The role of the pulmonary vasculature in the Fontan circulation

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Primary Objectives:- Determine the effect of pulmonary vasodilatation on indexed cardiac output during simulated exercise.- Characterization of structural properties of small pulmonary arteries.Secondary Objectives: - Investigate the effect of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital cardiac disorders
Study type	Observational invasive

Summary

ID

NL-OMON44674

Source
ToetsingOnline

Brief title
Fontan HC

Condition

- Congenital cardiac disorders
- Cardiac and vascular disorders congenital
- Pulmonary vascular disorders

Synonym
Fontan, Total cavopulmonary connection

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Fontan, nitric oxide, OCT, pulmonary vasculature

Outcome measures

Primary outcome

- Change in indexed cardiac output (l/min/m2) between condition 2 and condition

3

- Presence of intimal lesions in the small pulmonary arteries

Secondary outcome

Parameters derived from hemodynamic assessment:

- pressures caval veins, Fontan conduit, pulmonary arteries

- pulmonary capillary wedge pressure

- pressures single ventricle and aorta

- calculated flows and resistances; e.g. pulmonary flow, pulmonary/systemic

flow ratio pulmonary and systemic vascular resistance index

Parameters derived from pulmonary optical coherence tomography:

- Total wall thickness small pulmonary arteries

- intimal layer thickness small pulmonary arteries

- medial layer thickness small pulmonary arteries

- luminal area small pulmonary arteries

- fibrosis area small pulmonary arteries

Parameters derived from transthoracic echocardiography during study procedure:

- ventricular function

- valvular function

Demographic, clinical and functional parameters obtained from standardized

follow-up assessments:

- patient history: e.g. previous operations

- demographic parameters: e.g. age, sex, diagnosis, time after Fontan operation

- NYHA functional class

- Ergometry exercise tests: VO2max

- Pulmonary function tests: FVC, FEV1

- hemodynamic parameters from earlier cardiac catheterizations

- cardiac magnetic resonance imaging: diastolic and end-systolic stroke

volumes, ejection fraction from single ventricle

Study description

Background summary

The Fontan circulation is a definitive surgical palliation for patients with congenital heart defects for whom a biventricular correction is not possible, resulting in an non-physiologic pre- and afterload of the single ventricle, chronically increased systemic venous pressures and a chronic non-pulsatile flow in the pulmonary vascular bed. Since the Fontan procedure was introduced in the 1970s1 improvement in patient selection, surgical strategies, operation techniques and peri-operative care have led to improved short term survival of these patients.2
However with a growing number of Fontan patients reaching adulthood and longer follow-up time, it appears that a gradual attrition of the Fontan circulation occurs, eventually resulting in the so-called failing Fontan circulation. This situation may include protein-losing enteropathy, plastic bronchitis, ascites, hepatic cirrhosis and hepatic malignancy, ventricular dysfunction and a low cardiac output state. Multiple factors are suggested to contribute to the attrition of the Fontan circulation. However recently it has been hypothesized that the pulmonary vasculature, may form the common

denominator in these processes.3 To date medical or surgical treatment options to reverse or even slow down the failing of the Fontan circulation are extremely limited.

There are indications that the pulmonary circulation is of great importance in the Fontan circulation. Because of the absence of a subpulmonary ventricle to propel the blood through the pulmonary circulation a low pulmonary vascular resistance is a requisite. It has been shown that over time the pulmonary vascular resistance (PVR) gradually rises, the pathophysiological mechanism of this phenomenon still has to be elucidated. When the pulmonary vascular resistance rises, less blood returns to the single ventricle and a decreased preload is the consequence. It has been proposed that diminished preload is the controlling and limiting factor of cardiac output in Fontan patients.4 Fontan patients have impaired exercise capacity.5 During exercise, the body demands an increase in cardiac output and an increase in cardiac preload is required. In the Fontan circulation this can only be achieved by lowering PVR, which might be problematic in the Fontan patient.

Normally, pulsatile pulmonary blood flow is important for the release of endothelium-derived compounds such as nitric oxide (NO), which induces vasodilatation and lowers PVR. The non-pulsatile pulmonary flow in the Fontan circulation is suggested to induce endothelial dysfunction, associated with compromised vasodilatory capacity, adverse pulmonary vascular remodeling and local prothrombotic environment over time. Structural changes of the pulmonary vasculature and altered pulmonary vascular hemodynamics may play a role in the limited exercise capacity of Fontan patients. However, its exact role remains to be determined.

Optical Coherence Tomography (OCT) and pulmonary vasodilatation tests during cardiac catheterization are tools to assess this role in vivo. OCT is a catheter-based optical imaging modality which uses near-infrared light (1300nm). It produces an image of the vessel wall by optical scattering. OCT has a resolution 10-fold higher than intravascular ultrasound (IVUS) and allows for in vivo diagnosing of vascular lesions and structural wall remodeling.6 Pulmonary OCT has been used to diagnose peripheral pulmonary thrombi 7 and to asses pulmonary artery morphology.8 To date pulmonary vessel wall characterization using OCT has not been reported in Fontan patients.

Pulmonary vasodilator testing using NO is common clinical practice in pulmonary vascular diseases. 9 NO is frequently administered to Fontan patients post-operatively. 10-12 However little is known about the effects of NO at mid to long-term follow up in Fontan patients. Only one study has studied the effects of inhaled NO during cardiac catheterization (N=15) at mid-term follow up (under general anesthesia, median 12 years old, median 9 years after Fontan operation) and reported that pulmonary vascular resistance dropped significantly after administration of NO. 13 The possible beneficial effects of iNO on cardiac output during (pharmacologically simulated) exercise (with dobutamine) have not been reported in Fontan patients and should be subject of study.

In summary determination of the structural and functional characteristics of the pulmonary vasculature in the Fontan circulation would

identify the pulmonary circulation as a future treatment target in Fontan patients and may provide clues for new therapeutic treatment strategies to improve the long term outcome of these patients.

Study objective

Primary Objectives:

- Determine the effect of pulmonary vasodilatation on indexed cardiac output during simulated exercise.

- Characterization of structural properties of small pulmonary arteries.

Secondary Objectives:

- Investigate the effect of pulmonary vasodilatation during simulated exercise on hemodynamic characteristics (e.g. pulmonary vascular resistance index, end-diastolic pressure single ventricle).

- Investigate the effect of pulmonary vasodilatation during simulated exercise on ventricular and valvular function (based on echocardiographic assessment)

- Investigate the relationship between hemodynamic characteristics (all three conditions) and demographic (e.g. age, time since Fontan operation) and clinical and functional characteristics (e.g. NYHA class, VO2max).

- Investigate differences in hemodynamic characteristics (all three conditions) in sub-groups
(Based on e.g. NYHA class, presence of a fenestration)

- Investigate differences between the structural properties of small pulmonary arteries between the Fontan group, the PAH group and the Control group.

- Investigate the relationship between structural properties of small pulmonary arteries and demographic (e.g. age, time since Fontan operation) and clinical and functional characteristics (e.g. NYHA class, VO2max).

Study design

It is a cross-sectional observational cohort single center study with 2 control groups.

Fontan patients
The study protocol will be performed during a clinically indicated cardiac catheterization. The procedure is under conscious sedation, if necessary. The duration of the routine catheterization protocol for Fontan patients is 90

minutes. In the context of this study additional measurements will be done, this will take an additional 25 minutes.

Control group
The study protocol will be performed at the end of a clinically indicated right heart catheterization. The procedure is under conscious sedation, if necessary. The duration of the routine right heart catheterization protocol for the control group is 20 minutes. In the context of this study pulmonary OCT measurements will be done at the end of the routine catheterization protocol, this will take an additional 5 minutes. These measurements are necessary to provide normal pulmonary OCT control data to discriminate between the pulmonary OCT data from the Fontan group.

PAH group
The study protocol will be performed at the end of a clinically indicated right heart catheterization. The procedure is under conscious sedation, if necessary. The duration of the routine right heart catheterization protocol for the PAH group is 45 minutes. In the context of this study pulmonary OCT measurements will be done at the end of the routine catheterization protocol, this will take an additional 5 minutes. These measurements are necessary to provide abnormal pulmonary OCT control data to discriminate between the pulmonary OCT data from the Fontan group.

Procedures that the subjects will undergo:

Fontan group (N=15)

patient care
Cardiac catheterization (includes dobutamine stress test)

Additional study procedures:
- pulmonary OCT analysis
- inhaled nitric oxide 40ppm for 10 minutes
- 40 ug/kg/min dobutamine stress for 10 minutes
- pressure measurements and oximetry (6ml) after inhaled NO
- trans-thoracic echocardiography

Control group (N=5)

patient care:
- right heart catheterization

Additional study procedures:
- pulmonary OCT analysis

PAH group (N=5)

patient care:
- right heart catheterization

Additional study procedures:
- pulmonary OCT analysis

Study burden and risks

Fontan group:

Group relatedness
The Fontan circulation is a unique pathophysiological condition. There have been to date no long term experimental models designed to adequately study this condition. To eventually improve the treatment for Fontan patients it is necessary to investigate in vivo the mechanisms involved in the impaired exercise capacity and the gradual attrition over time.

Benefits
The participating patients wil not directly benefit from the potential results of this study. However It is possible that Fontan patients will benefit from participation because this study could identify the pulmonary circulation as a future treatment target in Fontan patients and may provide clues for new therapeutic treatment strategies to improve the long term outcome of these patients.*

Burden
- The catheterization protocol will be extended with 25 minutes. The duration of the standard catheterization protocol is approximately 90 minutes.
- NO inhalation for 10 minutes
- 20-30ml of additional contrast fluid (Xenetix 300mg I/ml) is necessary for pulmonary artery imaging using OCT.
- 1 minute of additional fluoroscopy is necessary for positioning of the OCT catheter for pulmonary artery imaging. The calculated additional radiation exposure is 0.1 - 0.16 mSv.
- 6ml of additional blood samples are necessary for oximetry.
- An additional amount of 40µg/kg/min dobutamine stress for 10 minutes.

Risks
Pulmonary vascular response tests using inhaled nitric oxide is a safe and a potent vasodilatation test routinely used in patients with pulmonary vascular disease such as pulmonary arterial hypertension in the cardiac catheterization laboratory. No major risks are associated with inhalation of NO. An overdose of nitric oxide (manifested in elevations of methaemoglobinaemia and NO2) is unlikely because of the short period of administration (10 minutes).

Abrupt discontinuation of the administration of inhaled nitric oxide may cause rebound reaction; decrease in oxygenation and increase in central pressure and

subsequent decrease in systemic blood pressure. Rebound reaction is the most common side effect in association with the clinical use of NO. Because the subject is gradually weaned from NO the occurrence of a rebound reaction is unlikely.

The use of an optical coherence tomography catheter implies risks associated with one additional catheter handling.

Control group:

Group relatedness
The control group is necessary to provide control values of the pulmonary artery optical coherence tomography measurements. Patients with a clinical indication for a right heart catheterization are included; therefore the additional burden and risks associated with these additional measurements are small.

Benefits
For the control subjects there are no benefits associated with the pulmonary artery optical coherence tomography measurements.

Burden
- The catheterization protocol will be extended with 5 minutes. The duration of a standard right heart catheterization protocol is approximately 20 minutes.
- 20-30ml of additional contrast fluid (Xenetix 300mg I/ml) is necessary for pulmonary artery imaging using OCT.
- 1 minutes of additional fluoroscopy is necessary for pulmonary artery imaging using OCT. The calculated additional radiation exposure is 0.1 - 0.16 mSv

Risks
The use of an optical coherence tomography catheter implies risks associated with one additional catheter handling.

PAH group:

Group relatedness
The PAH group is necessary to provide 'abnormal/pathological' control values of the pulmonary artery optical coherence tomography measurements. Patients with a clinical indication for a right heart catheterization are included; therefore the additional burden and risks associated with these additional measurements are small.

Benefits
For the PAH subjects there are no benefits associated with the pulmonary artery optical coherence tomography measurements.

Burden

- The catheterization protocol will be extended with 5 minutes. The duration of a standard right heart catheterization protocol is approximately 45 minutes.
- 20-30ml of additional contrast fluid (Xenetix 300mg I/ml) is necessary for pulmonary artery imaging using OCT.
- 1 minutes of additional fluoroscopy is necessary for pulmonary artery imaging using OCT. The calculated additional radiation exposure is 0.1 - 0.16 mSv

Risks
The use of an optical coherence tomography catheter implies risks associated with one additional catheter handling.

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

Fontan group:
- written informed consent
- Patients who underwent a TCPC/Fontan procedure
- Follow-up at UMCG
- adult 18 years or older
- Clinical indication for cardiac catheterization;Control group:
- written informed consent
- absence of Fontan circulation or univentricular heart-like diagnosis
- Follow-up at UMCG
- adult 18 years or older
- clinical indication for right heart catheterization
- absence of pulmonary vascular diseases
- normal pulmonary vascular hemodynamic profile;PAH group
- Written informed consent
- Clinical indication for right heart catheterization
- History of pulmonary arterial hypertension [PAH] diagnosis (criteria; mean pulmonary artery pressure > 25mmHg, pulmonary capillary wedge pressure <15mmHg, pulmonary vascular resistance index > 3 wood units, and other possible causes for pulmonary hypertension excluded).
- Reconfirmation of PAH diagnosis based on hemodynamic criteria during the right heart catheterization.

Exclusion criteria

Fontan group:
- Standard exclusion criteria for cardiac catheterization
- Obstruction in Fontan conduit
- Inability to measure a reliable cardiac index and PVR (rhythm instability, hemodynamic or anatomic reasons);Control group:
- No specific exclusion criteria apart from the standard exclusion criteria for right heart catheterization;PAH group
- No specific exclusion criteria apart from the standard exclusion criteria for right heart catheterization.
- Inability to perform a pulmonary OCT measurement during right catheterization (rhythm instability, hemodynamic or anatomic reasons)

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):	25-06-2015
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO Date:	12-06-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-01-2018
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
ClinicalTrials.gov	NCT02414321
CCMO	NL51128.042.15