Combined use of induced pluripotent stem cell derived cardiomyocytes and 3D-heart tissue to develop Therapies for pediatric heart failure in Tetratology of Fallot.

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

Summary

ID

NL-OMON51398

Source
ToetsingOnline

Brief title
CarkiT-Fallot

Condition

- Congenital cardiac disorders

Synonym
pulmonary atresia with ventricular septal defect, Tetralogy of Fallot

Research involving
Human

Sponsors and support

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

Intervention

Keyword: 3D-heart tissue, pluripotent stem cell derived cardiomyocytes, Tetratology of Fallot

Outcome measures

Primary outcome

To dissect genetic contribution to development of heart failure, i.e. dysfunction of cardiomyocytes, we intend to study induced pluripotent stem-cell derived cardiomyocytes (iPSC-CM) from patients with a known genetic mutation. The control group consists of iPSC-CMs from the same patients in which the mutation has been corrected in the stem cells using Crispr-cas9 technology, before the cardiomyocytes will be differentiated. Alternatively, we will use commercially available and other normal iPSC lines as controls. The main endpoints for the induced pluripotent stem-cell derived cardiomyocytes (iPSC-CM) are functional parameters: electrical conduction, calcium oscillations and force production. Corrected and uncorrected cardiomyocytes will be compared. We will perform RNA-sequencing and a modified form of RNA-sequencing (Ribo-Seq) to study the molecular consequences of the genetic mutation and stress-based effects. The iPSC-CM data will be correlated to the clinical phenotype of the patients. Due to the explorative nature of laboratory molecular research, endpoint of change of certain parameters cannot be given yet.

In the patients in which also cultured residual tissue obtained at surgery is available, the endpoints of these LTS are force production and force-frequency relationships.

Secondary outcome

Not applicable.

Study description

Background summary

Heart failure in congenital heart disease (ConHD) is the result of longstanding abnormal stress - or workload - for the heart even after surgery, in combination with a genetic mutation that leads to the ConHD itself. The most prevalent form of ConHD leading to heart failure is Tetralogy of Fallot (pulmonary atresia with ventricular septal defect). At present, no therapy exists to support the failing heart in ConHD. Hence, there is an urgent need to study mechanisms of pediatric heart failure in ConHD and test new therapeutic strategies. Recent studies suggest that genetic variations associated with the malformed heart in ConHD may also affect cardiomyocyte development and function and thereby contribute to heart failure. The research question of this study is to dissect the contribution of the genetic mutation to the development of pediatric heart failure in Tetralogy of Fallot (pulmonary atresia with ventricular septal defect) and to develop a platform to test therapeutic strategies. For that purpose, we aim to study cardiomyocytes derived from induced pluripotent stem cells (iPSCs), which in turn are generated from patients* blood. In patients in whom residual tissue will be available from surgery, we will compare the studies in cardiomyocytes with cardiac function studies obtained from cultures of residual tissues.

Study objective

The main objective of the study is to dissect the genetic and stress-based mechanisms on the development of pediatric heart failure in congenital heart disease (ConHD) with the use of induced pluripotent stem cell-derived cardiomycoytes (iPSC-CMs). The second objective is to develop a platform to test the efficacy of novel drugs / therapies on cardiomycyte function in iPSC-CMs from patients at risk to develop heart failure in ConHD. The third objective is to verify the results from iPS-CMs in cultured residual tisses obtained at surgery (LTS).

Study design

Observational, non-interventional, non-therapeutic patient-based study.

Study burden and risks

Burden: Single collection of 8 ml of blood will occur in combination with planned blood sampling or from cord blood. If the mutation is known before birth (in the case of antenatal diagnosis), blood will be collected from cord blood if possible, this will carry no burden. Alternatively, blood will be withdrawn before surgery or heart catheterization (if necessary), when the patient is under anaesthesia, which will not be painful, or during preparation before surgery in combination with routine blood sampling. Blood volume of patients during surgery is for children ~ 85 ml/kg, average weight at surgery 5 kg , hence 8 ml constitutes < 3% of total blood volume and can be withdrawn safely. Residual tissue obtained during surgery will be mounted in the 3D-LTS culture system. The other described investigations are all routine procedures during work up for surgery and follow up visits.
Benefits: there are no direct benefits for the patients associated with participation.
Group relatedness: This study can only be done in children with a ConHD since these patients are at risk or have developed heart failure. The children need surgery and hence residual tissue may become available. In addition, the genetic variation must be known, since routine genetic screening has become available for patients born last decade, this study can only be performed in children.

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)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

- Diagnosis as stated above
- Age between 0-18 years
- Known genetic mutation
- Written informed consent.

Exclusion criteria

- Non-consent to collect blood or residual tissue obtained at surgery or transplantation.
- Presence of multiple mutations or deletion of chromosome.

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):	25-03-2024
Enrollment:	5
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	23-09-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-07-2024
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	NL81863.078.22