# Implementation and effect of exercise and respiratory training on 6-minute walking distance in patients with severe chronic pulmonary hypertension: a randomized controlled multicenter trial in European countries

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

## Summary

### ID

NL-OMON46811

**Source**
ToetsingOnline

**Brief title**
effect of exercise and respiratory training in patients with severe PH

### Condition

- Heart failures
- Muscle disorders
- Pulmonary vascular disorders

**Synonym**
pulmonary hypertension; high bloodpressure in the lungs

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Vrije Universiteit Medisch Centrum
**Source(s) of monetary or material Support:** vumc PH-fonds

## Intervention

**Keyword:** Exercise, Pulmonary Hypertension, rehabilitation

## Outcome measures

### Primary outcome

Primary Study Objective

To investigate the effect of exercise training on 6-MWD in a multicenter setting and implement a low-dose, closely supervised training program for patients with pulmonary hypertension in European countries.

### Secondary outcome

Secondary Objectives

Investigate the effect on WHO functional class, quality of life, echocardiographic parameters, cardiopulmonary exercise testing, laboratory parameters such as inflammatory markers, markers for right heart impairment, safety parameters and optional assessment of epigenetic changes. Further effects on lung function/blood gases, safety parameters, adverse events and survival will be analyzed. Optionally, MRI parameters and DNA variations will be assessed to investigate effects of DNA mutations on treatment effects.

# Study description

## Background summary

Chronic pulmonary hypertension (PH) is associated with impaired exercise capacity, quality of life and right ventricular function.[1,2] The disease is characterized by an increase of pulmonary vascular resistance and pulmonary arterial pressure, leading to right heart insufficiency.[1,2] In later stages of the disease, the right heart is not able to further increase right ventricular contractility (cardiac index) during exercise. Within the last decade, new disease-targeted medical therapies have been approved for treatment of pulmonary arterial hypertension (PAH).[1-3] Sequential and upfront combinations of these agents have shown to further improve symptoms, 6-minute walking distance (6-MWD) and hemodynamics in PAH patients.[1-3]
Despite optimized combination-medical therapy most patients remain symptomatic, have reduced exercise capacity, quality of life and reduced survival rates, with an annual mortality rate of approximately 5 -15 % or even higher.[1] Most patients die due to chronic right heart insufficiency. Reduced exercise capacity in PH is associated with depression and anxiety disorders.[4] Thus, there is a high need of additional therapeutic strategies.
Previous training studies [5-11] have suggested that exercise training as add-on to medical treatment is highly effective improving exercise capacity, quality of life and symptoms. Prospective studies with a 24±12 months follow-up period suggested that exercise training may also improve the rate of clinical worsening events as the need for hospitalization, additional PH-medication, lung-transplantation and death.[5-11]
The current guidelines recommend exercise training only in specialized centres including both PH and rehabilitation specialists who are experienced in exercise training of severely compromised patients.[1]
A specialized PH-training program has been performed in Heidelberg since 2003 including >1200 patients with various forms of chronic PH, mostly pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). The exercise training program is performed in a special setting with an in-hospital start of the rehabilitation program. It is characterized by a low-dose closely supervised exercise training in small groups with additional psychological support and mental training.
This training program for patients with PH will be implemented in European centers to add exercise training to the existing PH therapies. The effect of the training on physical exercise capacity will be assessed by 6-minute walking distance (6-MWD). Further clinical parameters will be assessed to evaluate the effect on exercise capacity, quality of life and symptoms.

## Study objective

The aim of this study is to guide European PH-centers to become specialized centers for training in PH. This approach is in line with European PH-guidelines [12] which classified the exercise training in specialized centers with a closely monitored program as evidence-level A and recommended

further randomized controlled multicenter trials.

## Study design

Clinical Setting
This randomized, controlled multicenter trial will investigate the effect of exercise training on physical exercise capacity, measured by 6-MWD. 126 patients will be included, who either receive exercise training or continue their daily sedentary life style (1:1 randomization) for 15 weeks.
As inpatient settings are not available in all healthcare systems the training program will be adapted from the specific training program for PH patients developed in Heidelberg to a procedure, which is feasible in the local participating centres. Another objective of this study is to assess if the particular adopted training program specified for each participating centre and country is still safe and effective.
European health personnel will be taught the characteristics of the training to achieve comparable settings and implementation of the program.
All patients have to be on optimized, stable PH-therapy. Medication has to remain stable throughout the study. About three weeks are based on an in-hospital stay to adjust and teach the exercise training which will be continued at home for 12 more weeks. In-hospital stays will be arranged country specific and hospitalization time may range between 10-30 days.
Patients of the training group will perform an additional routine assessment at the end of in-hospital rehabilitation to adjust the program and receive advice for continuation at home.
All patients will visit the clinic at pre-study screening at Day -28 to -1 (Visit [V] 1), at baseline (BL) at Day 1 (V2) and Week 15 (V4). As regular control visits are usually performed every three months, the visits performed in this study will comprise of routine visit periods.
Patients will be carefully monitored and treated according to local clinical practice.

## Intervention

Randomized controlled trial to investigate primary and secondary endpoints in European centers with patients receiving exercise training compared to patients who continue their sedentary life-style for a period of 15 weeks.
The clinical investigation is performed as a prospective, randomized, controlled, investigator-blinded study. Patients will be assessed at baseline and after 15 weeks. Patients of the training group will also have an examination at the end of in-hospital rehabilitation.
The rehabilitation program comprises interval ergometer training, dumbbell training, respiratory therapy, mental training and guided walks for 5-7 times/week.
The clinical investigation across European countries will be initiated by training of practitioners and health personnel to build up comparable exercise

training programs. The medical personnel will be trained in the low-dose individually adjusted exercise program. On return to their country, these trained professionals will establish their own training center and implement PH rehabilitation therapy in their country.
Reference Treatment
Patients of the control group receive no exercise training and perform their daily activities at home as usual. Exercise training will be performed after 15 weeks of control intervention. Patients will then be offered to take part in the three-week training program (waiting-group design). The same measurements in both groups at each visit will be used to assess changes induced by exercise training.

**Study burden and risks**

Safety variables include and will be determined at each visit:
1. Electrocardiogram (ECG)
2. Vital signs: Blood pressure (BP), heart rate/pulse (HR), oxygen saturation
3. Clinical laboratory investigations
4. Concomitant medication
5. Concomitant diseases
6. Adverse events

A physical examination including vital signs and 12-lead ECG will be performed. Close in-hospital monitoring within the first 3 weeks, examinations and phone interviews will be used for assessment during the continuation of exercise training at home. Safety will be assessed by phone interview until 1 year of follow-up of the last patient. Patients will also be monitored during their regular control visits at their PH-center.

# 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

1. Female and male patients of any ethnic origin *18 years
2. WHO functional class II-IV
3. PH diagnosed by right heart catheter showing:
Baseline mean pulmonary arterial pressure (mPAP) * 25 mmHg
Baseline pulmonary vascular resistance (PVR) * 240 dyn x s x cm-5
Baseline pulmonary capillary wedge pressure (PCWP) * 15 mmHg
4. Patients receiving optimized conventional PH therapy including intensified treatment with diuretics and who have been stable for 2 months before entering the study.
5. Except for diuretics, medical treatment should not be expected to change during the entire 15-week study period.
6. Negative pregnancy test (*-HCG) at the start of the trial and appropriate contraception throughout the study for women with child-bearing potential.
7. Able to understand and willing to sign the Informed Consent Form

## Exclusion criteria

1. PH of any cause other than permitted in the entry criteria, e.g. concomitantly to portal hypertension, complex congenital heart disease, reversed shunt, HIV infection, suspected pulmonary veno-occlusive disease based on pulmonary edema during a previous vasoreactivity test or on abnormal findings compatible with this diagnosis (septal lines or pulmonary edema at high resolution computer tomography), congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension or unclear diagnosis
2. Pregnancy
3. Patients with signs of right heart decompensation
4. Walking disability
5. Acute infection

6. Pyrexia
7. Any change in disease-targeted therapy within the last 2 months
8. Any subject who is scheduled to receive an investigational drug during the course of this study
9. Severe lung disease: FEV1/FVC <0.5 and total lung capacity <70% of the normal value
10. Active myocarditis, instable angina pectoris, exercise induced ventricular arrhythmias, decompensated heart failure, active liver disease, porphyria or elevations of serum transaminases >3 x ULN (upper limit of normal) or bilirubin >1.5 x ULN
11. Hemoglobin concentration of less than 75% of the lower limit of normal
12. Systolic blood pressure <85 mmHg
13. History or suspicion of inability to cooperate adequately.

# Study design

## Design

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| Study phase: | 4 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Health services research |

## Recruitment

NL

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 01-10-2018 |
| Enrollment: | 10 |
| Type: | Actual |

# Ethics review

Approved WMO

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| Date: | 30-04-2018 |
| Application type: | First submission |

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 |
|---|---|
| ClinicalTrials.gov | NCT03345212 |
| CCMO | NL64021.029.17 |