: In all participants 24 hour monitoring of heart rhythm with locally available Holter monitors will be performed.

Echocardiography: Two-dimensional and 3-dimensional echocardiography will be used to assess the following variables of cardiac size and function:

Magnetic resonance imaging, using 1.5 Tesla scanners and dedicated coils will allow assessment of variables of cardiac size and function:

Exercise testing will be used in children > 5 years of age and adults to assess
- peak oxygen uptake (in VSD, ASD, Fallot and Fontan patient)
- peak workload (in VSD, ASD, Fallot and Fontan patient)

Assessment of neurohumoral markers and new candidate biomarkers In both patients group as well as healthy controls, NT-pro BNP will be assessed using commercially availalable kits. New candidate biomarkers as obtained from the animal experiments in the consortium research will be assessed using relevant and available methods, depending on findings in the course of the project.
A maximum 5 ml (age 0-4 years) to 20 ml (age 10 and up) of blood will be drawn from an Intravenous cannula, directly prior to heart catheterization, surgery or imaging procedures, after > 10 min. rest in supine position

Intervention

All study procedures in patients in group 1 and 2 will be part of normal clinical follow-up and are explained in the subheading ‘timepoints’

Contacts

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Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
Patients fitting the inclusion diagnoses (see 4.1) will be selected from 2 groups of patients:

Group 1) Patients with a recent indication for cardiac intervention
a. with a recent diagnosis fitting the inclusion criteria, primarily infants and (young) children, scheduled for surgical correction, palliation or start of medical therapy
(target: 100 patients (divided among the 4 diagnostic categories)).

b. with an indication for re-intervention or introduction of additional medical therapy
(target 100 patients (divided among the 4 diagnostic categories)).

Group 2) Patients at mid- to long-term after intervention

a. children and adults that have had previous systematic evaluation in an earlier research project (Dutch Heart Foundation (DHF) 2006B026 (ToF)/ DHF 2008B026 (ToF)/ WAKF 2007 (ToF)/ DHF 2008B095 (Fontan) / PhDLUMC2009 (ToF, Fontan, ASD) and pulmonary hypertension research UMCG).

b. additional patients with similar diagnoses to provide balanced numbers between the groups (target 200 patients in category 2a and b (divided among the 4 diagnostic categories)). Patients in category 2 will undergo repeat evaluation or new evaluation mid- to long-term after an intervention.

Main objective of this study is to validate favorable factors that stimulate maintenance of myocardial homeostasis as well as harmful factors related to impending failure, as identified in the studies related to this project.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

For patients:

- Patients with mental retardation,

- Patients who have contra-indications for exercise testing,

- Patients with contra-indications for MRI.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-10-2015
Enrollment:	400
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	01-06-2015
Application type:	First submission

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
NTR-new	NL5129
NTR-old	NTR5269
Other	Toetsingonline number, Approval number provided by the METC of the Erasmus Medical Centre Rotterdam. : MEC-2014-326, NL48188.078.14

Study results

Summary results
not yet