Cardiopulmonary aspects of hereditary haemorrhagic telangiectasia

Marco van Gent

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Cardiopulmonary aspects of hereditary haemorrhagic telangiectasia

Cardiopulmonale aspecten van hereditaire hemorrhagische teleangiectasieën
(met een samenvatting in het Nederlands)

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1

General introduction, aims, and outline of the thesis

General introduction

Hereditary haemorrhagic telangiectasia

Background

Hereditary haemorrhagic telangiectasia (HHT), also known as the Rendu-Osler-Weber syndrome, is a vascular disorder and inherited as an autosomal dominant trait. The estimated prevalence of HHT is 1 in 5000 individuals, but there is a wide geographic distribution.[1] For instance, a prevalence up to 1 in 1331 has been reported in the Afro-Caribbean population of the Netherlands Antilles.[2] The characteristic feature of vascular pathology in HHT is the presence of direct artery-to-vein communications which carry the risk for shunting and hemorrhage. These abnormal communications range from dilated microvessels, so-called telangiectases, to large arteriovenous malformations (AVMs). The latter are predominantly found in the pulmonary (PAVM), hepatic (HAVM) and cerebral (CAVM) circulation and are a source of significant morbidity in HHT patients. Predilection sites for telangiectases are the nose, buccal mucosa, skin, and gastro-intestinal tract (figure 1).

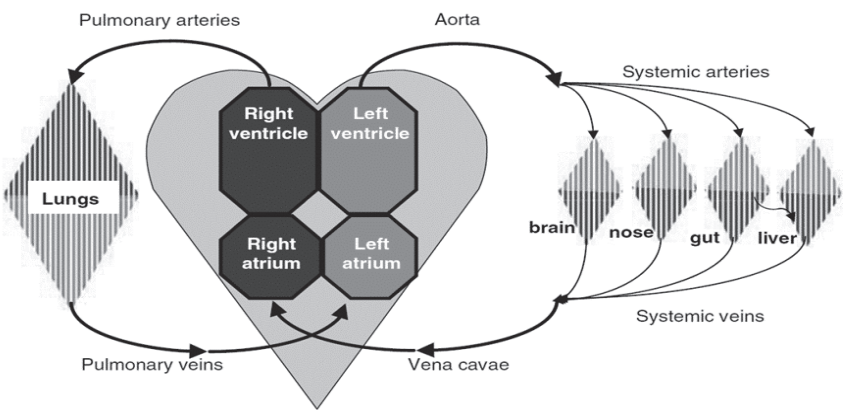

Figure 1 Schematic of systemic and pulmonary circulations showing capillary beds in which telangiectases or arteriovenous malformations occur (From reference 3, with permission of the publisher)

Molecular genetics and pathogenesis

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 endoglin,[3, 4 5] whereas HHT2 results from mutations in the activine receptor-like kinase (ACVRL1) gene on chromosome 12 encoding ALK-1.[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, 2 more loci causing HHT have been mapped to chromosome 5 (HHT type 3) and 7 (HHT type 4), although the causative genes have not been identified yet.[9, 10] However, the majority of HHT patients has type 1 or 2.[11] There are no mutations of the ENG and ACVRL1 genes that prevail, and all types of mutations have been reported (including missense, nonsense, deletions, insertions and splice site). Most families with HHT have a unique mutation.

Haploinsufficiency, resulting in an insufficient level of protein products for normal function, is the underlying cause of HHT.[12] Endoglin and ALK-1 proteins are endothelial receptors of the transforming growth factor β (TGF-β) superfamily. Both proteins cooperate in the TGF-β/ALK-1 signaling pathway, which is involved in angiogenesis (figure 2). Intracellular effectors of the SMAD protein family are also part of this pathway. Endoglin expression appears to be decreased in both HHT1 and HHT2 patients, suggesting the involvement of ALK-1 in ENG gene expression.[13, 14] In normal endothelial cells both ALK-5 and ALK-1 are involved in the TGF-β pathway. ALK-1 signaling promotes endothelial cell proliferation and migration, which is inhibited by ALK-5.[15] Therefore, a fine balance between these pathways is essential. In both HHT1 and HHT2 patients, the positive cooperation between endoglin and ALK-1 is impaired which compromises the ALK-1 pathway. A direct consequence of impaired TGF-β signaling is the failure to form cord-like structures that are typical for angiogenesis, and a disorganized cytoskeleton.[13] These are both common characteristics of endothelial cells from HHT patients and may lead to fragile vessels with bleeding and to an abnormal angiogenesis, which may explain the characteristic clinical symptoms associated with this disease.[13]

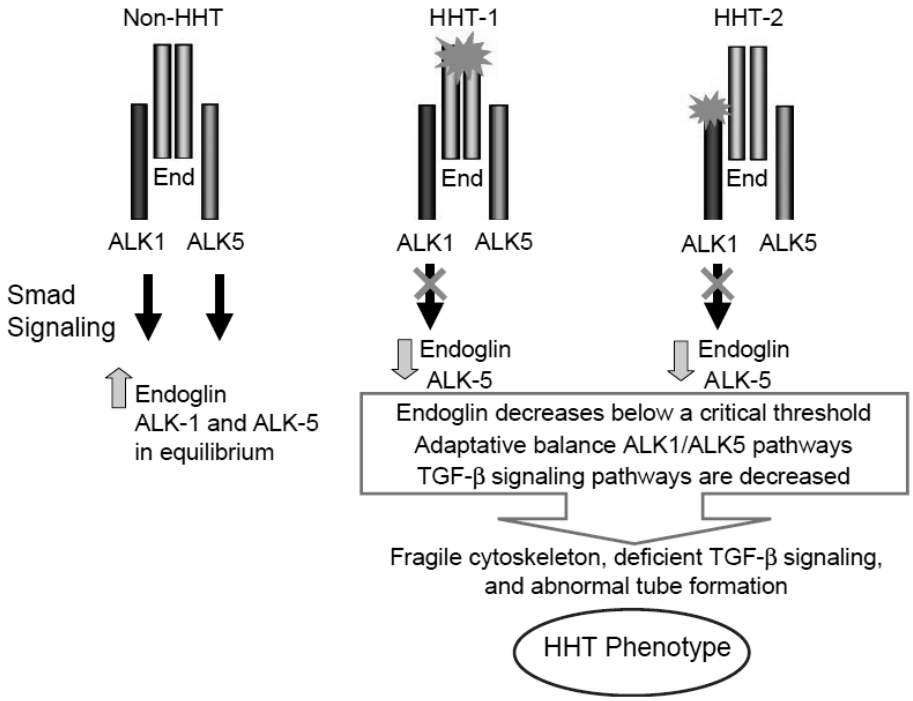

Figure 2 Hypothetical model for the pathogenesis of HHT; Schematic model representing TGF-β receptor complex in healthy (Non-HHT) compared to the situation in HHT1 and HHT2 endothelial cells. Normally (Non-HHT), ALK1 and endoglin are cooperating in the TGF-β/Smad pathway, and the endoglin levels are maintained to meet the physiological needs of the endothelial cells. However, in HHT1 and HHT2 cells, either endoglin or ALK1 fail as partners in the cooperative signaling. As a result, endoglin expression decreases below a critical threshold which leads to impaired TGF-β signaling, and abnormal cytoskeleton and tube formation in HHT endothelial cells. These altered endothelial functions may explain the HHT phenotype. (From reference 14, reproduced with permission of the authors).

Clinical diagnosis

A mutation detection rate of 72-93% for the ENG and ACVRL1 genes in patients with a clinical diagnosis of HHT has been reported.[16-18] Therefore, mutation analysis solely cannot be relied on to exclude HHT and a clinical evaluation remains important. This may relate to mutations in other genes that are not yet

identified. On the other hand, nose bleeds, and to a lesser degree telangiectases, are not uncommon in the general population, possibly causing false-positive diagnosis of HHT. Phenotypic expression is highly variable in HHT, even within members of the same family. This clinically heterogeneous presentation also precludes diagnosis of HHT subtypes. In addition, there appears to be age-related penetrance and therefore, the diagnosis should not be ruled out in asymptomatic children. The clinical diagnosis of HHT is based on a consensus statement, also known as the four Curaçao clinical criteria[19]:

- Recurrent, spontaneous epistaxis
- Multiple telangiectases at characteristic sites: lips, oral cavity, nose, fingers
- Visceral lesions, such as gastrointestinal telangiectases, PAVMs, cerebral AVMs, and hepatic AVMs
- Family history: a first degree relative with HHT according to these criteria

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'. The last two categories were introduced to reduce the number of patients overlooked and excluded from screening programs. However, this clinical classification has never been validated using genetic test results as the gold standard.

Pulmonary arteriovenous malformations

Definition and complications

PAVMs are caused by abnormal communications between pulmonary arteries and veins, resulting in a right-to-left shunt (RLS) which bypasses the pulmonary capillary filter. Consequently, both emboli of thrombotic and septic origin may reach the systemic circulation. This explains the high prevalence of brain abscess and ischemic stroke in HHT patients with untreated PAVMs, ranging from 8-19% and 10-36%, respectively.[20-24] Gas exchange may also be compromised, resulting in hypoxaemia and dyspnea. In addition, PAVMs may result in massive hemoptysis or hemothorax.[20, 21, 25, 26] Such severe complications may be the presenting manifestation in otherwise asymptomatic patients.

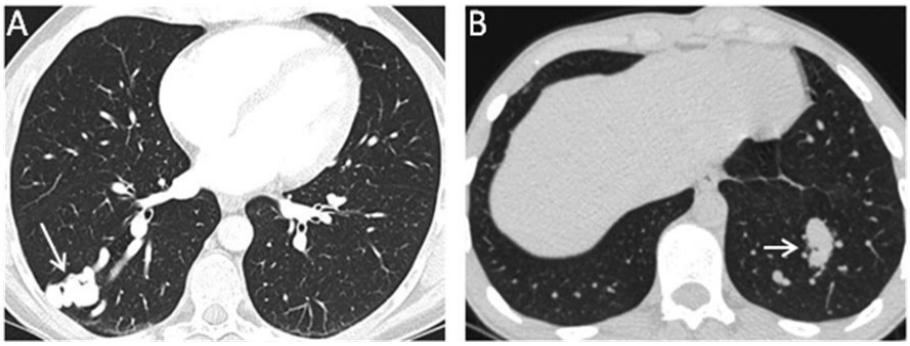

Figure 3. Examples of PAVMs on chest CT; A: Large PAVM (arrow) peripherally in the right lower lobe; B: Large PAVM (arrow) in the left lower lobe.

Prevalence

PAVMs are present in 15-45% of patients with HHT.[27, 28] It is estimated that at least 70% of PAVMs are associated with HHT,[27] but in our own experience this exceeds 90% of PAVMs.[21] Using chest computed tomography (CT), the prevalence of PAVMs in patients with HHT1 is 48-75%, compared to 5-44% in patients with HHT2.[29-32] Most PAVMs are multiple and in approximately 5% of HHT patients with PAVMs they are diffuse.[33, 34] The latter comprises a high-risk group that is much more susceptible to complications.[33, 34]

Intrapulmonary right-to-left shunt and migraine

Migraine is a common and recurrent headache disorder with an estimated prevalence of 12% in the general population.[35] In the management of HHT patients, a remarkably high prevalence of migraine has already been observed long ago.[36, 37] Migraine has important personal and socio-economic impact. Women are more frequently affected than men.[35] The diagnosis is based on criteria published by the International Headache Society.[38] The two main subgroups are migraine without aura (MA-) and migraine with aura (MA+). The pathogenesis of migraine is complex. The aura phenomenon is probably caused by the cortical spreading depression (CSD), characterized by neuronal excitation and subsequent prolonged suppression of neuronal activity.[39] It is not clear how the CSD is initiated. The migraine headache results from nociceptive input of the trigeminovascular system.[40]

Several studies have suggested an association between an interatrial RLS and migraine, as a patent foramen ovale (PFO) appeared to be more common among individuals with MA+, and MA+ more common among persons with a PFO.[41-44] MA- does not appear to be related to these shunts. A prospective study which randomized migraine patients with a PFO to percutaneous closure or a sham procedure did not show a reduction in migraine after PFO closure.[45] Furthermore, a recent population-based study did not show an association between PFO and migraine.[46] Therefore, the existence of a causal relationship between an interatrial RLS and migraine is still controversial. It is hypothesized that these shunts may provide an intermittent conduit for shunting of thrombi or vasoactive substances to the cerebral circulation, and from that trigger a migraine attack.[47-49] A PAVM is a source of permanent RLS, as opposed to only intermittent shunting in most PFOs. Retrospective studies have indeed suggested an increased prevalence of MA+ in patiens with HHT and PAVMs.[50, 51] Therefore, intrapulmonary shunting might explain the high prevalence of migraine in patients with HHT. However, large prospective studies on this association are lacking.

Treatment

PAVMs are treated by transcatheter embolisation with excellent long-term results.[21, 24, 52-54] Treatment of PAVMs with feeding vessels of 3mm or larger is usually recommended[55] but in some centres, including our own, smaller PAVMs are also treated when technically feasible.[56] The latter is supported by the finding that a substantial percentage of previously small (<3mm) PAVMs enlarge to a size requiring treatment during follow-up.[57] Nonetheless, many patients will have PAVMs that are too small to allow transcatheter embolotherapy. Because there is general consensus that it is unethical to withhold treatment of PAVMs, there are no prospective data on the natural history of PAVMs and there is no direct evidence for a reduction of neurological complications after embolisation. However, the available data suggest considerable morbidity and mortality in patients with PAVM.[21, 24, 26, 27, 57] Recently, indirect evidence for the effectiveness of embolotherapy was provided as no neurological complications were observed following obliteration of all angiographically visible PAVMs.[23] In addition, several

studies have demonstrated the occurrence of serious neurological complications during follow-up after treatment in patients with reperfused PAVMs, or enlargement of previously small, non-embolised PAVMs.[21, 53, 57]

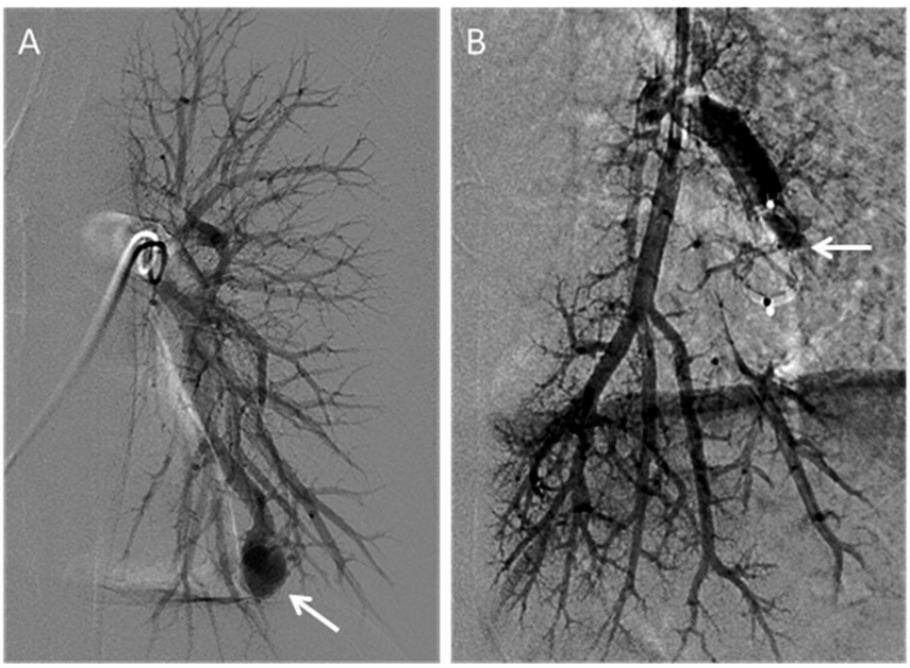

Figure 4. Pulmonary angiogram and embolisation in a patient with a PAVM in the left lower lobe on chest CT; A: Angiogram with pigtail in the left main pulmonary artery, showing a large PAVM (arrow) in the left lower lobe; B: Selective angiogram following embolisation, showing successful occlusion of the feeding artery after placement of an Amplatzer vascular plug (arrow).

Screening

Because of its high prevalence, its associated severe complications, and the possibility for an effective treatment, screening for PAVMs is routinely performed in all possible HHT patients. Screening has traditionally been done with chest radiography and arterial blood gas analysis including 100% oxygen shunt testing. However, these screening methods have a limited sensitivity and were replaced by

CT thorax as the accepted gold standard.[28] CT thorax allows selection of PAVMs that are amenable for embolotherapy, but a disadvantage is the concomitant radiation burden. This is particularly so for patients with PAVMs that have been embolised or that are too small for treatment, as repeated CT scans are usually performed over time in this group to detect reperfusion of treated PAVMs, or enlargement of untreated PAVMs. Transthoracic contrast echocardiography (TTCE) has a high diagnostic yield for the detection of intrapulmonary shunting through PAVMs. A high sensitivity has been reported in several, mainly small, retrospective studies.[28, 58-61] As a consequence, TTCE has gained much interest and has been increasingly employed as a first-line screening technique for PAVM. Radionuclide perfusion lung scanning and magnetic resonance imaging are also occasionally used for this purpose. The choice for an optimal screening test is continuously debated. However, there are only very few studies that directly compare different non-invasive methods, and none of them has been conducted prospectively.

HHT patients with PAVMs have a greatly increased risk for brain abscess.[23] The majority of bacterial isolates from brain abscesses are of dental origin.[23] Antibiotic prophylaxis for procedures with risk of bacteremia is recommended in patients with a PAVM.[62]

Contrast echocardiography

Technique

Originally, the so-called 'contrast-effect' of exogenous agents was unexpectedly observed in the era of M-mode echocardiography.[63] Later on it was recognized that microbubbles were in fact the source of this ultrasonic contrast effect.[64] Microbubbles are particularly strong reflectors because the gas within these bubbles has a markedly difference acoustic impedance relative to that of blood. This is even more pronounced for smaller bubbles. Following venous injection, microbubbles are not seen in the left-sided heart in physiologic conditions. This is for two reasons. Bubbles larger than the pulmonary capillary diameter are 'sieved', and those that are small enough to pass the capillaries dissolve rapidly.[65] However, in the presence of a right-to-left shunt (RLS), these microbubbles can be visible in the left heart. The simplest, least expensive and most commonly

used contrast agent is agitated saline. Saline-air solutions are usually used in conjunction with blood. Typically, 5-10ml of saline/blood is mixed with 0.1-1ml of air by repeat injection from one syringe to another via a three-way stopcock.[66] This agitated saline is then rapidly injected in the antecubital or femoral vein. Following contrast injection, the echocardiogram should be closely observed for the pattern and origin of contrast appearance, and its timing. The latter can be used to discern an intracardiac from an intrapulmonary shunt.

Intracardiac versus intrapulmonary shunting

The arrival of contrast in the left atrium is delayed when a large part of the pulmonary vasculature has to be traversed. A delay of at least 3 cardiac cycles from the moment that complete right atrial opacification is present is generally regarded as proof for a pulmonary origin of the RLS. It should be noted that this '3-beat rule' comes from a case report of a patient with diffuse PAVMs using M-mode echocardiography in 1976.[67] In the following years several authors have extended this to a '3- to 5-beat rule' for which there is no scientific basis.[68] Nonetheless, this practice is generally employed in echocardiographic laboratories to assess the origin of the shunt. It should be realized that earlier contrast appearance in patients with pulmonary shunts has also been described, especially with large shunts.[69-73] The majority of PFOs cannot be seen during a resting state and provocative manoeuvres are necessary to elicit a transient RLS. Therefore, a Valsalva manoeuvre is usually performed during contrast injection. During the strain phase venous return is interrupted due to the increased intrathoracic pressure. With release, the veins rapidly empty in the right atrium and the left atrium receives little blood from the pulmonary veins, favouring a right-to-left interatrial pressure gradient. PAVMs are a source of permanent RLS and do not need augmentation by provocative manoeuvres to show contrast appearance in the left heart. However, it should be realized that a PFO can in certain circumstances also be seen in a resting state. This seems comprehensible when right atrial pressure is elevated (e.g., pulmonary arterial hypertension, right ventricular dysfunction, or tricuspid valve disease), but can also be caused by inspiratory increase in right atrial pressure.[68, 74] Therefore, depending on the

respiratory rate, contrast may appear after 3-5 cardiac cycles in patients with a PFO and be misinterpreted as a pulmonary shunt. In addition, a brief interatrial pressure reversal has been shown during early ventricular systole in subjects with normal right-sided pressures.[75]

Because of its excellent resolution, transesophageal echocardiography (TEE) is considered the gold standard for the detection of shunts. However, it is often difficult to obtain a proper Valsalva manoeuvre during TEE (especially when the patient is sedated). The use of second harmonic imaging has improved the diagnostic yield of TTCE in the diagnosis of shunts, and has been reported to be as good as TEE.[76-78] Furthermore, because of its invasive character and patient discomfort, TEE is not attractive for routine screening purposes.

Instead of classifying a contrast study merely as positive or negative, semi-quantitative grading of shunt size might be valuable. The size of echocardiographic pulmonary shunting correlates with the presence and size of PAVM on angiography or chest CT.[58, 69] It is currently not known if classification of shunt size is also useful to guide treatment of PAVMs.

Aims of the thesis

The aims of this thesis are to answer the following questions:

1. Is TTCE a suitable screening test for PAVMs and how does it compare to other screening methods, in particular chest CT?
2. Can grading of shunt size with TTCE be used to discern small PAVMs that cannot be treated from larger PAVMs that require embolotherapy?
3. How do the prevalence and size of pulmonary shunts on TTCE differ between HHT type 1 and 2, and how does this affect the predictive value for treatable PAVMs?
4. What is the validity of the clinical criteria for HHT, and does TTCE improve clinical diagnosis?
5. Is there a real association between PAVMs and migraine in patients with HHT?
6. Does pulmonary shunt size influence the occurrence of migraine?

Outline of the thesis

In the first part we focus on the diagnostic value of TTCE as a screening tool for the detection of PAVM in HHT patients. Although previous studies have shown that TTCE is very sensitive for the detection of intrapulmonary shunting, this has never been systematically evaluated. In **chapter 2** we report on the diagnostic value of TTCE for the detection of intrapulmonary shunting. The presence of a PAVM on chest CT was the gold standard in this study involving almost 300 possible HHT patients who were screened in a prospective manner. The use of TTCE makes it possible to detect even small intrapulmonary shunts that are below the detection limit of chest CT. As a consequence, the positive predictive value of small shunts for the presence of (treatable) PAVMs on chest CT is expected to be limited. In **chapter 3** we test the hypothesis that the use of semi-quantitative grading of pulmonary shunt size might be used to predict both the presence and the possibility for treatment of PAVMs. Such an approach might be helpful to answer the question if there is a cutoff of shunt size below which treatable PAVMs are absent and CT thorax can be safely withheld.

In the *second part* we describe the differences between HHT1 and HHT2 in terms of prevalence and size of intrapulmonary shunts, and its consequences for clinical diagnosis and management. Studies on the genotype-phenotype correlation in HHT so far have used data from chest CT as the most sensitive technique to describe the prevalence of PAVM. In **chapter 4** we compare the prevalence of echocardiographic pulmonary shunts and the distribution of different shunt grades between HHT1 and HHT2. In addition, this chapter contains a comparison of the predictive value of intrapulmonary shunt size for the presence of treatable PAVMs in both HHT genotypes. The Curaçao criteria for the clinical diagnosis of HHT were drawn up in an era that genetic screening was hardly available. These criteria were quite stringent in order to avoid false-negative classification of HHT patients, and have never been validated. Therefore it is important to assess the diagnostic accuracy of the clinical criteria using genetic testing as the gold standard. This is described in **chapter 5**. Because of its high sensitivity, it is

tempting to use a pulmonary RLS on echocardiography as a clinical criterium. This assumption might theoretically improve the accuracy of clinical diagnosis of HHT. This hypothesis is also tested in chapter 5.

In the *third part* we investigate the relation between migraine and intrapulmonary shunting. In **chapter 6** the available evidence for a real association between MA+ and pulmonary shunting is reviewed. Most studies to date have evaluated this association retrospectively or did not discern between MA+ and MA-. **Chapter 7** discusses the first prospective data on migraine, both MA+ and MA-, in HHT patients with or without a PAVM on chest CT. However, chest CT can only be used to confirm the presence of a PAVM and does not provide any functional information on the size of intrapulmonary shunting. The RLS-migraine hypothesis would be further strengthened if a 'dose-response' relationship appears to be present. Therefore, we describe in **chapter 8** the influence of pulmonary shunt size on the occurrence of MA+ in a large cohort of individuals screened for possible HHT.

Reference List

1. Kjeldsen AD, Vase P, Green A. Hereditary haemorrhagic telangiectasia: a population-based study of prevalence and mortality in Danish patients. J Intern Med 1999;245:31-39.
2. Westermann CJ, Rosina AF, De V, V, de Coteau PA. The prevalence and manifestations of hereditary hemorrhagic telangiectasia in the Afro-Caribbean population of the Netherlands Antilles: a family screening. Am J Med Genet A 2003;116A:324-328.
3. Shovlin CL, Hughes JM, Tuddenham EG, Temperley I, Perembelon YF, Scott J, Seidman CE, Seidman JG. A gene for hereditary haemorrhagic telangiectasia maps to chromosome 9q3. Nat Genet 1994;6:205-209.
4. McDonald MT, Papenberg KA, Ghosh S, Glatfelter AA, Biesecker BB, Helmbold EA, Markel DS, Zolotor A, McKinnon WC, Vanderstoep JL, . A disease locus for hereditary haemorrhagic telangiectasia maps to chromosome 9q33-34. Nat Genet 1994;6:197-204.
5. McAllister KA, Grogg KM, Johnson DW, Gallione CJ, Baldwin MA, Jackson CE, Helmbold EA, Markel DS, McKinnon WC, Murrell J, . Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. Nat Genet 1994;8:345-351.
6. Johnson DW, Berg JN, Gallione CJ, McAllister KA, Warner JP, Helmbold EA, Markel DS, Jackson CE, Porteous ME, Marchuk DA. A second locus for hereditary hemorrhagic telangiectasia maps to chromosome 12. Genome Res 1995;5:21-28.
7. Vincent P, Plauchu H, Hazan J, Faure S, Weissenbach J, Godet J. A third locus for hereditary haemorrhagic telangiectasia maps to chromosome 12q. Hum Mol Genet 1995;4:945-949.
8. Gallione CJ, Repetto GM, Legius E, Rustgi AK, Schelley SL, Tejpar S, Mitchell G, Drouin E, Westermann CJ, Marchuk DA. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). Lancet 2004;363:852-859.
9. Cole SG, Begbie ME, Wallace GM, Shovlin CL. A new locus for hereditary haemorrhagic telangiectasia (HHT3) maps to chromosome 5. J Med Genet 2005;42:577-582.
10. Bayrak-Toydemir P, McDonald J, Akarsu N, Toydemir RM, Calderon F, Tuncali T, Tang W, Miller F, Mao R. A fourth locus for hereditary hemorrhagic telangiectasia maps to chromosome 7. Am J Med Genet A 2006;140:2155-2162.
11. Gallione CJ, Richards JA, Letteboer TG, Rushlow D, Prigoda NL, Leedom TP, Ganguly A, Castells A, Ploos van Amstel JK, Westermann CJ, Pyeritz RE, Marchuk DA. SMAD4 mutations found in unselected HHT patients. J Med Genet 2006;43:793-797.

12. Abdalla SA, Letarte M. Hereditary haemorrhagic telangiectasia: current views on genetics and mechanisms of disease. J Med Genet 2006;43:97-110.
13. Fernandez L, Sanz-Rodriguez F, Zarrabeitia R, Perez-Molino A, Hebbel RP, Nguyen J, Bernabeu C, Botella LM. Blood outgrowth endothelial cells from Hereditary Haemorrhagic Telangiectasia patients reveal abnormalities compatible with vascular lesions. Cardiovasc Res 2005;68:235-248.
14. Fernandez L, Sanz-Rodriguez F, Blanco FJ, Bernabeu C, Botella LM. Hereditary hemorrhagic telangiectasia, a vascular dysplasia affecting the TGF-beta signaling pathway. Clin Med Res 2006;4:66-78.
15. Goumans MJ, Valdimarsdottir G, Itoh S, Lebrin F, Larsson J, Mummery C, Karlsson S, ten DP. Activin receptor-like kinase (ALK)1 is an antagonistic mediator of lateral TGFbeta/ALK5 signaling. Mol Cell 2003;12:817-828.
16. Bossler AD, Richards J, George C, Godmilow L, Ganguly A. Novel mutations in ENG and ACVRL1 identified in a series of 200 individuals undergoing clinical genetic testing for hereditary hemorrhagic telangiectasia (HHT): correlation of genotype with phenotype. Hum Mutat 2006;27:667-675.
17. Letteboer TG, Zewald RA, Kamping EJ, de HG, Mager JJ, Snijder RJ, Lindhout D, Hennekam FA, Westermann CJ, Ploos van Amstel JK. Hereditary hemorrhagic telangiectasia: ENG and ALK-1 mutations in Dutch patients. Hum Genet 2005;116:8-16.
18. Prigoda NL, Savas S, Abdalla SA, Piovesan B, Rushlow D, Vandezande K, Zhang E, Ozcelik H, Gallie BL, Letarte M. Hereditary haemorrhagic telangiectasia: mutation detection, test sensitivity and novel mutations. J Med Genet 2006;43:722-728.
19. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, Kjeldsen AD, Plauchu H. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000;91:66-67.
20. Cottin V, Chinet T, Lavole A, Corre R, Marchand E, Reynaud-Gaubert M, Plauchu H, Cordier JF. Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: a series of 126 patients. Medicine (Baltimore) 2007;86:1-17.
21. Mager JJ, Overtoom TT, Blauw H, Lammers JW, Westermann CJ. Embolotherapy of pulmonary arteriovenous malformations: long-term results in 112 patients. J Vasc Interv Radiol 2004;15:451-456.

22. Moussouttas M, Fayad P, Rosenblatt M, Hashimoto M, Pollak J, Henderson K, Ma TY, White RI. Pulmonary arteriovenous malformations: cerebral ischemia and neurologic manifestations. Neurology 2000;55:959-964.
23. Shovlin CL, Jackson JE, Bamford KB, Jenkins IH, Benjamin AR, Ramadan H, Kulinskaya E. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. Thorax 2008;63:259-266.
24. White RI, Jr., Lynch-Nyhan A, Terry P, Buescher PC, Farmlett EJ, Charnas L, Shuman K, Kim W, Kinnison M, Mitchell SE. Pulmonary arteriovenous malformations: techniques and long-term outcome of embolotherapy. Radiology 1988;169:663-669.
25. Ference BA, Shannon TM, White RI, Jr., Zawin M, Burdge CM. Life-threatening pulmonary hemorrhage with pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia. Chest 1994;106:1387-1390.
26. Swanson KL, Prakash UB, Stanson AW. Pulmonary arteriovenous fistulas: Mayo Clinic experience, 1982-1997. Mayo Clin Proc 1999;74:671-680.
27. Gossage JR, Kanj G. Pulmonary arteriovenous malformations. A state of the art review. Am J Respir Crit Care Med 1998;158:643-661.
28. Cottin V, Plauchu H, Bayle JY, Barthelet M, Revel D, Cordier JF. Pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. Am J Respir Crit Care Med 2004;169:994-1000.
29. Lesca G, Olivieri C, Burnichon N, Pagella F, Carette MF, Gilbert-Dussardier B, Goizet C, Roume J, Rabilloud M, Saurin JC, Cottin V, Honnorat J, Coulet F, Giraud S, Calender A, Danesino C, Buscarini E, Plauchu H. Genotype-phenotype correlations in hereditary hemorrhagic telangiectasia: data from the French-Italian HHT network. Genet Med 2007;9:14-22.
30. Letteboer TG, Mager JJ, Snijder RJ, Koeleman BP, Lindhout D, Ploos van Amstel JK, Westermann CJ. Genotype-phenotype relationship in hereditary haemorrhagic telangiectasia. J Med Genet 2006;43:371-377.
31. Post MC, Letteboer TG, Mager JJ, Plokker TH, Kelder JC, Westermann CJ. A pulmonary right-to-left shunt in patients with hereditary hemorrhagic telangiectasia is associated with an increased prevalence of migraine. Chest 2005;128:2485-2489.

32. Sabba C, Pasculli G, Lenato GM, Suppressa P, Lastella P, Memeo M, Dicuonzo F, Guant G. Hereditary hemorrhagic telangiectasia: clinical features in ENG and ALK1 mutation carriers. J Thromb Haemost 2007;5:1149-1157.
33. Pierucci P, Murphy J, Henderson KJ, Chyun DA, White RI, Jr. New definition and natural history of patients with diffuse pulmonary arteriovenous malformations: twenty-seven-year experience. Chest 2008;133:653-661.
34. Faughnan ME, Lui YW, Wirth JA, Pugash RA, Redelmeier DA, Hyland RH, White RI, Jr. Diffuse pulmonary arteriovenous malformations: characteristics and prognosis. Chest 2000;117:31-38.
35. Lipton RB, Bigal ME. The epidemiology of migraine. Am J Med 2005;118 Suppl 1:3S-10S.
36. Boczko ML. Neurological implications of hereditary hemorrhagic telangiectasis. J Nerv Ment Dis 1964;139:525-536.
37. Hodgson CH, Burchell HB, Good CA, Clagett OT. Hereditary hemorrhagic telangiectasia and pulmonary arteriovenous fistula: survey of a large family. N Engl J Med 1959;261:625-636.
38. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24 Suppl 1:9-160.
39. Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. Brain 1994;117 (Pt 1):199-210.
40. Goadsby PJ. Pathophysiology of migraine. Neurol Clin 2009;27:335-360.
41. Anzola GP, Magoni M, Guindani M, Rozzini L, Dalla VG. Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. Neurology 1999;52:1622-1625.
42. Del SM, Angeli S, Leandri M, Ferriero G, Bruzzone GL, Finocchi C, Gandolfo C. Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. Cerebrovasc Dis 1998;8:327-330.
43. Ferrarini G, Malferrari G, Zucco R, Gaddi O, Norina M, Pini LA. High prevalence of patent foramen ovale in migraine with aura. J Headache Pain 2005;6:71-76.
44. Schwerzmann M, Nedeltchev K, Lagger F, Mattle HP, Windecker S, Meier B, Seiler C. Prevalence and size of directly detected patent foramen ovale in migraine with aura. Neurology 2005;65:1415-1418.

45. Dowson A, Mullen MJ, Peatfield R, Muir K, Khan AA, Wells C, Lipscombe SL, Rees T, De Giovanni JV, Morrison WL, Hildick-Smith D, Elrington G, Hillis WS, Malik IS, Rickards A. Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation 2008;117:1397-1404.
46. Rundek T, Elkind MS, Di Tullio MR, Carrera E, Jin Z, Sacco RL, Homma S. Patent foramen ovale and migraine: a cross-sectional study from the Northern Manhattan Study (NOMAS). Circulation 2008;118:1419-1424.
47. Buzzi MG, Moskowitz MA. The pathophysiology of migraine: year 2005. J Headache Pain 2005;6:105-111.
48. Schwedt TJ, Dodick DW. Patent foramen ovale and migraine--bringing closure to the subject. Headache 2006;46:663-671.
49. Wilmshurst P, Nightingale S. The role of cardiac and pulmonary pathology in migraine: a hypothesis. Headache 2006;46:429-434.
50. Thenganatt J, Schneiderman J, Hyland RH, Edmeads J, Mandzia JL, Faughnan ME. Migraines linked to intrapulmonary right-to-left shunt. Headache 2006;46:439-443.
51. Marziniak M, Jung A, Guralnik V, Evers S, Prudlo J, Geisthoff UW. An association of migraine with hereditary haemorrhagic telangiectasia independently of pulmonary right-to-left shunts. Cephalalgia 2009;29:76-81.
52. Dutton JA, Jackson JE, Hughes JM, Whyte MK, Peters AM, Ussov W, Allison DJ. Pulmonary arteriovenous malformations: results of treatment with coil embolization in 53 patients. AJR 1995;165:1119-1125.
53. Lee DW, White RI, Jr., Egglin TK, Pollak JS, Fayad PB, Wirth JA, Rosenblatt MM, Dickey KW, Burdge CM. Embolotherapy of large pulmonary arteriovenous malformations: long-term results. Ann Thorac Surg 1997;64:930-939.
54. Remy-Jardin M, Dumont P, Brillet PY, Dupuis P, Duhamel A, Remy J. Pulmonary arteriovenous malformations treated with embolotherapy: helical CT evaluation of long-term effectiveness after 2-21-year follow-up. Radiology 2006;239:576-585.
55. White RI, Jr. Pulmonary arteriovenous malformations: how do I embolize? Tech Vasc Interv Radiol 2007;10:283-290.

56. Remy-Jardin M, Wattinne L, Remy J. Transcatheter occlusion of pulmonary arterial circulation and collateral supply: failures, incidents, and complications. Radiology 1991;180:699-705.
57. Pollak JS, Saluja S, Thabet A, Henderson KJ, Denbow N, White RI, Jr. Clinical and anatomic outcomes after embolotherapy of pulmonary arteriovenous malformations. J Vasc Interv Radiol 2006;17:35-44.
58. Barzilai B, Waggoner AD, Spessert C, Picus D, Goodenberger D. Two-dimensional contrast echocardiography in the detection and follow-up of congenital pulmonary arteriovenous malformations. Am J Cardiol 1991;68:1507-1510.
59. Feinstein JA, Moore P, Rosenthal DN, Puchalski M, Brook MM. Comparison of contrast echocardiography versus cardiac catheterization for detection of pulmonary arteriovenous malformations. Am J Cardiol 2002;89:281-285.
60. Lee WL, Graham AF, Pugash RA, Hutchison SJ, Grande P, Hyland RH, Faughnan ME. Contrast echocardiography remains positive after treatment of pulmonary arteriovenous malformations. Chest 2003;123:351-358.
61. Nanthakumar K, Graham AT, Robinson TI, Grande P, Pugash RA, Clarke JA, Hutchison SJ, Mandzia JL, Hyland RH, Faughnan ME. Contrast echocardiography for detection of pulmonary arteriovenous malformations. Am Heart J 2001;141:243-246.
62. Faughnan ME, Palda VA, Garcia-Tsao G, Geisthoff UW, McDonald J, Proctor DD, Spears J, Brown DH, Buscarini E, Chesnutt MS, Cottin V, Ganguly A, Gossage JR, Guttmacher AE, Hyland RH, Kennedy SJ, Korzenik J, Mager JJ, Ozanne AP, Piccirillo JF, Picus D, Plauchu H, Porteous ME, Pyeritz RE, Ross DA, Sabba C, Swanson K, Terry P, Wallace MC, Westermann CJ, White RI, Young LH, Zarrabeitia R. International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia. J Med Genet 2009.
63. Weyman AE. Miscellaneous echocardiographic techniques I: Contrast echocardiography. Principles and practice of echocardiography. Second ed. Lea & Febiger, 1994:302-326.
64. Meltzer RS, Tickner EG, Sahines TP, Popp RL. The source of ultrasound contrast effect. J Clin Ultrasound 1980;8:121-127.
65. Meltzer RS, Tickner EG, Popp RL. Why do the lungs clear ultrasonic contrast? Ultrasound Med Biol 1980;6:263-269.

66. Soliman OI, Geleijnse ML, Meijboom FJ, Nemes A, Kamp O, Nihoyannopoulos P, Masani N, Feinstein SB, Ten Cate FJ. The use of contrast echocardiography for the detection of cardiac shunts. Eur J Echocardiogr 2007;8:S2-12.
67. Shub C, Tajik AJ, Seward JB, Dines DE. Detecting intrapulmonary right-to-left shunt with contrast echocardiography. Observations in a patient with diffuse pulmonary arteriovenous fistulas. Mayo Clin Proc 1976;51:81-84.
68. Woods TD, Patel A. A critical review of patent foramen ovale detection using saline contrast echocardiography: when bubbles lie. J Am Soc Echocardiogr 2006;19:215-222.
69. Zukotynski K, Chan RP, Chow CM, Cohen JH, Faughnan ME. Contrast echocardiography grading predicts pulmonary arteriovenous malformations on CT. Chest 2007;132:18-23.
70. Ahmed S, Nanda NC, Nekkanti R, Yousif AM. Contrast transesophageal echocardiographic detection of a pulmonary arteriovenous malformation draining into left lower pulmonary vein. Echocardiography 2003;20:391-394.
71. Attaran RR, Ata I, Kudithipudi V, Foster L, Sorrell VL. Protocol for optimal detection and exclusion of a patent foramen ovale using transthoracic echocardiography with agitated saline microbubbles. Echocardiography 2006;23:616-622.
72. Freeman JA, Woods TD. Use of saline contrast echo timing to distinguish intracardiac and extracardiac shunts: failure of the 3- to 5-beat rule. Echocardiography 2008;25:1127-1130.
73. Naqvi TZ, Nagai T, Atar S, Siegel RJ. Early appearance of echo-contrast simulating an intracardiac shunt in a patient with liver cirrhosis and intrapulmonary shunting. J Am Soc Echocardiogr 2002;15:379-381.
74. Vandenbossche JL, Englert M. Effects of respiration on an atrial septal aneurysm of the fossa ovale shown by echographic study. Am Heart J 1982;103:922-923.
75. Strunk BL, Cheitlin MD, Stulbarg MS, Schiller NB. Right-to-left interatrial shunting through a patent foramen ovale despite normal intracardiac pressures. Am J Cardiol 1987;60:413-415.
76. Clarke NR, Timperley J, Kelion AD, Banning AP. Transthoracic echocardiography using second harmonic imaging with Valsalva manoeuvre for the detection of right to left shunts. Eur J Echocardiogr 2004;5:176-181.
77. Daniels C, Weytjens C, Cosyns B, Schoors D, De SJ, Paelinck B, Muyldermans L, Van CG. Second harmonic transthoracic echocardiography: the new reference screening method for the detection of patent foramen ovale. Eur J Echocardiogr 2004;5:449-452.

78. Kuhl HP, Hoffmann R, Merx MW, Franke A, Klotzsch C, Lepper W, Reineke T, Noth J, Hanrath P. Transthoracic echocardiography using second harmonic imaging: diagnostic alternative to transesophageal echocardiography for the detection of atrial right to left shunt in patients with cerebral embolic events. J Am Coll Cardiol 1999;34:1823-1830.

Part I

Screening for pulmonary arteriovenous malformations using transthoracic contrast echocardiography

2

Screening for pulmonary arteriovenous malformations using transthoracic contrast echocardiography: a prospective study

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Abstract

Background: Pulmonary arteriovenous malformations (PAVMs) are associated with severe neurological complications in patients with hereditary haemorrhagic telangiectasia (HHT) and therefore screening is warranted. The objective of the present study was to prospectively establish the diagnostic value of transthoracic contrast echocardiography (TTCE) as a screening technique for PAVM using chest high resolution cimpited tomography (HRCT) as the gold standard for PAVMs.

Methods: All consecutive adult patients referred for HHT screening underwent a chest HRCT (n=299), TTCE (n=281), arterial blood gas analysis (n=291), shunt fraction measurement (n=111), and chest radiography (n=296).

Results: TTCE was positive in 87 (58.8%), 12 (16.7%) and 4 (6.7%), and chest HRCT was positive in 54 (36.5%), 3 (4.2%) and zero (0) patients with a definite, possible and negative clinical diagnosis of HHT. Two patients with a negative TTCE were diagnosed with PAVMs after CT; in both cases the PAVMs were too small to be treated by embolotherapy. The sensitivity of TTCE was 97% (95% confidence interval (CI) 93.6-98.3) and negative predictive value 99% (95% CI 96.9-99.8). The other diagnostic tests showed a considerable lower diagnostic value.

Conclusion: The present prospective study shows that transthoracic contrast echocardiography has an excellent diagnostic value and can be used as an initial screening procedure for pulmonary arteriovenous malformations. The high false-positive rate of transthoracic contrast echocardiography possibly represents microscopic pulmonary arteriovenous malformations.

Introduction

Background

A pulmonary arteriovenous malformation (PAVM) is a direct communication between a pulmonary artery and pulmonary vein. This results in a right-to-left shunt (RLS) causing hypoxemia and risk for paradoxal embolism through bypassing the filtering capillary network. Complications occurring in patients with PAVM and hereditary hemorrhagic telangiectasia (HHT) are stroke (10-19%), transient ischemic attacks (6-37%), cerebral abscess (5-9%), migraine headaches, seizures, massive hemoptysis and (spontaneous) hemothorax.[1-3] Antibiotic prophylaxis prior to procedures carrying risk for bacteremia is recommended.[3-5] At least 80% of PAVMs are associated with HHT.[3] HHT is an autosomal dominant disorder characterised by vascular abnormalities varying from small telangiectases to large arteriovenous malformations. The clinical diagnosis is based on the Curaçao Criteria.[6] Based on genetic analysis HHT is divided in types 1 and 2, corresponding with mutations in the genes ENG and ACVRL1, coding for endoglin and ALK1 (activin A receptor type-like kinase) respectively.[7, 8] The prevalence of PAVM, as documented by chest HRCT, in all HHT patients is 20 to 45%.[4, 9] The PAVM prevalence differs between these two subtypes, in HHT type 1 the prevalence is 48%, whereas the prevalence in HHT type 2 is 5%.[10] PAVMs can be effectively treated with transcatheter embolotherapy which has been proven safe and effective in long-term studies.[11-18] Recently it has been proven that embolisation of PAVMs is effective in the prevention of brain abscess and ischaemic stroke if complete occlusion of all PAVMs is achieved.[5] Because of the high incidence of severe complications, early diagnosis of PAVMs, and if possible treatment, is warranted.[3, 5] Therefore, patients with HHT are routinely screened for PAVMs, even if they are asymptomatic.

Screening for PAVMs

Screening tests used for detecting PAVMs are chest radiography, arterial oxygen measurement using the 100% oxygen technique, radionuclide lung scanning, magnetic resonance imaging, pulmonary angiography, chest computed tomography (CT) and transthoracic contrast echocardiography (TTCE). Chest

radiography, arterial blood gas analysis including shunt measurement using the 100% oxygen technique and radionuclide scanning lack sensitivity and are not recommended as a single procedure for excluding PAVMs and/or RLS.[1, 3, 4] Chest CT is presently referred to as the gold standard and has shown to be even more accurate than angiography.[19] Pulmonary angiography is indicated only for endovascular treatment of PAVMs.[1] The main disadvantage of CT is radiation exposure. TTCE is a simple, widely available and easy technique which can detect RLS and differentiate between intra-cardiac and pulmonary shunting. Although there might be concern about complications resulting from paradoxical cerebral air embolism, side effects of TTCE appear to be rare.[20] Its sensitivity for detecting PAVMs has been proven excellent in mainly retrospective studies.[4, 21-24] The aim of our prospective study is to establish the role of TTCE in screening for PAVM as compared to chest CT as 'gold standard'. The current authors hypothesized that TTCE can be used as a single first screening method in which further analysis with chest CT is only recommended for patients in whom TTCE suggests a pulmonary RLS. To the current authors' knowledge, this is the first prospective study systematically examining the screening of PAVM by TTCE compared with chest CT.

Methods

Patients

In total, 317 consecutive persons (> 16 years of age) were prospectively studied who were referred for possible HHT or were family members of index cases. Screening was performed in the period between May 2004 till June 2007. Almost all patients underwent a chest radiography, arterial blood gas analysis, chest CT and TTCE in a 1-day-protocol. In addition, on the same day all patients visited a pulmonologist and an otorhinolaryngist, both experienced in HHT patients. The clinical diagnosis HHT was established according to the Curaçao criteria.[6] At least three of the following four criteria were required for a clinical diagnosis: spontaneous and recurrent epistaxis, telangiectases at characteristic sites, visceral malformations (PAVM, cerebral arteriovenous malformations, hepatic arteriovenous malformations, or gastrointestinal (GI) telangiectases); and

a first degree relative with HHT. In the presence of two criteria the diagnosis was considered 'possible', and the clinical diagnosis was rejected in the presence of one criterium.

All patients were informed by letter about the screening protocol and procedures before visiting our clinic. TTCE is part of the present authors' routine screening protocol for possible HHT patients.

Study objective

The main objective of our study was to prospectively establish the diagnostic value of TTCE as a screening technique for PAVM using chest HRCT as the gold standard.

Diagnostic tests

The arterial oxygen tension ($P_{a,}O_2$) was measured at rest, breathing room air and an additional shunt measurement breathing 100% oxygen for ≥ 15 minutes was performed if $P_{a,}O_2$ <13 kPa or >12kPa for patients younger or older than 30 years, respectively. The shunt was estimated using the equation: $Q_s/Q_t = (C_{c,O2} - C_{a,O2}) / (C_{c,O2} - C_{v,O2})$ in which Q_s/Q_t = shunt as a fraction of cardiac output, $C_{c,O2}$ = oxygen content at the end of the pulmonary capillary, $C_{a,O2}$ = oxygen content of arterial blood, and $C_{v,O2}$ = oxygen content of mixed venous blood.[25] Partial pressure of carbon dioxide is assumed to equal partial pressure of oxygen (PO_2; barometric pressure (101.3 kPa) minus carbon dioxide arterial tension minus alveolar saturated water vapour pressure ($P_{A,H2O}$)). $P_{A,H2O}$ is 6.3 kPa at a body temperature of 37°C. Haemoglobin oxygen saturation (SO_2) at the end of the pulmonary capillary is assumed to be 100%. Oxygen content (C) was calculated as follows:

Oxygen content = $(0{,}0225 \times PO_2) + (2{,}24 \times \text{Haemoglobin} \times SO_2/100)$ ml O_2 / 100 ml blood. $C_{v,O2}$ was assumed to be as defined by the following equation:

$V_{v,O2} = C_{a,O2}$ – 4.4 ml O_2 / 100 ml blood. Using the 100% oxygen method, a shunt measurement of more than 5% was considered pathological.[3, 25]

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 PAVMs

was based on the presence of a nodular opacity with both an afferent and efferent vessel. A lower limit was not employed for the size of PAVMs. CTs were scored as positive, negative and indeterminate by two independent observers (a radiologist and a pulmonologist experienced in interpreting chest HRCT for the presence of PAVMs) both blinded to the other results of the protocol. In case of disagreement between both observers, the study was considered positive for PAVM. TTCE was performed by three experienced echocardiographists. An intravenous line (18-gauge) was preferentially placed in the right anticubital vein. Two 10-mL syringes were connected, one filled with 8 mL saline solution and 1 mL of air. The other syringe was used to draw 1mL of blood and mixed with the saline-filled syringe by reverse flushing, creating agitated saline (microbubbles). The patient was positioned in the left lateral decubitus position and 10 ml agitated saline was injected while projecting the four-chamber apical view without a Valsalva manoeuvre.[21] TTCE was considered positive for a pulmonary right-to-left shunt if (one or more) microbubbles appeared in the left atrium after four cardiac cycles.[3] The results were interpreted by a cardiologist without knowledge of the other test results and scored as positive, negative or indeterminate (no discrimination possible between patent foramen ovale and pulmonary RLS) or inappropriate for interpretation because of poor quality. Patients in whom the difference between an intracardiac and pulmonary shunt could not be made were considered positive for purpose of the analysis. A physician was present at all TTCE studies and checked for possible complications resulting from paradoxical air embolism. Chest CT was referred to as the gold standard for detecting PAVMs in the present study.

Statistical analysis

Descriptive statistics were used to describe patient characteristics. Continuous variables with normal distribution were presented as mean ± SD. Median (range) was used when normal distribution was absent. The sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) with their 95% confidence intervals (CI) were calculated for each screening test or a combination of two different tests, using the chest CT as the gold standard.

Results

Study population

In total 317 people were screened for possible HHT. From this group, 299 (94%) persons underwent chest CT scanning, which was regarded as the gold standard for detecting PAVMs. A total of 18 patients refused a chest CT or had a contraindication (*e.g.* pregnancy). Of all patients who underwent chest CT, chest radiography was performed in 296 (99%), arterial blood gas analysis in 291 (97%), and shunt measurement using the 100% oxygen method in 111 patients (37%). TTCE was performed in 283 patients (95%); in 16 patients placement of an *i.v.* line failed or was refused. In two patients, TTCE images could not be interpreted because of poor quality. A clinical diagnosis of HHT was definite, possible and rejected in 155 (51.8%), 80 (26.8%) and 64 (21.4%) patients, respectively. These data are summarised in table 1. The study population available for analysis (both CT and TTCE) consisted of 281 patients with a mean age of 44±15 yrs, of whom 61% were female.

Diagnostic value of screening methods

A chest CT was positive for PAVM in 60 (20,1%) patients, negative in 238 (79,6%) and indeterminate in 1 patient (0,3%). The κ coefficient for interobserver agreement concerning chest CT was 0.83. TTCE was positive for a pulmonary RLS in 107 patients (38,1%). The sensitivity (calculations are based on 281 patients) of TTCE for detecting PAVM was 96.5% (95% CI 93.6-98.3) and NPV 98.9% (95% CI 96.9-99.8). In contrast, specificity for TTCE was only 76.8% (95% CI 71.5–81.7). In two out of 174 patients with a negative TTCE there was evidence for PAVMs on chest CT (table 2). In these two patients with a false-negative result, chest CT showed PAVMs too small for embolisation therapy (in both patients afferent and efferent vessels were ≤ 1mm with a venous sac of respectively 3mm and 4mm diameter, respectively). In one of these two patients image quality of the echocardiogram was relatively poor but was sufficient for correct interpretation. In both of these false-negative patients P_aO2 measurements were below the prespecified threshold, but in neither of them the additional 100% oxygen method showed a shunt >5% (0,6% and 1,6%, respectively).

Table 1 Baseline characteristics

	n	%
Total	299	
Female	183	61,2
Age (mean±SD)	44±15	
PAVM screening method		
HRCT	299	100
TTCE	281	94
Chest radiograph	296	99
P_aO_2	291	97.3
RLS[#]	111	37.1

Data are presented as n (%) unless otherwise stated. PAVM: pulmonary arteriovenous malformation; HRCT: high-resolution computed tomography; TTCE: transthoracic contrast echocardiography; P_aO_2 = arterial oxygen tension; RLS = right-to-left shunt; [#]: A RLS measured with the 100% oxygen method was only performed if P_aO_2 was <13 kPa or >12kPa for patients younger or older than 30 years, respectively.

Table 2. Transthoracic contrast echocardiography (TTCE) versus chest high-resolution computed tomography (HRCT)

TTCE (n)		HRCT (n) **Positive**	**Negative**	**Indeterminate[#]**	**Total**
	Positive	54	49	0	103
	Negative	2	171	1	174
	Indeterminate[*]	1	3	0	4
	Total	57	223	1	281

[#]: Chest CT showed small nodules or opacities of uncertain origin, possibly pulmonary arteriovenous malformations; [*]: TTCE was indeterminate for discrimination between an intracardiac and pulmonary shunt

Chest radiography was negative in both false-negative patients. In total, 21 (7,5%) of all patients who underwent echocardiography had signs of a cardiac RLS, of whom 2 patients met criteria for both a pulmonary and cardiac shunt. In four patients there was doubt whether the RLS was based on a pulmonary or cardiac shunt (detection of contrast material in left atrium at 4 cardiac cycles).

When combining the TTCE and P_aO_2 the sensitivity increased to 100% (95% CI 98.7-100) and the NPV increased to 100% (95% CI 98.7-100). However, the specificity and PPV decreased to 40.6% (95% CI 34.8-46.6) and 30% (95% CI 24.6-

35.6), respectively. The sensitivity, specificity, NPV, and PPV for each test and the combination of different tests is summarised in table 3.
TTCE was positive in 87 (58.8%) out of 148 patients with a definite clinical diagnosis of HHT. In four (6.7%) patients without a clinical diagnosis HHT, TTCE showed a pulmonary shunt and 12 (16.7%) patients with possible HHT also showed positive TTCE. Chest HRCT was positive in 54 (36.5%) patients with clinically confirmed HHT and was negative in all patients without HHT. In seven patients, the presence of PAVMs on chest HRCT was required as a criterium for the (definite) clinical diagnosis HHT (table 4).

Discussion

The present study shows that TTCE has an excellent NPV for the detection of PAVM. No PAVMs treatable by embolisation were missed using TTCE. Therefore, TTCE can be used as an initial screening technique for PAVM. The high false-positive rate of TTCE may, in part, represent microscopic PAVMs below the detection limit of chest HRCT. In addition, TTCE also appears to be positive in a minority of patients without HHT, suggesting this might partially reflect normal variation in the general population.

Screening for PAVMs in all possible patients with HHT is warranted because of the high incidence of neurological complications in this population. Consensus exists that all PAVMs applicable for intervention should be treated.[1] This strategy is supported by a recent study that demonstrated that no strokes or brain abscesses occurred if obliteration of all angiographically visible PAVMs was achieved.[5] Furthermore, it appeared that the risk for stroke and brain abscess was independent of the severity of PAVMs.[5] TTCE has been studied as a screening technique for PAVMs in retrospective studies.[4, 21-24] Several studies compared TTCE with pulmonary angiography as a gold standard but the numbers of patients were limited and angiography was only performed when TTCE or other screening methods were positive.[23, 24, 26]

Table 3 Diagnostic value of the different screening methods for PAVM

	n	Positive (n,%)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
TTCE	281	107* (38,1)	96.5 (93.6-98.3)	76.8 (71.581.7)	98.9 (96.9-99.8)	51.4 (45.2-57.2)
Chest radiography	296	17 (5,7)	28,3 (23.0-33.5)	100 (99.0-100)	84,9 (80.2-88.7)	100 (99.0-100)
P_aO_2	291	156 (53,6)	74,6 (69.2-79.5)	51,7 (45.6-57.4)	88,9 (84.8-92.4)	28,2 (23.1-33.7)
Shunt using 100% O2	111	36 (32,4)	77,1 (68.6-84.9)	88,2 (80.8-93.6)	89,3 (81.9-94.3)	75,0 (65.7-82.5)
TTCE and chest radiography	298	107(38,1)	96,5 (93.9-98.4)	61,2 (55.3-66.6)	97,9 (95.7-99.3)	51,4 (45.5-57.2)
TTCE and P_aO_2	281	190 (67,6)	100 (98.7-100)	40,6 (34.8-46.6)	100 (98.7-100)	30 (24.6-35.6)
TTCE and shunt using 100% O2	281	115(40,9)	96,5 (93.6-98.3)	73,2 (67.7-78.4)	98,8 (96.9-99.8)	47,8 (41.7-53.7)
Chest radiography and P_aO_2	298	157 (52,7)	75,0 (69.9-80.0)	52,9 (47.2-58.6)	89,4 (85.2-92.5)	28,7 (23.8-34.4)

Data are presented as n (%) unless otherwise stated. CI: Confidence Interval; NPV: negative predictive value; PPV: positive predictive value; TTCE: transthoracic contrast echocardiography; P_aO_2: partial arterial oxygen pressure; #: Includes 4 patients with an indeterminate shunt (no clear differentiation possible between intracardiac and pulmonary shunt, see also methods section)

Table 4 Transthoracic contrast echocardiography (TTCE) and chest high-resolution computed tomography (HRCT) *versus* clinical diagnosis of hereditary haemorrhagic telangiectasia (HHT)

		Clinical diagnosis HHT			
		Yes	No	Possible	Total
TTCE	**Positive**	87 (58.8)	4 (6.7)	12 (16.7)	103
	Negative	59 (39.9)	55 (90)	60 (83.3)	174
	Indeterminate	2 (1.3)	2 (3.3)	0	4
	Total	148	61	72	281
HRCT	**Positive**	54 (36.5) #	0	3 (4.2)	57
	Negative	94 (63.5)	61 (100)	68 (94.4)	223
	Indeterminate	0	0	1 (1.4)	1
	Total	148	61	72	281

Data are presented as N (%) unless otherwise stated. This table is based on the population screened with both a TTCE and chest HRCT; #: In seven out of 54 patients a definite diagnosis of HHT was based on three Curaçao criteria, requiring a pulmonary arteriovenous malformation on chest HRCT as a diagnostic criterion

Therefore, true sensitivity and specificity values remain unknown. Cottin *et al*. made an important contribution to the literature on screening for PAVMs in HHT patients. They retrospectively studied 105 HHT patients with TTCE using chest CT and/or pulmonary angiography as a reference. TTCE proved to have a senstivity and predictive value for a negative test result of 93%.[4] TTCE has been proposed as an initial screening test in HHT patients.[4, 24, 26, 27] Chest CT is regarded as the current gold standard for detecting (treatable) PAVMs.

In the current prospective study, the diagnostic value of TTCE was evaluated in comparison with chest CT as a gold standard in a 1-day protocol in almost 300 subjects. For TTCE, a sensitivity of 97% and a predictive value for a negative test result of 99% was found. In two patients TTCE was false-negative. In both these patients chest CT showed PAVMs that were too small for embolisation therapy. Importantly, therefore, no treatable PAVMs were missed by TTCE. In the present authors' clinic, antibiotic prophylaxis is advised prior to nonsterile procedures in HHT patients, unless a RLS is excluded by TTCE. Consequently, when using TTCE as an initial screening method in the present population only two patients (<1%) would have been incorrectly denied antibiotic prophylaxis to prevent cerebral abscess. These two patients met all four Curaçao criteria.

As expected, the combination of TTCE with chest radiography did not improve NPV or sensitivity.

The combination of TTCE with $P_{a'}O_2$ measurements increased both the sensitivity and NPV to 100%. Patients screened for PAVMs in the present study underwent a $P_{a'}O_2$ measurement; shunt measurement was performed if $P_{a'}O_2$ was below our prespecified cut-off value. Both patients with false-negative TTCE appeared to have a low $P_{a'}O_2$ (explaining the 100% sensitivity and NPV when combining TTCE and $P_{a'}O_2$ measurement) but subsequent shunt measurement was within normal limits. Therefore it seems unlikely that pulmonary shunting caused the low $P_{a'}O_2$ in these patients. As a consequence, the current authors do not think it is justified to conclude that addition of $P_{a'}O_2$ measurement to TTCE improves diagnostic accuracy. A sensitivity for a shunt measurement of 77% and a predictive value for

a negative test result of 89% were found. However, it should be taken into account that shunt measurement was only performed in case of a low $P_{a'}O_2$ so a lower false-negative rate might be expected and these results should not be considered as representative for for the present study population overall. The diagnostic value of this screening test compares negatively to other studies of which a pooled analysis showed a sensitivity of 97,5%.[3] An explanation for this difference could be the fact that those data were only based on PAVMs large enough for embolisation therapy. Cottin *et al*. found a considerably lower sensitivity and negative predictive value (68% and 76%, respectively) but performed shunt measurement in all patients.[4]

In the current authors' opinion chest radiography, arterial blood gas analysis and shunt fraction measurement lack diagnostic value as screening methods for PAVM or RLS. However, shunt fraction measurement on 100% oxygen can be of value in the assessment of the severity of RLS, and follow-up after embolotherapy.

When a screening algorithm with TTCE as an initial screening technique (only followed by chest CT if positive) is followed it is of particular importance none of the treatable PAVMs are overlooked. No PAVMs suitable for embolotherapy were present in the current two patients with false-negative TTCE. In 52 (23,2%) patients, TTCE was positive in the absence of PAVMs on chest CT. In contrast, 172 (76,8%) patients did not have signs of pulmonary RLS and would not undergo chest CT in such a screening algorithm. In the present authors' hospital, this reduces impact on hospital resources and logistics given the fact that TTCE is a simple procedure that consumes little time and expense, but this depends on local facilities and logistics. In only two patients the acoustic window was inadequate for interpretation. However, inability to interpret and correctly judge TTCE outside specialised centres will probably be increased. The latter may reduce the sensitivity of TTCE. No adverse events were experienced as a result of TTCE. However, there may be concern about the risk for paradoxical air embolism. Data about cerebral air embolism are scarce. A survey of 363 physicians performing contrast echocardiography revealed neurologic and respiratory side-effects in 0.062% of all procedures, and no residual complications were observed.[20] Other

literature regarding this subject is predominantly based on case reports.[28-30] In the current study, 1mL of added air was used, but lower volumes of air have become customary in some centres to minimise risk of air embolism. Current guidelines for TTCE still recommend the use of 1mL of air.[31]

Concerns have been raised about the high false-positive rate and, therefore, high costs of TTCE as a screening technique.[27] False-positive might not be an accurate term because a pulmonary RLS seen on TTCE in the absence of PAVMs on chest CT might still represent microscopic PAVMs or telangiectases below the detection limit of CT scanning. This has also been suggested by a study which showed that TTCE frequently remains positive after embolotherapy of PAVMs, even if no residual PAVMs were seen on angiography.[23] Furthermore, microscopic PAVMs were histologically proven in a child with HHT and a pulmonary shunt on echocardiography but without visible PAVMs on chest CT, and in a report of two patients in whom this diagnosis was proven by autopsy.[32, 33] However, the present study also shows that TTCE is positive in 6.7% of patients without a clinical diagnosis of HHT, suggesting that positive TTCE studies, in part, reflect normal variation in the general population.

The influence of postural changes on pulmonary RLS in patients with PAVM (orthodeoxia) has been described in several studies.[17, 34-36] However, Cottin *et al*. did not find a different diagnostic value of TTCE in patients in whom echocardiography was performed in both the supine and upright position.[4] The current authors hypothesise that postural changes only influence the degree of shunting and not the diagnosis of a pulmonary RLS *per se.*

When there is evidence for a PAVM or a pulmonary RLS, antibiotic prophylaxis is recommended prior to procedures carrying risk for bacteremia.[3, 4] The importance of antibiotic prophylaxis in HHT patients was suggested by Shovlin *et al.* who indentified preceding events known to be associated with bacteremia in a high proportion of patients with a brain abscess.[5] However, it is not known what impact antibiotic prophylaxis in patients with microscopic PAVMs might have on neurological sequelae. Data about the follow-up of patients with positive TTCE are

lacking. There might be concern that possible microscopic PAVMs could evolve to treatable PAVMs and, therefore, follow-up to detect an opportunity for treatment seems justified. In addition to interpreting contrast echocardiography for the presence / absence of a pulmonary shunt, grading of TTCE has been shown to be able to predict the presence of PAVM on chest CT.[37] This modality might further improve the diagnostic value of TTCE.

Given the results of the current prospective study of almost 300 patients, it can be concluded that a screening algorithm for pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia patients can be based on initial transthoracic contrast echocardiography, because of its excellent sensitivity and predictive value for a negative test result. If there is evidence for a pulmonary right-to-left shunt on echocardiography, a chest computed tomography is performed, in order to detect pulmonary arteriovenous malformations that can be treated by embolisation. Obviously, the preferred screening strategy also depends on local institutional logistics and experience.

Reference List

1. Cottin V, Dupuis-Girod S, Lesca G, Cordier JF. Pulmonary vascular manifestations of hereditary hemorrhagic telangiectasia (rendu-osler disease). Respiration 2007;74:361-378.
2. Cottin V, Chinet T, Lavole A, Corre R, Marchand E, Reynaud-Gaubert M, Plauchu H, Cordier JF. Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: a series of 126 patients. Medicine (Baltimore) 2007;86:1-17.
3. Gossage JR, Kanj G. Pulmonary arteriovenous malformations. A state of the art review. Am J Respir Crit Care Med 1998;158:643-661.
4. Cottin V, Plauchu H, Bayle JY, Barthelet M, Revel D, Cordier JF. Pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. Am J Respir Crit Care Med 2004;169:994-1000.
5. Shovlin CL, Jackson JE, Bamford KB, Jenkins IH, Benjamin AR, Ramadan H, Kulinskaya E. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. Thorax 2008;63:259-266.
6. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, Kjeldsen AD, Plauchu H. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000;91:66-67.
7. McAllister KA, Grogg KM, Johnson DW, Gallione CJ, Baldwin MA, Jackson CE, Helmbold EA, Markel DS, McKinnon WC, Murrell J, . Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. Nat Genet 1994;8:345-351.
8. Berg JN, Gallione CJ, Stenzel TT, Johnson DW, Allen WP, Schwartz CE, Jackson CE, Porteous ME, Marchuk DA. The activin receptor-like kinase 1 gene: genomic structure and mutations in hereditary hemorrhagic telangiectasia type 2. Am J Hum Genet 1997;61:60-67.
9. Shovlin CL, Letarte M. Hereditary haemorrhagic telangiectasia and pulmonary arteriovenous malformations: issues in clinical management and review of pathogenic mechanisms. Thorax 1999;54:714-729.
10. Post MC, Letteboer TG, Mager JJ, Plokker TH, Kelder JC, Westermann CJ. A pulmonary right-to-left shunt in patients with hereditary hemorrhagic telangiectasia is associated with an increased prevalence of migraine. Chest 2005;128:2485-2489.

11. Sabba C, Pasculli G, Lenato GM, Suppressa P, Lastella P, Memeo M, Dicuonzo F, Guant G. Hereditary hemorrhagic telangiectasia: clinical features in ENG and ALK1 mutation carriers. J Thromb Haemost 2007;5:1149-1157.
12. White RI, Jr., Pollak JS, Wirth JA. Pulmonary arteriovenous malformations: diagnosis and transcatheter embolotherapy. J Vasc Interv Radiol 1996;7:787-804.
13. White RI, Jr., Lynch-Nyhan A, Terry P, Buescher PC, Farmlett EJ, Charnas L, Shuman K, Kim W, Kinnison M, Mitchell SE. Pulmonary arteriovenous malformations: techniques and long-term outcome of embolotherapy. Radiology 1988;169:663-669.
14. Lee DW, White RI, Jr., Egglin TK, Pollak JS, Fayad PB, Wirth JA, Rosenblatt MM, Dickey KW, Burdge CM. Embolotherapy of large pulmonary arteriovenous malformations: long-term results. Ann Thorac Surg 1997;64:930-939.
15. Remy-Jardin M, Dumont P, Brillet PY, Dupuis P, Duhamel A, Remy J. Pulmonary arteriovenous malformations treated with embolotherapy: helical CT evaluation of long-term effectiveness after 2-21-year follow-up. Radiology 2006;239:576-585.
16. Haitjema TJ, Overtoom TT, Westermann CJ, Lammers JW. Embolisation of pulmonary arteriovenous malformations: results and follow up in 32 patients. Thorax 1995;50:719-723.
17. Dutton JA, Jackson JE, Hughes JM, Whyte MK, Peters AM, Ussov W, Allison DJ. Pulmonary arteriovenous malformations: results of treatment with coil embolization in 53 patients. AJR Am J Roentgenol 1995;165:1119-1125.
18. Mager JJ, Overtoom TT, Blauw H, Lammers JW, Westermann CJ. Embolotherapy of pulmonary arteriovenous malformations: long-term results in 112 patients. J Vasc Interv Radiol 2004;15:451-456.
19. Remy J, Remy-Jardin M, Wattinne L, Deffontaines C. Pulmonary arteriovenous malformations: evaluation with CT of the chest before and after treatment. Radiology 1992;182:809-816.
20. Bommer WJ, Shah PM, Allen H, Meltzer R, Kisslo J. The safety of contrast echocardiography: report of the Committee on Contrast Echocardiography for the American Society of Echocardiography. J Am Coll Cardiol 1984;3:6-13.
21. Barzilai B, Waggoner AD, Spessert C, Picus D, Goodenberger D. Two-dimensional contrast echocardiography in the detection and follow-up of congenital pulmonary arteriovenous malformations. Am J Cardiol 1991;68:1507-1510.

22. Feinstein JA, Moore P, Rosenthal DN, Puchalski M, Brook MM. Comparison of contrast echocardiography versus cardiac catheterization for detection of pulmonary arteriovenous malformations. Am J Cardiol 2002;89:281-285.
23. Lee WL, Graham AF, Pugash RA, Hutchison SJ, Grande P, Hyland RH, Faughnan ME. Contrast echocardiography remains positive after treatment of pulmonary arteriovenous malformations. Chest 2003;123:351-358.
24. Nanthakumar K, Graham AT, Robinson TI, Grande P, Pugash RA, Clarke JA, Hutchison SJ, Mandzia JL, Hyland RH, Faughnan ME. Contrast echocardiography for detection of pulmonary arteriovenous malformations. Am Heart J 2001;141:243-246.
25. Mager JJ, Zanen P, Verzijlbergen F, Westermann CJ, Haitjema T, van HG, Lammers JW. Quantification of right-to-left shunt with (99m)Tc-labelled albumin macroaggregates and 100% oxygen in patients with hereditary haemorrhagic telangiectasia. Clin Sci (Lond) 2002;102:127-134.
26. Kjeldsen AD, Oxhoj H, Andersen PE, Elle B, Jacobsen JP, Vase P. Pulmonary arteriovenous malformations: screening procedures and pulmonary angiography in patients with hereditary hemorrhagic telangiectasia. Chest 1999;116:432-439.
27. Gossage JR. The role of echocardiography in screening for pulmonary arteriovenous malformations. Chest 2003;123:320-322.
28. Christin F, Bouffard Y, Rossi R, Delafosse B. Paradoxical symptomatic air embolism after saline contrast transesophageal echocardiography. Echocardiography 2007;24:867-869.
29. Holcomb BW, Loyd JE, Byrd BF, III, Wilsdorf TT, Casey-Cato T, Mason WR, Robbins IM. Iatrogenic paradoxical air embolism in pulmonary hypertension. Chest 2001;119:1602-1605.
30. Srivastava TN, Undesser EK. Transient ischemic attack after air contrast echocardiography in patients with septal aneurysm. Ann Intern Med 1995;122:396.
31. Attaran RR, Ata I, Kudithipudi V, Foster L, Sorrell VL. Protocol for optimal detection and exclusion of a patent foramen ovale using transthoracic echocardiography with agitated saline microbubbles. Echocardiography 2006;23:616-622.
32. Mache CJ, Gamillscheg A, Popper HH, Haworth SG. Early-life pulmonary arterial hypertension with subsequent development of diffuse pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia type 1. Thorax 2008;63:85-86.

33. HALES MR. Multiple small arteriovenous fistulae of the lungs. Am J Pathol 1956;32:927-943.
34. Terry PB, White RI, Jr., Barth KH, Kaufman SL, Mitchell SE. Pulmonary arteriovenous malformations. Physiologic observations and results of therapeutic balloon embolization. N Engl J Med 1983;308:1197-1200.
35. Thompson RD, Jackson J, Peters AM, Dore CJ, Hughes JM. Sensitivity and specificity of radioisotope right-left shunt measurements and pulse oximetry for the early detection of pulmonary arteriovenous malformations. Chest 1999;115:109-113.
36. Ueki J, Hughes JM, Peters AM, Bellingan GJ, Mohammed MA, Dutton J, Ussov W, Knight D, Glass D. Oxygen and 99mTc-MAA shunt estimations in patients with pulmonary arteriovenous malformations: effects of changes in posture and lung volume. Thorax 1994;49:327-331.
37. Zukotynski K, Chan RP, Chow CM, Cohen JH, Faughnan ME. Contrast echocardiography grading predicts pulmonary arteriovenous malformations on CT. Chest 2007;132:18-23.

3

Grading of pulmonary right-to-left shunt with transthoracic contrast echocardiography: does it predict the indication for embolotherapy?

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Abstract

Rationale: Pulmonary arteriovenous malformations (PAVMs) are associated with severe neurological complications in patients with hereditary hemorrhagic telangiectasia (HHT). Therefore, screening is warranted. Transthoracic contrast echocardiography (TTCE) can effectively detect pulmonary right-to-left shunt (RLS).

Objectives: To determine prospectively the predictive value of TTCE grading to detect PAVMs on high-resolution CT (HRCT) scans of the chest and the indication for embolotherapy.

Methods: Three hundred seventeen patients, referred for possible HHT, were screened for PAVMs. Patients who underwent both chest HRCT scanning and TTCE were included in the study (n=281). For the purposes of this study we used a 3-point grading scale, and shunt grades 3 and 4 according to the classification model of Barzilai et al were combined. Embolotherapy was performed of all PAVMs judged large enough for treatment.

Results: Echocardiographic criteria for a pulmonary RLS were present in 105 (41%) patients [mean (±SD) age, 43.7 ± 15.7 years; female gender, 63%). Chest HRCT scan findings were positive in 55 (52%) patients in this group. The positive predictive value of shunt grade for the presence of PAVMs on chest HRCT scans was 22.9% for grade 1 (n=35), 34.8% for grade 2 (n=23) and 83.0% for grade 3 (n=47), respectively. None of the patients with PAVMs seen on chest HRCT and a TTCE grade 1 (n=8) or 2 (n=8) were candidates for embolotherapy. Of 39 patients with TTCE grade 3 and PAVMs on chest HRCT, 26 (67%) underwent embolotherapy.

Conclusion: An increased echocardiographic shunt grade correlates with an increased probability of PAVMs seen on chest HRCT scans. Only patients with a TTCE grade 3 displayed PAVMs on chest HRCT scans that were large enough for embolotherapy.

Introduction

Pulmonary arteriovenous malformations (PAVM) are abnormal communications between pulmonary arteries and pulmonary veins. Complications occurring due to the presence of PAVM may be life-threatening and are often neurological due to paradoxical embolism in absence of a filtering capillary network.[1-3] PAVMs result in a right-to-left shunt (RLS), possibly causing hypoxemia and dyspnea on exertion. It is estimated that at least 80% of PAVMs are associated with hereditary hemorrhagic telangiectasia (HHT). HHT is an autosomal dominant disorder characterized by vascular abnormalities varying from small telangiectases to large arteriovenous malformations, predominantly in the brain, liver, and lungs. The clinical diagnosis of HHT is based on the Curaçao criteria.[4] Using chest CT scanning for PAVM screening, the overall prevalence of PAVM in patients with HHT is about 40%.[5] The prevalence of PAVMs tends to be higher in HHT type 1 than in HHT type 2 (48% vs 5%, respectively).[5] Rather than showing the presence of PAVMs as on chest CT scans, transthoracic contrast echocardiography (TTCE) tends to show a higher incidence of pulmonary RLS in HHT patients.[6, 7] Because of the high prevalence of PAVMs, its potentially severe consequences in HHT-affected patients, and the possibility for effective treatment[8, 9], systematic screening for PAVMs in all HHT patients is warranted. Several screening methods are available. Chest CT scanning is currently regarded as the "gold standard". However, a disadvantage of this technique is radiation exposure. TTCE is an alternative screening method. TTCE is a simple, minimally invasive and widely available technique that can effectively detect pulmonary RLS. Its diagnostic value has been proven excellent in retrospective studies.[6, 7, 10-12] There is a tendency towards the use of TTCE as a single first screening method only followed by chest CT scanning if findings are positive for a pulmonary RLS in order to establish the possibility for treatment.[7, 11, 13, 14] To increase the usefulness of TTCE as a screening technique for PAVMs, an echocardiographic grading system has been proposed.[10] Patients with larger shunts tended to have larger or multiple PAVMs. Recently, a retrospective study was performed to validate such a strategy.[15] Shunt grade on echocardiography proved to predict the presence of PAVM on chest CT scans. However, chest CT scanning remains obligatory to evaluate the opportunity for

embolotherapy. Therefore, it might be of help if echocardiographic shunt grading could predict not only the presence of PAVM on chest CTscans, but also the indication for treatment.

The aim of our prospective study was to determine the predictive value of shunt grade on TTCE for the presence of PAVMs on CT scans and for the indication whether or not to treat these PAVMs, to further increase the diagnostic value of TTCE as an initial screening technique in HHT patients.

Methods

Study population

In the period from May 2004 till June 2007, 317 consecutive persons were screened for possible HHT. Persons were screened as family members of patients with clinically or genetically confirmed HHT (index cases). All persons were routinely screened for the presence of PAVMs, intentionally with both chest HRCT scanning and TTCE with shunt grade measurement on the same day. Of the 317 persons, chest HRCT scanning was performed in 299; 18 persons refused a chest HRCT scan or had a contraindication (*eg*, pregnancy). Of these 299 persons, 283 underwent TTCE; in 16 patients placement of an IV line failed or was refused. Therefore, 283 persons underwent both TTCE and chest HRCT scanning and were available for analysis. All persons provided written informed consent, and the hospital review board approved the study.

TTCE

TTCE was peformed by placing an IV line 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, one 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 decubitus position and 10 mL of agitated saline was injected while projecting the four-chamber apical view without a Valsalva manoeuvre. TTCE was considered positive for a pulmonary RLS if microbubbles appeared in the left atrium after four cardiac cycles. When contrast was present in the left atrium within <4 cardiac

cycles, it was considered an intracardiac shunt. The results, interpreted by two independent echocardiographers unaware of the outcome of the CT scan, were scored as positive, negative, or indeterminate for distinction between the patent foramen ovale (PFO) and pulmonary RLS or inappropriate for interpretation because of poor quality. Opacification of the left ventricle was graded as 1 (maximum of 30 microbubbles in left ventricle), 2 (30-100 microbubbles in left ventricle), or 3 (>100 microbubbles in left ventricle). This division was based on the maximum number of microbubbles counted in one still-frame. These different shunt grades probably correspond with the divison into minimal, moderate and extensive (without endocardial outlining) shunts used in previous studies.[10, 15] We did not discern an extensive echocardiographic shunt with endocardial outlining (classified as a shunt grade 4 in previous studies), which was combined with a shunt grade 3 in our study. Patients in whom there was doubt between an intracardiac and extracardiac shunt were considered as positive for PAVMs for purpose of our analysis.

Chest CT

HRCT scanning (Philips Medical Systems, Best, the Netherlands) of the chest was performed without contrast using the single breath-hold technique with a slice thickness of 1 mm. Identification of PAVM was based on the presence of a nodular opacity with both an afferent and efferent vessel. CT scans were scored as positive, negative, and indeterminate by two independent observers, both blinded to the results of the TTCE.

Embolotherapy

PAVMs seen on chest CT with a feeding vessel diameter ≥ 3 mm were considered suitable for endovascular vaso-occlusion. When the feeding artery was <3 mm in diameter, treatment decisons were left to the judgement of the interventional radiologist and the clinical risk of complications like hematothorax. Transcatheter embolotherapy was performed using detachable stainless steel coils and, since 2004, also endovascular plugs.

Statistical analysis

Descriptive statistics were used to describe patients' characteristics. Continuous variables with normal distribution were presented as mean ± SD. Median with range was used when normal distribution was absent. The positive predictive value for each TTCE grade was calculated using chest CT as a reference. The Mantel-Haenszel χ^2 test was used to determine if there was a significant association between echocardiographic shunt grade and the presence of PAVMs on chest HRCT. Statistics were performed using a statistical software package (SPSS, version 13.0; SPSS Inc., Chicago, IL).

Results

Two-hundred eighty-three patients underwent both contrast echocardiography with shunt grade measurement and chest HRCT scanning. In two patients, echocardiographic image quality was too poor for adequate interpretation. Therefore, 281 patients could be included in our study (mean age, 44±15 years; female gender, 61%). In 22 patients (8%) there was evidence of an intracardiac shunt (PFO) on echocardiography. None of the patients with a PFO were diagnosed with PAVMs on CT scans. In three patients, no clear distinction was possible between an extracardiac and intracardiac shunt. In one of these patients, there was evidence of a PAVM on CT. Contrast echocardiography was positive for a pulmonary RLS in 105 patients (37.4%; mean age, 43.7 ± 15.7 years; female gender, 63%). PAVMs were visible on chest HRCT scans in 52% (n=55) of patients with a pulmonary RLS. Table 1 summarizes these data.

Table 1 Transthoracic contrast echocardiography grade (TTCE) grade vs pulmonary arteriovenous malformations (PAVMs) on chest computed tomography (CT) scans

		PAVM on chest CT (n)		Total
		-	+	
TTCE grade	**1**	27	8	35
	2	15	8	23
	3	8	39	47
Total		50	55	105

Data are presented as n (%) unless otherwise stated ; -: negative; +: positive

Table 2 Number of patients and positive predictive value (PPV) for transthoracic contrast echocardiography (TTCE) grade [#]

TTCE grade	No. of patients (%)	PPV	95% CI
1	35 (33.3)	0.23	0.10 – 0.40
2	23 (21.9)	0.35	0.16 – 0.57
3	47 (44.8)	0.83	0.69 – 0.92

CI: confidence interval; [#] Echocardiographic shunt grade was significantly associated with the presence of PAVMs on HRCT ($p < 0.0001$ for trend).

Pulmonary RLS grade 1 was diagnosed in 35 patients (33.5%), RLS grade 2 was diagnosed in 23 patients (21.9%), and RLS grade 3 was diagnosed in 47 patients (44.8%). The PPV of shunt grade measurement for the presence of PAVMs on chest HRCT scans was 22.9% for grade 1, 34.8% for grade 2, and 83.0% for grade 3, respectively. These data are summarized in table 2. Echocardiographic shunt grade was significantly associated with the presence of PAVMs on HRCT scans ($p < 0.0001$ for trend).

Of the patients with PAVMs seen on chest HRCT scans, none with a TTCE grade 1 (n=8) or 2 (n=8) underwent embolotherapy because PAVMs were too small for endovascular treatment. Of 39 patients with TTCE grade 3 and PAVMs on chest CT, 26 (67%) underwent transcatheter vaso-occlusion. These data are shown in table 3.

The κ coefficient for interobserver agreement concerning TTCE grade was 0.85.

Table 3 Number of patients who underwent embolotherapy for each transthoracic contrast echocardiography (TTCE) grade

TTCE grade	PAVM on chest CT scan	Embolotherapy
1	8	0
2	8	0
3	39	26 (67)

Data are presented as n (%) unless otherwise stated PAVM: pulmonary arteriovenous malformation

Discussion

PAVMs are associated with possibly severe, predominantly neurological, complications. Because of these serious complications, treatment of PAVMs is indicated, even in asymptomatic patients.[16] Therefore, in persons with possible HHT, screening for PAVMs is routinely performed. Retrospective studies have shown that TTCE has a good diagnostic value for detecting PAVMs on chest CT scans.[6, 7, 10-12] A good correlation between echocardiographic shunt grade and probability of PAVM on chest CT was shown in a retrospective study.[15] In our prospective study, we also found an increase in the PPV with larger shunt grades for diagnosing PAVMs on chest CT. Furthermore, only in patients with TTCE grade 3 were the PAVMs on chest CT scans large enough for subsequent embolotherapy.

The shunt grading measurement used in previous studies was based on a classification model proposed by Barzilai et al.[10] This classification relies on the relative opacification of the left ventricle with microbubbles on a scale of 1 to 4. On this scale grade 1 means minimal; grade 2, moderate; grade 3, extensive opacification without outlining the endocardium; and grade 4, extensive opacification with clear endocardial definition. A disadvantage of this classification model is the absence of objective characteristics to differentiate between minimal, moderate and extensive shunts. Therefore, such a strategy is susceptible for subjective interpretation. However, good interobserver agreement seems possible using this model.[15] Furthermore, the distinction between grade 3 and 4 shunts can be rather difficult in clinical practice because, on our opinion, there is not always a clear cutoff point between the presence and absence of endocardial definition. Because of these constraints we have chosen to use a model based on the maximum number of micro-bubbles visible in the left ventricle (in one still-frame). Using cutoff points of 30 and 100 microbubbles we discern three shunt grades (see methods section). In practice, this means that the grade 4 as described by Barzilai, is included in our grade 3. We found a high inter observer agreement with a Kappa coefficient of 0.85.

Our results show an increased probability of detecting PAVMs on chest CT with a higher TTCE grade. Most patients with pulmonary RLS grade 1 or 2 appeared not

to have a PAVM on chest CT (table 1). A shunt with the maximal shunt grade has a PPV of 0.83, which means that only 17% of patients with a grade 3 intrapulmonary shunt do not have PAVMs on chest CT scans. Zukotynski and colleagues found a PPV of 100% for a grade 4 shunt using a 4 scale classification model.[15] So, in their study the presence of clear endocardial outlining could predict the presence of PAVMs on chest CT with certainty. Even with such a high predictive value of a high-grade pulmonary RLS on TTCE, chest CT scans remain obligatory to guide treatment decisions. Our study shows that, using a TTCE grading system, it is possible to predict the necessity of endovascular treatment. None of the patients with a pulmonary shunt grade 1 or grade 2 appeared to have PAVMs large enough for subsequent embolotherapy. Hence TTCE grading may make it possible to discern insignificant from treatable PAVMs, which is of particular importance in clinical practice. The results suggest that in patients with a low pulmonary shunt grade, a CT scan might be withheld, whereas patients with a shunt grade 3 should be referred for a CT scan to evaluate if PAVMs are present and suitable for treatment. However, given the serious impact of complications from a missed treatable PAVM, further data are warranted before discontinuing chest CT scanning in the initial screening for patients with PAVMs and a low pulmonary shunt grade on TTCE.

In accordance with our findings, Zukotynski et al. showed that the majority of patients with low-grade shunts (grade 1 or 2) had no PAVMs seen on chest CT. These so-called false-positive echocardiographic findings probably represent microscopic PAVMs or telangiectasia below the detection limit of CT-scanning. If these intrapulmonary telangiectasia are widely present, it seems conceivable that they can cause a high-grade intrapulmonary shunt.[17] The latter could explain a PPV for the presence of PAVM on chest CT of only 0.83 despite a grade 3 shunt on contrast echocardiography. This was also suggested by a study which showed that TTCE frequently remains positive after embolotherapy of PAVMs, despite the absence of residual PAVMs on angiography.[6] When a pulmonary shunt is suggested only by echocardiography, antibiotic prophylaxis in procedures carrying risk for bacteremia is recommended. Furthermore, because of the possibility of growth of (microscopic) PAVMs we recommend follow-up of these patients with supposedly

false-positive echocardiograms in order to detect indications for treatment. These days, follow-up is performed with chest HRCT scanning, which means that often young people undergo numerous scans in their lives with the concomitant radiation exposure. However, regarding the predictive value of a grade 3 pulmonary shunt for treatment possibilities, it seems conceivable that follow-up of patients with a TTCE grade 1 or 2 could be performed by contrast echocardiography. A chest HRCT would than only be indicated if the echocardiographic shunt increases. Of course, for patients with a TTCE grade 3 without visible PAVMs on chest HRCT, follow-up should still be performed with chest HRCT scanning.

Concerns have been expressed about the diagnostic accuracy in discerning an intrapulmonary RLS from a PFO.[18] Usually, the presence of contrast material in the left atrium in more than four cardiac cycles after right atrial opacification is regarded as proof for a pulmonary RLS. Less than four cardiac cycles is regarded as a PFO. PFO has a prevalence of 25% in the general population based on a large autopsy study and according to a meta-analysis of case-control studies a PFO was present in 16% of 721 control subjects using TTCE with the Valsalva manoeuvre.[19, 20] In our study, the PFO prevalence was 8%, and none of the patients with a PFO appeared to have PAVMs on chest CT. Transesophageal echocardiography (TEE) using the Valsalva manoeuvre has been propagated as the gold standard for differentiating a pulmonary from an intracardiac RLS.[18] With this technique the atria, the interatrial septum and pulmonary veins can be visualized and so clarify the origin of the RLS. TTCE with the Valsalva manoeuvre has a similar yield as contrast enhanced TEE for detecting an atrial RLS.[21-23] However, this has not been proven to discriminate the origin of the shunt. In the absence of a provocative Valsalva manoeuvre, as in our study, the sensitivity of TEE and TTCE for diagnosing a PFO decreases significantly.[24] This might explain the low rate of 8% PFOs found in our and previous PAVM screening studies. Although TEE could clarify this issue, in our opinion, it is not a preferred screening technique, because of its invasive character. In our study, none of the patients with an intracardiac RLS showed PAVMs on chest HRCT scan. Thus, defining the origin of the shunt with a TEE in patients with contrast appearance in the left atrium at 4 cardiac cycles would not have had any therapeutic implications in these patients (except

for prophylactic use of antibiotics, to prevent cerebral abscess). Nonetheless, a definite diagnosis of a PFO would discharge patients from otherwise unnecessary follow-up for possible PAVMs. Currently in our center we do not routinely perform a TEE to establish the origin of the shunt. In our opinion the absence of therapeutic consequences and patient discomfort outweigh the possible benefits for follow-up.

In conclusion, our prospective study shows that TTCE grading predicts the presence and the indication for treatment of PAVMs on chest HRCT scans. This is relevant for clinical practice because our findings imply that in patients with a low pulmonary shunt grade, chest HRCT scanning may be withheld because PAVMs in these patients are too small for embolotherapy. In addition, contrast echocardiography could also be useful for follow-up of this patient group. Given the impact of a missed treatable PAVM, our data need to be confirmed in future studies before implementing such a screening algorithm.

Acknowledgement:
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Reference List

1. Cottin V, Dupuis-Girod S, Lesca G, Cordier JF. Pulmonary vascular manifestations of hereditary hemorrhagic telangiectasia (rendu-osler disease). Respiration 2007;74:361-378.
2. Cottin V, Chinet T, Lavole A, Corre R, Marchand E, Reynaud-Gaubert M, Plauchu H, Cordier JF. Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: a series of 126 patients. Medicine (Baltimore) 2007;86:1-17.
3. Gossage JR, Kanj G. Pulmonary arteriovenous malformations. A state of the art review. Am J Respir Crit Care Med 1998;158:643-661.
4. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, Kjeldsen AD, Plauchu H. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000;91:66-67.
5. Post MC, Letteboer TG, Mager JJ, Plokker TH, Kelder JC, Westermann CJ. A pulmonary right-to-left shunt in patients with hereditary hemorrhagic telangiectasia is associated with an increased prevalence of migraine. Chest 2005;128:2485-2489.
6. Lee WL, Graham AF, Pugash RA, Hutchison SJ, Grande P, Hyland RH, Faughnan ME. Contrast echocardiography remains positive after treatment of pulmonary arteriovenous malformations. Chest 2003;123:351-358.
7. Nanthakumar K, Graham AT, Robinson TI, Grande P, Pugash RA, Clarke JA, Hutchison SJ, Mandzia JL, Hyland RH, Faughnan ME. Contrast echocardiography for detection of pulmonary arteriovenous malformations. Am Heart J 2001;141:243-246.
8. Mager JJ, Overtoom TT, Blauw H, Lammers JW, Westermann CJ. Embolotherapy of pulmonary arteriovenous malformations: long-term results in 112 patients. J Vasc Interv Radiol 2004;15:451-456.
9. White RI, Jr., Lynch-Nyhan A, Terry P, Buescher PC, Farmlett EJ, Charnas L, Shuman K, Kim W, Kinnison M, Mitchell SE. Pulmonary arteriovenous malformations: techniques and long-term outcome of embolotherapy. Radiology 1988;169:663-669.
10. Barzilai B, Waggoner AD, Spessert C, Picus D, Goodenberger D. Two-dimensional contrast echocardiography in the detection and follow-up of congenital pulmonary arteriovenous malformations. Am J Cardiol 1991;68:1507-1510.
11. Cottin V, Plauchu H, Bayle JY, Barthelet M, Revel D, Cordier JF. Pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. Am J Respir Crit Care Med 2004;169:994-1000.

12. Feinstein JA, Moore P, Rosenthal DN, Puchalski M, Brook MM. Comparison of contrast echocardiography versus cardiac catheterization for detection of pulmonary arteriovenous malformations. Am J Cardiol 2002;89:281-285.
13. Gossage JR. The role of echocardiography in screening for pulmonary arteriovenous malformations. Chest 2003;123:320-322.
14. Kjeldsen AD, Oxhoj H, Andersen PE, Elle B, Jacobsen JP, Vase P. Pulmonary arteriovenous malformations: screening procedures and pulmonary angiography in patients with hereditary hemorrhagic telangiectasia. Chest 1999;116:432-439.
15. Zukotynski K, Chan RP, Chow CM, Cohen JH, Faughnan ME. Contrast echocardiography grading predicts pulmonary arteriovenous malformations on CT. Chest 2007;132:18-23.
16. Shovlin CL, Jackson JE, Bamford KB, Jenkins IH, Benjamin AR, Ramadan H, Kulinskaya E. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. Thorax 2008;63:259-266.
17. Oliveira GH, Seward JB, Cortese DA, Dines DE. Contrast transesophageal echocardiography in the diagnosis and localization of diffuse pulmonary telangiectasias. Chest 2000;118:557-559.
18. Frazin LJ. Patent foramen ovale or pulmonary arteriovenous malformation: an appeal for diagnostic accuracy. Chest 2007;132:5-6.
19. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984;59:17-20.
20. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. Neurology 2000;55:1172-1179.
21. Clarke NR, Timperley J, Kelion AD, Banning AP. Transthoracic echocardiography using second harmonic imaging with Valsalva manoeuvre for the detection of right to left shunts. Eur J Echocardiogr 2004;5:176-181.
22. Kuhl HP, Hoffmann R, Merx MW, Franke A, Klotzsch C, Lepper W, Reineke T, Noth J, Hanrath P. Transthoracic echocardiography using second harmonic imaging: diagnostic alternative to transesophageal echocardiography for the detection of atrial right to left shunt in patients with cerebral embolic events. J Am Coll Cardiol 1999;34:1823-1830.

23. Daniels C, Weytjens C, Cosyns B, Schoors D, De SJ, Paelinck B, Muyldermans L, Van CG. Second harmonic transthoracic echocardiography: the new reference screening method for the detection of patent foramen ovale. Eur J Echocardiogr 2004;5:449-452.
24. Chen WJ, Kuan P, Lien WP, Lin FY. Detection of patent foramen ovale by contrast transesophageal echocardiography. Chest 1992;101:1515-1520.

Part II

Clinical diagnosis of hereditary haemorrhagic telangiectasia

4

Real prevalence of pulmonary right-to-left shunt according to genotype in patients with hereditary haemorrhagic telangiectasia: a transthoracic contrast echocardiography study

Chest (in press)

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Abstract

Background: transthoracic contrast echocardiography (TTCE) can detect pulmonary right-to-left shunting (RLS) and is used to screen for pulmonary arteriovenous malformations (PAVMs) in patients with hereditary haemorrhagic telangiectasia (HHT). We studied the prevalence and size of pulmonary RLS in HHT type 1, HHT type 2, and HHT negative controls, and its positive predictive value (PPV) and negative predictive value (NPV) for PAVMs that can be treated by embolotherapy.

Methods: In 343 consecutive persons, referred for possible HHT as first degree family members of index patients, a TTCE and chest CT were performed. All persons were offered genetic analysis.

Results: An HHT causing mutation was confirmed in 92 (mean age 41±15 yr; 59% female) HHT1 relatives, and in 97 (mean age 47±14 yr; 52% female) HHT2 relatives. TTCE showed a pulmonary RLS in 78 (85%) HHT1, and in 34 (35%) HHT2 related mutation carriers, respectively ($p<0.0001$). In HHT1 relatives, 29 of 53 (55%) PAVMs; and in HHT2 relatives, 3 of 17 (18%) PAVMS were treated, resulting in a PPV of TTCE for treatable PAVMs of 36.3% and 8.3%, respectively. The accompanying NPV was 100%. A minimal, moderate and large shunt was present in 12 (13%), 24 (26%) and 42 (46%) HHT1, and in 20 (21%), 6 (6%) and 8 (8%) HHT2 related mutation carriers, respectively (p for trend < 0,0001). A large shunt predicted treatable PAVMs in 55.8% of HHT1, and in 37.5% of HHT2 relatives. TTCE was positive in 4 (6%) of 63 persons without HHT.

Conclusion: A pulmonary shunt on TTCE is more prevalent and larger in HHT1, as compared with HHT2 related mutation carriers. Shunt grading is helpful to predict treatable PAVMs, particularly in the HHT2 group. TTCE is also positive in a small fraction of persons without HHT.

Introduction

Hereditary hemorrhagic telangiectasia (HHT) is a disorder with an autosomal dominant inheritance pattern which is characterized by vascular malformations, predominantly in the lungs, brain and liver.[1-4] Lung involvement causes a right-to-left shunt (RLS) which may lead to severe neurological complications such as stroke, transient ischemic attack, and cerebral abscess. Pulmonary arteriovenous malformations (PAVMs) can be effectively treated with transcatheter embolotherapy.[5-11] Therefore, systematic screening for PAVMs in patients with HHT is recommended, as is treatment, even in asymptomatic patients.[1, 2, 4] Transthoracic contrast echocardiography (TTCE) can effectively detect pulmonary RLS, which makes this technique particularly helpful for PAVM screening.[12-18] Compared to chest HRCT as a gold standard for detecting PAVMs, pulmonary shunting as shown by TTCE has an excellent negative predictive value.[12, 16] In addition, grading of pulmonary shunt size with TTCE is helpful to predict the presence of PAVMs on chest HRCT, and the indication for subsequent embolotherapy.[19, 20] Furthermore, TTCE is a simple and safe technique in experienced hands.[18, 21] Because of these favourable properties, TTCE is used as an initial screening technique for PAVMs in HHT patients in many specialized centres.[12, 13, 16, 18, 22, 23] It is currently not known if the predictive value of TTCE for the presence of a treatable PAVM on chest CT differs largely according to the HHT genotype involved.

HHT is divided in type 1 (HHT1) and 2 (HHT2), corresponding with mutations in the genes ENG and ACVRL1 coding for endogline and activin A receptor type-like kinase (ALK1), respectively. Using chest HRCT, PAVMs are more prevalent in patients with HHT1, as compared with HHT2 affected patients.[24-28] Furthermore, PAVMs tend to be larger in HHT1 patients and brain involvement is more frequent.[25, 27, 28].

We report on the prevalence and size of pulmonary RLS detected by contrast echocardiography in a large cohort of first-degree relatives of HHT patients with an identified causative mutation, compared to family members without an HHT causing mutation. In addition, we compared the predictive value of TTCE for the presence of PAVMs that are suitable for embolotherapy in both HHT1 and HHT2 relatives.

Methods

Study population

In the period from May 2004 till December 2008, 466 consecutive persons were screened for possible HHT in the St. Antonius Hospital. In order to guarantee a uniform group of screened persons, we only included first-degree relatives of proven HHT patients (index cases). We excluded 20 persons because they were referred for suggestive findings for HHT and not as family members of known HHT patients, and 78 persons who were family members but not in the first degree. In 20 persons no TTCE was performed (because an intravenous line was refused or could not be placed, or because of logistic difficulties), in 5 subjects echocardiographic images were too poor for interpretation. These persons were also excluded from the study database, leaving 343 persons available for analysis. Of this group, we only included 252 patients in whom mutation analysis was performed (see flow chart in figure 1). The clinical diagnosis HHT was established according to the Curaçao criteria.[29] These criteria consist of spontaneous and recurrent epistaxis, telangiectases at characteristic sites, visceral arteriovenous malformations 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. All persons were screened clinically and underwent complete history and physical examination by a pulmonologist, and consultation by an otorhinolaryngist, both experienced in HHT. In addition, screening for the presence of PAVMs was routinely performed with intentionally both a chest HRCT and TTCE with shunt grade measurement, on the same day.

All patients provided written informed consent, and the study was approved by the hospital review board.

Diagnosis of PAVM

TTCE

TTCE was performed as previously described.[12] In short, the patient was positioned in the left lateral decubitus position and 10 ml agitated saline (1ml of air and 1 ml of blood) was injected while projecting the four-chamber apical view without a Valsalva manoeuvre. TTCE was considered positive for a

pulmonary RLS if microbubbles appeared in the left atrium after four cardiac cycles. When contrast was present in the left atrium within less than 4 cardiac cycles, this was considered as an intracardiac shunt. The results were interpreted by two independent echocardiographers unaware of the outcome of the CT-scan, and scored as positive, negative, or indeterminate for distinction between patent foramen ovale and pulmonary RLS, or inappropriate for interpretation because of poor quality. Opacification of the left venticle was graded as either 1 (small or minimal shunt; maximum of 29 microbubbles in the left ventricle), 2 (moderate shunt; 30-99 microbubbles in the left ventricle) and 3 (large shunt; 100 microbubbles or more in the left ventricle).[19] This division was based on the maximum number of microbubbles counted in one still-frame. Patients in whom there was doubt between an intracardiac and extracardiac shunt (2 patients in the present study) were considered as positive for PAVMs for purpose of the analysis.

Chest HRCT

High resolution HRCT scanning (HRCT; Philips, Best, The Netherlands) of the chest was performed without contrast using the single breath-hold technique with a slice thickness of 1mm.

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 (a radiologist and an experienced pulmonologist), both blinded to the results of the TTCE. When both observers disagreed, the chest CT was considered as positive for PAVM. PAVMs on chest CT with a diameter of the feeding vessel ≥3 mm were considered suitable for endovascular vaso-occlusion. When the feeding artery was <3 mm in diameter, treatment was performed when judged technically feasible by the interventional radiologist.

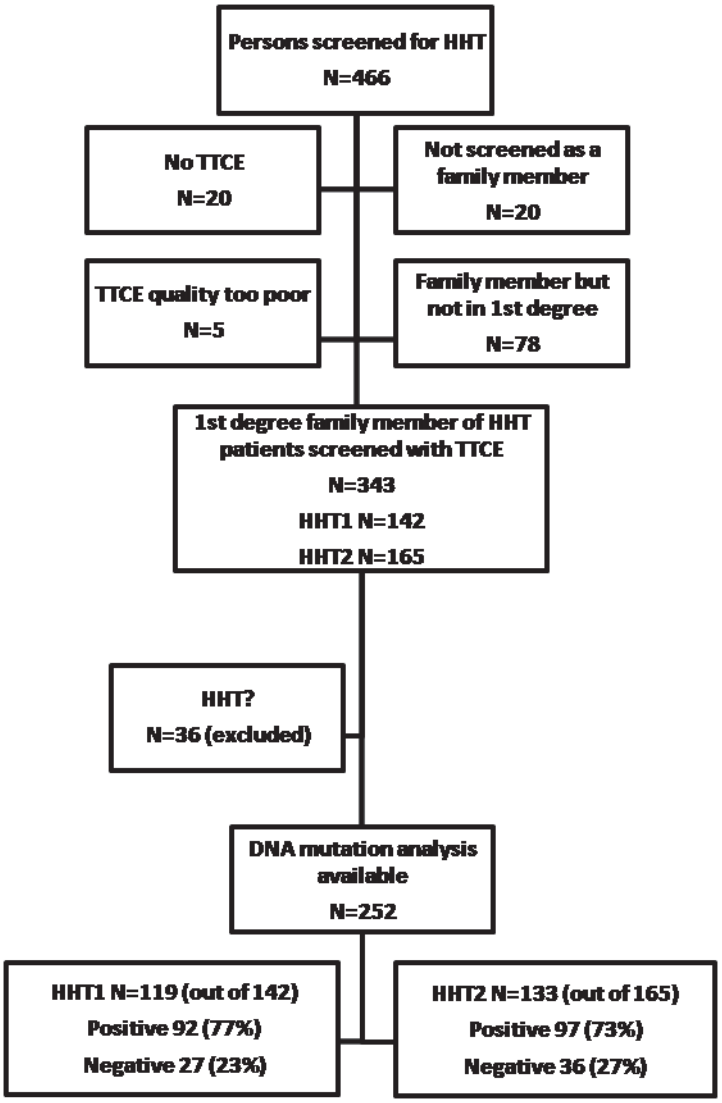

Figure 1 Selection of study patients

HHT = hereditary hemorrhagic telangiectasia (HHT1: mutation in the gene ENG; HHT2: mutation in the gene ACVLR1; HHT?: HHT causing mutation was not found or DNA analysis was not yet performed in the probands). TTCE = transthoracic contrast echocardiography

Mutation analysis

Mutation analysis was performed as previously reported.[30] A genetic diagnosis was established when the mutation causing HHT in the patient's family was present or when the patient was an obligate carrier. Affected patients were divided in HHT1, HHT2 and HHT? on the basis of mutation findings. In patients classified as HHT?, the HHT causing mutation was not found or DNA analysis was not yet performed in the probands.

Statistics

Descriptive statistics were used to describe patients characteristics. Continuous variables with normal distribution were presented as mean ± SD. Median with range was used when normal distribution was absent. Differences between groups were analyzed by the χ^2 test for nominal variables. Between-groups comparison of the presence and different grades of pulmonary shunting was done by the Mann-Whitney U test; $p < 0.05$ was considered statistically significant. Statistics were performed using a statistical software package (SPSS Inc., version 17.0; Chicago, IL, USA).

Results

Three-hundred forty-three persons (mean age 42±15 years; female gender, 58%) were screened for possible HHT as first degree family members of index cases (clinically or genetically confirmed HHT) and had an appropriate TTCE. All persons underwent a TTCE including shunt grade measurement. In 335 of 343 (98%) persons a chest HRCT was performed. In 307 (90%) persons the HHT subtype of the index patient was known. One-hundred and forty-two of screened persons (mean age 39±15 years; 60% female) were first-degree family members of index HHT1 patients; 165 were relatives of HHT2 (mean age 46±19 years; 58% female), and 36 were relatives of HHT? patients (mean age 44±14 yr; 55% female). DNA analysis was performed in 119 (84%) HHT1 relatives, and 133 (81%) HHT2 relatives and showed a genetic mutation in 92 (77%; mean age 41±15 yr; 59% female) and 97 (73%; mean age 47±14 yr; 52% female), respectively (see table 1 and figure 1).

A definite clinical diagnosis was present in 96% of ENG mutation carriers and 89% of ACVRL1 mutation carriers. One HHT2 relative with a confirmed causative mutation was clinically judged as 'unlikely'. This was a 28-year-old male with only a positive family history, and no clinical signs of HHT (see table 1).
In mutation carriers overall, 65 of 104 (62.5%) women and 47 of 85 (55.3%) men showed a pulmonary shunt on TTCE (p=0.32). Based on chest CT, 47 of 102 (46.1%) females and 23 of 84 (27.4%) males displayed a PAVM (p=0.013). The distribution of the different shunt grades differed significantly between both sexes: small, moderate, and large shunts were present in 29.8%, 36.2%, and 34.0% of men, compared with 30.8%, 16.9%, and 52.3% of women, respectively (p=0.048). We did not find a significant difference for pulmonary involvement and distribution of shunt size between both sexes in the separate HHT subtypes (p=0.9 for TTCE, p=0.34 for CT, and p=0.15 for shunt size in the HHT1 cohort; p=0.53 for TTCE, p=0.1 for CT, and p=0.15 for shunt size in the HHT2 cohort).

Table 1 Baseline characteristics and contrast echocardiography results in HHT subtypes

Family member*	**HHT1**		**HHT2**	
DNA mutation†	**Yes**	**No**	**Yes**	**No**
N	92	27	97	36
Age (yr)	41.2±15.4	32.8±11.1	47.4±13.5	40.4±13.1
Female	54 (58.7)	16 (59.3)	50 (51.6)	18 (50.0)
Male	38 (42.4)	11 (40.7)	47 (48.4)	18 (50.0)
PAVM (HRCT)‡	53 (57.6)	0	17 (17.5)	0
Clinical diagnosis#				
Definite	88 (95.7)	0	86 (88.7)	0
Possible	4 (4.3)	12 (44.4)	10 (10.3)	15 (41.7)
Unlikely	0	15 (55.6)	1 (1.0)	21 (58.3)
TTCE				
Positive	78 (84.8)	2 (7.4)	34 (35.1)	2 (5.6)
Grade 1	12 (13.0)	1 (3.7)	20 (20.6)	2 (5.6)
Grade 2	24 (26.1)	0	6 (6.2)	0
Grade 3	42 (45.7)	1 (3.7)	8 (8.2)	0

*Data are presented as n (%) unless otherwise stated; HHT: hereditary hemorrhagic telangiectasia; PAVM: pulmonary arteriovenous malformation; HRCT: high-resolution computed tomography; *: based on first degree family member with an identified HHT subtype;†: Mutations in the genes ENG (HHT1) and ACVRL1 (HHT2); ‡: Chest CT was performed in 96% of individuals [91 (99%) of ENG mutation carriers, 24 (89%) of relatives without an ENG mutation; 95 (98%) of ACVLR1 mutation carriers, 34 (94%) of relatives without an ACVRL1 mutation]; #: Clinical diagnosis based on the Curaçao clinical criteria (see methods)*

TTCE studies were positive in 78 (84.8%) and 34 (35.8%) of ENG and ACVRL1 mutation carriers, respectively (p<0.0001). Twenty-three persons (6.7%) showed a PFO on contrast echocardiography. None of these persons showed a PAVM on chest CT. CT thorax was performed in 91 (99%) ENG, and 95 (98%) ACVRL1 mutation carriers, respectively. None of the individuals without a chest CT showed an intrapulmonary shunt on TTCE. PAVMs on chest CT were present in 57.6% of HHT1, and 17.5% of HHT2 causing mutation carriers (p<0.0001). Of these PAVMs on chest CT, 29 (55%) were large enough for embolotherapy in ENG mutation carriers, and 3 (18%) in ACVRL1 mutation carriers (see table 2). The distribution of the three shunt grades differed between both subtypes: large shunts tended to be more frequent in HHT1 (53.8% of all shunts in HHT1 were grade 3), whereas small shunts were predominant in HHT2 (58.8% of all shunts in HHT2 were grade 1) (p < 0,0001, see table 1 and figure 2). The κ coefficient for interobserver agreement concerning TTCE shunt grade was 0.85, and 0.84 for the diagnosis of PAVM on chest CT.

Table 2 Predictive value of TTCE for the presence of a treatable PAVM on chest CT in both HHT genotypes

	Intrapulmonary shunt on TTCE	**Treatable PAVM on chest HRCT***		**PPV**	**NPV**
		No	yes		
HHT1†	**No shunt**	37	0	-	100
	Any shunt	51	29	36.3	-
	Grade 1	13	0	0	-
	Grade 2	19	5	20.8	-
	Grade 3	19	24	55.8	-
HHT2†	**No shunt**	93	0	-	100
	Any shunt	33	3	8.3	-
	Grade 1	22	0	0	-
	Grade 2	6	0	0	-
	Grade 3	5	3	37.5	-

*Data are presented as n (%) unless otherwise stated; TTCE: transthoracic contrast echocardiography; HHT: hereditary hemorrhagic telangiectasia; PAVM: pulmonary arteriovenous malformation; HRCT: high-resolution computed tomography; PPV: positive predictive value; NPV: negative predictive value; *: PAVM on chest CT judged large enough for embolotherapy; †: First-degree family members of HHT patients with known mutation analysis results (based on data in table 1)*

TTCE was positive in 4 (6.3%) of 63 persons with a negative genetic screening test for HHT. Of this group, 2 persons were screened as family members of HHT1 patients and one of them showed a grade 1 (3 microbubbles on TTCE), and one showed a grade 3 pulmonary shunt on TTCE. Both patients who were negative for HHT2 and showed a pulmonary shunt on echocardiography, appeared to have a small shunt (6 and 14 microbubbles on TTCE).

The negative predictive value (NPV) of TTCE for the presence of a treatable PAVM on chest CT was 100%. The positive predictive value (PPV) of a pulmonary shunt per se was 36.3% for family members of HHT1 patients, and 8.3% for HHT2 relatives. None of the family members with a small shunt displayed treatable PAVMs on chest CT. The positive predictive value of a large shunt was 55.8% and 37.5% for screened relatives of HHT1 and HHT2 patients, respectively (see table 2).

Discussion

We report for the first time on the prevalence of pulmonary shunting on TTCE in a large homogeneous group of first-degree HHT relatives with an identified HHT causing mutation. We found a pulmonary right-to-left shunt in 85% of HHT1, and in 35% of HHT2 related mutation carriers, respectively. Furthermore, pulmonary shunts are larger in HHT1 compared to HHT2 relatives. TTCE appears to be also positive in 6% of persons without an HHT causing mutation. Only a small fraction of PAVMs in the HHT2 subgroup is large enough for embolotherapy and this explains the poor PPV of 8.8% for an intrapulmonary shunt on TTCE *per se*. However, this may be overcome using semiquantitative shunt grading, as only moderate and large shunts were associated with treatable PAVMs in both HHT genotypes.

Contrast echocardiography according to HHT subtype

Previous studies have shown a higher prevalence of PAVMs in HHT1 as compared with HHT2 patients, using chest CT as the most sensitive technique to detect PAVMs.[24-28] Bayrak et al. used contrast echocardiography, but only in a fraction of patients, and pulmonary angiography and chest CT in others.[24]

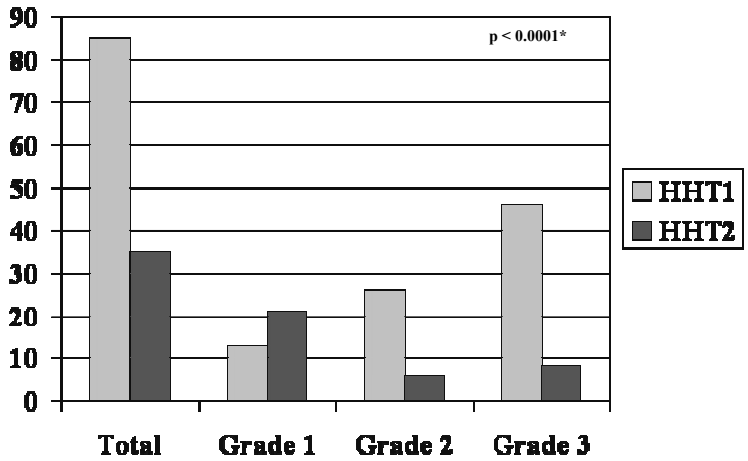

Figure 2 Prevalence and size of pulmonary shunts on TTCE according to HHT genotype
*TTCE: transthoracic contrast echocardiography; HHT: hereditary haemorrhagic telangiectasia; Y-axis: % positive TTCE; X-axis: distribution of positive TTCE studies and shunt grades according to HHT genotype; *: p<0.0001 for trend of distribution of different shunt grades*

Based on chest CT, PAVMs occur in 48-75% and 5-44 % of patients with HHT1 and HHT2, respectively.[24-28] We report a positive chest HRCT in HHT1 and HHT2 relatives with a causative mutation in 58% and 18% persons, respectively. Our results show that a pulmonary shunt is present in 85% of patients with an HHT1 causing mutation, and in 35% of patients with an HHT2 genotype (p<0.0001). Thus, the prevalence of pulmonary shunts with TTCE is markedly higher than for PAVMs on chest HRCT. This discrepancy might be explained by microscopic shunts which are not visualized by chest HRCT.[14]

The distribution of pulmonary shunt grades also differed significantly (p <0,0001 for trend; figure 2). HHT1 related mutation carriers with a positive TTCE study showed a large pulmonary shunt in 54%, versus predominantly small shunts in the HHT2 group (59%).This corresponds with the higher prevalence of treatable PAVMs in the HHT1 subgroup of patients in this study, as with previous studies that showed a higher percentage of large and symptomatic PAVMs in HHT1 patients.[24, 25, 28]

Contrast echocardiography is used as an initial screening procedure for PAVMs in many specialized centers. Only a positive TTCE is followed by chest HRCT to detect PAVMs that can be treated by embolotherapy in such an algorithm. This strategy is supported by the excellent NPV of TTCE for PAVMs on chest CT in previous studies.[12, 16] In line with this is the present study which shows a NPV of 100% regarding treatable PAVMs. However, the PPV of an echocardiographic pulmonary shunt per se was low, especially in family members of HHT2 patients (8.8%). This reflects the low proportion of treatable PAVMs on PAVMs overall in ACVRL1 mutation carriers. The use of shunt grading can be used to improve this PPV, as clinically meaningful PAVMs were only seen in patients with moderate and large shunts. This classification of shunt size, rather than merely its presence, might also be supported by our finding that 85% of HHT1 relatives had a positive 'echo-bubble'. This raises questions about the cost-effectiveness of contrast echocardiography for screening in this group. Alternatively, we can think of a strategy which comprises a chest HRCT as a first-line screening technique for PAVMs in HHT1 relatives with a high clinical suspicion of the disease, without a preceding TTCE. This perspective does not refer to HHT2 patients, as the prevalence of pulmonary shunts in this group is much lower.

HHT patients with pulmonary shunts have a highly increased risk for brain abscess as a result of bypassing the capillary filter.[1] Therefore, antibiotic prophylaxis is recommended preceding interventions carrying the risk of bacteraemia.[2, 16, 31, 32] Surprisingly, a recent study showed that different markers of PAVM severity (oxygen saturation, RLS using 100% oxygen, feeding artery diameter; TTCE was not used) could not predict the risk for stroke or brain abscess.[1] In our centre we recommend the use of antibiotic prophylaxis to all patients with an echocardiographically proven RLS. In institutions where a chest HRCT (and not a TTCE) is performed to screen for PAVMs, antibiotic prophylaxis is routinely recommended to all HHT patients. The latter is the result of the much higher sensitivity for pulmonary shunting on contrast echocardiography as compared to chest HRCT. The high incidence of pulmonary shunts on contrast echocardiography in our study, especially in HHT1 patients, reinforces this routine.

Women displayed PAVMs on chest HRCT significantly more frequently than men. Previous studies have shown a higher prevalence of PAVM in female HHT patients using chest CT as a screening procedure, but only in the HHT1 group.[26, 28] We were not able to demonstrate a difference in the prevalence of PAVM between female and male patients in the HHT1 and 2 subgroups, probably due to the lower number of patients. Unlike PAVM on chest CT, the presence of intrapulmonary shunting on TTCE did not differ between both sexes. This suggests that PAVMs may be larger in women, which is supported by our finding that women displayed significantly more large shunts than men.

Contrast echocardiography in subjects without HHT

TTCE appears to be positive in 4 (6%) persons in whom genetic testing for HHT was negative. Notably, one person without an HHT1 causing mutation showed a grade 3 pulmonary shunt (and no PAVMs on chest HRCT). This patient was clinically classified as 'possible' HHT (first degree family member with proven HHT and telangiectases), and she has an 8-year old son with epistaxis and telangiectases who has not been genetically screened yet. These findings might be suggestive for the presence of HHT nonetheless. In order to exclude an error in sample logistics and look for other mutations than the family mutation, repeated genetic testing in this patient would be of interest. Unfortunately, this was refused. None of these four persons with pulmonary shunts had comorbidity that could explain these findings. Recently, similar results were published showing a prevalence of pulmonary shunts on TTCE of 7% in a group of 100 controls (all grade 1 shunts).[18] Sensu stricto a PFO should be excluded in these subjects before it is assumed that pulmonary shunting is not unusual in the general population. In the absence of a Valsalva manoeuvre, delayed appearance of left-sided contrast might also be caused by increases in right atrial pressure at end inspiration which may be enough to cause a transient right-to-left shunt through a PFO.[33] Because a provocative Valsalva manoeuvre was not routinely performed in our study, a PFO might have been missed, particularly so because the overall prevalence of PFO was only 6.7% in the present population. As a consequence, we have recently started to routinely perform a Valsalva manoeuvre in all screened persons undergoing

TTCE. Transesophageal echocardiography (TEE) might clarify the origin of the shunt, but as it is an invasive technique, this is not routinely used. Furthermore, in the absence of PAVMs on chest HRCT, a TEE has no therapeutic consequences. Therefore, we did not perform TEE studies. So, pulmonary shunting on TTCE might be present as a normal variant in the general population, but a PFO should be properly excluded to prove this assumption. A limitation of the present study was the absence of detailed data on echocardiographic measures of left ventricular function, valvular heart disease, and right ventricular systolic pressure, as these might theoretically influence the delay and size of contrast appearance in the left ventricle.

In conclusion, our results show that TTCE identifies pulmonary shunts in 85% of HHT1 versus 35% of HHT2 related mutation carriers, and that pulmonary shunts are larger in the former. TTCE studies also suggest a pulmonary RLS in 6% of a control group without HHT. The presence of an intrapulmonary shunt on TTCE per se does not select the patients with PAVMs that meet criteria for embolotherapy. However, grading of shunt size is helpful to detect treatable PAVMs. Alternatively, because of the high prevalence of pulmonary shunting in HHT1 related mutation carriers, a direct chest CT without preceding TTCE may be considered in individuals with a high clinical suspicion of HHT.

Reference List

1. Shovlin CL, Jackson JE, Bamford KB, Jenkins IH, Benjamin AR, Ramadan H, Kulinskaya E. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. Thorax 2008;63:259-266.
2. Gossage JR, Kanj G. Pulmonary arteriovenous malformations. A state of the art review. Am J Respir Crit Care Med 1998;158:643-661.
3. Cottin V, Chinet T, Lavole A, Corre R, Marchand E, Reynaud-Gaubert M, Plauchu H, Cordier JF. Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: a series of 126 patients. Medicine (Baltimore) 2007;86:1-17.
4. Cottin V, Dupuis-Girod S, Lesca G, Cordier JF. Pulmonary vascular manifestations of hereditary hemorrhagic telangiectasia (rendu-osler disease). Respiration 2007;74:361-378.
5. Dutton JA, Jackson JE, Hughes JM, Whyte MK, Peters AM, Ussov W, Allison DJ. Pulmonary arteriovenous malformations: results of treatment with coil embolization in 53 patients. AJR Am J Roentgenol 1995;165:1119-1125.
6. Haitjema TJ, Overtoom TT, Westermann CJ, Lammers JW. Embolisation of pulmonary arteriovenous malformations: results and follow up in 32 patients. Thorax 1995;50:719-723.
7. Lee DW, White RI, Jr., Egglin TK, Pollak JS, Fayad PB, Wirth JA, Rosenblatt MM, Dickey KW, Burdge CM. Embolotherapy of large pulmonary arteriovenous malformations: long-term results. Ann Thorac Surg 1997;64:930-939.
8. Mager JJ, Overtoom TT, Blauw H, Lammers JW, Westermann CJ. Embolotherapy of pulmonary arteriovenous malformations: long-term results in 112 patients. J Vasc Interv Radiol 2004;15:451-456.
9. Remy-Jardin M, Dumont P, Brillet PY, Dupuis P, Duhamel A, Remy J. Pulmonary arteriovenous malformations treated with embolotherapy: helical CT evaluation of long-term effectiveness after 2-21-year follow-up. Radiology 2006;239:576-585.
10. White RI, Jr., Lynch-Nyhan A, Terry P, Buescher PC, Farmlett EJ, Charnas L, Shuman K, Kim W, Kinnison M, Mitchell SE. Pulmonary arteriovenous malformations: techniques and long-term outcome of embolotherapy. Radiology 1988;169:663-669.
11. White RI, Jr., Pollak JS, Wirth JA. Pulmonary arteriovenous malformations: diagnosis and transcatheter embolotherapy. J Vasc Interv Radiol 1996;7:787-804.

12. van Gent MW, Post MC, Luermans JG, Snijder RJ, Westermann CJ, Plokker HW, Overtoom TT, Mager JJ. Screening for pulmonary arteriovenous malformations using transthoracic contrast echocardiography: a prospective study. Eur Respir J 2009;33:85-91.
13. Nanthakumar K, Graham AT, Robinson TI, Grande P, Pugash RA, Clarke JA, Hutchison SJ, Mandzia JL, Hyland RH, Faughnan ME. Contrast echocardiography for detection of pulmonary arteriovenous malformations. Am Heart J 2001;141:243-246.
14. Lee WL, Graham AF, Pugash RA, Hutchison SJ, Grande P, Hyland RH, Faughnan ME. Contrast echocardiography remains positive after treatment of pulmonary arteriovenous malformations. Chest 2003;123:351-358.
15. Feinstein JA, Moore P, Rosenthal DN, Puchalski M, Brook MM. Comparison of contrast echocardiography versus cardiac catheterization for detection of pulmonary arteriovenous malformations. Am J Cardiol 2002;89:281-285.
16. Cottin V, Plauchu H, Bayle JY, Barthelet M, Revel D, Cordier JF. Pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. Am J Respir Crit Care Med 2004;169:994-1000.
17. Barzilai B, Waggoner AD, Spessert C, Picus D, Goodenberger D. Two-dimensional contrast echocardiography in the detection and follow-up of congenital pulmonary arteriovenous malformations. Am J Cardiol 1991;68:1507-1510.
18. Gazzaniga P, Buscarini E, Leandro G, Reduzzi L, Grosso M, Pongiglione G, Pedrinazzi C, Lanzarini L, Portugalli V, Blotta P, Forner P, Boccardi E, Pagella F, Manfredi G, Olivieri C, Zambelli A, Danesino C, Inama G. Contrast echocardiography for pulmonary arteriovenous malformations screening: does any bubble matter? Eur J Echocardiogr 2009;10:513-518.
19. van Gent MW, Post MC, Snijder RJ, Swaans MJ, Plokker HW, Westermann CJ, Overtoom TT, Mager JJ. Grading of Pulmonary Right-to-Left Shunt With Transthoracic Contrast Echocardiography: Does It Predict the Indication for Embolotherapy? Chest 2009;135:1288-1292.
20. Zukotynski K, Chan RP, Chow CM, Cohen JH, Faughnan ME. Contrast echocardiography grading predicts pulmonary arteriovenous malformations on CT. Chest 2007;132:18-23.
21. Bommer WJ, Shah PM, Allen H, Meltzer R, Kisslo J. The safety of contrast echocardiography: report of the Committee on Contrast Echocardiography for the American Society of Echocardiography. J Am Coll Cardiol 1984;3:6-13.

22. Gossage JR. The role of echocardiography in screening for pulmonary arteriovenous malformations. Chest 2003;123:320-322.
23. Kjeldsen AD, Oxhoj H, Andersen PE, Elle B, Jacobsen JP, Vase P. Pulmonary arteriovenous malformations: screening procedures and pulmonary angiography in patients with hereditary hemorrhagic telangiectasia. Chest 1999;116:432-439.
24. Bayrak-Toydemir P, McDonald J, Markewitz B, Lewin S, Miller F, Chou LS, Gedge F, Tang W, Coon H, Mao R. Genotype-phenotype correlation in hereditary hemorrhagic telangiectasia: mutations and manifestations. Am J Med Genet A 2006;140:463-470.
25. Lesca G, Olivieri C, Burnichon N, Pagella F, Carette MF, Gilbert-Dussardier B, Goizet C, Roume J, Rabilloud M, Saurin JC, Cottin V, Honnorat J, Coulet F, Giraud S, Calender A, Danesino C, Buscarini E, Plauchu H. Genotype-phenotype correlations in hereditary hemorrhagic telangiectasia: data from the French-Italian HHT network. Genet Med 2007;9:14-22.
26. Letteboer TG, Mager JJ, Snijder RJ, Koeleman BP, Lindhout D, Ploos van Amstel JK, Westermann CJ. Genotype-phenotype relationship in hereditary haemorrhagic telangiectasia. J Med Genet 2006;43:371-377.
27. Post MC, Letteboer TG, Mager JJ, Plokker TH, Kelder JC, Westermann CJ. A pulmonary right-to-left shunt in patients with hereditary hemorrhagic telangiectasia is associated with an increased prevalence of migraine. Chest 2005;128:2485-2489.
28. Sabba C, Pasculli G, Lenato GM, Suppressa P, Lastella P, Memeo M, Dicuonzo F, Guant G. Hereditary hemorrhagic telangiectasia: clinical features in ENG and ALK1 mutation carriers. J Thromb Haemost 2007;5:1149-1157.
29. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, Kjeldsen AD, Plauchu H. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000;91:66-67.
30. Letteboer TG, Zewald RA, Kamping EJ, de HG, Mager JJ, Snijder RJ, Lindhout D, Hennekam FA, Westermann CJ, Ploos van Amstel JK. Hereditary hemorrhagic telangiectasia: ENG and ALK-1 mutations in Dutch patients. Hum Genet 2005;116:8-16.
31. Faughnan ME, Palda VA, Garcia-Tsao G, Geisthoff UW, McDonald J, Proctor DD, Spears J, Brown DH, Buscarini E, Chesnutt MS, Cottin V, Ganguly A, Gossage JR, Guttmacher AE, Hyland RH, Kennedy SJ, Korzenik J, Mager JJ, Ozanne AP, Piccirillo JF, Picus D, Plauchu H, Porteous ME, Pyeritz RE, Ross DA, Sabba C, Swanson K, Terry P, Wallace

MC, Westermann CJ, White RI, Young LH, Zarrabeitia R. International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia. J Med Genet 2009.

32. Shovlin C, Bamford K, Wray D. Post-NICE 2008: Antibiotic prophylaxis prior to dental procedures for patients with pulmonary arteriovenous malformations (PAVMs) and hereditary haemorrhagic telangiectasia. Br Dent J 2008;205:531-533.
33. Woods TD, Patel A. A critical review of patent foramen ovale detection using saline contrast echocardiography: when bubbles lie. J Am Soc Echocardiogr 2006;19:215-222.

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Hereditary haemorrhagic telangiectasia:

how accurate are the clinical criteria?

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Abstract

Background: The clinical diagnosis of hereditary haemorrhagic telangiectasia (HHT) is based on the Curaçao criteria. One out of the four criteria is the presence of visceral arteriovenous malformations (AVMs). Transthoracic contrast echocardiography (TTCE) has a high sensitivity for the detection of pulmonary right-to-left shunting (RLS) as an expression of pulmonary AVM. We report on the diagnostic accuracy of the clinical criteria and hypothesized that this might be improved by TTCE.

Methods: A total of 489 consecutive persons were screened for HHT between May 2004 and May 2009. We included 263 first-degree relatives of disease-causing mutation carriers who underwent mutation analysis and both a chest CT and TTCE. Genetic test results were considered the gold standard.

Results: The family mutation was present in 186 patients (mean age 43±15 yr; 55% female). A clinical diagnosis was definite (at least 3 criteria), 'possible' (2 criteria), and unlikely (0 or 1 criterion) 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, 60% female). In this group a clinical diagnosis was definite, 'possible' and unlikely in zero (0), 35 (45.5%), and 42 (54.5%) persons, respectively. The use of TTCE as a criterion raised the number of patients with a correct diagnosis of definite HHT to 175 (94.1%), but also the number of falsely positives among persons without the family mutation to 5 (6.5%).

Conlusion: The Curaçao clinical criteria have a good diagnostic performance. The use of TTCE as a criterion resulted in a modestly increased sensitivity, but also raised the number of falsely positives, limiting its additional benefit for the clinical diagnosis of HHT.

Introduction

Hereditary haemorrhagic telangiectasia (HHT) is a disorder with an autosomal dominant inheritance pattern. HHT causes vascular pathology, ranging from telangiectases to large visceral arteriovenous malformations (AVMs), predominantly in the lung, brain, liver, and gastrointestinal tract. Most feared are neurological complications such as cerebral abscess and ischaemic stroke, resulting from paradoxical embolic events through right-to-left shunting (RLS) of pulmonary AVMs (PAVMs). The incidence of brain abscess and stroke in patients with untreated PAVMs appears to be high, ranging from 8-19% and 10-36%, respectively.[1-5] Transcatheter embolotherapy is used to treat PAVMs.[2, 4, 6-10] Because of its potential detrimental consequences and possibility for treatment, presymptomatic screening for PAVMs in all HHT patients is warranted. PAVM screening is performed by chest CT or transthoracic contrast echocardiography (TTCE).[11-13] The prevalence of pulmonary RLS in HHT patients as shown by TTCE appears to be much higher than for PAVMs on chest CT or pulmonary angiography. For example, TTCE has been shown to be positive for an intrapulmonary shunt in 22% of patients without PAVMs on chest HRCT.[13] This is probably due to visualization of small shunts below the detection limit of CT.[13-16]

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.[17-19] The clinical diagnosis is established according to the consensus clinical diagnostic criteria which were published in 2000, also known as the Curaçao criteria.[20] These criteria consist of spontaneous and recurrent epistaxis, telangiectases at characteristic sites, visceral arteriovenous malformations 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 renders the diagnosis unlikely. No studies on the sensitivity and specificity of these clinical criteria have been reported to date. The presence of an intrapulmonary shunt on TTCE, as a proof for visceral involvement in HHT, might support the establishment of the clinical diagnosis, as has recently been suggested.[21]

The vascular anomalies in HHT patients are associated with mutations in genes implicated in the transforming growth factor β (TGF-β) signalling pathway in vascular endothelium.[22] 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. A third disease-causing mutation has been shown in the SMAD4 gene which causes a combined syndrome of juvenile polyposis and HHT.[23] In addition, 2 more loci causing HHT have been mapped to chromosome 5 (HHT type 3) and 7 (HHT type 4), although the causative genes have not been identified yet.[24, 25] Genetic testing is being increasingly performed to establish the HHT causing mutation in affected families, and to diagnose HHT in asymptomatic individuals, especially young adults and children. A mutation detection sensitivity has been reported between 72 and 93% in individuals with a confirmed clinical diagnosis HHT.[26-28]

We report on the diagnostic accuracy of the clinical Curaçao criteria in a large group of first-degree family members of HHT patients in whom genetic testing for the family mutation was performed. We hypothesized that TTCE, as a very sensitive technique to detect pulmonary shunting, might be used as an alternative argument for the presence of visceral AVMs, and from that improve the clinical diagnosis of HHT.

Methods

Study population

In the period from May 2004 till May 2009, 489 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. Screening for the presence of PAVMs was routinely performed with intentionally both a chest HRCT and TTCE, on the same day. Screening for gastro-intestinal telangiectases and hepatic AVMs (HAVM) 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 (CAVMs). All persons were offered genetic testing.

In order to validate the clinical criteria, we decided to use the presence or absence of a disease-causing mutation as the gold standard. So, carriers of the disease-causing mutation were considered the true positives and non-carriers the true negatives. 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 guaranteed that no patients with a clinical diagnosis of HHT were included in whom the disease-causing mutation was not detected (and would otherwise be falsely classified as true negatives; theoretically another causative mutation might be present but this chance is negliglibly small). In addition, we excluded all index cases. 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. Consequently, this would introduce a bias in the study. Both a CT thorax and TTCE were also required for inclusion in the study. TTCE studies allowed us to test the value of its use as a clinical criterion. We included 263 first-degree relatives of HHT patients with a proven disease-causing mutation who all underwent mutation analysis, and both a chest CT and TTCE. Of this group, 87 were ENG mutation carriers, 99 ACVRL1 mutation carriers, and in 77 persons the family mutation was not found (figure 1). The clinical diagnosis HHT was established according to the Curaçao criteria.[20] All patients provided written informed consent, and the study was approved by the hospital review board.

TTCE

TTCE was performed as previously described.[13] The patient was positioned in the left lateral decubitus position and 10 ml agitated saline was injected while projecting the four-chamber apical view without a Valsalva manoeuvre. TTCE was performed by three experienced echocardiographers. TTCE was considered positive for a pulmonary right-to-left shunt if microbubbles appeared in the left atrium after four cardiac cycles. When contrast was present in the left atrium within less than 4 cardiac cycles, this was considered as a patent foramen ovale (PFO). We diagnosed a PFO in 19 (7.2%) individuals. The results were scored as

positive, negative, or indeterminate for distinction between PFO and pulmonary RLS, or inappropriate for interpretation because of poor quality. Five patients in whom there was doubt between an intracardiac and extracardiac shunt were considered positive for PAVMs for purpose of the analysis.

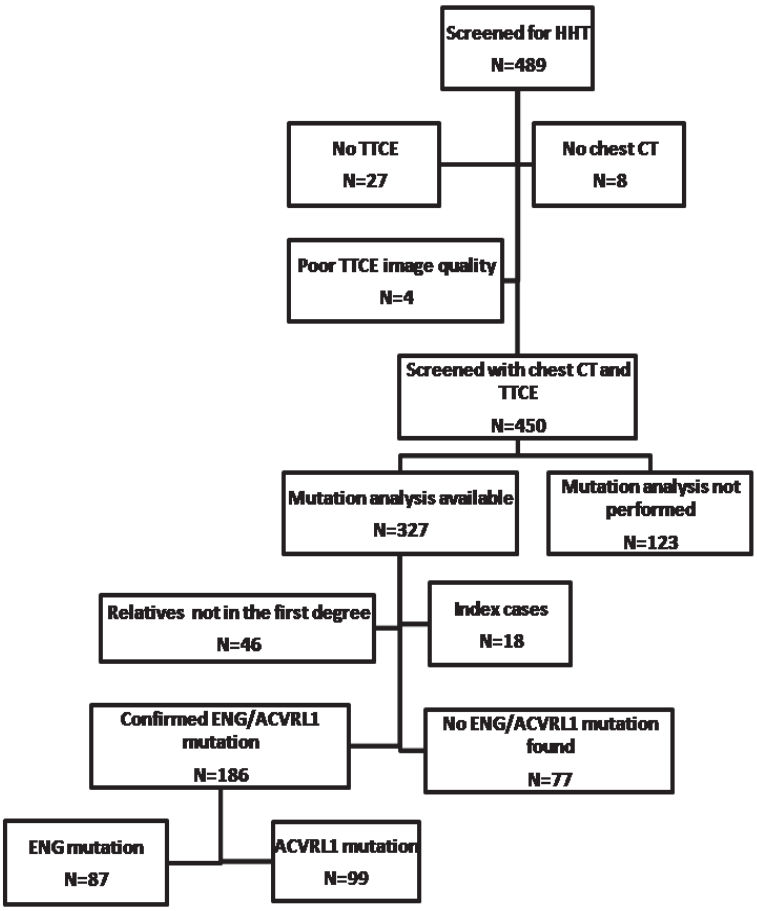

Figure 1 Selection of study population

Selection of first-degree relatives who underwent both a chest CT and contrast echocardiogram, and mutation analysis. All included individuals were relatives of HHT patients with a proven disease-causing mutation; HHT: hereditary hemorrhagic telangiectasia; TTCE: transthoracic contrast echocardiography; CT: computed tomography; EN: gene coding for endoglin (HHT type 1); ACVRL1: gene coding for ALK-1 (HHT type 2)

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 a PAVM.

Mutation analysis

Mutation analysis was performed as previously reported.[28] 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 a the family mutation was not found.

Statistics

Descriptive statistics were used to describe patients characteristics. Continuous variables with normal distribution were presented as mean ± SD. 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 proven 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 a statistical software package (SPSS Inc., version 17.0; Chicago, IL, USA).

Results

The study population consisted of 263 patients (mean age 41.2±14.2 yr; 56% female), of whom 87 patients with a confirmed mutation of the ENG gene (mean age 41.5±15.7 yr; 59% female), and 99 patients with an ACVRL1 gene mutation (mean age 44.1±13.6 yr; 50% female; see table 1). In 77 persons the family mutation was not found (mean age 37.1±12.3 yr; 60% female). Clinical diagnosis was definite in 83 (95%), 'possible' in 4 (5%), and unlikely in none of the ENG mutation carriers (table 1). Within ACVRL1 mutation carriers, a clinical diagnosis was definite in 85 (86%) patients, possible in 13 (13%) patients, and unlikely in 1 (1%) patient. The latter patient was 28-years-old at the time of screening, and had no clinical signs of HHT. A positive clinical diagnosis predicted mutation carriers in 100% correctly. The negative predictive value of an unlikely clinical diagnosis was 97.7%. (table 2).

Of persons in whom the family mutation was absent, clinical diagnosis was definite in zero (0%), possible in 35 (45.5%), and unlikely in 42 (55%) persons.

TTCE showed a pulmonary shunt in 75 (86%) patients with HHT1, 38 (38%) patients with HHT2, and 7 (9%) persons without HHT. When a positive TTCE study was considered as proof for visceral AVM, 2 and 4 patients would be clinically judged as having definite instead of possible HHT in the HHT1 and 2 groups, respectively (table 1). This would improve the sensitivity of a confirmed clinical diagnosis from 95% to 98% in the HHT1 group, and from 86% to 90% in the HHT2 cohort. In persons in whom no family mutation was found, 5 (6.5%) persons would be clinically falsely reclassified as having definite instead of possible HHT. For clarity, this 'reclassification' concerns patients with a possible clinical diagnosis who do not meet the criterion of organ involvement (all patients underwent a chest HRCT to detect PAVM), except for an intrapulmonary shunt on TTCE.

Table 1 Baseline characteristics and results of clinical diagnosis in first-degree relatives of HHT patients in whom genetic testing for the family mutation was performed

	ENG + ACVRL1	ENG	ACVRL1	No mutation found
Total	186	87	99	77
Age (yr±SD)	42.9±14.6	41.5±15.7	44.1±13.6	37.1±12.3
Female	102 (54.8)	53 (60.9)	49 (49.5)	46 (59.7)
Male	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
PAVM (CT)	66 (35.5)	53 (60.9)	13 (13.1)	0
CAVM[b]	4 (2.2)	4 (4.6)	0	0
HAVM[c]	7 (3.8)	1 (1.1)	6 (6.1)	0
GI[d]	10 (5.4)	5 (5.7)	5 (5.1)	0
TTCE positive[e]	113 (60.8)	75 (86.2)	38 (38.4)	7 (9.1)
Clinical diagnosis				
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)
Clinical diagnosis using TTCE[f] **as a criterion**				
Definite	175 (94.1)	85 (97.7)	89 (89.9)	5 (6.5)
Possible	10 (5.4)	2 (2.3)	9 (9.1)	30 (39.0)
Unlikely	1 (0.5)	0	1 (1.0)	42 (54.5)

Data are presented as N (%) unless otherwise stated; HHT: hereditary haemorrhagic telangiectasia; ENG: endoglin; ACVRL1: activin receptor-like kinase; AVM: arteriovenous malformation; PAVM: pulmonary AVM; CAVM: cerebral AVM; HAVM: hepatic AVM; GI: gastro-intestinal; TTCE: transthoracic contrast echocardiography; [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; [e] Evidence for a pulmonary shunt on TTCE; [f] A positive TTCE study was regarded as proof for visceral AVM

Table 2 Clinical diagnosis versus ENG or ACVRL1 mutation

		ENG or ACVRL1 mutation[a]		
		Yes	**No**	**Total**
Clinical diagnosis[b]	**Definite**	168	0	169
	Unlikely	1	42	43
	Possible	17	35	51
	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%; specificity: 54.5%; positive predictive value of a definite diagnosis: 100%; negative predictive value of an unlikely diagnosis: 97.7%

Discussion

The present study reports on the validity of the Curaçao criteria. Of 186 patients with an HHT causing family mutation, a definite clinical diagnosis was present in 90%. Importantly, only 1 (0.5%) patient was clinically assessed as 'unlikely'. The addition of intrapulmonary shunting on contrast echocardiography as a diagnostic criterion resulted in a slightly improved sensitivity, but also raised falsely positive clinical assessment in persons without HHT.

Diagnostic accuracy of the Curaçao criteria

The clinical diagnostic criteria were originally drawn up as a consensus statement.[20] Until then, 2 criteria were enough for diagnosis of HHT.[17] 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, 3 criteria were required for a definite diagnosis, a 'possible' diagnosis was incorporated for patients with 2 criteria, and persons with 0 or 1 criterion were regarded as 'unlikely' of having HHT. Of notice, the latter group should probably only be reserved for persons older than 30-40 years, especially so for first-degree relatives of HHT patients.[29] This is supported by the present study which showed that the single patient with 1 criterion (family history) within the group of disease-causing mutation carriers was a 28-year-old man.

Ever since the Curaçao criteria were designed, molecular diagnostic tests are improved and have become more widely available. However, mutations are not found in approximately 20% of HHT families.[26, 28, 30] Consequently, establishing a clinical diagnosis remains an important instrument in the care of HHT families. 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.[20] This issue was reminded in the recently published guidelines.[31] In order to assess its accuracy, 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 a sensitivity of a certain clinical diagnosis of 90% within HHT patients overall, which appeared to be higher in ENG (95%) than ACVRL1 mutation carriers (86%).This difference should be interpreted with caution as screening for HAVM was only performed when clinically suggested in the present study. A prevalence of HAVM in HHT2 up to 83% has been reported.[32] Hence, the fact that HAVMs were not systematically screened for might well have lead to underestimation of the number of patients with visceral AVMs, and from that reduce the sensitivity of the clinical criteria. This may also apply to the ENG mutation carriers, in whom a prevalence of 44-60% for HAVM has been previously described.[32, 33]

When a clinical screening program is being implemented, it is trivial that no HHT patients are overlooked. This relates to the potential lethal complications of organ involvement, and consequences for screening of descendants of possible HHT affected individuals. In this respect, the present data are reassuring because only 1 of 186 mutation carriers had 1 clinical criterion. Bossler et al. described only one clinical criterion in 5 of 77 (6%) HHT1, and 4 of 50 (8%) HHT2 patients with confirmed gene mutations, respectively.[34] However, 70% of genetically screened patients had a positive family history for HHT in this study, and only 68% of proven mutation carriers had 3 criteria. The sensitivity of the clinical criteria will probably be increased when screening is performed predominantly in first-degree family members (already meeting one criterion), as in the present study. In general, comparison of diagnostic accuracy of clinical criteria and genotype-

phenotype association should be assessed carefully because of patient selection (indication for referral) and screening methods for organ involvement.
A high percentage (45.5%) of individuals without a disease-causing mutation was classified as 'possible' HHT patients. This reflects the fact that the criteria are very stringent in order to prevent falsely negative diagnosis, as mentioned before. For the same reason, it seems also conceivable that epistaxis or telangiectases are more liberately diagnosed in first-degree family members of known HHT patients. This might have caused the high number of telangiectases and epistaxis (20% and 16%, respectively) of non-mutation carriers in our study.

Contrast echocardiography as a clinical diagnostic criterion
The clinical manifestations of HHT are often subtle. Currently, chest HRCT still is the gold standard for detecting PAVMs. However, small pulmonary AVMs or telangiectases may not be visible on CT. In this respect, TTCE is of interest because it is a very sensitive technique for the detection of intrapulmonary shunting.[15, 35, 36] In the present study, TTCE showed a pulmonary RLS in 61% of ENG and ACVRL1 mutation carriers, compared with a 36% detection rate of PAVMs on chest CT. As a result, the use of contrast echocardiography might theoretically improve the sensitivity of clinical assessment when an intrapulmonary shunt is regarded as proof for organ involvement in HHT. On the other hand, TTCE (without the Valsalva manoeuvre) has been shown to be also positive in 7% of persons without a clinical diagnosis of HHT, possibly reducing specificity.[13, 21] The present data showed a pulmonary RLS on TTCE in 9% of persons without a family mutation for HHT.
TTCE increased the diagnostic sensitivity of the Curaçao criteria from 90% to 94%, as a result of reclassification of patients previously judged as having 'possible' HHT. However, TTCE also increased the number of falsely positives from 0% to 6.5%. This unfavourable effect largely counterbalances the modest benefit for clinical diagnostics. In our opinion a pulmonary shunt, as visualized by contrast echocardiography without the Valsalva manoeuvre, should therefore not be automatically interpreted as a diagnostic criterion, as was recently proposed.[21] An explanation for these falsely positive TTCE results might be the fact that our

echo studies were performed without the Valsalva manouevre. A PFO might therefore have been mistaken for an intrapulmonary shunt. It has been shown that the inspiratory increase in right atrial pressure can be enough to induce a right-to-left shunt through a PFO.[37] This mechanism might be responsible for the appearance of contrast in the left heart after 4 cardiac cycles. The use of TTCE with the Valsalva manoeuvre, as has recently become routine in our centre, might prevent this misinterpretation Alternatively, pulmonary shunts may be present as a normal variant in the general population.[13] In this respect, TTCE might be oversensitive for the purpose of clinical diagnosis..

In conclusion, the Curaçao clinical criteria have a good diagnostic performance. The sensitivity in patients with a mutation of the ENG gene was higher than in patients with an ACVRL1 gene mutation, but it should be noticed that screening for HAVM was not routinely performed. Importantly, only 1 out of 186 HHT patients, a 28-year-old male, was incorrectly classified as 'unlikely'. The additional use of TTCE as a clinical criterion resulted in a modestly increased sensitivity, but this benefit was largely counterbalanced by a higher false-positive rate of clinical diagnoses.

Reference List

1. Cottin V, Chinet T, Lavole A, Corre R, Marchand E, Reynaud-Gaubert M, Plauchu H, Cordier JF. Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: a series of 126 patients. Medicine (Baltimore) 2007;86:1-17.
2. White RI, Jr., Lynch-Nyhan A, Terry P, Buescher PC, Farmlett EJ, Charnas L, Shuman K, Kim W, Kinnison M, Mitchell SE. Pulmonary arteriovenous malformations: techniques and long-term outcome of embolotherapy. Radiology 1988;169:663-669.
3. Shovlin CL, Jackson JE, Bamford KB, Jenkins IH, Benjamin AR, Ramadan H, Kulinskaya E. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. Thorax 2008;63:259-266.
4. Mager JJ, Overtoom TT, Blauw H, Lammers JW, Westermann CJ. Embolotherapy of pulmonary arteriovenous malformations: long-term results in 112 patients. J Vasc Interv Radiol 2004;15:451-456.
5. Moussouttas M, Fayad P, Rosenblatt M, Hashimoto M, Pollak J, Henderson K, Ma TY, White RI. Pulmonary arteriovenous malformations: cerebral ischemia and neurologic manifestations. Neurology 2000;55:959-964.
6. Dutton JA, Jackson JE, Hughes JM, Whyte MK, Peters AM, Ussov W, Allison DJ. Pulmonary arteriovenous malformations: results of treatment with coil embolization in 53 patients. AJR Am J Roentgenol 1995;165:1119-1125.
7. Haitjema TJ, Overtoom TT, Westermann CJ, Lammers JW. Embolisation of pulmonary arteriovenous malformations: results and follow up in 32 patients. Thorax 1995;50:719-723.
8. Lee DW, White RI, Jr., Egglin TK, Pollak JS, Fayad PB, Wirth JA, Rosenblatt MM, Dickey KW, Burdge CM. Embolotherapy of large pulmonary arteriovenous malformations: long-term results. Ann Thorac Surg 1997;64:930-939.
9. Remy-Jardin M, Dumont P, Brillet PY, Dupuis P, Duhamel A, Remy J. Pulmonary arteriovenous malformations treated with embolotherapy: helical CT evaluation of long-term effectiveness after 2-21-year follow-up. Radiology 2006;239:576-585.
10. White RI, Jr., Pollak JS, Wirth JA. Pulmonary arteriovenous malformations: diagnosis and transcatheter embolotherapy. J Vasc Interv Radiol 1996;7:787-804.
11. Faughnan ME, Granton JT, Young LH. The pulmonary vascular complications of hereditary haemorrhagic telangiectasia. Eur Respir J 2009;33:1186-1194.

12. Cottin V, Dupuis-Girod S, Lesca G, Cordier JF. Pulmonary vascular manifestations of hereditary hemorrhagic telangiectasia (rendu-osler disease). Respiration 2007;74:361-378.
13. van Gent MW, Post MC, Luermans JG, Snijder RJ, Westermann CJ, Plokker HW, Overtoom TT, Mager JJ. Screening for pulmonary arteriovenous malformations using transthoracic contrast echocardiography: a prospective study. Eur Respir J 2009;33:85-91.
14. Nanthakumar K, Graham AT, Robinson TI, Grande P, Pugash RA, Clarke JA, Hutchison SJ, Mandzia JL, Hyland RH, Faughnan ME. Contrast echocardiography for detection of pulmonary arteriovenous malformations. Am Heart J 2001;141:243-246.
15. Lee WL, Graham AF, Pugash RA, Hutchison SJ, Grande P, Hyland RH, Faughnan ME. Contrast echocardiography remains positive after treatment of pulmonary arteriovenous malformations. Chest 2003;123:351-358.
16. Kjeldsen AD, Oxhoj H, Andersen PE, Elle B, Jacobsen JP, Vase P. Pulmonary arteriovenous malformations: screening procedures and pulmonary angiography in patients with hereditary hemorrhagic telangiectasia. Chest 1999;116:432-439.
17. Plauchu H, de Chadarevian JP, Bideau A, Robert JM. Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. Am J Med Genet 1989;32:291-297.
18. Porteous ME, Burn J, Proctor SJ. Hereditary haemorrhagic telangiectasia: a clinical analysis. J Med Genet 1992;29:527-530.
19. Berg J, Porteous M, Reinhardt D, Gallione C, Holloway S, Umasunthar T, Lux A, McKinnon W, Marchuk D, Guttmacher A. Hereditary haemorrhagic telangiectasia: a questionnaire based study to delineate the different phenotypes caused by endoglin and ALK1 mutations. J Med Genet 2003;40:585-590.
20. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, Kjeldsen AD, Plauchu H. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000;91:66-67.
21. Gazzaniga P, Buscarini E, Leandro G, Reduzzi L, Grosso M, Pongiglione G, Pedrinazzi C, Lanzarini L, Portugalli V, Blotta P, Forner P, Boccardi E, Pagella F, Manfredi G, Olivieri C, Zambelli A, Danesino C, Inama G. Contrast echocardiography for pulmonary arteriovenous malformations screening: does any bubble matter? Eur J Echocardiogr 2009;10:513-518.
22. Abdalla SA, Letarte M. Hereditary haemorrhagic telangiectasia: current views on genetics and mechanisms of disease. J Med Genet 2006;43:97-110.

23. Gallione CJ, Repetto GM, Legius E, Rustgi AK, Schelley SL, Tejpar S, Mitchell G, Drouin E, Westermann CJ, Marchuk DA. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). Lancet 2004;363:852-859.
24. Cole SG, Begbie ME, Wallace GM, Shovlin CL. A new locus for hereditary haemorrhagic telangiectasia (HHT3) maps to chromosome 5. J Med Genet 2005;42:577-582.
25. Bayrak-Toydemir P, McDonald J, Akarsu N, Toydemir RM, Calderon F, Tuncali T, Tang W, Miller F, Mao R. A fourth locus for hereditary hemorrhagic telangiectasia maps to chromosome 7. Am J Med Genet A 2006;140:2155-2162.
26. Prigoda NL, Savas S, Abdalla SA, Piovesan B, Rushlow D, Vandezande K, Zhang E, Ozcelik H, Gallie BL, Letarte M. Hereditary haemorrhagic telangiectasia: mutation detection, test sensitivity and novel mutations. J Med Genet 2006;43:722-728.
27. Bossler AD, Richards J, George C, Godmilow L, Ganguly A. Novel mutations in ENG and ACVRL1 identified in a series of 200 individuals undergoing clinical genetic testing for hereditary hemorrhagic telangiectasia (HHT): correlation of genotype with phenotype. Hum Mutat 2006;27:667-675.
28. Letteboer TG, Zewald RA, Kamping EJ, de HG, Mager JJ, Snijder RJ, Lindhout D, Hennekam FA, Westermann CJ, Ploos van Amstel JK. Hereditary hemorrhagic telangiectasia: ENG and ALK-1 mutations in Dutch patients. Hum Genet 2005;116:8-16.
29. Govani FS, Shovlin CL. Hereditary haemorrhagic telangiectasia: a clinical and scientific review. Eur J Hum Genet 2009;17:860-871.
30. Bossler AD, Richards J, George C, Godmilow L, Ganguly A. Novel mutations in ENG and ACVRL1 identified in a series of 200 individuals undergoing clinical genetic testing for hereditary hemorrhagic telangiectasia (HHT): correlation of genotype with phenotype. Hum Mutat 2006;27:667-675.
31. Faughnan ME, Palda VA, Garcia-Tsao G, Geisthoff UW, McDonald J, Proctor DD, Spears J, Brown DH, Buscarini E, Chesnutt MS, Cottin V, Ganguly A, Gossage JR, Guttmacher AE, Hyland RH, Kennedy SJ, Korzenik J, Mager JJ, Ozanne AP, Piccirillo JF, Picus D, Plauchu H, Porteous ME, Pyeritz RE, Ross DA, Sabba C, Swanson K, Terry P, Wallace MC, Westermann CJ, White RI, Young LH, Zarrabeitia R. International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia. J Med Genet 2009.

32. Sabba C, Pasculli G, Lenato GM, Suppressa P, Lastella P, Memeo M, Dicuonzo F, Guant G. Hereditary hemorrhagic telangiectasia: clinical features in ENG and ALK1 mutation carriers. J Thromb Haemost 2007;5:1149-1157.
33. Lesca G, Olivieri C, Burnichon N, Pagella F, Carette MF, Gilbert-Dussardier B, Goizet C, Roume J, Rabilloud M, Saurin JC, Cottin V, Honnorat J, Coulet F, Giraud S, Calender A, Danesino C, Buscarini E, Plauchu H. Genotype-phenotype correlations in hereditary hemorrhagic telangiectasia: data from the French-Italian HHT network. Genet Med 2007;9:14-22.
34. Bossler AD, Richards J, George C, Godmilow L, Ganguly A. Novel mutations in ENG and ACVRL1 identified in a series of 200 individuals undergoing clinical genetic testing for hereditary hemorrhagic telangiectasia (HHT): correlation of genotype with phenotype. Hum Mutat 2006;27:667-675.
35. van Gent MW, Post MC, Luermans JG, Snijder RJ, Westermann CJ, Plokker HW, Overtoom TT, Mager JJ. Screening for pulmonary arteriovenous malformations using transthoracic contrast echocardiography: a prospective study. Eur Respir J 2008.
36. Cottin V, Plauchu H, Bayle JY, Barthelet M, Revel D, Cordier JF. Pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. Am J Respir Crit Care Med 2004;169:994-1000.
37. Woods TD, Patel A. A critical review of patent foramen ovale detection using saline contrast echocardiography: when bubbles lie. J Am Soc Echocardiogr 2006;19:215-222.

Part III

Pulmonary arteriovenous malformations and migraine

6

The relation between intrapulmonary right-to-left shunt and migraine: a review

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Abstract

Migraine is a common and disabling disorder. Pulmonary arteriovenous malformations (PAVMs) cause a right-to-left shunt (RLS). An increased prevalence of migraine, particularly migraine with aura (MA+), has been shown in patients with a RLS of both pulmonary and cardiac origin. The prevalence of PAVM in patients with hereditary haemorrhagic telangiectasia (HHT) is 15-45%. Therefore, the HHT population provides a unique opportunity to study the RLS-migraine hypothesis. Embolisation of PAVMs might reduce the prevalence of migraine, and an association between PAVM in HHT patients and MA+ was recently shown in a prospective study. The current review focuses on the evidence of a real association between an intrapulmonary RLS and migraine, and summarizes the possible underlying pathogenesis.

Introduction

Following the early observations of an increased prevalence of a patent foramen ovale (PFO) in patients with stroke at young age or decompression sickness,[1-4] a possible link between PFO and migraine was also suggested during the late nineties.[5, 6] Although this association between an intracardiac right-to-left shunt (RLS) and migraine has been extensively studied since then, it is nowadays still surrounded by much controversy. As the pathogenesis of migraine in patients with an interatrial RLS might be related to the RLS per se, an increased prevalence of migraine might as well be expected in patients with an intrapulmonary RLS. In this respect, it is of interest that clinicians have reported on a remarkably high prevalence of migraine in patients with hereditary haemorrhagic telangiectasia (HHT) for already a long time.[7 8] The prevalence of pulmonary arteriovenous malformations (PAVM), a specific pulmonary RLS, in HHT patients is high. These observations might suggest a possible link between intrapulmonary shunting and migraine. In this review, we will focus on the available evidence in support of this hypothesis.

Pulmonary arteriovenous malformations

Definition and complications

A PAVM is a direct communication between a pulmonary artery and a pulmonary vein, bypassing the pulmonary capillary filter. Consequently, a PAVM elicits a RLS and may result in hypoxaemia and paradoxical embolism, both of thromboembolic and septic origin (figure 1). This is believed to underly the high incidence of severe neurological complications such as stroke (8-19%) and brain abscess (10-36%) in patients with HHT.[9-13]

PAVMs can have a simple or complex angioarchitecture. In a simple PAVM, a single artery feeds an aneurysmal communication with a single draining vein; in a complex PAVM, one or more artery branches feed an aneurysmal sac with two or more draining veins.[14] Most PAVMs are multiple but ~5% of HHT patients have diffuse PAVMs, which result in a particular high rate of complications.[15, 16]

Prevalence

It is estimated that at least 70% of PAVMs can be attributed to HHT. However, in our experience, in a tertiary care hospital, HHT is diagnosed in more than 90% of patients with a PAVM. Using chest CT, the prevalence of PAVM in HHT patients is 15-45%.[17-20] A pulmonary shunt on contrast echocardiography has been reported in 59% of HHT patients.[21]

Besides HHT, pulmonary shunting is most frequently found in patients with hepatic cirrhosis (hepatopulmonary syndrome).[22]

The exact prevalence of PAVM in the general population is unknown. We and others have reported on an echocardiographic pulmonary RLS in 6-9% of a control group of persons in whom HHT was excluded.[21, 23] However, a Valsalva manoeuvre was not routinely performed in these studies. A large pulmonary shunt has also been reported in 5% of the patients in the MIST trial, although the percentage of pulmonary RLS overall was not mentioned.[24] A pulmonary shunt has been reported in 4% of patients referred for transesophageal echocardiography (TEE) for various indications.[25] A secondary source of RLS, most likely intrapulmonary shunting, was diagnosed in 17 of 84 (20%) patients during balloon occlusion of a PFO.[26]

Hereditary haemorrhagic telangiectasia

HHT is a vascular disorder and inherited as an autosomal dominant trait. The estimated prevalence is 1/5000.[27] The vascular malformations in HHT patients are associated with mutations in genes implicated in the transforming growth factor β (TGF-β) signalling pathway in vascular endothelium.[28] Vascular anomalies in HHT range from telangiectases to large visceral AVMs and are predominantly found in the lung, brain and liver. HHT is divided in two main subtypes. HHT type 1 (HHT1) is caused by mutations in the ENG gene encoding endoglin, whereas HHT type 2 (HHT2) is caused by mutations in the ACVRL1 (activin receptor-like kinase) gene encoding ALK-1. HHT1 is characterized by a more aggressive phenotype as a result of a higher prevalence of PAVM compared with HHT2. PAVMs on chest CT are present in 48-75% of HHT1 patients, and in 5-44% of HHT2 patients.[19, 29-32] A prevalence of pulmonary shunts on echocardiography up

to 85% in HHT1 patients has been documented, compared with 35% in patients with HHT2.[21]

Diagnosis

Although chest CT has traditionally been the screening method of choice, transthoracic contrast echocardiography (TTCE) is being increasingly used to detect intrapulmonary shunting in HHT patients. TTCE has proven to be very sensitive for the detection of intrapulmonary shunts that are not visible on chest CT or pulmonary angiography.[18, 20, 33] In order to avoid the radiation exposure of chest CT, TTCE is used as a first-line screening technique in many specialized HHT centers, as was recently recommended in the international guidelines for the diagmosis and treatment of HHT patients.[34] However, a chest CT remains ultimately needed to guide treatment decisions when a shunt is detected by TTCE. Because of its possible detrimental consequences, screening for PAVMs is routinely performed in all possible HHT patients.

Treatment

PAVMs are treated by transcatheter embolotherapy. Long-term results with this technique are excellent.[10, 13, 35] PAVMs with a feeding artery ≥ 3mm should inevitably be embolized,[36] but smaller PAVMS are also treated in many specialized centres when technically feasible. It appears that neurological complications can be completely abolished if all angiographically visible PAVMs are embolised.[12]

In order to prevent brain abscess, antibiotic prophylaxis is recommended prior to procedures carrying the risk of bacteraemia in HHT patients with pulmonary shunts.[12, 37]

Migraine

Migraine is a common, chronic and intermittent headache disorder with disabling consequences. The estimated prevalence in the general population is ~12%, affecting women 3 to 4 time more frequently than men.[38] The prevalence increases with age until 40 years and declines thereafter.[39] The diagnosis is based on criteria drawn up by the International Headache Society (table 1).[40] Two main subgroups

are migraine with (MA+) and without aura (MA-). Aura has been described in one third of migraineurs.[41]

The pathophysiology of migraine is complex. There appears to be a strong genetic component, particularly in MA+, while both genetic and environmental factors are important in MA-.[42] The migraine aura is thought to be caused by cortical spreading depression (CSD).[43] This comes down to neuronal excitation which is followed by prolonged inhibition of neuronal activity.[43] This hypothesis is supported by human blood flow studies which showed a focal hyperaemia preceding the spreading oligaemia (reduced cortical blood flow) in the occipital cortex during migraine with aura.[44] In addition, a recent randomised placebo-controlled trial studying tonabersat, a drug with a known inhibitory effect on CSD, demonstrated a preventive effect on MA+, but not MA-, further supporting this pathogenesis in aura.[45] The origin of the migraine headache relates to nociceptive stimuli of the trigeminovascular system which can be modulated centrally through input from the thalamus and midbrain, and activated by the CSD.[46]

Pulmonary arteriovenous malformations and migraine

Migraine in HHT patients: is it related to HHT, PAV M, or both?

Following the early observations of an unusual high prevalence of headache disorders in HHT patients,[7, 8] Steele and colleagues specifically addressed the subject of migraine in HHT patients for the first time.[47] By means of a headache questionnaire they compared the prevalence of migraine in 53 HHT patients and 35 controls. The most striking finding in their study was a MA+ prevalence of 55% in HHT patients compared to 14% in controls ($p<0.001$).[47] The prevalence of MA- differed non-significantly between both groups (8% in HHT patients versus 26% in controls). Bayrak and colleagues observed a higher prevalence of migraine in patients with the HHT1 subtype (35% of 61 patients) compared to HHT2 patients (16% in 50 patients; $p=0.042$).[48] They did not discern MA+ from MA- in this study. The question at this point was what the causal factor of migraine in HHT might be and both cerebral AVM (CAVM) and PAVM were proposed. An association between CAVM and migraine had been suggested,[49, 50] but as pointed out by Steele and colleagues the prevalence of CAVM in HHT is probably too low to explain these findings.[47]

Table 1. Diagnostic criteria for migraine without aura and migraine with aura according to the criteria of the International Classification of Headache Disorders (International Headache Society)[40]

Migraine without aura	Migraine with aura
A. At least 5 attacks fulfilling criteria B–D	**A. At least 2 attacks fulfilling criteria B–D**
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)	**B. Aura consisting of at least one of the following, but no motor weakness:** 1. fully reversible visual symptoms including positive features (*eg*, flickering lights, spots or lines) and/or negative features (*ie*, loss of vision) 2. fully reversible sensory symptoms including positive features (*ie*, pins and needles) and/or negative features (*ie*, numbness) 3. fully reversible dysphasic speech disturbance
C. Headache has at least two of the following characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing avoidance of routine physical activity (*eg*, walking or climbing stairs)	**C. At least two of the following:** 1. homonymous visual symptoms and/or unilateral sensory symptoms 2. at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes 3. each symptom lasts ≥5 and 60 minutes
D. During headache at least one of the following 1. nausea and/or vomiting 2. photophobia and phonophobia	**D. Headache fulfilling criteria B–D for Migraine without aura;** begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder	**E. Not attributed to another disorder**

Several small observational studies concerning patients with symptomatic PAVMs, for the larger part HHT patients, have reported a migraine prevalence of 38% to 59%.[13, 51, 52] However, further specification was not available as migraine was not the main subject of interest in these studies. Following these observations, subsequent studies have focused on the role of PAVM as an explanatory factor for the increased prevalence of migraine in HHT patients. Our group reported a large retrospective series of 538 confirmed (clinically or genetically) HHT patients, the prevalence of self-reported migraine was 16.4%.[19] Furthermore, migraine was significantly more frequently diagnosed in the subset of 208 patients with a

documented PAVM compared to patients without a PAVM (21 vs 13%; p=0.02). Although CAVM was significantly more frequent in migraineurs than non-migraineurs, the association between PAVM and migraine
was sustained after exclusion of patients with CAVM.[19] However, brain imaging was only performed in 13% of patients, and no distinction made between MA+ and MA- in this study. Thenganatt and colleagues also reported on migraine and its relationship to PAVM in HHT patients.[53] They retrospectively studied 124 HHT patients of whom 38% had a history of migraine. Of migraineurs, 81% reported symptoms compatible with MA+. After correction for sex and age, PAVM appeared to be an independent predictor for migraine in HHT patients (OR 2.2; 95% CI 1.1-5.5; p=0.04).[53] Marziniak and colleagues compared migraine in 106 patients with a clinically confirmed diagnosis of HHT to an identical number of age and gender pair-matched controls.[54] In their study the prevalence of migraine in HHT patients was 40% compared to 20% in controls (OR 3.0; 95% CI 1.6-5.7l p<0.001). Of note, this difference could be largely attributed to a higher prevalence of MA- in HHT patients compared to controls (OR 2.29; 95% CI 1.08-4.87; p=0.043), whereas MA+ was not significant more frequently diagnosed in HHT patients (OR 2.21; 95% CI 0.94-5.16; p=0.098).[54] However, when evaluating the association of PAVM with migraine in the HHT group, the prevalence of MA+ was 39% in HHT patients with a PAVM compared with 10% in those without a PAVM (p=0.003).[54] Conversely, MA- was significantly more prevalent in HHT patients without PAVMs (26% vs 12%). The authors hypothesized that the increased prevalence of MA- in HHT patients might be related to an abnormality of TGF-β levels or the impaired TGF-β signaling pathway, the principle abnormality involved in HHT related vasculopathy.[54] Recently we were able to confirm the association of PAVM with MA+ prospectively in 196 HHT patients (see chapter 7 of this thesis).[55] A PAVM was present in 68% of 25 MA+ patients compared to 32% of 157 non-migraineurs. The presence of a PAVM was an independent predictor for MA+ after multivariate analysis (OR 3.0; 95% CI 1.0-9.2; p=0.05).[56] Consistent with previous studies, MA- was not associated with PAVM in this study either. An overview of reported studies is provided in table 1.

The question remains if MA+ in HHT can be attributed solely to pulmonary shunting, as it seems also conceivable that a yet unknown HHT related factor is involved. However, the only study using a control group of persons without HHT found no difference in MA+ prevalence between HHT patients overall and controls, but showed indeed a largely increased prevalence of MA+ in the HHT subgroup with PAVMs.[54] Futhermore, in 200 patients with a history of decompression illness, Wilmshurst and Nightingale described MA+ in 29% of 14 patients with echocardiographic evidence of a pulmonary shunt, as compared to 14% in the group without a shunt.[57] These findings are in support of an intrapulmonary RLS per se as the causal link with migraine, apart from HHT. Given the fact that the larger part of intrapulmonary shunts is related to HHT,[17] it will be difficult to study this causality in a sufficient number of patients without HHT.

Table 2. Prevalence of migraine in HHT patients with and without a PAVM

Authors	Patients (n)	Design	Female (%)	Age (yr)	Migraine (%)	MA+ (%)	PAVM (%)	Migraine[19,53] or MA+[54,55] (%)			P
								PAVM+	PAVM-	OR (95% CI)	
Thenganatt et al.[53]	124	retrospective	65	43(15-87)	38	31	41	46	33	2.4 (1.1-5.5)	0.04
Post et al.[19]	538	retrospective	58	39±19	16	-	39	21	13	-	0.02
Marziniak et al.[54*]	106	case-control	63	54±15	40	23	25	39	10	-	0.003
Post et al.[55]	196	prospective	57	45±15	20	13	36	24	6	4.6 (1.84-11.2)	0.001

*MA+=migraine with aura; PAVM=pulmonary arteriovenous malformation; HHT = Hereditary hemorrhagic telangiectasia; OR: Odds ratio; CI: Confidence interval; *Only data of HHT patients in this table (not the control group)*

Does the size of intrapulmonary shunting correlate with migraine?

To date no studies have specifically addressed this issue. In a study using pulmonary angiography, migraine was diagnosed in 50% of 26 patients with a single PAVM compared to 63% of patients with multiple PAVMs (p=0.27).[11] In another study the size of RLS was evaluated by MR angiography, and it was reported that PAVMs were not larger in patients with MA+ compared to MA- or non-migraineurs, although no specific data on this subject were provided.[54] Other studies did not distinguish between different size and number of PAVMs.[53, 56] However, patients with a visible PAVM on chest CT or angiography are expected to have a relatively large RLS. Of note, the absence of a visisble PAVM on chest CT or angiography does not imply that a meaningful shunt is also absent.[33, 58] As mentioned earlier, this is probably explained by microscopic shunting below the detection limit of chest CT. Both Thenganatt and Marziniak used contrast echocardiography studies but these were not semi-quantitatively assessed.[53, 54] As TTCE is capable to determine the functional potential of RLS, it would be interesting to evaluate the influence of shunt size on migraine prevalence. In patients with a PFO, shunt size appears to be related to MA+.[59-62] This could establish if smaller pulmonary shunts, as frequently shown in HHT (particularly HHT2) patients, also relate to migraine.

Does treatment of PAVM reduce migraine?

In a retrospective series of 84 HHT patients with PAVMs who underwent embolotherapy, the prevalence of migraine overall decreased from 45% before to 35% after embolisation (p=0.01).[63] The prevalence of MA+ also decreased, from 33% before to 19% after embolotherapy (p=0.002). Median follow-up was 48 months in this study. Thenganatt and colleagues shortly described a decrease in frequency of migraine in 44% of 18 patients undergoing PAVM closure.[53] Obviously, the retrospective study design is prone to recall bias and placebo effects, the latter being a known interfering factor in migraine studies. Therefore, prospective studies on this subject are awaited.

Migraine with aura appears to be consistently related to intrapulmonary shunting, so why is its association with patent foramen ovale still controversial?

Although an association between MA+ and PFO has been suggested in several case-control studies,[5, 6, 59, 64] a true relationship has been questioned in a recent population-based study.[65] Notably, as in patients with pulmonary shunts, the association with migraine appears to be restricted to MA+. No consistent increase in MA- prevalence has been shown.[66] The only prospective study evaluating the effect of PFO closure on migraine did not show a beneficial effect, but has been debated for some methodological constraints.[24] However, the functional capacity of a PFO to cause a RLS, rather than merely its presence, appears to be also of importance. This was suggested by Wilmshurst and colleagues who showed that migraine is stronger related to a RLS that is present during normal breathing as opposed to a RLS that can only be provoked by strain manoeuvres.[62] In addition, an increased prevalence of MA+ has been shown in patients with a large RLS compared to those with smaller shunts.[59-61] Likewise, Giardini and coworkers have shown that in patients with a PFO, those with MA+ had a higher prevalence of both spontaneous and large shunts than non-migraineurs. Unlike the situation in most PFOs, PAVMs do not need provocative manoeuvres to cause a RLS. Therefore, it might be speculated that the increased time of an effectively present RLS in PAVMs explains a more consistent association with MA+ than has been shown for PFO.

What is the pathogenesis of migraine in patients with an intrapulmonary shunt?

The exact nature of the relation between migraine and intrapulmonary RLS is not clear. There are two main theories proposed (figure 1).[67, 68] The first is paradoxical embolisation to the brain of venous thrombi. This may be supported by the finding that migraine patients appear to have more subclinical white matter lesions on brain MRI than controls.[69] Furthermore, migraine, stroke, and brain abscess have a high prevalence in patients with PAVMs, suggesting RLS as a common cause. In addition, acetylsalicylic acid and coumarins may have a beneficial effect on migraine.[70, 71] The second theory is based on a shunt of chemical substances to the arterial circulation. Normally, a considerable amount of biogenic amines is

filtered in the pulmonary capillary network,[72] which is in part bypassed in the presence of PAVM. Serotonin has been the most frequently proposed vasoactive peptide involved. In this respect, it is of interest that triptans, which interfere with a subgroup of serotonin receptors, are effective in the treatment migraine.[73] It is speculated that these proposed mechanisms might initiate the CSD and from that cause the aura phenomenon. Indeed, local cerebral hypoperfusion appears to be a final common event for CSD initiation, and cerebral microembolisation has been proven to trigger the CSD in animal experiments, probably by inducing brief hypoxic-ischaemic episodes.[74] Vasoactive substances may induce hypoperfusion by affecting local cerebral blood flow.[74]

Coinheritance might theoretically also be involved in the increased prevalence of RLS in MA+ patients. A dominant inheritance pattern of atrial shunts has been shown which was linked to inheritance of MA+ as well.[75] However, the observation that both cardiac and pulmonary shunts are related to MA+ renders this less likely as an explanation. Furthermore, the association between MA+ and PAVM has shown to be sustained in both HHT1 and HHT2 which are caused by gene mutations on different chromosomes.[56] Finally, the beneficial effect of shunt closure on migraine contradicts this hypothesis.

Increased hemoglobin levels have also been linked to migraine,[76] but this is uncommon in HHT patients, and the opposite (anaemia) is frequently observed as these patients often suffer from epistaxis and gastrointestinal blood loss due to telangiectases.

Large pulmonary shunts may cause hypoxaemia, which has also been proposed as a causal factor in migraine.[77, 78] However, we have shown that arterial oxygen tension was only non-significantly reduced in MA+ patients compared to non-migraineurs (10.2 vs 11.0 kPa; p=0.17) in HHT patients.[56]

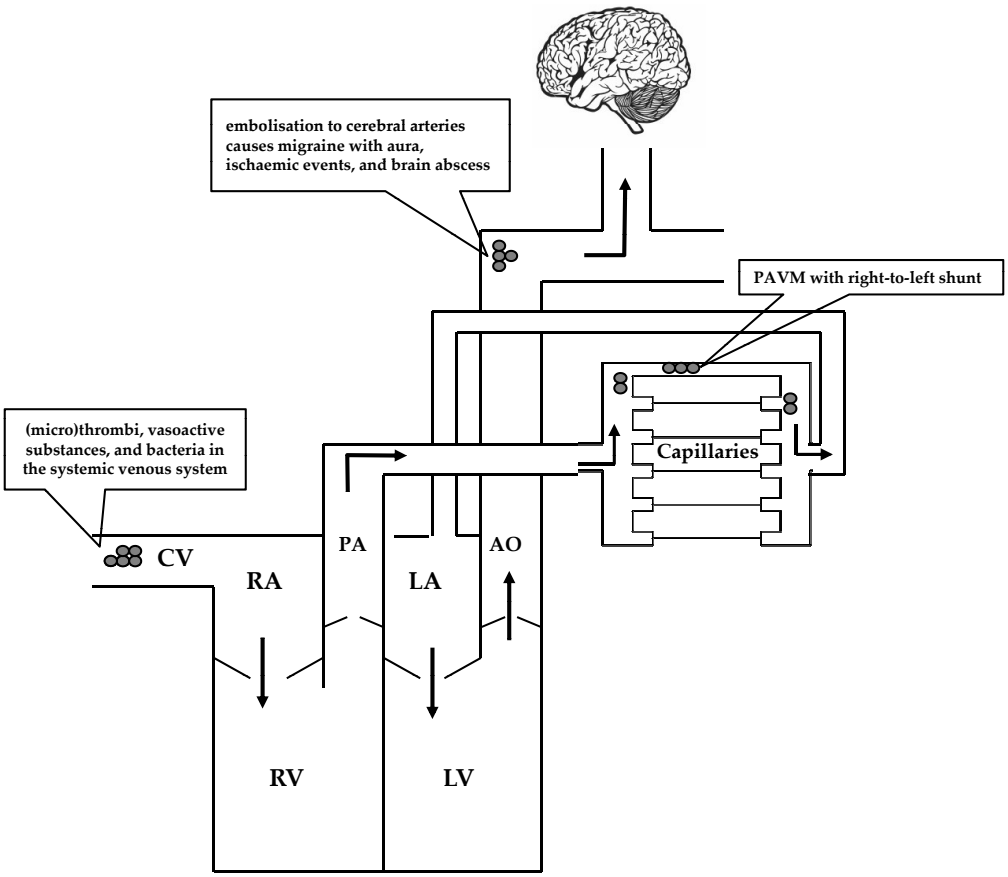

Figure 1. Pathogenesis of paradoxical embolisation through pulmonary arteriovenous malformations and its consequences

(Micro)thrombi, vasoactive substances, and bacteria in the systemic venous system are under normal conditions filtered in the pulmonary capillary network. In the presence of a PAVM, this filter is bypassed and paradoxical embolisation occurs. As a consequence, migraine with aura, cerebral ischaemic events, and brain abscess may occur.

CV: caval veins; RA: right atrium; RV: right ventricle; PA: pulmonary artery; LA: left atrium; LV: left ventricle; AO: aorta; PAVM: pulmonary arteriovenous malformation

Limitations of published studies on right-to-left shunt and migraine

As migraine is particularly prone for confounding factors, it is important to address the methodological aspects of studies on the association of RLS and migraine. For example, retrospective data collection is less reliable, and recall bias and placebo effects[79] may be present. In addition, few studies report on medication use. The concept of case-control studies, on which most data on an association of RLS and migraine are based, risks an overestimation of migraine as control-populations are frequently healthier or have RLS associated conditions, resulting in a selection bias.[80] These biases may be overcome by using a population-based approach. However, these studies are often hampered by data on self-reported migraine.[65]
Direct comparison of different studies is also restricted because different methods are used to detect RLS. TTCE, TEE, TCD, and chest CT have been used, and results from these techniques are not always interchangeable. Even between studies using the same diagnostic modality, comparison is difficult as very different cut-off values for small or large shunts are employed.

Clinical implications of published studies and future directions for research

It appears that PAVMs, which constitute a permanent RLS, are indeed associated with MA+. This information is important for the approach of RLS per se, and PFO in particular, when studying its association with MA+. In our opinion, the functional potential of a RLS should specifically be addressed. In this respect, it is not unexpected that conflicting results have been reported on an association of PFO with migraine when all PFOs are regarded as equal. It is important to differentiate PFOs that can only be visualized with provocative manoeuvres from PFOs that are spontaneously present. Information on these aspects of RLS should be routinely implemented in future studies on the RLS-migraine relationship. The importance to focus on patients with MA+ and large shunts was recently shown, as a beneficial effect of PFO closure was reported in patients with large shunts through a PFO who also had evidence of paradoxical cerebral embolism.[81, 82]
Although the question whether or not to treat a RLS does not apply to PAVMs, that are already routinely embolised whenever large enough, it would be interesting to know if treatment of PAVMs reduces migraine. A reduction in migraine after

embolisation of PAVMs would provide substantial support for the RLS-migraine hypothesis. Because it is regarded unethical to withhold treatment of PAVMs, this cannot be studied in a randomized fashion. Therefore, the concluding piece of evidence is expected from large, multi-centre, sham-controlled trials on the effect of PFO closure on MA+. Lessons should be learned from the MIST-trial.[24] This implies that data on shunt size post-embolisation are essential, patients with paradoxical embolisation should not be excluded, and detailed data on use of migraine attack medication should be reported. Several of such trials are currently enrolling patients.

Conclusion

Surveying the available evidence, there appears to be a consistent association between intrapulmonary shunting and MA+, but not MA-. Although less decisive, comparable findings have been shown for the association of PFO with migraine. This suggests that a RLS per se might play a role in the pathogenesis of MA+, independent of its location. Prospective trials on the efficacy of shunt closure on migraine could provide more clarity on the existence of a real causal relationship in this subgroup of migraineurs.

Reference List

1. Webster MW, Chancellor AM, Smith HJ, Swift DL, Sharpe DN, Bass NM, Glasgow GL. Patent foramen ovale in young stroke patients. Lancet 1988;2:11-12.
2. Lechat P, Mas JL, Lascault G, Loron P, Theard M, Klimczac M, Drobinski G, Thomas D, Grosgogeat Y. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988;318:1148-1152.
3. Moon RE, Camporesi EM, Kisslo JA. Patent foramen ovale and decompression sickness in divers. Lancet 1989;1:513-514.
4. Wilmshurst PT, Byrne JC, Webb-Peploe MM. Neurological decompression sickness. Lancet 1989;1:731.
5. Del SM, Angeli S, Leandri M, Ferriero G, Bruzzone GL, Finocchi C, Gandolfo C. Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. Cerebrovasc Dis 1998;8:327-330.
6. Anzola GP, Magoni M, Guindani M, Rozzini L, Dalla VG. Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. Neurology 1999;52:1622-1625.
7. Boczko ML. Neurological implications of hereditary hemorrhagic telangiectasis. J Nerv Ment Dis 1964;139:525-536.
8. Hodgson CH, Burchell HB, Good CA, Clagett OT. Hereditary hemorrhagic telangiectasia and pulmonary arteriovenous fistula: survey of a large family. N Engl J Med 1959;261:625-636.
9. Cottin V, Chinet T, Lavole A, Corre R, Marchand E, Reynaud-Gaubert M, Plauchu H, Cordier JF. Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: a series of 126 patients. Medicine (Baltimore) 2007;86:1-17.
10. Mager JJ, Overtoom TT, Blauw H, Lammers JW, Westermann CJ. Embolotherapy of pulmonary arteriovenous malformations: long-term results in 112 patients. J Vasc Interv Radiol 2004;15:451-456.
11. Moussouttas M, Fayad P, Rosenblatt M, Hashimoto M, Pollak J, Henderson K, Ma TY, White RI. Pulmonary arteriovenous malformations: cerebral ischemia and neurologic manifestations. Neurology 2000;55:959-964.
12. Shovlin CL, Jackson JE, Bamford KB, Jenkins IH, Benjamin AR, Ramadan H, Kulinskaya E. Primary determinants of ischaemic stroke/brain abscess risks are independent

of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. Thorax 2008;63:259-266.

13. White RI, Jr., Lynch-Nyhan A, Terry P, Buescher PC, Farmlett EJ, Charnas L, Shuman K, Kim W, Kinnison M, Mitchell SE. Pulmonary arteriovenous malformations: techniques and long-term outcome of embolotherapy. Radiology 1988;169:663-669.
14. Remy J, Remy-Jardin M, Wattinne L, Deffontaines C. Pulmonary arteriovenous malformations: evaluation with CT of the chest before and after treatment. Radiology 1992;182:809-816.
15. Pierucci P, Murphy J, Henderson KJ, Chyun DA, White RI, Jr. New definition and natural history of patients with diffuse pulmonary arteriovenous malformations: twenty-seven-year experience. Chest 2008;133:653-661.
16. Faughnan ME, Lui YW, Wirth JA, Pugash RA, Redelmeier DA, Hyland RH, White RI, Jr. Diffuse pulmonary arteriovenous malformations: characteristics and prognosis. Chest 2000;117:31-38.
17. Gossage JR, Kanj G. Pulmonary arteriovenous malformations. A state of the art review. Am J Respir Crit Care Med 1998;158:643-661.
18. Cottin V, Plauchu H, Bayle JY, Barthelet M, Revel D, Cordier JF. Pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. Am J Respir Crit Care Med 2004;169:994-1000.
19. Post MC, Letteboer TG, Mager JJ, Plokker TH, Kelder JC, Westermann CJ. A pulmonary right-to-left shunt in patients with hereditary hemorrhagic telangiectasia is associated with an increased prevalence of migraine. Chest 2005;128:2485-2489.
20. van Gent MW, Post MC, Luermans JG, Snijder RJ, Westermann CJ, Plokker HW, Overtoom TT, Mager JJ. Screening for pulmonary arteriovenous malformations using transthoracic contrast echocardiography: a prospective study. Eur Respir J 2009;33:85-91.
21. van Gent MW, Post MC, Snijder RJ, Westermann CJ, Plokker HW, Mager JJ. Real prevalence of pulmonary right-to-left shunt according to genotype in patients with hereditary hemorrhagic telangiectasia: a transthoracic contrast echocardiography study. Chest 2010.
22. Rodriguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome--a liver-induced lung vascular disorder. N Engl J Med 2008;358:2378-2387.

23. Gazzaniga P, Buscarini E, Leandro G, Reduzzi L, Grosso M, Pongiglione G, Pedrinazzi C, Lanzarini L, Portugalli V, Blotta P, Forner P, Boccardi E, Pagella F, Manfredi G, Olivieri C, Zambelli A, Danesino C, Inama G. Contrast echocardiography for pulmonary arteriovenous malformations screening: does any bubble matter? Eur J Echocardiogr 2009;10:513-518.
24. Dowson A, Mullen MJ, Peatfield R, Muir K, Khan AA, Wells C, Lipscombe SL, Rees T, De Giovanni JV, Morrison WL, Hildick-Smith D, Elrington G, Hillis WS, Malik IS, Rickards A. Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation 2008;117:1397-1404.
25. Daniels C, Weytjens C, Cosyns B, Schoors D, De SJ, Paelinck B, Muyldermans L, Van CG. Second harmonic transthoracic echocardiography: the new reference screening method for the detection of patent foramen ovale. Eur J Echocardiogr 2004;5:449-452.
26. Jesurum JT, Fuller CJ, Renz J, Krabill KA, Spencer MP, Reisman M. Diagnosis of secondary source of right-to-left shunt with balloon occlusion of patent foramen ovale and power M-mode transcranial Doppler. JACC Cardiovasc Interv 2009;2:561-567.
27. Kjeldsen AD, Vase P, Green A. Hereditary haemorrhagic telangiectasia: a population-based study of prevalence and mortality in Danish patients. J Intern Med 1999;245:31-39.
28. Abdalla SA, Letarte M. Hereditary haemorrhagic telangiectasia: current views on genetics and mechanisms of disease. J Med Genet 2006;43:97-110.
29. Bayrak-Toydemir P, McDonald J, Markewitz B, Lewin S, Miller F, Chou LS, Gedge F, Tang W, Coon H, Mao R. Genotype-phenotype correlation in hereditary hemorrhagic telangiectasia: mutations and manifestations. Am J Med Genet A 2006;140:463-470.
30. Lesca G, Olivieri C, Burnichon N, Pagella F, Carette MF, Gilbert-Dussardier B, Goizet C, Roume J, Rabilloud M, Saurin JC, Cottin V, Honnorat J, Coulet F, Giraud S, Calender A, Danesino C, Buscarini E, Plauchu H. Genotype-phenotype correlations in hereditary hemorrhagic telangiectasia: data from the French-Italian HHT network. Genet Med 2007;9:14-22.
31. Letteboer TG, Mager JJ, Snijder RJ, Koeleman BP, Lindhout D, Ploos van Amstel JK, Westermann CJ. Genotype-phenotype relationship in hereditary haemorrhagic telangiectasia. J Med Genet 2006;43:371-377.

32. Sabba C, Pasculli G, Lenato GM, Suppressa P, Lastella P, Memeo M, Dicuonzo F, Guant G. Hereditary hemorrhagic telangiectasia: clinical features in ENG and ALK1 mutation carriers. J Thromb Haemost 2007;5:1149-1157.
33. Lee WL, Graham AF, Pugash RA, Hutchison SJ, Grande P, Hyland RH, Faughnan ME. Contrast echocardiography remains positive after treatment of pulmonary arteriovenous malformations. Chest 2003;123:351-358.
34. Faughnan ME, Palda VA, Garcia-Tsao G, Geisthoff UW, McDonald J, Proctor DD, Spears J, Brown DH, Buscarini E, Chesnutt MS, Cottin V, Ganguly A, Gossage JR, Guttmacher AE, Hyland RH, Kennedy SJ, Korzenik J, Mager JJ, Ozanne AP, Piccirillo JF, Picus D, Plauchu H, Porteous ME, Pyeritz RE, Ross DA, Sabba C, Swanson K, Terry P, Wallace MC, Westermann CJ, White RI, Young LH, Zarrabeitia R. International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia. J Med Genet 2009.
35. Lee DW, White RI, Jr., Egglin TK, Pollak JS, Fayad PB, Wirth JA, Rosenblatt MM, Dickey KW, Burdge CM. Embolotherapy of large pulmonary arteriovenous malformations: long-term results. Ann Thorac Surg 1997;64:930-939.
36. White RI, Jr. Pulmonary arteriovenous malformations: how do I embolize? Tech Vasc Interv Radiol 2007;10:283-290.
37. Shovlin C, Bamford K, Wray D. Post-NICE 2008: Antibiotic prophylaxis prior to dental procedures for patients with pulmonary arteriovenous malformations (PAVMs) and hereditary haemorrhagic telangiectasia. Br Dent J 2008;205:531-533.
38. Lipton RB, Bigal ME. The epidemiology of migraine. Am J Med 2005;118 Suppl 1:3S-10S.
39. Silberstein SD. Migraine. Lancet 2004;363:381-391.
40. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24 Suppl 1:9-160.
41. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology 1999;53:537-542.
42. Russell MB. Genetic epidemiology of migraine and cluster headache. Cephalalgia 1997;17:683-701.
43. Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. Brain 1994;117 (Pt 1):199-210.

44. Olesen J, Larsen B, Lauritzen M. Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Ann Neurol 1981;9:344-352.
45. Hauge AW, Asghar MS, Schytz HW, Christensen K, Olesen J. Effects of tonabersat on migraine with aura: a randomised, double-blind, placebo-controlled crossover study. Lancet Neurol 2009;8:718-723.
46. Goadsby PJ. Pathophysiology of migraine. Neurol Clin 2009;27:335-360.
47. Steele JG, Nath PU, Burn J, Porteous ME. An association between migrainous aura and hereditary haemorrhagic telangiectasia. Headache 1993;33:145-148.
48. Bayrak-Toydemir P, McDonald J, Markewitz B, Lewin S, Miller F, Chou LS, Gedge F, Tang W, Coon H, Mao R. Genotype-phenotype correlation in hereditary hemorrhagic telangiectasia: mutations and manifestations. Am J Med Genet A 2006;140:463-470.
49. Bruyn GW. Intracranial arteriovenous malformation and migraine. Cephalalgia 1984;4:191-207.
50. Silvestrini M, Cupini LM, Calabresi P, Floris R, Bernardi G. Migraine with aura-like syndrome due to arteriovenous malformation. The clinical value of transcranial Doppler in early diagnosis. Cephalalgia 1992;12:115-119.
51. Puskas JD, Allen MS, Moncure AC, Wain JC, Jr., Hilgenberg AD, Wright C, Grillo HC, Mathisen DJ. Pulmonary arteriovenous malformations: therapeutic options. Ann Thorac Surg 1993;56:253-257.
52. White RI, Jr., Lynch-Nyhan A, Terry P, Buescher PC, Farmlett EJ, Charnas L, Shuman K, Kim W, Kinnison M, Mitchell SE. Pulmonary arteriovenous malformations: techniques and long-term outcome of embolotherapy. Radiology 1988;169:663-669.
53. Thenganatt J, Schneiderman J, Hyland RH, Edmeads J, Mandzia JL, Faughnan ME. Migraines linked to intrapulmonary right-to-left shunt. Headache 2006;46:439-443.
54. Marziniak M, Jung A, Guralnik V, Evers S, Prudlo J, Geisthoff UW. An association of migraine with hereditary haemorrhagic telangiectasia independently of pulmonary right-to-left shunts. Cephalalgia 2009;29:76-81.
55. Post MC, van Gent MW, Plokker HW, Westermann CJ, Kelder JC, Mager JJ, Overtoom TT, Schonewille WJ, Thijs V, Snijder RJ. Pulmonary arteriovenous malformations associated with migraine with aura. Eur Respir J 2009;34:882-887.
56. Post MC, van Gent MW, Plokker HW, Westermann CJ, Kelder JC, Mager JJ, Overtoom TT, Schonewille WJ, Thijs V, Snijder RJ. Pulmonary arteriovenous malformations associated with migraine with aura. Eur Respir J 2009.

57. Wilmshurst P, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. Clin Sci (Lond) 2001;100:215-220.
58. van Gent MW, Post MC, Snijder RJ, Swaans MJ, Plokker HW, Westermann CJ, Overtoom TT, Mager JJ. Grading of Pulmonary Right-to-Left Shunt With Transthoracic Contrast Echocardiography: Does It Predict the Indication for Embolotherapy? Chest 2009;135:1288-1292.
59. Schwerzmann M, Nedeltchev K, Lagger F, Mattle HP, Windecker S, Meier B, Seiler C. Prevalence and size of directly detected patent foramen ovale in migraine with aura. Neurology 2005;65:1415-1418.
60. Anzola GP, Morandi E, Casilli F, Onorato E. Different degrees of right-to-left shunting predict migraine and stroke: data from 420 patients. Neurology 2006;66:765-767.
61. Jesurum JT, Fuller CJ, Velez CA, Spencer MP, Krabill KA, Likosky WH, Gray WA, Olsen JV, Reisman M. Migraineurs with patent foramen ovale have larger right-to-left shunt despite similar atrial septal characteristics. J Headache Pain 2007;8:209-216.
62. Wilmshurst P, Pearson M, Nightingale S. Re-evaluation of the relationship between migraine and persistent foramen ovale and other right-to-left shunts. Clin Sci (Lond) 2005;108:365-367.
63. Post MC, Thijs V, Schonewille WJ, Budts W, Snijder RJ, Plokker HW, Westermann CJ. Embolization of pulmonary arteriovenous malformations and decrease in prevalence of migraine. Neurology 2006;66:202-205.
64. Ferrarini G, Malferrari G, Zucco R, Gaddi O, Norina M, Pini LA. High prevalence of patent foramen ovale in migraine with aura. J Headache Pain 2005;6:71-76.
65. Rundek T, Elkind MS, Di Tullio MR, Carrera E, Jin Z, Sacco RL, Homma S. Patent foramen ovale and migraine: a cross-sectional study from the Northern Manhattan Study (NOMAS). Circulation 2008;118:1419-1424.
66. Schwerzmann M, Nedeltchev K, Meier B. Patent foramen ovale closure: a new therapy for migraine. Catheter Cardiovasc Interv 2007;69:277-284.
67. Post MC, Budts W. The relationship between migraine and right-to-left shunt: Fact or fiction? Chest 2006;130:896-901.
68. Post MC, van Gent MW, Snijder RJ, Mager JJ, Schonewille WJ, Plokker HW, Westermann CJ. Pulmonary arteriovenous malformations and migraine: a new vision. Respiration 2008;76:228-233.

69. Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD, Launer LJ. Migraine as a risk factor for subclinical brain lesions. JAMA 2004;291:427-434.
70. Fragoso YD. Reduction of migraine attacks during the use of warfarin. Headache 1997;37:667-668.
71. Lipton RB, Goldstein J, Baggish JS, Yataco AR, Sorrentino JV, Quiring JN. Aspirin is efficacious for the treatment of acute migraine. Headache 2005;45:283-292.
72. Gillis CN, Pitt BR. The fate of circulating amines within the pulmonary circulation. Annu Rev Physiol 1982;44:269-281.
73. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 2001;358:1668-1675.
74. Dalkara T, Nozari A, Moskowitz MA. Migraine aura pathophysiology: the role of blood vessels and microembolisation. Lancet Neurol 2010;9:309-317.
75. Wilmshurst PT, Pearson MJ, Nightingale S, Walsh KP, Morrison WL. Inheritance of persistent foramen ovale and atrial septal defects and the relation to familial migraine with aura. Heart 2004;90:1315-1320.
76. Aamodt AH, Borch-Iohnsen B, Hagen K, Stovner LJ, Asberg A, Zwart JA. Headache prevalence related to haemoglobin and ferritin. The HUNT Study. Cephalalgia 2004;24:758-762.
77. Schoonman GG, Sandor PS, Agosti RM, Siccoli M, Bartsch P, Ferrari MD, Baumgartner RW. Normobaric hypoxia and nitroglycerin as trigger factors for migraine. Cephalalgia 2006;26:816-819.
78. Amery WK. Brain hypoxia: the turning-point in the genesis of the migraine attack? Cephalalgia 1982;2:83-109.
79. Diener HC, Schorn CF, Bingel U, Dodick DW. The importance of placebo in headache research. Cephalalgia 2008;28:1003-1011.
80. Kurth T, Tzourio C, Bousser MG. Migraine: a matter of the heart? Circulation 2008;118:1405-1407.
81. Papa M, Gaspardone A, Fragasso G, Ajello S, Gioffre G, Iamele M, Iani C, Margonato A. Usefulness of transcatheter patent foramen ovale closure in migraineurs with moderate to large right-to-left shunt and instrumental evidence of cerebrovascular damage. Am J Cardiol 2009;104:434-439.

82. Vigna C, Marchese N, Inchingolo V, Giannatempo GM, Pacilli MA, Di VP, Impagliatelli M, Natali R, Russo A, Fanelli R, Loperfido F. Improvement of migraine after patent foramen ovale percutaneous closure in patients with subclinical brain lesions: a case-control study. JACC Cardiovasc Interv 2009;2:107-113.

7

Pulmonary arteriovenous malformations associated with migraine with aura

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Abstract

Background: Migraine with aura (MA) is associated with cardiac right-to-left shunt. We prospectively studied the association between pulmonary arteriovenous malformations (PAVMs) and MA in hereditary haemorrhagic telangiectasia (HHT).

Methods: All 220 consecutive HHT patients who underwent a high-resolution chest computed tomography for PAVM screening were included prospectively. Prior to screening, a structured validated headache questionnaire was completed by 196 patients (57% female, mean age 45±15 years). Two neurologists diagnosed migraine according to the International Headache Society Criteria.

Results: A PAVM was present in 70 (36%) patients. The prevalence of MA was 24% in the presence of a PAVM compared with 6% in the absence of a PAVM (OR 4.6: 95% CI 1.84-11.2; p=0.001), and MA was an independent predictor for the presence of PAVM using multivariate analysis (OR 3.6: 95% CI 1.21-10.5; p=0.02). A PAVM was present in 68% of the patients with MA compared with 32% in the non-migraine controls (OR 4.6: 95% CI 1.84-11.2; p=0.001), and a PAVM was an independent predictor for MA using multivariate analysis (OR 3.0: 95% CI 1.00-9.20; p=0.05).

Conclusion: PAVMs are associated with MA in HHT patients.

Introduction

Migraine is a disorder that occurs in 12% of the general population.[1] In one-third of patients a migraine attack is accompanied by an aura.[2] Migraine is a complex disease and multiple factors seem to play a role in the pathogenesis. In the last decade, an association between a cardiac right-to-left shunt through the patent foramen ovale (PFO) and migraine has been described.[3] In particular, the prevalence of migraine with aura (MA) seems to be increased in the presence of a PFO.[4]

Interestingly, an association between overall migraine and the presence of a pulmonary right-to-left shunt, a pulmonary arteriovenous malformation (PAVM), has been observed in a retrospective study.[5] A PAVM is an abnormality of the pulmonary vascular system, characterised by direct communication between the pulmonary artery and vein. In patients with PAVM, >70% have hereditary hemorrhagic teleangiectasia (HHT), an autosomal dominant disorder caused mainly by a mutation of endoglin (HHT type 1) or activin receptor-like kinase 1 (HHT type 2).[6] A PAVM is present in ~40% of the patients with HHT, with a higher prevalence (≤50%) in HHT type 1.[7, 8]

The aim of the current prospective study was to evaluate the prevalence of migraine and especially MA in the presence or absence of a PAVM.

Methods

Patient selection

All 417 consecutive persons (>16 yrs of age) who were referred to our hospital (St. Antonius Hospital, Nieuwegein, The Netherlands) for screening for possible HHT, most of them family members of index cases, were studied prospectively between May 2004 and April 2008. Informed consent was obtained from all patients and the local ethical committee approved the study.

HHT screening

A clinical diagnosis of HHT was based on the presence of at least 3 clinical characteristics in accordance to the Curaçao criteria. These criteria consist of spontaneous and recurrent epistaxis, teleangiectasia at characteristic sites, visceral

arteriovenous malformations or teleangiectasia, and a first degree relative with HHT.[9] A genetic diagnosis was considered to be positive either when the family mutation was present or when the patient was an obligate carrier of the mutation. The affected patients were divided into three groups: 1) HHT type 1, 2) HHT type 2, and 3) HHT unknown on the basis of the mutations findings. The HHT unknown subgroup consisted of patients in whom the mutation was neither found nor investigated. A definite diagnosis of HHT could be made in 236 patients out of 417 screened persons. HHT type 1 was present in 95 patients, HHT type 2 in 118 patients, and the HHT was unknown in 23 patients.

HRCT of the chest

In 228 patients (97%), a high-resolution computer tomography (HRCT) scan of the chest was performed without contrast using the single breath-hold technique with a slice thickness of 1 mm (16-slice HRCT, Philips Medical Systems, Best, The Netherlands). Eight patients refused the HRCT or had a contraindication. HRCT is currently the gold standard in diagnosing a PAVM.[10] Identification of PAVM was based on the presence of a nodular or round opacity with both an afferent and efferent vessel. The eight patients in whom the diagnosis of PAVM was uncertain were excluded. A radiologist, blinded to the migraine diagnosis, diagnosed the presence of a PAVM.

Migraine diagnosis

A structured headache questionnaire was sent to all patients prior to the outpatient-screening visit. The same questionnaire was used in previous studies.[11] The patients were asked about the presence, time of onset, frequency, severity, duration, type and site of headache, accompanying symptoms, and the impact on activities. The questionnaire was focused on the six months time period prior to the screening visit. Two independent neurologists, blinded to the patients' data, diagnosed migraine or migraine with aura by reviewing the questionnaires according to the International Headache Society (IHS) criteria.[12] Migraine was defined if at least one migraine attack occurred during the predefined period. The headache questionnaire was fully completed by 196 out of 220 (89%) patients in whom an adequate HRCT of the chest was performed.

Neurological event

The history of stroke or a transient ischaemic event was diagnosed by a neurologist, and confirmed by the appropriate imaging techniques. Screening for cerebral arteriovenous malformations (CAVM) was recommended in patients who suffered HHT type 1 using magnetic resonance imaging of the brain, because the prevalence of CAVM in patients with HHT type 1 is much higher in comparison with the prevalence in HHT type 2 patients (15% versus 1%).[8]

Statistical analysis

Descriptive statistics were used to describe patients and migraine characteristics. Differences between groups were analyzed by unpaired Student's *t* test for continuous variables and Chi-squared test for nominal variables. Data are given as mean ± SD or n (% of total), and the level of significance was set at $p<0.05$. Univariate and multivariate statistical analysis with logistic regression were used to identify and estimate risk factors for overall migraine and MA compared to non-migraine controls. Following univariate analysis, variables with $p \leq 0.1$ were entered into a multivariate model. The odds ratios (OR) with their 95% confidence intervals (CI) were calculated. Interobserver variability was evaluated by measuring the kappa coefficient. Statistical analysis was performed with the SPSS software for Windows XP version 14.0.1 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

A total of 196 HHT patients (57% female, mean age 44.6±15.2 years) could be included in the study. The baseline characteristics are given in table 1.

Pulmonary arteriovenous malformation

The prevalence of PAVM in our study population was 35.7%. The prevalence of migraine in patients with a PAVM was 28.6% compared with 15.1% in the patients without a PAVM (OR 2.25: 95% CI 1.11–4.59; p=0.03). The prevalence of MA was 24.3% in patients with a PAVM and 6.3% in patients without a PAVM (OR 4.55: 95% CI 1.84–11.2; p=0.001). These data are shown in figure 1. In the presence of a PAVM the lifetime prevalence of a cerebral ischaemic event (both transient

Table 1. Baseline characteristics

	Number	Percentage
Total	196	-
Age ± SD (years)	44.6±15.2	-
Female	112	57.1
Male	84	42.9
Blood pressure (mmHg)		
Systolic ± SD	131±16	-
Diastolic ± SD	77±9	-
Neurological event		
TIA	3	1.5
CVA	4	2.0
TIA or CVA	7	3.6
CAVM*	11	15.1
Migraine	39	19.9
Migraine with aura	24	12.8
Migraine without aura	14	7.1
PAVM		
No	126	64.3
Yes	70	35.7
HHT		
type 1	73	37.2
type 2	105	53.6
unknown	18	9.2

*Data are presented as mean ± SD or n (%) unless otherwise indicated. TIA: transient ischaemic attack; CVA: cerebral vascular accident; CAVM: cerebral arteriovenous malformation; PAVM, pulmonary arteriovenous malformation; HHT, hereditary haemorrhagic telangiectasia; *: data available in 73 patients*

ischaemic attack and cerebrovascular accident) was 7.1% compared with 1.6% in the absence of a PAVM (OR 4.77: 95% CI 0.90–25.3; p=0.10). HHT type 1 was a predictor for the presence of a PAVM (OR 7.01: 95% CI 3.50–14.1; p<0.001). In a multivariate analysis model, MA (OR 3.57: 95% CI 1.21–10.5; p=0.02) and HHT type 1 (OR 6.33: 95% CI 3.10–12.9; p<0.001) were independent predictors for the presence of a PAVM after correction for the history of a cerebral ischaemic event. These data are summarised in table 2.

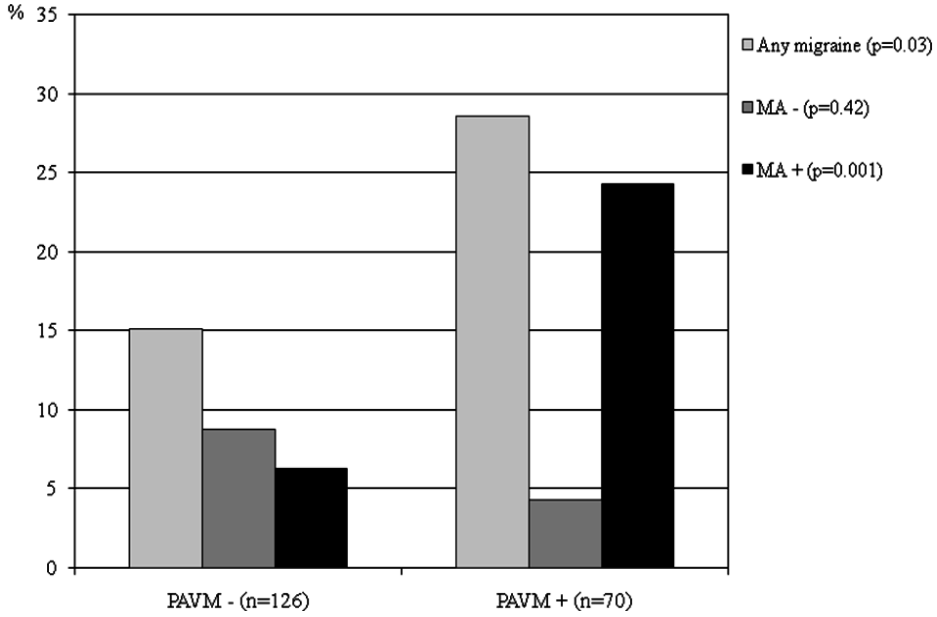

Figure 1. The prevalence of migraine with (MA+) and without aura (MA-) in the presence (+) or absence (-) of of a pulmonary arteriovenous malformation (PAVM).

Migraine

The overall prevalence of any migraine was 19.9% (82% female, 41.3±15.5 years). MA was present in 12.8% of the HHT patients. The patients with any migraine were predominantly female (OR 4.40: 95% CI 1.83–10.6; p<0.001), had a higher lifetime prevalence of a cerebral ischaemic event (OR 5.87: 95% CI 1.26–27.4; p=0.03), had a higher prevalence of PAVM (OR 2.25: 95% CI 1.11–4.59; p=0.03), and suffered HHT type 2 (OR 1.96: 95% CI 0.93-4.13; p=0.09), compared to the non-migraine controls. In a multivariate analysis model, female sex was the only predictor for the presence of any migraine, after correction for the history of a cerebral ischaemic event, the presence of a PAVM and type of HHT (OR 4.50: 95% CI 1.72-11.7; p=0.002).

Table 2. Characteristics of patients with (+) and without (-) pulmonary arteriovenous malformation (PAVM), and the univariate and multivariate analysis for the prediction of PAVM.

	PAVM -	PAVM +	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Basic characteristics, n (%)						
Total	126 (64.3)	70 (35.7)	-	-		
Age ± SD (years)	44.5±14.5	44.9±16.4	1.00 (0.98 – 1.02)	0.87	-	
Female	68 (54.0)	44 (62.9)	1.44 (0.79 – 2.63)	0.29	-	
Male	58 (46.0)	22 (37.1)	-			
Bloodpressure (mmHg)						
Systolic ± SD	132±16	128±16	0.99 (0.97 – 1.00)	0.14	-	
Diastolic ± SD	78±8	76±10	0.97 (0.94 – 1.01)	0.16	-	
Neurological event, n (%)						
TIA	1 (0.8)	2 (2.9)	3.68 (0.33 – 41.3)	0.29	-	
CVA	1 (0.8)	3 (4.3)	5.60 (0.57 – 54.9)	0.13	-	
TIA or CVA	2 (1.6)	5 (7.1)	4.77 (0.90 – 25.3)	0.10	1.41 (0.17 – 11.9)	0.75
CAVM*	4 (11.8)	7 (17.9)	1.64 (0.44 – 6.18)	0.52	-	
Migraine overall	19 (15.1)	20 (28.6)	2.25 (1.11 – 4.59)	0.03	-	-
Migraine with aura	8 (6.3)	17 (24.3)	4.55 (1.84 – 11.2)	0.001	3.57 (1.21 – 10.5)	0.02
Migraine without aura	11 (8.7)	3 (4.3)	0.42 (0.16 – 2.19)	0.42	0.61 (0.14 – 2.63)	0.51
No migraine	107 (84.9)	55 (72.4)	Reference	-	Reference	-
HHT, n (%)#						
Type 1	31 (42.5)	42 (57.5)	7.01 (3.50 – 14.1)	<0.001	6.33 (3.10 – 12.9)	<0.001
Type 2	88 (83.8)	17 (16.2)	-		-	-
Unknown	7 (38.9)	11 (61.5)	n.a.		-	-

*Data are presented as mean ± SD or n (%) unless otherwise indicated. OR: odds ratio; CI: confidence interval; TIA: transient ischaemic attack; CVA: cerebral vascular accident; CAVM: cerebral arteriovenous malformation; PAVM: pulmonary arteriovenous malformation; HHT: hereditary haemorrhagic telangiectasia; *: data available in 73 patients (34 without PAVM and 39 with PAVM); #: uni- and multivariate analysis without unknown subgroup*

Table 3. Characteristics of patients with migraine with aura (MA) compared with non-migraine controls with the univariate and multivariate analysis for the prediction of MA

	No migraine	Migraine with aura	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Basic characteristics, n (%)						
Total	157(86.3)	25 (13.7)	-	-	-	-
Age ± SD (years)	45.5±15.0	41.1±16.5	0.98 (0.95 – 1.00)	0.18	-	-
Female	80(51.0)	21 (84.0)	5.05 (1.66 – 15.4)	0.002	5.60 (1.51 – 20.7)	0.01
Male	77 (49.0)	4 (16.0)	-	-	-	-
Bloodpressure (mmHg)						
Systolic ± SD	131±15	126±17	0.98 (0.95 – 1.00)	0.15	-	-
Diastolic ± SD	78±9	76±8	0.97 (0.92 – 1.03)	0.34	-	-
Neurological event, n (%)						
TIA	2 (1.3)	1 (4.0)	3.23 (0.28 – 37.0)	0.36	-	-
CVA	1 (0.6)	2 (8.0)	13.6 (1.18 – 155)	0.05	-	-
TIA or CVA	3 (1.9)	3 (12.0)	7.00 (1.33 – 36.9)	0.02	2.51 (0.28 – 22.5)	0.41
CAVM*	6 (12.2)	3 (18.8)	1.65 (0.36 – 7.55)	0.68	-	
PAVM, n (%)						
No	107 (68.2)	8 (32.0)	-	-	-	-
Yes	50 (31.8)	17 (68.0)	4.55 (1.84 – 11.2)	0.001	3.01 (1.00 – 9.20)	0.05
HHT, n (%)[#]						
Type 1	54 (79.4)	14 (20.6)	3.30 (1.25 – 8.68)	0.02	2.10 (0.68 – 6.47)	0.20
Type 2	89 (92.7)	7 (7.3)	-		-	-
Unknown	14 (77.8)	4 (22.2)	n.a.		-	-

*Data are presented as mean ± SD or n (%) unless otherwise indicated. OR: odds ratio; CI: confidence interval; TIA: transient ischaemic attack; CVA: cerebral vascular accident; CAVM: cerebral arteriovenous malformation; PAVM: pulmonary arteriovenous malformation; HHT: hereditary haemorrhagic telangiectasia; *: data available in 77 patients (60 non-migraine controls and 17 MA) [#]: uni- and multivariate analysis without unknown subgroup*

Patients who suffer MA were predominantly female, had a higher lifetime prevalence of a cerebral ischaemic event, a higher prevalence of PAVM, and a HHT type 1 genotype, compared with non-migraine controls. The prevalence of a PAVM was 68% in the patients with MA compared with 32% in the non-migraine controls (OR 4.55: 95% CI 1.84–11.2; p=0.001). In a multivariate analysis model the presence of a PAVM (OR 3.01: 95% CI 1.00-9.20; p=0.05) and female sex (OR 5.60: 95% CI 1.51–20.7; p=0.01) were both independent predictors for having MA, after correction for the history of a cerebral ischaemic event and HHT genotype. These data are summarised in table 3.

The saturation fraction in 17 HHT patients with a PAVM and MA was significantly lower compared with 49 non-migraine HHT patients with a PAVM, 95% versus 97%, respectively (OR 0.78: 95% CI 0.62–0.99; p=0.02). The arterial oxygen tension tended to be lower in the MA subgroup, at 10.2 kPa versus 11.0 kPa (OR 0.81: 95% CI 0.60–1.09; p=0.17).

The kappa coefficient for interobserver variability for migraine was 0.93 ($p<0.0001$).

Discussion

Migraine occurs in 10 to 12% of the general population, and the prevalence increases with age until a peak prevalence of 18% is reached in the fourth decade of life.[1] The migraine prevalence varies according to age, sex, ethnic origin, and income. In one-third of patients with migraine, the attack is associated with transient focal neurological symptoms, *i.e.* the aura phenomenon.[2] The aura phenomenon is related to cortical activation followed by a temporary depression of neuronal activity, the so-called "cortical spreading depression".[13, 14] Coupled with these "cortical spreading depressions" are cerebral blood flow changes that manifest themselves as initial hyperaemia followed by oligaemia. These changes in cortical blood flow are seen during the aura phenomenon in migraine. Different migraine triggers can initiate an attack; however, the exact mechanism behind the initial start of the cortical cascade is still unknown.

Migraine, especially MA, is associated with the presence of a right-to-left shunt.[15] In the presence of a right-to-left shunt, the prevalence of MA is ~48%

compared with 14% in those without a shunt[16], and seems to be independent of the localisation of the right-to-left shunt.[3] In the presence of a pulmonary or cardiac right-to-left shunt, the prevalence of MA is increased compared with those without a shunt.[4, 17] In our study, we have described the association between the presence of a pulmonary right-to-left shunt and the occurrence of MA, and found that the presence of a PAVM was an independent predictor for having MA in HHT patients. Interestingly, we found that the presence of MA is an independent predictor for the presence of a PAVM in HHT patients.

Three small observational studies reported the efficacy of treatment of a large PAVM, and described the prevalence of self-reported migraine prior to the treatment. The prevalence of migraine in these patients with a large PAVM varies between 38 and 59%.[18-20]

Wilmshurst and Nightingale[16] described the relationship between the presence of a right-to-left shunt and the prevalence of MA in 200 patients with a history of a decompression illness. The diagnosis of migraine was based on the International Headache Society criteria. The MA prevalence was 29% in the presence of a pulmonary shunt (n=14) compared to 14% in patients without a shunt.

We previously reported the prevalence of self-reported migraine in 538 HHT patients. The overall prevalence of any migraine was 16%. In the presence of a PAVM, 21% of the patients suffered from any migraine, compared with 13% in the patients without a PAVM (p=0.02). In that study, the difference between migraine with or without aura could not be made.[7] Furthermore, embolisation of PAVM seems to reduce the prevalence of migraine, especially MA. In an observational retrospective study, the MA prevalence decreased from 33% before to 19% after embolisation of large PAVMs.[21] Thenganatt et al. described the relationship between a PAVM and migraine in 124 HHT patients.[17] The overall prevalence of migraine and MA in their study population was 38% and 31%, respectively. The prevalence of any migraine in patients with a PAVM was 46% compared with 33% in those without a PAVM (p=0.14). However, the presence of PAVM was associated with migraine after adjustment for age and sex (OR 2.4, p=0.04).[17] In our study, we found an overall prevalence of any migraine of 29% in the presence of a PAVM compared with 15% in patients without a PAVM, without difference in age and sex

between those two groups. The MA prevalence was 24% in patients with a PAVM and 6% in those without a PAVM. The prevalence of any migraine in the absence of a PAVM is the same as the peak prevalence in the general population found during the fourth decade of life. The presence of a PAVM was not associated with overall prevalence of any migraine. However, a PAVM was a strong independent predictor for MA, after adjustment for sex, a history of a cerebral ischaemic event and type of HHT.

It is suggested that paradoxical embolism might play a role in the pathophysiology of migraine, especially in MA. The (micro)emboli might trigger the migraine attack, and induce the cascade of "cortical spreading depression".[22, 23] Paradoxical thromboembolism through a right-to-left shunt has been postulated as a possible mechanism in the development of a (cryptogenic) cerebral ischaemic event.[6, 24] An increased prevalence of cerebral ischemic events is found in patients with a PAVM.[25] The prevalence of sub-clinical brain infarction, diagnosed by magnetic resonance imaging, is higher in patients with MA compared with non-migraine controls.[26] Furthermore, patients with MA have an increased life-time risk for a cerebral ischaemic event.[27] In our study, we found a higher lifetime prevalence of a cerebral ischaemic event in the presence of a PAVM compared with those without. Interestingly, the lifetime prevalence of a cerebral ischaemic event was significantly higher in patients suffering MA compared with non-migraine controls. All these findings support the hypothesis that (micro)emboli might play a role in the pathogenesis of MA.

Several authors have described the association between migraine and the presence of a CAVM.[28, 29] In a study by Steele et al., it is suggested that cerebral AVM might play a role in the pathogenesis of migraine in HHT patients.[30] In the present study, we found no association between the presence of a CAVM and overall prevalence of neither any migraine nor MA. The same observation was made by Thenganatt et al.[17], and was also reported in our large retrospective study.[7] However, the prevalence of cerebral AVM might be underestimated because only a subgroup of patients has been screened for cerebral AVM.

An autosomal dominant inherited pattern was found for the occurrence of a cardiac shunt and was linked to the inheritance of MA in some families.[31] As mentioned

earlier, HHT is an autosomal dominant inherited disorder caused predominantly by two mutations, which lead to different types of HHT, each with their own phenotype.[8, 32] These two mutations, or a mutation that has not been specified yet, might determine both HHT and MA. However, we found no difference in the prevalence of any migraine or MA between both types of HHT in the presence of a PAVM. In support of this, the HHT genotype was not an independent predictor for MA.

An important limitation of our study might be the presence of a selection bias. Firstly, our patient population was a selected cohort referred to our tertiary care centre. Migraine prevalence in our HHT population might differ from the prevalence in the overall worldwide group of patients suffering HHT. It is possible that environmental and other unidentified factors interact to trigger a migraine attack,[33] and these factors might differ between countries, and especially between ethnic origin and income. Secondly, 11% of the selected patients did not fill in the questionnaire accurately, which could either under – or overestimate the prevalence of migraine. Thirdly, we were not able to control for other risk factors for a cerebral ischaemic event, and this might influence the prevalence of migraine.

In conclusion, in this large prospective study, the presence of a PAVM is associated with migraine with aura in HHT patients. Migraine with aura is a strong independent predictor for the presence of a PAVM, regardless of the HHT genotype.

Reference List

1. Stewart WF, Shechter A, Rasmussen BK. Migraine prevalence. A review of population-based studies. Neurology 1994;44:S17-S23.
2. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology 1999;53:537-542.
3. Post MC, Budts W. The relationship between migraine and right-to-left shunt: Fact or fiction? Chest 2006;130:896-901.
4. Schwerzmann M, Nedeltchev K, Lagger F, Mattle HP, Windecker S, Meier B, Seiler C. Prevalence and size of directly detected patent foramen ovale in migraine with aura. Neurology 2005;65:1415-1418.
5. Post MC, van Gent MW, Snijder RJ, Mager JJ, Schonewille WJ, Plokker HW, Westermann CJ. Pulmonary arteriovenous malformations and migraine: a new vision. Respiration 2008;76:228-233.
6. Shovlin CL, Letarte M. Hereditary haemorrhagic telangiectasia and pulmonary arteriovenous malformations: issues in clinical management and review of pathogenic mechanisms. Thorax 1999;54:714-729.
7. Post MC, Letteboer TG, Mager JJ, Plokker TH, Kelder JC, Westermann CJ. A pulmonary right-to-left shunt in patients with hereditary hemorrhagic telangiectasia is associated with an increased prevalence of migraine. Chest 2005;128:2485-2489.
8. Letteboer TG, Mager JJ, Snijder RJ, Koeleman BP, Lindhout D, Ploos van Amstel JK, Westermann CJ. Genotype-phenotype relationship in hereditary haemorrhagic telangiectasia. J Med Genet 2006;43:371-377.
9. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, Kjeldsen AD, Plauchu H. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000;91:66-67.
10. Remy J, Remy-Jardin M, Wattinne L, Deffontaines C. Pulmonary arteriovenous malformations: evaluation with CT of the chest before and after treatment. Radiology 1992;182:809-816.
11. Mortelmans K, Post M, Thijs V, Herroelen L, Budts W. The influence of percutaneous atrial septal defect closure on the occurrence of migraine. Eur Heart J 2005;26:1533-1537.
12. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24 Suppl 1:9-160.

13. Olesen J, Larsen B, Lauritzen M. Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Ann Neurol 1981;9:344-352.
14. Olesen J, Friberg L, Olsen TS, Iversen HK, Lassen NA, Andersen AR, Karle A. Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. Ann Neurol 1990;28:791-798.
15. Wammes-van der Heijden EA, Tijssen CC, Egberts AC. Right-to-left shunt and migraine: the strength of the relationship. Cephalalgia 2006;26:208-213.
16. Wilmshurst P, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. Clin Sci (Lond) 2001;100:215-220.
17. Thenganatt J, Schneiderman J, Hyland RH, Edmeads J, Mandzia JL, Faughnan ME. Migraines linked to intrapulmonary right-to-left shunt. Headache 2006;46:439-443.
18. Puskas JD, Allen MS, Moncure AC, Wain JC, Jr., Hilgenberg AD, Wright C, Grillo HC, Mathisen DJ. Pulmonary arteriovenous malformations: therapeutic options. Ann Thorac Surg 1993;56:253-257.
19. White RI, Jr., Lynch-Nyhan A, Terry P, Buescher PC, Farmlett EJ, Charnas L, Shuman K, Kim W, Kinnison M, Mitchell SE. Pulmonary arteriovenous malformations: techniques and long-term outcome of embolotherapy. Radiology 1988;169:663-669.
20. Moussouttas M, Fayad P, Rosenblatt M, Hashimoto M, Pollak J, Henderson K, Ma TY, White RI. Pulmonary arteriovenous malformations: cerebral ischemia and neurologic manifestations. Neurology 2000;55:959-964.
21. Post MC, Thijs V, Schonewille WJ, Budts W, Snijder RJ, Plokker HW, Westermann CJ. Embolization of pulmonary arteriovenous malformations and decrease in prevalence of migraine. Neurology 2006;66:202-205.
22. Post MC, Luermans JG, Plokker HW, Budts W. Patent foramen ovale and migraine. Catheter Cardiovasc Interv 2007;69:9-14.
23. Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. Lancet 2000;356:1648-1651.
24. Webster MW, Chancellor AM, Smith HJ, Swift DL, Sharpe DN, Bass NM, Glasgow GL. Patent foramen ovale in young stroke patients. Lancet 1988;2:11-12.
25. Maher CO, Piepgras DG, Brown RD, Jr., Friedman JA, Pollock BE. Cerebrovascular manifestations in 321 cases of hereditary hemorrhagic telangiectasia. Stroke 2001;32:877-882.

26. Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD, Launer LJ. Migraine as a risk factor for subclinical brain lesions. JAMA 2004;291:427-434.
27. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. BMJ 2005;330:63.
28. Goadsby PJ. Neurovascular headache and a midbrain vascular malformation: evidence for a role of the brainstem in chronic migraine. Cephalalgia 2002;22:107-111.
29. Haas DC. Migraine and intracranial vascular malformations. Headache 1994;34:287.
30. Steele JG, Nath PU, Burn J, Porteous ME. An association between migrainous aura and hereditary haemorrhagic telangiectasia. Headache 1993;33:145-148.
31. Wilmshurst PT, Pearson MJ, Nightingale S, Walsh KP, Morrison WL. Inheritance of persistent foramen ovale and atrial septal defects and the relation to familial migraine with aura. Heart 2004;90:1315-1320.
32. Bayrak-Toydemir P, McDonald J, Markewitz B, Lewin S, Miller F, Chou LS, Gedge F, Tang W, Coon H, Mao R. Genotype-phenotype correlation in hereditary hemorrhagic telangiectasia: mutations and manifestations. Am J Med Genet A 2006;140:463-470.
33. Rapoport A, Edmeads J. Migraine: the evolution of our knowledge. Arch Neurol 2000;57:1221-1223.

8

The relation between migraine and size of intrapulmonary right-to-left shunt: results of a prospective study in 420 individuals

Submitted

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Abstract

Background: An increased prevalence of both intracardiac and intrapulmonary right-to-left shunt (RLS) has been shown in patients with migraine. We prospectively investigated whether the size of intrapulmonary RLS was associated with migraine with (MA+) and without aura (MA-) in persons screened for hereditary haemorrhagic telangiectasia (HHT).

Methods: A total of 462 consecutive persons underwent transthoracic contrast echocardiography (TTCE). A pulmonary shunt was established when contrast appeared in the left atrium >4 cardiac cycles. Shunt size was assessed semiquantitatively as small (<30 microbubbles), moderate (30-100 microbubbles), or large (>100 microbubbles). A headache questionnaire was completed by 420 (91%) persons. Two independent neurologists diagnosed migraine according to the International Headache Society criteria.

Results: Of 420 participants (mean age 43.4±15.4 yr, 61.4% female), 44 (10.5%) had MA+, and 45 (10.7%) MA-. MA+ was an independent predictor for an intrapulmonary RLS (OR 2.96; 95% CI 1.36-6.47; p=0.006) in multivariate analysis. MA- did not correlate with RLS (OR 1.21; 95% CI 0.56-2.64; p=0.6). When comparing MA+ patients with nonmigraineurs in a multivariate analysis, the presence of an intrapulmonary shunt predicted MA+ (OR 2.5; 95% CI 1.2-5.2; p=0.01), as did female gender (OR 3.15; 95% CI 1.29-7.65; p<0.01). The correlation of MA+ and RLS could be entirely attributed to large intrapulmonary shunts (OR 7.61; 95% 3.11-18.61; p<0.001), as small (OR 0.6; 95% CI 0.13-2.78; p=0.52) and moderate (OR 1.33; 95% CI 0.35-5.02; p=0.68) shunts did not appear to be risk factors for MA+.

Conclusion: Patients with a large intrapulmonary RLS have an increased risk for MA+.

Introduction

Despite the fact that migraine is a common disorder in the general population, knowledge about its pathophysiology is limited. Several case-control studies have suggested that a patent foramen ovale (PFO) is more common among individuals with migraine with aura (MA+) and that MA+ is more often observed in individuals with a PFO.[1-4] A possible causal relation might be the right-to-left shunt (RLS) accompanying a PFO through which vasoactive substances and microthrombi are permitted in the arterial circulation, and from that trigger a migraine attack.[5, 6] In support of this hypothesis is the observation that migraineurs with a PFO seem to have a larger RLS than controls.[4, 7-9] However, a recent population-based study has questioned the relationship between migraine headaches and PFO.[10]

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by vascular malformations. HHT is mainly divided in type 1 (HHT1) and type 2 (HHT2), corresponding with mutations in the genes ENG and ACVRL1 coding for endogline and activin A receptor type-like kinase (ALK1), respectively. Using chest CT, the overall prevalence of pulmonary arteriovenous malformations (PAVMs) among HHT affected individuals ranges from 20% to 45%.[11-13] The incidence of brain abscess (8-19%), stroke (10-36%), and migraine (16-57%) in HHT patients appears to be high.[12, 14-21] These neurological sequelae are believed to result from paradoxical embolism through intrapulmonary right-to-left shunting caused by PAVMs. In support of retrospective studies linking migraine in HHT patients to intrapulmonary RLS[12, 21], a recent prospective study showed that the presence of PAVM on chest HRCT was an independent predictor for MA+ in HHT patients.[22] Treatment of PAVMs with transcatheter embolotherapy has been shown to reduce the incidence of migraine in a retrospective design.[23] These findings suggest that a RLS per se might play a role in the origin of migraine, independent of its intracardiac or extracardiac localization. The intrapulmonary shunting through a PAVM is continuously present, as opposed to most PFOs, and therefore the HHT population provides a unique opportunity to study the association of RLS with migraine.

We prospectively studied the association of intrapulmonary shunt size, as documented semi-quantitatively by transthoracic contrast echocardiography (TTCE), with migraine in a large group of subjects screened for possible HHT.

Methods

Study population

In the period from May 2004 till May 2009, 492 consecutive persons were screened for possible HHT in the St Antonius Hospital, the Netherlands. A total of 350 persons were screened as first degree family members of index HHT patients, 9 persons as second-degree family members, 2 persons as third-degree family members, and in 59 persons there was no positive family history for HHT (the latter group consisted of persons with symptoms which suggested HHT, or in whom a PAVM was detected on chest CT). All persons provided informed consent and the study was approved by the hospital review board.

Screening for HHT

The screening protocol included systematic history taking and physical exmanination by a pulmonologist specialized in HHT. Screening for PAVMs was performed with both a chest HRCT and a TTTCE on the same day. Blood gas analysis was also routinely performed in all subjects. The clinical diagnosis HHT was established according to the Curaçao criteria.[24] These criteria consist of spontaneous and recurrent epistaxis, telangiectasia at characteristic sites, visceral arteriovenous malformations 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 no or one criterium renders the diagnosis unlikely. Genetic testing for the HHT causing family mutation was offered to all screened persons, and performed as previously described.[25] The diagnosis of HHT relied on the results of genetic testing, and when these were not available, on clinical judgement according to the diagnostic criteria.

TTCE

Contrast echocardiography was performed as previously described.[26] Briefly, the patient was positioned in the left lateral decubitus position and 10 ml agitated saline was injected while projecting the four-chamber apical view without a Valsalva manoeuvre. A Valsalva manoeuvre was not performed because the objective of the TTCE was to screen for the permanent intrapulmonary RLS in

HHT patients. TTCE was performed by three experienced echocardiographers. TTCE was considered positive for a pulmonary right-to-left shunt if microbubbles appeared in the left atrium after four cardiac cycles. When contrast was present in the left atrium within less than 4 cardiac cycles, this was considered a PFO (27 patients in the study, 6.4% of 420 study patients). The results were scored as positive or negative for a pulmonary shunt, or inappropriate for interpretation because of poor quality (5 patients in the present study). If the difference between an intracardiac or pulmonary shunt was not clear, the TTCE was assessed as positive for a pulmonary shunt. Opacification of the left ventricle was graded as either 1 (maximum of 30 microbubbles in left ventricle), 2 (30-100 microbubbles in left ventricle) and 3 (more than 100 microbubbles in left ventricle). This division was based on the maximum number of microbubbles counted in one still-frame.

Migraine

A structured headache questionnaire was sent to all patients prior to the screening visit in the outpatient clinic. Patients were asked about the presence, frequency, severity, duration, type and site of headache. Furthermore, they were asked about the occurrence of scotoma, paresthesia, paresis, aphasia and aggravating factors, accompanying symptoms such as nausea, vomiting, sono- and/or photophobia, and if they were able to continue daily activities. The relative frequency of migraine attacks had to be reported by the patients in a score from 0 to 6, ranging from no headaches to daily episodes. The severity of the headache attacks had to be scored on a scale ranging from 0 (no pain) to 10 (severe pain). The questions focused on the 6 months prior to the day of screening. Two independent neurologists, blinded to the other screening tests results, reviewed the questionnaires[27] and diagnosed migraine and MA according to the International Headache Society classification.[28] (see figure 1) Migraine was defined if at least one migraine attack occurred during the predefined period. When both neurologists disagreed about the presence of migraine or MA+, the patient was classified as positive for one of these diagnoses.

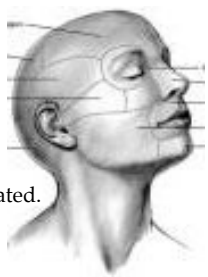
Figure 1

Headache Questionnaire

1. Do you often have a headache? Yes O No O
2. How frequently do you have a headache?
   - O never
   - O once a month
   - O several times a month
   - O once a week
   - O several times a week
   - O once a day
   - O several times a day
3. If you have a headache, how severe is this headache (scale from 0 to 10)? (indicate below)

   Minimal |——————|——————|——————|——————| Very severe

   0 5 10
4. Do you experience visual disturbances prior to or during the headache episodes?
   Yes O No O
5. Do you experience tingling in arms or legs before or during the headache episodes?
   Yes O No O
6. Do you have difficulties in speaking before or during the headache episodes?
   Yes O No O
7. Do you experience weakness (at one side of the body) before or during the headache episodes?
   Yes O No O
8. How long do the visual disturbances last? ……minutes
9. How long does the tingling last? ……minutes
10. How long do the speech disturbances last? ……minutes
11. How long does the weakness last? ……minutes
12. When you have a headache, do you experience:
    - Nausea? Yes O No O
    - Vomiting? Yes O No O
    - Increase in pain while walking? Yes O No O
13. When you have a headache, do you avoid:
    - Light? Yes O No O
    - Noise? Yes O No O
14. Is the headache throbbing? Yes O No O
15. Is the headache located on one side or both sides of the head?
    One O Two O
16. Can you continue your duties/activities during a headache episode?
    Yes O No O
17. How long does the headache last? ……minutes
18. Indicate with an arrow in this picture where the headache is mainly located.



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Neurological event

The history of stroke and transient ischemic attack was diagnosed by a neurologist and in nearly all patients confirmed by CT or MRI of the brain. Screening for CAVM was recommended to all HHT patients, particularly so for HHT type 1 patients as the incidence of CAVM in this patient group (15%) is higher than in patients with HHT type 2 (1%).

Statistical analysis

Descriptive statistics were used to describe patients and migraine characteristics. Differences between groups were analyzed by unpaired t-test for continuous variables and χ^2 test for nominal variables. Data are given either as mean ± SD or n (% of total). The level of significance was set at p,0.05. Univariate and multivariate statistical analysis with logistic regression were used to identify and estimate risk factors for pulmonary shunting, and MA+ compared with nonmigraineurs. Following univariate analysis, variables with $p<0.1$ were entered into a multivariate model. The comparison of the distribution of shunt grades between migraine categories was performed using the Mann-Whitney U-test. The odds ratios with their 95% confidence intervals were calculated. Interobserver variability was evaluated by measuring the κ coefficient. Statistical analysis was performed with SPSS software (version 17.0.0, Chicago, IL, USA).

Results

Of 492 consecutive persons screened for HHT (mean age 43.4±15.4 years; female gender, 61.4%), a TTCE with shunt grading was available in 462 individuals (figure 2). Four-hundred-and-twenty (91%) persons completed the headache questionnaire and these were included in the study. The overall prevalence of migraine in the study participants was 21.2%, and 10.5% for MA+ (table 1). A pulmonary shunt was present in 36.6% of individuals without migraine, 31.1% of migraineurs without aura, and 63.6% of migraineurs with aura. MA+ patients displayed a large intrapulmonary shunt in 52.3%. The distribution of different shunt grades differed significantly between MA+ patients and non-migraineurs (Mann-Whitney U-test, $p<0.001$) or MA- patients ($p<0.001$) (figure 3). Of 163

individuals with a pulmonary shunt, 141 (86.5%) were HHT patients, 11 (6.7%) were patients with a 'possible' clinical diagnosis HHT, and 11 (6.7%) did not have HHT. Baseline characteristics of migraineurs and controls are shown in table 1.

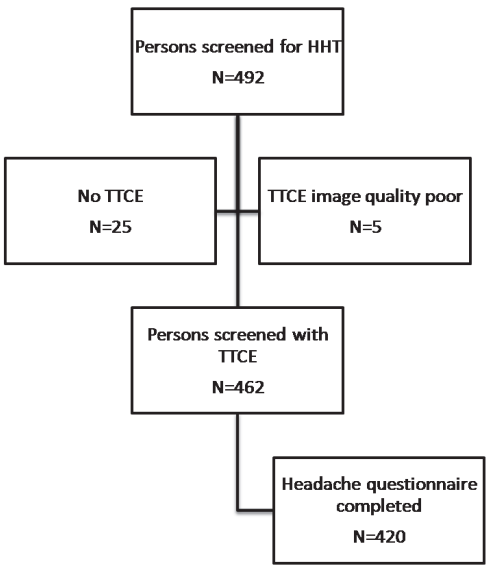

Figure 2 Selection of study population

HHT: Hereditary Haemorrhagic Telangiectasia; TTCE:Transthoracic Contrast Echocardiography

MA- was not associated with the presence of an intrapulmonary RLS (OR 1.21; 95% CI 0.56-2.64; p=0.63; table 2). Conversely, MA+ was an independent predictor for the presence of a pulmonary shunt in both univariate and multivariate analysis (OR 2.96; 95% CI 1.36-6.47; p=0.006). Lifetime risk for stroke or TIA did not appear to be a predictor for pulmonary shunting (OR 2.03; 95% CI 0.51-8.17; p=0.32), but the absolute number of documented strokes (n=8) and TIA (n=5) was low. The arterial oxygen tension showed a trend for an association with any pulmonary shunt after correction for other risk factors. However, patients with a large pulmonary shunt displayed a significantly lower partial oxygen pressure (10.5±1.8 kPa) compared to patients without (12.2±1.5 kPa; p<0.001), small (12.3±1.4 kPa; p<0.001) or moderate (12.8±1.5 kPa; p<0.001) shunts, respectively. These data are summarized in table 2.

Table 1 Baseline characteristics of study population

	N	No migraine	Migraine without aura	Migraine with aura
N	420	331	45	44
Male / Female	162/258	148/183	6/39	8/36
Age (yr±SD)	43.4±15.4	44.3±15.6	40.9±13.8	39.5±14.6
Oral contraceptive	52 (12.4)	34 (10.3)	8 (17.8)	10 (22.7)
Platelet inhibitor	10 (3.8)	1 (0.3)	1 (2.2)	8 (18.2)
Stroke or TIA	13 (3.1)	10 (3.0)	0	3 (6.8)
CAVM*	9 (2.1)	7 (2.1)	1 (2.2)	1 (2.3)
HHT#	217 (51.7)	169 (51.1)	18 (40.0)	30 (68.2)
No pulmonary shunt	257 (61.2)	210 (63.4)	31 (68.9)	16 (36.4)
Any pulmonary shunt	163 (38.8)	121 (36.6)	14 (31.1)	28 (63.6)
Small pulmonary shunt	58 (13.8)	47 (14.2)	9 (20.0)	2 (4.5)
Moderate pulmonary shunt	37 (8.8)	32 (9.7)	2 (4.4)	3 (6.8)
Large pulmonary shunt	68 (16.2)	42 (12.7)	3 (6.7)	23 (52.3)

*Data are presented as n (%) unless otherwise stated; SD: standard deviation; TIA: transient ischaemic attack; CAVM: cerebral arteriovenous malformation; HHT: hereditary haemorrhagic telangiectasia; *Data available for 101 patients; # Definite HHT, based on confirmed genetic mutation or Curaçao clinical criteria (see methods section)*

When comparing MA+ patients with nonmigraineurs, the prevalence of an intrapulmonary RLS was higher in the former group of patients (OR 2.53; 95% CI 1.23-5.18; p=0.01; table 3). Moreover, a large intrapulmonary shunt was a powerful independent predictor for MA+ (OR 7.61; 95% CI 3.11-18.61; p<0.001), but small or moderate shunts did not appear to be risk factors for MA+. Except for large shunts, only female gender was an independent predictor for MA+ (OR 3.15; 95% CI 1.29-7.65; p<0.01). MA+ patients showed a trend towards a younger age but this association was not sustained after correction. These data are summarized in table 3.

The κ coefficient for interobserver variability for the diagnosis of migraine between both neurologists was 0.89.

Table 2 Characteristics of patients with and without an intrapulmonary shunt on contrast echocardiography, and the univariate and multivariate analysis for the prediction of intrapulmonary shunting

	Pulmonary shunt on TTCE		Univariate analysis OR (95% CI)	P	Multivariate analysis OR (95% CI)	P
	No (%)	Yes (%)				
Total	257	163				
Age (±SD)	43.8±15.4	42.8±15.4	1.00 (0.98-1.01)	0.51		
Gender						
Female	152 (59.1%)	106 (65.0)	1.30 (0.86-1.93)	0.23		
Male	105 (40.9)	57 (34.8)				
Medication						
Beta-blocker	15 (6.0)	12 (7.5)	1.26 (0.57-2.77)	0.57		
Platelet inhibitor	7 (2.8)	3 (1.9)	0.66 (0.17-2.60)	0.56		
Oral contraceptive use	27 (10.7)	25 (15.7)	1.54 (0.86-2.77)	0.15		
Neurological event						
Stroke	1 (0.4)	7 (4.3)	11.4 (1.40-94.25)	0.02		
TIA	3 (1.2)	2 (1.2)	1.05 (0.17-6.36)	0.96		
Stroke or TIA	4 (1.6)	9 (5.5)	3.67 (1.11-12.13)	0.03	2.03 (0.51-8.17)	0.32
CAVM*	4 (11.1)	5 (7.7)	0.62 (0.18-2.80)	0.70		
Migraine						
No migraine	210 (81.7)	121 (74.2)	Reference		Reference	
MA-	31 (12.1)	14 (8.6)	0.81 (0.41-1.58)	0.53	1.21 (0.56-2.64)	0.63
MA+	16 (6.2)	28 (17.2)	3.03 (1.58-5.82)	0.001	2.96 (1.36-6.47)	0.006
HHT#						
Unlikely	124 (48.2)	12 (7.4)	Reference		Reference	
Possible	35 (13.6)	11 (6.7)	3.25 (1.32-7.99)	0.007	3.35 (1.34-8.39)	0.01
Definite	98 (38.1)	141 (85.9)	14.8 (7.74-28.17)	<0.001	13.53 (7.00-26.17)	<0.001
P_aO_2 (kPa)	12.2±1.5	11.7±1.9	0.81 (0.72-0.92)	0.001	0.87 (0.76-1.00)	0.06
Hemoglobin(mmol/l)	8.7±1.0	8.6±1.4	0.95 (0.81-1.12)	0.54		

*Data are presented as n (%) unless otherwise stated; TTCE : transthoracic contrast echocardiography; OR :Odds Ratio; CI: Confidence Interval; TIA: transient ischaemic attack; CAVM: cerebral arteriovenous malformation; MA+: migraine with aura; MA-: migraine without aura; HHT: hereditary haemorrhagic telangiectasia; P_aO_2 = partial oxygen tension; *Data available for 101 patients; #Diagnosis based on the four Curaçao clinical criteria (see text), Unlikely = 0 or 1 criterium, Possible = 2 criteria, Definite = ≥3 criteria*

Table 3 Characteristics of patients without migraine and with migraine with aura (MA+) and the univariate and multivariate analysis for the prediction of MA+

	No migraine	Migraine with aura	Univariate analysis OR (95% CI)	P	Multivariate analysis OR (95% CI)	P
Total	331 (88.3)	44 (11.7)				
Age	44.3±15.6	39.5±14.6	0.98 (0.96-1.00)	0.06	0.98 (0.95-1.00)	0.08
Gender						
Female	183 (55.3)	36 (81.8)	3.64 (1.64-8.07)	0.001	3.15 (1.29-7.65)	0.011
Male	148 (44.7)	8 (18.2)				
Medication						
Beta blocker	23 (6.9)	2 (4.5)	0.64 (0.15-2.80)	0.55		
Platelet inhibitor	8 (2.4)	1 (2.3)	0.94 (0.12-7.69)	0.95		
Oral contraceptive	34 (10.3)	10 (22.7)	2.56 (1.16-5.64)	0.02	1.21 (0.44-3.33)	0.71
Neurological event						
Stroke	6 (1.8)	2 (4.5)	2.58 (0.50-13.19)	0.26		
TIA	4 (1.2)	1 (2.3)	1.90 (0.21-17.40)	0.57		
CAVM*	7 (10.0)	1 (5.9)	0.56 (0.06-4.91)	0.60		
Pulmonary shunt on TTCE						
None	210 (63.4)	16 (36.4)	Reference		Reference	
Small	47 (14.2)	2 (4.5)	0.56 (0.12-2.51)	0.45	0.60 (0.13-2.78)	0.52
Moderate	32 (9.7)	3 (6.8)	1.23 (0.34-4.46)	0.75	1.33 (0.35-5.02)	0.68
Large	42 (12.7)	23 (52.3)	7.19 (3.50-14.75)	<0.001	7.61 (3.11-18.61)	<0.001
HHT#						
Unlikely	109 (32.9)	10 (22.7)	Reference			
Definite	189 (57.1)	30 (68.2)	1.73 (0.81-3.67)	0.15		
Possible	33 (10.0)	4 (9.1)	1.32 (0.39-4.49)	0.66		
P_aO_2 (kPa)	12.0±1.6	11.5±2.1	0.83 (0.69-0.99)	0.04	1.00 (0.80-1.25)	0.99
Hemoglobin (mmol/l)	8.7±1.3	8.8±1.2	1.08 (0.82-1.40)	0.59		

*Data are presented as n (%) unless otherwise stated; TTCE: transthoracic contrast echocardiography; OR: odds ratio; CI: Confidence Interval; TIA: Transient Ischaemic Attack; CAVM: Cerebral Arteriovenous Malformation; MA+: Migraine with aura; MA-: Migraine without aura; HHT: Hereditary Hemorrhagic Telangiectasia; P_aO_2: Partial oxygen tension; *Data available for 101 patients; #: Diagnosis based on the four Curaçao clinical criteria (see text), unlikely: 0 or 1 criterium, possible: 2 criteria; definite: ≥3 criteria*

Discussion

This study demonstrates that in patients with a large intrapulmonary shunt the odds for migraine with aura is increased more than 7-fold. More than half of patients with migraine with aura displayed a large shunt on contrast echocardiography. We did not find a correlation between a lesser degree of intrapulmonary right-to-left shunt and migraine with aura. To our knowledge, this is the first prospective study specifically addressing the relationship between pulmonary shunt size and migraine.

The association of migraine with PFO is still a matter of debate. As opposed to selected patient groups in case-control studies,[1-4, 27, 29, 30] a recent population-based study has debated the association of an interatrial shunt and migraine.[10] However, in addition to merely the presence of a RLS, its functional characteristics appear be of particular importance. Studies using both transcranial Doppler and transesophageal echocardiography have shown that the degree of shunt is associated with MA+.[4, 7-9] Moreover, a RLS that is present during normal breathing seems to carry a higher risk for migraine than PFOs that need augmentation by provocative manoeuvres to cause a RLS.[9] Comparable findings have been shown for the association of PFO with stroke.[31]

These findings seem comprehensible from a pathophysiological point of view, as shunts that are already present during quiet breathing permit an increased time for paradoxical embolisation and shunting of vasoactive substances. In this respect, the association of PAVM with migraine is of interest. PAVMs cause a permanent intrapulmonary RLS and are predominantly (>80%) seen in patients with HHT. Although initially attributed to possible cerebral AVMs,[20] studies later on have shown the correlation of PAVM with MA+ in HHT affected patients.[21, 22, 32] The data of the present study are consistent with these findings as MA+ appeared to be an independent predictor for a pulmonary RLS on echocardiography. Otherwise, the presence of an intrapulmonary shunt did correlate with MA+. However, the most cardinal finding of the study was that a large shunt on TTCE was a powerful independent predictor for MA+ after multivariate analysis, increasing the odds for MA+ more than 7-fold. Of all patients with MA+, 52% displayed a large intrapulmonary shunt, as opposed to 7% and 13% of patients with MA- or without migraine, respectively.

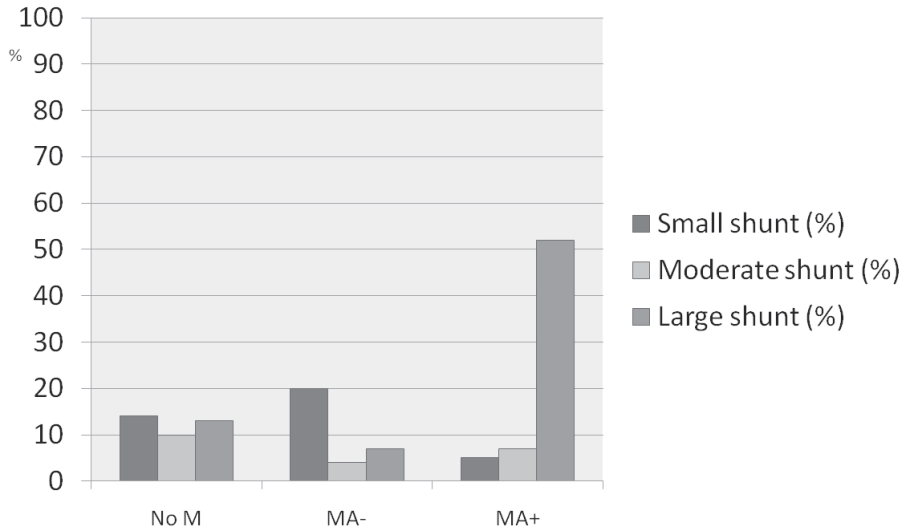

Figure 3 Prevalence and size of intrapulmonary shunts for different migraine categories
M: migraine; MA-: migraine without aura; MA+: migraine with aura; The distribution of different intrapulmonary shunt sizes differed significantly between MA+ patients and non-migraineurs (Mann-Whitney U-test; p<0.001) or MA- patients (p<0.001), but not between MA- patients and non-migraineurs (p=0.32)

Notably, there was no gradual increase in migraneous aura with increasing shunt size, as small and moderate pulmonary shunts appeared not be associated with MA+. Similar results have been published by Schwerzmann et al. who also found a significant difference only for large interatrial shunts in MA+ patients compared with controls without migraine.[4] Accordingly, using TCD with a 0-5 grading scale, Jesurum *et al.* only found significantly more large interatrial shunts (grade IV or V) among migraineurs compared to controls.[8] Hypothetically, these findings may be explained by some sort of 'neuronal threshold' above which migraine is triggered. Such a mechanism was also put forward in a recent study which showed a similar reduction in migraine relief for patients with and without (residual RLS on TCD) complete closure of a PFO.[33]

We did not find a significant difference in intrapulmonary RLS in patients with MA- compared to non-migraineurs. Steele et al. did also find a higher prevalence

of MA+, but not MA-, in HHT patients compared to controls.[20] Marziniak et al. also showed an increased prevalence of MA- in HHT patients but this could not be linked to an increased prevalence of PAVM.[32] In the study by Thenganatt et al. this difference could not be attributed as only 3 of 47 migraineurs were without aura.[21] Several studies with regard to the migraine prevalence in patients with PFO and vice versa also showed an association solely for MA+, and not for MA-.[1, 29, 34, 35] However, others have reported an increased RLS in MA- patients as well.[7, 8]

Although stroke appeared to be a predictor for pulmonary RLS univariately in our study population, a history of combined stroke or TIA was not associated with a pulmonary RLS after multivariate analysis. In the present study, the prevalence of ischaemic neurologic events was non-significantly higher in MA+ patients compared to non-migraineurs. This might be an unexpected finding in light of a presumed common pathogenesis in our study population, namely RLS, underlying both MA+ and stroke. Migraine has been associated with an increased risk for stroke, particularly so in young women, [1, 36, 37] and neuroimaging studies have shown an increase in subclinical white-matter lesions in MA+ and MA- patients.[38] However, our data with regard to ischaemic neurologic events should be interpreted with caution as the absolute number of patients with stroke or TIA was low, and we were not able to correct for cerebrovascular risk factors. A high incidence of stroke has been reported in patients with PAVMs.[14-18] The low prevalence of stroke and TIA in our study is probably explained by the relatively young age (mean age 43±15 years) of screened subjects who were for the larger part asymptomatic family members of proven HHT patients.

Hypoxaemia has also been proposed as a mechanism that may facilitate migraine attacks in patients with RLS.[39] Because all screened persons routinely underwent blood gas analysis, we were able to verify this hypothesis. Although an association was suggested univariately, the partial oxygen tension did not correlate with MA+ after correction for multiple factors, contradicting this hypothesis.

The influence of oral contraceptive (OC) use on migraine has been shown to be very variable.[40] After correction for multiple factors, an association between OC and MA+ was not sustained in our study.

This study presents some limitations. First of all, there are some differences in methodological aspect of contrast echocardiography compared to other studies. For example, Wilmshurst et al. used a cutoff value of 20 microbubbles for a large shunt,[9] compared to a cutoff of 30 and 100 microbubbles for medium and large shunts in the present study, respectively. This, as well as the different techniques (TTE, TEE, and TCD) used, makes comparison of results in different studies more difficult. Because the main purpose of TTCE in our population was the detection of intrapulmonary shunts, which permit a permanent RLS independent of provocative manoeuvres, a Valsalva manoeuvre was not routinely performed. This explains the low detection rate (6.4%) of PFO in the present study. Consequently, we were not able to correct for a possible separate effect of interatrial shunting on the prevalence of migraine. Secondly, we studied the association of pulmonary RLS with migraine in a selected cohort of persons screened for possible HHT. However, we were able to show that not the presence of HHT per se predicts MA+, but its associated pulmonary RLS. Similar results have been published by Marziniak et al. who found no significant difference in MA+ prevalence between HHT patients and a control group, except for those with PAVMs.[32] Thirdly, 9% of patients did not complete the headache questionnaires, but this percentage is probably too small to significantly influence the prevalence of migraine. Fourthly, we were not able to correct for risk factors for ischaemic cerebral events.

In conclusion, the present study shows that migraine with aura is an independent predictor for intrapulmonary RLS, and that a large shunt increases the odds for migraine with aura more than 7-fold. We could not demonstrate an association between migraine without aura and pulmonary shunting, and neither was there a relationship between shunts of a lesser degree and migraine with aura. Our data underline the importance of the functional potential of right-to-left shunts when studying its association with migraine, rather than merely its presence.

Reference List

1. Anzola GP, Magoni M, Guindani M, Rozzini L, Dalla VG. Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. Neurology 1999;52:1622-1625.
2. Del SM, Angeli S, Leandri M, Ferriero G, Bruzzone GL, Finocchi C, Gandolfo C. Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. Cerebrovasc Dis 1998;8:327-330.
3. Ferrarini G, Malferrari G, Zucco R, Gaddi O, Norina M, Pini LA. High prevalence of patent foramen ovale in migraine with aura. J Headache Pain 2005;6:71-76.
4. Schwerzmann M, Nedeltchev K, Lagger F, Mattle HP, Windecker S, Meier B, Seiler C. Prevalence and size of directly detected patent foramen ovale in migraine with aura. Neurology 2005;65:1415-1418.
5. Schwedt TJ, Dodick DW. Patent foramen ovale and migraine--bringing closure to the subject. Headache 2006;46:663-671.
6. Wilmshurst P, Nightingale S. The role of cardiac and pulmonary pathology in migraine: a hypothesis. Headache 2006;46:429-434.
7. Anzola GP, Morandi E, Casilli F, Onorato E. Different degrees of right-to-left shunting predict migraine and stroke: data from 420 patients. Neurology 2006;66:765-767.
8. Jesurum JT, Fuller CJ, Velez CA, Spencer MP, Krabill KA, Likosky WH, Gray WA, Olsen JV, Reisman M. Migraineurs with patent foramen ovale have larger right-to-left shunt despite similar atrial septal characteristics. J Headache Pain 2007;8:209-216.
9. Wilmshurst P, Pearson M, Nightingale S. Re-evaluation of the relationship between migraine and persistent foramen ovale and other right-to-left shunts. Clin Sci (Lond) 2005;108:365-367.
10. Rundek T, Elkind MS, Di Tullio MR, Carrera E, Jin Z, Sacco RL, Homma S. Patent foramen ovale and migraine: a cross-sectional study from the Northern Manhattan Study (NOMAS). Circulation 2008;118:1419-1424.
11. Cottin V, Plauchu H, Bayle JY, Barthelet M, Revel D, Cordier JF. Pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. Am J Respir Crit Care Med 2004;169:994-1000.
12. Post MC, Letteboer TG, Mager JJ, Plokker TH, Kelder JC, Westermann CJ. A pulmonary right-to-left shunt in patients with hereditary hemorrhagic telangiectasia is associated with an increased prevalence of migraine. Chest 2005;128:2485-2489.

13. Shovlin CL, Letarte M. Hereditary haemorrhagic telangiectasia and pulmonary arteriovenous malformations: issues in clinical management and review of pathogenic mechanisms. Thorax 1999;54:714-729.
14. White RI, Jr., Lynch-Nyhan A, Terry P, Buescher PC, Farmlett EJ, Charnas L, Shuman K, Kim W, Kinnison M, Mitchell SE. Pulmonary arteriovenous malformations: techniques and long-term outcome of embolotherapy. Radiology 1988;169:663-669.
15. Shovlin CL, Jackson JE, Bamford KB, Jenkins IH, Benjamin AR, Ramadan H, Kulinskaya E. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. Thorax 2008;63:259-266.
16. Moussouttas M, Fayad P, Rosenblatt M, Hashimoto M, Pollak J, Henderson K, Ma TY, White RI. Pulmonary arteriovenous malformations: cerebral ischemia and neurologic manifestations. Neurology 2000;55:959-964.
17. Mager JJ, Overtoom TT, Blauw H, Lammers JW, Westermann CJ. Embolotherapy of pulmonary arteriovenous malformations: long-term results in 112 patients. J Vasc Interv Radiol 2004;15:451-456.
18. Cottin V, Chinet T, Lavole A, Corre R, Marchand E, Reynaud-Gaubert M, Plauchu H, Cordier JF. Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: a series of 126 patients. Medicine (Baltimore) 2007;86:1-17.
19. Bayrak-Toydemir P, McDonald J, Markewitz B, Lewin S, Miller F, Chou LS, Gedge F, Tang W, Coon H, Mao R. Genotype-phenotype correlation in hereditary hemorrhagic telangiectasia: mutations and manifestations. Am J Med Genet A 2006;140:463-470.
20. Steele JG, Nath PU, Burn J, Porteous ME. An association between migrainous aura and hereditary haemorrhagic telangiectasia. Headache 1993;33:145-148.
21. Thenganatt J, Schneiderman J, Hyland RH, Edmeads J, Mandzia JL, Faughnan ME. Migraines linked to intrapulmonary right-to-left shunt. Headache 2006;46:439-443.
22. Post MC, van Gent MW, Plokker HW, Westermann CJ, Kelder JC, Mager JJ, Overtoom TT, Schonewille WJ, Thijs V, Snijder RJ. Pulmonary arteriovenous malformations associated with migraine with aura. Eur Respir J 2009.
23. Post MC, Thijs V, Schonewille WJ, Budts W, Snijder RJ, Plokker HW, Westermann CJ. Embolization of pulmonary arteriovenous malformations and decrease in prevalence of migraine. Neurology 2006;66:202-205.

24. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, Kjeldsen AD, Plauchu H. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000;91:66-67.
25. Letteboer TG, Zewald RA, Kamping EJ, de HG, Mager JJ, Snijder RJ, Lindhout D, Hennekam FA, Westermann CJ, Ploos van Amstel JK. Hereditary hemorrhagic telangiectasia: ENG and ALK-1 mutations in Dutch patients. Hum Genet 2005;116:8-16.
26. van Gent MW, Post MC, Luermans JG, Snijder RJ, Westermann CJ, Plokker HW, Overtoom TT, Mager JJ. Screening for pulmonary arteriovenous malformations using transthoracic contrast echocardiography: a prospective study. Eur Respir J 2008.
27. Mortelmans K, Post M, Thijs V, Herroelen L, Budts W. The influence of percutaneous atrial septal defect closure on the occurrence of migraine. Eur Heart J 2005;26:1533-1537.
28. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24 Suppl 1:9-160.
29. Dalla VG, Guindani M, Zavarise P, Griffini S, Pezzini A, Padovani A. Prevalence of patent foramen ovale in a large series of patients with migraine with aura, migraine without aura and cluster headache, and relationship with clinical phenotype. J Headache Pain 2005;6:328-330.
30. Carod-Artal FJ, da Silveira RL, Braga H, Kummer W, Mesquita HM, Vargas AP. Prevalence of patent foramen ovale in migraine patients with and without aura compared with stroke patients. A transcranial Doppler study. Cephalalgia 2006;26:934-939.
31. De CS, Cartoni D, Fiorelli M, Rasura M, Anzini A, Zanette EM, Beccia M, Colonnese C, Fedele F, Fieschi C, Pandian NG. Morphological and functional characteristics of patent foramen ovale and their embolic implications. Stroke 2000;31:2407-2413.
32. Marziniak M, Jung A, Guralnik V, Evers S, Prudlo J, Geisthoff UW. An association of migraine with hereditary haemorrhagic telangiectasia independently of pulmonary right-to-left shunts. Cephalalgia 2009;29:76-81.
33. Jesurum JT, Fuller CJ, Kim CJ, Krabill KA, Spencer MP, Olsen JV, Likosky WH, Reisman M. Frequency of migraine headache relief following patent foramen ovale "closure" despite residual right-to-left shunt. Am J Cardiol 2008;102:916-920.
34. Wilmshurst P, Nightingale S. Relationship between migraine and cardiac and pulmonary right-to-left shunts. Clin Sci (Lond) 2001;100:215-220.

35. Domitrz I, Mieszkowski J, Kaminska A. Relationship between migraine and patent foramen ovale: a study of 121 patients with migraine. Headache 2007;47:1311-1318.
36. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. BMJ 2005;330:63.
37. Wilmshurst P, Nightingale S, Pearson M, Morrison L, Walsh K. Relation of atrial shunts to migraine in patients with ischemic stroke and peripheral emboli. Am J Cardiol 2006;98:831-833.
38. Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD, Launer LJ. Migraine as a risk factor for subclinical brain lesions. JAMA 2004;291:427-434.
39. Amery WK. Brain hypoxia: the turning-point in the genesis of the migraine attack? Cephalalgia 1982;2:83-109.
40. Silberstein SD, Merriam GR. Estrogens, progestins, and headache. Neurology 1991;41:786-793.

9

General discussion

This thesis addresses the outcomes of our studies on several clinical aspects of pulmonary arteriovenous malformations (PAVMs) in patients with hereditary haemorrhagic telangiectasia (HHT). Amongst others, the contribution of transthoracic contrast echocardiography (TTCE) for the diagnosis and treatment of PAVMs was extensively explored.

Screening for pulmonary arteriovenous malformations

PAVMs are, through paradoxical embolisation, associated with a high prevalence of severe, predominantly neurological, complications. Therefore, screening for PAVMs is a crucial part of the clinical management of HHT patients. Different non- or minimally invasive screening modalities are available, such as chest radiography, arterial blood gas analysis with oxygen shunt testing, radionuclide scanning, magnetic resonance imaging, chest computed tomography (CT), and transthoracic contrast echocardiography (TTCE). The choice between one of these methods depends on its diagnostic accuracy, personal experience, patient harm and discomfort, and cost. Given the impact of a missed treatable PAVM, it is particularly important that the number of false-negatives is low. Which screening test best fulfils these criteria?

Chest radiography, arterial blood gas analysis and shunt measurement with 100% oxygen

In the second chapter of this thesis we demonstrate that chest radiography, arterial blood gas analysis, and shunt measurement using 100% oxygen can be definitely regarded as obsolete screening techniques for PAVM.[1] This relates to the limited sensitivity of these techniques (28% for chest radiography, 75% for $P_aO_{2,}$ and 77% for shunt measurement) compared with TTCE (sensitivity 97%) and chest CT (gold standard), resulting in missed PAVMs. Chest radiography will only detect (very) large PAVMs, and measurement of P_aO_2 only reveals PAVMs that affect oxygenation importantly. However, small PAVMs may still participate in gas exchange, especially when alveolar PaO2 is high[2], as with 100% oxygen shunt measurement. This results in an underestimation of the actual right-to-left shunt (RLS), although these small PAVMs may not be treatable. Likewise, arterial

oxygenation is not necessarily impaired in vessels responsible for the transmission of microbubbles with TTCE.[3] In line with our results, it has previously been shown that TTCE is more sensitive than oxygen shunt testing.[4, 5, 6, 7] However, a shunt fraction >5% detects 97.5% of treatable PAVMs and can be useful for follow-up in individual patients after embolotherapy.[8, 9]

Magnetic resonance angiography

The experience with contrast-enhanced magnetic resonance angiography (CE-MRA) is limited thus far. CE-MRA has only been compared to chest CT in a few small retrospective studies.[10-12] As for now, it appears that CE-MRA may be useful for the detection of large PAVMs, and to determine its angioarchitecture before embolisation therapy.[13] However, diagnosis of small PAVMs may be less accurate. We do not have experience with CE-MRA in the diagnosis and management of HHT patients in our centre, and MRI availability is limited.

Radionuclide lung scanning

Radionuclide perfusion lung scanning can be used for the quantification of intrapulmonary shunting.[14, 15] This method uses 99mTc labeled macroaggregates of albumin which are normally trapped in the pulmonary capillaries, but pass through PAVMs. In a study of 93 patients screened for PAVM using chest CT as the gold standard, the sensitivity of radionuclide lung scanning was only 71%, as compared with 93% for TTCE.[6] Radionuclide perfusion scanning is cumbersome for routine clinical practice, costly, and has a limited availability. It is only occasionally employed for screening purposes and follow-up after embolotherapy in specialized centres.

Chest computed tomography

Chest CT has the advantage that not only the presence of PAVMs can be determined, but also the opportunity for endovascular treatment. In addition, it can detect PAVMs without the need for contrast enhancement.[16] However, the use of contrast media might enhance the differential diagnosis from other nodules.[17, 18, 19] Contrast enhanced CT imaging may also improve the identification of bronchial

or non-bronchial systemic artery blood supply in previously embolised PAVMs.[20, 21] Three-dimensional reconstructions may be helpful to confirm the diagnosis of a PAVM. Chest CT also visualizes thrombosed PAVMs that are missed when functional screening tests are used.

The major disadvantage of CT is its radiation-induced risk of cancer.[22] This risk is increased in children and young adults, as they are more radiosensitive and have more remaining years of life during which a radiation-induced cancer can develop.[22] Radiation exposure is increased when multiple CTs are performed during follow-up to detect reperfusion of embolised PAVMs, or enlargement of previously small PAVMs. A CT of the thorax has been regarded as the gold standard for the detection of PAVM until recently.[23]

Transthoracic contrast echocardiography: the first line diagnostic method for screening

TTCE is a simple, minimally invasive, and patient-friendly technique that enables the detection of intrapulmonary RLS. In chapter 2 and 3 of this thesis we show that TTCE is a very sensitive technique for the detection of intrapulmonary shunting.[1, 24] Compared to PAVMs on CT thorax as the gold standard, it has an excellent negative predictive value (NPV) of 99%.[1] Our findings are in line with previous studies that reported a NPV of 93% [6] and 100% [25] for TTCE. Importantly, no treatable PAVMs are overlooked when TTCE is used as a first-line screening test.[1] The latter is an important requisite with regard to screening for PAVMs.

TTCE can be hampered by poor image quality. However, this was a problem in only 0.8% of our study patients. This percentage may be exceeded outside specialized centers.

Neurological complications of TTCE have sporadically been described in the literature,[26-28] but the overall safety profile of contrast echocardiography appears to be good.[29] A recent study systematically evaluated complications of TTCE in a total of 190 HHT patients and controls.[30] Complications occurred in three (1.6%) patients with a large pulmonary shunt and consisted of migraine in two patients, and peripheral paresthesias in one patient.[30] Both spontaneously recovered completely within a few minutes. We have seen a migraine attack directly

following TTCE in one patient with an extensive pulmonary shunt once, but we have not routinely documented possible side-effects of TTCE. However, serious neurological complications of TTCE have never been observed following contrast echocardiography in our hospital.

Hence, TTCE appears to be both highly sensitive and safe which renders it an attractive screening test for PAVM. However, the ability of TTCE to detect even very small intrapulmonary shunts raises an important question: is contrast echocardiography oversensitive for clinical use? As we report in chapter 2, only in 51% of patients with a pulmonary shunt on TTCE, a PAVM was detected with chest CT.[1] Furthermore, a positive TTCE *per se* does not predict the candidates for endovascular treatment, and demands an additional chest CT. This limitation of TTCE can, in part, be overcome by the use of a grading system for intrapulmonary shunting.

Graded contrast echocardiography

Shunt size has previously been shown to predict the presence of PAVM on pulmonary angiography[31] and chest CT,[32] but these findings are not indicative of treatable PAVMs. In chapter 3 we show for the first time that the use of 'grading' of shunt size (figure 1) guides clinical decision making: in patients with small (grade 1) shunts, a chest CT can be safely withheld as treatable PAVMs were absent in this group.[24] We propose a step-wise, graded TTCE guided screening algorithm that reduces radiation exposure and unnecessary additional diagnostic tests in a substantial part of screened patients (figure 2). In support of our proposed screening strategy is a recent report that showed no PAVMs on chest CT at all in patients with small shunts, although a different cut-off of 20 microbubbles was employed (we used a cut-off of 30 microbubbles, see figure 1).[25]

With growing experience, we have documented 5 HHT patients with a moderate shunt and PAVMs amenable for embolotherapy.[24] This outcome explains the apparent discrepancy with the initial results in chapter 2, that became available 1,5 year earlier and showed that patients with a moderate shunt did not display treatable PAVMs either.[1]

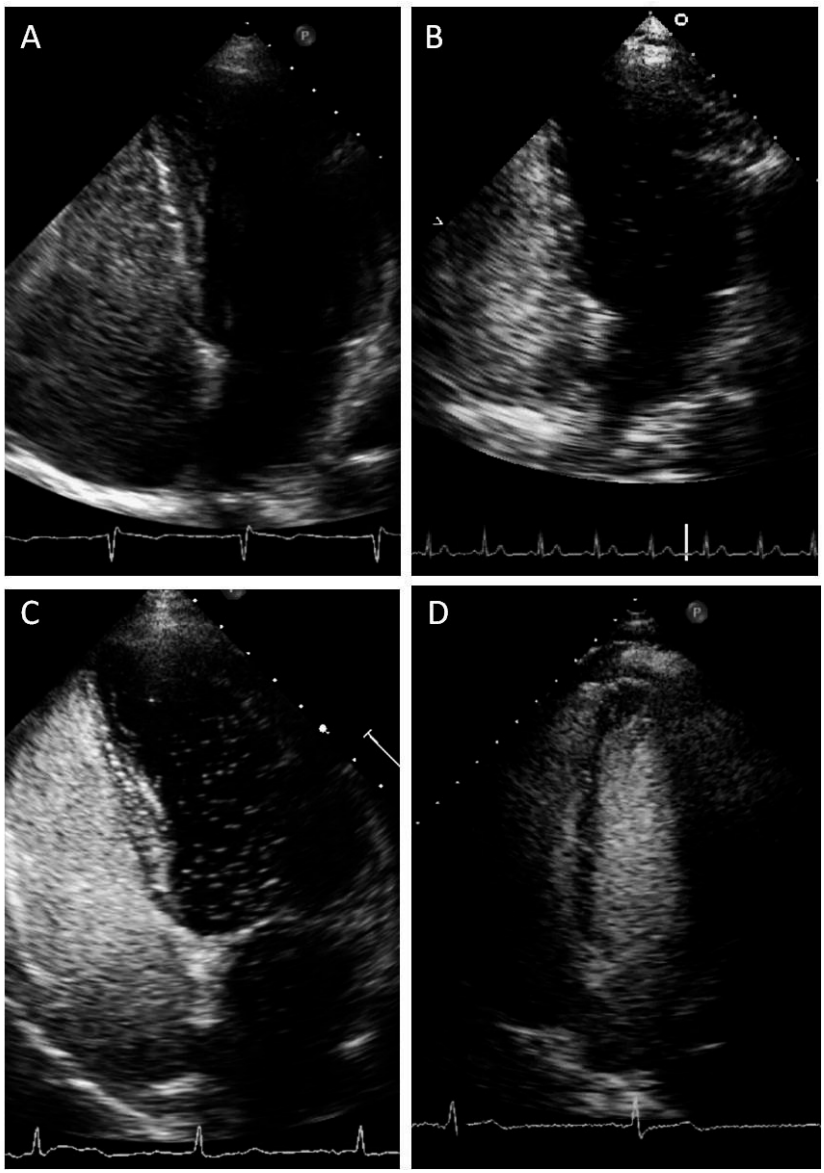

Figure 1 Different degrees of left ventricular opacification on contrast echocardiography following injection of agitated saline in patients with intrapulmonary shunts; A: Normal, no appearance of 'microbubbles' in the left ventricle; B: Small shunt (grade 1; < 30 microbubbles); C: Moderate shunt (grade 2; 30-100 microbubbles); D: Large shunt (grade 3; >100 microbubbles).

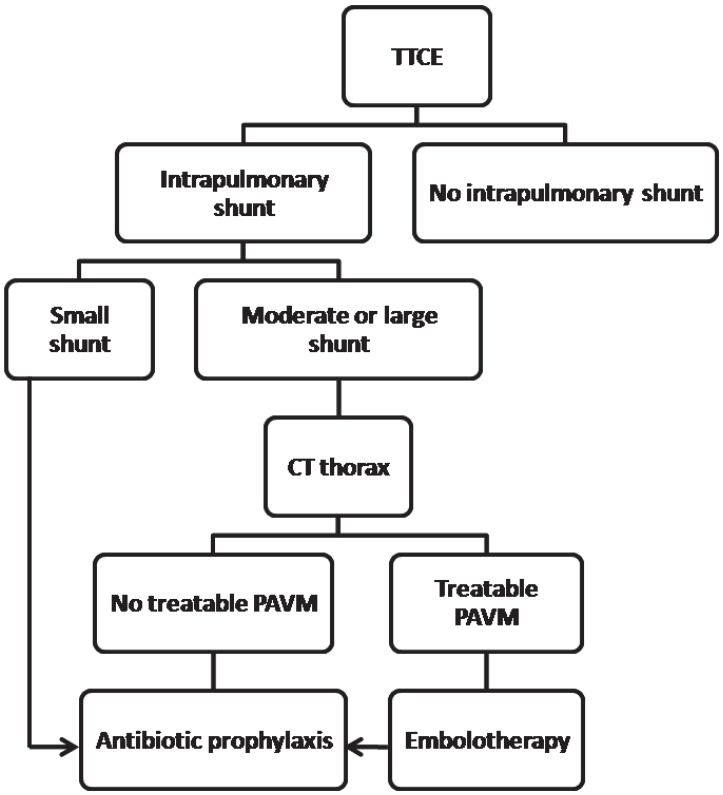

Figure 2 Proposed screening algorithm for PAVM; TTCE: transthoracic contrast echocardiography; CT: computed tomography; PAVM: pulmonary arteriovenous malformation

Intrapulmonary shunting in HHT type 1 and 2

Graded contrast echocardiography is also helpful to depict the differences of intrapulmonary shunting between HHT1 and HHT2 patients. In chapter 4 we report an echocardiographic intrapulmonary shunt in 85% of HHT1 patients and in 35% of HHT2 patients. This outcome indicates that in only a very small number of HHT1 patients a chest CT can be withheld. Consequently, one might argue that a TTCE could be left behind when the clinical suspicion of HHT1 in a screened family member of an ENG mutation carrier is high. We have also illustrated that the presence of treatable PAVMs in patients with HHT2 is uncommon.

This explains the poor PPV of only 8.3% of a positive TTCE study in this group. The use of a grading scale of shunt size increases the PPV considerably in both HHT genotypes, but particularly in HHT2 patients. The low number of PAVMs amenable for embolotherapy in HHT2 affected subjects is reflected by the different distribution of echocardiographic shunt size between patients with HHT1 and HHT2. HHT1 patients show predominantly large shunts as opposed to mainly small shunts in the HHT2 group.

Positive contrast echocardiography studies in healthy controls

As outlined in chapter 4 and 5, a pulmonary shunt on TTCE appeared to be present in 6-9% of individuals without HHT. These shunts were nearly all small (except for one patient with a large shunt and negative DNA test results for HHT who was clinically suspected of HHT nonetheless; this has been discussed in chapter 4). These findings could not be explained by comorbidity that is known to be associated with intrapulmonary shunting (e.g. hepatic cirrhosis). The common opinion is that the appearance of microbubbles in the left-sided heart is pathological. Should these apparently healthy persons now be regarded as having pulmonary shunts, or is shunting of a small amount of microbubbles a normal variant in the general population? Before answering this question, we emphasize that the larger part of TTCE studies used for this thesis was performed without a provocative Valsalva manoeuvre. As outlined in the introduction (chapter 1), it is possible that a patent foramen ovale (PFO) results in late appearance of left-sided microbubbles, depending on the phase of the respiratory cycle.[33] Therefore, we cannot exclude that some of the shunts that were apparently of pulmonary origin, were in fact PFOs. However, late appearance of microbubbles in the left-sided heart with use of the Valsalva manoeuvre has also been reported in 5% of patients with migraine,[34] and 4% of patients referred for a TEE for various indications.[35]

Explanation of false-positive findings on contrast echocardiography

The normal pulmonary capillary diameter is about 7-10 μm, and does not exceed 13 μm even under high, non-physiological perfusion pressures.[36] Microbubbles above this diameter will therefore be 'sieved'. However, these bubbles can shrink

or fracture in smaller ones that can traverse the capillary network.[37] These very small bubbles have a high internal pressure due to surface tension effects. Gas inside these bubbles will rapidly diffuse down its concentration gradient into blood which decreases bubble size and accelerates total dissolution.[37] The contrast bubble diameter in vivo is not exactly known but it is estimated that the size of bubbles entering the pulmonary circulation is 60 to 90 μm.[38] A 8 μm bubble will completely dissolve in 190 to 550 ms .[39] The mean pulmonary capillary transit time of red blood cells is at least 750 ms and decreases during exercise.[40, 41] However, transit time does not fall below 450ms, even with a cardiac output of 30 l/min.[42] A transit time from the main pulmonary artery to the left atrium of at least 6 seconds has also been reported.[41] Either way, bubbles smaller than the capillary diameter will dissolve to a radius undetectable by M-mode or fundamental imaging before they reach the left atrium. However, second-harmonic imaging has dramatically enhanced the contrast effect of microbubbles.[43] It is not known if this technique also visualizes bubbles < 8 μm,[33] but given the instability of these very small bubbles (which dissolve even more rapidly) this seems unlikely. Can we therefore conclude that these direct connections are present in a part of the general population? There is indeed evidence for the presence of large-diameter intrapulmonary arteriovenous anastomoses in humans.[44] Furthermore, it has been shown that microspheres of 25 to 50 μm are able to traverse the pulmonary vasculature of human lungs under physiologic perfusion and ventilation pressures.[38] Transpulmonary passage of agitated saline has also been documented during exercise in the greater part of healthy persons.[45] This probably indicates recruitment of intrapulmonary arteriovenous conduits.

In conclusion, it appears that that direct arteriovenous communications are present in at least some healthy individuals and this probably explains the positive echo contrast studies in patients without HHT.

Antibiotic prophylaxis

Because of its very high sensitivity, we only advise antibiotic prophylaxis in HHT patients with proven intrapulmonary shunts on TTCE (figure 1). Although the clinical impact of prophylaxis is uncertain, the risk for a brain abscess in HHT

patients with a PAVM is dramatically increased compared with the general population.[46] Antibiotic prophylaxis is generally recommended to patients in whom a PAVM is suspected,[8, 23, 47, 48] but given the high prevalence of pulmonary shunts on TTCE in patients with HHT, antibiotic prophylaxis might be recommended to all patients with HHT when less sensitive screening tests for PAVM are used.

Contrast echocardiography versus chest CT

Because of the limitations of the other screening methods mentioned above, the choice for an appropriate screening test is between the two most sensitive techniques: TTCE and chest CT.

Chest CT provides anatomic images but does not provide any functional information on the size of the RLS, as opposed to TTCE. Although it is probably true that large PAVMs on chest CT usually cause large shunts, the opposite frequently does not hold. This is shown in chapter 2, as a substantial number of patients with intrapulmonary shunts do not display PAVMs on chest CT.[1] Furthermore, we report in chapter 3 that even 17% of patients with an echocardiographic large shunt did not have visible PAVMs on CT.[24] As discussed in these chapters, these findings most likely relate to small PAVMs that are not visualized by chest CT. This explains the excellent NPV, and the limited PPV of TTCE for the presence of PAVMs when chest CT is taken as the gold standard. It is important to realize that chest CT and TTCE detect two different entities, that is an anatomic PAVM with a visible feeding vessel versus intrapulmonary shunting. These two tests are not always interchangeable. As it comes down to intrapulmonary shunting, TTCE should be regarded the true gold standard, and this is represented by chest CT for the detection of PAVMs amenable for treatment.

An overview of advantages and disadvantages of contrast echocardiography and CT as a screening test for PAVM is provided in table 1.

Table 1 Main characteristics of chest CT and contrast echocardiography as screening techniques for PAVM

	CT thorax	Contrast echocardiography
Radiation exposure	+	-
Detection of treatable PAVMs	+	-[#]
Invasive	-	-[*]
Reliable image quality	+	±[¶]
Detects reperfusion or enlargement of PAVM	+	?
Anatomic information on PAVM	+	-
Functional information on shunt	-	+
Safe	±[‡]	+
Selection of candidates for antibiotic prophylaxis	-	+
Detects other intrathoracic abnormalities	+	-
Detects cardiac abnormalities	-	+

[#]: additional CT needed if positive, can be partially overcome using shunt grading; [*]: minimally invasive, i.v. access needed; [¶]: patient and operator dependent; [‡]: radiation; CT: computed tomography; PAVM: pulmonary arteriovenous malformation;

Currently, chest CT is recommended for the follow-up of previously embolized PAVMs.[23] TTCE might not be suitable for this purpose as it remains positive in the majority of patients after embolotherapy, even if no PAVMs are angiographically visible anymore.[5] However, echocardiographic shunt size has been shown to decrease after embolotherapy.[5] At present, it is not known if our findings that small pulmonary shunts are not associated with treatable PAVMs can also be applied to the post-embolotherapy period.

Conclusion

Contrast echocardiography has been proposed as the initial screening technique of choice in the recently published international guidelines for the diagnosis and management of HHT.[23] In these guidelines, the use of CT thorax to detect treatable PAVMs is reserved for patients in whom any echocardiographic intrapulmonary shunt is shown. This decision was based on clinical experience and a few small retrospective studies, but not led by proper studies directly comparing TTCE with CT. We have now provided these data and confirm the value of contrast echocardiography as an evidence based screening method for PAVM. TTCE has

the favourable combination of a high sensitivity and a low risk. However, TTCE appears to be extremely sensitive and also detects very small PAVMs that are not clinically relevant. Unnecessary additional testing in patients with these small PAVMs can be overcome by the use of graded TTCE. Therefore, we underline the importance of an echocardiographic classification of intrapulmonary shunt size, which should be an integral part of TTCE when screening for PAVM.

Clinical diagnosis of HHT

Validity of the clinical criteria for HHT

In chapter 5 we report on the validity of the HHT clinical criteria in first-degree relatives of patients with a proven HHT causing mutation. This selection was done in order to guarantee that all screened persons had a comparable a priori probability. For HHT, with an autosomal dominant inheritance pattern, 50% of screened persons would be mutation carriers in a perfectly distributed population. However, symptomatic patients will be presented for screening more frequently and will probably be more frequently genetically tested. This is shown in chapter 5, as 71% of persons that underwent DNA testing were positive for their family mutation. It is important to realize that we tested the validity of the clinical criteria in these conditions, because measures as sensitivity, specificity, and predictive value are dependent on the prevalence of HHT in the screened population. The age-dependent penetrance of HHT is a complicating factor for clinical diagnosis. Ideally, the validity of the Curaçao criteria should be stratified for different categories of age, but our study was not adequately powered for this purpose. This phenomenon of age-related phenotypic appearance was the reason to introduce a third category of 'possible' HHT patients (2 clinical criteria). As a consequence, our concept of sensitivity and specificity differs from the usual intent of these measures in a two-by-two table. We report a sensitivity of 90% for a definite, and 55% for an unlikely clinical diagnosis, respectively. However, for the clinician sitting in front of a possible HHT patient, the predictive value of this clinical diagnosis is more important than sensitivity and specificity. We show that, in a population with a disease prevalence of 71%, the PPV is 100% for a definite clinical diagnosis, and report a NPV of 98% for an unlikely clinical

diagnosis. Of patients with a possible clinical diagnosis, 33% proved positive for the family mutation. For clinical practice, this implies 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.

Echocardiographic intrapulmonary shunting for the clinical diagnosis of HHT

The clinical diagnosis of HHT is based on four criteria of which one is the involvement of visceral organs.[49] PAVMs are by far the most frequent manifestation of organ involvement in HHT patients in our clinic, but we do not routinely screen for liver AVMs. When chest CT is used to detect PAVMs and extra-pulmonary involvement is absent, small PAVMs may be missed, resulting in underdiagnosis of HHT. We theorized that these false-negative results may be overcome by using TTCE as a more sensitive technique to diagnose intrapulmonary shunts. In fact, the late appearance of contrast in the left atrium is already regarded as a valid clinical criterium by some authors.[30]

In chapter 5 we indeed prove that TTCE increases the sensitivity of a definite clinical diagnosis of HHT (from 90 to 94% in HHT patients overall). However, specificity was substantially reduced as the percentage of falsely positive diagnoses increased from 1 to 6.5%. As outlined previously, this probably relates to small pulmonary shunts in the general population. Our data are an example of how clinical intuition may be a dangerous direction to follow exclusively. In our opinion, a small pulmonary shunt on echocardiography should not be routinely used as a criterium for the clinical diagnosis of HHT.

Intrapulmonary right-to-left shunt and migraine

Migraine with aura (MA+),[50, 51] paradoxical embolism,[46, 52-57] and decompression illness[58, 59, 60] have been linked to both intracardiac and pulmonary shunts. This suggests that a RLS per se might explain this association. However, conflicting results have been reported on the influence of PFO closure on migraine,[34, 50] and therefore doubt remains whether a real association exists. But is this area of uncertainty confined to PFO, or also to a pulmonary RLS?

Based on the review presented in chapter 6, describing the association between migraine with aura (MA+) and pulmonary shunts, it appears that the available data strongly suggest a causal relationship between these two entities. However, available studies included only a small number of patients[61-63], or were retrospective in design.[64, 65] Obviously, there is also the issue of publication and recall bias. In chapter 7 and 8 we report two large prospective studies showing an increased prevalence of MA+ in HHT patients with pulmonary shunts, and otherwise an increased prevalence of pulmonary RLS in MA+ patients. In chapter 7, we show that PAVMs on chest CT are independently associated with MA+.[66] As aforementioned, PAVMs on chest CT are not necessarily proportional to the effective shunt size. The importance of shunt size is reported in chapter 8, which shows that only large pulmonary shunts on TTCE are related to MA+: the odds for MA+ is increased more than seven-fold in this group of patients. The influence of shunt size has been reported previously in the context of an association between PFO and migraine.[60, 67-69] We did not find evidence for a link between smaller shunts and MA+.

Our findings suggest that the occurrence, or recurrence, of MA+ during follow-up of HHT patients might indicate an increase in pulmonary shunt size, as with reperfusion of treated PAVMs, or enlargement of previously small PAVMs. Because of the independent strong association of MA+ and PAVM, a repeated TTCE or chest CT should be considered in HHT patients with new onset MA+ to detect PAVMs amenable for treatment.

Our data may also be important for the approach of intracardiac shunts and their relation to migraine. Our data underline the need to specifically address the functional potential of a RLS, rather than merely its presence. We show that a RLS that is both permanently present and large, is associated with MA+. From this point of view it seems plausible that when all PFOs are regarded as equal, conflicting results have been reported on their association with migraine. A substantial part of all PFOs only causes a RLS with provocative manoeuvers, a situation which is completely different from the shunt characteristics of PAVMs. It has previously been reported that a large RLS at rest constitutes the highest risk for MA+.[60] In other words, proper selection of patients with an intracardiac RLS who might

benefit most from closure seems to be important. This is emphasized by recent studies that showed an important reduction in migraine when PFOs with only a large RLS were closed in subjects with radiologic evidence of paradoxical cerebral embolism.[70, 71]

Conclusions

TTCE can be used as a first-line screening test for PAVM. A graded approach of intrapulmonary shunting should be employed to identify patients with small pulmonary shunts in whom unnecessary additional testing can be prevented. A pulmonary shunt on TTCE should not automatically be regarded as a clinical criterium for HHT because it raises false-positive diagnosis. This relates to the presence of small intrapulmonary shunts in a part of the general population. A large intrapulmonary shunt, but not shunts of lesser degree, is a strong independent predictor for MA+.

Future perspectives

Several questions concerning the screening for PAVMs, clinical diagnosis of HHT, and the association of MA+ and pulmonary shunts have been answered in this thesis. However, there are still important areas of uncertainty that will need to be attended in future research.

1. It will be intriguing to study the results of graded TTCE in the follow-up of patients with embolised PAVMs. The value of assessment of shunt size for screening has been shown in this thesis, but it would also be important to evaluate whether these results also apply to the time after embolisation. A TTCE should ideally be performed shortly after embolotherapy, to examine whether a significant decrease in shunt size has emerged, and compared with chest CT results during follow-up. Chest CT is currently recommended for follow-up after treatment of PAVMs, but cannot be repeated without limit because of the use of ionizing radiation. Follow-up would be markedly facilitated if it can be shown that patients with small shunts on TTCE after treatment can be managed conservatively, similar to the initial screening. Of note, TTCE will not be able to detect reperfusion of PAVMs by collateral systemic arteries which cause a left-to-left shunt.
2. The natural history of patients with isolated pulmonary shunting on TTCE (no visible PAVMs on CT thorax) is unknown. Preliminary reports indicate that the risk for complications related to PAVM in this group might be low.[72] We are currently undertaking a study in our centre in which repeated TTCE is performed 5 years after initial echocardiographic assessment. This might provide insight in the natural history and guide regimens for follow-up.
3. Data are warranted on the validity of the clinical criteria in different groups of age and HHT genotypes. The age-related penetrance of HHT renders this a complex disease with regard to clinical diagnosis. It would be important to know if the predictive value of the clinical categories 'definite', 'possible', and 'unlikely' differ according to age. Furthermore, such data might also clarify if this clinical classification can be simplified for patients older than a certain age, as they might have 'complete phenotypic appearance' of HHT. However, to study different strata of age, large numbers of patients with known results from mutation analysis are needed for adequate statistical power.

4. In this thesis we provide evidence for an association between pulmonary RLS and MA+. These findings would be reinforced if a decrease in migraine can be shown in patients after embolisation of PAVMs. As for now, this has been shown in a retrospective cohort of HHT patients. However, these studies are prone to recall bias and placebo effect of embolisation. In our hospital a prospective observational study is currently being conducted to test if embolotherapy of PAVMs indeed reduces the occurrence of MA+. More randomized, sham-controlled trials on the closure of PFO and the occurrence of migraine (PREMIUM, PRIMA) are also underway. In addition, more fundamental research is needed on the precise mechanism that provokes migraine in patients with RLS.
5. The pathogenesis of HHT needs to be further elucidated. As outlined in the introduction, a decrease in endoglin appears to be crucial for the development of abnormal blood vessels in both HHT type 1 and type 2. However, the specific intracellular pathways and influencing factors that ultimately cause abnormal endothelial cells and vascular anomalies need to be better understood.

Reference List

1. van Gent MW, Post MC, Luermans JG, Snijder RJ, Westermann CJ, Plokker HW, Overtoom TT, Mager JJ. Screening for pulmonary arteriovenous malformations using transthoracic contrast echocardiography: a prospective study. Eur Respir J 2009;33:85-91.
2. Genovesi MG, Tierney DF, Taplin GV, Eisenberg H. An intravenous radionuclide method to evaluate hypoxemia caused by abnormal alveolar vessels. Limitation of conventional techniques. Am Rev Respir Dis 1976;114:59-65.
3. Hopkins SR, Olfert IM, Wagner PD. Point: Exercise-induced intrapulmonary shunting is imaginary. J Appl Physiol 2009;107:993-994.
4. Nanthakumar K, Graham AT, Robinson TI, Grande P, Pugash RA, Clarke JA, Hutchison SJ, Mandzia JL, Hyland RH, Faughnan ME. Contrast echocardiography for detection of pulmonary arteriovenous malformations. Am Heart J 2001;141:243-246.
5. Lee WL, Graham AF, Pugash RA, Hutchison SJ, Grande P, Hyland RH, Faughnan ME. Contrast echocardiography remains positive after treatment of pulmonary arteriovenous malformations. Chest 2003;123:351-358.
6. Cottin V, Plauchu H, Bayle JY, Barthelet M, Revel D, Cordier JF. Pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. Am J Respir Crit Care Med 2004;169:994-1000.
7. Kjeldsen AD, Oxhoj H, Andersen PE, Elle B, Jacobsen JP, Vase P. Pulmonary arteriovenous malformations: screening procedures and pulmonary angiography in patients with hereditary hemorrhagic telangiectasia. Chest 1999;116:432-439.
8. Gossage JR, Kanj G. Pulmonary arteriovenous malformations. A state of the art review. Am J Respir Crit Care Med 1998;158:643-661.
9. Gossage JR. The role of echocardiography in screening for pulmonary arteriovenous malformations. Chest 2003;123:320-322.
10. Khalil A, Farres MT, Mangiapan G, Tassart M, Bigot JM, Carette MF. Pulmonary arteriovenous malformations. Chest 2000;117:1399-1403.
11. Ohno Y, Hatabu H, Takenaka D, Adachi S, Hirota S, Sugimura K. Contrast-enhanced MR perfusion imaging and MR angiography: utility for management of pulmonary arteriovenous malformations for embolotherapy. Eur J Radiol 2002;41:136-146.
12. Maki DD, Siegelman ES, Roberts DA, Baum RA, Gefter WB. Pulmonary arteriovenous malformations: three-dimensional gadolinium-enhanced MR angiography-initial experience. Radiology 2001;219:243-246.

13. Schneider G, Uder M, Koehler M, Kirchin MA, Massmann A, Buecker A, Geisthoff U. MR angiography for detection of pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. AJR 2008;190:892-901.
14. Mager JJ, Zanen P, Verzijlbergen F, Westermann CJ, Haitjema T, van HG, Lammers JW. Quantification of right-to-left shunt with (99m)Tc-labelled albumin macroaggregates and 100% oxygen in patients with hereditary haemorrhagic telangiectasia. Clin Sci (Lond) 2002;102:127-134.
15. Whyte MK, Peters AM, Hughes JM, Henderson BL, Bellingan GJ, Jackson JE, Chilvers ER. Quantification of right to left shunt at rest and during exercise in patients with pulmonary arteriovenous malformations. Thorax 1992;47:790-796.
16. Pollak JS, Saluja S, Thabet A, Henderson KJ, Denbow N, White RI, Jr. Clinical and anatomic outcomes after embolotherapy of pulmonary arteriovenous malformations. J Vasc Interv Radiol 2006;17:35-44.
17. Maillard JO, Cottin V, Etienne-Mastroianni B, Frolet JM, Revel D, Cordier JF. Pulmonary varix mimicking pulmonary arteriovenous malformation in a patient with Turner syndrome. Respiration 2007;74:110-113.
18. Halbsguth A, Schulze W, Ungeheuer E, Hoer PW. Pitfall in the CT diagnosis of pulmonary arteriovenous malformation. J Comput Assist Tomogr 1983;7:710-712.
19. Remy J, Remy-Jardin M, Wattinne L, Deffontaines C. Pulmonary arteriovenous malformations: evaluation with CT of the chest before and after treatment. Radiology 1992;182:809-816.
20. Lacombe P, Blivet S, Blondel JH, Bourgalt I, Chinet TH, Lesur G, Ozanne A, Raffestin B, Roume J, Soubrier F, Cellerin L, Corre R, Pelage JP. Embolization of pulmonary arteriovenous malformations in 70 consecutive patients over a 3-year period: results with the use of multidetector computed tomography - In: Hematology Meeting Reports - 8th International Hereditary Haemorrhgaic Telangiectasia Scientific Conference, Santander, Spain. 3 ed. 2009:26.
21. Sagara K, Miyazono N, Inoue H, Ueno K, Nishida H, Nakajo M. Recanalization after coil embolotherapy of pulmonary arteriovenous malformations: study of long-term outcome and mechanism for recanalization. AJR 1998;170:727-730.
22. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med 2007;357:2277-2284.

23. Faughnan ME, Palda VA, Garcia-Tsao G, Geisthoff UW, McDonald J, Proctor DD, Spears J, Brown DH, Buscarini E, Chesnutt MS, Cottin V, Ganguly A, Gossage JR, Guttmacher AE, Hyland RH, Kennedy SJ, Korzenik J, Mager JJ, Ozanne AP, Piccirillo JF, Picus D, Plauchu H, Porteous ME, Pyeritz RE, Ross DA, Sabba C, Swanson K, Terry P, Wallace MC, Westermann CJ, White RI, Young LH, Zarrabeitia R. International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia. J Med Genet 2009.
24. van Gent MW, Post MC, Snijder RJ, Swaans MJ, Plokker HW, Westermann CJ, Overtoom TT, Mager JJ. Grading of Pulmonary Right-to-Left Shunt With Transthoracic Contrast Echocardiography: Does It Predict the Indication for Embolotherapy? Chest 2009;135:1288-1292.
25. Parra JA, Bueno J, Zarauza J, Farinas-Alvarez MC, Cuesta JM, Ortiz P, Zarrabeitia R, Del Molino AP, Bustamante M, Botella LM, Delgado MT. Graded contrast echocardiography in pulmonary arteriovenous malformations. Eur Respir J 2009.
26. Christin F, Bouffard Y, Rossi R, Delafosse B. Paradoxical symptomatic air embolism after saline contrast transesophageal echocardiography. Echocardiography 2007;24:867-869.
27. Holcomb BW, Loyd JE, Byrd BF, III, Wilsdorf TT, Casey-Cato T, Mason WR, Robbins IM. Iatrogenic paradoxical air embolism in pulmonary hypertension. Chest 2001;119:1602-1605.
28. Srivastava TN, Undesser EK. Transient ischemic attack after air contrast echocardiography in patients with septal aneurysm. Ann Intern Med 1995;122:396.
29. Bommer WJ, Shah PM, Allen H, Meltzer R, Kisslo J. The safety of contrast echocardiography: report of the Committee on Contrast Echocardiography for the American Society of Echocardiography. J Am Coll Cardiol 1984;3:6-13.
30. Gazzaniga P, Buscarini E, Leandro G, Reduzzi L, Grosso M, Pongiglione G, Pedrinazzi C, Lanzarini L, Portugalli V, Blotta P, Forner P, Boccardi E, Pagella F, Manfredi G, Olivieri C, Zambelli A, Danesino C, Inama G. Contrast echocardiography for pulmonary arteriovenous malformations screening: does any bubble matter? Eur J Echocardiogr 2009;10:513-518.
31. Barzilai B, Waggoner AD, Spessert C, Picus D, Goodenberger D. Two-dimensional contrast echocardiography in the detection and follow-up of congenital pulmonary arteriovenous malformations. Am J Cardiol 1991;68:1507-1510.

32. Zukotynski K, Chan RP, Chow CM, Cohen JH, Faughnan ME. Contrast echocardiography grading predicts pulmonary arteriovenous malformations on CT. Chest 2007;132:18-23.
33. Woods TD, Patel A. A critical review of patent foramen ovale detection using saline contrast echocardiography: when bubbles lie. J Am Soc Echocardiogr 2006;19:215-222.
34. Dowson A, Mullen MJ, Peatfield R, Muir K, Khan AA, Wells C, Lipscombe SL, Rees T, De Giovanni JV, Morrison WL, Hildick-Smith D, Elrington G, Hillis WS, Malik IS, Rickards A. Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation 2008;117:1397-1404.
35. Daniels C, Weytjens C, Cosyns B, Schoors D, De SJ, Paelinck B, Muyldermans L, Van CG. Second harmonic transthoracic echocardiography: the new reference screening method for the detection of patent foramen ovale. Eur J Echocardiogr 2004;5:449-452.
36. Glazier JB, Hughes JM, Maloney JE, West JB. Measurements of capillary dimensions and blood volume in rapidly frozen lungs. J Appl Physiol 1969;26:65-76.
37. Weyman AE. Miscellaneous echocardiographic techniques I: Contrast echocardiography. Principles and practice of echocardiography. Second ed. Lea & Febiger, 1994:302-326.
38. Lovering AT, Stickland MK, Kelso AJ, Eldridge MW. Direct demonstration of 25- and 50-microm arteriovenous pathways in healthy human and baboon lungs. Am J Physiol Heart Circ Physiol 2007;292:H1777-H1781.
39. Meltzer RS, Tickner EG, Popp RL. Why do the lungs clear ultrasonic contrast? Ultrasound Med Biol 1980;6:263-269.
40. Johnson RL, Jr., SPICER WS, Bishop JM, Forster RE. Pulmonary capillary blood volume, flow and diffusing capacity during exercise. J Appl Physiol 1960;15:893-902.
41. Wagner WW, Jr., Latham LP, Gillespie MN, Guenther JP, Capen RL. Direct measurement of pulmonary capillary transit times. Science 1982;218:379-381.
42. Warren GL, Cureton KJ, Middendorf WF, Ray CA, Warren JA. Red blood cell pulmonary capillary transit time during exercise in athletes. Med Sci Sports Exerc 1991;23:1353-1361.
43. Porter TR, Xie F. Contrast ultrasound imaging: Methods, Analysis, and Applications. In: Otto CM, ed. The practice of clinical echocardiography. Third ed. Saunders Elsevier, 2007.
44. Lovering AT, Eldridge MW, Stickland MK. Counterpoint: Exercise-induced intrapulmonary shunting is real. J Appl Physiol 2009;107:994-997.

45. Eldridge MW, Dempsey JA, Haverkamp HC, Lovering AT, Hokanson JS. Exercise-induced intrapulmonary arteriovenous shunting in healthy humans. J Appl Physiol 2004;97:797-805.
46. Shovlin CL, Jackson JE, Bamford KB, Jenkins IH, Benjamin AR, Ramadan H, Kulinskaya E. Primary determinants of ischaemic stroke/brain abscess risks are independent of severity of pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia. Thorax 2008;63:259-266.
47. Shovlin CL, Letarte M. Hereditary haemorrhagic telangiectasia and pulmonary arteriovenous malformations: issues in clinical management and review of pathogenic mechanisms. Thorax 1999;54:714-729.
48. Shovlin C, Bamford K, Wray D. Post-NICE 2008: Antibiotic prophylaxis prior to dental procedures for patients with pulmonary arteriovenous malformations (PAVMs) and hereditary haemorrhagic telangiectasia. Br Dent J 2008;205:531-533.
49. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, Kjeldsen AD, Plauchu H. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 2000;91:66-67.
50. Butera G, Biondi-Zoccai GG, Carminati M, Caputi L, Usai S, Bussone G, Meola G, Delogu AB, Sheiban I, Sangiorgi G. Systematic review and meta-analysis of currently available clinical evidence on migraine and patent foramen ovale percutaneous closure: Much ado about nothing? Catheter Cardiovasc Interv 2009.
51. Post MC, van Gent MW, Snijder RJ, Mager JJ, Schonewille WJ, Plokker HW, Westermann CJ. Pulmonary arteriovenous malformations and migraine: a new vision. Respiration 2008;76:228-233.
52. Webster MW, Chancellor AM, Smith HJ, Swift DL, Sharpe DN, Bass NM, Glasgow GL. Patent foramen ovale in young stroke patients. Lancet 1988;2:11-12.
53. Lechat P, Mas JL, Lascault G, Loron P, Theard M, Klimczac M, Drobinski G, Thomas D, Grosgogeat Y. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988;318:1148-1152.
54. Cottin V, Chinet T, Lavole A, Corre R, Marchand E, Reynaud-Gaubert M, Plauchu H, Cordier JF. Pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia: a series of 126 patients. Medicine (Baltimore) 2007;86:1-17.

55. Mager JJ, Overtoom TT, Blauw H, Lammers JW, Westermann CJ. Embolotherapy of pulmonary arteriovenous malformations: long-term results in 112 patients. J Vasc Interv Radiol 2004;15:451-456.
56. Moussouttas M, Fayad P, Rosenblatt M, Hashimoto M, Pollak J, Henderson K, Ma TY, White RI. Pulmonary arteriovenous malformations: cerebral ischemia and neurologic manifestations. Neurology 2000;55:959-964.
57. White RI, Jr., Lynch-Nyhan A, Terry P, Buescher PC, Farmlett EJ, Charnas L, Shuman K, Kim W, Kinnison M, Mitchell SE. Pulmonary arteriovenous malformations: techniques and long-term outcome of embolotherapy. Radiology 1988;169:663-669.
58. Wilmshurst PT, Byrne JC, Webb-Peploe MM. Neurological decompression sickness. Lancet 1989;1:731.
59. Moon RE, Camporesi EM, Kisslo JA. Patent foramen ovale and decompression sickness in divers. Lancet 1989;1:513-514.
60. Wilmshurst P, Pearson M, Nightingale S. Re-evaluation of the relationship between migraine and persistent foramen ovale and other right-to-left shunts. Clin Sci (Lond) 2005;108:365-367.
61. Steele JG, Nath PU, Burn J, Porteous ME. An association between migrainous aura and hereditary haemorrhagic telangiectasia. Headache 1993;33:145-148.
62. Thenganatt J, Schneiderman J, Hyland RH, Edmeads J, Mandzia JL, Faughnan ME. Migraines linked to intrapulmonary right-to-left shunt. Headache 2006;46:439-443.
63. Bayrak-Toydemir P, McDonald J, Markewitz B, Lewin S, Miller F, Chou LS, Gedge F, Tang W, Coon H, Mao R. Genotype-phenotype correlation in hereditary hemorrhagic telangiectasia: mutations and manifestations. Am J Med Genet A 2006;140:463-470.
64. Post MC, Letteboer TG, Mager JJ, Plokker TH, Kelder JC, Westermann CJ. A pulmonary right-to-left shunt in patients with hereditary hemorrhagic telangiectasia is associated with an increased prevalence of migraine. Chest 2005;128:2485-2489.
65. Marziniak M, Jung A, Guralnik V, Evers S, Prudlo J, Geisthoff UW. An association of migraine with hereditary haemorrhagic telangiectasia independently of pulmonary right-to-left shunts. Cephalalgia 2009;29:76-81.
66. Post MC, van Gent MW, Plokker HW, Westermann CJ, Kelder JC, Mager JJ, Overtoom TT, Schonewille WJ, Thijs V, Snijder RJ. Pulmonary arteriovenous malformations associated with migraine with aura. Eur Respir J 2009.

67. Schwerzmann M, Nedeltchev K, Lagger F, Mattle HP, Windecker S, Meier B, Seiler C. Prevalence and size of directly detected patent foramen ovale in migraine with aura. Neurology 2005;65:1415-1418.
68. Anzola GP, Morandi E, Casilli F, Onorato E. Different degrees of right-to-left shunting predict migraine and stroke: data from 420 patients. Neurology 2006;66:765-767.
69. Jesurum JT, Fuller CJ, Velez CA, Spencer MP, Krabill KA, Likosky WH, Gray WA, Olsen JV, Reisman M. Migraineurs with patent foramen ovale have larger right-to-left shunt despite similar atrial septal characteristics. J Headache Pain 2007;8:209-216.
70. Papa M, Gaspardone A, Fragasso G, Ajello S, Gioffre G, Iamele M, Iani C, Margonato A. Usefulness of transcatheter patent foramen ovale closure in migraineurs with moderate to large right-to-left shunt and instrumental evidence of cerebrovascular damage. Am J Cardiol 2009;104:434-439.
71. Vigna C, Marchese N, Inchingolo V, Giannatempo GM, Pacilli MA, Di VP, Impagliatelli M, Natali R, Russo A, Fanelli R, Loperfido F. Improvement of migraine after patent foramen ovale percutaneous closure in patients with subclinical brain lesions: a case-control study. JACC Cardiovasc Interv 2009;2:107-113.
72. Wong HH, Leaong-Poi H, Prabhudesai R, Nijarchi R, Fuaghnan ME. Outcomes in isolated intrapulmonary shunts in HHT - In: Hematology Meeting Reports - 8th International Hereditary Haemorrhgaic Telangiectasia Scientific Conference, Santander, Spain. 3 ed. 2009.

10

Summary

This thesis reports on several clinical aspects of pulmonary arteriovenous malformations (PAVMs) in patients with hereditary haemorrhagic telangiectasia (HHT). In particular, the value of transthoracic contrast echocardiography (TTCE) for the screening of PAVMs and clinical diagnosis of HHT was explored, as was the association of PAVMs with migraine.

Chapter 1 provides an introduction to the main clinical characteristics of HHT and PAVMs. HHT, also known as the Rendu-Osler-Weber syndrome, is a rare vascular disorder with an autosomal dominant inheritance pattern. Depending on the causative mutation involved, two major subtypes of HHT are recognized; HHT type 1 (HHT1) and 2 (HHT2). HHT is characterized by vascular anomalies which can present as both telangiectases and large arteriovenous malformations (AVMs). When located in the pulmonary circulation, these AVMs cause a right-to-left shunt (RLS) through a direct connection between the pulmonary arteries and veins, without an intervening capillary network. As a consequence, paradoxical embolisation of both thrombotic and septic origin may occur, resulting in possibly severe neurological complications such as stroke and brain abscess. For this reason, HHT patients are routinely screened for PAVMs.

Part I of this thesis describes the use of transthoracic contrast echocardiography (TTCE) as a screening technique for PAVMs.

Chapter 2 attends a prospective study in 281 individuals on the diagnostic value of TTCE for PAVM screening, as compared with chest HRCT (high-resolution computed tomography) as the gold standard. Chest HRCT showed a PAVM in 57 (20%) persons, compared with a pulmonary shunt on TTCE in 107 (38%) individuals. TTCE was false-negative in 2 out of 174 persons without a pulmonary shunt on TTCE. PAVMs in both these patients were too small for treatment. The sensitivity of TTCE was 97%, and its negative predictive value (NPV) 99%. Because TTCE detects even small pulmonary shunts that are not visible as PAVMs on chest HRCT, its positive predictive value (PPV) was only 51%. The primary outcome of this study was the excellent NPV of TTCE for PAVMs on chest CT. As a

consequence, TTCE can be used as a first-line screening technique for PAVMs, only followed by a CT scan to detect treatable PAVMs when positive for a pulmonary shunt. In addition, contrast echocardiography appears to be highly sensitive, as even microscopic PAVMs below the detection limit of HRCT are detected.

Because TTCE detects these small pulmonary shunts, a chest HRCT is subsequently performed in a considerable number of patients without treatable PAVMs. Therefore, the aim of **chapter 3** was to determine if a cut-off size of intrapulmonary shunting could be found at which chest HRCT would be redundant. In 281 patients who underwent both a TTCE and chest CT, the pulmonary shunt on TTCE was classified as small (<30 microbubbles), moderate (30-100 microbubbles), or large (>100 microbubbles). TTCE studies were positive in 105 patients (41%). A PAVM was present on HRCT in 23% of patients with a small pulmonary shunt, 35% with a moderate shunt, and 83% with a large pulmonary shunt. Moreover, none of the patients with a small or moderate shunt displayed PAVMs that were large enough for embolisation. In contrast, 76% patients with a large pulmonary shunt underwent embolotherapy. In conclusion, grading of pulmonary shunt size with contrast echocardiography is useful to discern insignificant from treatable PAVMs. A chest HRCT can be withheld in patients with low-grade shunts.

In Part **II**, the results of contrast echocardiography studies in different HHT genotypes are discussed, as well as the applicability of TTCE for the clinical diagnosis of HHT.

In **chapter 4** we describe the prevalence and size of intrapulmonary shunts in HHT type 1 and 2. A pulmonary shunt on TTCE was present in 78 of 92 (85%) HHT1, and 34 of 97 (35%) HHT2 relatives with a proven mutation. The majority of shunts (54%) in HHT1 patients were large, as opposed to predominantly small shunts (59%) in HHT2 patients. The PPV of a pulmonary shunt *per se* for treatable PAVMs was 36% in HHT1, and only 8% in HHT2 relatives. For large shunts only, the PPV increased to 56% and 38%, respectively. Unlike the results in chapter 3, we found 5 patients with a moderate shunt but a treatable PAVM nonetheless. This is probably explained by the growing number of patients over time. TTCE appeared

to be also positive in 6% of 63 individuals without HHT. These data show that pulmonary shunts are highly prevalent and predominantly large in HHT1 patients. In our opinion, the use of a graded approach of shunt size is inevitable, particularly in the HHT2 subgroup. However, as 85% of TTCE studies is positive in HHT1 patients, a first-line chest HRCT may also be considered in relatives with a high clinical suspicion for HHT when TTCE without shunt grading is used.

The aim of **chapter 5** was to assess the diagnostic accuracy of the clinical criteria for HHT in a large group of patients with an identified genotype. The clinical diagnosis of HHT is divided in 'definite' (≥3 criteria), 'possible' (2 criteria), and 'unlikely' (0 or 1 criterion). One of the criteria is the presence of visceral AVMs. Because of its high sensitivity, we were particularly interested in the usefulness of a pulmonary shunt on TTCE as proof for the presence of these visceral AVMs. From that we hypothesized that TTCE may improve clinical diagnosis of HHT. Of 186 first-degree relatives with a proven family mutation, a clinical diagnosis was definite in 168 (90%), possible in 17 (9%), and unlikely in 1 (0.5%) patient. Of 77 persons without a mutation, none had a definite diagnosis, and 42 (55%) were correctly classified as 'unlikely'. When a positive TTCE would be considered a valid criterion, the percentage of 'definite' patients increased to 94.1% of mutation carriers. However, this benefit was counterbalanced by 6.5% false-positives. In conclusion, a small pulmonary shunt appears to be a normal variant in the general population, and should therefore not be regarded as a clinical criterion for HHT.

Part III encompasses studies on the relation of intrapulmonary RLS and migraine.

Chapter 6 is a review of the literature on the association between migraine and intrapulmonary RLS. The proposed mechanisms that link these two entities are mainly shunting of (micro)thrombi or vasoactive substances to the arterial circulation. Surveying the available studies, there appears to be a consistent relationship between migraine with aura, but not migraine without aura, and intrapulmonary RLS. However, this association has only been studied retrospectively in small groups, which can lead to potential selection and recall bias.

In **chapter 7** we present the results of the first prospective study on an association of PAVMs with migraine. A total of 196 consecutive HHT patients underwent a HRCT and completed a structured headache questionnaire prior to screening. Two neurologists, blinded to the other patient data, diagnosed migraine according to the International Headache Society criteria. A PAVM on CT was present in 70 (36%) patients. Of patients with a PAVM, 24% met criteria for migraine with aura, compared with 6% of those without a PAVM. Otherwise, a PAVM was present in 68% of patients with migraine with aura, compared with 32% in non-migraineurs (odds ratio (OR) 4.6). Using multivariate analysis, migraine with aura appeared to be an independent predictor for PAVM (OR 3.6), and PAVM independently predicted migraine with aura (OR 3.0). This study shows an unequivocal association between PAVMs and migraine with aura in patients with HHT.

Chapter 8 describes the influence of pulmonary shunt size on the occurrence of migraine. In 462 consecutive persons who were screened for possible HHT, the echocardiographic size of pulmonary RLS was semi-quantitatively assessed as small, moderate, or large. A headache questionnaire was completed before their hospital visit by 420 persons of whom 44 (10.5%) were diagnosed with migraine with aura. Migraine with aura independently predicted the presence of an intrapulmonary RLS (OR 2.96). The most striking finding was that a large intrapulmonary shunt (> 100 microbubbles) appeared to be a powerful predictor for migraine with aura in multivariate analysis, with an odds ratio of 7.6. Lesser degrees of shunting were not associated with migraine. This study demonstrates that it is important to specifically address the functional potential of a RLS when studying its association with migraine.

In **Chapter 9**, which represents the general discussion, the main findings of this thesis are placed in a broader clinical perspective. We propose an adjusted screening algorithm for PAVMs, based on graded contrast echocardiography. In addition, a possible explanation is provided for the presence of small pulmonary shunts in persons without HHT. We also discuss the significance of our finding that an indisputable relationship exists between large intrapulmonary shunts and migraine with aura.

Samenvatting

Dit proefschrift behandelt een aantal klinische aspecten van pulmonale arterioveneuze malformaties (PAVM's) bij patiënten met hereditaire haemorrhagische teleangiectasieën (HHT). In het bijzonder wordt aandacht besteed aan de waarde van transthoracale contrast-echocardiografie (TTCE) voor de screening naar PAVM's en de klinische diagnose van HHT, evenals aan de relatie tussen PAVM's en migraine.

Hoofdstuk 1 geeft een introductie tot de belangrijkste klinische aspecten van HHT en PAVM's. HHT, ook wel bekend als de ziekte van Rendu-Osler-Weber, is een zeldzame vaataandoening met een autosomaal dominant overervingspatroon. Afhankelijk van de oorzakelijke genetische mutatie wordt er onderscheid gemaakt tussen 2 belangrijke subtypes van HHT: HHT type 1 (HHT1) en type 2 (HHT2). HHT wordt gekenmerkt door vaatafwijkingen die kunnen variëren van teleangiectasieën tot grotere arterioveneuze malformaties (AVM's). Als deze AVM's gelokaliseerd zijn in de pulmonale circulatie veroorzaken ze een rechts-links shunt (RLS) door een directe verbinding tussen het arteriële en veneuze systeem, zonder een tussenliggend capillair netwerk. Dientengevolge kan paradoxale embolisatie van zowel thrombotische als septische aard optreden, met potentieel ernstige neurologische complicaties zoals een cerebrovasculair accident of hersenabces tot gevolg. Om deze reden worden patiënten met HHT routinematig gescreend op de aanwezigheid van PAVM's.

Deel I van deze thesis beschrijft het gebruik van TTCE als screeningsmethode naar PAVM's.

Hoofdstuk 2 behandelt de resultaten van een prospectieve studie met 281 patiënten over de diagnostische waarde van TTCE voor de screening naar PAVM's, in vergelijking met high-resolution computed tomography (HRCT) van de thorax als de gouden standaard. HRCT toonde een PAVM in 57 (20%) personen, vergeleken met een pulmonale shunt op TTCE in 107 (38%) personen. TTCE was vals-negatief in 2 van de 174 personen zonder een pulmonale shunt op TTCE. De sensitiviteit van TTCE was 97% en de negatief predictieve waarde (NPW) 99%. Omdat TTCE

ook kleine pulmonale shunts visualiseert die niet als PAVM's zichtbaar zijn op HRCT, was de positief predictieve waarde (PPW) slechts 51%. De belangrijkste uitkomst van dit onderzoek is de uitstekende NPW van TTCE voor PAVM's op HRCT. Daarom kan TTCE worden toegepast als initiële screeningsmethode naar PAVM's, enkel gevolgd door een HRCT om behandelbare PAVM's te identificeren. Verder lijkt TTCE een uiterst sensitieve techniek, omdat zelfs de RLS van zeer kleine PAVM's onder de detectiegrens van HRCT zichtbaar kan worden gemaakt.

Omdat met TTCE deze kleine pulmonale shunts worden gevisualiseerd, wordt een HRCT gemaakt in een aanzienlijk aantal patiënten dat vervolgens geen behandelbare PAVM's zal blijken te hebben. Dit was de reden om te onderzoeken of een afkappunt kan worden vastgesteld voor de grootte van de shunt waarbij een HRCT overbodig is. Deze vraag wordt beantwoord in **hoofdstuk 3**. In 281 patiënten die allen een TTCE en HRCT ondergingen, werd de pulmonale shunt op TTCE ingedeeld in gering (<30 microbubbles), matig (30-100 microbubbles), of groot (>100 microbubbles). TTCE was positief in 105 patiënten (41%). Een PAVM op HRCT was aanwezig in 23% van de patiënten met een geringe, 35% met een matige en 83% met een grote pulmonale shunt. Bij geen van de patiënten met een geringe of matige shunt werd een PAVM gezien die voldoende groot was om voor embolisatie in aanmerking te komen. Daartegenover staat dat 76% van de patiënten met een grote shunt wel geëmboliseerd werd. Concluderend is het door graderen van de grootte van de pulmonale shunt mogelijk om onbelangrijke van behandelbare PAVM's te onderscheiden. Daarenboven kan een HRCT achterwege worden gelaten bij patiënten met kleinere shunts.

In **deel II** worden de resultaten van contrast echocardiografie bij patiënten met HHT1 en HHT2 besproken, evenals de toepasbaarheid van TTCE voor de klinische diagnose van HHT.

In **hoofdstuk 4** beschrijven we de prevalentie en grootte van intrapulmonale shunts in HHT type 1 en 2. Een echocardiografische long-shunt was aanwezig in 78 van 92 (85%) HHT1, en 34 van 97 (35%) HHT2 familieleden met een bewezen

mutatie. Het merendeel van de shunts (54%) in HHT1 patiënten was groot, in tegenstelling tot overwegend kleine shunts (59%) in HHT2 patiënten. De PPW van een pulmonale shunt in het algemeen voor behandelbare PAVM's was 36% in HHT1, en slechts 8% in HHT2 familieleden. Echter, voor alleen grote shunts steeg de PPW naar respectievelijk 56% en 38%. In tegenstelling tot hoofdstuk 3, waren er in deze studie 5 patiënten met een matige shunt die toch een behandelbare PAVM vertoonden. Een verklaring hiervoor is hoogstwaarschijnlijk het grotere aantal patiënten dat ten tijde van deze studie was gescreend. Verder was een TTCE ook positief in 6% van 63 personen zonder HHT. Naar onze mening is het graderen van de shunt-grootte van groot belang, met name in de HHT2 groep. In verband met het feit dat 85% van de HHT1 patiënten een positief TTCE laat zien, kan bij familieleden met een sterke klinische verdenking op de aanwezigheid van HHT1 ook worden overwogen om direct een HRCT te verrichten.

Het doel van **hoofdstuk 5** was het vaststellen van de validiteit van de klinische criteria voor HHT in een grote groep patiënten met een bekende mutatie. De klinische diagnose wordt ingedeeld in 'definitief' (≥3 criteria), 'mogelijk' (2 criteria) en 'onwaarschijnlijk' (0 of 1 criterium). Eén van de criteria is de aanwezigheid van viscerale AVM's. Omwille van de hoge sensitiviteit waren we in het bijzonder geïnteresseerd in de bruikbaarheid van een pulmonale shunt op TTCE als bewijs voor deze viscerale AVM's. Dit zou heoretisch de klinische diagnostiek van HHT kunnen verbeteren. De klinische diagnose van HHT was 'definitief' in 168 (90%), 'mogelijk' in 17 (9%) en 'onwaarschijnlijk' in 1 (0,5%) van de 186 eerstegraads familieleden met een bewezen mutatie. Van 77 personen zonder mutatie was er niemand met een 'definitieve' diagnose en 42 (55%) personen werden correct geclassificeerd als 'onwaarschijnlijk'. Het percentage met een 'definitieve' diagnose steeg naar 94 % van de dragers van een mutatie, indien een positief TTCE als geldig criterium werd beschouwd. Echter, dit ging ten koste van 6,5 % vals-positieven. Concluderend lijkt een kleine pulmonale shunt aanwezig te zijn als een normale variant in de algemene populatie en dient deze bevinding niet te worden gebruikt als een criterium voor de klinische diagnose HHT.

Deel III omvat studies met betrekking tot de relatie tussen intrapulmonale RLS en migraine.

Hoofdstuk 6 is een review van de beschikbare literatuur over de associatie tussen migraine en intrapulmonale RLS. De vooropgestelde mechanismen die deze twee entiteiten met elkaar verbinden zijn hoofdzakelijk een shunt van (micro)thrombi of vasoactieve stoffen naar de arteriële circulatie. Op basis van de beschikbare studies lijkt er een consistent verband te bestaan tussen migraine met aura, maar niet migraine zonder aura, en pulmonale RLS. Echter, deze associatie is alleen onderzocht in retrospectieve studies hetgeen kan leiden tot selectie en 'recall´ bias.

In **hoofdstuk 7** laten we de resultaten zien van de eerste prospectieve studie naar een relatie tussen PAVM's en migraine. In totaal 196 HHT patiënten ondergingen een HRCT en vulden voorafgaand aan de screening een gestructureerde hoofdpijnvragenlijst in. Twee neurologen, die geblindeerd waren voor de overige patiëntengegevens, stelden de diagnose migraine volgens de International Headache Society criteria. Bij 70 (36%) patiënten werd een PAVM op CT gezien. Van patiënten met een PAVM had 24 % migraine met aura, in vergelijking met 6% van de groep zonder PAVM. Andersom was een PAVM aanwezig in 68% van de patiënten met migraine met aura, vergeleken met 32 % van de patiënten zonder migraine. Na multivariate analyse bleek migraine met aura een onafhankelijke voorspeller voor PAVM (odds ratio (OR) 3,6) en PAVM een voorspeller voor migraine met aura (OR 3,0). Deze studie laat ontegenzeggelijk een verband zien tussen PAVM's en migraine met aura in patiënten met HHT.

Hoofdstuk 8 beschrijft de invloed van de grootte van de pulmonale shunt op het optreden van migraine. In 462 opeenvolgende personen die werden verwezen voor screening naar HHT, werd de shuntgrootte echocardiografisch semi-kwantitatief beoordeeld als gering, matig of groot. Een hoofdpijnvragenlijst werd ingevuld voorafgaand aan het ziekenhuisbezoek door 420 personen van wie 44 (10,5%) voldeden aan de criteria voor migraine met aura. Migraine met aura was een onafhankelijke voorspeller voor een intrapulmonale RLS (OR 2,96). De meest

opvallende bevinding was dat een grote shunt (> 100 microbubbles) een krachtige voorspeller was voor migraine met aura in multivariate analyse, met een odds ratio van 7,6. Kleinere shunts waren niet geassocieerd met migraine. Deze studie laat zien dat het belangrijk is om specifiek aandacht te schenken aan de functionele shunt-grootte wanneer men de associatie van rechts-links shunts met migraine bestudeert.

In **hoofdstuk 9**, de algemene discussie, worden de belangrijkste bevindingen van deze thesis in een breder klinisch perspectief geplaatst. Wij stellen een aangepast screeningsalgoritme voor, gebaseerd op gegradeerde contast-echocardiografie. Daarenboven wordt een potentiële verklaring gegeven voor de aanwezigheid van kleine pulmonale shunts in personen zonder HHT. Verder bespreken we de betekenis van onze bevinding dat er een duidelijk verband bestaat tussen grote intrapulmonale shunts en migraine met aura.

Dankwoord

Velen hebben een bijdrage geleverd aan de totstandkoming van dit proefschrift. Ik wil op deze plaats een aantal mensen persoonlijk danken voor hun hulp en inzet.

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Curriculum Vitae

De auteur van dit proefschrift werd op 13 augustus 1977 geboren in het Pieter Pauw ziekenhuis te Wageningen. In 1995 werd het diploma Voorbereidend Wetenschappelijk Onderwijs behaald aan "Het Wagenings" in de gelijknamige stad. In datzelfde jaar begon hij aan de studie Geneeskunde aan de Universiteit Antwerpen. Gedurende deze studies werd zijn interesse voor de cardiologie gewekt tijdens de colleges cardiovasculaire fysiologie. Aan het Universitair Ziekenhuis te Antwerpen vond het afstudeeronderzoek getiteld "Primaire PTCA versus rescue PTCA in the treatment of ST-elevation myocardial infarction" plaats (o.l.v. Prof. dr. M. Claeys). Op 20 juni 2003 werd het artsexamen behaald. Hierna was hij tot juli 2005 werkzaam als arts-assistent niet-in-opleiding op de afdelingen interne geneeskunde en cardiologie van het Amphia Ziekenhuis te Breda. Hierop volgde de overstap naar het Sint Antonius Ziekenhuis te Nieuwegein waar vanaf januari 2006 aanvang werd genomen met de opleiding tot cardioloog (opleider: Dr. W. Jaarsma). Na gedurende een jaar van zijn opleiding werkzaam te zijn geweest op de afdeling cardiologie van het Gelre Ziekenhuis te Apeldoorn (opleider: Dr. W.T.J. Jap Tjoen San), volgde hij gedurende 2 jaar de vooropleiding interne geneeskunde in het Sint Antonius Ziekenhuis te Nieuwegein (opleiders: Dr. D.H. Biesma en Dr. A.B. Geers). In januari 2009 volgde de terugkeer naar de afdeling cardiologie in hetzelfde ziekenhuis. In het eerste jaar van zijn opleiding werd hij door Dr. M.C. Post geënthousiasmeerd voor klinisch wetenschappelijk onderzoek, hetgeen heeft geresulteerd in dit proefschrift. In 2006 trouwde hij met Marleen Wagemakers met wie hij in januari 2008 een zoon kreeg, Ruben.