Human induced pluripotent stem cells to unravel the pathophysiology of peripartum cardiomyopathy

Published: 04-06-2014
Last updated: 11-07-2024

Employing PPCM patient-derived iPSCs, we aim to test our hypothesis that cardiomyocytes from PPCM patients exhibit (epi)genetically determined differences in protein expression profiles and functional behavior in comparison to those from healthy…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Observational invasive

Summary

ID

NL-OMON40927

Source
ToetsingOnline

Brief title
PPCM-iPSC

Condition

- Heart failures

Synonym
Peripartum cardiomyopathy, pregnancy-related heart failure

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: NWO,Hartstichting

Intervention

Keyword: cardiomyocytes, differentiation, induced pluripotent stem cells, reprogramming

Outcome measures

Primary outcome

- IPS cells can be generated from skin fibroblasts of test subjects and can be differentiated into cardiomyocytes.

- Cardiomyocytes derived from test subjects via IPS reprogramming show differences in expression profiles and in responses to stress in comparison to those of healthy controls.

Secondary outcome

Not applicable

Study description

Background summary

Peripartum Cardiomyopathy (PPCM) is a pregnancy-associated myocardial disease characterized by signs and symptoms of heart failure (HF). The etiology of PPCM is largely unknown. Using tissue of patients with PPCM may be helpful in unraveling the pathophysiology of the disease. However, in human this is challenged by the fact that myocardial biopsies are taken only in a minority of patients. The procedure is associated with the risk of myocardial perforation and gives only a limited amount of tissue. Furthermore, if biopsies are taken, this is mostly done in patients with already far advanced disease, and therefore the early changes in cardiomyocyte structure and signaling pathways remain unknown. Therefore a novel and innovative approach is needed.
With the use of human induced pluripotent stem cells (hiPSC) we will generate patient-specific cardiomyocytes that will be subjected to pregnancy related stress. This allows us to explore new pathways in PPCM. Finally, the influence of the target genes and microRNA's identified in the hiPSC experiments will be studied in relation to new onset HF in the general population.

Study objective

Employing PPCM patient-derived iPSCs, we aim to test our hypothesis that cardiomyocytes from PPCM patients exhibit (epi)genetically determined differences in protein expression profiles and functional behavior in comparison to those from healthy controls. We will therefore follow specific aims: Aim 1: To isolate skin fibroblasts from PPCM patients and healthy control individuals by punch biopsy under local anesthesia and store them after in vitro multiplication.
Aim 2: To reprogram the patient-derived skin fibroblasts into induced pluripotent stem cells (iPSCs) and, after full iPSC characterization/verification, differentiate them in vitro into cardiomyocytes.
Aim 3: To compare the characteristics of PPCM patient-derived cardiomyocytes with control ones using RNA sequencing, proteomic analyses and epigenomic profiling.
Aim 4: To expose PPCM patient and control-derived cardiomyocytes to different types of stress (stretch, oxidative, and hormonal) in vitro and compare their responses by analyzing their behavior and expression profiles.
Aim 5: To correlate findings in iPS cells to bloodlevels of certain proteins and microRNAs.

Study design

Non-therapeutic study, exploring 2 groups of 6 Dutch PPCM-patients and 2 groups of healthy controls, one visit research.
For the whole study, fibroblasts from 2 groups of 6 PPCM patients and 2 groups of 6 healthy controls will be used. One group of patients that suffered a severe case of PPCM and one group of patients that have recovered from (mild) PPCM will be selected. Each control group will consist of sisters of the PPCM patients. When sisters are unavailable, nieces will be selected. In total, 24 subjects will be selected.
After patient selection, a skin punch biopsy (6mm) will be performed according to standard procedures under sterile conditions and after local anesthesia at the cardiology outpatient clinic, UMCG. The skin biopsies will be collected in sterile physiological salt solution and transported to the lab of the dept. of Experimental Cardiology, UMCG. After tissue dissociation, fibroblasts will be cultured and multiplied under fibroblast specific/selective culture conditions. Part of these fibroblasts will be stored frozen; another part will be used for reprogramming into iPSCs and subsequently differentiated into cardiomyocytes according to procedures developed in the dept. of Experimental Cardiology, UMCG. Subsequently, the iPSC-derived cardiomyocytes will be subjected to extensive analyses, comprising proteomics, gene expression and epigenomic profiling. These characteristics will be compared with cardiomyocytes generated from iPSC lines derived from healthy controls. Control iPSC lines will be obtained from and equal number of healthy sisters. Healthy controls are all women aged of 18 years and older with no signs of HF development. All included subjects have to have been pregnant at least once.
In order to obtain baseline values, bloodsamples will be taken from all individuals involved and an echocardiogram will be made. The bloodsamples will

be stored for future reference to which we can compare findings obtained from the iPS cells; certain protein and microRNA levels will be determined from those bloodsamples.

Study burden and risks

From the PPCM patients and healthy control subjects, a small (6mm) skin biopsy will be taken from the inner side of the upper arm using a standard punch technique under local anesthesia. The only minimal risk involved in particpation may be the occurrence of infection (despite intense desinfection of the site of biopsy) (<1% of cases) ; effective treatment with antibiotic ointment.
The extent of risks involved in taken a blood sample is small. Minor complications may occur as an hematoma or an infection. These complications are very rare and blood samples will be taken by an expert.

Contacts

Public
Universitair Medisch Centrum Groningen

Antonius Deusinglaan 1
Groningen 9713 AV
NL
Scientific
Universitair Medisch Centrum Groningen

Antonius Deusinglaan 1
Groningen 9713 AV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients:
• Ages from 18 and older.
• Diagnosis PPCM according to the revised European Society of Cardiology guidelines 2012.
• Participation of healthy sister (or female cousin) that has been pregnant at least once without diagnosis of PPCM.
• Possibility of adequate communication.
• Informed consent is obtained.;Controls:
• Ages from 18 and older.
• Sister or (female) first cousin of patient.
• Generally in good health.
• Has been pregnant without cardiac complications.
• Possibility of adequate communication.
• Informed consent is obtained.

Exclusion criteria

Patients:
• Other etiology of heart failure other than PPCM.
• A healthy sister (or female cousin) cannot be included, for any reason.
• Severe complications during pregnancy (aside from PPCM).
• Extensive skin disorder precluding a biopsy from unaffected skin area.
• Known allergy for local anesthetics.
• Informed consent can, for whatever reason, not be obtained.;Controls:
• Has never been pregnant.
• Severe complications during pregnancy (including cardiac complications)
• Extensive skin disorder precluding a biopsy from unaffected skin area.
• Known allergy for local anesthetics.
• Informed consent can, for whatever reason, not be obtained.

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:	Recruitment stopped
Start date (anticipated):	02-12-2014
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO

Date:	04-06-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	24-06-2015
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	NL48062.042.14