# ACE inhibition in Fontan patients: its effect on body fluid regulation.

No registrations found.

| | |
|---|---|
| **Ethical review** | Positive opinion |
| **Status** | Recruiting |
| **Health condition type** | - |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON27721

**Source**
NTR

**Brief title**
SAFE

**Health condition**

Fontan patients/palliation/circulation/surgery

Single ventricle, univentricular heart

ACE-inhibition, Enalapril

### Sponsors and support

**Primary sponsor:** Leiden University Medical Centre (LUMC)
**Source(s) of monetary or material Support:** Sponsor

### Intervention

### Outcome measures

**Primary outcome**

- Cardiopulmonary exercise stress test: VO2peak.

- Cardiac autonomic nervous activity: heart rate variability and pre-ejection period.

- Outcome of passive leg raising and head up tilt table testing: cardiac output and cardiac autonomic tone.

**Secondary outcome**

- Echocardiography: Complete echocardiographic evaluation will be performed. This includes 2D imaging, colour Doppler and pulse wave velocity measurements of inflow and outflow through the cardiac valves. Tissue Doppler imaging as well as speckle tracking strain imaging will be performed. Special attention will be paid to hepatic venous blood flow patterns and superior caval venous (Glenn) flow patterns.

- Cardiopulmonary Exercise Stress Testing: A symptom limited maximal exercise stress test will be performed on a bicycle ergometer. During the stress test heart rate, and carbon dioxide production will be measured. This enables the assessment of maximal oxygen consumption, VE/VCO2 relationship and the measurement of the Oxygen Uptake Efficiency Slope (OUES).

- Blood Sampling: From a venous puncture blood will be taken to assess electrolytes (Na and K), kidney function (Creatinine and Urea), liver function (ASAT, ALAT, alkalic phosphatase, gamma globulin and bilirubin levels), albumin and NT-pro BNP levels.

- 24-hour monitoring of electrocardiography and impedance cardiography: To monitor ECG and ICG non-invasively, continuously during 24 hours we will use the VU-AMS device. By the use of seven electrodes on the thorax this ambulatory device continuously records the electrocardiogram, impedance cardiogram and movement (by means of a three axial accelerometer). VU-AMS makes it possible to monitor non-invasively in a continuous way during daily life activities heart rate, heart rate variability, stroke volume and pre ejection period. Respiratory sinus arrhythmia (derived from the electrocardiogram and respiration) is a measure of the cardiac parasympathetic activity; the pre ejection period (derived from combining electrocardiogram and impedance cardiogram signals) is an index of cardiac contractility and a reflection of cardiac sympathetic control. Respiratory sinus arrhythmia measured by the VU-AMS is based on the peak-valley method. The time between two successive R peaks in the electrocardiogram (the inter beat interval) is calculated by the VU-AMS software. The difference between the shortest interval during inspiration and the longest interval during exhalation is defined as the respiratory sinus arrhythmia and is used as a measure of cardiac vagal tone, representing the parasympathetic nervous activity. Pre-ejection period is defined as the time between the onset of the depolarization of the ventricles (reflected by the Q-onset in the electrocardiogram) and the opening of the aortic valves (reflected by the B-point in the impedance cardiogram) In addition, the impedance cardiogram can be used to assess stroke volume (changes).

- Aortic stiffness: By means of the arteriograph the pulse wave velocity of the aorta can be measured. This measurement is a surrogate of aortic stiffness. By means of the arteriograph, pulse wave velocity, augmentation index and central blood pressure can be measured non-invasively in a reliable and easy way.

- Outcome of passive leg raising and head up tilt table testing: After the baseline cardiovascular parameters have been performed the patient will undergo a passive leg raising test and a head up tilt table testing. There will be a period of at least 30 minutes between the two tests to allow the circulation to return to baseline levels.

- Passive leg raising: By means of passive leg raising an easy, safe and reversible fluid load can be given. After stabilization aortic pulse wave velocity will be measured by the arteriograph,
while using echocardiography changes inand hepatic venous blood flow can be measured. Cerebral blood flow will be measured by Doppler recordings.

- Head up tilt table testing: Passive head-up-tilt testing induces an easily and fast reversible unloading of the central blood volume. After stabilization aortic distensibility will be measured by the arteriograph, while using echocardiography changes in hepatic venous blood flow can be measured. Cerebral blood flow will be measured by Doppler recordings. A Finapres device will be used to continuously non-invasively measure blood pressure.

# Study description

**Background summary**

Rationale: There is no consensus on the use of ACE inhibition in Fontan patients without ventricular dysfunction. Multiple centres prescribe enalapril on a routine base for patients with a Fontan circulation and a preserved ventricular function, while other centres have considerable doubt about its effectiveness. Too little research has been done to the effectiveness of ACE inhibition in Fontan patients. There are as yet no studies available that investigate the effect of ACE inhibition on various cardiovascular parameters in patients with a Fontan circulation. By studying the effect of ACE inhibition on cardiovascular parameters as systolic and diastolic ventricular function, cardiac output, and the sensitivity of the cardiovascular system to fluid changes, the basic effects of ACE inhibition on the cardiovascular system of Fontan patients will become more clear. This will result in a more appropriate selection of patients that will profit of the use of ACE inhibitors.

Main objective: To treat Fontan patients for 3 months with the ACE inhibitor enalapril and compare a set of cardiovascular measurements before and after treatment in order to study its effect on the cardiovascular system and the effect of a reversible fluid challenge and depletion in Fontan patients, and to correlate all these results with the results of a symptom limited maximal exercise test.
Study design: This study consists of a longitudinal intervention study and a cross-sectional study.

Study population: 55 patients with a univentricular heart after palliation with the Fontan circulation will be included from an age of 8 until 18 years old. Patients who already use enalapril will be excluded. A number of fifty healthy age and gender matched subjects will

serve as controls.

Intervention (if applicable): To all Fontan patients enalapril will be given twice daily at a dose of 0,5 mg/kg/day with a maximum of 20 mg per day. All Fontan patients will undergo all the investigations before and after treatment and healthy controls will undergo all the investigations once.

Main study parameters/endpoints:

- Cardiopulmonary exercise stress test: VO2peak.

- Cardiac autonomic nervous activity: heart rate variability and pre-ejection period.

- Outcome of passive leg raising and head up tilt table testing: cardiac output and cardiac autonomic tone.

**Study objective**

ACE-inhibition will exaggerate the responsiveness to central blood volume depletion, will increase the responsiveness to fluid challenges, will result in a decrease aortic pulse wave velocity, a better cardiac autonomic profile and an increase in cardiopulmonary stress testing.

**Study design**

All Fontan patients will be undergo all the investigations before and after treatment, with a treatment duration of 3 months, and healthy controls will undergo all the investigations once.

**Intervention**

This study consists of a longitudinal intervention study and a cross-sectional study

In the present study we will compare several cardiovascular measurements before and after treatment of enalapril, in patients with a univentricular heart after palliation with the Fontan circulation. Patients will start with treatment of enalapril after all cardiovascular measurements at baseline have been performed. After a 3-month period of treatment with enalapril (0,5mg/kg/day with a maximum of 20mg per day), all cardiovascular measurements will be repeated.

Healthy age and gender matched subjects will serve as controls. All cardiovascular measurements, except blood testing, will be performed just once in healthy controls. They will not be treated with enalapril.

# Contacts

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# Eligibility criteria

## Inclusion criteria

Patients with a univentricular heart after palliation with the Fontan circulation from 8-18 years old.

## Exclusion criteria

Patients who already use ACE-inhibition.

# Study design

## Design

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|---|---|
| Study type: | Interventional |
| Intervention model: | Other |
| Allocation: | Non controlled trial |

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| Masking: | Open (masking not used) |
| Control: | N/A , unknown |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 01-05-2017 |
| Enrollment: | 110 |
| Type: | Anticipated |

### IPD sharing statement

**Plan to share IPD:** Undecided

## Ethics review

Positive opinion

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| Date: | 20-07-2017 |
| Application type: | First submission |

## Study registrations

### Followed up by the following (possibly more current) registration

ID: 46953
Bron: ToetsingOnline
Titel:

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
|---|---|
| NTR-new | NL6415 |
| NTR-old | NTR6591 |
| CCMO | NL59498.058.17 |

| Register | ID |
| --- | --- |
| OMON | NL-OMON46953 |

# Study results

**Summary results**

Harteveld LM, Blom NA, Terol C, Kuipers IM, Rammeloo LAJ, Hazekamp MG, Van Dijk JG, Ten Harkel ADJ. 3-month Enalapril Treatment in Pediatric Fontan Patients with Moderate to Good Systolic Ventricular Function. Am J Cardiol. 2021 Nov 10:S0002-9149(21)01007-9
Harteveld LM, Blom NA, Terol C, Van Dijk JG, Kuipers IM, Rammeloo LAJ, De Geus EJC, Hazekamp MG, Ten Harkel ADJ. Determinants of exercise limitation in contemporary paediatric Fontan patients with an extra cardiac conduit. Int J Cardiol. 2021 Oct 15;341:31-38.
Two other following (submitted)