COBRA3 Congenital heart defects: Bridging the gap between Growth, Maturation, Regeneration, Adaptation, late Attrition and Ageing

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1. to gain mechanistic insight into the impact of ConHD on growth, renewal and homeostasis of the heart, especially the RV2. to improve identification of patients at risk for attrition of heart function in ConHD3. to establish the context to develop...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Congenital cardiac disorders
Study type	Observational invasive

Summary

ID

NL-OMON41820

Source
ToetsingOnline

Brief title
The power of a child's heart

Condition

- Congenital cardiac disorders

Synonym
congenital heart disease

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Nederlandse Hartstichting

Intervention

Keyword: Cardiac arrhythmias, Congenital heart disease, Heart failure, Regeneration

Outcome measures

Primary outcome

1. Right and/or left ventricular or single ventricular end-systolic volume

indexed to body surface area (ml/m2 BSA) (patients > 7 years of age)

2. 2. Maximal oxygen uptake (adjusted for age, gender and weight) (children > 5

years of age, adults) (in VSD with PAH, ASD II, Fallot en Fontan patients not

in PAH patients)

Secondary outcome

a. Maximal work load (patients > 5 years of age)(in VSD, ASD II, Fallot en

Fontan patients) / walking distance in 6 min (only PAH patients)

b. Right and/or left ventricular or single ventricular ejection fraction,

c. Regional right and/or left ventricular or single ventricular strain / strain

rate,

d. 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.

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 loading conditions during childhood, keeping attrition at bay.

Study objective

1. to gain mechanistic insight into the impact of ConHD on growth, renewal and homeostasis of the heart, especially the RV
2. to improve identification of patients at risk for attrition of heart function in ConHD
3. to establish the context to develop therapies to prevent or reverse heart failure or arrhythmias in ConHD patients.

Study design

Prospective as well as cross-sectional patient-based study.

Study burden and risks

All clinical examinations, with the exception of myocardial biopsies, in the participating patients are the same as are routinely performed during follow-up of patients from the 4 diagnostic groups, including dobutamine stress MRI in Fallot and Fontan patients. For the purpose of the research proposal examinations will be clustered, and will be repeated before and after surgery, catheter intervention or change in drug regimen, if
applicable. All examinations will be performed on the same day, unless the patient prefers to participate on 2 consecutive days. The total duration of these examinations is a maximum of 2,5 hours all the medical examinations combined. Burden and risk are similar to those of regular clinical procedures and follow-up, that apply to all children and adults in this research proposal. During regular follow-up blood samples will be obtained with every check-up related to the current research proposal. The amount of blood drawn and the mode of acquisition will be in line with the local biobank protocol for study specific biobanking.

Only in those patients in whom a clinical indication exists for cardiac surgery, myocardial samples will be obtained according to clinical guidelines. Blood and myocardial biopsies will be stored in local university hospital biobanks for later use in the course of the current project.
Myocardial sampling is done strictly for scientific reasons. Samples will be taken from the region of the heart that will need to be approached by surgery for clinical reasons in tetralogy of Fallot patients and most patients with a univentricular heart. In patients with an ASD II, VSD and some univentricular heart patients with a body weight of > 8 kg, a surgical myocardial biopsy will be taken from the right ventricle (ASD II / VSD) or from the dominant ventricle in univentricular heart patients strictly for scientific reasons.
Group-relatedness exists because the study cannot be done in adults with similar disease types, since growth and growth related myocardial renewal and homeostasis cannot be studied in subjects in whom growth has ceased.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)

Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Prospective as well as cross-sectional patient-based study.
A total of 400 patients will be included, with 1 of following diagnoses:
- tetralogy of Fallot (ToF),
- atrial septal defect (ASD),
- univentricular heart
- pulmonary arterial hypertension (PAH). ;These patients will be selected from 2 groups of patients: ;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 heart catherization
(target: 100 patients (4 diagnostic categories)).
b. with an indication for re-intervention
(target 100 patients (4 diagnostic categories)). ;2) Patients at mid- to long-term after intervention
a. 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 (4 diagnostic categories)). ;In patients from group 1 changes in outcome parameters prior to and after intervention (surgery, catheter intervention, medical) will be assessed.
In patients from group 2a changes in these parameters between current and available baseline measurements will be assessed.

The different groups of ConHD will be age-matched which will allow identification of factors (in blood and myocardium) related to maintenance of homeostasis, in relation to type of diagnosis, residual loading abnormality, clinical state and age. ;Ad group 1: These patients will be studied prior to intervention and at regular time points until approximately 1 year after intervention (no longer because of time restrictions imposed by the format of the funding grant). ;Ad group 2: In category 2a data that is highly relevant for the current project of a total of approximately 400 patients with a diagnosis of ToF, ASD,Fontan or PAH, more than 1 year after intervention is already available. This data includes detailed information on medical history, past and current clinical status, ECG, regional ventricular function and ejection fraction (using TDi and speckle tracking echocardiography), metabolic exercise testing and of MRI-derived RV and LV volumes, wall mass and ejection fraction (at rest and with stress) and stored blood samples.

Exclusion criteria

patients with mental retardation,
patients who have contra-indications for exercise testing,
patients with contra-indications for MRI.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

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

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	16-02-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-02-2016

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL48188.078.14