The pressure overloaded right ventricle: a deformation imaging study

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1. To characterize and compare RV myocardial structure, contraction patterns, and functional capacity of (A) PH patients (group 1 or 4, the latter are to be inoperable), (B) patients with pressure overloaded RV due to CHD and (C) healthy controls. 2…

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

Summary

ID

NL-OMON38071

Source
ToetsingOnline

Brief title
RV-DEF

Condition

- Congenital cardiac disorders
- Pulmonary vascular disorders

Synonym
aangeboren hartafwijking, pressure overloaded right heart chamber, pulmonale hypertensie

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ICIN (onderdeel KNAW)

Intervention

Keyword: CHD, PAH, pressure-overloaded, right ventricle

Outcome measures

Primary outcome

Study parameters:

- For the first objective

o Echocardiographic characteristics of RV deformation and RV volumetrics in the patients with pressure overloaded right ventricles, measuring strain and strain rate.

o Deformation pattern of the RV in these patients characterized by MR tagging, including torsion and twist of left and right ventricle. Volumetric data derived from MR imaging.

o Functional parameters obtained by cardiopulmonary exercise testing; VO2 max, anaerobic threshold, Ve/VCO2 and non-invasive cardiac output measurements; stroke volume and dP/dt.

o Delayed enhancement MRI to quantify fibrosis; spectroscopy of the septum.

o Pulmonary perfusion data obtained by MR scanning.

- For the second objective (only PH patients):

o Standard 2D&3D echocardiographic parameters and speckle tracking in 2D and 3D.

o Cardiopulmonary exercise testing including the measurements mentioned above.

- For the third objective:

o RV strain values derived by 3D speckle tracking and MR tagging (to establish validity of 3D with MR tagging as a reference).

- For the fourth objective:

o Strain values for circumferential, longitudinal and radial strain (and if possible torsion of the RV) of healthy volunteers.

o Volumetric data of the RV obtained with Ventripoint.

End points (for prognostic part of study in PH patients):

- Total time to clinical worsening, defined as: all cause mortality, nonelective hospital stay for PH and disease progression defined as a reduction from baseline in the 6MWT by 15% (confirmed by 2 studies done within 2 weeks) plus worsening in functional class.

Secondary outcome

Secondary endpoints:

- Mortality

- Onset to right ventricular failure (clinical diagnosis)

Study description

Background summary

Patients with pulmonary hypertension (PH) have a poor prognosis, with pulmonary arterial hypertension (PAH) having a 3-year survival in the current medical era ranging from 58.2-72.1%. The main reason for death in PH patients is failure of the chronically pressure overloaded right ventricle (RV). In patients that have a chronically pressure overloaded right ventricle due to congenital heart disease (CHD), however, time to RV failure is much longer, generally occurring in the 3rd to 5th decade of life depending on the underlying pathology. Apparently, the possibility to adapt to an increased afterload is less for a RV that has been subject to normal afterload for years, than for a RV that has never known a normal low afterload. A logical explanation for this difference would be that a structurally different composition of the myocardial wall is present, which gives rise to different contraction patterns and different endurance to the high afterload. A second possible explanation would be a difference in metabolic response of the myocardium and a difference in ventilatory capacity between these different patient groups.
Over the last years, imaging studies and anatomical studies have provided

indications that the RV contraction pattern changes in response to high pressure, from a longitudinal to a more circumferential contraction pattern. Furthermore, it was also found that the myocardial wall is structurally different for right ventricular hypertrophy (RVH) seen in Tetralogy of Fallot (ToF) patients. However, whether this is true in all patients with chronically pressure overloaded right ventricles due to congenital heart disease, let alone, in patients with PH, is as yet unknown. Recently, several new imaging techniques to evaluate RV myocardial structure and contraction have emerged, such as tagging on Magnetic Resonance Imaging (MRI) and three-dimensional (3D) speckle tracking on echocardiography. Furthermore diffusion tensor imaging (DTI) on MRI is being applied in hearts and has been validated in both ventricles, ex vivo and, in experimental setting, in vivo. This will not yet be part of the current protocol because the abilities to do this in vivo are still in under development and would vastly prolong the scan time. Using MR tagging, lung perfusion scanning, gadolinium late enhancement and spectroscopy, we thus aim to describe the RV myocardial structure, RV contraction pattern, proximal pulmonary vasculature, and lung perfusion in patients with PH, in patients with a pressure overloaded RV due to CHD, and in healthy volunteers. Conceivably, following comparison of parameters derived from these new techniques between the patients groups, differences in RV structure and contraction may be unveiled. All imaging modalities reflect the function of the heart in a resting condition. However it is also important compare how the heart reacts to stress, as this does not always correlate to cardiac function in rest. Therefore patients will be asked to participate in a cardiopulmonary exercise testing (CPX). Also we can use these results to investigate the correlation of cardiac function during exercise to the echocardiographic and MR derived functional parameters (in rest).
More insight in to the underlying RV pathophysiology may help in better understanding the course of the disease, adaptive abilities of the heart as well as generate new insight into treatment.

Secondly, even though many studies have attempted to find prognosticators in PH patients. Up to now no good early and non-invasive predictors for a more rapid deteroriation are available. Only a few two dimensional (2D) echocardiographic prognostic markers have been identified so far: Tricuspid annular plane systolic excursion (TAPSE) < 20 mm, Indexed right atrial area and pericardial effusion.18 But these parameters are also markers that arise late in the disease course. This study will focus on 2D and 3D speckle tracking, as these techniques have proven, in other patient groups, to be able to detect subtle and subclinical RV dysfunction more sensitively than the above mentioned parameters.
CPX, measuring: maximum oxygen uptake (VO2max), relation between ventilation and carbon dioxide production (Ve/VCO2), anaerobic threshold, stroke volume and rate of pressure rise (dP/dt), can also detect subtle deterioration in different patient categories. These measurements have shown predictive value in patients with congenital heart disease, heart failure and a recent review recognized that this technique can provide valuable information in patients

with PH and that further prognostic research is needed in this field.19-22
The PH patients - group 1 or 4 - will therefore be followed during two years, using the endpoint *clinical worsening* as defined in the statistics section, to determine which echocardiographic parameters and which parameters derived from cardiopulmonary exercise testing have (additive) predictive value. And as important: to determine the prognostic significance of deterioration in these parameters. Known predictors will be recorded in our database, derived from the patient*s file: 6 Minute Walking Test (6MWT), hemodynamic parameters (when measured) and NYHA class and NT-proBNP.

Thirdly, 3D speckle tracking of the right ventricle is a novel technique which has not been validated satisfactorily. Nor has it been used in studies large enough to establish reference values. Therefore, we aim to validate this new technique through comparison with MR tagging as a reference and to establish its clinical utility - by means of feasibility and reproducibility - in healthy controls and patients with right ventricular pathology. Furthermore we will use Ventripoint, a system using 2D echocardiography in a 3D magnetic space to determine anatomic landmarks and reconstruct RV volumes and EF, will be validated against MR data.

Study objective

1. To characterize and compare RV myocardial structure, contraction patterns, and functional capacity of (A) PH patients (group 1 or 4, the latter are to be inoperable), (B) patients with pressure overloaded RV due to CHD and (C) healthy controls.
2. To evaluate the prognostic value of 2D and 3D echocardiographic parameters (emphasizing on deformation imaging) and of cardiopulmonary exercise parameters, for time to clinical worsening in PAH patients.
3. To validate RV 3D speckle tracking against MR tagging in healthy controls and patients with RV dysfunction and to asses its clinical utility by means of feasibility and reproducibility.
4. To establish reference values for the novel 3D speckle tracking of the RV and to provide the first data on 3D speckle tracking in RV dysfunction.

Study design

Observational study, partly cross sectional (CHD patients and healthy controls) and partly follow-up (PH patients).

Study burden and risks

The risk associated with participation is considered to be very low. Gadolinium is considered a safe contrast medium with very low complication rate (< 1 on 10.000 with serious adverse event).26 The risk associated with insertion of an intravenous (i.v.) catheter is negligible. Furthermore a very small risk of

complication was reported during and directly after a symptom-limited maximal cardiopulmonary exercise test. A trial evaluating over 6000 exercise test reported no serious adverse events. During a safety trial in heart failure patients (over 4000 tests), both ventricular tachycardia and fibrillation occurred once and were successfully converted. However this test is also part of standard follow-up in PH patients and CHD patients.
For all participants the major burden will be time-related. For healthy controls this will be a one-time visit of 2 hours. This will consist of; 15-30 minutes for short physical examination, history and ECG, 45 minutes for echocardiogram and 60 minutes for MRI.
For the congenital heart disease group this will also be a one-time visit with an additional cardiopulmonary exercise test, cumulating to about 2.5 hours (excluding travelling time).
The PH patient group will be asked to pay two visits to the UMCU, the first visit will be approximately 2.5 hours (MRI, echocardiogram, exercise test), the second visit 1 hour (only echocardiogram). Note that only the first 17 patients with PAH associated with connective tissue disease (CTD), the first 17 CTEPH and the first 17 with Eisenmenger's syndrome will be asked to undergo MRI.
For CHD patients and, partly, PH patients the results of echocardiogram, MRI and cardiopulmonary exercise test are also part of the regular patient care and will be available for treating physicians and recorded in the patient file. All investigations will be planned in consensus with the patients to minimize the burden as much as possible.
Patients and healthy controls have no benefit for participating in this study. The results are mostly important for scientific purposes; to gain more insight into the adaptive mechanisms of the heart and a better understanding of the various disease processes. Furthermore there is a possible advantage for future PAH patients as these new insights might yield new focus areas for therapy. Prognostic parameters are also very important since they aid physicians in making decisions for the individual patient (therapeutic/diagnostic).
Even though there are no direct advantages for participants, we believe the burden of participation is rather minimal, thereby justifying participation.

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

18 years or older
PAH group 1, inoperable CTEPH
or simple ccTGA, TGA after Mustard or Senning, RVOTO/PS, Tetralogy of Fallot
Healthy control subject ;All 18 years or over

Exclusion criteria

Clinically unstable/deteroriating
For healthy controls: abnormalities in physical examination, ECG or echocardiography, top athlete
legally incapable/unwilling to give informed consent

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):	04-08-2011
Enrollment:	270
Type:	Actual

Ethics review

Approved WMO

Date:	01-04-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO

Date:	11-04-2012
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	NL34856.041.11