Experimental in vitro characterization of chronic thromboembolic pulmonary hypertension.

Published: 15-07-2019
Last updated: 09-04-2024

The primary objective of this study is to investigate the role of vascular cells, with focus on pulmonary arterial endothelial cells (PAEC), in the development and pathogenesis of extensive thromboembolisms as observed in CTEPH.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Observational non invasive

Summary

ID

NL-OMON48197

Source
ToetsingOnline

Brief title
in vitro CTEPH

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Pulmonary vascular disorders

Synonym
chronic thromboembolic pulmonary hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,ICaR-VU

Intervention

Keyword: Chronic Thromboembolic Pulmonary Hypertension, Endothelial cells, Thrombosis

Outcome measures

Primary outcome

The main objective of this study is to investigate the role of the CTEPH endothelium in platelet adhesion and clot formation. Pulmonary arterial endothelial cells (ECs) will be characterized before and after interaction with peripheral blood under shear stress. Cellular phenotypes of PAECs from CTEPH patients are compared to PAECs from control subjects, and possible underlying mechanisms will be investigated based on gained results.

Secondary outcome

1. Characterize PAECs coagulation factors expression profile. We will compare control and CTEPH-PAECs to identify differences.

2. Study endothelial-blood interaction under high levels of fluid shear stress to investigate how the diseased endothelium influences coagulation under conditions resembling human hemodynamics. We will compare control, CTEPH and PAH-PAECs to identify differences.

3. Characterize plasma from PH patients on soluble protein markers that influences cellular behavior to express pro-thromboembolic proteins. We will compare plasma from control, CTEPH and PAH-PAECs to identify differences.

4. Confirm if increased thrombosis found in CTEPH is a vascular problem rather than a hemostatic problem. We will do this by studying endothelial-blood interaction where control, CTEPH and PAH blood will be perfused over control PAECs to compare and identify differences.

5. Investigate potential drug treatments that could act on the coagulation

pathway to prevent recurrent or to treat CTEPH.

Study description

Background summary

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension (PH), a group of deadly lung disorders, that is characterized by obstruction or occlusion of the pulmonary arteries by thrombotic material and occlusive vascular remodelling. The mechanisms driving the disease remain unclear. Recurrent thromboembolisms as a result from a pulmonary embolism (PE) or inadequate fibrinolysis are thought to be the two major contributors to the development of CTEPH. Moreover, many patients have pre-existing CTEPH when a PE is diagnosed, therefore in situ thrombosis should be considered as a potential third factor.
Thrombosis and haemostasis are tightly regulated processes that includes timely controlled interactions of endothelial cells, platelets, red and white blood cells, and fibrin. Injury to vascular beds activate the formation of a thrombus, while healthy vascular beds will prevent coagulation or regulate lysis of a thrombus. This indicates the importance of the endothelium to play an important role in the progression the disease.
CTEPH can be considered as a dual vascular disorder with obstructions in the major vessels and secondary pulmonary arteriopathy in the microvasculature, similar as in pulmonary arterial hypertension (PAH). PAH is a different form of PH and has been well characterized by endothelial hyperproliferation with microvascular dysfunction. Although classified in a different group, CTEPH and PAH show similar hemodynamic and pathological features, and therefore some of the patients share drug treatment, although robust scientific evidence is lacking.

Study objective

The primary objective of this study is to investigate the role of vascular cells, with focus on pulmonary arterial endothelial cells (PAEC), in the development and pathogenesis of extensive thromboembolisms as observed in CTEPH.

Study design

This is an experimental in vitro study using cells from surgical material from CTEPH patients and, healthy control and patient derived blood samples. This makes it possible to study endothelial-blood interaction involved in

coagulation in a functional assay.

Study burden and risks

The pulmonary endarterectomy surgery will not be performed for the purpose of this study. Therefore, tissue sample collection from surgical material, that is removed to clear the pulmonary vasculature, will not have an additional risk for the patient. Drawing venous blood is a regular diagnostic technique and the volume of 50 mL will have a minimal risk on the healthy subject or patient. The blood collection is performed during the regular hospital visits and blood sampling for diagnostic purposes.

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

PH patients diagnosed with pulmonary hypertension older than 18 years can be included in this study. Cells will be only isolated from chronic thromboembolic pulmonary hypertension (CTEPH) patients undergoing a pulmonary endarterectomy. Blood will be drawn from CTEPH as wel as pulmonary arterial hypertension patients and healthy controls

Exclusion criteria

PH patients who are categorized in group 2, 3 and 5 of the WHO classes pulmonary hypertension (PH), are excluded from this study. Blood from control subjects are only considered as controls if they do not have PH and/or do not do have any bleeding disorders or take any medication that acts on the coagulation cascade.

Study design

Design

Study type:	Observational non 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):	09-09-2019
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	15-07-2019
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
CCMO	NL69167.029.19