Balloon pulmonary angioplasty versus pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension: a non-inferiority randomized trial

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To evaluate if balloon pulmonary angioplasty (BPA) is non-inferior to pulmonary endarterectomy (PEA) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) who are eligible for both treatments.

Ethical review	Approved WMO
Status	Pending
Health condition type	Pulmonary vascular disorders
Study type	Interventional

Summary

ID

NL-OMON57458

Source
ToetsingOnline

Brief title
GO-CTEPH

Condition

- Pulmonary vascular disorders
- Vascular injuries

Synonym
blood clots, High blood pressure in the small vessels in lungs

Research involving
Human

Sponsors and support

Primary sponsor: Aarhus University Hospital
Source(s) of monetary or material Support: Novo Nordisk Foundation

Intervention

Keyword: Angioplasty, Balloon, Endarterectomy, Hypertension, Pulmonary / surgery, Vascular Resistance

Outcome measures

Primary outcome

Change in pulmonary vascular resistance from baseline to 4-months (+/- 28 days)

after the procedure(s). Patients on medical treatments at baseline will remain

on medical treatments until the assessment of the primary endpoint, and be

taken off if hemodynamics permit.

Secondary outcome

Change from baseline in:

- mean pulmonary arterial pressure (mPAP), cardiac index (CI), right atrial

pressure (RAP)

- 6 minute walking distance (6MWD)

- Clinical worsening

- World Health Organization (WHO) functional class

- Nt-pro brain natriuretic peptide (BNP)

- Quality of life (QoL) measures

Study description

Background summary

CTEPH is a rare and potentially life-threatening disease. CTEPH evolves from unresolved pulmonary embolism that over time becomes fibrotic and obstructs the pulmonary arteries. The crude incidence of CTEPH is 2-5 cases per 100,000 population but the disease is underdiagnosed and undertreated. CTEPH is a progressive disease. The increase in pulmonary artery pressure induced by mechanical obstruction induces microvascular remodeling which further increases pulmonary vascular resistance and worsens pulmonary hypertension. The progressive increase in pulmonary vascular resistance increases strain on the right ventricle and eventually leads to right ventricular failure and death.
If left untreated, mean life expectancy of patients with CTEPH is less than three years.

Gold standard treatment for CTEPH is PEA, although no controlled studies exist. Surgical management of CTEPH is complex and requires institutional skills and experience. The results after PEA are excellent and patients treated in experienced centers have a reported three years survival of 89%. Few centers are available across the world and we know that only ~60% of patients referred to CTEPH centers undergo PEA which leaves a large proportion of CTEPH patients untreated. Main reasons for not undergoing PEA are distribution of the vascular lesions making the patient technically inoperable, co-morbidities or patient choice. For patients not eligible for PEA, medical treatments and interventional balloon BPA have emerged as effective treatment strategies. BPA can be performed in most inoperable patients. As a classical percutaneous procedure, BPA may offer faster recovery and the procedure can be done in patients in whom risks of complex surgery outweigh benefits. Because of small vessel access, BPA can be done in patients with predominantly distal vascular lesions who are deemed technically inoperable. Registry data suggest that one-year mortality may be higher in PEA than in BPA but, that decrease of pulmonary vascular resistance may be more substantial with PEA.9-12 However, all current knowledge in that regard is based on retrospective observations. Because BPA is commonly performed in patients not eligible for PEA, differences may be due to selection bias.

The diagnosis of CTEPH, disease characterization, distribution of lesions and recommended treatment is done at a multidisciplinary team conference at the local CTEPH centre. This evaluation is based on patient history, right heart catheterization, imaging (pulmonary angiograms and computed tomography pulmonary angiograms and echocardiography) and blood sampling (cardiac biomarkers, kidney function etc.).
Common practice is that PEA is performed in patients with predominantly proximal disease, and BPA is performed in patients with more distal disease, but in a subset of patients, the lesions are accessible by both PEA and BPA as shown in Figure 2. The guideline recommended approach in patients, with lesions accesible for both PEA and BPA is to perform PEA,6 but several centers with limited surgical acces have reported good results of BPA in this patient population11, 12 and we do not know if BPA or PEA are equally good for treating this subgroup of patients with CTEPH. Common practice is that PEA is performed

in patients with more proximal disease, and BPA is performed in patients with more distal disease, but local expertise determines individual treatment selections in CTEPH centers, sometimes leading to PEA in more distal CTEPH, and BPA in more proximal CTEPH in selected cases.7 In a subgroup of patients, both BPA and PEA may be safely performed. Therefore, there is an unmet need for a comparative study of PEA versus BPA in patients with CTEPH who are eligible for both procedures.

Study objective

To evaluate if balloon pulmonary angioplasty (BPA) is non-inferior to pulmonary endarterectomy (PEA) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) who are eligible for both treatments.

Study design

This is an investigator-initiated multicenter prospective, randomized, controlled, open label non-inferiority trial. The study will randomize 139 patients with CTEPH who are eligible for both PEA and BPA. Patients will be screened for eligibility for study inclusion at the local CTEPH multidisciplinary team (MDT) conference and eligibility for both PEA and BPA will be confirmed by a central adjudication committee. If eligible for study inclusion patients will be included after informed consent and randomized 1:1 to PEA or BPA at the first patient visit following the MDT conference. If PAH targeted therapy is instituted or changed after MDT this should be done during a run-in period of up to 3 months before randomization. The run-in period allows for up-titration of medical treatment and a minimum of one-month stabilization on medical treatment after target dose is reached. Baseline right heart catheterization will be done before MDT, but an additional baseline RHC should be performed if changes in PAH targeted medical therapy have been instituted after the screening RHC or if >3 months from screening RHC till PEA/BPA. PEA or BPA will be completed within 6 months from randomization. Follow up visit with right heart catheterization will be completed at 4 months after PEA or last BPA session, to assess the primary end point, and at 12 months after PEA or last BPA session. (Figure 1)

No changes in PAH medical therapies shall be instituted until after the follow-up evaluation unless the treating physician finds it un-safe not to institute, increase dose of, or terminate PAH medical therapies in this period of time.

No biobank or collection/retention of bodily materials is planned for this clinical investigation.

Intervention

Patients randomized to BPA will undergo and have finalized the procedures within 6 months after randomization and optional run-in phase. Pre-planning of target lesions will be done by pulmonary CT angiogram and conventional pulmonary angiography. In local anesthesia, a guiding catheter will be advanced to the pulmonary circulation through a femoral venous access and lesions will be crossed with standard percutaneous coronary intervention (PCI) wires. A balloon sized to the diameter of the target vessel (typically 2-6 mm) will be advanced over the PCI wire and inflated with a pressure of 4-12 atm to restore flow in the targeted vessel. Several vessels will be treated at each session, but due to the vast number of lesions, radiation dose, amount of contrast, and the risk of reperfusion edema, all lesions cannot be treated in one session and several sessions (typically 4-8) are needed to treat the patient.9 After the procedure, the patient will be managed and discharged according to local guidelines. The specific pre-planning protocol, choice of wires and balloons, the number of vessels treated per session, and the decision that no further BPA sessions are needed is at the discretion of the treating physician. Standard equipment for percutaneous interventions are used for BPA. BPA is performed as standard and guideline based treatmsent for CTEPH at investigation sites and choice of the specific utensils for the procedure is at the discretion of the investigation site. All including centers are expert BPA centers with experienced operators and BPA teams and BPA operators should have been properly trained according to local guidelines. For details regarding BPA and medical dilatation balloon devices used in this study with regards to technical documentation, functional features traceability and materials, please see the Investigator Brochure and respective instructions for use submitted for the GO-CTEPH trial. The manufacturers are aware of the use of these devices in routine practice for CTEPH indication. Procedural operations for BPA will follow routine practice and will not deviate from routine clincal practice. Tracability of the devices will be available through the CRF.

Study burden and risks

study related risk:
An additional Right heart catheterization guided with pressure wave forms if changes in PAH targeted medical therapy have been substituted after RHC or if >3 months from screening RHC till PEA/PEA.

Patients included in the trial and randomized to BPA will be exposed to additional radiation exposure, but with a total load of less than 80 mSv. See also section 8.7.1 in the protocol.

non health related risk: quality of life questionnaire, more frequent and longer visit to the hospital, which can be inconvenient.

risk related to routine practice:
We know that PEA is an effective treatment with excellent long-term outcome for patients with proximal CTEPH. However, in the subpopulation of CTEPH patients

with more distal CTEPH, where both procedures PEA and BPA could be considered. PEA is a complex surgical procedure and it is not without risks. BPA is a procedure where observational data suggest it to be as effective as PEA regarding the reduction of pulmonary vascular resistance in short and intermediate term, and with a lower periprocedural risk for the patient, but a randomized trial is lacking. A patient included in the trial will be randomly treated with either PEA as standard treatment or with BPA where preliminary data suggest it to be as good, but with lower interventional risk than PEA. Complications of BPA and PEA are mitigated through adherence to routine practice and standard of care for these both treatments in CTEPH patients. The principal complications for BPA are related to pulmonary vascular injury, vessel injury/rupture, haemorrhage, pulmonary oedema and haemorrhagic plueral effusion which are risks largely due to procedural error. The interventional cardiologists and support staff at all participating sites are experienced in performing both the BPA and PEA procedures in line with current guidelines and are well trained to manage and reduce any procedural risks. Rigorous study monitoring will ensure that all sites adhere to the study protocol and reporting requirements in the case of protocol deviations, adverse events, device deficiencies or use errors. Patient will be covered by the Hospitals insurance sceems in the different countries.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-Diagnosed with CTEPH according to current European Society of Cardiology (ESC)/ European Respiratory Society (ERS) guidelines and eligible for both PEA and BPA by decision at the local CTEPH multidisciplinary team (MDT) conference and by central adjudication committee (CAC)
-Written informed consent from the patient
-Patient age Patient age >17 years
-Able to understand and follow instructions and to participate in the entire study period

Exclusion criteria

-Life expectancy <12 months
-Co morbidities evaluated at the MDT conference, that contributes significantly to the
patients PH
-Not possible to perform BPA or PEA within 4 months after randomization. Evaluated at MDT that changes in PAH targeted therapy between baseline and 4 months follow-up is inevitable*
-Known pregnancy or positive urine hCG screening test in fertile women
-Previous BPA/PEA
-Highly calcified lesions
-Large amount of adjacent acute or subacute thrombus
-Uncorrected bleeding disorders
-Patients who cannot tolerate antiplatelet therapy and anticoagulant therapy

* Patients are allowed to be on PAH targeted medical therapy before study inclusion

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2023
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Generic name:	Cordis;Ikazuchi Zero PTCA balloon
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	24-04-2025
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	NCT05110066
CCMO	NL81297.018.24