Exploring the use of venous blood samples for diagnosis and monitoring of patients with pulmonary hypertension, and determining the genetic base of disease.

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The main objective of this study is to obtain valuable biomarkers that are useful in the prediction of the presence of (subtypes of PH) and/or treatment responses. Nucleic acid expression patterns will be determined in plasma and peripheral blood....

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Observational invasive

Summary

ID

NL-OMON55700

Source
ToetsingOnline

Brief title
Venous blood sampling in pulmonary hypertension

Condition

- Cardiac disorders, signs and symptoms NEC
- Cardiac and vascular disorders congenital
- Vascular hypertensive disorders

Synonym
elevated lung pressure, Pulmonary Hypertension

Research involving

Human

Sponsors and support

Primary sponsor: Longziekten
Source(s) of monetary or material Support: Ministerie van OC&W,NWO;KNAW,Hartstichting;NFU

Intervention

Keyword: Blood, Diagnosis/evaluation of disease, Genetic reseach, Pulmonary Hypertension

Outcome measures

Primary outcome

The main objective of the study is to explore the use of peripheral blood to yield biomarkers for diagnostic and monitoring purposes in PH. For this we will use platelets and plasma, PBMCs, and ECFCs. Secondary objectives of this study are:

Secondary outcome

1. To determine whether disease specific expression patterns of nucleic acids in plasma and platelets can be used to identify the presence of (subtypes of) pulmonary hypertension.

2. To determine unknown genetic determinants of pulmonary hypertension. This part of the study is performed in collaboration with the University of Cambridge. PBMCs are used for new generation sequencing techniques (combination of whole genome sequencing and exome sequencing). Patient consent for this part of the project will be requested separately.

3. To characterize key phenotypic abnormalities of endothelial dysfunction in ECFCs from patients with PH regarding reaction to un-physiological high flow, apoptosis, proliferation rate and protein expression. To determine whether

ECFCs can be used as reliable alternatives for MVECs, direct comparison of

ECFCs and MVECs will be made when paired samples are available.

4. To explore whether some of the established abnormal behavioural aspects of

ECFCs are already present in unaffected carriers of disease causing genes,

thereby suggesting that they play a direct role in the generation of disease.

Study description

Background summary

Pulmonary hypertension (PH) is a fatally progressive disease leading to right heart failure and death. Lung ECs from PH patients exhibit unbalanced production of vaso-constrictive, proliferation inducing vascular mediators such as endotheline-1 and thromboxane, in excess of the countering vasodilators prostaglandin and nitric oxide, ultimately leading to vasoconstriction, proliferation and a progressive increase in pulmonary vascular pressure and resistance.

Diagnosis of PH and assessment of hemodynamic status in response to treatment is done by invasive right heart catheterisation. An elevation of mean pulmonary arterial pressure exceeding 25 mmHg confirms the presence of PH. This procedure is a recurrent burden for the patient, as the effect of treatment is under constant evaluation and many catheterisations are needed. Direct assessments of the primary disease process in PH, such as proliferation of lung microvascular endothelial cells (MVECs), is only rarely possible as it requires biopsy of lung tissue. Therefore, an alternative method to assess the vasculature of patients with PH is warranted. These methods would not only aid in the management of patients, but also in research on the pathophysiology of PH, which now relies on tissue samples obtained after lung transplantation or autopsy.

In this study, we will explore the use of venous blood sampling as an alternative for invasive diagnostic tests. Platelets will be isolated from blood to study expression patterns of DNA and RNA and quantify processes of proliferation and inflammation. Endothelial colony forming cels (ECFCs) will be isolated from venous blood to cell to determine whether these cells are valid alternatives for lung MVECs.

Third part of the study is completely optional; subjects choose wether they

want to participate in this study. It is possible to participate in the rest of the study, without undergoing genetical research. Using this research, we aim to identify mutations explaining and predicting the onset of pulmonary hypertension. Hereby we'll be able to identify patient groups at risk in the future. We perform this research in collaboration with the university of Cambridge. All subjects will be offered a consult with the clinical genetics, who will explain the possible consequences of genetic screening. Patients choose wether they want to be informed about possible relevant mutations explaining the onset of pulmonary hypertension. Accidental findings will never be shared with the patient.

Study objective

The main objective of this study is to obtain valuable biomarkers that are useful in the prediction of the presence of (subtypes of PH) and/or treatment responses. Nucleic acid expression patterns will be determined in plasma and peripheral blood. ECFCs from patients with PH are compared to ECFCs from control subjects regarding key phenotypic abnormalities and their reaction to un-physiologically high flow. In addition we'll use genetic sreening to identify the genetic basis of pulmonary hypertension. This part of the study is ' optional' and will be performed in collaboration with the University of Cambridge.

Study design

The VU University Medical Center (VUmc) is the national referral center for suspected PH patients, who are all potential study candidates. Although the routine diagnostic work-up at the time of diagnosis and during work-up is extensive (including invasive hemodynamic assessment), patients are highly motivated to undergo these investigations, as they have a strong desire to know the exact nature of their disease and response to therapy. In this setting and infrastructure, patients undergo diagnostic right heart catheterization to confirm the diagnosis of PH or the establish the current hemodynamic status under treatment. During this essential clinical procedure, a 80 mL blood draw can be considered as a minimal burden.

As a control group, age matched healthy subjects will be included. Blood will be drawn by venous punction, which is a very low risk, routine procedure done by experienced doctors from the VUmc. All mentioned techniques are operational at our institute. We aim to include 50 samples from healthy control subjects. Control subjects will be recruited from our department, from healthy volunteers and out of the direct environment of the patient (relatives, friends), from patients undergoing a right heart catheterization for diagnostic purposes, but with a normal hemodynamic profile and healthy volunteers. Experiments will be performed on samples matched for age, gender and smoking status.

The procedure of extracting nucleic acids from plasma/platelets and culturing ECFCs from blood samples is an operational procedure in our research lab. ECFCs from patients with PH have successfully been grown. For the purpose of our research we will examine prospectively collected ECFCs from PAH patients and control subjects, as well as MVECs cultured from explanted PAH lung tissue and lungs derived from major lung resections for cancer treatment. We will prospectively collect ECFCs and MVECs from single patients (blood draw prior to lung transplantation or lung surgery), but our ECFC-MVEC comparisons will also be done on unrelated sample pairs. In all cell types, proliferation rates, apoptosis resistance and protein expression will be determined. In addition, ECFC reaction to flow will be quantified and compared to MVEC. The underlying signalling cascades and genome expression leading to abnormal EC behaviour will be investigated. Furthermore, for those patients who have consented, genetic screening will be performed on PBMCs (whole genome and exome sequencing). This part of the study will be done in collaboration with the University of Cambridge.

Study burden and risks

Overall benefit
By the development of blood derived biomarkers we can decrease the invasiveness of patient diagnosis of PH and follow up. By these methods we expect to be able to diagnose earlier, provide better follow up and identify groups at risk as well as predict treatment response in individual patients.

Risk assessment
Venous punction will be done by highly qualified medical doctors of the Department of Pulmonology VUMc. Occasionally punction can cause a hematoma. The total amount of blood withdrawn will be 80 ml per patient for the complete study. The total time taken for the procedure will not exceed 10 min.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients with (suspected) PH who are diagnosed with PH and/or undergo diagnostic right heart catheterization in our clinic are eligible for our study. PH is diagnosed conform ESC/ERS guidelines. We include treated and untreated patients. In addition we aim to include an age and gender matched control population containing persons with a normal hemodynamic profile. For this we'll ask volunteers as well as patient suspected of heart disease but with hemodynamic profile and partners, friends and/or family members accompanying the patient in the clinic. Our goal is to form an age matched population.

Exclusion criteria

Not applicable. Control persons with co-morbidities can serve as a control for patients with significant co-morbidity.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-10-2015
Enrollment:	1600
Type:	Actual

Ethics review

Approved WMO Date:	23-09-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2021
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	NL53211.029.15