Ajmaline provocation in early detection of Arrhythmogenic Cardiomyopathy

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Describe the electrocardiographic changes and areas of late myocardial activation encountered in PLN and PKP2 mutation carriers during ajmaline provocation and the relation of these differences to the development for early stages of arrhythmogenic...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Myocardial disorders
Study type	Interventional

Summary

ID

NL-OMON46598

Source
ToetsingOnline

Brief title
Ajmaline provocation in early detection of Arrhythmogenic Cardiomyopathy

Condition

- Myocardial disorders
- Cardiac and vascular disorders congenital

Synonym
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), Arrhythmogenic Right Ventricular Dysplasia (ARVD)

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Hartstichting door middel van het e-DETECT consortium

Intervention

Keyword: Ajmaline provocation, Arrhythmogenic Cardiomyopathy, Asymptomatic mutation carriers, early detection

Outcome measures

Primary outcome

The mean difference in local Activation Time Duration before ajmaline administration and at the maximal amount of ajmaline administration in the subtricuspid area, the mid right ventricle area, right ventricular outflow tract, the left ventricle anterior area and left ventricle posterolateral area as calculated by ECG imaging.

Secondary outcome

Mean differences in epicardial and endocardial Activation Time Duration before and at the maximal amount of ajmaline administration in these specified areas (subtricuspid area, the mid RV area, RVOT, the LV anterior and LV posterolateral) as calculated by ECG imaging.
Electrocardiographic parameters (PQ, QRS and QTc intervals, the occurrence of the type I Brugada pattern, terminal activation duration) before, during and directly after ajmaline provocation.

Other study parameters:
Patient demographics: Sex, Age, Past medical history (including previous episodes of ventricular tachycardia and the results of cardiovascular diagnostic test, for example cardiac holters, cardiac MRI and echocardiography), Allergies, Family history of sudden cardiac death, the

amount of 2010 Task Force Criteria points for arrhythmogenic cardiomyopathy

(ACM) currently used medication, Weight (kg), Length (cm), Body mass index.

Laboratory parameters: Before ajmaline provocation: Creatinine and GFR, Sodium,

Potassium, ALAT, ASAT, GGT, AF, bilirubin.

Two weeks after ajmaline provocation: ALAT, ASAT, GGT, AF, bilirubin.

Study description

Background summary

Arrhythmogenic Cardiomyopathy (ACM) is a disease with a genetic origin and involves cardiac desmosomes dysfunction and fibrofatty replacement of the myocardium. Clinically, patients present with ventricular arrhythmias or sudden cardiac death. Genetic testing in family members of patients with ACM shows incomplete penetrance and variable expression, especially in the early disease state. Unfortunately, currently used diagnostic test are unable to predict the development of ACM in asymptomatic mutation carriers. This is bothersome, since life threatening arrhythmias and sudden cardiac death might be the first signs of disease progression.

Studies have shown that plakophilin-2 (PKP2) insufficiency due to PKP2 mutation leads to down regulation of cardiac sodium channels along with the desmosomes. This down regulation of sodium channels results in conduction slowing due to dysfunction of the cardiac desmosomes and gap junctions. Earlier imaging studies have shown that the electromechanical interval and RV deformation imaging is abnormal in the subtricuspid area of the right ventricle (RV) even in the early stage of disease. We hypothesize that provocation with a sodium blocker such as ajmaline induces more pronounced electrical dysfunction of those myocardial areas that are affected in the early stage of ACM. Therefore, this ajmaline challenge could identify those mutation carriers who are at risk for the development of ACM, arrhythmias and/or sudden cardiac death.

Study objective

Describe the electrocardiographic changes and areas of late myocardial activation encountered in PLN and PKP2 mutation carriers during ajmaline provocation and the relation of these differences to the development for early

stages of arrhythmogenic cardiomyopathy.

Study design

Multicentre, diagnostic trial and cohort study.
T0. Inclusion of patients ((1) patients with arrhythmogenic cardiomyopathy, (2) asymptomatic mutation carriers, (3) controls.)
T1. Ajmaline provocation (T1): Electrocardiographic imaging will be performed before and after ajmaline infusion.
T2. Laboratory follow up (T2) Two weeks after the ajmaline challenge the liver parameters will be tested using a single peripheral blood sample.

Intervention

Ajmaline (class 1c sodium channel blocker, with a short half-life) infusion in fractions of 10mg every minute up to a target dose of 1mg/kg.

Study burden and risks

Participants will undergo an ajmaline provocation test with a duration of approximately 2 hours. During the provocation, electrocardiographic imaging and the standard 12 lead ECG will be used to record cardiac activation times and the effects of ajmaline on de- and repolarization parameters. This test will be scheduled together with the other outpatients appointments. The risks of this intervention are low when using the generally accepted infusion protocol and the cardiac monitoring protocol, although there is a small risk of ventricular arrhythmias. This risk is short term (during infusion and cardiac monitoring) and minimalized with the protocol used for the ajmaline challenge. Ajmaline provocation is widely used and has been proven to be safe in patients with the suspicion of the Brugada syndrome.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Age >=18 years
Pathogenic PLN mutation, pathogenic PKP2 mutation or patients without structural heart disease who are referred for ajmaline provocation to exclude Brugada syndrome.
Referral for cardiac MRI during routine clinical practice
New York Heart Association functional class <= 1.

Exclusion criteria

Severe hepatic impairment (Child-Pugh class C)
Severe renal dysfunction (eGFR <30 ml/min/kg)
Symptomatic heart failure, NYHA >= 2
Women who are currently pregnant
Known intolerance or contraindication to Ajmaline
Sick sinus syndrome, second or third degree AV block
Recent myocardial infarction
Known strong allergic reaction to ECG electrodes
Current use of anti-arrhythmic drugs (Bruagdadrugs.org list class I, IIa, IIb)
Current or recent use of amiodarone (within 6 months)

Study design

Design

Study type:	Interventional
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):	25-04-2019
Enrollment:	72
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gilurytmal
Generic name:	Ajmaline

Ethics review

Approved WMO Date:	24-01-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	19-02-2019
Application type:	First submission
Review commission:	METC NedMec

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
EudraCT	EUCTR2018-000752-18-NL
CCMO	NL65196.041.18