Pulmonary arteriovenous malformations: strategies for detection, treatment and follow-up.

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	-

Summary

ID

NL-OMON25616

Source
Nationaal Trial Register

Brief title
PAVMOPT

Health condition

Hereditary haemorrhagic telangiectasia (HHT)
Trans thoracic contract echocardiography (TTCE)
Pulmonary arteriovenous malformations (PAVMs)
Magnetic resonance imaging (MRI)
Computed tomography (CT)

Sponsors and support

Primary sponsor: St. Antonius Hospital
Source(s) of monetary or material Support: ZonMw
Bakhuys Roozeboom fund

Intervention

Outcome measures

Primary outcome

In a retrospective cohort we will study the accuracy of the current clinical diagnostic criteria, compared to
genetic testing in correlation with age. We will study the additional value of different pulmonary shunt grading on TTCE, not only
in the screenings algorithm, but also in follow-up of untreated PAVMs. The potential spontaneous increase or decrease of
pulmonary shunting on TTCE after five years will be evaluated. In a prospective analysis we will compare the diagnostic
accuracy of MRI to CT in both the detection and follow-up of (treated) PAVMS. We will determine potential differences in
long-term results of PAVM embolotherapy with either coils or plugs and determine potential patterns in PAVM feeding arteries
involved in persistent perfusion after embolotherapy. A comparison of HHT versus sporadic PAVMs and embolisation results
will be made.

Secondary outcome

Survival and cause of mortality will also be analysed and correlated to demographic and clinical characteristics to
find prognostic factors of survival.

Study description

Background summary

Background: Hereditary haemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is an autosomal
dominant inherited disorder, with an age-related penetrance, characterized by vascular abnormalities varying from small
telangiectases in skin and mucosal membranes, to large arteriovenous malformations, predominantly in the brain, liver and -especially - lungs. Pulmonary arteriovenous malformations (PAVMs) replace normal capillaries between the pulmonary arterial and venous circulation, which result in a permanent pulmonary right-to-left shunt. This carries the risk of strokes and brain
abscesses, due to paradoxical embolisations. PAVMs are detected in 35-85% of patients. Because of this high prevalence and potential severe complications, screening for PAVMs is warranted in all persons with (suspected) HHT. Sporadic PAVMs occur, but 90% of the PAVMs is related to HHT. Transthoracic contrast echocardiography (TTCE) has become the initial screening test for the detection of PAVMs. The current international guidelines require the

confirmation of all shunts on TTCE by chest computed tomography (CT), in order to evaluate the necessity for transcatheter embolotherapy of PAVMs with coils or – more and more frequently - Amplatzer plugs. Six months after the embolotherapy, a chest CT is repeated and in case of persistent perfusion of the PAVM, embolotherapy is repeated. The standard protocol consists of yearly follow-up, with CT every 2 to 4 years, as reperfusion of PAVMs may occur, despite initial successful occlusion. This results in a high radiation exposure in mainly young adults.

Objective: The aim of this project is to optimize the current screenings algorithm for the detection of PAVMs in (suspected)
HHT, as well as the options for treatment and follow-up.

Hypotheses: A pulmonary shunt grading system can be used to characterize the pulmonary shunt size on TTCE and guide
further decision making in the initial screening algorithm for the detection and treatment of PAVMs in (suspected) HHT. Whether the pulmonary shunt size on TTCE may increase over time is currently unknown. In order to reduce radiation exposure, both
TTCE and magnetic resonance imaging (MRI) may be used in the follow-up of (un)treated PAVMS, but a comparison with chest CT is currently lacking. A multidisciplinary approach using TTCE, chest CT and MRI, and regular discussion with a cardiologist, pulmonologist and intervention radiologist may result in an optimised tailored made approach for the patient. We hypothesise that embolotherapy with plugs is at least as effective as with coils.

Study design: Retrospective and prospective cohort study.

Study population and dataset: All consecutive persons screened for HHT and/or PAVMs from 2004 until present at the St. Antonius Hospital will be included in the dataset. This dataset includes all diagnostic and clinical important characteristics.
Intervention: All persons are screened for the presence of HHT and PAVMs by a standardized diagnostic approach. CT and
MRI will be performed depending on the presence of pulmonary shunting on TTCE. The indication for embolotherapy is
evaluated in a multidisciplinary consensus meeting.

Outcome measures: In a retrospective cohort we will study the accuracy of the current clinical diagnostic criteria, compared to
genetic testing in correlation with age. We will study the additional value of different pulmonary shunt grading on TTCE, not only
in the screenings algorithm, but also in follow-up of untreated PAVMs. The potential spontaneous increase or decrease of
pulmonary shunting on TTCE after five years will be evaluated. In a prospective analysis we will compare the diagnostic
accuracy of MRI to CT in both the detection and follow-up of (treated) PAVMS. We will determine potential differences in
long-term results of PAVM embolotherapy with either coils or plugs and determine potential patterns in PAVM feeding arteries
involved in persistent perfusion after embolotherapy. A comparison of HHT versus sporadic

PAVMs and embolisation results
will be made. Survival and cause of mortality will also be analysed and correlated to demographic and clinical characteristics to
find prognostic factors of survival.

Sample size: 1500 HHT patients (1300 currently known and 50 new patients prospectively every year). Approximately 100
embolisations are performed each year.

Data analysis: All data will be analyzed using an appropriate statistical software application.

Collaboration/Connection: A multidisciplinary approach with the pulmonology, cardiology, radiology and neurology departments
of the St. Antonius Hospital has already been established. The St. Antonius Hospital is acknowledged as a HHT centre of
excellence (by the International HHT Foundation). There is a close collaboration with the Genetic and Neurology department of
the UMCU. The collaboration with the LUMC resulted in a publication in Nature Medicine.

Time schedule: Four years (2014-2018)

Study objective

A pulmonary shunt grading system can be used to characterize the pulmonary shunt size on TTCE and guide
further decision making in the initial screening algorithm for the detection and treatment of PAVMs in (suspected) HHT. Whether
the pulmonary shunt size on TTCE may increase over time is currently unknown. In order to reduce radiation exposure, both
TTCE and magnetic resonance imaging (MRI) may be used in the follow-up of (un)treated PAVMS, but a comparison with chest
CT is currently lacking. A multidisciplinary approach using TTCE, chest CT and MRI, and regular discussion with a cardiologist,
pulmonologist and intervention radiologist may result in an optimised tailored made approach for the patient. We hypothesise
that embolotherapy with plugs is at least as effective as with coils.

Study design

Inclusion: till 2017. Final data analysis 2018, preliminary analysis will be perfomed in between.

Intervention

The study is a retrospective and prospective cohort study. Depending on the different subquestions the next interventions will be performed:
- Patients included in the study will undergo an MRI-scan with contrast (Gadolinium) in

addition to the normal CT-scan of the
lungs.
- A trans thoracic contract echocardiogram (TTCE) will be made at baseline and at 5 (or 6) years follow-up.
- The screening and follow-up of children aged 4 years and older, is based on the HHT guidelines and consists of full
examination by a pulmonologist and/or paediatrician (cyanosis, dyspnoea, clubbing), supine and upright pulse oximetry, and
otorhinolaryngologist and a chest X-ray. A chest CT is only made when PAVMs are suspected based on clinical examination or chest X-ray.
- All persons are screened for the presence of HHT by a standardized diagnostic approach to identify the presence of the
Curacao Criteria. The diagnostic approach
includes examination by a pulmonologist and otorhinolaryngologist, chest X-ray, TTCE and laboratory tests. Screening for
hepatic arteriovenous malformations (HAVMs) with ultrasound is performed when significant HAVMs are expected by clinical
examination or laboratory tests. Screening for cerebral arteriovenous malformations (CAVMs) is performed in all patients with
HHT-I (prevalence of CAVM about 15%) and proposed to patients with HHT-II (prevalence of CAVM 1-3%).
- Embolisation of PAVMs with coils or Amplatzer vascular plugs. Six months after the embolotherapy, a chest CT is repeated.
The standard protocol consists of yearly follow-up, with chest CT every two to four years, as reperfusion of PAVMs may occur,
despite initial successful occlusion.

Contacts

Public
Dr. J.J. Mager, Pulmonology department, Postbus 2500, 3430 EM NIEUWEGEIN,
J.J. Mager,
Nieuwegein 3430 EM
The Netherlands
0883201458
Scientific
Dr. J.J. Mager, Pulmonology department, Postbus 2500, 3430 EM NIEUWEGEIN,
J.J. Mager,
Nieuwegein 3430 EM
The Netherlands
0883201458

Eligibility criteria

Inclusion criteria

All consecutive persons screened for HHT and/or PAVMs from 2004 until present at the St. Antonius Hospital will be included in the dataset.

Exclusion criteria

Patients without HHT and without PAVMs and no family history of HHT

Study design

Design

Intervention model: Other
Control: N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-10-2014
Enrollment:	1500
Type:	Anticipated

Ethics review

Positive opinion

Date:	19-11-2014
Application type:	First submission

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
NTR-new	NL4793
NTR-old	NTR4933
Other	R&D/Z14.061 : w14.074

Study results

Summary results

Recent publications:

1. Velthuis S, Buscarini E, Mager JJ, Vorselaars VMM, van Gent MWF, Gazzaniga P, Manfredi G, Danesino C, Diederik AL,
Vos JA, Gandolfi S, Snijder RJ, Westermann CJJ and Post MC. Predicting the size of pulmonary arteriovenous malformations
on chest computed tomography: a role for transthoracic contrast echocardiography. European Respiratory Journal 2014; [Epub
ahead of print]
2. Vorselaars VMM, Velthuis S, Mager JJ, Snijder RJ, Bos W-J, Vos JA, Strijen MJL and Post MC. Direct haemodynamic effects
of pulmonary arteriovenous malformation embolisation. Netherlands Heart Journal 2014; [Epub ahead of print]
3. de Gussem EM, Lausman AY, Beder AJ, Edwards CP, Blanker MH, Terbrugge KG, Mager JJ and Faughnan ME. Outcomes
of Pregnancy in Women With Hereditary Hemorrhagic Telangiectasia. Obstetrics & Gynecology 2014; 123(3):514-520
4. van Gent MWF, Velthuis S, Post MC, Snijder RJ, Westermann CJJ, Letteboer TGW and Mager JJ. Hereditary hemorrhagic
telangiectasia: how accurate are the clinical criteria? American Journal of Medical Genetics Part A 2013; 161(3):461-466.
5. Velthuis S, Buscarini E, van Gent MW, Gazzaniga P, Manfredi G, Danesino C, Schonewille WJ, Westermann CJ, Snijder RJ,
Mager JJ and Post MC. Grade of pulmonary right-to-left shunt on contrast echocardiography

and cerebral complications; a striking association. Chest 2013; 144(2):542-548.
6. Velthuis S, Vorselaars VM, van Gent MW, Westermann CJ, Snijder RJ, Mager JJ and Post MC. Role of transthoracic
contrast echocardiography in the clinical diagnosis of hereditary hemorrhagic telangiectasia. Chest 2013; 144(6):1876-1882.