Clinical implications of pulmonary shunting on contrast echocardiography

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Clinical implications of pulmonary shunting on contrast echocardiography

Klinische implicaties van pulmonale shunts bij contrast echocardiografie
(met een samenvatting in het Nederlands)

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"Nil sine magno labore vita dedit mortalibus"

Horatius

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CHAPTER 1

General introduction

Based on:
Clinical implications of pulmonary shunting on contrast echocardiography.

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HEREDITARY HAEMORRHAGIC TELANGIECTASIA

Background.

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant inherited vascular disorder with an estimated prevalence of 1 in 5000 individuals [1]. HHT is also known as Rendu-Osler-Weber syndrome (ROW), named after Henri Rendu, William Osler and Frederick Weber, who first described the syndrome in the late 19th and early 20th centuries. HHT is characterized by the presence of abnormal direct artery-to-vein communications, which carry the risk for shunting and hemorrhage with significant morbidity and mortality. The abnormal vascular communications range from dilated micro vessels in skin and mucosal membranes (so-called telangiectases), to large arteriovenous malformations in predominantly the pulmonary, hepatic and cerebral circulation [2]. HHT consists of two main subtypes, HHT type 1 (HHT1) and type 2 (HHT2). HHT1 results from mutations in the ENG gene on chromosome 9, encoding the protein endoglin [3], whereas HHT2 results from mutations in the activin receptor-like kinase (ACVRL1) gene on chromosome 12, encoding the protein ALK-1 [4]. A third disease-causing mutation has been shown in the SMAD4 gene, which causes a combined syndrome of juvenile intestinal polyposis and HHT [5]. In addition, two more loci causing HHT have been mapped to chromosome 5 (HHT3) and 7 (HHT4), although the exact causative genes have not been identified yet [6, 7]. Most families with HHT have a unique mutation and more than 600 types of mutations have been reported (see www.hhtmutation.org). The majority of HHT patients (>80%) have a mutation in either ENG (HHT1) or ACVRL1 (HHT2), with ENG mutations being more common than ACVRL1 mutations [8], but geographical variations exist [9-13]. Although genetic testing for an HHT-causing gene mutation improved in the past few years and became more widely available, DNA analysis per se is not always sufficient in diagnosing HHT and an accurate clinical evaluation remains essential in all persons with suspected HHT. The clinical diagnosis of HHT is established according to the four Curaçao criteria [14], which is described in more detail in the discussion section of this thesis.

What exactly causes the pathogenesis of HHT is still controversial and the precise sequence of events remains to be determined. Both endoglin and ALK-1, as well as SMAD4, are involved in angiogenesis, the process in which new blood vessels are formed from pre-existing ones. During angiogenesis, mural cells (smooth muscle cells and pericytes) detach, after which brief periods of endothelial cell activation, proliferation and migration are coordinated to provide stabilisation of developing new blood vessels. In HHT, several complex biological activities lead to over-expression of ALK-1 or under-expression of endoglin, which can either promote or inhibit the above described specific endothelial cell responses. This results in an abnormal angiogenesis and the formation of fragile vessels with bleeding tendency, which explains the characteristic clinical features associated with HHT [15-17].

Arteriovenous malformations in HHT.

Under normal conditions, a capillary network of microscopic vessels lies interposed between high-pressure arteries and thin-walled veins. In case of an arteriovenous malformation

(AVM), arteries or arterioles connect directly to the venous system, bypassing the capillary network [18]. Clinical consequences of these AVMs may result from rupture, increase in blood flow, or loss of capillary functions such as nutrient exchange and filtering function. AVMs have been described in almost every tissue or organ, but are predominantly found in brain, liver and lungs. Approximately 18-23% of HHT patients will harbour a cerebral arteriovenous malformation (CAVM) [19-21], with a predilection for HHT1 [12]. A CAVM in HHT has a retrospectively estimated bleeding risk of 0.5% per year [22], but some CAVMs carry a more favourable natural history. Despite the lack of evidence of treatment effectiveness for asymptomatic CAVMs in HHT, the current international guideline for the diagnosis and management of HHT do recommend screening for CAVMs with MRI in adults with possible or definite HHT [23]. HHT patients with CAVMs discovered during screening should be referred to a centre with neurovascular expertise to be considered for an individualised management (e.g. conservative expectative approach, invasive angiography, microsurgery, stereotactic radiation or embolisation).

A hepatic arteriovenous malformation (HAVM) is found in 41-78% of HHT patients [24, 25], with a predilection for HHT2 [12]. Although there are no published data regarding the natural history of HAVMs in HHT, it is estimated that symptoms occur in only 8% of these patients [24, 25], which include high-output heart failure, portal hypertension and biliary disease [26]. Abdominal Doppler ultrasound or computed tomography (CT) is recommended in HHT patients with abnormal liver enzymes and/or clinical picture suggesting complications from HAVMs, to confirm its presence [23]. Furthermore, screening for HAVMs can be advised in persons with only one or two clinical Curaçao criteria to clarify the diagnosis of HHT when genetic testing is either inconclusive or unavailable. Hepatic artery embolisation in patients with HAVMs should be avoided, since this appears to be a temporising procedure with significant morbidity and mortality [27]. Referral for liver transplantation should be considered in patients with HAVMs who develop ischaemic biliary necrosis, portal hypertension, or high-output heart failure refractory to medical therapy [23]. After liver transplantation, symptoms resolve in the majority of patients and the procedure has a relatively favourably 5-year survival rate of 83% [28].

PULMONARY ARTERIOVENOUS MALFORMATIONS (PAVMs)

As the current thesis focuses on the clinical implications of PAVM related pulmonary shunting on TTCE, important aspects of these PAVMs are described below in more detail.

Definition and anatomy of PAVMs.
PAVMs (also called pulmonary arteriovenous fistulas) are low-resistance, high-flow abnormal vascular structures that most often connect a pulmonary artery directly to a pulmonary vein. PAVMs thereby bypass the normal pulmonary capillary network, which results in permanent pulmonary right-to-left shunting [29]. In rare cases, the afferent supply of the PAVM may also derive from the systemic circulation, such as bronchial or intercostal arteries. PAVMs can be

single or multiple, unilateral or bilateral, and simple or complex (figure 1). Simple PAVMs receive blood through a single artery, while complex AVMs receive blood through two or more arteries. A PAVM may involve a large single vascular sac or a compilation of dilated tortuous vascular communications between pulmonary artery and vein. The efferent vessel of the PAVM often communicates with branches of the pulmonary vein, although direct communications with the inferior vena cava or left atrium have been described [30].

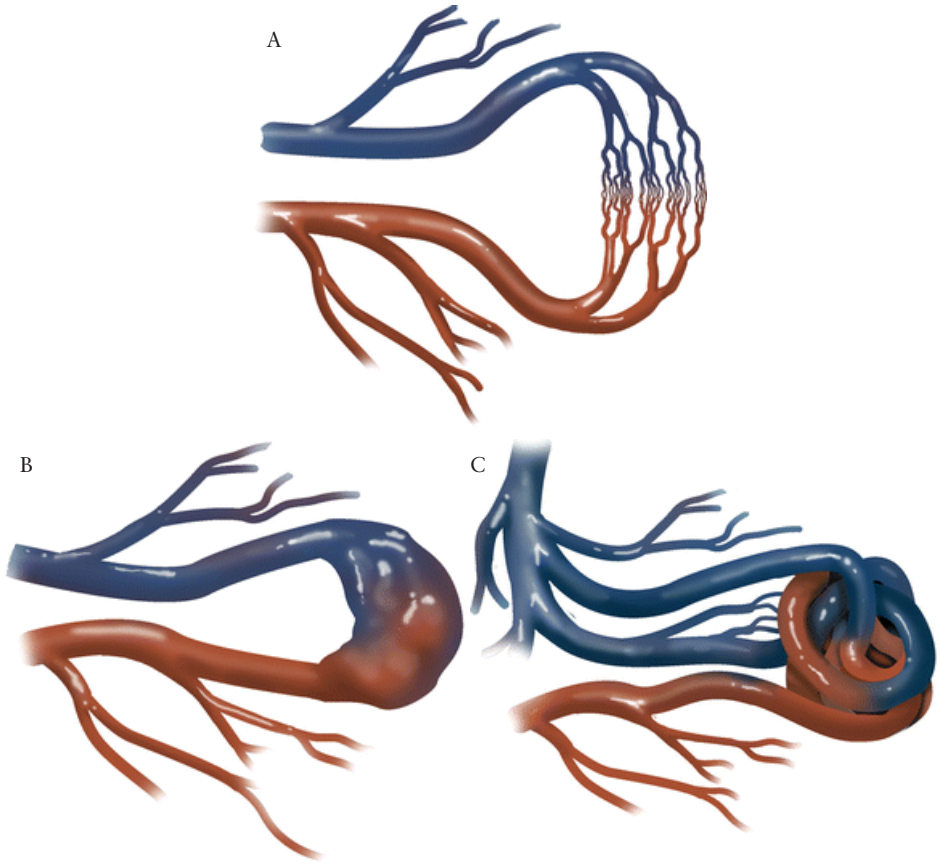

Figure 1. (**A**) Normal pulmonary capillary network; (**B**) Simple PAVM; (**C**) Complex PAVM.
Adapted from Trerotola et al. [31] and reprinted with permission from the American Journal of Roentgenology.

Prevalence of PAVMs.

There is only one known population-based study that determined the prevalence of PAVMs in a general population [32]. This study retrospectively identified eight persons with PAVMs out of 21,235 individuals screened for lung cancer and thereby estimated a 0.04% prevalence of PAVMs in the general population [32]. The majority of PAVMs (up to 94%) is however associated with HHT [33]. Using chest CT, the prevalence of PAVMs in patients with HHT1 is 61%, compared to 14% in patients with HHT2 [34]. Most non-HHT related PAVMs are idiopathic, but other sporadic causes have been described, which include infections (schistosomiasis [35] and actinomycosis [36]), Fanconi syndrome [37], or secondary to hepatopulmonary syndrome [38]. Evidence is lacking on the potential rate of growth of PAVMs and its determinants, although puberty and pregnancy have been described as potential factors that induce growth [39, 40]. Furthermore, literature indicates that the clinical presentation of HHT is age-dependant [41], which may also be the case for PAVMs.

PAVM related complications.

The normal pulmonary capillary network measures 8 to 10 μm in diameter, which acts as a filter for blood coming from the pulmonary arteries. The presence of PAVMs therefore predisposes to complications from paradoxical systemic embolisation of both thrombotic and septic origin, including stroke and brain abscess [33, 42-44]. It has been hypothesized that the risk of these cerebral paradoxical embolizations depends on the relative perfusion of the PAVM, but conflicting data exist. This concept is also suggested in patients with a patent foramen ovale (PFO), in which a larger diameter and a more extensive, or permanent, right-to-left interatrial shunt on contrast echocardiography is associated with a significantly higher prevalence of cerebral ischemic stroke [45-47]. PAVMs are also associated with an increased prevalence of migraine with aura [48-50], where it has been suggested that paradoxical (micro)embolisms trigger the migraine attack and play a role in its pathophysiology by inducing a cascade of cortical spreading depression [51]. Furthermore, the abnormal segment of the PAVM between the pulmonary artery and vein is fragile and may rupture, which then results in haemoptysis or haemothorax [52]. PAVMs may also result in hypoxaemia, dyspnea and cyanosis, depending on the degree of right-to-left shunt, as blood flows directly from the pulmonary artery to the pulmonary vein, bypassing the capillary-alveolar barrier without effective gas exchange. Platypnea (worsening dyspnea when upright) may also be present, because the majority of PAVMs are in the lower lung fields. These PAVM related potential severe complications may be the presenting manifestation of HHT in otherwise asymptomatic persons.

Treatment of PAVMs.

PAVMs can be treated with percutaneous transcatheter embolotherapy, which replaced surgical resection as the present treatment of choice. Transcatheter embolotherapy is an endovascular intervention that occludes the feeding artery of the PAVM with a coil or plug, in order to reduce the risk of PAVM-related complications (figure 2) [31]. Because withholding treatment of PAVMs large enough for endovascular closure is considered unethical, there is no direct, prospective evidence for a reduction of PAVM-related complications after embolotherapy. However, available data from observational studies showed considerable

morbidity and mortality in patients with untreated PAVMs [43,53,54] and indirect evidence exists suggesting the effectiveness of embolotherapy, as no further neurological complications were observed following endovascular closure of angiographically visible PAVMs in one recent study [33]. Transcatheter embolotherapy demonstrated to be safe with excellent long-term results in both adults and children [55-62]. The procedure is performed through a femoral vein approach by an interventional radiologist.

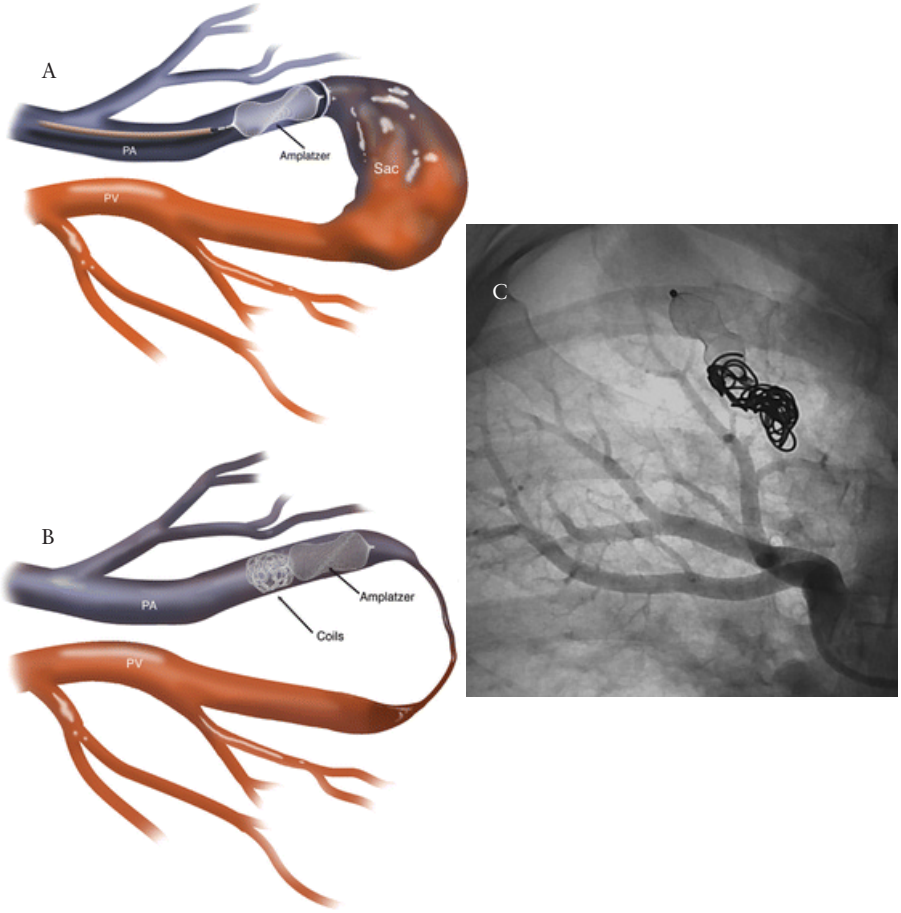

Figure 2. Transcatheter embolotherapy with (A) Amplatzer device, (B) additional coil. (C) Post-embolization result on pulmonary angiography shows occlusion of PAVM.
Abbbreviations: PA, pulmonary artery; PV, pulmonary vein. Adapted from Trerotola et al. [31] and reproduced with permission from the American Journal of Roentgenology.

Screening for PAVMs.

Because of the high prevalence of PAVMs in HHT, its associated severe complications and effective transcatheter treatment options, screening for PAVMs is recommended in all persons with possible or confirmed HHT [23]. The screening algorithm traditionally consisted of chest X-ray, arterial blood gas analysis and pulmonary shunt fraction measurements (using the 100% oxygen method or ^{99m}Tc radionuclide scanning), followed by pulmonary angiography in case of high suspicion for PAVMs. Large studies investigating the value of these diagnostic tests demonstrated that chest X-ray, blood gas analysis and shunt fraction measurements lack sensitivity [63-65] and they were therefore replaced by chest CT with thin-cut reconstructions as the gold standard for the detection of PAVMs (figure 3) [63, 66]. Chest CT appeared to be as sensitive and specific as pulmonary angiography in diagnosing PAVMs [66]. A disadvantage of screening solely based on chest CT was the need for repetitive radiation exposure in a large proportion of persons screened for HHT without PAVMs [63, 66].

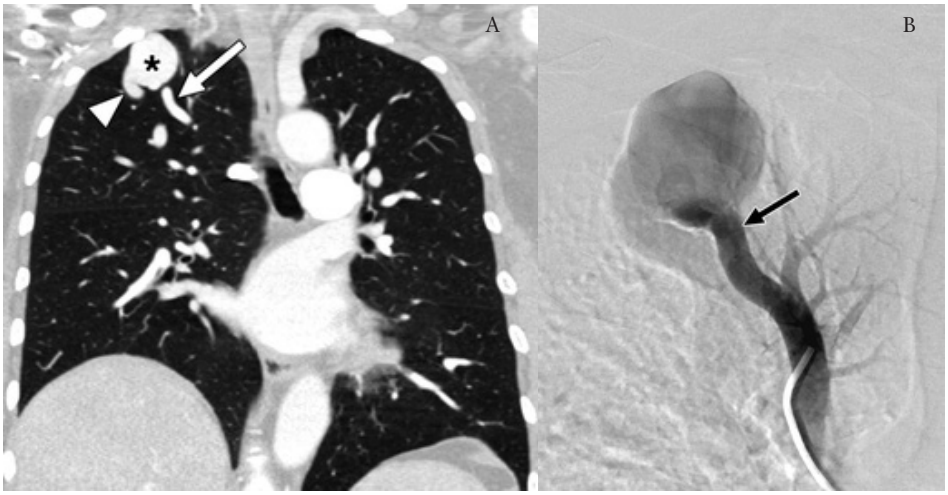

Figure 3. (**A**) Chest CT and (**B**) pulmonary angiography, demonstrating a simple PAVM in the right upper lobe.
Arrow, PAVM feeding artery; asterisk, sac; arrowhead, PAVM draining vein. Adapted from Trerotola et al. [31] and reproduced with permission from the American Journal of Roentgenology.

The last few years however, revealed that transthoracic contrast echocardiography (TTCE) has an excellent sensitivity and negative predictive value in detecting PAVMs, with lower risks and costs, and therefore TTCE is currently advised as the first-line screening technique for the detection of PAVMs in HHT [23, 65, 67-69]. Chest CT is no longer part of the standard screening algorithm for PAVMs. If there is evidence for pulmonary right-to-left shunting on TTCE, chest CT is performed in order to select PAVMs amenable for subsequent transcatheter embolotherapy [23, 65].

TRANSTHORACIC CONTRAST ECHOCARDIOGRAPHY

Technique.
Transthoracic contrast echocardiography (TTCE) is an excellent technique for the evaluation of PAVM related pulmonary RLS. The procedure can be performed by placing an intravenous line in preferably the right ante-cubital vein to which two 10mL syringes are connected, one filled with an 8mL physiologic saline solution and the other with 1mL air. Subsequently, 1mL blood is drawn in the air-filled syringe and mixed with the saline-filled syringe by reverse flushing between both syringes, creating agitated saline with microbubbles. The patient is then positioned in the left lateral position and 5mL of fresh agitated saline is injected within three seconds, while simultaneously projecting the four-chamber apical view with 2-D echocardiography. The agitated saline contains microbubbles which are easily visualised as contrast in the right-sided heart chambers, compared to the normally echo lucent blood. In persons without right-to-left shunting, the contrast appearing in the right-sided heart chambers gradually dissipates as the microbubbles become trapped in the pulmonary circulation [70]. TTCE is preferably performed in specialized HHT centers, where it can be performed by a constant group of trained echocardiographists and interpreted by cardiologists with expertise in both pulmonary and cardiac right-to-left shunting, in order to achieve the accuracy reported in literature.

Pulmonary versus cardiac right-to-left shunting on TTCE.
After contrast injection, the left-sided heart chambers should be closely observed for the potential appearance of microbubbles, its timing and especially shunt origin. All right-to-left shunting visualised through a pulmonary vein should be classified as pulmonary shunts. Only on the occasion of poor visualisation of shunt origin, TTCE has been variably defined as positive for pulmonary shunting based on a delay of more than three [68] or four [63, 65] cardiac cycles before microbubbles appear in the left atrium after its first appearance in the right atrium. There is no clear scientific evidence for a precise delay of three or four cardiac cycles to distinguish cardiac form pulmonary shunts [71]. In case of a PAVM, the delay of contrast appearance in the left atrium depends on the quantity, anatomical location and size of the PAVM, and a delay of two to eight cardiac cycles has been previously described for pulmonary shunting [65, 68, 72-76]. Anaemia and parameters such as left ventricular function, valvular heart disease, right ventricular systolic pressure, heart rate and cardiac output may in theory also influence the timing of left-sided microbubbles, but are not recorded in a standard manner in literature. In our opinion, a delay of more than three cardiac cycles should be accepted as the low threshold for pulmonary shunting on TTCE, when shunt origin cannot be visualised. In daily practice, microbubbles appearing in the left atrium with a delay between two to three cardiac cycles and no clear shunt origin can be considered as indeterminate right-to-left shunting, where additional transesophageal echocardiography or chest CT may be performed. In experienced centers this scenario occurs in only 4.0% of persons screened for HHT [34].

In case of a cardiac right-to-left shunt (PFO, atrial septal defect, ventricular septal defect), microbubbles are visualized in the left-sided heart chambers within two cardiac cycles after

contrast appearance in the right atrium. The majority of PFOs cannot be seen during a resting state and require a provocative manoeuvre to elicit a transient cardiac right-to-left shunt. Therefore, TTCE is usually combined with a Valsalva manoeuvre after a second contrast injection. Venous return of blood is interrupted during the straining phase due to increased intra-thoracic pressure. With release, intra-thoracic pressure suddenly declines and veins rapidly empty in the right atrium favouring a right-to-left interatrial pressure gradient and potential visualization of right-to-left shunting due to a PFO.

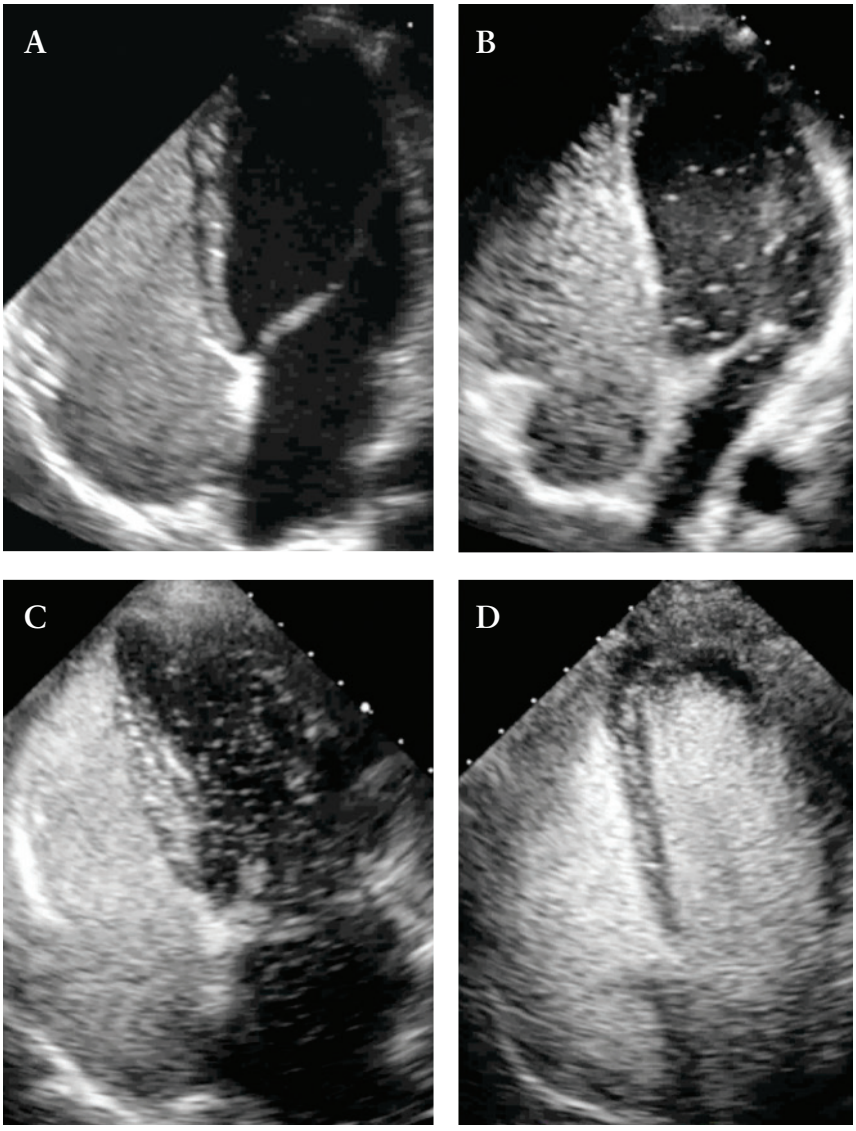

Figure 4. Different pulmonary shunt grades on TTCE.
(A) no shunt; (B) grade 1; (C) grade 2; (D) grade 3. Adapted from Velthuis et al. [34] and reproduced with permission from the European Respiratory Society.

Different pulmonary shunt grades on TTCE.
To increase the usefulness of TTCE as first-line screening technique for the detection of PAVMs, an echocardiographic pulmonary shunt grading system was previously proposed by Barzilai et al. [72]. Their classification relied on the relative opacification of the left ventricle with microbubbles on a scale of 1 to 4, representing respectively minimal, moderate and extensive opacification without or with outlining the endocardial definition. As this classification lacks objective characteristics to differentiate between exact shunt sizes, it might be susceptible for subjective interpretation. Furthermore, the distinction between grade 3 and 4 pulmonary shunts can be rather difficult in clinical practice, as the cut-off point between presence or absence of endocardial outlining is not always clear. Therefore, our group and others [77, 78] choose to use a quantitative grading system, based on the maximum number of microbubbles counted in the left ventricle in one still-frame. With this system, a pulmonary shunt can be graded as 1 (maximum of 29 microbubbles), 2 (30-100 microbubbles) or 3 (>100 microbubbles), meaning that the grade 4 shunts as described by Barzilai et al. are included in our grade 3 pulmonary shunts on TTCE (figure 4). A high inter-observer agreement with a Kappa coefficient of 0.85 up to 0.94 has been reported for this quantitative echocardiographic pulmonary shunt grading system [77, 79].

This echocardiographic pulmonary shunt grading system improves the diagnostic value of TTCE in the detection of PAVMs. Currently, we are already comfortable deferring both additional chest CT and antibiotic prophylaxis when initial TTCE is negative [23, 76], but an important question remains whether we should be no less comfortable deferring it in all persons with only a pulmonary shunt grade 1 on TTCE?

AIMS OF THIS THESIS

In order to investigate the clinical implications of different pulmonary shunt grades on TTCE in (suspected) HHT, the present thesis tries to answer the following questions:

1. Should we accept the presence of any pulmonary shunt on TTCE as a new Curaçao criterion in the clinical diagnosis of HHT?
2. Is there a relation between pulmonary shunt size on TTCE and prevalence of neurological complications due to paradoxical embolizations?
3. Is there a relation between pulmonary shunt size on TTCE and feasibility for transcatheter embolotherapy of PAVMs on chest CT?
4. How to handle small pulmonary shunts on TTCE; does any bubble matter?
5. Can we improve the current screening algorithm for the detection of PAVMs in (suspected) HHT?

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CHAPTER 2

Hereditary hemorrhagic telangiectasia: how accurate are the clinical criteria?

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ABSTRACT

Background: The clinical diagnosis of hereditary hemorrhagic telangiectasia (HHT) is based on the Curaçao criteria. Three out of four criteria are required for a definite clinical diagnosis HHT, two criteria are considered "possible" HHT, and 0 or 1 criterion makes the diagnosis unlikely. However, these consensus diagnostic criteria have not been validated. We report on the diagnostic accuracy of the clinical criteria.

Method: A total of 450 consecutive persons ≥16 years of age were screened for HHT between May 2004 and September 2009, including a chest CT to screen for pulmonary arteriovenous malformations (AVMs). We selected 263 first-degree relatives of disease-causing mutation carriers who underwent mutation analysis. Genetic test results were considered the gold standard.

Results: The family mutation was present in 186 patients (mean age 42.9 ± 14.6 yr; 54.8% female). A clinical diagnosis was definite, "possible", and unlikely in 168 (90.3%), 17 (9.1%), and 1 (0.5%) patient, respectively. In 77 persons the family mutation was absent (mean age 37.1 ± 12.3 yr, 59.7% female). In this group a clinical diagnosis was definite, possible, and unlikely in 0, 35 (45.5%), and 42 (54.5%) persons, respectively. The positive predictive value of a definite clinical diagnosis was 100% (95% CI 97.8–100), the negative predictive value of an unlikely diagnosis 97.7% (95% CI 87.9–99.6). Of 52 patients with "possible" HHT, 17 (32.7%) displayed an HHT-causing mutation.

Conclusion: The Curaçao clinical criteria have a good diagnostic performance. Genetic testing is particularly helpful in patients with a "possible" clinical diagnosis HHT.

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is a disorder with an autosomal dominant inheritance pattern. HHT causes vascular pathology, ranging from telangiectases on the skin and mucosal membranes to large visceral arteriovenous malformations (AVMs), predominantly in the lung, brain, and liver. The vascular anomalies in HHT patients are associated with mutations in genes implicated in the transforming growth factor β (TGF-β) signaling pathway in vascular endothelium [1]. HHT is divided in two main subtypes. HHT1 (OMIM 187300) is caused by mutations in the *ENG* gene encoding endoglin, whereas HHT2 (OMIM 600376) is caused by mutations in the *ACVRL1* (activin receptor-like kinase) gene encoding ALK-1. Most feared are neurological complications such as cerebral abscess and ischemic stroke, resulting from paradoxical embolic events through right-to-left shunting (RLS) of pulmonary AVMs (PAVMs) [2-6]. Therefore, presymptomatic screening for PAVMs in all HHT patients is warranted [7]. PAVM screening is performed by chest CT or transthoracic contrast echocardiography (TTCE). The clinical presentation of HHT varies considerably, even among members of the same family, and penetrance is age-dependent, making clinical diagnosis at young age more difficult [8-10]. The clinical diagnosis is established according to the consensus clinical diagnostic criteria, which were published in 2000, also known as the Curaçao criteria [11]. These criteria consist of spontaneous and recurrent epistaxis, telangiectases at characteristic sites, visceral AVMs or telangiectases, and a first degree relative with HHT. Three criteria suffice for a definitive diagnosis of HHT, two criteria are considered as possible HHT, and one or no criterion makes the diagnosis unlikely. Although genetic testing is increasingly performed to establish the diagnosis HHT, a mutation is not found in approximately 20% of patients who meet the clinical criteria for HHT [12-14]. Consequently, establishing a clinical diagnosis remains an important instrument in the care of HHT families. However, data on the sensitivity and specificity of the Curaçao criteria are scarce. This was also reminded in the practice guidelines of HHT [7]. We report on the validity of the clinical criteria in a large homogeneous group of persons screened for HHT in whom gene mutation analysis was performed.

METHODS

Study Population.

In the period from May 2004 till May 2009, 458 consecutive persons were screened for possible HHT. All persons were screened clinically and underwent complete history and physical examination by a pulmonologist, and consultation by an otorhinolaryngist, both experienced in HHT. Epistaxis had to be both recurrent and spontaneous to fulfill a criterion. For telangiectases, at least three had to be present at characteristic sites (lips, oral cavity, nose, fingers) to satisfy a clinical criterion. Screening for the presence of PAVMs was routinely performed with chest HRCT. A definite diagnosis of a PAVM was based upon chest CT, as a pulmonary shunt on contrast echocardiography is currently not an accepted clinical criterion. Chest CT was available for 450 of 458 (98%) screened persons. Screening for

gastro-intestinal telangiectases and hepatic AVMs was only performed when suggested by history, physical examination, or blood test results. Patients who were definitely (clinically or genetically) diagnosed with HHT were offered a brain MRI to detect cerebral AVMs. All persons were offered genetic testing. In order to validate the clinical criteria, we decided to use the presence or absence of the family mutation as the gold standard. So, carriers of the disease-causing mutation were considered the true positives and non-carriers the true negatives. In addition, we selected only first-degree family members of patients with a proven mutation of ENG or ACVRL1. Because the family mutation was known in all included individuals, this strategy guarantees that no patients with a clinical diagnosis of HHT were included in whom the disease-causing mutation was not detected. In addition, we excluded all sporadic cases of the families involved (18 patients, all with positive genetic test results). This was done because it can be expected that these persons are more symptomatic than relatives who are screened as first-degree family members of known mutation carriers, which would introduce a bias in the study. We were able to include 263 first-degree relatives of HHT patients with a proven disease-causing mutation who all underwent mutation analysis and were screened for PAVMs with chest CT. Of this group 87 were *ENG* mutation carriers, 99 ACVRL1 mutation carriers, and in 77 persons the family mutation was not found. The latter group consisted of persons with a negative or possible clinical diagnosis and they were excluded from clinical follow-up. The included patients represented a total of 75 HHT families. The selection of the study population is presented in figure 1. The clinical diagnosis HHT was established according to the Curaçao criteria [11]. All patients provided written informed consent, and the study was approved by the hospital review board.

Chest HRCT.

High resolution CT scanning (Philips, The Netherlands) of the chest was performed without contrast using the single breath-hold technique with a slice thickness of 1 mm. Both sagittal and coronal reformats were used. Identification of PAVM was based on the presence of a nodular opacity with both an afferent and efferent vessel. CTs were scored as positive, negative, and indeterminate by two independent observers, both blinded to the results of the TTCE (a radiologist and an experienced pulmonologist). When both observers disagreed, the chest CT was considered as positive for PAVM.

Mutation Analysis.

Mutation analysis was performed as previously reported [12]. When the mutation was identified, relatives were offered clinical evaluation, genetic counseling, and DNA analysis for the disease causing mutation. A genetic diagnosis was confirmed when the family mutation was present or when the patient was an obligate carrier. Affected individuals were divided in HHT1 and HHT2 patients depending on the causative mutation. A third group consisted of persons in whom the family mutation was not found.

Statistics.

Descriptive statistics were used to describe patient's characteristics. Continuous variables with normal distribution were presented as mean ± standard deviation. Median with range was used when normal distribution was absent. Sensitivity was expressed as the number

of patients with a clinically confirmed diagnosis HHT (≥3 criteria) divided by the number of patients with a confirmed family mutation. Specificity was expressed as the number of patients with an unlikely (0 or 1 criterion) clinical diagnosis divided by the number of persons in whom the family mutation was not found. Statistics were performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL).

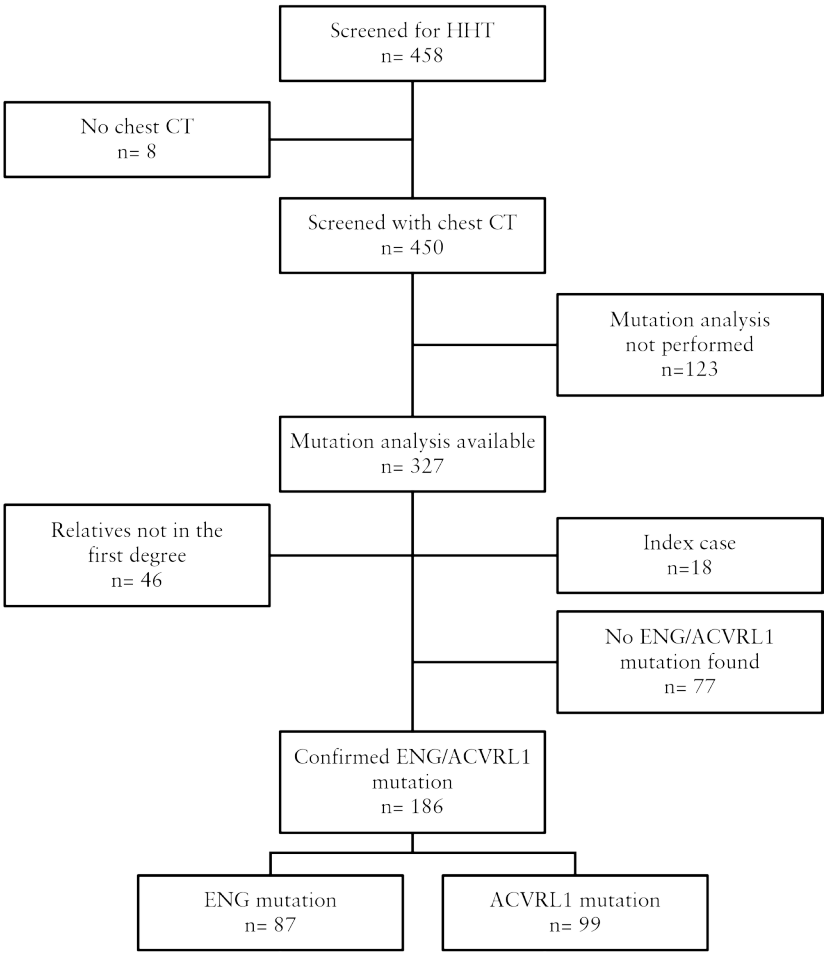

Figure 1. Selection of study population of first-degree relatives of HHT patients who underwent a chest CT, and mutation analysis.

All included individuals were relatives of HHT patients with a proven disease-causing mutation. Abbreviations: HHT, hereditary hemorrhagic telangiectasia; CT, computed tomography; ENG, gene coding for endoglin (HHT type 1); ACVRL1, gene coding for ALK-1 (HHT type 2).

RESULTS

The study population consisted of 263 patients (range 16–76 yr; 56.3% female), of whom 87 patients with a confirmed mutation of the ENG gene (mean age 41.5 ± 15.7 yr; 60.9% female), and 99 patients with an *ACVRL1* gene mutation (mean age 44.1 ± 13.6 yr; 49.5% female; see table 1). In 77 persons the family mutation was not found (mean age 37.1 ± 12.3 yr; 59.7% female). Clinical diagnosis was definite in 83 (95.4%), "possible" in four (4.6%; mean age 28.5 ± 14.9 yr) and unlikely in none of the *ENG* mutation carriers (table 1). Within *ACVRL1* mutation carriers, a clinical diagnosis was definite in 85 (85.9%), possible in 13 (13.1%; mean age 31.2 ± 10.2 yr), and unlikely in one (1.0%) patient, respectively. The latter patient was a 28-years-old man at the time of screening, and he had no clinical signs of HHT. A positive clinical diagnosis predicted 100% (95% CI 97.8–100) of mutation carriers correctly (table 2). The negative predictive value of an unlikely clinical diagnosis was 97.7% (95% CI 87.9–99.6). Of persons in whom the family mutation was absent, clinical diagnosis was definite in none, possible in 35 (45.5%), and unlikely in 42 (54.5%) persons. Of the 123 patients who denied genetic testing, 50 individuals displayed three or more clinical criteria, 53 showed two criteria, and in 20 persons there were no clinical signs of HHT.

Table 1. Clinical characteristics of the study population according to genetic test results.

	ENG + ACVRL1	ENG	ACVRL1	No mutation found
Total (N)	186	87	99	77
Age (yr±SD)	42.9±14.6	41.5±15.7	44.1±13.6	37.1±12.3
Female, n (%)	102 (54.8)	53 (60.9)	49 (49.5)	46 (59.7)
Male, n (%)	84 (45.2)	34 (39.1)	50 (50.5)	31 (40.3)
HHT criteria, n (%)				
Family member[a]	186 (100)	87 (100)	99 (100)	77 (100)
Epistaxis	170 (91.4)	81 (93.1)	89 (89.9)	12 (15.6)
Telangiectases	167 (89.8)	81 (93.1)	86 (86.9)	15 (19.5)
Visceral AVM	75 (40.3)	55 (63.2)	20 (20.2)	0
Pulmonary AVM on CT	66 (35.5)	53 (60.9)	13 (13.1)	0
Cerebral AVM[b]	4 (2.2)	4 (4.6)	0	0
Hepatic AVM[c]	7 (3.8)	1 (1.1)	6 (6.1)	0
GI telangiectases[d]	10 (5.4)	5 (5.7)	5 (5.1)	0
Clinical diagnosis, n (%)				
Definite	168 (90.3)	83 (95.4)	85 (85.9)	0
Possible	17 (9.1)	4 (4.6)	13 (13.1)	35 (45.5)
Unlikely	1 (0.5)	0	1 (1.0)	42 (54.5)

Abbreviations: ENG, endoglin; ACVRL1, activin receptor-like kinase; N, number of patients; SD, standard deviation; AVM, arteriovenous malformation; GI, gastro-intestinal.

[a] First-degree relative of HHT patient with a proven mutation; [b] Screening performed in 58 patients; [c] Screening performed in 36 patients; [d] Screening performed in 17 patients

Table 2. Clinical diagnosis versus ENG or ACVRL1 mutation.

		ENG or ACVRL1 mutation[a]		
		Yes	No	Total
Clinical diagnosis[b]	**Definite**	168 (90.3%)	0	168
	Possible	17 (9.1%)	35 (45.5%)	52
	Unlikely	1 (0.6%)	42 (54.5%)	43
	Total	186	77	263

[a] ENG = Gene coding for endoglin (HHT type 1); ACVRL1 = Gene coding for ALK-1 (HHT type 2).

[b] Clinical diagnosis based on the Curaçao criteria (see text).

Calculated sensitivity: 90.3 (95% CI 85.2-93.8%); specificity: 54.5 (95% CI 43.5-65.2%); Positive predictive value: 100% (95% CI 97.8-100) for a definite diagnosis HHT; Negative predictive value: 97.7% (95% CI 87.9-99.6) for an unlikely diagnosis HHT

DISCUSSION

We report on the diagnostic accuracy of the Curaçao criteria. Of 186 patients with an HHT causing mutation, a definite clinical diagnosis was present in 90.3% and one patient (0.5%) was clinically assessed as unlikely. Within the group without a genetic mutation, 54.5% was clinically classified as unlikely and none were diagnosed with definite HHT. The clinical diagnostic criteria were originally drawn up as a consensus statement [11]. Until then, two criteria were enough for diagnosis of HHT [9]. However, manifestations such as epistaxis are common in the general population, and non-florid telangiectases may present as an expression of other pathologies, which may raise the number of false positives. On the other hand, because of age-related penetrance, the diagnosis should not be ruled out in apparently unaffected children who may become symptomatic later in their lives. Therefore, in the Curaçao classification, three criteria were required for definite diagnosis, a "possible" diagnosis was incorporated for patients with two criteria, and persons with 0 or 1 criterion were regarded as "unlikely" of having HHT. Ever since the Curaçao criteria were designed, molecular diagnostic tests have been improved and have become more widely available. A mutation detection rate of 72–93% of patients with clinically confirmed HHT has been reported [11-13, 15]. Richards-Yutz et al. [14] provided data on 600 individuals who were referred for mutation analysis. They found a mutation in the *ENG* or *ACVRL1* gene in 87% of patients with four clinical criteria and 42–80% in patients with 3 criteria (depending on the different combinations of the individual criteria). Therefore, mutation analysis per se is not always sufficient and clinical evaluation of possible HHT patients is still important. In addition, a clinical evaluation is also essential for at-risk relatives who deny genetic testing. This is emphasized by the high percentage of patients with three clinical criteria in this group in our study. The underuse of genetic screening by at-risk relatives has been observed previously [16]. Common barriers for genetic testing were lack of knowledge, access problems, and emotional issues. As was recognized by the authors of the original report, the accuracy

of the clinical criteria should be re-evaluated when more data on mutation analysis would be available [7, 11]. No previous studies have specifically addressed this subject. In order to assess its validity, we tested the Curaçao criteria in a large group of first-degree relatives of HHT patients with a proven mutation, and used genetic test results as the gold standard. We report on a sensitivity of a certain clinical diagnosis of 90.3% overall, which appeared to be higher in *ENG* (95.4%) than *ACVRL1* mutation carriers (85.9%). This difference should be interpreted with caution as screening for HAVMs, that are more prevalent in HHT2, was not routinely performed. Only 1 of 186 mutation carriers, the aforementioned 28-year-old man, had one clinical criterion (family member of an HHT2 patient), but again, diagnostic workup for involvement of digestive tract and liver was not performed in this patient. We report 45.5% possible HHT patients in the group without a disease-causing mutation. This rather high percentage possibly reflects a more liberate diagnosis of epistaxis or telangiectases in first-degree family members of known HHT patients. It also suggests that a more stringent clinical assessment could improve the diagnostic value of the Curaçao criteria. Although this was not the main subject of interest of their report, Richards-Yutz et al. [14] showed a sensitivity of 72% for a definite clinical diagnosis (given mutation analysis as the gold standard). Six percent of mutation carriers had one clinical criterion, and 35% of patients without a mutation presented three or four criteria. Clinical data were based on test requisition forms that accompanied samples for molecular diagnosis. This contrasts with the diagnostic performance of the clinical criteria in our study and probably relates to the requisites for inclusion in our study population (first-degree family members of patients with a proven HHT causing mutation), as opposed to an unselected population in the Richards-Yutz report. In addition, no information on the methods of clinical screening was available. Obviously, assessment of the validity of the clinical criteria is influenced by patient selection (indication for referral) and screening methods. Therefore, we selected a uniform group of patients who all underwent an identical and systematic clinical screening program.

Our results imply that a definite diagnosis of HHT can clinically be assessed with 100% certainty in a population of first-degree family members of HHT mutation carriers. We report a high prevalence of 70.7% mutation carriers in individuals that were genetically tested. This is probably the result of symptomatic patients that will present for (genetic) screening more frequently. This high prevalence of genetically confirmed HHT might well have raised the positive predictive value of clinical diagnosis. We report on a negative predictive value of 97.7% for an unlikely clinical diagnosis. Of patients with a possible clinical diagnosis, 32.7% proved to be positive for the family mutation. For the clinician this means that genetic testing has limited additional value for the diagnosis of HHT in persons with a definite or unlikely clinical diagnosis, but should be strongly recommended to relatives with possible HHT. However, knowledge of the specific mutation allows diagnosis in relatives, especially in children and young adults with limited phenotypic appearance of HHT. Because of this age-dependent penetrance, the validity of the clinical criteria should ideally be stratified for different categories of age. However, our study was not adequately powered for this purpose. For the same reason, we were not able to test different combinations of individual clinical criteria. Another limitation of our study is that no routine screening for liver AVMs, cerebral

AVMs, and gastrointestinal telangiectases was performed. This might even have caused under-appreciation of the performance of the clinical criteria. Future directions to improve the performance of the diagnostic criteria are expected from contrast echocardiography. TTCE is a sensitive technique for the detection of intrapulmonary shunting [17]. It has been suggested that moderate or large pulmonary shunts on its own are enough as a criterion [18]. This will be subject of further study in our institution.

CONCLUSIONS

The Curaçao clinical criteria, which were based on expert opinion in 2000, prove to have a good diagnostic performance in first-degree relatives of HHT patients with a known family mutation. For diagnostic purposes, genetic testing is particularly helpful in subjects with a clinical diagnosis of possible HHT and individuals at young age.

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CHAPTER 3

Role of transthoracic contrast echocardiography in the clinical diagnosis of hereditary hemorrhagic telangiectasia.

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ABSTRACT

Background: Hereditary hemorrhagic telangiectasia (HHT) can be diagnosed according to the four clinical Curaçao criteria, including the presence of pulmonary arteriovenous malformations (PAVMs). In the past few years, transthoracic contrast echocardiography (TTCE) replaced chest high-resolution CT (HRCT) imaging for the screening of PAVMs. The objective of this study was to determine whether the presence of any pulmonary shunt on TTCE can be accepted as a new clinical Curaçao criterion in diagnosing HHT.

Methods: Between 2004 and 2012, we included 487 first-degree relatives of known HHT-causing mutation carriers who underwent both TTCE and chest HRCT imaging to screen for PAVMs. A quantitative three-point grading scale was used to differentiate among minimal, moderate, or extensive pulmonary shunt on TTCE (grade 1-3). Genetic testing was performed in all people and considered the gold standard for the diagnosis of HHT.

Results: Chest HRCT imaging demonstrated PAVMs in 114 of 218 patients (52.3%) with a pulmonary shunt on TTCE. The addition of any pulmonary shunt on TTCE to the current clinical Curaçao criteria increased the number of positive criteria in 92 of 487 individuals (18.9%), which increased the sensitivity in diagnosing HHT from 88% to 94% at the expense of a decreased specificity from 74% to 70%. Accepting only pulmonary shunt grades ≥ 2 on TTCE as a diagnostic criterion for HHT enhanced the number of positive criteria in 30 (6.2%) individuals, which led to an increased sensitivity of 90% with no decrease in specificity (74%).

Conclusion: The addition of only pulmonary shunt grades ≥ 2 on TTCE to the current clinical Curaçao criteria increases its sensitivity without affecting specificity in the diagnosis of HHT.

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal-dominant inherited disorder characterized by vascular abnormalities varying from small telangiectases in skin and mucosal membranes to large arteriovenous malformations (AVMs) predominantly in the brain, liver, and lungs [1]. There are mainly two types of HHT that correspond with gene mutations coding for endoglin (HHT1) and ALK1 (HHT2) [2, 3]. A third disease-causing mutation has been shown in SMAD4, which causes a combined syndrome of juvenile polyposis and HHT [4]. HHT commonly presents with epistaxis and anemia but carries the risk of more severe complications when visceral AVMs are involved. Most feared are intracranial hemorrhages from ruptured cerebral AVMs [5] and cerebral ischemic events or brain abscesses from paradoxical embolizations through pulmonary AVMs (PAVMs) [6]. Because effective treatment options can prevent these severe complications, early and accurate recognition of HHT is important. The clinical diagnosis of HHT is established according to the four Curaçao criteria [7], which comprise spontaneous and recurrent epistaxis, telangiectases at characteristic sites, a first-degree relative with HHT, and the presence of visceral AVMs. Three criteria suffice for a definite diagnosis of HHT, two criteria are considered as possible HHT, and one or no criterion makes the diagnosis unlikely. Screening for PAVMs traditionally has been done with chest high-resolution CT (HRCT) imaging [8, 9], but the past few years demonstrated that transthoracic contrast echocardiography (TTCE) has an excellent sensitivity, negative predictive value (NPV), and wide availability with lower risks and costs; therefore, TTCE is now advised in the international guidelines as the first-line screening technique for the detection of PAVMs [10-14]. However, to our knowledge, the exact role of a pulmonary shunt on TTCE as a potential new diagnostic criterion for HHT has never been evaluated. Therefore, the aim of the present large prospective study was to determine whether the presence of any pulmonary shunt on TTCE can be accepted as a clinical Curaçao criterion in diagnosing HHT.

METHODS

Study population.

From May 2004 until October 2012, 872 consecutive people aged > 15 years were screened for HHT as family members of index patients or in cases of clinical symptoms suggesting HHT. Both TTCE and chest HRCT scan were performed in 799 of 872 screened people (91.6%) to detect potential PAVMs. Patients with previously treated PAVMs were not included in the analysis. From February 2011, a subsequent chest HRCT scan was withheld in the absence of a pulmonary shunt on TTCE [10, 13, 15]. Because validation of the clinical Curaçao criteria is strongly influenced by the composition of the study population, we selected a highly uniform group of first-degree family members of patients with genetically proven HHT1 or HHT2. This prevented patients with clinically diagnosed HHT in whom genetic testing could not detect a disease-causing mutation from being falsely classified as HHT negative. In addition, we excluded all index patients with HHT because they might be

more symptomatic than their subsequently screened relatives, which would have introduced a bias in the study. Therefore, the present study included 487 first-degree relatives of patients with HHT who all underwent genetic testing and screening for PAVMs with both TTCE and chest HRCT scan. Genetic testing was performed as described earlier [16] and used as the gold standard for the presence or absence of HHT. The selection of the study population is illustrated in figure 1. A complete history and physical examination was performed in all individuals by a pulmonologist and otorhinolaryngologist with dedicated expertise in HHT. The clinical diagnosis of HHT was established according to the current Curaçao criteria. Epistaxis had to be both spontaneous and recurrent to fulfill a criterion. At least three telangiectases had to be present at characteristic sites (lips, oral cavity, nose, fingers) to satisfy a clinical criterion. Screening for GI telangiectases and hepatic AVMs was performed only when suggested by history, physical examination, or blood test results. Patients who were given a definite diagnosis of HHT were offered a brain MRI scan to exclude cerebral AVMs. All participants provided informed consent, and the study was approved by the hospital review board (LTME/Z-12.41).

TTCE was performed as previously described [6]. Two experienced cardiologists with dedicated expertise in HHT interpreted the shunt on TTCE. In case of right-to-left shunting, visualization of shunt origin was pursued in every TTCE. All shunts visualized through a pulmonary vein were classified as pulmonary shunts. On the occasion of poor visualization of shunt origin, we used a delay of four cardiac cycles to distinguish between a pulmonary or cardiac shunt. TTCE results were considered positive for a pulmonary shunt if microbubbles appeared in the left atrium after four cardiac cycles [13, 14, 17]. Right-to-left shunts within four cardiac cycles with poor visualization of shunt origin were classified as indeterminate shunts (n = 7) and excluded from further analysis. Opacification of the left ventricle was graded as 1 (maximum of 29 microbubbles), 2 (30-100 microbubbles), or 3 (> 100 microbubbles). This division was based on the maximum number of microbubbles in the left ventricle counted in one still frame, which was confirmed by checking the five frames before and after the chosen frame. A good κ coefficient of 0.85 was found for interobserver agreement regarding pulmonary shunt grade on TTCE in previous studies [14, 15, 18]. In cases of disagreement on presence, quantity, or timing of microbubbles in the left ventricle, the TTCE was reviewed again by both cardiologists together to agree on the final determination. A patent foramen ovale was diagnosed only after a positive Valsalva maneuver without a spontaneous right-to-left shunt.

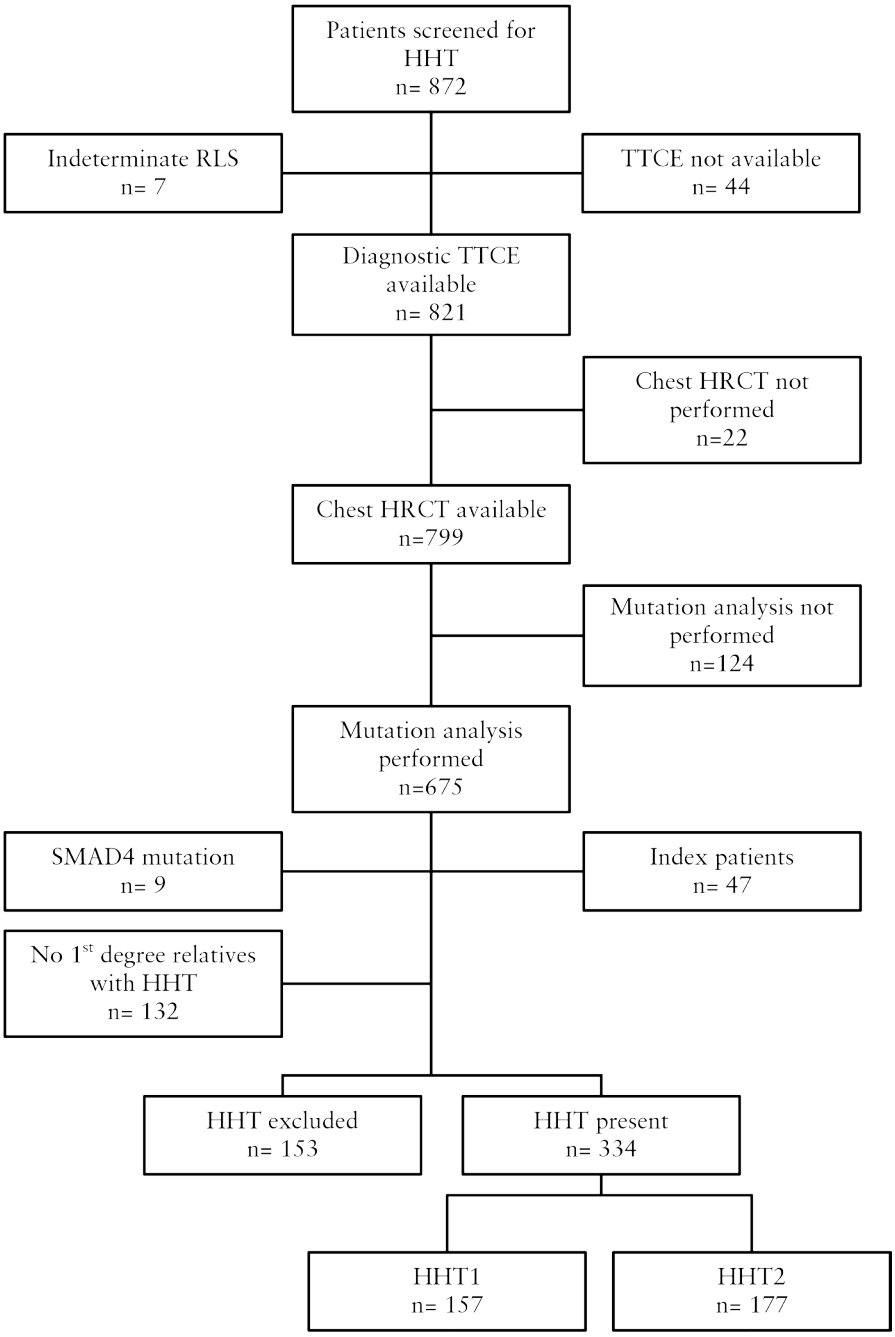

Figure 1: Selection of the study population.
Abbreviations: HHT, hereditary hemorrhagic telangiectasia; RLS, right-to-left shunt; n, number; HRCT, high-resolution computed tomography; TTCE,Transthoracic contrast echocardiography.

Chest HRCT scan.
Chest HRCT scanning (Koninklijke Philips NV) was performed without contrast with the use of the single breath-hold technique and a slice thickness of 1 mm. Identification of PAVMs was based on the presence of a nodular opacity with both an afferent and an efferent vessel. The HRCT scans were evaluated by two independent observers (a radiologist and an experienced pulmonologist), both blinded to the TTCE results. When both observers disagreed, the chest HRCT images were considered positive for a PAVM, and angiography of the pulmonary artery was performed given the impact of complications from a potentially missed treatable PAVM.

Statistical analysis.
Descriptive statistics were used to describe patient characteristics. Continuous variables with normal distribution were presented as mean ± SD. Sensitivity was expressed as the number of patients with clinically confirmed HHT (three or more Curaçao criteria) divided by the number of patients with a confirmed HHT-causing mutation on genetic testing. Specificity was expressed as the number of patients with an unlikely clinical diagnosis (no or one Curaçao criterion) divided by the number of individuals in whom genetic testing excluded the known HHT family mutation. Positive predictive values (PPVs) and NPVs were subsequently calculated with their 95% CIs. Statistical analyses were performed with SPSS, version 17.0 (IBM Corporation) software.

RESULTS

Study population.
The selected study population comprised 487 people (mean age, 42.2 ± 14.7 years, 56.3% women) in whom genetic testing confirmed HHT1 in 157 (32.2%), HHT2 in 177 (36.3%), and no HHT in 153 (31.4%) (table 1).

TTCE and chest HRCT imaging.
TTCE documented a pulmonary shunt in 134 patients (85.4%) with HHT1, 75 (42.4%) with HHT2, and nine (5.9%) without HHT (table 1). All nine individuals without HHT had a pulmonary shunt grade 1 on TTCE. The distribution of the three pulmonary shunt grades differed between both HHT subtypes. Grade 3 shunts tended to be more frequent in HHT1 (53.7% of all shunts in HHT1), whereas grade 1 shunts were predominant in HHT2 (64.0% of all shunts in HHT2). Of the 136 individuals with a pulmonary shunt grade 1 and 2 on TTCE, only five (3.7%) had a maximum number of microbubbles close to the cutoff point between these two shunt grades (eg, five of 136 had between 27 and 32 bubbles in the left ventricle). The mean number of left-sided microbubbles was 10 and 49 for a pulmonary shunt grade 1 and 2, respectively on TTCE. Chest HRCT scan confirmed the presence of PAVMs in 114 of 218 patients (52.3%) with a pulmonary shunt on TTCE, whereas all patients with a PAVM on chest HRCT scan demonstrated a pulmonary shunt on TTCE.

Table 1. Clinical characteristics of the study population.

	HHT1	HHT2	No HHT
Total, n	157	177	153
Age (years±SD)	41.6±15.4	46.0±14.0	38.3±13.7
Female, n (%)	96 (61.1)	95 (53.7)	83 (54.2)
Male, n (%)	61 (38.9)	82 (46.3)	70 (45.8)
HHT criteria, n (%)			
First degree family member with HHT, n (%)	157 (100)	177 (100)	153 (100)
Epistaxis	146 (93.0)	167 (94.4)	22 (14.4)
Telangiectases	145 (92.4)	158 (89.3)	20 (13.1)
Visceral AVM[a]	107 (68.2)	42 (23.7)	1 (0.7)
Pulmonary AVM (chest HRCT scan)	97 (61.8)	17 (9.6)	0
Cerebral AVM [b]	13 (8.3)	1 (0.6)	n/a
Hepatic AVM [c]	4 (2.5)	19 (10.7)	1 (0.7)
GI telangiectases [d]	17 (10.8)	11 (6.2)	n/a
Clinical diagnosis, n (%) [e]			
Definite	145 (92.4)	149 (84.2)	3 (2.0)
Possible	12 (7.6)	28 (15.8)	37 (24.2)
Unlikely	0	0	113 (73.8)
Pulmonary RLS on TTCE, n (%)	134 (85.4)	75 (42.4)	9 (5.9)
Grade 1	25 (18.7)	48 (64.0)	9 (100)
Grade 2	37 (27.6)	17 (22.7)	0
Grade 3	72 (53.7)	10 (13.3)	0

Abbreviations: HHT, hereditary hemorrhagic telangiectasia; n, number; SD, standard deviation; AVM, arteriovenous malformation; HRCT, high-resolution computed tomography; n/a, not applicable.

[a]29 persons with two different localisations of visceral AVMs and one person with three different visceral localisations of AVMs.

[b]Screening performed in 174 patients.

[c]Screening performed in 53 patients.

[d]Screening performed in 36 patients.

[e]According to the current clinical Curaçao criteria (using chest HRCT for the presence of PAVMs).

The presence of a pulmonary shunt on TTCE as a clinical Curaçao criterion for diagnosing HHT.

According to the current clinical Curaçao criteria (use of chest HRCT scan to detect the presence of PAVMs), HHT was definite in 294 patients (88.0%) and possible in 40 (12.0%) with a genetically proven HHT-causing mutation (table 1). There were no patients with genetically proven HHT in whom the current criteria suggested HHT to be unlikely. Genetic testing excluded HHT in three individuals (1.9%) given a definite clinical diagnosis on the

basis of the current criteria. All three had a first-degree relative with HHT, frequent and spontaneous epistaxis, and at least three telangiectasia on the characteristic sites but no visceral AVMs. The first-degree family mutations of these individuals with negative DNA findings were clearly pathogenic. The sensitivity, specificity, PPV, and NPV of the current clinical Curaçao criteria for diagnosing HHT were 88.0% (95% CI, 0.84-0.91), 73.9% (95% CI, 0.66-0.80), 99.0% (95% CI, 0.97-0.99), and 100% (95% CI, 0.97-1.0), respectively (table 2).

Table 2. Diagnosis of HHT according to current clinical Curaçao criteria without TTCE.

Clinical Diagnosis	HHT Mutation	No HHT Mutation	Total
Definite	294 (88.0)	3 (1.9)	297
Possible	40 (12.0)	37 (24.2)	77
Unlikely	0	113 (73.9)	113
Total	334	153	487

Data are presented as No. (%) unless otherwise indicated. Calculated sensitivity, 88.0% (95% CI, 0.84-0.91); specificity, 73.9% (95% CI, 0.66-0.80); positive predictive value; 99.0% (95% CI, 0.97-0.99) for a definite diagnosis of HHT; negative predictive value, 100% (95% CI, 0.97-1.0) for an unlikely diagnosis of HHT. See table 1 legend for expansion of abbreviations.

Accepting the presence of any pulmonary shunt on TTCE as a clinical Curaçao criterion enhanced the number of positive criteria in 92 of 487 individuals (18.9%), which actually changed the clinical diagnosis in 30 of them (32.6%). The remaining 62 (67.4%) changed from three to four positive criteria, which had no clinical consequences because three Curaçao criteria already suffice for a definite diagnosis of HHT (table 3). This increased criteria sensitivity from 88.0% (95% CI, 0.84-0.91) to 94.3% (95% CI, 0.91-0.96) at the expense of a decreased specificity from 73.9% (95% CI, 0.66-0.80) to 69.9% (95% CI, 0.62-0.77) (table 4). This decline in specificity was completely related to the presence of grade 1 pulmonary shunts in individuals without HHT; all nine of the 153 people (5.9%) without HHT incorrectly given a diagnosis of possible or definite HHT showed a pulmonary shunt grade 1 on TTCE. The range of microbubbles counted in the left side of the heart in these nine individuals was between three and 19, which illustrates that there was no doubt about the presence of a pulmonary shunt grade 1 (and not grade 2) on TTCE. In contrast, genetic testing confirmed the presence of HHT in all individuals with a pulmonary shunt grade ≥ 2 on TTCE. Therefore, we also determined the diagnostic accuracy of the clinical Curaçao criteria with the addition of only pulmonary shunt grades ≥ 2 on TTCE as a positive criterion. This strategy enhanced the number of positive criteria in 30 of 487 individuals (6.2%), which correctly changed the clinical diagnosis in seven of 30 (23.3%) and prevented additional incorrect clinical diagnoses of HHT, with no difference between HHT1 and HHT2 (table 5). Accepting the presence of only pulmonary shunt grades ≥ 2 on TTCE as a positive clinical Curaçao criterion actually improved the overall diagnostic accuracy of the current criteria, resulting in a sensitivity, specificity, PPV, and NPV of 90.1% (95% CI, 0.86-0.93), 73.9% (95% CI, 0.66-0.80), 99.0% (95% CI, 0.97-0.99), and 100% (95% CI, 0.97-1.0), respectively, in diagnosing HHT (table 6).

Table 3. Changes in the number of positive Curaçao criteria with the addition of any pulmonary shunt on TTCE

No. Criteria	HHT1	HHT2	No HHT
0→1	n/a	n/a	n/a
1→2	0	0	6 (3.9)
2→3	6 (3.8)	15 (8.4)	3 (2.0)
3→4	28 (17.8)	34 (19.2)	0
Total	34 (21.7)	49 (27.7)	9 (5.9)

Data are presented as No. (%). See table 1 legend for expansion of abbreviations.

Table 4. Diagnosis of HHT with the addition of any pulmonary shunt on TTCE to the current clinical Curaçao criteria

Clinical Diagnosis	HHT Mutation	No HHT Mutation	Total
Definite	315 (94.3)	6 (3.9)	321
Possible	19 (5.7)	40 (26.1)	59
Unlikely	0	107 (69.9)	107
Total	334	153	487

Data are presented as No. (%). Calculated sensitivity, 94.3% (95% CI, 0.91-0.96); specificity, 69.9% (95% CI, 0.62-0.77); positive predictive value, 98.1% (95% CI, 0.96-0.99) for a definite diagnosis of HHT; negative predictive value, 100% (95% CI, 0.97-1.0) for an unlikely diagnosis of HHT. See table 1 legend for expansion of abbreviations.

Table 5. Changes in the number of positive Curaçao criteria with the addition of only pulmonary shunt grades ≥ 2 on TTCE

No. Criteria	HHT1	HHT2	No HHT
0→1	n/a	n/a	n/a
1→2	0	0	0
2→3	3 (1.9)	4 (2.3)	0
3→4	13 (8.3)	10 (5.6)	0
Total	16 (10.2)	14 (7.9)	0

Data are presented as No. (%). See table 1 legend for expansion of abbreviations.

Table 6. Diagnosis of HHT with the addition of only pulmonary shunt grades ≥ 2 on TTCE to the current clinical Curaçao criteria

Clinical Diagnosis	HHT Mutation	No HHT Mutation	Total
Definite	301 (90.1)	3 (1.9)	304
Possible	33 (9.9)	37 (24.2)	70
Unlikely	0	113 (73.9)	113
Total	334	153	487

Data are presented as No. (%). Calculated sensitivity, 90.1% (95% CI, 0.86-0.93); specificity, 73.9% (95% CI, 0.66-0.80); positive predictive value, 99.0% (95% CI, 0.97-0.99) for a definite diagnosis of HHT; negative predictive value, 100% (95% CI, 0.97-1.0) for an unlikely diagnosis of HHT. See table 1 legend for expansion of abbreviations.

DISCUSSION

To our knowledge, this large prospective study is the first to evaluate the role of a pulmonary shunt on TTCE in the clinical Curaçao criteria for diagnosing HHT. The results demonstrate that the addition of only pulmonary shunt grades ≥ 2 on TTCE to the current Curaçao criteria increases its sensitivity without affecting specificity, suggesting that a pulmonary shunt grade 1 on TTCE should not be accepted as a diagnostic criterion for HHT.

The characteristic feature of vascular pathology in HHT is the presence of direct artery-to-vein communications, which carries the risk of complications from shunting and hemorrhage. HHT has an estimated prevalence of 1 in 5,000 individuals [19], but many do not receive a diagnosis and are at risk for potential preventable complications [20,21]. Although genetic testing for an HHT-causing mutation has been improved and has become more widely available in the past few years, mutation analysis per se is not always sufficient in the diagnosis of HHT. Previous studies described a mutation detection rate of 72% to 93% in patients with clinically confirmed HHT [16,22-24], and underuse of genetic testing has been reported in relatives at risk for HHT [25]. Therefore, an accurate clinical evaluation remains essential in all persons with suspected HHT. The original clinical Curaçao criteria were designed in the year 2000 as a consensus statement and consist of spontaneous and recurrent epistaxis, telangiectases at characteristic sites, a first-degree relative with HHT, and the presence of visceral AVMs [7]. Our group previously demonstrated that these criteria already have a good diagnostic performance compared with genetic testing [26]. However, further improvement of the criteria remains desirable, as was already recognized by the authors of the original clinical Curaçao criteria [8,9]. Although TTCE replaced chest HRCT scanning in the past few years as the first-line screening technique for detecting PAVMs [10], it remains unknown whether a pulmonary shunt on TTCE can stand on its own as a (new) Curaçao criterion in the clinical diagnosis of HHT. This question can be of special importance because the present study confirms that chest HRCT scanning demonstrates a PAVM in only 52.3% of patients with a pulmonary shunt on TTCE.

In the present study, the addition of any pulmonary shunt on TTCE to the current clinical Curaçao criteria resulted in an increased sensitivity from 88% to 94%, but decreased specificity from 74% to 70%. Although a pulmonary shunt grade 1 on TTCE was present in 73 of 334 patients (21.9%) with HHT and correctly changed the clinical diagnosis from possible to definite HHT in 14 (4.2%), this small pulmonary shunt was also found in nine individuals (5.9%) without HHT and falsely changed the clinical diagnosis from possible to definite in three (2.0%). This finding suggests a limited diagnostic significance of a pulmonary shunt grade 1 on TTCE. The presence of small pulmonary shunts on TTCE has been previously described in around 6% of healthy subjects [14, 18] and may represent a normal variant in the general population in the absence of an underlying patent foramen ovale (excluded in all people with a pulmonary shunt grade 1 without HHT in the present study). Woods et al [27] described a relatively high prevalence of small pulmonary right-to-left shunts on TTCE (28%) in a healthy volunteer population compared with the 5.9% found in the present study. A potential explanation for this discrepancy might be that the study by Woods et al [27] could have been biased toward volunteers with migraines (because the study advertisements described a research study investigating shunts and migraines), a population in which a higher prevalence of pulmonary shunts has been reported [28]. This potential advertisement-based bias might also explain the relatively high prevalence of individuals with a patent foramen ovale (38%) and migraine (40%) [27] compared with the percentages in other studies (15%-27% [29-31] and 6%-18% [32], respectively). However, because we cannot think of other plausible explanations for this different finding, we should consider that small pulmonary shunts on TTCE might be more common in healthy subjects than previously appreciated. Therefore, we believe that only pulmonary shunt grades ≥ 2 on TTCE should be accepted as a positive clinical Curaçao criterion in diagnosing HHT. With this strategy, the sensitivity of the current clinical criteria is increased to 90% without decreasing specificity.

This study had several limitations. First, the study included a selected group of first-degree family members of patients with genetically proven HHT1 or HHT2 (who all fulfilled already one Curaçao criterion), and caution is needed in extrapolating the results to less selected screening populations. However, it can be expected that the diagnostic significance of the pulmonary shunt grade on TTCE is even higher in patients with no known first-degree family member with HHT. Second, the study population was screened in an HHT clinic with specific expertise in TTCE, and it remains uncertain whether the results also apply to a general population in hospitals without this specific expertise. However, screening for PAVMs with TTCE is preferably performed in specialized HHT clinics to achieve the accuracy reported in the literature. Third, the clinical presentation of HHT is age dependent [33], and validity of the clinical Curaçao criteria ideally should be stratified for different age categories. The present study was not adequately powered for this purpose, and caution should be taken in extrapolating the results to young people with a pulmonary shunt grade 1 on initial TTCE and those aged < 15 years because this last age category was not included in the present study. Fourth, routine screening for liver, cerebral, or GI AVMs was absent in the study. This might have caused an underappreciation of the current clinical Curaçao criteria

but does reflect a more realistic representation of the screening algorithm for HHT in daily practice. Finally, the present study is a single-center investigation, and different results may be found by a different set of investigators.

CONCLUSIONS

The addition of only pulmonary shunt grades ≥ 2 on TTCE to the current clinical Curaçao criteria further increases its sensitivity without affecting specificity in diagnosing HHT. A pulmonary shunt grade 1 on TTCE should not be accepted as a diagnostic criterion for HHT.

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CHAPTER 4

Pulmonary shunt fraction measurement compared to contrast echocardiography in HHT patients; time to abandon the 100% oxygen method?

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ABSTRACT

Background: Presence of pulmonary right-to-left shunting (RLS) is associated with severe neurological complications from paradoxical embolisation in patients with hereditary haemorrhagic telangiectasia (HHT) and screening is warranted. Pulmonary shunt fraction measurement with the 100% oxygen method can be used for the detection and quantification of functional pulmonary RLS, although transthoracic contrast echocardiography (TTCE) appeared as gold standard during the last few years.

Objective: Determining the true diagnostic accuracy of the established 100% oxygen method in detecting pulmonary RLS, as compared to TTCE.

Methods: We analysed 628 persons screened for HHT between 2004 and 2010, who all underwent TTCE. A quantitative three-point grading scale was used to differentiate between minimal, moderate or extensive pulmonary RLS on TTCE (grade 1-3 respectively). Additional shunt fraction measurement with the 100% oxygen method was pursued in case of pO_2 <13kPa or <12kPa in patients younger or older than 30 years respectively. A shunt fraction >5% was considered pathological.

Results: Both TTCE and 100% oxygen method were performed in 210 persons. Although the presence of a pathological shunt fraction correlated with an increased pulmonary shunt grade on TTCE, the 100% oxygen method confirmed a >5% shunt fraction in only 51% of patients with pulmonary RLS on TTCE (14%, 20% and 72% for respectively grade 1, 2 and 3).

Conclusion: Pulmonary shunt fraction measurement with the 100% oxygen method is not a useful screening technique for the detection of pulmonary RLS in HHT, as its sensitivity is too low and large pulmonary shunts on TTCE may remain undetected using this method.

INTRODUCTION

Pulmonary arteriovenous malformations (PAVMs) are thin walled abnormal vessels replacing normal capillaries between the pulmonary arterial and venous circulation [1]. A PAVM causes permanent pulmonary right-to-left shunting (RLS), thereby bypassing the pulmonary capillary filter. Consequently, both emboli of thrombotic and septic origin may directly reach the systemic circulation, causing potential severe neurological complications, such as ischemic strokes or brain abscesses [2]. Gas exchange may also be compromised in the presence of pulmonary RLS, resulting in hypoxaemia and dyspnea. The majority of PAVMs (70-90%) is associated with hereditary haemorrhagic telangiectasia (HHT) [3, 4]. HHT is an autosomal dominant inherited disorder, characterized by vascular abnormalities varying from small telangiectases in skin and mucosal membranes, to large arteriovenous malformations, predominantly in the brain, liver and lungs. There are mainly two types of HHT, corresponding with gene mutations coding for Endoglin (HHT1) and ALK1 (HHT2) [5, 6]. Pulmonary RLS has been reported in 91% of HHT1, and in 53% of HHT2 patients [7]. Because of this high prevalence, its potential severe complications and effective treatment options with transcatheter embolotherapy, screening for pulmonary RLS is recommended in all persons with possible or confirmed HHT [8-10]. Pulmonary shunt fraction measurement with the 100% oxygen method has long been performed as initial screening technique, based on alveolar-arterial oxygen differences after breathing 100% oxygen [3], but during the last few years transthoracic contrast echocardiography (TTCE) evolved as the recommended first-line screening technique for the detection of pulmonary RLS [9, 11]. However, the 100% oxygen method has never been directly compared to TTCE and is still in use for the detection and quantification of pulmonary RLS and analysis of unexplained hypoxaemia. Therefore, the present large observational study determined the true diagnostic accuracy of pulmonary shunt fraction measurement with the established 100% oxygen method in detecting functional pulmonary RLS compared to TTCE as modern gold standard.

METHODS

Study population.

Between May 2004 and December 2010 669 persons above fifteen years of age were screened for HHT in the St. Antonius Hospital, Nieuwegein, the Netherlands. Subjects were screened in a one-day protocol, as family members of index patients or in case of clinical symptoms suggesting HHT. Complete history and physical examination were performed by a pulmonologist with dedicated expertise in HHT. The clinical diagnosis of HHT was established according to the Curaçao criteria [12]. These criteria consist of spontaneous and recurrent epistaxis, telangiectasias at characteristic sites, visceral arteriovenous malformations, and a first-degree relative with HHT. Genetic testing for the HHT-causing gene mutation was offered to all screened subjects and performed as published before [13]. A definite diagnosis of HHT was established in case of three or more clinical Curaçao criteria, or when genetic testing identified the HHT-causing mutation. The diagnosis of HHT

was “possible” in patients with two clinical Curaçao criteria without genetic testing or if no mutation had been found in the family. The diagnosis of HHT was “unlikely” in the presence of less than two clinical Curaçao criteria without genetic testing or if no mutation had been found in the family. HHT was rejected when genetic testing excluded the known HHT-causing family mutation. The study was approved by the institutional review board (LTME/Z-12.41).

Pulmonary shunt fraction measurement with the established 100% oxygen method.
The arterial partial oxygen pressure (pO_2, kPa) was measured at rest, breathing room air in a semi-recumbent position. An additional shunt fraction measurement with the 100% oxygen method was pursued in case of a pO_2 <13kPa or <12kPa in patients younger or older than 30 years respectively. Patients breathed 100% oxygen from a Douglas bag, via a closely fitting mouthpiece and two-way valve, while wearing a nose clip and taking a deep inspiration every minute. An arterial blood sample was obtained after breathing 100% oxygen for 30 minutes and the samples were cooled on ice and analysed immediately for oxygen and carbon dioxide tensions. The pulmonary shunt fraction was calculated using the established classical equation: $Q_s/Q_t = (C_{c,O2} - C_{a,O2}) / (C_{c,O2} - C_{v,O2})$, in which Q_s/Q_t is the RLS as a fraction of the cardiac output, $C_{c,O2}$ is the oxygen content at the end of the pulmonary capillary, $C_{a,O2}$ is the oxygen content of arterial blood and $C_{v,O2}$ is the oxygen content of mixed venous blood [14]. The $C_{v,O2}$ was defined as the $C_{a,O2}$ - 4.4ml O_2/100ml blood [15]. Since the total blood oxygen content is composed of dissolved O_2 plus HbO_2 and the solubility of oxygen in blood is 0.0225ml/100ml/kPa, the oxygen content (C) was calculated as follows: Oxygen content (ml O_2/100ml blood) = (0.0225 x pO_2) + (2.24 x haemoglobin x SaO_2/100), where pO_2 is the partial oxygen pressure (kPa), haemoglobin is expressed in mmol/L and SaO_2 is the arterial oxygen saturation (%). The haemoglobin oxygen saturation at the end of the pulmonary capillary is assumed to be 100%. The partial pressure of carbon dioxide (pCO_2) is assumed to equal the alveolar partial pressure of oxygen (pO_2) and can be calculated as follows; pO_2 = barometric pressure (101.3 kPa) - pCO_2 - alveolar saturated water vapour pressure ($P_{A,H2O}$). $P_{A,H2O}$ is 6.3 kPa at a body temperature of 37°C. Using the 100% oxygen method, a pulmonary shunt fraction of >5% was considered pathological [3, 15]. Patients with previously treated PAVMs were not included in our analysis.

Transthoracic contrast echocardiography.
TTCE was performed by placing an intravenous line in the right ante-cubital vein to which two 10mL syringes were connected, one filled with an 8mL physiologic saline solution and the other with 1mL air. Subsequently, 1mL blood was drawn in the air-filled syringe and mixed with the saline-filled syringe by reverse flushing between both syringes, creating agitated saline (microbubbles). The patient was positioned in the left lateral position and 5mL of fresh agitated saline was injected within three seconds, while projecting the 4-chamber apical view, with and without a Valsalva manoeuvre. TTCE was performed by a constant group of three trained echocardiographists. Interpretation of RLS was performed by two cardiologists with dedicated expertise in both TTCE and HHT, who were unaware of the patients medical history or prior shunt fraction measurement. In case of RLS, visualization

of shunt origin was pursued in every TTCE. All RLS visualized through a pulmonary vein was classified as pulmonary RLS. On the occasion of poor visualization of shunt origin, we used a delay of 4 cardiac cycles to distinguish pulmonary from cardiac RLS, in which TTCE was considered positive for pulmonary RLS if microbubbles appeared in the left atrium after 4 cardiac cycles, as published before [11, 16, 17]. This delay in appearance of microbubbles in the left atrium was measured in number of cardiac cycles after the first appearance of microbubbles in the right atrium. Opacification of the left ventricle was quantitatively graded as 1 (maximum of 29 microbubbles in left ventricle), 2 (30-100 microbubbles, or 3 (>100 microbubbles). This division was based on the maximum number of microbubbles in the left ventricle counted in one still-frame. A good κ coefficient of 0.85 up to 0.94 was found for inter-observer agreement concerning this pulmonary shunt grade on TTCE in previous studies [17, 18]. RLS within 4 cardiac cycles with poor visualization of shunt origin was classified as indeterminate shunting and excluded from further analysis. A patent foramen ovale (PFO) was diagnosed only after a positive Valsalva manoeuvre, without spontaneous RLS. The presence of an atrial septum defect (ASD) was routinely excluded in all RLS using colour Doppler or potential negative contrast in the right atrium [19].

Chest computed tomography.

Chest CT images were routinely obtained on a 16+ multi-detector CT scanner (Philips Medical Systems), with a dedicated high-resolution algorithm and maximum slice thickness of 1 mm. Identification of PAVMs on chest CT was based on presence of a nodular opacity with both an afferent and efferent vessel. Chest CT scans were evaluated by two independent observers highly experienced in evaluating PAVMs (a radiologist and pulmonologist), both blinded to the results from TTCE and shunt fraction measurement. When both observers disagreed, chest CT was considered positive for a PAVM and additional angiography of the pulmonary artery was performed given the impact of potential complications from a missed treatable PAVM.

Statistics.

Descriptive statistics were used to describe patient characteristics. Continuous variables with normal distribution were presented as mean ± standard deviation. A median range was used when normal distribution was absent. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) with their 95% confidence intervals (CI) and the area under the receiver operating characteristic (ROC) curve were determined for shunt fraction measurement with the 100% oxygen method compared to TTCE as gold standard. Statistical analyses were performed using the statistical software application SPSS (version 17.0; SPSS Inc., Chicago).

RESULTS

Study population.

Out of the 669 persons screened for HHT, a diagnostic TTCE was available in 628 persons (93.9%). Arterial blood gas analysis was performed in 614 out of these 628 persons (97.8%). Based on the previous described pO_2 values, 210 persons (34.2%) underwent additional pulmonary shunt fraction measurement with the 100% oxygen method, and were included for further analysis (figure 1). Out of these 210 persons, presence of HHT was definite in 135 patients (64.3%), possible in 17 persons (8.1%), unlikely in 19 persons (9.0%) and excluded in 39 individuals (18.6%). Genetic testing was performed in 188 out of 210 persons (89.5%), which identified 62 patients (29.5%) with HHT1 and 62 patients (29.5%) with HHT2. The baseline characteristics of our final study population are described in table 1.

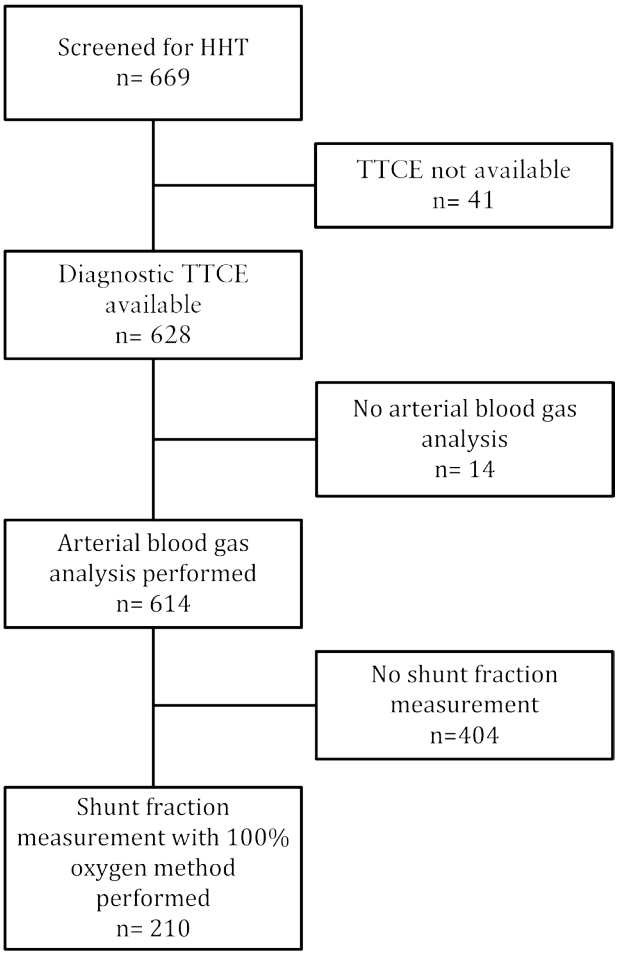

Figure 1. Flow-chart of selected study population

Abbreviations: HHT, hereditary haemorrhagic telangiectasia; n, number; TTCE, transthoracic contrast echocardiography.

Table 1. Baseline characteristics of 210 persons with both TTCE and 100% oxygen method.

Total	210
Female	128 (61,0)
Age (mean±SD)	46,8 ± 15,1
HHT	
definite	135 (64,3)
HHT 1	62 (29,5)
HHT2	62 (29,5)
possible	17 (8,1)
unlikely	19 (9,0)
excluded	39 (18,6)
Pulmonary shunt on TTCE	
grade 1	22 (10,5)
grade 2	15 (7,1)
grade 3	61 (29,0)
No pulmonary shunt on TTCE	112 (53,3)
PFO, n (%)	10 (4,8)
Shunt fraction ≤ 5%	144 (68,6)
Shunt fraction > 5%	66 (31,4)
PAVM on chest CT	
yes	66 (31,4)
no	141 (67,1)

Abbreviations: SD, standard deviation; HHT, hereditary haemorrhagic telangiectasia; TTCE, transthoracic contrast echocardiography; PFO, patent foramen ovale; PAVM, pulmonary arteriovenous malformation; CT, computed tomography.

Pulmonary shunt fraction measurement with the 100% oxygen method compared to TTCE. Pulmonary RLS on TTCE was present in 98 out of 210 persons (46.7%). A pulmonary shunt grade 1 was diagnosed in 22 patients (22.4%), grade 2 in 15 patients (15.3%) and grade 3 in 61 patients (62.2%). The 100% oxygen method documented a pathological shunt fraction of >5% in 13.6%, 20.0% and 72.1% of patients with respectively a pulmonary shunt grade 1, 2 or 3 on TTCE (figure 2). The mean pulmonary shunt fraction in patients with a pulmonary shunt grade 1, 2 and 3 on TTCE was respectively 2.2%, 3.8% and 10.1% (figure 3). Using TTCE as gold standard for the detection of functional pulmonary RLS, the 100% oxygen method had a sensitivity of 51% (95% CI 0.41-0.61) and specificity of 86% (95% CI 0.78-0.91) (table 2), with an area under the ROC curve of 0.74 (95% CI 0.67-0.81). The diagnostic accuracy of the 100% oxygen method in detecting only moderate to

large pulmonary shunts on TTCE (grade 2 and 3) slightly increased to a sensitivity of 62% (95% CI 0.51-0.72) and specificity of 86% (95% CI 0.79-0.9) (table 2), with an area under the ROC curve of 0.82 (95% CI 0.75-0.88).

The 100% oxygen method revealed a pathological shunt fraction of >5% in 14.3% of persons without any RLS on TTCE. A mean shunt fraction of 9.1% was found in these false positive cases. Chest CT demonstrated regions with atelectasis and/or pulmonary fibrosis in 53.3% of these persons, but no alternative explanation was found in the other 46.7% of false positive cases.

TTCE showed a PFO in 10 out of 210 persons (4.8%), where the 100% oxygen method revealed a pathological shunt fraction of >5% in only 3 of these patients. No ASD was documented.

Chest CT was performed in 207 out of 210 persons (98.6%) with both TTCE and shunt fraction measurement. Although already selected by a lower pO_2, chest CT confirmed the presence of PAVMs in 66 out of 98 patients (67.3%) with pulmonary RLS on TTCE. Pulmonary shunt fraction measurement with the 100% oxygen method identified a pathological shunt fraction in 46 out of 66 patients with a PAVM on chest CT (69.7%); the 100% oxygen method did not reveal an abnormal shunt fraction in the other 41.7% of patients with visible PAVMs on chest CT.

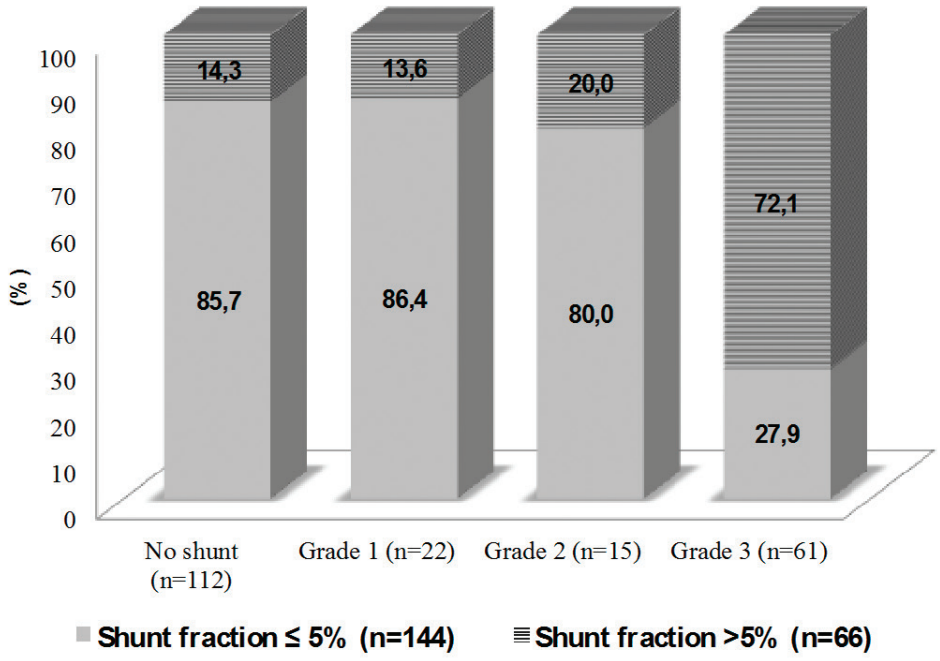

Figure 2. Pulmonary shunt fraction measurement with the 100% oxygen method compared to different pulmonary shunt grades on TTCE (n=210).

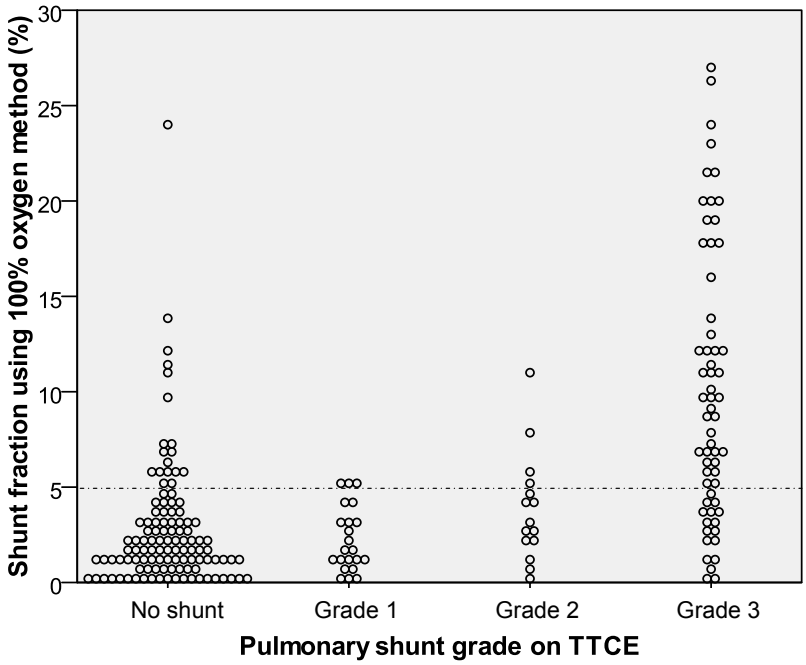

Figure 3. Dot plot demonstrating the shunt fractions measured with the 100% oxygen method compared to graded TTCE as gold standard (n=210).

Table 2. Pulmonary shunt fraction measurement using100% oxygen method compared to TTCE.

	Shunt fraction ≤ 5%, n	Shunt fraction >5%, n	
No pulmonary shunt on TTCE, n	96	16	112
Any pulmonary shunt on TTCE, n	48	50	98
	144	66	210

Diagnostic accuracy of the 100% oxygen method in detecting any pulmonary RLS on TTCE: Sensitivity 51% (CI 0,41-0,61), specificity 86% (CI 0,78-0,91), PPV 76% (CI 0,64-0,84), NPV 67% (CI 0,58-0,74).

	Shunt fraction ≤ 5%, n	Shunt fraction >5%, n	
No or grade 1 pulmonary shunt on TTCE, n	115	19	134
Only pulmonary shunt grade 2 or 3 on TTCE, n	29	47	76
	144	66	210

Diagnostic accuracy of the 100% oxygen method in detecting only pulmonary shunt grades 2 and 3 on TTCE:
Sensitivity 62% (95% CI 0,51-0,72), specificity 86% (CI 0,79-0,9), PPV 71% (CI 0,59-0,81), NPV 80% (CI 0,73-0,86).

DISCUSSION

To our knowledge, this is the first large study evaluating the true diagnostic accuracy of pulmonary shunt fraction measurement with the 100% oxygen method in detecting functional pulmonary RLS compared to TTCE as modern gold standard. Our results firmly indicate that pulmonary shunt fraction measurement with the 100% oxygen method is not a reliable test to screen for PAVMs in patients with HHT.

Screening for PAVMs is warranted in all patients with possible or confirmed HHT, given the high risk of neurological complications that may be prevented by transcatheter embolotherapy. Arterial blood gas analysis and additional pulmonary shunt fraction measurement with the 100% oxygen method have been used as non-invasive screening tests for the detection of functional pulmonary RLS in these subjects. Under normal conditions, the fraction of cardiac output that shunts from right-to-left (=shunt fraction) is ≤ 5%. A pathological shunt fraction of >5% has been reported in up to 97.5% of patients with PAVMs, prior to transcatheter embolotherapy [20-25] and the 100% oxygen method has long been assumed accurate enough for the detection of clinically important pulmonary RLS. However, a retrospective study of 105 persons screened for HHT by Cottin et al. previously suggested a markedly lower sensitivity (up to 68%) of the 100% oxygen method in detecting pulmonary RLS compared to anatomical-based tests like chest CT and pulmonary angiography [26]. During the last few years, TTCE now evolved as first-line screening technique for the detection of functional pulmonary RLS, based on its excellent sensitivity, high negative predictive value and wide availability with low risks and costs [9, 11, 17, 27-29], but studies directly comparing the 100% oxygen method to TTCE are lacking. The current analysis is warranted to reveal the true diagnostic accuracy of pulmonary shunt fraction measurement with the 100% oxygen method, as we know that chest CT confirms the presence of PAVMs in only 45% of patients with pulmonary RLS on TTCE [7]. The present study demonstrates that the 100% oxygen method detects a pathological shunt fraction of >5% in only 51% of patients with any pulmonary RLS on TTCE. The majority of patients with a pulmonary shunt grade 1 or 2 on TTCE remain undetected using the 100% oxygen method (86.4% and 80.0% respectively). Even in patients with a large, pulmonary shunt grade 3 on TTCE, the 100% oxygen method fails to detect an abnormal shunt fraction in 27.9% of cases. Our group recently described that only pulmonary shunt grades 2 and 3 on TTCE have clinical implications [2, 7, 30], as neurological complications due to paradoxical embolisations are encountered in up to 14.2% of these shunts [2] and transcatheter embolotherapy of PAVMs is indicated in 52.5% of these patients [7]. However, the present study reveals that the 100% oxygen method fails to detect a pathological shunt fraction of >5% in 38.2% of patients with a pulmonary shunt grade 2 or 3 on TTCE. Furthermore, the current international guideline on diagnosis and management of HHT recommends the use of antibiotic prophylaxis before procedures with risk of bacteraemia in patients with any documented pulmonary RLS, in order to prevent the occurrence of brain abscesses [9]. The current study illustrates that up to 49% of these patients will not be identified using shunt fraction measurements with the 100% oxygen method.

On the other hand, we documented a pathological shunt fraction of >5% in 14.3% of persons without any RLS on TTCE. Additional chest CT imaging showed regions with atelectasis and/or pulmonary fibrosis in 53.3% of these persons, but no alternative explanation for the increased shunt fraction was found in the remaining 46.7% (true false positives). Besides the fact that a small degree of physiologic RLS normally takes place via the bronchiolar system of the lung perfusion and Thebesian veins, there may be several sources of error resulting in false positive or negative findings with the 100% oxygen method. The detection of pulmonary RLS using TTCE is based on the true anatomical and functional shunt, while the 100% oxygen method measures the alveolar-arterial oxygen difference, which is then converted into a shunt magnitude. The 100% oxygen method will be influenced by presence of multiple small PAVMs, where oxygen uptake may still take place and the actual RLS is underestimated. Furthermore, the arteriovenous difference in oxygen content is not routinely measured in the established 100% oxygen method and deviations from the assumed value could therefore result in deviations from the calculated shunt fraction. Measurement of the actual individual arteriovenous difference would improve the accuracy of the 100% oxygen method, but is not feasible in daily practice because of its invasive character. In addition, an accurate test can only be obtained when the patient truly receives 100% oxygen. A small leak in the oxygen delivery system will overestimate the degree of shunt fraction by lowering the true alveolar partial oxygen pressure. Similarly, breathing 100% oxygen for an inadequate period of time may result in an overestimation of shunt fraction, owing to inadequate denitrogenation of poorly ventilated alveoli (which was not the case in the present study). It has also been reported that breathing 100% oxygen can occasionally cause a small amount of pulmonary RLS (up to 11%) in healthy subjects, due to complete denitrogenation and micro-atelectasis [31]. Taking a deep inspiration every minute helps to prevent this 100% oxygen related micro-atelectasis [20]. Further study limitations are the fact that additional shunt fraction measurement was not routinely performed in all 669 screened persons and that the 100% oxygen method was tested in a population at high pre-test risk for PAVMs (HHT). Therefore, our results do not automatically support generalization to all other etiologies of pulmonary shunting.

CONCLUSION

Pulmonary shunt fraction measurement with the 100% oxygen method is not a useful screening technique for the detection of pulmonary RLS in HHT, as its sensitivity is too low and a large proportion of clinically important pulmonary RLS remains undetected.

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CHAPTER 5

Grade of pulmonary right-to-left shunt on contrast echocardiography and cerebral complications; a striking association.

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ABSTRACT

Background: A pulmonary right-to-left shunt (RLS) carries the risk of cerebral paradoxical embolization and severe neurologic complications. Recognizing patients at risk is important to facilitate appropriate management strategies, but a direct relation between pulmonary shunt size and risk of complications remains controversial. This study evaluated the potential relation between pulmonary shunt grade on transthoracic contrast echocardiography (TTCE) and prevalence of cerebral manifestations in patients screened for hereditary hemorrhagic telangiectasia (HHT).

Methods: We conducted a two-center, cross-sectional study of all consecutive patients screened for HHT between 2004 and 2011. Pulmonary shunt grading on TTCE (grade 0, no microbubbles; grade 1, < 30 microbubbles; grade 2, 30-100 microbubbles; grade 3, > 100 microbubbles) was performed according to contrast opacification of the left ventricle. Cerebral complications were defined as ischemic stroke, transient ischemic attack, or brain abscess diagnosed by a neurologist and confirmed by appropriate imaging techniques.

Results: A pulmonary RLS was present in 530 out of 1,038 patients (51.1%; mean age, 44.3 ± 15.6 years; 58.6% women). The presence of a cerebral manifestation (n = 51) differed significantly among pulmonary shunt grades on TTCE: 1.4%, 0.4%, 6.5%, and 20.9% for grades 0, 1, 2 and 3, respectively. A pulmonary shunt grade 1 was not associated with an increased prevalence of cerebral manifestations (OR, 0.44; 95% CI, 0.05-4.13; P = .47), whereas pulmonary shunt grade 2 (OR, 4.78; 95% CI, 1.14-20.0; P = .03) and grade 3 (OR, 10.4; 95% CI, 2.4-45.3; P = .002) were both independent predictors for the prevalence of a cerebral ischemic event or brain abscess.

Conclusion: The pulmonary RLS grade on TTCE is strongly associated with the prevalence of cerebral complications in patients screened for HHT.

INTRODUCTION

A pulmonary arteriovenous malformation (PAVM) is a thin-walled abnormal vessel that replaces normal capillaries between the pulmonary arterial and venous circulation. A PAVM causes a permanent right-to-left shunt (RLS) that bypasses the pulmonary capillary filter, which carries the risk of cerebral paradoxical embolization of both thrombotic and septic origin [1]. A paradoxical embolization is considered the likely predominant mechanism of cerebral ischemia or brain abscesses in patients with PAVMs [2, 3]. According to the literature, 70% to 90% of PAVMs are associated with hereditary hemorrhagic telangiectasia (HHT) [2, 4]. HHT is an autosomal-dominant inherited disorder characterized by vascular abnormalities varying from small telangiectases in skin and mucosal membranes, to large arteriovenous malformations, predominantly in the brain, liver, and lungs. The diagnosis is based on the clinical Curaçao criteria [5], or the presence of responsible gene mutations. There are two main types of HHT, corresponding to gene mutations coding for endoglin (HHT1) and ALK1 (HHT2) [6, 7]. A third disease-causing mutation has been shown in the SMAD4 gene, which causes a combined syndrome of juvenile polyposis and HHT [8]. In addition, two more loci causing HHT have been mapped to chromosomes 5 and 7, although the causative genes have not yet been identified [9, 10]. Transthoracic contrast echocardiography (TTCE) is recommended as initial screening for the presence of PAVMs in all patients with (suspected) HHT [2, 9-13]. Based on TTCE, a pulmonary RLS is present in 85% of patients with HHT1 and in 35% of patients with a HHT2 genotype [13]. TTCE is used to guide further decisions in the screening algorithm for PAVMs, in which a quantitative grading system is used to characterize the pulmonary shunt size [14]. Additional chest high-resolution CT (HRCT) scanning is deferred in the absence of a pulmonary RLS on TTCE [15]. Several authors questioned whether we should also defer chest HRCT scanning in patients with a small pulmonary RLS on TTCE [14-16], but a direct relation between pulmonary shunt size and risk of cerebral complications remains a matter of debate. According to the current guideline for the diagnosis and management of HHT, all patients with any pulmonary RLS on TTCE currently receive a chest HRCT scan and it is recommended that antibiotic prophylaxis be used for procedures with risk of bacteremia to prevent cerebral abscesses [11]. Understanding which patients with PAVMs are indeed at risk of cerebral paradoxical embolizations is important to improve PAVM management strategies. To our knowledge, we present the first large cross-sectional study investigating the potential relation between (functional) pulmonary shunt size on TTCE and the prevalence of cerebral complications in patients screened for HHT.

METHODS

Study Population.

From May 2004 to March 2011, 1,129 people were screened for HHT at two specialized clinics: the St. Antonius Hospital in Nieuwegein, The Netherlands, and the Maggiore Hospital in Crema, Italy. People > 15 years of age were screened as family members of index patients with HHT or with clinical symptoms suggesting HHT. All patients underwent a

complete history and physical examination by a physician with dedicated expertise in HHT. The clinical diagnosis of HHT was established according to the Curaçao criteria [5]. These criteria consist of spontaneous and recurrent epistaxis, telangiectases at characteristic sites, visceral arteriovenous malformations, and a first-degree relative with HHT. Genetic testing for the HHT-causing gene mutation was offered to all screened subjects and was performed as published previously [17]. A definite diagnosis of HHT was established in the case of three or more Curaçao criteria, or when genetic testing identified the HHT-causing gene mutation. HHT was considered a possibility in patients with two clinical Curaçao criteria, in whom no genetic testing was performed or no gene mutation was found after genetic testing. Patients with zero to one clinical Curaçao criterion in whom no genetic testing was performed or no gene mutation was found after genetic testing were defined as "HHT unlikely." HHT was rejected when genetic testing excluded the HHT-causing family mutation. Patients with previously treated PAVMs were not included in the analysis. All patients provided informed consent and the study was approved by the institutional review board of both hospitals (17/2004 and LTME/Z-12.41).

Pulmonary RLS on TTCE.

TTCE was performed by placing an IV line in the right hand, to which two 10-mL syringes were connected, one filled with an 8-mL physiologic saline solution and the other with 1-mL air. Subsequently, 1 mL blood was drawn in the air-filled syringe and mixed with the saline-filled syringe by reverse flushing between both syringes, creating agitated saline (microbubbles). The patient was positioned in the left lateral position, and 5 mL of agitated saline was injected within 3 s, while projecting the four-chamber apical view, with and without a Valsalva maneuver. The TTCEs were performed by the same group of three trained echocardiographers. Shunt interpretation was performed by two experienced cardiologists with dedicated expertise in HHT, who were unaware of the patient's medical history. In the case of an RLS, visualization of shunt origin was pursued in every TTCE. All shunts visualized through a pulmonary vein were classified as pulmonary shunts. In the case of poor visualization of shunt origin, we used a delay of four cardiac cycles to distinguish a pulmonary from a cardiac RLS, in which TTCE was considered positive for a pulmonary RLS if microbubbles appeared in the left atrium after four cardiac cycles, as published previously [13, 14, 18]. The delay in the appearance of microbubbles in the left atrium was measured in the number of cardiac cycles after the first appearance of microbubbles in the right atrium. Opacification of the left ventricle was graded as 1 (maximum of 29 microbubbles in left ventricle), 2 (30-100 microbubbles), or 3 (> 100 microbubbles). This division was based on the maximal number of microbubbles in the left ventricle counted in one still-frame. Local institutional logistics and experience in the TTCE procedure are important requirements for an optimal and accurate RLS grading system. A good κ coefficient of 0.85 was found for interobserver agreement concerning pulmonary shunt grade in previous studies [13-15]. Shunts within four cardiac cycles and poor visualization of shunt origin were classified as "indeterminate" shunts. A patent foramen ovale (PFO) was diagnosed only after a positive Valsalva maneuver, without spontaneous RLS. The presence of an atrial septum defect was excluded routinely in all shunts using color Doppler and potential negative contrast in the right atrium.

Prevalence of Cerebral Manifestations.

All available medical records were analyzed for the prevalence of potential cerebral manifestations. The presence of cerebral ischemic stroke, transient ischemic attack (TIA), or brain abscess was diagnosed by a neurologist based on clinical evaluation and appropriate brain imaging. Cerebral ischemic stroke was defined as a sudden focal neurologic deficit of presumed cerebrovascular cause that persisted beyond 24 h. An event matching this definition but lasting < 24 h was considered to be a TIA. A brain abscess was diagnosed in the case of a focal intracranial infection of parenchyma that evolved into collections of pus enclosed by a well-vascularized capsule.

Statistical Analysis.

Descriptive statistics were used to describe patient characteristics. Differences between groups were analyzed by the unpaired Student *t* test for continues variables and $\chi 2$ test for nominal variables. Data are given as mean ± SD or No. (%). The level of significance was set at $P < .05$. Univariate and multivariate statistical analyses with logistic regression were used to identify and estimate risk factors for the presence of cerebral manifestations. ORs and 95% CIs were calculated. Statistics were performed using a statistical software package (SPSS version 17.0; SPSS Inc).

RESULTS

Study Population.

A diagnostic TTCE was available in 1,088 of 1,129 screened patients (96.4%). An indeterminate RLS was found in 50 of 1,088 patients (4.6%), who were excluded to ensure that only purely pulmonary shunts were included in our analysis. In these 50 patients, only one TIA was documented (2%), and their exclusion probably did not influence our results. The remaining 1,038 patients were included for further analysis. Genetic testing was performed in 853 of the 1,038 screened patients (82.2%). HHT was definite in 689 patients (66.4%), possible in 84 (8.1%), unlikely in 99 (9.5%), and excluded in 166 (16.0%). HHT1 was found in 218 patients (21.0%), and 294 patients (28.3%) had HHT2. The baseline characteristics of our study population are listed in table 1.

Table 1. Baseline characteristics

Characteristic	Value
Patients, No.	1,038
Age, mean ± SD, y	44.3 ± 15.6
Sex	
Male	430 (41.4)
Female	608 (58.6)
Pulmonary RLS on TTCE	
Yes	530 (51.1)
No	508 (48.9)
HHT	
Definite	689 (66.4)
Possible	84 (8.1)
Unlikely	99 (9.5)
Excluded	166 (16.0)
Genetic testing	853 (82.2)
HHT1	218 (21.0)
HHT2	294 (28.3)
SMAD4 mutation	6 (0.6)
HHT excluded	166 (16.0)
Gene mutation not found	169 (16.3)
Not performed	185 (17.8)
PFO[a]	58 (5.6)

Data are presented as No. (%) unless indicated otherwise. Abbreviations: HHT, hereditary hemorrhagic telangiectasia; PFO, patent foramen ovale; RLS, right-to-left shunt; TTCE, transthoracic contrast echocardiography. [a] Only Valsalva induced.

Pulmonary RLS on TTCE.

A pulmonary RLS on TTCE was present in 530 of 1,038 patients (51.1%) (table 2). Out of 530 patients with a pulmonary RLS, definite HHT was diagnosed in 460 (86.8%) and possible HHT in 25 (4.7%); HHT remained unlikely in 24 patients (4.5%), and it was excluded in 21 patients (4.0%). A pulmonary shunt grade 1, 2, or 3 was present in 228 (22.0%), 139 (13.4%), and 163 (15.7%) patients, respectively. Only six patients (1.1%) had a pulmonary shunt grade 2 or 3 in which HHT was unlikely or excluded. None of these patients had comorbidities that could explain the shunt. They were diagnosed with an idiopathic, solitary PAVM, which may have been caused by referral bias in our HHT screening program. In 58 patients (5.6%), there was evidence of a clear Valsalva-induced PFO. No atrial septum defects were detected in our screening population.

Table 2. Characteristics of patients with different pulmonary shunt grades on transthoracic contrast echocardiography

Characteristics	No RLS	Grade 1 RLS	Grade 2 RLS	Grade 3 RLS
Patients	508 (48.9)	228 (22.0)	139 (13.4)	163 (15.7)
Age, mean ± SD, y	45.5 ± 15.4	42.7 ± 16.1	42.6 ± 15.7	44.6 ± 14.8
Sex				
Male	225 (44.3)	91 (39.9)	62 (44.6)	52 (31.9)
Female	283(55.7)	137 (60.1)	77 (55.4)	111 (68.1)
HHT				
Definite	229 (45.1)	176 (77.2)	132 (95.0)	152 (93.3)
Possible	59 (11.6)	13 (5.7)	4 (2.9)	8 (4.9)
Unlikely	75 (14.8)	19 (8.3)	2 (1.4)	3 (1.8)
Excluded	145 (28.5)	20 (8.8)	1 (0.7)	0
Cerebral manifestation	7 (1.4)	1 (0.4)	9 (6.5)	34 (20.9)[a]
Ischemic stroke	2 (0.4)	1 (0.4)	3 (2.2)	22 (13.5)
TIA	4 (0.8)	0	3 (2.2)	5 (3.1)
Brain abscess	1 (0.2)	0	3 (2.2)	9 (5.5)
Hemorrhagic complication	2 (0.4)	0	2 (1.4)	9 (5.5)
Hemoptysis	2 (0.4)	0	1 (0.7)	9 (5.5)
Hemothorax	0	0	1 (0.7)	0

Data are presented as No. (%) unless indicated otherwise. Abbreviations: TIA, transient ischemic attack. See table 1 legend for expansion of other abbreviations.

Prevalence of Cerebral Manifestations.

The overall prevalence of a cerebral manifestation (ischemic stroke, TIA, or brain abscess) in patients with a pulmonary RLS on TTCE was 8.3% compared with 1.4% in patients without a pulmonary RLS ($P < .001$). The prevalence of a cerebral manifestation differed significantly among the pulmonary shunt grades: 1.4%, 0.4%, 6.5%, and 20.9% for pulmonary shunt grade 0, 1, 2, and 3 on TTCE, respectively (table 2). The time course between the neurologic event and the TTCE was 4.8 ± 5.7 years. Using multivariate analysis, pulmonary shunt grades 2 and 3 on TTCE were strong significant predictors for the prevalence of a cerebral manifestation ($P = .03$ and $P = .002$, respectively) (table 3). Interestingly, there was no significant difference in the prevalence of cerebral manifestations between patients with a pulmonary shunt grade 1 on TTCE and patients without a pulmonary RLS ($P = .47$) (figure 1).

Table 3. Predictors of cerebral manifestations inpatients screened for HHT

	Univariate		Multivariate	
Cerebral manifestation (n=51)	**Odds ratio (95% CI)**	**P value**	**Odds ratio (95% CI)**	**P value**
Age (y)	1.02 (1.00-1.04)	0.08	1.02 (1.00-1.04)	0.11
Sex (female)	1.20 (0.67-2.15)	0.54		
HHT, n (%)				
Definite	11.5 (1.6-84.3)	0.02	1.06 (0.11-10.3)	0.96
Possible	4.02 (0.36-45.0)	0.26	1.13 (0.08-15.4)	0.93
Unlikely	5.16 (0.53-50.3)	0.16	3.23 (0.31-33.9)	0.33
Excluded (ref)	*ref*	*ref*	*ref*	*ref*
Pulmonary RLS on TTCE	6.51 (2.90-14.6)	*<0.001*		
Grade 1 RLS	0.32 (0.04-2.58)	*0.28*	0.44 (0.05-4.13)	0.47
Grade 2 RLS	4.96 (1.81-13.6)	*0.002*	4.78 (1.14-20.0)	0.03
Grade 3 RLS	18.9 (8.18-43.5)	<0.001	10.4 (2.4-45.3)	0.002
No RLS (ref)	*ref*	*ref*	*ref*	*ref*
PAVM on chest HRCT	16.3 (7.74-34.0)	<0.001	3.73 (1.29-10.8)	0.02

A cerebral manifestation was documented in 51 patients. Abbreviations: HRCT, high-resolution CT; PAVM, pulmonary arteriovenous malformation; Ref, reference. See table 1 legend for expansion of other abbreviations.

A chest HRCT scan was available in all 44 patients (100%) with a pulmonary RLS on TTCE and a cerebral manifestation, and it identified a PAVM in 40 of these patients (90.9%). There were two grade 2 and two grade 3 pulmonary shunts on TTCE in the four patients (9.1%) without a PAVM on chest HRCT scan and a prior cerebral manifestation. These shunts probably represent diffuse, microscopic shunts not detectable on chest HRCT scan. As expected, the presence of a PAVM on chest HRCT scan was also a significant predictor for the prevalence of a cerebral manifestation using multivariate analysis (P = .02) (table 3). There were no cerebral manifestations documented in the 58 patients with a Valsalva-induced PFO.

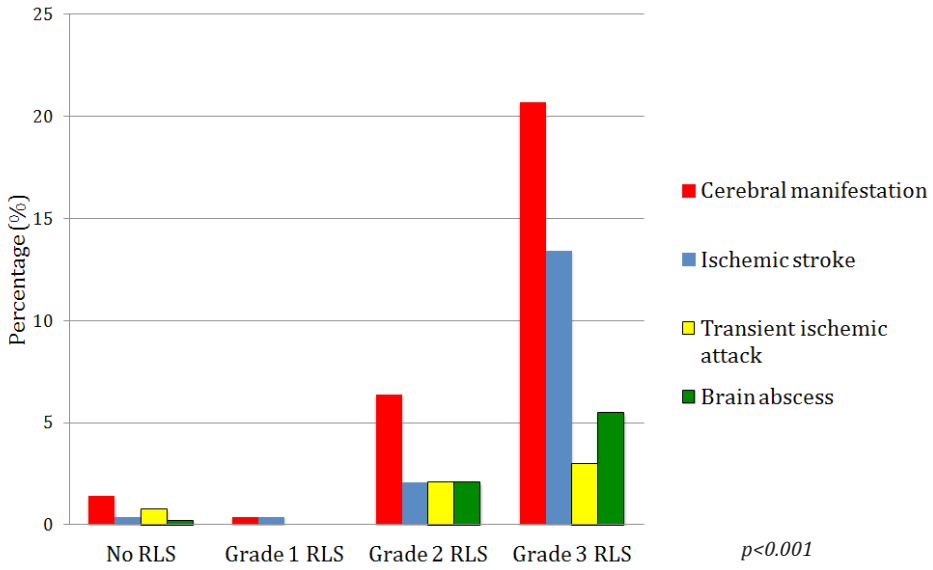

Figure 1. Prevalence of cerebral manifestations within different pulmonary shunt grades on transthoracic contrast echocardiography.
Abbreviations: RLS, right-to-left shunt; TIA, transient ischemic attack.

DISCUSSION

To our knowledge, this is the first large cross-sectional study to evaluate the potential relation between pulmonary shunt size on TTCE and prevalence of cerebral complications. Our study demonstrates that the occurrence of a cerebral ischemic event or brain abscess is strongly associated with the pulmonary shunt grade on TTCE, which has not been established before.

A pulmonary RLS carries the risk of cerebral paradoxical embolization by bypassing the pulmonary capillary filtering system, resulting in cerebral ischemic stroke, TIA, or brain abscess [13]. In our study, the overall prevalence of a cerebral manifestation was 8.3% in patients with a pulmonary shunt on TTCE. Previous studies showed a higher prevalence of neurologic complications (9%-47%) when using pulmonary angiography or chest HRCT scan for the detection of PAVMs [19-22]. TTCE is a more sensitive screening method and detects microscopic PAVMs as well, which are not visualized by pulmonary angiography or chest HRCT scan. Therefore, our study population is different and also includes PAVMs that would not have been included in prior studies solely based on angiography and chest HRCT scan.

In addition to the potentially high rate of cerebral complications from paradoxical embolization, PAVMs may also cause pulmonary hemorrhagic complications [23]. These are caused by intrabronchial or intrapleural rupture of PAVMs resulting in hemoptysis or hemothorax. In our study population we encountered only 12 patients (1.2%) with hemoptysis and one patient (0.1%) with a hemothorax (table 2).

It is hypothesized that the risk of cerebral paradoxical embolization depends on the relative perfusion of PAVMs. This concept is also suggested in patients with a PFO, in which a larger diameter and a more extensive, or permanent, interatrial RLS on TTCE is associated with a significantly higher prevalence of cerebral ischemic stroke [24-26]. The existence of a relation between pulmonary shunt size and risk of cerebral complications remains controversial. Moussouttas et al. [21] previously evaluated the presence of cerebral paradoxical embolizations in patients with PAVMs on pulmonary angiography. They included 75 patients with a PAVM-feeding artery diameter of ≥ 3 mm on pulmonary angiography. The prevalence of ischemic stroke increased from 14% in patients with a single PAVM to 27% in those with multiple PAVMs on pulmonary angiography. Similar to their findings for ischemic stroke, the prevalence of brain abscess also increased twofold in patients with multiple PAVMs, suggesting an increased predisposition for cerebral complications in patients with a greater number of PAVMs. This correlation was also shown by Gazzaniga et al. [12], who described a potential relation between echocardiographic pulmonary shunt grading and a history of neurologic complications related to paradoxical embolization. However, because their analysis dealt with only nine complications in 36 patients with PAVMs, they emphasized that this correlation could have been biased by the low number of events.

In a well-performed study by Shovlin et al. [22], no association was found between PAVM-feeding artery diameter on chest HRCT scan and risk of cerebral ischemic stroke or brain abscess in a cohort of 219 patients with PAVMs. A possible explanation for the different findings in our study is the use of TTCE instead of chest HRCT scan. Echocardiographic shunt grading represents a more functional measurement of pulmonary RLS, compared with the anatomic shunt measurements with chest HRCT scan. We know that up to 50% of pulmonary shunts on TTCE remain undetected by chest HRCT scanning [14]. Diffuse small PAVMs can be missed on HRCT scan, whereas there may be a large functional shunt on TTCE, which carries a risk of cerebral paradoxical embolization as well [16]. In the study by Shovlin et al. [22], functional pulmonary shunt size was measured with technetium and oximetry. Pulmonary shunt grade 1 and 2 on TTCE are still small shunts, usually associated with normal oximetry, and were probably not detected with the methods used in the study by Shovlin et al. [22].

Clinical Relevance.

Previously, van Gent et al. [14] suggested that patients with a pulmonary shunt grade 1 on TTCE do not have PAVMs on chest HRCT scan that are large enough for transcatheter embolotherapy, which implies that chest HRCT scanning may be withheld in these patients. The results of our current study suggest that a pulmonary shunt grade 1 on TTCE is not associated with an increased prevalence of cerebral ischemic events, brain abscesses, or pulmonary hemorrhagic complications. We believe that a conservative management strategy (without chest HRCT scan and antibiotic prophylaxis) is probably justified in patients with a pulmonary shunt grade 1 on TTCE, considering the absence of treatable PAVMs and the negligible risk of cerebral paradoxical embolizations in this subset of patients. Deferring

chest HRCT scans in these patients could result in a tremendous cost saving and reduction of radiation exposure in mainly young adults [16]. Additional chest HRCT scans may than be reserved for patients with a pulmonary shunt grade 2 or 3 on initial TTCE to evaluate the opportunity for transcatheter embolotherapy.

Although we do not have sufficient long-term data on the potential growth of PAVMs, it seems advisable that follow-up of patients with no or grade 1 pulmonary RLS on initial TTCE, and those with a pulmonary shunt grade 2 and no treatable PAVM on chest HRCT scanning, be performed by TTCE every 5 years. An additional chest HRCT scanning would then be indicated only if the echocardiographic pulmonary shunt grade increases to a grade 2 or 3 shunt. Of course, follow-up should still be performed with chest HRCT scanning in patients with a pulmonary shunt grade 3 on TTCE without visible PAVMs on chest HRCT scan. Given the impact of a missed treatable PAVM and the subsequent risk of cerebral complications, our data and hypotheses need to be confirmed in future prospective studies.

Study Limitations.
This study has some limitations. First of all, we are well aware of its cross-sectional nature, which makes a real causal inference difficult. The study was not designed primarily to analyze the diagnostic value of TTCE in predicting the risk of neurologic complications. Cross-sectional studies can be used for hypothesis generation and show associations rather than causalities. Cross-sectional studies cannot accurately describe the temporal relationship between risk factors and disease development, in this case, pulmonary shunt grade and cerebral manifestation. Furthermore, cross-sectional studies carry the risk of selection bias, which may have contributed to a less precise prevalence of both PAVMs and complications in our study population, compared with a prospective study design. Despite the cross-sectional design, we do think our study presents a firm observation and contributes important elements to the challenging discussion about the optimal approach to the patient with a pulmonary shunt grade 1 on initial TTCE screening.

A second limitation of our study is the fact that we did not record the classic vascular risk factors, such as smoking status, arterial hypertension, known diabetes mellitus, hypercholesterolemia, atrial fibrillation, and cardiac and carotid artery disease. Although our study population was relatively young, we cannot exclude atherosclerotic disease in both patients with and without a pulmonary RLS and a cerebral ischemic event.

A third limitation may be the absence of detailed echocardiographic data on left ventricular function, valvular heart disease, right ventricular systolic pressure, heart rate, cardiac output, and anemia. This may have influenced the pulmonary grading system.

A fourth limitation is that patients with a pulmonary shunt on TTCE were not routinely screened for the prevalence of cerebral ischemic events, because this seems to have few clinical consequences. Asymptomatic cerebral ischemic events were missed, and this may have influenced the prevalence of cerebral manifestations in our study population, which may be higher than reported.

CONCLUSIONS

The pulmonary RLS grade on TTCE is strongly associated with the prevalence of a cerebral ischemic event or brain abscess in patients screened for HHT. Patients with a pulmonary shunt grade 1 on TTCE do not appear to have an increased risk of cerebral complications.

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CHAPTER 6

Predicting the size of pulmonary arteriovenous malformations on chest CT: a role for transthoracic contrast echocardiography

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ABSTRACT

Objective: This study aimed to investigate whether pulmonary shunt grade on transthoracic contrast echocardiography (TTCE) predicts the size of pulmonary arteriovenous malformations (PAVMs) on chest CT and subsequent feasibility for transcatheter embolotherapy.

Methods: We prospectively included 772 persons with possible or definite hereditary haemorrhagic telangiectasia, who underwent both TTCE and chest CT for screening of PAVMs. A quantitative three-point grading scale was used to classify the pulmonary shunt size on TTCE (grade 1-3). Transcatheter embolotherapy was performed for PAVMs deemed large enough for endovascular closure on chest CT.

Results: TTCE documented pulmonary shunting in 510 patients (66.1%). The positive predictive value of a pulmonary shunt grade 1, 2 and 3 on TTCE for presence of PAVMs on chest CT was 13.4%, 45.3% and 92.5% respectively ($p<0.001$). None of the 201 persons with a pulmonary shunt grade 1 on TTCE had PAVMs on chest CT large enough for transcatheter embolotherapy, while 38 (25.3%) and 123 (77.4%) individuals with respectively a pulmonary shunt grade 2 and 3 on TTCE underwent endovascular closure of PAVMs.

Conclusion: Pulmonary shunt grade on TTCE predicts the size of PAVMs on chest CT and their feasibility for subsequent transcatheter embolotherapy. Chest CT can be safely withheld in all persons with a pulmonary shunt grade 1 on TTCE, since any PAVM found in these subjects will be too small for transcatheter embolotherapy.

INTRODUCTION

Pulmonary arteriovenous malformations (PAVMs) are thin walled abnormal vessels replacing normal capillaries between the pulmonary arterial and venous circulation, resulting in a permanent right-to-left shunt. The majority of PAVMs (±90%) are associated with hereditary haemorrhagic telangiectasia (HHT) [1]. HHT is an autosomal dominant inherited disorder, characterized by vascular abnormalities varying from small telangiectasias in skin and mucous membranes, to large arteriovenous malformations, predominantly in the brain, liver and lungs [2]. Most HHT patients have a gene mutation coding for Endoglin (HHT1) or ALK1 (HHT2) [3,4]. A pulmonary shunt has been reported in up to 85% of HHT1 and in 35% of HHT2 patients [5]. PAVMs are associated with disabling and life-threatening complications, such as cerebral ischemic strokes, brain abscesses, massive haemoptysis or hemothorax [6,7]. The neurological complications occur via paradoxical embolizations of thrombotic or septic origin that bypass the pulmonary capillary filter, whereas the hemorrhagic complications are due to spontaneous rupture of PAVMs. Transcatheter embolotherapy is an endovascular intervention that occludes the feeding artery of the PAVM with a coil or plug, in order to reduce the risk of PAVM-related complications [8]. Because of the high prevalence, potential severe complications and effective treatment options, screening for PAVMs is recommended in all persons with possible or confirmed HHT. During the last few years, transthoracic contrast echocardiography (TTCE) has become the initial screening test for detecting PAVMs, based on its excellent sensitivity, negative predictive value, good inter-observer reproducibility and non-invasive character, with low risks and costs [5,9-11]. TTCE can be used to estimate the pulmonary shunt size, varying from small (grade 1), moderate (grade 2), to large (grade 3) right-to-left shunts (figure 1). Irrespective of this echocardiographic pulmonary shunt grade, the current international guideline for diagnosis and management of HHT and PAVMs requires the confirmation of all pulmonary shunts on TTCE by chest CT with thin-cut reconstructions, in order to evaluate the necessity for transcatheter embolotherapy [9]. However, it remains unclear whether additional chest CT is indeed mandatory in all persons with only a small pulmonary shunt on TTCE, as these shunts may be too small for subsequent transcatheter embolotherapy [12-14]. Therefore, this large prospective two-center study investigated whether pulmonary shunt grade on TTCE predicts the size of PAVMs on chest CT and subsequent feasibility for transcatheter embolotherapy.

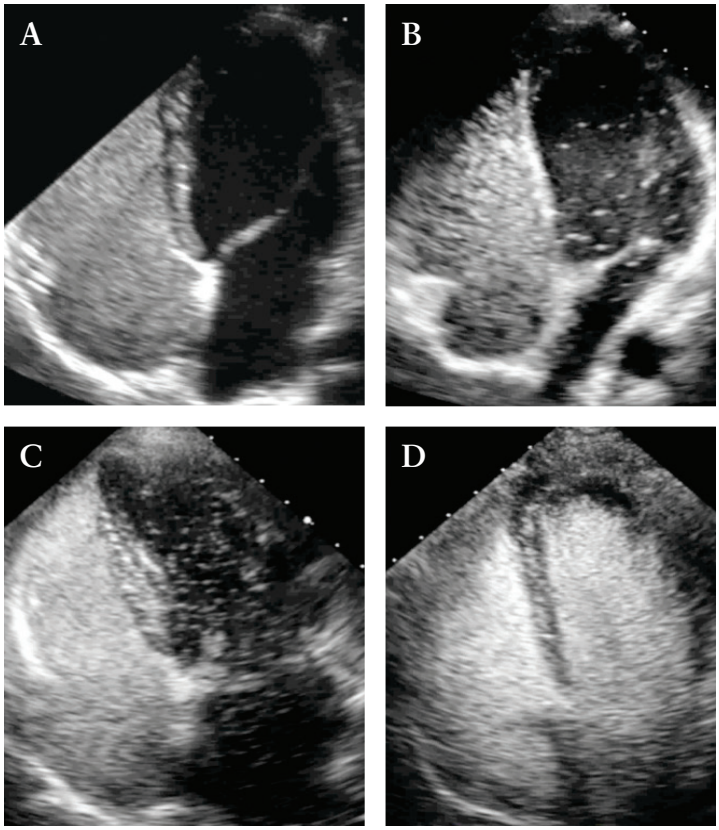

Figure 1. Different pulmonary shunt grades on TTCE.
(A) no shunt; (B) grade 1; (C) grade 2; (D) grade 3.

METHODS

Study population.

From May 2004 till October 2012, 1280 consecutive individuals were screened for HHT at two specialised clinics: the St. Antonius Hospital in Nieuwegein (the Netherlands) and the Maggiore Hospital in Crema (Italy). Persons aged > 15 years were screened as family members of index patients with HHT, or in case of clinical symptoms suggesting HHT. TTCE was performed in 1240 individuals (96.9%); placement of an intravenous line failed or was refused in the other 40 persons (3.1%). In 50 out of these 1240 persons (4.0%), no clear distinction was possible between a pulmonary or cardiac right-to-left shunt and these "indeterminate" shunts were excluded from further analysis. Chest CT was performed in 1020 out of the remaining 1190 individuals (85.7%), as chest CT was withheld in patients without a pulmonary shunt on TTCE from January 2011. All 1020 persons underwent

complete history and physical examination by a physician with dedicated expertise in HHT. The clinical diagnosis of HHT was established according to the Curaçao criteria [15]. These criteria consist of spontaneous and recurrent epistaxis, telangiectasias at characteristic sites, visceral arteriovenous malformations, and a first-degree relative with HHT. Genetic testing for the HHT-causing gene mutation was offered to all subjects and performed as published earlier [16, 17]. A definite diagnosis of HHT was established in case of three or more clinical Curaçao criteria, or when genetic testing identified the HHT-causing mutation. The diagnosis of HHT was "possible" in patients with two clinical Curaçao criteria without genetic testing or if a mutation could not be found without knowing a specific family mutation. The diagnosis of HHT was "unlikely" in the presence of less than two clinical Curaçao criteria, without genetic testing or if a mutation could not be found without knowing a specific family mutation. HHT was rejected when genetic testing excluded the known HHT-causing family mutation. Because the pre-test probability of having PAVMs is smaller in persons without HHT, we excluded all persons where HHT was rejected (n=157) or unlikely (n=91). Therefore, a total of 772 patients with possible or definite HHT in which both TTCE and chest CT were performed are included in the present study for statistical analyses (figure 2). Patients with previously treated PAVMs were not included in the analysis. The study was approved by the institutional review board of both hospitals (17/2004 and LTME/Z-12.41).

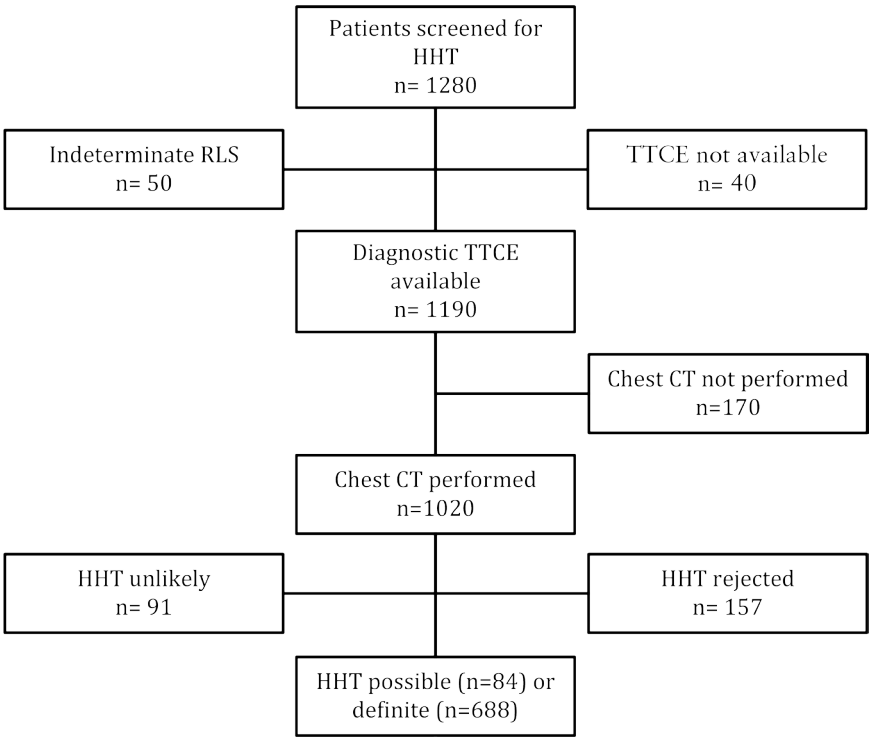

Figure 2. Selection of study population

* Additional chest CT was withheld in the absence of a pulmonary shunt on TTCE from January 2012. Abbreviations: HHT, hereditary haemorrhagic telangiectasia; n, number; RLS, right-to-left shunt; TTCE, transthoracic contrast echocardiography; CT, computed tomography.

Transthoracic contrast echocardiography.
TTCE was performed by placing an intravenous line in the right ante-cubital vein to which two 10mL syringes were connected, one filled with an 8mL physiologic saline solution and the other with 1mL air. Subsequently, 1mL blood was drawn in the air-filled syringe and mixed with the saline-filled syringe by reverse flushing between both syringes, creating agitated saline with microbubbles. The patient was positioned in the left lateral position and 5mL of agitated saline was injected within three seconds, while projecting the four-chamber apical view, with and without a Valsalva manoeuvre. TTCE was performed by a constant group of three trained echocardiographists. Shunt interpretation was performed by two experienced cardiologists with dedicated expertise in HHT, who were unaware of the patient's medical history. In case of a right-to-left shunt, visualization of shunt origin was pursued in every TTCE. All right-to-left shunts visualized through a pulmonary vein were classified as pulmonary shunts. On the occasion of poor visualization of shunt origin, we used a delay of four cardiac cycles to distinguish a pulmonary from a cardiac right-to-left shunt, in which TTCE was considered positive for a pulmonary shunt if microbubbles appeared in the left atrium after four or more cardiac cycles, as published before [5, 11, 14]. Based on the maximum number of microbubbles counted in the left sided heart in one still-frame, the shunt was graded as 1 (maximum of 29 microbubbles), 2 (30-100 microbubbles) or 3 (>100 microbubbles), as reported earlier [10, 11, 18]. In case of disagreement on presence, quantity, or timing of microbubbles in the left ventricle, the TTCE was reviewed again by both cardiologists together to agree on the final determination.

Chest CT.
Chest CT was routinely obtained on a 16+ multi-detector CT scanner (Philips Medical Systems), with a dedicated high-resolution algorithm and maximum slice thickness of 1 mm in both hospitals. Identification of PAVMs on chest CT was based on the presence of a nodular opacity with both an afferent and efferent vessel. Chest CT images were evaluated in a multidisciplinary consensus meeting with dedicated interventional radiologists and vascular pulmonologists, who were blinded for the results from TTCE. When observers disagreed, chest CT was considered as positive for a PAVM and additional pulmonary angiography of the pulmonary artery was performed given the impact of complications from a potentially missed treatable PAVM.

Transcatheter embolotherapy of PAVMs.
Based on the collective experience of the present HHT community, all PAVMs with a feeding artery diameter of ≥3mm were deemed accessible for transcatheter embolotherapy, whereas diameters <2mm were considered to indicate inaccessibility for endovascular closure. Feasibility for transcatheter embolotherapy of PAVMs with a feeding artery diameter between 2.0-3.0mm was based on technical aspects of the endovascular intervention, which was also assessed in the above described multidisciplinary consensus meeting. Features taken into account in these cases included location, tortuosity, angulation and multiplicity of PAVMs. The decision to treat PAVMs was blinded for the results from TTCE and potential clinical significance of the PAVM (for example a prior cerebral paradoxical complication),

as treatment decisions could otherwise have been influenced, which was not the case in the present study. The feeding artery diameters of embolized PAVMs on both chest CT and pulmonary angiography (based on the caliber of the embolisation catheter) were measured in order to analyse their degree of agreement. Transcatheter embolotherapy of PAVMs was performed by a constant group of respectively three and two interventional radiologists in Nieuwegein and Crema, using platinum or stainless steel coils, endovascular plugs, or a combination of these materials.

Statistical analysis.
Descriptive statistics were used to describe the patient characteristics. The positive predictive value (PPV) for the different pulmonary shunt grades on TTCE was calculated using chest CT as a reference. The Mantel-Haenszel χ^2 test was used to determine whether there was a significant association between the pulmonary shunt grade on TTCE and the presence of PAVMs on chest CT. A Bland-Altman analysis was performed to evaluate the degree of agreement in PAVM feeding artery diameter on chest CT and pulmonary angiography. Statistical analyses were performed using the statistical software application SPSS (version 17.0; SPSS Inc., Chicago).

RESULTS

Study population.
A total of 772 patients with possible or definite HHT (mean age 45.5±15.4 years, 58.2% female) underwent both TTCE with pulmonary shunt grade measurement and chest CT for the detection of PAVMs (n=497 in St. Antonius Hospital and n=275 in Maggiore Hospital). The patient characteristics and homogeneity between these centers are described in table 1a+b. Notably, a proportion of these HHT patients has been described before [10, 11]. . tably, hese centres is described in tables; es., computed tomography.roups. Presence of HHT was definite in 688 patients (89.1%) and remained possible in 84 persons (10.9%). Genetic testing identified 224 patients with HHT1 (29.0%), 305 patients with HHT2 (39.5%) and 10 patients with a SMAD4 mutation (1.3%). DNA analysis could not detect an HHT-causing mutation or was not performed in the other 233 patients (30.2%).

Table 1a. Overall patient characteristics, according to each pulmonary shunt grade on TTCE

	No shunt	Grade 1	Grade 2	Grade 3	Total
Total, n (%)	262 (33.9)	201 (26.1)	150 (19.4)	159 (20.6)	772
Age, yr±SD	47.3±15.1	44.9±16.1	43.7±16.0	44.8±14.2	45.5±15.4
Sex, n (%)					
Female	146 (32.5)	113 (25.2)	79 (17.6)	111 (24.7)	449 (58.2)
Male	116 (35.9)	88 (27.2)	71 (22.0)	48 (14.9)	323 (41.8)
HHT, n (%)					
Definite	204 (29.7)	186 (27.0)	145 (21.1)	153 (22.2)	688 (89.1)
Possible	58 (69.0)	15 (17.9)	5 (6.0)	6 (7.1)	84 (10.9)
Genetic testing, n (%)					
HHT1	21 (9.4)	39 (17.4)	57 (25.4)	107 (47.8)	224 (29.0)
HHT2	145 (47.5)	104 (34.1)	38 (12.5)	18 (5.9)	305 (39.5)
SMAD4	1 (10.0)	4 (40.0)	2 (20.0)	3 (30.0)	10 (1.3)
Unknown #	95 (40.8)	54 (23.2)	53 (22.7)	31 (13.3)	233 (30.2)

Abbreviations: yr, year; SD, standard deviation; n, number; HHT, hereditary haemorrhagic telangiectasia. # Unknown; unknown family mutation or genetic testing not performed. Data are presented as number of patients and percentage.

TTCE and chest CT.

TTCE documented a pulmonary shunt grade 1 in 201 patients (26.1%), grade 2 in 150 patients (19.4%) and grade 3 in 159 patients (20.6%). We found a good κ-coefficient of 0.85 for inter-observer agreement concerning the pulmonary shunt grade on TTCE, which is in line with prior reports [5, 10, 19]. Chest CT confirmed the presence of a PAVM in 242 out of 510 patients (47.5%) with a pulmonary shunt on TTCE. The remaining 268 patients (52.5%) represented diffuse or microscopic pulmonary shunts under the detection limit of chest CT. In total, 203/224 HHT1 patients (90.6%) had a pulmonary shunt on TTCE, 137 of them (61.2%) also had a PAVM on chest CT. A pulmonary shunt on TTCE was documented in 160/305 HHT2 patients (52.5%), 42 of them (13.8%) had a PAVM on chest CT.

The positive predictive value of the different pulmonary shunt grades on TTCE for the presence of PAVMs on chest CT was 13.4% (95% CI 9.4-18.8), 45.3% (95% CI 37.6-53.3) and 92.5% (95% CI 87.3-95.6) for respectively a pulmonary shunt grade 1, 2 and 3 ($p<0.001$, figure 3). There were six out of 772 patients (0.8%) with a PAVM-like structure on chest CT without a pulmonary shunt on TTCE. This could not be explained by poor quality of TTCE, chest CT or disagreement between interpreters. These sporadic cases were considered as false positive chest CT and antibiotic prophylaxis was not advised. In 22 out of 262 patients (8.4%) without a pulmonary shunt on TTCE there was evidence of a patent foramen ovale. None of these persons were diagnosed with PAVMs on chest CT.

Table 1b. Homogeneity of study population.

	St. Antonius Hospital, Netherlands	Maggiore Hospital, Italy
Persons, n (%)	497 (64.4)	275 (35.6)
Age (yr) ±SD	44.8±15.5	46.6±15.2
Sex, n (%)		
Female	296 (59.6)	153 (55.6)
Male	201 (40.4)	122 (44.4)
HHT, n (%)		
Definite	428 (86.1)	260 (94.5)
Possible	69 (13.9)	15 (5.5)
Genetic testing, n (%)		
HHT1	177 (35.6)	47 (17.1)
HHT2	208 (41.9)	97 (35.3)
SMAD4	9 (1.8)	1 (0.4)
Unknown #	103 (20.7)	130 (47.2)
Pulmonary shunt on TTCE, n (%)		
No shunt	196 (39.4)	66 (24.0)
Grade 1	109 (21.9)	92 (33.5)
Grade 2	76 (15.3)	74 (26.9)
Grade 3	116 (23.4)	43 (15.6)
PAVM on chest CT, n (%)	158 (31.8)	90 (32.7)
Transcatheter embolotherapy performed, n (% of positive chest CT)	92/158 (58.2)	69/90 (76.7)

[#] Unknown; unknown family mutation or genetic testing not performed.

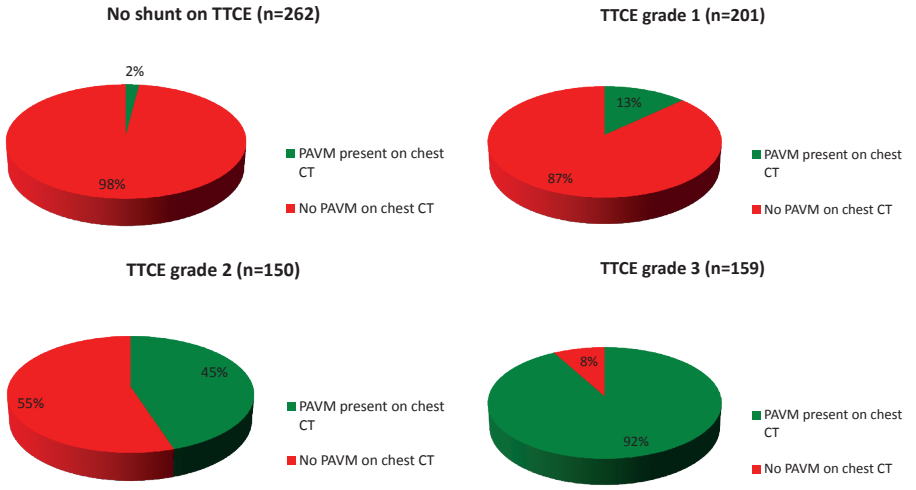

Figure 3. Pulmonary shunt grade on TTCE predicts presence of PAVMs on chest CT
Abbreviations: TTCE, transthoracic contrast echocardiography; PAVMs, pulmonary arteriovenous malformations; CT, computed tomography

Transcatheter embolotherapy of PAVMs.

Transcatheter embolotherapy of PAVMs was performed in 161 out of 510 patients (31.6%) with a pulmonary shunt on TTCE. Most patients had a PAVM feeding artery diameter on chest CT of ≥3mm (88%), while only 12% had a feeding artery diameter between 2.0-2.9mm (table 2). Our Bland-Altman analysis (figure 4) demonstrated that chest CT accurately estimated the PAVM feeding artery diameter on pulmonary angiography, with a mean difference of -0.03mm (95% CI -1.12–1.06mm) between these techniques and concordance correlation coefficient of 0.94. The majority of transcatheter embolotherapy was performed in patients with HHT1 (59.0% HHT1, 13.7% HHT2, 1.2% SMAD4, 26.1% unknown mutation or DNA analysis not performed). In total, 95/224 HHT1 patients (42.4%) underwent transcatheter embolotherapy, versus only 22/305 HHT2 patients (7.2%). The necessity for endovascular closure of PAVMs was strongly related to the pulmonary shunt grade on TTCE (table 3). The positive predictive value of a pulmonary shunt grade 1, 2 and 3 on TTCE for their feasibility of transcatheter embolotherapy of PAVMs was respectively 0%, 25.3% (95% CI 19.1-32.9) and 77.4% (95% CI 70.3-83.2) (table 3 and figure 5). Based on chest CT, none of the 262 and 201 patients with respectively no or grade 1 pulmonary shunt on TTCE had PAVMs large enough for subsequent transcatheter embolotherapy, whereas endovascular closure was performed in 38/150 and 123/159 patients with respectively a pulmonary shunt grade 2 and 3 on TTCE.

Table 2. Distribution of PAVM feeding artery diameter on chest CT of embolized PAVMs.

PAVM feeding artery diameter on chest CT (mm)	**Number of patients, n (%)**
2.0-2.9	18 (12.0)
3.0-3.9	51 (34.0)
4.0-4.9	40 (26.7)
5.0-5.9	17 (11.3)
6.0-6.9	10 (6.7)
7.0-7.9	7 (4.7)
8.0-8.9	4 (2.6)
9.0-9.9	1 (0.7)
>10.0	2 (1.3)

Measurement of PAVM feeding artery diameters on chest CT available in 150 out of 161 embolized patients (93.2%). Largest diameter used in case of multiple PAVMs or feeders in one patient.

Table 3. Number of patients who underwent transcatheter embolotherapy of PAVMs, according to different pulmonary shunt grades on TTCE.

TTCE	**PAVM on chest CT,** n (%)	**Transcatheter embolotherapy performed,** n (% of positive chest CT)	**PPV,** % (95% CI)
No shunt (n=262)	6 (2.3)	0 (0)	0 (0)
Grade 1 (n=201)	27 (13.4)	0 (0)	0 (0)
Grade 2 (n=150)	68 (45.3)	38 (55.9)	25.3 (19.1-32.9)
Grade 3 (n=159)	147 (92.5)	123 (83.7)	77.4 (70.3-83.2)
Total (n=772)	248 (32.1)	161 (64.9)	

Abbreviations: TTCE, transthoracic contrast echocardiography; PAVM, pulmonary arteriovenous malformation; CT, computed tomography; n, number; PPV, positive predictive value of pulmonary shunt grade on TTCE for feasibility of transcatheter embolotherapy of PAVM; CI, confidence interval.

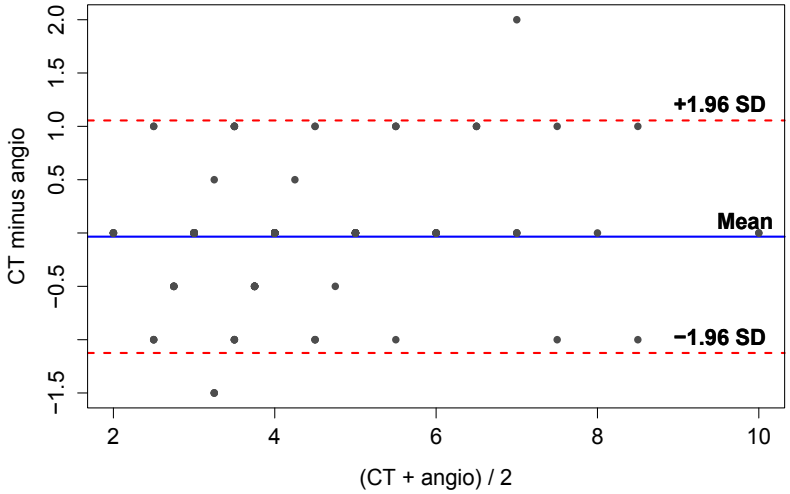

Figure 4. Bland-Altman analysis demonstrating good degree of agreement in PAVM feeding artery diameter between chest CT and pulmonary angiography.
Mean difference -0.03mm (95% CI -1.12 - 1.06mm), concordance correlation coefficient 0.94.
Measurement of PAVM feeding artery diameters on both chest CT and pulmonary angiography available in 146 out of 161 embolized patients (90.7%). Largest diameter used in case of multiple PAVMs or feeders. Diameter on pulmonary angiography based on caliber of the embolisation catheter.

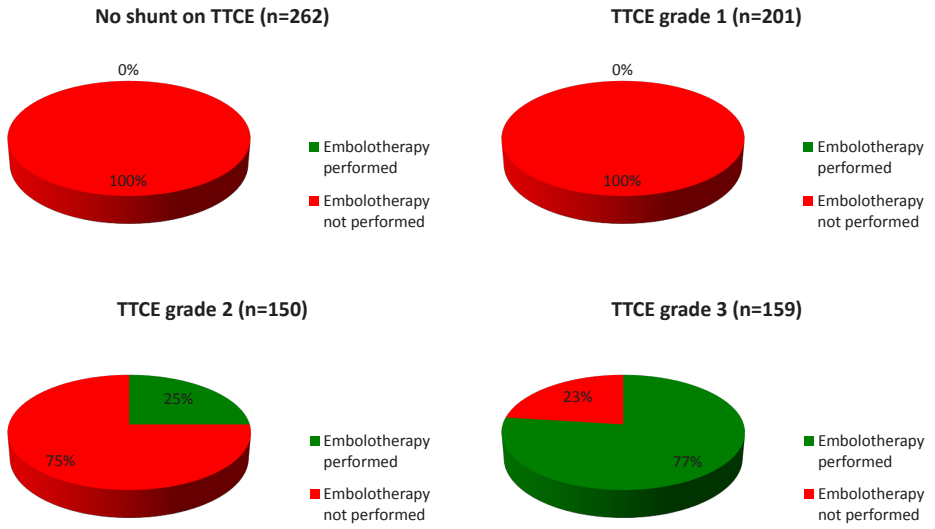

Figure 5. Pulmonary shunt grade on TTCE predicts feasibility for transcatheter embolotherapy of PAVMs on chest CT.
Abbreviations: TTCE, transthoracic contrast echocardiography; PAVMs, pulmonary arteriovenous malformations; n, number.

DISCUSSION

The present large prospective study demonstrates that pulmonary shunt grade on TTCE not only correlates with the probability of detecting PAVMs on chest CT, but most importantly also predicts the feasibility for subsequent transcatheter embolotherapy. The main strength of our study is the finding that persons with a pulmonary shunt grade 1 on TTCE do not have PAVMs large enough for transcatheter embolotherapy. Therefore, additional chest CT can be safely withheld in all these individuals, which may improve the current management strategy of pulmonary right-to-left shunts.

The present guideline for the diagnosis and treatment of HHT recommends TTCE as the initial screening test for pulmonary shunts [9], in order to detect PAVMs before the development of potential severe complications. Some centers advocate to perform chest radiography before TTCE in order to rule out large PAVMs, where TTCE might be withheld. With a low sensitivity of only 28% compared to chest CT [11], we believe that chest radiography lacks diagnostic value as screening test for PAVMs since large pulmonary shunts will still be missed in the majority of patients and unnecessary radiation exposure can be prevented. Furthermore, the safety of TTCE has been well documented [20], which is supported by a very low incidence of minimal and self-resolving side effects in recent literature [10, 13].

In the last few years, a quantitative three-point grading scale was developed to classify the pulmonary shunt size on TTCE, differentiating between grade 1, 2 and 3 (small, moderate or large respectively) [14]. Our present study confirms that an increased pulmonary shunt grade on TTCE correlates with an increased probability of detecting PAVMs on chest CT [13]. Still, chest CT remains negative in 54.7% and 7.5% of patients with respectively a pulmonary shunt grade 2 and 3 on TTCE. These shunts represent diffuse microscopic PAVMs below the detection limit of chest CT. This underscores the importance of TTCE, as these moderate to large pulmonary shunts are missed with chest CT, but do carry an increased risk of paradoxical cerebral complications and deserve antibiotic prophylaxis for procedures with high risk of bacteraemia [18].

The present international guideline on diagnosis and management of HHT recommends to confirm every pulmonary shunt on TTCE by chest CT, in order to evaluate the opportunity for transcatheter embolotherapy [9]. Currently, selection of PAVMs suitable for transcatheter embolotherapy is based on the PAVM feeding artery diameter on chest CT, generally 3 mm or greater, although targeting PAVMs with a feeding artery diameter as low as 2 mm may be appropriate [9]. It has been hypothesized that additional chest CT might be withheld in persons with only a small pulmonary shunt on initial TTCE, because these PAVMs might be too small for endovascular closure, but large studies are lacking [12, 14]. Given the impact of a potential complication from a missed treatable PAVM, more data were required before re-evaluating the necessity of additional chest CT in persons with only a small pulmonary shunt on TTCE. The present large prospective two-center study now demonstrates that only 13% of patients with a pulmonary shunt grade 1 on TTCE have detectable PAVMs on chest CT and none of these PAVMs are large enough for transcatheter embolotherapy. Therefore, TTCE may

predict the feasibility for transcatheter embolotherapy and discerns clinically insignificant from treatable PAVMs. Interestingly, our group recently published that pulmonary shunt grade on TTCE is also associated with the prevalence of neurological complications in patients screened for HHT [18]. In that large cross-sectional study [18], a pulmonary shunt grade 1 on TTCE did not appear to be a risk factor for the presence of neurological complications. Together with the findings in the present study, these data contribute important new elements to the challenging discussion about the optimal approach to persons with only a small pulmonary shunt on initial TTCE. In the present study, a pulmonary shunt grade 1 on TTCE was present in 26.0% of patients with possible or definite HHT, where additional chest CT could have been withheld. This percentage can even be higher in a general screening population for HHT, as small pulmonary shunts are also described in 6-28% of healthy subjects [5, 10, 21]. Deferring additional chest CT in all persons with a pulmonary shunt grade 1 on TTCE could result in a significant cost saving and reduction of radiation exposure in mainly young adults [12]. Using this strategy, additional chest CT would have been indicated in only 40% of our study population with possible or definite HHT.

Study limitations.

First, our study population consisted of HHT patients screened at two hospitals with specific experience in pulmonary shunt grading with TTCE and it remains uncertain whether our results also apply to a general population in centers without this expertise. However, screening for PAVMs with TTCE is preferably performed in specialized HHT centers, in order to achieve the accuracy reported in the literature. Second, it can be challenging to discern an early pulmonary shunt from an intra-cardiac patent foramen ovale using TTCE. In the present study, no clear distinction between shunt origin was possible in 50 out of 1040 initially screened persons (4.0%), who were excluded from further analysis. In this small subset of individuals with an indeterminate right-to-left shunt, the diagnostic accuracy of TTCE is limited and additional chest CT remains indicated for the detection of potential treatable PAVMs. Third, our study did not record detailed echocardiographic data on left ventricular function, valvular heart disease, right ventricular systolic pressure, heart rate, cardiac output or anemia, which may have influenced the delay and size of contrast appearance in the left ventricle. Fourth, not all patients in our study underwent a pulmonary angiography to confirm the results from chest CT, as this is unethical and not advised in the current guideline. Chest CT is therefore essentially elevated to being the gold standard for determining the feasibility for transcatheter embolotherapy of PAVMs. Although our Bland-Altman analysis indicates that chest CT accurately estimates the feeding artery diameter of large PAVMs on pulmonary angiography, this remains unknown for smaller PAVMs (where pulmonary angiography was not performed). Fifth, feasibility for transcatheter embolotherapy of PAVMs with a feeding artery diameter <3mm was based on technical aspects of the endovascular intervention, but in daily practise this decision will at least partly remain subject to personal judgment as international accepted treatment criteria are currently lacking. Furthermore, treatment decisions may be influenced by pulmonary shunt grade on TTCE and potential clinical significance of the PAVM, which was not the case in the present study. These decisions to treat PAVMs are preferentially based on consensus meetings

in centers with specific expertise in this endovascular intervention. Finally, we do not yet have sufficient long-term data on potential growth of PAVMs, but it seems conceivable that follow-up of patients with a pulmonary shunt grade 1 on initial TTCE might be performed by TTCE every five years. Chest CT should then only be performed if the echocardiographic pulmonary shunt size increases.

CONCLUSIONS

Pulmonary shunt grade on TTCE not only correlates with the probability of detecting PAVMs on chest CT, but most importantly also predicts the feasibility for subsequent transcatheter embolotherapy. Additional chest CT can be safely withheld in all persons with a pulmonary shunt grade 1 on TTCE, since any PAVM found in these subjects will be too small for transcatheter embolotherapy.

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CHAPTER 7

Direct haemodynamic effects after transcatheter embolotherapy of pulmonary arteriovenous malformations

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ABSTRACT

Background: Transcatheter embolisation is widely used to close pulmonary arteriovenous malformations (PAVMs) in patients with hereditary haemorrhagic telangiectasia (HHT). Data on the direct cardiovascular haemodynamic changes induced by this treatment are scarce.

Objectives: We investigated the direct haemodynamic effects of transcatheter embolisation of PAVMs, using non-invasive finger pressure measurements.

Methods: During the procedure, blood pressure, heart rate (HR), stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR) and delta pressure/ delta time (dP/dt) were continuously monitored using a Finometer®. Potential changes in these haemodynamic parameters were calculated from the pressure registrations using Modelflow® methodology. Absolute and relative changes were calculated and compared using the paired sample t-test.

Results: The present study includes 29 HHT patients (mean age 39±15 years, 11 men) who underwent transcatheter embolotherapy of PAVMs. The total number of embolisations was 72 (mean per patient 2.5). Directly after PAVM closure, SV and CO decreased significantly with -11.9% (p=0.01) and -9.5% (p=0.01) respectively, without a significant change in HR (1.8%). Mean arterial blood pressure increased by 4.1% (p=0.02), while the TPR and dP/dt did not increase significantly (5.8% and 0.2%, respectively).

Conclusion: Significant haemodynamic changes occur directly after transcatheter embolisation of PAVMs, amongst which a decrease in stroke volume and cardiac output are most important.

INTRODUCTION

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant inherited disease characterized by vascular malformations, ranging from small telangiectases in skin and mucosal membranes to large visceral arteriovenous malformations (AVMs) predominantly localized in the lungs, brain and liver [1-3]. Pulmonary arteriovenous malformations (PAVMs) are abnormal dilated vessels between pulmonary arteries and veins that cause a permanent extra-cardiac right-to-left shunt (RLS), which carries the risk of cerebral paradoxical embolisations of both thrombotic and septic origin [3]. Transcatheter embolisation of PAVMs can be safely performed, in order to prevent these potential severe neurological complications, such as ischaemic stroke or cerebral abscess [1, 4]. Currently, there are no data regarding the potential haemodynamic changes occurring directly after PAVM embolisation. Therefore, the present study investigated the direct haemodynamic effects of PAVM embolisation, using non-invasive finger pressure measurements.

METHODS

Patient population.
Between 2008 and 2010, we included 29 patients who underwent transcatheter embolisation of PAVMs in the St. Antonius Hospital Nieuwegein, which is a national HHT referral centre in the Netherlands. All patients provided informed consent.

Transcatheter embolotherapy of PAVMs.
A PAVM was defined as a direct communication between a pulmonary artery and a pulmonary vein, bypassing the pulmonary capillary filter [5], and was diagnosed using transthoracic contrast echocardiography (TTCE) and subsequent chest computed tomography (CT). Before and after PAVM embolisation, the right-to-left shunt fraction was measured using the 100% oxygen method as previously described [6]. All patients were discussed in a multidisciplinary team including a pulmonologist and interventional radiologist. PAVMs with a feeding artery diameter of 2-3 millimeter or greater were found suitable for embolisation therapy [7]. The procedure (figure 1a-c) was performed under local anaesthesia (lidocain 1%). Percutaneous access was derived through the right femoral vein and a six French sheath was inserted. Selection of the PAVM closure device was based on the diameter and anatomy of the PAVM by the interventional radiologist. The most preferred closure device was the Amplatzer® vascular plug (AGA Medical, Golden Valley, MN, USA) (figure 1d). Plugs with a diameter of 4 to 12 millimeter were used. If PAVM closure with a plug was not possible, detachable coils (Boston Scientific, Natick, Ma) were used. The embolic material was implanted under fluoroscopic guidance, with a maximum contrast volume of 300 ml (Xenetix; Iobitrol, Guerbet, Villepinte, France). Within 24 hours after embolisation, a chest X-ray was performed. No standard medication was given.

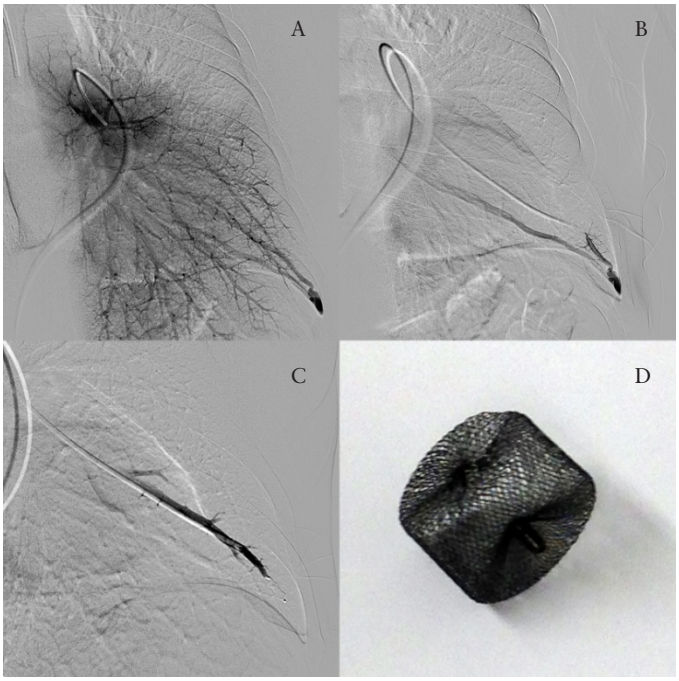

Figure 1. Transcatheter embolotherapy of a PAVM in the left lower lobe
(A) Pulmonary angiogram; (B) Selective angiogram; (C) Embolisation Amplatzer® vascular plug (D)

Haemodynamic changes after PAVM embolisation, using non-invasive finger pressure measurements.

During the transcatheter embolisation of PAVMs, arterial pressure was measured in a finger of the left hand using a Finometer® device (FMS, Finapres Medical Systems, Amsterdam, the Netherlands). The Finometer® measures blood pressure by a combination of the volume clamp method of Penaz and the 'Physiocal' criteria developed by Wesseling [8-10]. The hand was kept at heart level and a cuff was wrapped around the same arm for individual blood pressure calibration using the return-to-flow calibration [8,11]. Because of potential distortion of the measurements at the time of PAVM closure, parameters were recorded after stabilization of the finger pressure signal during a blanking period of one minute immediately before and after placement of the first and the last plug.

Data registration and analysis.

During the PAVM embolisation, finger pressure measurements with the associated event marks were monitored and digitally stored. Review of these data was performed using BeatScope® software. Five minute averages of systolic (SBP), diastolic (DBP) and mean blood pressure (MBP), heart rate (HR), stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR) and delta pressure/delta time (dP/dt) were calculated after an electronic calibration procedure. SV and CO (CO is the product of SV and HR) were calculated from the finger pressure wave using the Modelflow® methodology [12]. The cardiac index was calculated from the CO and the body surface area (BSA). TPR was defined as MAP divided by CO [8].

Return-to-flow calibration, using the arm cuff, was used for calibration of the blood pressure. There was no calibration with invasive determinations for the CO, SV and TPR. Both absolute values and absolute and relative changes (delta absolute and delta percent) are presented.

Statistical analysis.
The statistics were performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to describe patient characteristics. Continuous variables with normal distribution were presented as mean ± SD. Differences within groups were analyzed performing paired samples t-tests. A significance level of $p < 0.05$ was considered significant.

RESULTS

Patient population.
A total of 29 HHT patients (62% female, mean age 39.2 ± 15.3 years) were included, in which 72 PAVMs were embolised (mean per patient 2.5). An Amplatzer® plug was used in 54 cases and a detachable coil in the remaining 18 cases. The baseline characteristics are presented in tables 1 and 2.

Table 1. Baseline characteristics of patients

Total		29
Gender	Male	11 (37.9)
	Female	18 (62.1)
Age (years)		39.2 ± 15.3
BMI (kg/m²)		24.0 ± 5.0
BSA (m²)		1.9 ± 0.2
HHT	Definite	28 (96.6)
	Type 1	19 (65.5)
	Type 2	2 (6.9)
	Type unknown	8 (27.6)
SaO2 (%)	Before procedure	95.5 ± 3.5
	After procedure	98.4 ± 2.3
Shunt fraction (%)	Before procedure	13.6 ± 8.3
	After procedure	4.9 ± 6.6

Abbreviations: BMI, body mass index; BSA, body surface area; Kg, kilogram; kg/m², kilogram per square meter; HHT, hereditary haemorrhagic telangiectasia; SaO_2, saturation level of oxygen in hemoglobin, PAVM, pulmonary arteriovenous malformation.
All characteristics are written in number of patients with percentage or mean with standard deviation.

Table 2. Baseline characteristics of embolisation procedure

Treated PAVMs	1 PAVM	9 (31.0)
	2 PAVMs	9 (31.0)
	3 PAVMs	2 (6.9)
	4 PAVMs	8 (27.6)
	> 4 PAVMs	1 (3.4)
Closure device	Amplatzer plug	54 (75.0)
	Coil	18 (25.0)
Plug diameter *	< 4 (mm)	1 (1.9)
	4 (mm)	13 (24.1)
	6 (mm)	13 (24.1)
	8 (mm)	9 (16.7)
	10 (mm)	10 (18.5)
	> 10 (mm)	6 (11.1)
	Not known	2 (3.7)

Abbreviations: PAVM, pulmonary arteriovenous malformation; mm, millimeter.
All characteristics are written in number with percentage. * Diameter of coils are not know.

Haemodynamic changes using non-invasive finger pressure measurements.
Directly after PAVM embolisation the SV and CO decreased significantly: - 6.4 ± 13.0 ml (range -45.9 to 17.9 ml; -11.9%, p=0.01) and -0.4 ± 0.8 l/min (range -3.0 to 1.58 l/min; -9.5%, p=0.01). As expected, the CI decreased as well (range -1.5 to 0.9 l/min/m^2; -9.5%, p=0.01). DBP and MBP increased significantly with 5.2 ± 10.3 mmHg (range -9.0 to 32.9 mmHg; 5.9%, p=0.01) for DBP and 5.7 ± 12.1 mmHg (range -12.7 to 32.6 mmHg; 4.1 %, p=0.02) for MBP, respectively. There was no significant change in SBP (4.0 ± 16.3 mmHg (range -25.5 to 38.5 mmHg; 1.7%, p=0.20). The dP/dt did not change significantly: 2.1 ± 290.0 mmHg/sec (range -750.0 to 848.2 mmHg/sec; 0.2%, p=0.97). There was a correlation between the delta dP/dt and the SBP (pearson coefficient r= 0.73, r^2=0.53, p< 0.0001). HR en TPR increased, but this appeared to be non-significant: 1.6 ± 7.4 beats/min (range -17.4 to 21.2 beats/min; 1.8%, p=0.24) and 0.1 ± 0.5 Woods units (range -1.62 to 1.39 Woods units; 5.8%, p=0.16). These data are summarized in table 3.

Table 3. Haemodynamic measurements before and after embolisation with absolute and relative changes

	Before ± SD	After ± SD	Delta absolute	Delta percent	P
SBP (mmHg)	144.9 ± 25.3	148.9 ± 28.4	4.0	1.7	0.20
DPB (mmHg)	85.5 ± 11.5	90.7 ± 16.3	5.2	5.9	0.01
MBP (mmHg)	108.0 ± 16.0	113.7 ± 19.9	5.7	4.1	0.02
HR (beats/min)	78.8 ± 14.6	80.4 ± 13.9	1.6	1.8	0.24
SV (ml)	70.9 ± 20.9	64.5 ± 19.3	-6.4	-11.9	0.01
CO (l/min)	5.5 ± 1.6	5.1 ± 1.4	-0.4	-9.5	0.01
CI (l/min/m^2)	3.0 ± 0.8	2.8 ± 0.8	-0.2	-9.5	0.01
TPR (woods units)	1.4 ± 0.5	1.5 ± 0.5	0.1	5.8	0.16
dP/dt (mmHg/sec)	1233.7 ± 463.8	1235.8 ± 481.7	2.1	0.2	0.97

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; CI, cardiac index; TPR, total peripheral resistance; dP/dt, delta pressure/delta time; SD, standard deviation; min, minutes; ml, milliliters; l/min, liters per minute; mmHg, millimetres of mercury ; sec, second.

DISCUSSION

To our knowledge, this is the first study describing the occurrence of significant haemodynamic changes directly after transcatheter embolisation of PAVMs. Using the Finometer® and Modelflow® methodology, our study accurately recorded beat-to-beat non-invasive finger pressure measurements and thereby the immediate haemodynamic changes after PAVM embolisation, amongst which a decrease in stroke volume and cardiac output were most important.

Only one case report previously documented haemodynamic changes four months after PAVM embolisation with a marked reduction in cardiac output of -5.1 L/min (41%) [13]. This seems to be in line with the results in our current study in 29 HHT patients who all underwent transcatheter embolisation of PAVMs. However, we found a less pronounced decrease in CO, which can be explained by the smaller right-to-left shunts in our study population, with a mean shunt fraction before closure of 14% versus 31% described by Andrivet et al [13]. It is possible that the CO may further decrease over time as a result of additional thrombosis of the plug or coil in the PAVM feeding artery. However, the long-term haemodynamic changes after PAVM embolisation remain hard to predict, since new PAVMs may occur and existing PAVMs may grow, so this is still subject for larger studies in the future.

The haemodynamic responses after PAVM embolisation may differ between HHT patients, which can be related to difference in number and size of PAVMs at baseline [3]. In the present study, nine patients underwent embolisation of at least 4 PAVMs in one session, whereas less PAVMs were embolised in the remaining 20 patients. Furthermore, a total of 16 PAVMs

were treated with a large plug (diameter ≥10 mm), whereas 14 PAVMs could be treated with smaller endovascular plugs (diameter ≤4mm). Unfortunately, we could not find a significant association between plug size (size of the PAVM) and the changes in haemodynamic parameters. Furthermore, the haemodynamic response can be influenced by a different prevalence of underlying hepatic arteriovenous malformations (HAVMs) in different HHT subtypes [5, 14, 15]. HAVMs may cause a hyperdynamic circulation with high CO [7]. In our cohort, only one patient had a history of HAVMs, which might be an underestimation, since screening for HAVMs was only performed when clinically or biochemically suspected. Clinically significant HAVMs seemed to be absent in the present study, as a hyperdynamic circulation with an abnormal high CI at baseline was not documented in the present study (mean CI within the normal range of 3.0±0.8 L/min/m^2). The amount of microscopic PAVMs under the detection limit of chest CT may further influence the shunt percentage and different haemodynamic responses in HHT patients.

Due to the decrease in pulmonary right-to-left shunt from 14% to 5% after PAVM embolisation, a consequent decrease in preload and SV can be expected (mean change -12% in the current study). As there was no change in HR, the CO decreased as well (-9.5%). The MBP increased with 4% after PAVM embolisation, which is probably due to the non-significant increase in TPR (6%), as the MBP is a product of TPR and CO. As blood pressure is inversely related to indoor temperature [16], the fall in ambient temperature during the procedure may have caused further vasoconstriction and thereby an increase in blood pressure. In a previous study about the association between brachial pulse dP/dt and other haemodynamic parameters in a chronic haemodialysis population, a pearson coefficient of r=0.6 (r^2=0.36, p< 0.001) was reported for the correlation between the delta blood pressure and the delta dP/dt [17]. This is in line with the results found in our study (r=0.73, r^2=0.53, p< 0.0001) and demonstrates that the dP/dt is responsible for more than 50% of variance in the blood pressure. Because of the significant increase in MBP and decrease in CO, we also expected a significant increase in TPR. A possible explanation might be an increase in central venous pressure due to the embolisation. Unfortunately, no measurements of the right atrium pressure were performed during the embolisation procedure.

A potential clinical implication of our findings might be associated with the presence of pulmonary hypertension (PH) in HHT [18, 19]. PH can both occur as the gene related pulmonary arterial hypertension and as a response to high output due to HAVMs [15]. As PAVMs are abnormal dilated vessels between pulmonary arteries and veins they provide low resistance pathways for the pulmonary blood flow and one may therefore expect an elevation in pulmonary artery pressure (PAP) after transcatheter closure. Surprisingly, in a prior study by Shovlin et al. there was no described increase in PAP after transcatheter embolisation of PAVMs [15]. It was suggested that this might be caused by other haemodynamic changes, for example recruitment of the pulmonary vasculature or a decrease in cardiac output, although this has been previously suggested in only one case report [13]. We now present the first study that confirms the decrease in CO after embolisation in a larger population of HHT patients, which may indeed provide a potential explanation for the absent increase

in PAP after embolisation. Furthermore, PAVM related hypoxemia can induce pulmonary vasoconstriction with a concomitant increase in pulmonary vascular resistance (PVR). In our study there was indeed an increase in saturation after embolisation of PAVMs (table 1) with probably a decrease in pulmonary vasoconstriction and PVR.

Study limitations.
First, our study is limited by its small sample, which may have influenced the results. Second, the Modelflow® model seems not to be accurate in measuring absolute values of SV, CO and TPR. The differences between the uncalibrated model and invasive determinations (measured with the thermodilution method) in individual patients are usually small, but can be substantial and unreliable in some [8, 20]. However, the Modelflow® methodology is an accurate model to compare changes in haemodynamics within one patient and the British Hypertension Society has recommended the Finometer® for measurements in the clinical set-up as well as for research purposes [8, 21].

CONCLUSIONS

The present study shows that significant haemodynamic changes occur directly after embolisation of pulmonary arteriovenous malformations, amongst which a decrease in stroke volume and cardiac output are most important. This may especially provide additional insights into the haemodynamic responses after PAVM embolisation in HHT patients prone to PH.

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CHAPTER 8

Left atrial appendage closure for stroke prevention in patients with atrial fibrillation and hereditary haemorrhagic telangiectasia

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ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting millions of individuals worldwide, and a major risk factor for disabling cerebral embolic stroke.

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant inherited disorder, characterized by vascular abnormalities with high bleeding tendency and therefore intolerance for oral anticoagulation.

We report a case of percutaneous closure of the left atrial appendage, which might be a good alternative strategy instead of chronic oral anticoagulation to protect patients with high-risk AF and HHT from cerebral embolic strokes.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and a major risk factor for cerebral embolic stroke. Although oral anticoagulation (OAC) is highly effective in stroke prevention, a substantial number of patients is unable to sustain chronic OAC because of high bleeding risks. Among these are patients with hereditary hemorrhagic telangiectasia (HHT), who frequently encounter inconvenient epistaxis, gastro-intestinal bleedings, or life-threatening bleedings from cerebral or pulmonary arteriovenous-malformations. Since most thrombo-embolic complications in patients with AF arise from the left atrial appendage (LAA), a percutaneous transcatheter LAA closure device was recently developed.

This is the first report about the feasibility of percutaneous LAA closure in patients with high-risk AF and HHT, which can be a promising strategy to protect these patients against embolic stroke, while avoiding the need for long-term OAC.

Case presentation.
We present a 79-year-old man who had previously been diagnosed with HHT, based on the clinical Curaçao criteria [1]; his family history revealed numerous first-degree relatives with HHT, physical examination demonstrated several telangiectasia on hands, face, lips and ears, and he suffered from recurrent epistaxis. DNA analysis confirmed the clinical diagnosis with an ALK-1 gene mutation on chromosome 12. Visceral AVMs in the brain, lungs, liver or gastro-intestinal tract were excluded with magnetic resonance imaging, echocardiography, computed-tomography and endoscopy. In addition to HHT, the patient was known with arterial hypertension, a recent cerebral ischemic stroke and permanent AF. His $CHADS_2$-score of four indicated a high risk of recurrent stroke (8.5%/year) [2]. Since visceral sources of life-threatening hemorrhages were ruled out, a trial of OAC (warfarin) was started. This resulted in extensive epistaxis, requiring repeated blood transfusions despite treatment with iron supplements and nasal cauterizations. Because of this clinical dilemma, the patient was referred to our HHT-specialized cardiology department and accepted for percutaneous LAA closure to protect against recurrent stroke, while avoiding the need for long-term OAC. A 27mm Watchman LAA Occlusion Device (Atritech Inc., Plymouth, Minnesota) was implanted in the LAA using biplane fluoroscopy and 3D-transoesophageal echocardiography (TEE) guidance, according to recent literature (figure 1) [3]..REF).t of thess increased bleeding risk. a ruptured endobronchial or subpleural AVM and is reported in up to lantation. but nc Because of the patient's high bleeding risk, post-procedural anticoagulation was limited to aspirin for at least six weeks to allow for device endothelialization and to prevent thrombotic complications. Control TEE at 45-days demonstrated successful closure of the LAA without thrombus formation on the atrial surface of the device (figure 2) and aspirin was discontinued. During one-year follow-up, no thrombo-embolic complications or severe HHT-related bleedings occurred.

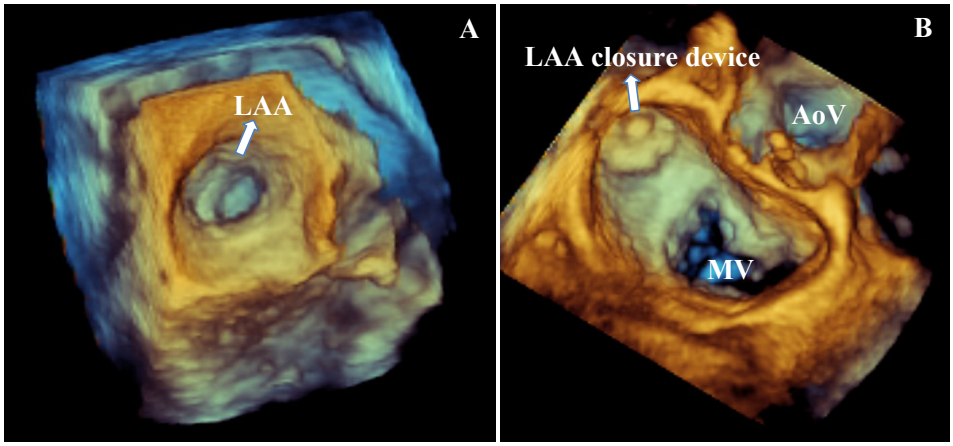

Figure 1. Real-time-three-dimensional transoesophageal echocardiographic imaging of the left atrial appendage as seen from the left atrial perspective.
(A) Pre-procedural view of LAA. (B) LAA closure device deployed. Abbreviations: LAA, left atrial appendage; AoV, aortic valve; MV, mitral valve

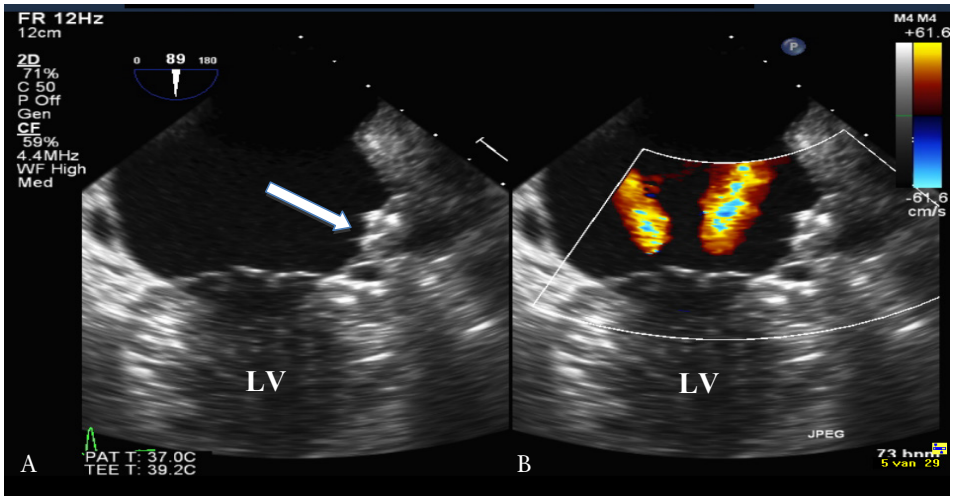

Figure 2. Two-dimensional transoesophageal echocardiographic imaging of the left atrium at 45-days follow-up.
(A) Successful occlusion of the LAA without thrombus formation on the atrial surface of the device despite the limited use of anticoagulation therapy (aspirin only). (B) No residual flow around the device. Abbreviation: LV, left ventricle.

DISCUSSION

This is the first report about the feasibility of a percutaneous LAA closure device in patients with high-risk AF and HHT. Percutaneous closure of the LAA might be a new strategy to protect this population against cerebral embolic stroke without the need for chronic OAC and subsequent high bleeding risks.

HHT-related gene mutations result in abnormal angiogenesis and fragile vessels with increased bleeding tendency [4]. Recurrent epistaxis is the most common symptom of HHT, affecting 78-96% of patients [5]. Epistaxis often leads to iron-deficiency anemia and is an important factor reducing quality of life [6]. Gastro-intestinal (GI) telangiectasia are present in 80% of HHT patients, from which 30% will develop GI-bleedings and causes increased morbidity and mortality [7]. Approximately 23% of HHT patients has cerebral AVMs. The bleeding risk from cerebral AVMs in HHT is estimated around 0.5% per year [8], which may have devastating consequences. Pulmonary AVMs are present in up to 58% of HHT patients [9] and carry the risk of hemoptysis or hemothorax, which is caused by a ruptured endobronchial or subpleural AVM and reported in up to 8% [10] REF))ount manuscript: 734ragilit in abnormal angiogenesis and fragilie vessels with increased bleeding tendency. some HHT pati.

Because of this inconvenient and sometimes life-threatening bleeding tendency, the decision to start OAC in patients with high-risk AF and HHT should be based on a careful, individual risk-assessment of both thrombo-embolic and hemorrhagic complications.

Previous studies demonstrated that the LAA is the source of thrombi in more than 90% of patients with non-valvular AF [11], which led to the development of the Watchman left atrial appendage occlusion device. This percutaneous transcatheter device excludes the LAA from the systemic circulation and protects against embolic stroke, without the need for long-term OAC. The Watchman device was investigated in the PROTECT-AF trial, which demonstrated that percutaneous closure of the LAA was non-inferior to chronic OAC therapy [3]. After device implantation, all patients in the PROTECT-AF trial were treated with warfarin for 45-days, clopidogrel and aspirin for six months and then aspirin lifelong. Therefore, the exact safety and efficacy of percutaneous LAA device closure in patients with high bleeding risks and intolerance for short-term OAC remains unknown. At our institution, HHT patients must be eligible for at least 6 weeks of aspirin therapy, which is tested before device implantation using a nosebleed diary. A careful risk-benefit assessment is made prior to LAA device implantation for every individual with HHT, in order to arrange a tailored-made post-procedural anticoagulation treatment. We underscore that the optimum strategy to prevent device-related thrombo-embolic complications without raising the risk of bleeding in patients with contraindications for OAC has to be established in future studies. At present, percutaneous LAA occlusion may be an acceptable option in selected HHT patients with high-risk AF who are not candidates for long-term OAC.

CONCLUSION

Percutaneous closure of the LAA might provide an alternative strategy to chronic anticoagulation therapy for stroke prevention in patients with high-risk AF and HHT.

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CHAPTER 9

General discussion

Based on:
Clinical implications of pulmonary shunting on contrast echocardiography.

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This discussion section addresses the outcome of our studies on clinical implications of pulmonary right-to-left shunting on transthoracic contrast echocardiography (TTCE) in patients with (suspected) hereditary haemorrhagic telangiectasia (HHT). Using a quantitative three-point grading scale, differentiating between minimal, moderate and extensive pulmonary shunting (grade 1-3 respectively), the clinical significance of especially small pulmonary shunts on TTCE is explored and challenged.

Pulmonary shunt grade on TTCE and clinical diagnosis of HHT.

Although genetic testing for an HHT-causing gene mutation improved in the past few years and became more widely available, DNA analysis per se is not always sufficient in diagnosing HHT. Previous studies described a mutation detection rate of 72-93% in patients with clinically confirmed HHT [1-4] and underuse of genetic testing has been reported in first-degree relatives at risk for HHT [5]. Therefore, an accurate clinical evaluation remains essential in all persons with suspected HHT. This clinical diagnosis can be established according to the four Curaçao criteria, consisting of spontaneous and recurrent epistaxis, telangiectases at characteristic sites, a first-degree relative with HHT and the presence of visceral arteriovenous malformations. Three criteria suffice for a definite diagnosis of HHT, two criteria are considered as possible HHT, and one or no criterion makes the diagnosis unlikely [6]. Using these clinical Curaçao criteria, it remains important to consider the observations that the phenotypic expression of HHT is highly variable, even within members of the same family, and that its clinical presentation can be age-dependant [7]. For patients with a definite clinical diagnosis of HHT additional genetic testing is not required to confirm the diagnosis, but may further assist in the management of other family members. Additional genetic testing is especially recommended in case of a possible clinical diagnosis of HHT.

The current clinical Curaçao criteria, based on chest CT for the detection of PAVMs, already have a good diagnostic performance compared to genetic testing [8]. PAVMs have traditionally been diagnosed by chest CT [9,10], but since a few years the international guidelines recommend TTCE as first-line screening technique for their detection [11]. Recent literature however, demonstrates that chest CT confirms the presence of PAVMs in only 47.5% of patients with pulmonary shunting on TTCE [12] and the exact influence of TTCE on the diagnostic clinical Curaçao criteria for HHT remained unknown. We therefore specifically evaluated the role of pulmonary shunting on TTCE as a new clinical Curaçao criterion [13]. Pulmonary shunting on TTCE is present in 91% of HHT1 patients, compared to 53% of HHT2 related mutation carriers [12]. The distribution of pulmonary shunt grades on TTCE differs between HHT subtype, where large pulmonary shunts are more frequently found in HHT1 than HHT2 [14]. Although a pulmonary shunt grade 1 on TTCE is significantly more often found in HHT patients compared to a control population [15], we demonstrated that the addition of only pulmonary shunt grades ≥ 2 on TTCE to the current clinical Curaçao criteria further increases its sensitivity to 90%, without affecting specificity (74%) [13]. A pulmonary shunt grade 1 on TTCE is also documented in 6-28% of healthy individuals without HHT [14-16] and accepting these small pulmonary shunts as a positive Curaçao criterion leads to more false-positive clinical diagnoses of HHT [13], which should be prevented in our opinion.

Pulmonary shunt grade on TTCE and risk for neurological complications.
A paradoxical embolisation is considered the likely predominant mechanism of stroke and/or brain abscess in patients with HHT and PAVMs [17, 18]. Recognizing patients at risk for these complications is important to facilitate appropriate PAVM management strategies. In patients with a PFO, it has been shown that a larger diameter and more extensive, or permanent inter-atrial shunt right-to-left shunt on TTCE is associated with a significantly higher prevalence of cerebral ischemic strokes [19-21]. Therefore, it has been hypothesized that the risk of paradoxical embolisation in patients with pulmonary shunts also depends on the relative perfusion of the PAVM, but evidence remained conflicting. Moussouttas et al. previously included 75 patients with a PAVM feeding artery diameter of ≥3mm on pulmonary angiography and evaluated the presence of cerebral paradoxical embolisation [22]. The prevalence of ischemic stroke in that study increased from 14% in patients with a single PAVM to 27% in those with multiple PAVMs on pulmonary angiography and the prevalence of brain abscess also increased two-fold in patients with multiple PAVMs, which suggested an increased predisposition for neurological complications in patients with a greater number of PAVMs [22]. However, another cohort of 219 patients with PAVMs on chest CT could not find an association between PAVM feeding artery diameter on chest CT and risk for stroke or brain abscess [23]. Gazzaniga et al. was the first to suggest a potential relation between pulmonary shunt size on TTCE and neurological complications [15]. TTCE represents a functional measurement of pulmonary right-to-left shunting, instead of the anatomic shunt measurement by chest CT, which may explain their different findings. More recently, the study by Gazzaniga et al. [15] was confirmed in our large two-center, retrospective study, which demonstrated a striking association between pulmonary shunt size on TTCE and prevalence of neurological complications in 1038 persons with (suspected) HHT [24]. A neurological complication was found in 0.4%, 6.5% and 20.9% of patients with respectively a pulmonary shunt grade 1, 2 and 3 on TTCE [24]. A pulmonary shunt grade 1 on TTCE was not significantly associated with an increased prevalence of neurological complications (0.4%), compared to patients with a negative TTCE (1.4%) [24].

Pulmonary shunt grade on TTCE and feasibility for transcatheter embolotherapy of PAVMs.
Based on the collective experience of the present HHT community [11], all PAVMs with a feeding artery diameter of ≥3mm are deemed accessible for transcatheter embolotherapy, whereas diameters <2mm are generally considered to indicate inaccessibility for endovascular closure. Feasibility for transcatheter embolotherapy of PAVMs with a feeding artery diameter between 2.0-2.9mm is based on technical aspects of the endovascular intervention, which include location, tortuosity, angulation and multiplicity of PAVMs. Additional considerations may include patient preference and past history of possible embolic complications. A Bland-Altman analysis demonstrated that chest CT accurately estimates the PAVM feeding artery diameter on pulmonary angiography (concordance correlation coefficient of 0.94) [12], which is important as chest CT is presently elevated to being gold standard for determining whether a PAVM is sizeable enough for transcatheter embolotherapy (instead of pulmonary angiography). It has been demonstrated that the probability of detecting PAVMs on chest CT increases with a higher pulmonary shunt grade on TTCE [12, 15, 25-27]. Our recent study

confirmed that the positive predictive value of a pulmonary shunt grade 1, 2 and 3 on TTCE for the presence of PAVMs on chest CT is respectively 13%, 45% and 93% [12]. Interestingly, our and other recent studies revealed that the feasibility for transcatheter embolotherapy of PAVMs on chest CT is strongly related to the pulmonary shunt grade on TTCE [12, 15, 25-27]. Persons with a pulmonary shunt grade 1 on TTCE do not have treatable PAVMs on chest CT, whereas transcatheter embolotherapy of PAVMs can be performed in 25% and 77% of patients with respectively a pulmonary shunt grade 2 and 3 on TTCE [12].

Is it safe (not) to perform TTCE?

There have been concerns about the safety of TTCE and therefore screening for PAVMs still takes place with chest CT in some centers. Potential complications of TTCE might be related to the injection of a small amount of air (1 ml) in combination with the presence of possible right-to-left shunting and subsequent risk for systemic air emboli. However, the safety of TTCE has been well documented in a large retrospective survey of 363 physicians regularly performing contrast echocardiography, conducted by the American Society of Echocardiography [28]. In this survey [28], an estimated total of 27,000 contrast echocardiographic procedures were performed over a 16-year period. TTCE indeed appeared to carry some risk for side effects (transient neurologic deficits, light-headedness, visual sparks, flashing lights, scotomata, central and peripheral numbness, nausea, vagal symptoms and anxiety), but this risk was low (prevalence of 0.062%) and, importantly, no residual side effects or complications were reported. Of special interest was a survey patient who re-experienced her initial symptoms during a second examination, during which no contrast injections were made. The needle puncture and visualization of blood may induce vagal symptoms in reactive patients in a medical environment and a clear causal relation between symptoms and contrast injections remains difficult to ascertain in many cases. The observations by Bommer et al. [28] are supported by a very low incidence of minimal and self-resolving side effects in more recent literature [15, 25] and our own experience. In addition, we would rather reverse the question to "Is it safe nót to perform TTCE?", as it has been demonstrated that chest CT remains negative in 55% and 8% of patients with respectively a pulmonary shunt grade 2 and 3 on TTCE [12]. These pulmonary shunts probably represent diffuse microscopic PAVMs below the detection limit of chest CT, but should be regarded as a positive Curaçao criterion in the clinical diagnosis of HHT [13] and appear to have an increased risk for neurological complications [24], where transcatheter embolotherapy might be indicated [12] and antibiotic prophylaxis should be prescribed before procedures with high risk of bacteraemia to prevent brain abscesses, according to the international guideline for the diagnosis and management of HHT [11]. We are convinced that the benefits of TTCE strongly outweigh its potential (minor) risk.

How to handle small pulmonary shunts on TTCE; does any bubble matter?

Additional chest CT and antibiotic prophylaxis is already deferred in HHT patients with a negative TTCE [11, 27], but whether this strategy is also safe in all persons with only a pulmonary shunt grade 1 on TTCE is currently unknown. This question can be of additional interest, as the presence of small pulmonary shunts on TTCE has also been reported in a

significant proportion of healthy individuals without HHT [14-16]. The common opinion is that the appearance of microbubbles in the left-sided heart chamber is pathological, in the absence of a PFO. The normal pulmonary capillary diameter does not exceed 13μm (even under high perfusion pressures [29]), so therefore all microbubbles above this diameter will be sieved. The diameter of a microbubble in vivo is not exactly known, but it is estimated that the size of bubbles entering the pulmonary circulation is 60 to 90μm [30]. Although it has been described that microbubbles can shrink or fracture in smaller ones that may traverse the pulmonary capillary network [31], microbubbles smaller than the normal pulmonary capillary network will dissolve at least to a radius undetectable by echocardiography before they reach the left atrium [32]. Therefore, presence of minuscule direct pulmonary arteriovenous communications may explain the small pulmonary shunts found on TTCE in some healthy individuals without HHT [14-16]. At present, there are however no clinical recommendations how to manage these small pulmonary shunts in the general population.

The current guidelines on diagnosis and management of HHT advise additional chest CT in case of any pulmonary shunt on TTCE [11], in order to confirm the presence of PAVMs and its necessity for transcatheter embolotherapy. We believe that chest CT can be safely withheld in the presence of a pulmonary shunt grade 1 on TTCE, as any PAVM found on chest CT will be too small for subsequent transcatheter embolotherapy [12, 15, 25-27] and these small echocardiographic shunts do not appear to be associated with an increased risk for neurological complications [24]. Deferring chest CT in these persons could result in a tremendous cost saving and reduction of radiation exposure in mainly young adults [33]. This strategy would be in line with a recently published position paper from the European Society of Cardiology, that cautions against inappropriate radiation exposure if the needed information can also be obtained with non-ionizing tests of comparable accuracy [34].

In addition, the current guidelines on diagnosis and management of HHT also recommend prescription of antibiotic prophylaxis before procedures with risk of bacteraemia in HHT patients with pulmonary shunting on TTCE, in order to prevent brain abscesses [11]. This thesis now sets the stage for further discussion about the need for antibiotic prophylaxis in all persons with only a pulmonary shunt grade 1 on TTCE, as these shunts are not associated with an increased prevalence of neurological complications in our recent large retrospective study [24] and there are no other data to support the use of antibiotic prophylaxis in these subjects. It may be interesting to extrapolate this question to the recent discussion about antibiotic prophylaxis in the prevention of infective endocarditis, which is, like brain abscesses in HHT, also an uncommon but serious and often life-threatening condition [35, 36]. Despite lack of evidence, the traditional empirical approach for antibiotic prophylaxis in endocarditis has long been accepted, primarily due to the apprehension among both physicians and patients about the serious nature of endocarditis, which was further reinforced by previous recommendations from professional societies. Several factors however contributed to the recent extensive revision of this seemingly sound empirical approach. First of all, there have been no studies proving the concept that antibiotic prophylaxis indeed decreases the incidence of endocarditis. Second, it is known that procedures like dental

extractions can cause bacteraemia [37], but so do everyday activities like brushing teeth [38]. The cumulative exposure to bacteraemia from routine daily activities in one year may be as high as $5.6x10^6$ times greater as that resulting from a single tooth extraction [39]. Furthermore, the evidence that antibiotic prophylaxis prevents or reduces bacteraemia is even conflicting and those studies showing a reduction in bacteraemia did not show a subsequent reduction in endocarditis [40, 41]. Therefore, it appears unlikely that severe infective complications from micro-organisms, like endocarditis or brain abscesses, can be completely prevented by antibiotic prophylaxis. The lack of evidence for benefit of antibiotic prophylaxis in dental procedures and lack of good epidemiological data for non-dental procedures (respiratory, gastrointestinal and genitourinary), together with the more frequent occurrence of antibiotic resistance and side-effects as significant public health problems, led to the recently extensive revised international guideline on the prevention of endocarditis [36]. It is striking that the restricted indications for antibiotic prophylaxis to prevent endocarditis were not based on new data, but more on a change in philosophy. The aim to narrow the indication for antibiotic prophylaxis seems to be a healthy trend and the true role of antibiotic prophylaxis in all patients with only a pulmonary shunt grade 1 on TTCE is questionable and needs to be reconsidered.

Follow-up of pulmonary shunts on TTCE.

The current guideline on diagnosis and management of HHT recommends long-term follow-up for patients with PAVMs, in order to detect growth of untreated PAVMs and also reperfusion of treated PAVMs [11]. In patients with pulmonary shunting on TTCE without (treatable) PAVMs on chest CT, follow-up is currently advised with chest CT approximately every 1-5 year on a case-by case basis, with consideration for limiting radiation exposure [11]. Although we do not yet have sufficient long-term data on potential growth of PAVMs, it now ing radiation exposure (ref)ly on TTCE not detected or treatable on chest CT follow up discussed at the next consensus confseems conceivable that follow-up of HHT patients with no or grade 1 pulmonary shunt on TTCE could be performed by TTCE every five years, also depending on age. Additional chest CT would then only be indicated if the echocardiographic pulmonary shunt size increases to ≥ grade 2. A pulmonary shunt grade 2 and 3 on initial TTCE should be followed by chest CT every five years, as well as patients with treated PAVMs, since TTCE remains positive in 90% of cases after transcatheter embolotherapy [42].

Proposed new screening algorithm for the detection of PAVMs in (suspected) HHT.

Considering the above described recent advances in understanding the clinical implications of pulmonary shunting on TTCE, we suggest a new screening algorithm for the detection of PAVMs in patients with (suspected) HHT (figure 1). Using this proposed strategy, additional chest CT and antibiotic prophylaxis may be prevented in around 22% of individuals screened for HHT [24].

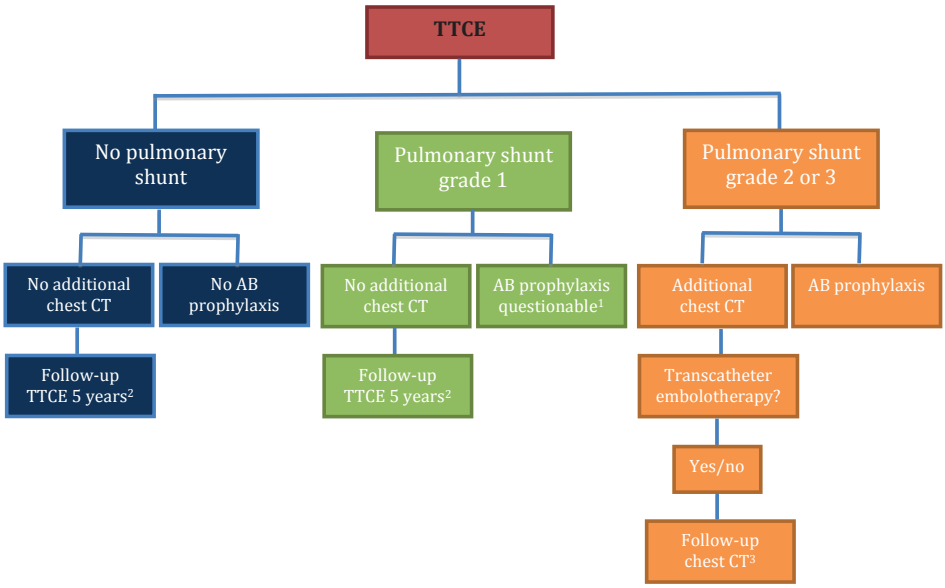

Figure 1. Proposed new screening algorithm for the detection of PAVMs in (suspected) HHT.
[1] Although still advised by the present guideline, the true role of antibiotic prophylaxis for patients with only a pulmonary shunt grade 1 on TTCE is currently unclear and needs to be reconsidered. [2]Only in case of proven HHT. [3]Chest CT 4-6 months after embolisation, followed by every three years. Chest CT every five years in case of no treatable PAVM.
Abbreviations: TTCE, transthoracic contrast echocardiography; RLS, right-to-left shunt; AB, antibiotic; CT, computed tomography; PAVM, pulmonary arteriovenous malformation.

CONCLUSIONS

The present thesis reports on recent advances in understanding the clinical implications of pulmonary shunting on TTCE and addresses its safety issues. Currently, additional chest CT and antibiotic prophylaxis are both recommended in case of any pulmonary shunting on TTCE, to evaluate the feasibility for transcatheter embolotherapy of PAVMs and prevent the occurrence strokes and brain abscesses related to paradoxical embolisation after procedures with risk for bacteraemia respectively. However, the current thesis suggests that small pulmonary shunts on TTCE lack any clinical implication, as these shunts cannot be used as a diagnostic criterion for HHT, are not associated with an increased risk for neurological complications and represent PAVMs that are too small for subsequent endovascular treatment. This implies that additional chest CT can be safely withheld in all HHT patients with only a small pulmonary shunt on TTCE and also sets the stage for further discussion about the need for antibiotic prophylaxis in these subjects. Besides further optimization of the current

screening algorithm for the detection of PAVMs in HHT, these recent observations can be of additional clinical importance, as small pulmonary shunts on TTCE are also documented in up to 28% of healthy individuals without HHT.

Not any bubble matters!

FUTURE PERSPECTIVES

Several important questions concerning clinical implications of different pulmonary shunt grades on TTCE in HHT have been addressed in this thesis. However, there are still important areas of uncertainty that needs to be investigated in future research.

1) In an epidemiological view and given the impact of a potential missed treatable PAVM with subsequent risk for cerebral complications, it should be encouraged to confirm our observations described in chapter five in a large prospective study. Although it seems unethical to perform such a study on the natural incidence of neurological complications in patients with a treatable pulmonary shunt grade 2 and 3 on TTCE, a conservative approach to all persons with a pulmonary shunt grade 1 on TTCE can now be considered and they should then be followed to document the incidence of neurological complications and compare this to persons without a pulmonary shunt on initial TTCE. Other cardiovascular risk factors, like smoking, diabetes, hypertension and hypercholesterolemia should then be reported as well. A disadvantage of such a large prospective study will however be its time consuming aspect and these results cannot be expected within the next few years.

2) Besides the neurological complications related to paradoxical embolization through PAVMs in HHT, the prevalence of pulmonary hypertension is increasingly recognized as a potential important complication in HHT [23, 43-46]. Pulmonary hypertension in HHT may result from a high cardiac output state associated with hepatic AVMs. Furthermore, the HHT-related gene mutations in ALK-1 or endoglin appear to predispose HHT patients to the development of pulmonary arterial hypertension. Echocardiography is currently the most useful screening tool for the detection of pulmonary hypertension [47] and it would be interesting to prospectively evaluate the exact prevalence of pulmonary hypertension in a large cohort of patients with HHT.

3) Recent literature suggests that patients with HHT might be at higher risk for thrombotic events than previously suspected [48]. Considering the documented increased prevalence of cerebral ischemic events in patients with HHT and PAVMs, it may be interesting to further analyze this pro-thrombotic state in HHT patients and investigate their platelet function assays, which have been collected during the last few years in our center.

4) We do not have sufficient long-term data on the potential growth of PAVMs on chest CT and pulmonary shunts on TTCE. In our center, follow-up of patients without a pulmonary shunt or a grade 1 shunt on TTCE is currently performed with TTCE after five years. Whether this strategy is also safe for those patients with a pulmonary shunt grade 2 on TTCE and no PAVMs on chest CT, remains also unknown. In order to recommend an evidence based follow-up op these patients, it is crucial to perform a large prospective study that compares the pulmonary shunt grade on TTCE five years after the initial screening. This study is currently undertaken in our center and may further guide regimens for follow-up of echocardiographic pulmonary shunts in HHT.

5) Chest CT is currently recommended for the follow-up after treatment of PAVMs [11], but should not be repeated without limits because of the use of ionizing radiation. It would be interesting to explore the role of magnetic resonance angiography (MRA) for both the detection and follow-up of (treated) PAVMs in HHT.

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CHAPTER 10

Summary

Nederlandse samenvatting

List of publications

Awards

Dankwoord

Curriculum Vitae

SUMMARY

Hereditary haemorrhagic telangiectasia (HHT), or Rendu-Osler-Weber disease, is an autosomal dominant inherited vascular disorder, characterized by the presence of abnormal direct artery-to-vein communications. These abnormal vascular communications range from dilated micro vessels in skin and mucosal membranes (so-called telangiectases), to large arteriovenous malformations (AVMs) in predominantly the pulmonary, hepatic and cerebral circulation. There are mainly two types of HHT, corresponding with gene mutations coding for Endoglin (HHT1) and ALK1 (HHT2). The clinical diagnosis of HHT is established according to the four Curaçao criteria, consisting of spontaneous and recurrent epistaxis, telangiectases at characteristic sites, a first-degree relative with HHT and the presence of visceral arteriovenous malformations (AVMs). Three criteria suffice for a definite diagnosis of HHT, two criteria are considered as possible HHT, and one or no criterion makes the diagnosis unlikely. In **chapter 2** we demonstrated that these clinical criteria already have a good diagnostic performance, compared with genetic testing as gold standard.

The rest of this thesis focused on the diagnosis and clinical implications of pulmonary arteriovenous malformations (PAVMs) in HHT. PAVMs are abnormal vascular structures that most often connect a pulmonary artery directly to a pulmonary vein, thereby bypassing the normal pulmonary capillary network. This results in a permanent pulmonary right-to-left shunt, which carries the risk of severe complications from paradoxical systemic embolizations, such as ischemic stroke or brain abscess. A pulmonary right-to-left shunt is found in 91% of HHT1 and 53% of HHT2 patients. Large PAVMs can be treated with transcatheter embolotherapy, which is an endovascular intervention that occludes the feeding artery of the PAVM with a coil or plug, in order to prevent the occurrence of the complications described above. Because of the high prevalence of PAVMs, its potential severe complications and effective treatment options, screening for PAVMs is recommended in all persons with possible or confirmed HHT. This screening was traditionally performed by chest CT, but has been replaced by transthoracic contrast echocardiography (TTCE) during the last few years, based on its excellent sensitivity and negative predictive value with lower risks and costs. Using TTCE, our group previously developed a quantitative pulmonary shunt grading system, in order to increase the usefulness of TTCE as a first-line screening technique for the detection of PAVMs. Depending on the number of contrast microbubbles counted in one still frame of the left-sided heart chamber, a pulmonary shunt is graded as 1 (maximum of 29 microbubbles), 2 (30-100 microbubbles) or 3 (>100 microbubbles). The aim of the current thesis was to further investigate the clinical implications of different pulmonary shunt grades on TTCE in (suspected) HHT.

In **chapter 3**, we demonstrated that a pulmonary shunt grade 1 on TTCE should not be accepted as a new diagnostic clinical Curaçao criterion for HHT, as this decreases the specificity of the criteria, resulting in more false positive diagnoses. However, we also revealed that the addition of pulmonary shunt grades ≥2 on TTCE to the current clinical Curaçao criteria increases its sensitivity without affecting the specificity and thereby further improves the diagnostic value of the current clinical Curaçao criteria.

In **chapter 4** we determined the diagnostic accuracy of pulmonary shunt measurements using the 100% oxygen method in detecting pulmonary right-to-left shunts, compared to different pulmonary shunt grades on TTCE. The 100% oxygen method, based on alveolar-arterial oxygen differences after breathing 100% oxygen for 30 minutes, is still performed in some centers in order to assess the presence of potential pulmonary shunting. Our study now firmly demonstrated that the sensitivity of the 100% oxygen method in detecting pulmonary shunts is low (51%). A large proportion of pulmonary shunt grades 2 and 3 on TTCE remained undetected and we therefore suggested that the 100% oxygen method should be abandoned as screening technique for pulmonary shunts in daily clinical practise.

In **chapter 5** we combined our scientific efforts with the HHT center in Crema (Italy) and created a large study cohort of persons screened for HHT with TTCE. In this retrospective study we demonstrated that the prevalence of neurological complications differs significantly between pulmonary shunt grades on TTCE; 0.4%, 6.5% and 20.9% for respectively grade 1, 2 and 3. Recognising patients at risk can be important to further facilitate and improve appropriate PAVM management strategies.

In **chapter 6** we confirmed that an increased pulmonary shunt grade on TTCE clearly relates to the probability of detecting PAVMs on chest CT, with a positive predictive value of 13%, 45% and 93% for a pulmonary shunt grade 1, 2 and 3 on TTCE respectively. More importantly, we demonstrated that the necessity for transcatheter embolotherapy of PAVMs on chest CT is strongly related to the pulmonary shunt grade on TTCE. In the sporadic case of a PAVM on chest CT in patients with a pulmonary shunt grade 1 on TTCE, this PAVM appeared to be too small for subsequent transcatheter embolotherapy in all cases.

Chapter 7 describes the direct cardiovascular hemodynamic changes that occurred after transcatheter embolotherapy of PAVMs. Using a non-invasive Finometer® device on a finger of the left hand and Modelflow® methodology, we most notably measured a decrease in stroke volume and cardiac output directly after endovascular closure of PAVMs.

In **chapter 8** we presented the first case worldwide of a percutaneous closure of the left atrial appendage with a "Watchmann device" in an HHT patient. In the near future, this might become a good alternative strategy to protect HHT patients with both atrial fibrillation and high-bleeding risk from strokes, without the need for chronic oral anticoagulation.

In **chapter 9** we further discuss on the safety of contrast echocardiography and clinical implications of different pulmonary shunt grades on TTCE in (suspected) HHT. We strongly believe that a pulmonary shunt grade 1 on TTCE lacks any clinical implications, as it cannot be used as a diagnostic criterion for HHT, it is not associated with an increased risk of neurological complications and in those sporadic cases where a PAVM is found on additional chest CT it will be too small for transcatheter embolotherapy. This implies that additional chest CT can be safely withheld in all persons with a pulmonary shunt grade 1 on TTCE, which could result in a tremendous cost saving and reduction of radiation exposure in mainly young adults. Furthermore, we challenged the present indication for

antibiotic prophylaxis in patients with only a pulmonary shunt grade 1 on TTCE to prevent the occurrence of brain abscess. In the opinion of the current author, we should change our philosophy despite the lack of large prospective studies and restrict the use of antibiotic prophylaxis to HHT patients with a pulmonary shunt grade ≥2 on TTCE. This discussion in chapter 9 resulted in a proposed new screening algorithm for the detection of PAVMs in (suspected) HHT.

SAMENVATTING

Hereditaire haemorrhagische teleangiectasie (HHT), ook wel bekend als de ziekte van Rendu-Osler-Weber (ROW), is een vaataandoening met een autosomaal dominant overervingspatroon, welk gekenmerkt wordt door de aanwezigheid van abnormale directe verbindingen tussen de arteriële en veneuze circulatie. Deze vaatafwijkingen kunnen variëren van gedilateerde zeer kleine bloedvaatjes in onder andere de huid en slijmvliezen (zogenaamde teleangiectasieën), tot grote arterioveneuze vaatmalformaties (AVMs) in voornamelijk de long, lever en hersenen.

Er bestaan hoofdzakelijk twee soorten HHT, welke overeenkomen met gen mutaties in ofwel het Endoglin (HHT1), ofwel ALK-1 (HHT2) eiwit.

De klinische diagnose van HHT wordt gesteld aan de hand van de vier Curaçao criteria, welke bestaan uit spontane en recidiverende bloedneuzen, teleangiectasieën op karakteristieke lokaties, een eerste-graads familie lid met HHT en de aanwezigheid van viscerale AVMs. Met drie positieve criteria is de klinische diagnose definitief, met twee criteria blijft de diagnose mogelijk, en bij afwezigheid of slechts één positief criterium is de klinische diagnose onwaarschijnlijk. In **hoofdstuk 2** beschreven wij dat deze klinische criteria reeds een goede diagnostische waarde kennen, vergeleken met het genetisch testen op HHT als gouden standaard.

Vervolgens richt dit proefschrift zich voornamelijk op de diagnostiek en klinische consequentie van pulmonale arterioveneuze vaatmalformaties (PAVMs) in patiënten met HHT. PAVMs zijn abnormale vaatstructuren die meestal een pulmonaal arterie direct verbinden met een pulmonaal vene, en daarbij het normale capillaire vaatnetwerk van de long deels overslaan. Dit resulteert in een permanente abnormale pulmonale rechts-links shunt van bloed, wat het risico op ernstige complicaties door paradoxale systemische embolieën met zich mee brengt, zoals een herseninfarct of hersenabces. Een pulmonale rechts-links shunt wordt aangetroffen in 91% en 53% van respectievelijk HHT1 en HHT2 patiënten. Grote PAVMs kunnen behandeld worden middels een transcatheter embolotherapie, welk een endovasculaire interventie is waarbij het aanvoerende bloedvat van de PAVM wordt afgesloten met een coil of plug, om zo het optreden van boven beschreven complicaties te voorkomen. Wegens de hoge prevalentie van PAVMs, de mogelijke ernstige complicaties en de aanwezigheid van een effectieve behandeling, wordt het aangeraden alle personen met mogelijk of bewezen HHT te screenen op aanwezigheid van PAVMs. Dit screenen gebeurde initieel voornamelijk met een CT-thorax, maar dit werd in de afgelopen jaren vervangen door transthoracale contrast echocardiografie (TTCE), gezien de excellente sensitiviteit en negatief voorspellende waarde hiervan met tevens lagere gezondheid risico's en kosten.

Onze onderzoeksgroep ontwikkelde reeds eerder een kwantitatief echografisch gradering systeem voor pulmonale rechts-links shunts, om zo de waarde van TTCE als initiële screening techniek verder te verhogen. Afhankelijk van het in een stilstaand frame getelde aantal contrast microbubbles in de linker ventrikel van het hart, wordt onderscheid gemaakt tussen

een pulmonale shunt graad 1 (maximaal 29 microbubbles), graad 2 (30-100 microbubbles), of graad 3 (>100 microbubbles). Het voornaamste doel van het huidige proefschrift bestond uit het bepalen van de klinische consequenties van deze verschillende pulmonale shunt graderingen op TTCE in patiënten met (mogelijk) HHT.

In **hoofdstuk 3**, toonden wij aan dat een pulmonale shunt graad 1 op TTCE niet geaccepteerd zou moeten worden als nieuw diagnostisch Curaçao criterium voor HHT, aangezien dit de specificiteit van de criteria verlaagt en resulteert in meer fout-positieve diagnoses. Hetzelfde hoofdstuk toonde echter ook aan dat het toevoegen van alleen pulmonale shunt graad ≥2 op TTCE de sensitiviteit van de criteria verhoogt zonder de specificiteit negatief te beïnvloeden, en zodoende de diagnostische waarde van de huidige Curaçao verder verbetert.

In **hoofdstuk 4** bepaalden wij de diagnostische accuraatheid van de 100% zuurstof methode in het detecteren van pulmonale shunts, in vergelijking met TTCE. Deze 100% zuurstof methode, gebaseerd op alveolaire-arteriële verschillen in zuurstof concentraties na inademen van 100% zuurstof gedurende 30 minuten, wordt in verschillende ziekenhuizen toegepast om de aanwezigheid van mogelijke pulmonale rechts-links shunts te onderzoeken als oorzaak van een hypoxie. Onze studie toont echter duidelijk aan dat de sensitiviteit van deze 100% zuurstof methode erg laag is (51%). Een groot deel van de pulmonale shunt graad 2 en 3 op TTCE wordt niet gedetecteerd middels deze methode en daarom adviseren wij dat de 100% zuurstof methode niet meer gebruikt dient te worden als diagnosticum voor pulmonale rechts-links shunts in de kliniek.

In **hoofdstuk 5** bundelden wij onze wetenschappelijke krachten met een HHT centrum in Crema (Italië) en creëerden zo een groot studie-cohort van personen met (mogelijk) HHT die middels TTCE gescreend waren op PAVMs. In de hieruit voortgekomen retrospectieve studie toonden wij aan dat de prevalentie van neurologische complicaties duidelijk afhankelijk is van de pulmonale shunt graad op TTCE; een complicatie kwam namelijk voor bij 0.4%, 6.5% en 20.9% van de patiënten met respectievelijk een pulmonale shunt graad 1, 2 en 3. Het herkennen van HHT patiënten die daadwerkelijk een verhoogd risico lopen op mogelijk ernstige neurologische complicaties is belangrijk, om de juiste behandel strategie voor PAVMs op te kunnen stellen en verder te verbeteren.

In **hoofdstuk 6** bevestigden wij dat de pulmonale shunt graad op TTCE de kans voorspelt op aanwezigheid van een PAVM op CT-thorax, met een positief voorspellende waarde van 13%, 45% en 93% voor respectievelijk een pulmonale shunt graad 1, 2 en 3 op TTCE. Nog belangrijker was onze observatie dat de echocardiografische pulmonale shunt graad gerelateerd is aan de mogelijkheid tot percutane behandeling van PAVMs op CT-thorax. In het sporadische geval dat CT-thorax een PAVM toont bij een persoon met een pulmonale shunt graad 1 op TTCE, blijkt deze PAVM in alle gevallen namelijk te klein om endovasculair te behandelen.

In **hoofdstuk 7** beschreven wij de directe hemodynamische veranderingen, die optreden na transcatheter embolotherapie van PAVMs. Middels een niet-invasieve Finometer®, bevestigt aan een vinger van de linker hand, en bijbehorende Modelflow® methode, toonden wij met name een afname in slagvolume en cardiac output aan direct na het afsluiten van een PAVM.

Hoofdstuk 8 omvat de wereldwijd eerst beschreven casus van een percutane, endovasculaire afsluiting van het linker hartoor met een "Watchman device" in een HHT patiënt. In de toekomst zou dit mogelijk een goed alternatief kunnen vormen, om HHT patiënten met zowel een verhoogde bloedingsneiging als atriumfibrilleren te beschermen tegen herseninfarcten, zonder gebruik te hoeven maken van chronische orale antistolling.

In **hoofdstuk 9** discussieerden wij verder over de veiligheid van contrast echocardiografie en de klinische consequenties van de verschillende pulmonale shunt gradering op TTCE in patiënten met (mogelijk) HHT. Wij zijn ervan overtuigd dat een pulmonale shunt graad 1 op TTCE geen klinische consequenties bezit, aangezien deze shunt niet beschouwd kan worden als diagnostisch criterium voor HHT, deze niet geassocieerd lijkt te zijn met een verhoogd risico op neurologische complicaties, en deze in die enkele gevallen waar een PAVM op CT-thorax wordt aangetroffen te klein blijkt te zijn voor succesvolle endovasculaire behandeling. Dit betekent dat een aanvullende CT-thorax veilig achterwege kan blijven in alle personen met een pulmonale shunt graad 1 op TTCE, wat een enorme kosten besparing en afname van stralingsbelasting kan betekenen voor een grote groep van voornamelijk jong volwassenen.

Verder stelden wij in dit hoofdstuk vraagtekens bij de indicatie voor antibiotica profylaxe ter preventie van hersenabcessen in patiënten met slechts een pulmonale shunt graad 1 op TTCE. Naar onze mening moeten we van gedachten veranderen en ondanks de afwezigheid van grote prospectief gerandomiseerde studies het gebruik van antibiotica profylaxe beperken tot HHT patiënten met een pulmonale shunt graad ≥ 2 op TTCE. Wij sloten hoofdstuk 9 dan ook af met een nieuw voorgesteld screening algoritme voor het detecteren van PAVMs in (mogelijk) HHT.

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Koning en **Keizer**, jullie zijn stout en lief en jullie weten het.

CURRICULUM VITAE

Sebastiaan Velthuis werd geboren op 5 augustus 1984 in Alkmaar. In 2003 behaalde hij cum laude zijn Gymnasium diploma aan het Willem Blaeu College, waarna hij de Universiteit van Maastricht verkoos voor zijn verdere studie Geneeskunde. Het laatste jaar van deze opleiding werd volbracht op de afdeling Cardiologie van het Academisch Ziekenhuis Maastricht. Onder leiding van Prof. Dr. S. Heymans deed hij tevens onderzoek naar verschillende oorzaken van inflammatoire cardiomyopathie binnen het Cardiovascular Research Institute Maastricht (CARIM). Vervolgens werd klinische ervaring opgedaan als arts-assistent cardiologie in zowel het Meander Medisch Centrum te Amersfoort als het Gelre Ziekenhuis te Apeldoorn, om vervolgens in 2011 te starten met zijn klinische opleiding tot cardioloog in het St. Antonius Ziekenhuis te Nieuwegein (opleider: Dr. J.M. ten Berg). Deze opleiding combineerde hij met het verrichten van wetenschappelijk onderzoek naar contrast echocardiografie onder leiding van Dr. M.C. Post, hetgeen in 2014 resulteerde in dit proefschrift. Naar verwachting rond hij zijn cardiologie opleiding af op 1 maart 2017.

Sebastiaan Velthuis was born on Augustus 5th in Alkmaar, the Netherlands. In 2003 he graduated his Gymnasium cum laude at the Willem Blaeu College, after which he started his medical training at the Maastricht University. The last year of this training he participated in the cardiology department of the Academic Medical Hospital Maastricht. Supervised by Prof. Dr. S. Heymans, he also performed scientific research with a focus on inflammatory cardiomyopathy in the Cardiovascular Research Institute Maastricht (CARIM). Afterwards, he gained clinical experience in cardiology at the Meander Medical Center in Amersfoort and the Gelre Hospital in Apeldoorn. In 2011 he started his official training in cardiology at the St. Antonius Hospital in Nieuwegein, which is supervised by Dr. J.M. ten Berg. During these years, he combined his training in cardiology with a PhD project on contrast echocardiography under supervision of Dr. M.C. Post, which resulted in this thesis in 2014. As expected, he will finish his training in cardiology on the first of March 2017.