Towards a better understanding of patients in the *TWILIGHT zone* of Pulmonary Hypertension (OPTIEK2)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON41571

Source
ToetsingOnline

Brief title
OPTIEK2

Condition

- Heart failures
- Pulmonary vascular disorders

Synonym
diastolic heart failure = heart failure with preserved ejection fraction =HFPEF

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Actelion

Pharmaceuticals,Bayer,GlaxoSmithKline,onvoorwaardelijk onderzoeksgeld;ter beschikking gesteld door de farmaceutische industrie (zie G2),United Therapeutics

Intervention

Keyword: diagnosis, diastolic heart failure, fluid challenge, pulmonary arterial hypertension, pulmonary capillary wedge pressure

Outcome measures

Primary outcome

Improvement in exercise capacity, as measured by 6-minute walk testing (6MWT)

will be used as primary outcome measure.

Secondary outcome

Change in PCWP after treatment, as measured by RHC during follow up, will be

evaluated as secondary outcome measure. Other physiological parameters of

interest are: diastolic pressure gradient, reaction of PCWP to fluid challenge

at the time of the first RHC, reaction of PCWP on NO inhalation at first RHC,

exercise echocardiography measures, NT-proBNP, cardiac index, LV (diastolic)

function, additional CMR measures (including assessment of diastolic strain and

left atrial dimensions), use and dosage of diuretics and quality of life.

Study description

Background summary

Pulmonary hypertension (PH) due to left heart failure is a common form of PH. Distinguishing PH due to heart failure with preserved ejection fraction (HFPEF) is notoriously difficult but is of particular importance as therapeutic management in this group is different.

Traditionally, patients with an increased mean pulmonary artery pressure (mPAP) and high pulmonary capillary wedge pressure (PCWP >15 mmHg) will be diagnosed with heart failure (including HFPEF) and clinicians focus mainly on treating

the underlying cardiac diseases. In the contrary in patients with a low PCWP, pulmonary arterial hypertension (PAH) is diagnosed and these patients benefit from PAH specific medication (provided other causes of PH are excluded).

However in some cases the cut-off value of 15 mmHg seems arbitrary. Especially in the twilight zone of PH (when PCWP is between 10-15 mmHg) uncertainties remain regarding the best diagnostic and treatment strategy.

We hypothesize that the twilight zone of PH is a heterogeneous group of patients in which both patients with HFPEF like- and PAH phenotype can be found. If this hypothesis proves to be correct, this raises the question whether the use of PAH specific medication in all patients in the Twilight zone of PH is beneficial. Nevertheless, differences in treatment response and the correlation to clinical characteristics in this sub-group of PH has never been investigated.

By characterizing patients in the twilight zone of PH and evaluating initial response to PAH-specific medication we will gain insight in pathophysiological differences in this group and we will be able to develop a more disease-targeted therapy in the future.

Study objective

The main objective of the current study is to evaluate which patients in the twilight zone of PH will benefit from PAH specific therapy. We will assess the (early) response to PAH specific treatment and determine potential predictors of adverse treatment outcome.

Study design

In this explorative, prospective, single centre intervention study, all adult patients referred for new evaluation of PH and suspected of either PAH (with a PCWP between 8-15 mmHg) or HFPEF (PCWP >15 mmHg) will be included. Treatment response on initial PAH-specific medication, following a standardized treatment protocol, will be our primary outcome parameter. Clinical and physiological characteristics of responders and non-responders to treatment will be compared. Clinical parameters of interest are: change in pulmonary capillary wedge pressure and mPAP after treatment at 4 months of follow-up, diastolic pressure gradient, several cardiac MRI (CMR) parameters (including strains, atrial dimensions and 4Dflow velocities), (exercise) echocardiographic measures (e.g. LV (diastolic) function and left atrial dimensions), NT-proBNP, cardiac index, quality of life (QoL) and the use and dosage of diuretics.

Intervention

Right heart catheterisation, CMR, echocardiography, NT-proBNP and 6MWD at

baseline and at follow-up are already part of our routine diagnostic work-up. For the purpose of this study, we will extend the routine diagnostic work-up by adding a fluid challenge, exercise echocardiography and additional CMR measures. In addition, patients will be requested to complete QoL questionnaires.

Study burden and risks

The proposed tests are safe and operational at the VUmc. They add little discomfort to the patients, as the study measurements only extend routine clinical investigations. In this study, we will treat patients with a PCWP >15 mmHg with PAH-specific medication. Although this is in contrast with current guidelines (which recommend only treating patients with a wedge below 15mmHg), this treatment strategy is not uncommon in PH expert centres and is considered safe. Importantly, it is not known whether HFPEF patients with PH and an elevated PCWP higher wedge pressures and HFPEF-like PH may benefit from PAH-specific medication. This is very well possible as they may still express PAH-like pathophysiology. As such, withholding therapy from these patients may not be justified.
Although participating patients will not directly profit from the additional measurements obtained in this study, they might benefit from the results of this study in the future.
We consider the burden and risks associated with participation to be low, whereas the benefit for the PH-patient group in general is considered high.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Referred to the VUmc for analyses of PH;
- Suspected of PAH(PCWP 8-15mmHg) or
- PH secondary to HFPEF (wedge pressure >15mmHg) AND out of proportion PH (defined as pulmonary vascular resistance (PVR) > 3 Woods units (WU) or PVR between 2.5 -3.0 WU AND elevated transpulmonary gradient >12)

Exclusion criteria

- Hemodynamic instability
- Contra-indication for diagnostic right heart catheterisation, MRI, echocardiography (e.g. pregnancy)
- Other diagnosis than PAH/ diastolic heart failure
- No informed consent for the complete study protocol

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped

Start date (anticipated):	25-08-2015
Enrollment:	65
Type:	Actual

Ethics review

Approved WMO Date:	07-05-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2015
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	NL46196.029.14