ACE inhibition in Fontan patients: its effect on body fluid regulation
(SAFE trial)

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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, except for blood testing and the symptom limited exercise test which will not be performed in healthy controls.

Main study parameters/endpoints:
- Cardiopulmonary exercise stress test: VO_{2}peak.
- 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.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients with a Fontan circulation will have to visit the LUMC twice and these visits will be instead of normal appointments. In the future, Fontan patients could possibly have advantage from this research. For healthy subjects, this research means that they have to come only once to the LUMC. The exams themselves are not harmful to health, will cost three hours per visit and have a low burden. Only venapunction, which only will be done in the group of Fontan patients, can be painful, but we will thrive to soften the pain by using, for example, emla cream.
1. Introduction and Rationale

At present more than 90% of patients with congenital heart disease reach adulthood. However, their life expectancy is less than normal, and many patients suffer from heart failure or pulmonary hypertension (Nieminen et al). A group of patients that is especially prone to these long-term sequelae are patients with a univentricular heart. Although heart failure may be treated medically by anti-heart failure medication, most studies evaluating the effectiveness of these medications are performed in patients with a biventricular circulation.

Patients with a univentricular heart usually undergo a stepwise Fontan procedure. This technique consists of a stepwise approach with first connecting the superior vena cava with the pulmonary arteries and at a later stage connecting the inferior vena cava with the pulmonary arteries, either as an intra-atrial tunnel, or as an extra cardiac conduit (Total Cavopulmonary Connection; TCPC). After Fontan palliation these patients lack a heart chamber that pumps the blood through the pulmonary circulation. Therefore venous pressure is necessary to overcome pulmonary resistance. Any increase in pulmonary vascular resistance will lead to increased central venous pressure and venous congestion. On the other end of the circulation there is downstream decreased flow (Gewillig et al). This results in a critical fluid balance and dependence of cardiac output on adequate preload (La Gerche et al). While a volume challenge can increase cardiac output in patients (De Mey et al), fluid overload can lead to increased central venous pressure, resulting in venous congestion and ascites and pleural effusion, while dehydration immediately has a negative effect on cardiac output and may result in signs of clinical forward failure. In Fontan patients there is a delicate balance between systemic and pulmonary vascular resistance, while systemic circulation is highly preload dependent. In most Fontan patients a fluid challenge resulted in an increase in end-diastolic pressure and an increase in cardiac output as well (De Mey et al). On the other hand, an increase in end-diastolic pressure may have detrimental effects on the Fontan circulation due to a decrease of the transpulmonary gradient.

Fontan patients show a slightly diminished diastolic and systolic ventricular function already 10 years after completion of the TCPC (Bossers et al). During adulthood an increasing number of patients will suffer from clinical signs of ventricular dysfunction (Ohuchi J Cardiol 2016). Furthermore, a decrease in aortic distensibility is now being recognized as an important factor for increased afterload of these ventricles (Ohuchi et al), thereby increasing the process of ventricular deterioration.

Furthermore, the normal mechanisms that can counteract the negative effects of changes in fluid volume have been described to be diminished in Fontan patients as well. The main regulatory mechanisms in healthy individuals to counteract the effects of fluid changes on cardiovascular
parameters are the possibility of the heart to change stroke volume, the autonomic nervous system and the aortic stiffness or aortic distensibility.

**Ventricular function:**
During longer-term follow-up a significant number of patients show impaired ventricular function (Ono et al). When dobutamine stress is used in Fontan patients even those with a normal ventricular function lack the possibility to increase their stroke volume (Robbers-Visser et al). These cardiovascular changes in most patients result in a diminished exercise capacity (Bossers et al 2014).

**Cardiac autonomic Nervous Activity:**
Failure of the autonomic nervous system to adapt to differing circumstances is one of the key markers in the development of heart failure and may result in an increased risk of rhythm disturbances (Dekker et al 1997; La Rovere et al 2001; Nolan et al 1998; Saul et al 1988; Schwartz et al 1992). Assessment of cardiac autonomic function has important clinical implications as cardiac autonomic balance can be positively modified by exercise training (Groehs et al 2015) and a variety of other pharmacological and more invasive measures (Schwartz et al 2015), contributing to improvement of prognosis. Reports in patients with congenital heart disease including Fontan patients have shown a reduction in cardiac autonomic nervous activity, although its relation to symptoms and prognosis remains as yet unclear (Ohuchi et al 2003; Ohuchi et al 2011). In Fontan patients parasympathetic activity seems to be reduced as assessed by the heart rate recovery after cessation of exercise. In addition, various aspects of heart rate variability (HRV) are reduced in Fontan patients, reflecting both parasympathetic as well as sympathetic cardiac autonomic nervous activity (Bossers et al 2015). The clinical value of HRV in Fontan patients has yet to be established, but it has been demonstrated previously that HRV analysis might contribute to early detection of patients who will develop arrhythmias (Dahlqvist et al 2011).

**Aortic stiffness:**
In addition to reduced ventricular function, in many congenital heart disease patients, the vascular function of especially the aortic arch show significant differences from normal (Kojima et al). Several studies have investigated vascular function in Fontan patients. Both in paediatric patients as well as in adult patients arterial stiffness and pulse wave velocity are increased (Tomkiewicz et al; Lambert et al; Biglione et al; Myers et al). However, no clear relation with ventricular function could be made. In the assessment of cardiovascular risk factors the measurement of pulse wave velocity of the aorta has become a key factor. Aortic pulse wave velocity is a surrogate of aortic stiffness. Since arterial baroreceptors are present in the aortic arch it is understandable from a physiological standpoint that arterial stiffness and cardiac autonomic function have a relationship. Various studies have found a
correlation between cardiovascular autonomic function and indices of arterial stiffness (Chrysohoou et al; Nemes et al).

In the present study we will evaluate 46 patients with functional univentricular hearts after TCPC. A fluid challenge will be given by passive leg raising. Passive leg raising has shown to be an effective and reversible and safe method of studying the effect of a fluid challenge on various cardiovascular parameters (Cherpanath et al). This method is extensively being used in intensive care units to predict the effect of fluid challenge on the circulation of various groups of patients. Depletion of central and splanchnic blood volume will be induced by a passive head-up-tilt test. In a previous study the reduction of portal venous flow is more pronounced in symptomatic Fontan patients (Hsia et al. J Thorac Cardiovasc Surg).

**Enalapril:**

Enalapril, an angiotensin converting enzyme (ACE) inhibitor, has been shown to be effective in reducing mortality in patients with heart failure and reduced systolic function for more than 25 years. In subsequent studies its effectiveness has also been proven in patients with mild to moderate symptomatic heart failure. In recent guidelines ACE inhibition has therefore become the cornerstone of therapeutic interventions in patients with systolic heart failure. The effectiveness of ACE inhibition has been ascribed to its effect on various cardiovascular and pulmonary parameters, including systemic vascular resistance, cardiac autonomic tone (KD Maida et al), aortic pulse wave velocity (PWV) and lung function (Contini et al; Abraham et al). The success of ACE inhibition in patients with systolic heart failure and a biventricular heart has also led to the introduction of ACE inhibition to improve the Fontan circulation in patients with a univentricular heart.

The use of ACE inhibition in patients with a univentricular heart is, however, controversial. There is consensus on the use of ACE inhibition in Fontan patients with ventricular dysfunction. However, many centres also prescribe enalapril on a routine base for patients with a Fontan circulation and a preserved ventricular function, while other centers have considerable doubt about its effectiveness (Wilson et al; Int J Cardiol; Wilson et al Heart Lung and circulation). In a small study no effect of enalapril on exercise capacity in Fontan patients has been found (Kouatli et al, circulation). However, when enalapril is used in univentricular pre-Fontan patients a decrease in end-diastolic pressure (Yim et al Cardiol Young) and a redirection of blood flow to the systemic circulation (Lee et al; Heart 2011) has been found. These cardiovascular effects, however, did not improve somatic growth, ventricular function or heart failure severity score during the first year of life (Hsu et al Circulation 2010).
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 most of the use of ACE inhibitors.
2. Objectives

The objectives of the present study are as follows:

- To assess autonomic parasympathetic and sympathetic function as well as vascular function in a population of patients with univentricular hearts palliated by the Fontan procedure and compare it with the results in healthy subjects.

- To assess the effects of central fluid depletion by means of a passive head-up-tilt test and central fluid loading by passive leg raising on cardiac output, aortic distensibility and hepatic venous blood flow patterns in a group of patients with a Fontan circulation and compare it with the results in healthy controls.

- To correlate the above mentioned results with the results of a symptom limited maximal exercise test.

- 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 in Fontan patients.

- To study the effect of a reversible fluid challenge and fluid depletion on cardiovascular parameters before and after a period of enalapril treatment in order to study changes in fluid susceptibility in Fontan patients.
3. Study design

In the present study we will compare several cardiovascular measurements (described below at ‘6. Study parameters’) 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, all cardiovascular measurements will be repeated.

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

Population:
Patients, who have been operated in the Leiden University Medical Centre (LUMC), with a univentricular heart after palliation with the Fontan circulation will be included. We strive for including 55 patients. A number of 55 healthy age and gender matched subjects will serve as controls.

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

Exclusion criteria:
Patients who already use enalapril.

Sample size calculation:
To detect statistical significant difference of our main study parameter VO$_2$peak (ml/kg/min), between Fontan patients before and after treatment with enalapril, we calculated a group size of 52 will be sufficient. We calculated this sample size for paired observations with a clinical relevant effect of 10% elevation after treatment, with a mean of 33.5 and SD of 6.8 before treatment (Bossers et al.; J Thorac Cardiovasc Surg 2014) and an elevation of the mean to 36.85 with an expected same SD after treatment and calculated a SD of the difference of 6.8 with a correlation coefficient of 0.5. We used an alpha of 0.01 with 80% power. We used a lower alpha of 0.01 to correct for multiple comparison according to the Bonferroni correction, because we have five main study parameters. Moreover, we also need to take the change of drop out into account, which means we need 55 patients per group when we expect a 5% drop out. This means a group size of in total 55 Fontan patients and a group of 55 healthy subjects will be sufficient.
5. **Treatment of subject:**

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. Enalapril will be titrated on average in two steps, by blood pressure measurements, which will be measured by the general practitioners of the patients. When a fall of more than 20% of the systolic blood pressure occurs, enalapril dosage will be lowered to a maximum acceptable dosage at which a fall of more than 20% of the systolic blood pressure does not occur. Dosage will also be lowered when Fontan patients feel light-headed or have complaints of dizziness. After a period of three months all procedures that are performed at the start of the study will be repeated.

This is a study of medicinal products within the meaning of the “WMO”. Which means preparation and labelling of the investigational medicinal products will be done according to the relevant GMP guidelines. The medicinal products in this study will be labelled and issued by the hospital pharmacy of the LUMC, which has a GMP license.
6. Study parameters

Main study parameters:
- **Cardiopulmonary exercise stress test**: VO$_2$peak.
- **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 study parameters:
- **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/VCO$_2$ 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 (De Geus et al 1995; Riese et al 2003; Van Lien et al 2013; Willemsen et al 1996). 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 (Horvath et al 2010). 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 in and 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.
7. Data analysis
The study has a cross-sectional between-subject design paired with prospective within-subject design. Baseline cardiovascular measurements will be compared between the Fontan patients and their age and gender matched healthy controls. Comparisons between the groups will be made using the independent T-test in case of normal distribution and Mann-Whitney U test in case of non-normal distribution (SPSS for Windows, recent version). After a period of 3 months treatment with enalapril all baseline cardiovascular measurements will be repeated and compared to pre-treatment values (echocardiography, cardiopulmonary exercise stress testing, blood testing, 24-hour monitoring of electrocardiography and impedance cardiography, and aortic distensibility). Also the fluid challenge by passive leg raising as well as the depletion of central and splanchnic blood volume by head up tilt testing will be repeated and compared to pre-treatment values.

Statistics
In general data will be expressed as mean (standard deviation) in case of normal distribution, or median (interquartile range) in case of non-normal distribution.
8. Expected results

- In this study we expect to find a more prominent effect of fluid challenges on cardiovascular parameters in patient with a Fontan circulation as compared to healthy controls.

- We expect that the use of enalapril in Fontan patients will exaggerate the responsiveness to central blood volume depletion and will increase the responsiveness to fluid challenge as well.

- We expect that the use of enalapril will result in a decreased aortic pulse wave velocity, a better cardiac autonomic profile and an increase in cardiopulmonary exercise stress testing.

- By evaluating the basic characteristics of patients who respond best on enalapril treatment with those who respond the least will probably result in the identification of a basic profile of those patients who will profit best of enalapril treatment.
9. Administrative aspects of participants data

All the data of all participants that will be collected during this study will be treated anonymously and confidentially.

Confidentially of participants data
Each study subject will receive a specified code that will be connected to the study data. This will be done to protect the privacy of each participant. This specific code will not consist of personal information that can lead to the study participant. Only the responsible and principle investigators will have the key of the code to know which code stands for which participant. The key of this code is safely stored at the local institution where the research is carried out. Data of this study can be used in reports or scientific publications, but data will then still not be traceable to individual participants.

Access to data of participants
Several persons are allowed to access the medical and personal records. This is needed to verify that this research project is carried out in a good and reliable way. The people allowed to access these records are: the research team, the monitors that monitor this research and the Dutch “Health and Youth Care Inspectorate. All these persons will keep the records of the participants secret. Non-authorised outsiders will not have access to these records.

Retention period of participants data
All data from this research will be collected and then stored for at least 15 years.

Information about unexpected results
During this research it is possible that accidentally something is found that is not important for the research, but is important for the healthcare of the participant. In this case the concerning participant will be informed. The participant can discuss with his or her treating paediatric cardiologist or general practitioner what has to be done with these results. The participant gives permission for this.

Withdrawal of consent
The participant can always withdraw the consent for this research. When a participant withdraws the consent, already collected data will still be used for the research.
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More information about rights and processing of participants data
For general information about participant’s rights at processing participant’s data, the website of the Dutch authority of personal data or Leiden University Medical Centre can be consulted.

Participants can contact the principal investigator for questions about their rights. The principal investigator is Dr. A.D.J. ten Harkel, Tel: +3171-5262835, E-mail: A.D.J. ten_Harkel@lumc.nl.

Participants who have questions or complaints about processing of personal data can contact the research location first. They can also contact the officer of data protection of the LUMC (Yvonne Zegers, E-mail: infoavg@lumc.nl, Albinusdreef 2, 2333 ZA Leiden; central phone number: +31715269111) or the Dutch authority of personal data.

Registration of this research
Information about this research is also included in an overview of medical-scientific research, called the Dutch trial registry (http://www.trialregister.nl/trialreg/index.asp). Data about this research on this website is not traceable to individual participants. After the research has been ended, this website can give a summary of the results. This research can be found under: “ACE inhibition in Fontan patients; its effect on body fluid regulation”; acronym: SAFE, NTR number: NTR6591.
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