Myocardial function, oxygen consumption and efficiency assessment in the right ventricle of patients with idiophathic pulmonary hypertrophy using positron emission tomography.

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Ethical review	Approved WMO
Status	Pending
Health condition type	Heart failures
Study type	Observational invasive

Summary

ID

NL-OMON31568

Source
ToetsingOnline

Brief title
Cardiac function and efficiency of the RV in idiopathic PH

Condition

- Heart failures
- Respiratory disorders congenital
- Pulmonary vascular disorders

Synonym
(idiopathic) pulmonary hypertension or chronically increased pressure in the lungvessels resulting in enlarged right ventricle muscle and deterioration

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Stichting Medicina Interna (50%)

Intervention

Keyword: (Idiophathic) pulmonary hypertension, Cardiac efficiency, Myocardial oxygen consumption, Right ventricle

Outcome measures

Primary outcome

- Oxygen consumption measurements of hypertrophic/failing RV with 11C-acetate

and 15O-O2

- Cardiac efficiency of RV

- Myocardial glucose uptake of RV

- Myocardial perfusion reserve of RV (see also Study Objectives no. 1 to 4)

Secondary outcome

Relation between the efficiency, glucose uptake and perfusion to the wall

stress of the RV (p. 9, wall stress explained)

Oxygen consumption and glucose uptake measurements in the intraventricular

septum

Test-retest of the oxygen gas tracer for measurement of myocardial oxygen

consumption

Study description

Background summary

The transition of right ventricular (RV) hypertrophy to the often-fatal right heart failure in pulmonary hypertension (PH) is poorly understood. Based on preclinical research with monocrotaline-injected PH rats, we have suggested that cellular hypoxia is the probable cause of the transition to heart failure (Des Tombe et al., 2002). A mismatch of oxygen supply and demand can develop during hypertrophic growth, which can result in myocyte hypoxia, mitochondrial dysfunction, ROS production, cytochrome C release, and ultimately right heart failure (fig. 1 in protocol).
The current study. The development of hypoxia in the cell cores depends on the oxygen demand. This is in turn dependent on the myocardial workload, and on the cardiac efficiency: the ratio of the cardiac power (= cardiac output × mean PAP) to the total amount of energy produced with cardiac oxygen consumption (MVO2). The efficiency of both healthy LV and RV is ~20%. Decrease of the cardiac efficiency is a sign of failure; and it is also an increased risk for myocyte hypoxia. The MVO2 in the hypertrophic RV in PH is increased as a result of an elevated myocardial workload. The MVO2 rises even more with RV failure, partly due to increased oxidative stress, e.g. ROS production in the cardiomyocytes. The MVO2 can be measured with PET with two methods: firstly, 11C-acetate tracer is directly cleared via the Krebs cycle . Its clearance rate is an indirect measure for the MVO2. Secondly, with 15O-O2 gas tracer it is possible to measure the total oxygen use during cardiac metabolism, in which a small amount of oxygen is also used in other reactions, e.g. ROS production. The difference between 11 C-acetate and 15O-O2 gas tracer can thus be used as a measure of the oxidative stress, which would be a possible indication for RV failure. A second mechanism which can be observed in the failing heart is a shift to an increased glucose oxidation (473 kJ/mol O2), instead of oxidizing free fatty acids (439 kJ/mol O2), which is the preferred energy substrate in the healthy heart. Little is known about substrate alterations in the hypertrophic and failing RV. The coronary perfusion can also influence the cardiac oxygen supply. Our hypotheses are:
1. The RV efficiency is decreased as the RV function deteriorates in the progression of PH; simultaneously the glucose uptake per gram tissue is increased in the decompensated RV. In contrast, the (assumed) unaffected LV would have a normal efficiency, while the glucose uptake per gram tissue is less compared to the RV in PH.
2. The oxygen consumption measured with the 15O2 tracer is higher than that measured with 11C-acetate, the difference relates to the severity of RV failure. (assessment RV function explained on p. 9, paragraph 'Hemodynamic Data')

Study objective

The study investigates the role of the RV efficiency in the deterioration of RV function to failure in PH (measured with stroke volume index as the parameter

of RV function); efficiency will be related to MVO2, alterations in substrate metabolism and myocardial perfusion (reserve) of RV:
1. Measurement of the RV efficiency in patients with different stages of PH. For calculation of the efficiency is it necessary to measure the MVO2 and the cardiac power (obtained from CO × mPAP from right heart catheterisation).
2. Measurement of MVO2 with 11C-acetate and 15O-O2, relate the difference to RV function.
3. Measurement of glucose uptake by the hypertrophic RV with 18FDG.
4. Measurement of the myocardial perfusion on exertion and in rest with 15O-H2O, from which the myocardial perfusion reserve (MPR, ratio of the myocardial blood flow on exertion to that at rest) is calculated to relate with the RV efficiency and function; the perfusion in rest will be related with MVO2 and glucose uptake (see also ch. 5.1, p. 13).
Correlation of the parameters between the RV en LV will be made.

Study design

PET scan research in order of inclusion, a single PET scan measurement (performed in one or two days) as part of the
work-up protocol to evaluate the diseased in known iPH patients, under optimal medicine therapy for PH.

Study burden and risks

- An extensive study protocol, which should be scanned preferably on one day. The alternative scheme will also be offered to the patients, in which the scan protocol - and thus the scan time and burden - is divided over two days. Any participant can choose for the 'two-day' protocol if he/she finds the 'one-day' protocol too extensive. Moreover, the choice for the 'one or two-day' scan will also be based on the clinical condition of the patient. During the scanning the patient must lie still. Mobilisation can be carried out during the two breaks between the scans.
- Placement of one intravenous and one intra-arterial line in the arms; the tracer injections are given through the iv-line, the blood samplings are drawn via one of both lines. On the second day (of the two-day protocol), it is strived to re-use the iv-entry of the first day, by the means of a 'waaknaald' overnight.
- The total amount of blood sampling is 150ml during the entire protocol. Patiens are excluded from this study if they have anemia. The patient will receive extra oral fluid to compensate the blood drawn.
- Radiation dose is 9.05 mSv. This stays below the maximal radiation dose of 10 mSv, allowed to conduct biomedical research with ionized radiation on subjects, according to the IRCP-guidelines.
- During a perfusion scan the patients perform a light exercise for 10 minutes on the recumbent bike at 40% of their maximal workload previously acquired.

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

Newly diagnosed idiopathic PH, NYHA functional classification II to IV, not yet started with PH-medication, age 18 yrs and older

Exclusion criteria

Secundary PH, anemia (Hb <8.0), previously known coronary disease, atrial fibrillation, diabetes mellitus, known malignancy, pregnancy

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2008
Enrollment:	20
Type:	Anticipated

Ethics review

Approved WMO Date:	20-02-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-06-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL19143.029.07