Whole exome sequencing in patients with Idiopathic Ventricular Fibrillation and familial Atrial Fibrillation

Published: 08-06-2015
Last updated: 21-04-2024

Genotyping the population of patients with iVF and AF and detecting novel genes associated with iVF and AF. Secondary endpoints are correlation of the presence of gene defects and response to catheter ablation in AF patients and create a better...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac and vascular disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON42277

Source
ToetsingOnline

Brief title
The W-IVF/W-AF study

Condition

- Cardiac and vascular disorders congenital

Synonym
atrial fibrillation of unknown origin, life-threatening ventricular rythm disorder of unknown origin

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Familial atrial fibrillation, Idiopathic ventricular fibrillation, Whole exome sequencing

Outcome measures

Primary outcome

The detection of the underlying genetic cause of patients with IVF and fAF by:

1. The evaluation of the genetic burden of pathogenic mutations in a diagnostic panel of 212 cardiomyopathy genes.

2. The detection of novel genes/genetic factors responsible for IVF and fAF.

Secondary outcome

1. The correlation of the presence of gene defects and response to catheter ablation in AF patients.

2. The understanding of the pathophysiological mechanism and disease pathways of iVF and familial lone AF with functional studies using the extensive UMCU network with collaboration of the departments of biostatistics, medical physiology, experimental cardiology and the Hubrecht institute.

Study description

Background summary

Ventricular fibrillation (VF) is a major cause of SCD and around 25% of the patients with an out-of-hospital cardiac arrest (OHCA) show VF as initial rhythm. Most of these are caused by ischemia in patients with coronary artery disease.
The definition of idiopathic ventricular fibrillation (iVF) is an episode of documented VF without a causal connection to the clinical circumstances. The term idiopathic implies that up until present day, research has failed to

identify an underlying cause. In 95% of the patients with documented VF, an underlying structural or primary electrical cardiac disease is found. 5% of all patients with VF are diagnosed with iVF.
In several other forms of primary arrhythmia syndromes, a genetic cause has been detected. For instance in the long QT syndrome (LQTS), once thought to be idiopathic, 13 genes responsible for this disease have been identified. Possibly this applies to iVF as well.
20% of the patients with iVF have a family history positive for sudden death. This suggests a genetic origin in patients with familial iVF. Genetic testing is becoming more important and new genes responsible for iVF have been identified, such as the DPP6-haplotype. With the discovery of the DPP6-haplotype, more evidence is becoming available that iVF does not exist, but currently unknown genetic defects are responsible for a high susceptibility for VF. In order to detect this genetic origin, Whole Exome Sequencing (WES) should be performed in patients with iVF, where the regular genetic screening has failed to detect a genetic cause.

Mostly AF is secondary to, or associated with cardiovascular conditions such as hypertension, coronary artery disease, valvular disease and cardiomyopathies. AF sometimes develops in a subset of young patients with no underlying identifiable cardiopulmonary causes or other comorbid disease. This is referred as *lone* or *idiopathic* AF. The diagnosis lone AF is made by excluding all underlying causes. The true prevalence of lone AF is unknown. It varies between 1.6% and 30%, depending on the definition used for lone AF and the population studied.
Lone AF can occur in patients with and without a positive family history of AF. Increasing evidence is becoming available that familial lone AF has an underlying genetic origin. 9 Multiple target genes responsible for AF have been identified, such as KCNQ1, KCNE2, KCNJ2, SCN5A, GJA5, GJA1 and NPPA and novel genes are still being identified.

Study objective

Genotyping the population of patients with iVF and AF and detecting novel genes associated with iVF and AF. Secondary endpoints are correlation of the presence of gene defects and response to catheter ablation in AF patients and create a better understanding in the pathophysiological mechanism and disease pathways of iVF and familial lone AF.

Study design

The study is a single-center cohort study, where patients with iVF and familial lone AF will undergo WES. If necessary, reference databases are used (such as the genome of the Netherlands) to determine the pathogenicity of a found genetic mutation.

Study burden and risks

Discovering the aetiology of iVF is a necessary first step to improve the detection, treatment and follow-up in patients with iVF and to prevent the occurrence of sudden cardiac death. In AF-patients, the knowledge of having genetic predisposition to AF can be useful in risk-stratification and starting prophylactic treatment to prevent morbidity, such as heart failure and stroke, and mortality. WES has a relatively low burden and has no risks. In patients where no DNA is available, it will be obtained by the withdrawal of 2x 10 mL of blood by venepuncture. This is the only invasive study procedure. Information on the possible outcomes of WES is provided, and the possibility of disclosure of unsolicited findings is addressed as well, so all patients can make a well-informed decision.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients with iVF:
All documented patients with:
• A sudden cardiac arrest with initial rhythm of VF.
• Who were diagnosed with iVF after careful phenotyping and exclusion of all structural or primary electrical cardiac disease.
• In whom regular genetic testing has not detected a known gene mutation associated with the occurrence of VF. ;Patients with (familial) lone AF
• Patients with at least 1 episode of documented AF
• No present structural or systemic cause for AF, excluded by past medical history, anamnesis, physical examination, laboratory results, electrocardiogram, X-thorax and echocardiography
• <60 years of age at the time of the first presentation of AF
• Who have at least 1 first degree family member with *lone* atrial fibrillation.

Exclusion criteria

• Patients not capable of giving inform consent
• <18 years
• Objection to the reporting of unsolicited findings in category A

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-09-2015
Enrollment:	70
Type:	Actual

Ethics review

Approved WMO Date:	08-06-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL50981.041.14