A CELL-based platform to study the role of the micRotubule network in pediatric inHeritable arrhYTHMia patients and Improve the effiCacy of drug treatment

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Primary objectives: The first aim is to examine the role of microtubule network in electrical conduction, protein localization and function in induced cardiomyocytes from pediatric BrS patients, life threatening ventricular arrhythmia patients and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac arrhythmias
Study type	Observational invasive

Summary

ID

NL-OMON54599

Source
ToetsingOnline

Brief title
CELLRHYTHMIC STUDY

Condition

- Cardiac arrhythmias
- Cardiac and vascular disorders congenital

Synonym
cardiac arrhythmia and sudden cardiac death

Research involving
Human

Sponsors and support

Primary sponsor: Kindercardiologie
Source(s) of monetary or material Support: MRACE subsidie van het ErasmusMC en Subsidie van de Vrienden van het Sophia (geworven bij bedrijven en stichtingen)

Intervention

Keyword: Inheritable arrhythmia, Microtubuli, Pediatric, Sudden cardiac death

Outcome measures

Primary outcome

Spontaneous cellular contractions, electrical conduction and calcium oscillations in induced cardiomyocytes will be measured. Using fluorescence-based microscopy experiments, the effect of altered microtubule dynamics on electrical conduction will be studied as well as on the localization of important proteins and protein-protein interactions in the intercalated disk. We will test the efficacy of novel drugs by performing the same measurements. We will perform T2C measurements, RNA-Sequencing, and a modified form of RNA-Sequencing called Ribo-Seq, in order to study the transcription factor-based regulation of SCN5A expression, general molecular mechanism underlying the function of SCN5A, and molecular consequences of its dysfunction in arrhythmia patients. The induced cardiomyocytes data will be correlated to the clinical phenotype of the patients investigated by ECG, 24-hours 12-lead Holter monitoring, ECG during exercise testing, ECG during fever or ECG during Ajmaline testing, Signal Averaged ECG and echocardiography. Due to the explorative nature of laboratory molecular research (statistical consultation provided by Prof. dr. ir. H. Boersma, professor in clinical epidemiology of cardiovascular disease), endpoints of change in certain

parameters cannot be given yet.

Secondary outcome

Not applicable

Study description

Background summary

Sudden Cardiac Death (SCD) contributes 10% to Dutch pediatric mortality. At least 30% of SCD in children is caused by inheritable arrhythmia syndromes, mainly channelopathies like Brugada Syndrome (BrS), Long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). Timely prophylactic treatment of disease carriers will result in reduction of mortality and post-resuscitation morbidity. Phenotypic expression of BrS differs with respect to age of onset and severity of arrhythmia, even between patients with identical (SCN5A) mutations. However, for the majority of BrS patients (70-80%) no mutation has currently been identified. Knowledge of additional contributing factors responsible for a specific phenotypic expression is lacking, as is the identification of ultimate effective medical therapy to prevent potential life-threatening arrhythmia. Ventricular arrhythmia in BrS patients usually present between the 3rd and 4th decade. However currently also pediatric BrS patients are increasingly described in literature and seen in daily practice of pediatric cardiology. Underlying factors responsible for phenotypic expression or non-expression of BrS in the pediatric age group are unknown. Medical treatment to prevent life-threatening arrhythmia in these children is yet unavailable.
Recently, the microtubule cytoskeleton has been shown to fine-tune the function, transport, localization and turnover of proteins that are mutated in BrS and to be essential for electrical conduction in the heart.
We hypothesize that increasing microtubule stability ameliorates stability of electrical conduction and cardiac rhythm in pediatric BrS patients. This will provide new targets for arrhythmia treatment. A cell based platform, allowing to test efficacy of (novel) medication, will provide opportunities to develop and test tailor-made treatments for specific phenotypes of inheritable arrhythmia. In this project, pediatric BrS serves as a model for inheritable arrhythmia in pediatric patients that can be extended to other types of inheritable arrhythmia in children.

Study objective

Primary objectives: The first aim is to examine the role of microtubule network in electrical conduction, protein localization and function in induced

cardiomyocytes from pediatric BrS patients, life threatening ventricular arrhythmia patients and controls.
The second aim is to test the efficacy of novel drugs -potentially effective in the (prophylactic) treatment of arrhythmia in BrS- on the electrical and molecular properties of cultured induced cardiomyocytes derived from pediatric BrS patients and pediatric survivors of an out of hospital cardiac arrest due to ventricular arrhythmia. The third aim is to develop a model that allows prediction which children at risk for Brugada syndrome will develop a Brugada phenotype at what time in the future.

Study design

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

Study burden and risks

The risk and burden associated with the one-time collection of 10ml blood by venepuncture is that it will be painful for the child and can cause a localized, temporary hematoma. We aim to combine all the investigations on a regularly planned outpatient clinic visit. Drawing blood is usually not performed during regular outpatient clinic examinations and is therefore mentioned as study related (invasive) procedure. The other described investigations, except the non-invasive Signal Averaged ECG, are standardly used investigations during regular follow up of the described patient population. Of course for the healthy controls, the burden of participation is extended to an outpatient clinic visit with all the investigations described above because they do not need regular follow up in a cardiology outpatient clinic. We will ask patients planned for ear - nose - throat (ENT) surgery as control patients. Blood will then be drawn during general anaesthesia used for the surgery to minimize the burden of pain related to the venipuncture. The other investigations in control patients will be combined during other outpatient clinic visits that are obligatory in order to prepare the patient for the planned ENT surgery. There are no direct benefits to the patients associated with participation. Group relatedness: The study can only be done in the pediatric age group because we aim to search for specific factors that particularly predispose to a pediatric phenotype of BrS or life threatening arrhythmia. We expect to determine molecular changes either responsible for a BrS phenotype or protective against a BrS phenotype in childhood. Conversely, the phenotype of adult BrS patients is also influenced by myocardial changes related to aging of the heart and coronaries resulting in cardiac conduction and functional changes. These age-related changes might interfere with our phenotype analysis if we would study adult BrS patients. Since we aim to develop a cell based platform to test novel medication that eventually will be used to medically treat the pediatric phenotypes of BrS/life threatening arrhythmia, we need pediatric derived induced cardiomyocytes. These will optimally approximate the clinical and cellular phenotype and are therefore the

best model in order to predict medication effectiveness for the prevention of life threatening arrhythmia in pediatric patients.

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)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Age >= 0.5 and < 18 years and
Patient population/ cases
- Proven SCN5A mutation with phenotypic BrS,
- or a SCN5A mutation without phenotypic BrS,

- or phenotypic BrS, proven without specific genetically recognized mutation,
- or aborted SCD due to ventricular arrhythmia proven without recognized genetic mutations in currently known arrhythmia genes.
Control population:
- Phenotypic cardiac healthy persons with a negative family history of (non coronary related) SCD < 45 years of age, inheritable arrhythmia syndromes, pacemaker or ICD implantation and heart failure.
- Same age range as the patient cases
- Same gender proportion as the cases
- Planned Ear Nose Throat surgery without cardiac involvement in surgery or underlying disease
- Control patients will not be subjected to DNA testing because of the ethical inappropriateness to perform DNA diagnostics in healthy children under 18 years and the psychological burden and societal implications of eventual unexpected accidental genetic abnormalities found. The risk however to include a phenotypic cardiac healthy control patient accidently carrying a mutation in one of the known cardiac arrhythmia genes will be minimized by exclusion of controls with a family history of a potential inheritable arrhythmia syndrome.E,v#Î
- Non SCN5A mutation carrier without phenotypic BrS, sibling of a SCN5A mutation carrier with phenotypic BrS

Exclusion criteria

A potential subject patient population or control who meets any of the following criteria will be excluded from participation in this study:
- Non-consent for the collection of blood
- Presence of any other (anatomic) cardiac disease or cardiac conduction disturbance other than the ones described for the inclusion criteria.
- Additional known genetic mutations other than the ones described for the inclusion criteriaIn addition to the above exclusion criteria, healthy controls will be excluded if
- they have a positive family history for a potential inheritable arrhythmia syndrome defined as a positive family history for SCD < 45 years of age (exception: proven coronary disease), inheritable arrhythmia syndromes (e.g. BrS, LQTS, CPVT, idiopathic ventricular fibrillation or short QT syndrome), pacemaker or ICD implantation, or heart failure in first or second degree family members.

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:	Recruiting
Start date (anticipated):	14-12-2018
Enrollment:	16
Type:	Actual

Ethics review

Approved WMO Date:	09-07-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-04-2020
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	NL62724.078.18