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Open Med. 2015; 10: 285-293

Research Article

Open Access

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Carotid ultrasound for pulmonary arteriovenous malformation screening

Abstract: Objective: In patients with hereditary hemorrhagic telangiectasia (HHT), pulmonary arteriovenous malformations (PAVMs) can cause serious neurological complications. Our aim was to evaluate the potential of contrast-enhanced Doppler ultrasound (CE-US) of the common carotid artery as a screening test for detection of PAVMs. Methods: A total of 124 consecutive patients with HHT or a positive family history underwent screening for PAVMs with CE-US and thoracic contrast-enhanced magnetic resonance angiography (CE-MRA). CE-US was performed after receiving (D)-galactose microparticulate, and CE-MRA with gadobenate dimeglumine. Twenty-five patients with confirmed PAVMs were referred to conventional pulmonary catheter angiography (PA). Findings on CE-US and CE-MRA were evaluated using contingency tables and McNemar's test. Results: Using CE-MRA as the reference test, CE-US had a sensitivity of 100%, a specificity of 87%, and a negative predictive value of 100%. In 25 patients who underwent PA, PAVMs that had been diagnosed on CE-US and CE-MRA were confirmed. Of the PAVMs detected by CE-MRA, 24% were not identified on PA. Conclusion: CE-US is a simple, minimally invasive screening method that can easily be performed in different settings. CE-US can predict PAVMs with high probability of success. CE-US may be a simple alternative to transthoracic echocardiography in the assessment of PAVMs in certain HHT-patients.

Keywords: Hereditary hemorrhagic telangiectasia, pulmonary arteriovenous malformation, screening, contrast-enhanced ultrasound

DOI 10.1515/med-2015-0040

Received: December 19, 2014; accepted: April 4, 2015

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1 Introduction

Pulmonary arteriovenous malformations (PAVMs) occur in up to 50% of patients suffering from hereditary hemorrhagic telangiectasia (HHT) [1, 2], also known as Osler-Weber-Rendu disease. PAVMs are abnormally dilated vessels resulting in right-to-left shunts.

After remaining asymptomatic for years, PAVMs can suddenly cause life-threatening complications, such as paradoxical embolism leading to neurological problems, including brain abscess and stroke, or lung hemorrhage [3-5]. PAVMs can enlarge over time [5, 6], especially during pregnancy [7, 8]. PAVMs with a feeding artery ≥ 3 mm require transcatheter coiling [1, 3, 9, 10].

In accordance with the international guidelines for the diagnosis and management of HHT, the consensus is that patients with suspected or confirmed HHT should be screened for PAVMs [1].

Contrast-enhanced transthoracic echocardiography has been shown to be the most sensitive screening method for detection of PAVMs among the non-invasive screening methods available [2, 11-15], and it is recommended for initial screening, followed by chest computed tomography (CT) [1].

Other screening methods include radionuclide perfusion [16], and gas exchange or pulse oximetry methods [13, 16]. Due to different reference methods used, comparison of sensitivities is problematic.

In the present study, echo-enhanced Doppler ultrasound (CE-US) of the common carotid artery (Fig. 1) was compared to thoracic contrast-enhanced magnetic resonance angiography (CE-MRA) (Fig. 2) and conventional pulmonary angiography (PA) to evaluate its efficacy as a screening procedure for PAVMs.

2 Material and methods

2.1 Study design

Overall, 124 patients aged 9–79 years (median 46 years, mean 47 years, standard deviation 15 years) underwent screening by CE-US and CE-MRA. The majority were females (54 males, 70 females). PA was performed in 25 of the 124 patients aged 21-67 years (median 46 years, mean 47 years, standard deviation 14 years) comprising 17 females and 8 males.

Patients were diagnosed with HHT based on the Curaçao criteria as agreed upon by the Scientific Advisory Board of HHT Foundation International in 2000 [17], or were first-degree relatives of affected individuals. The

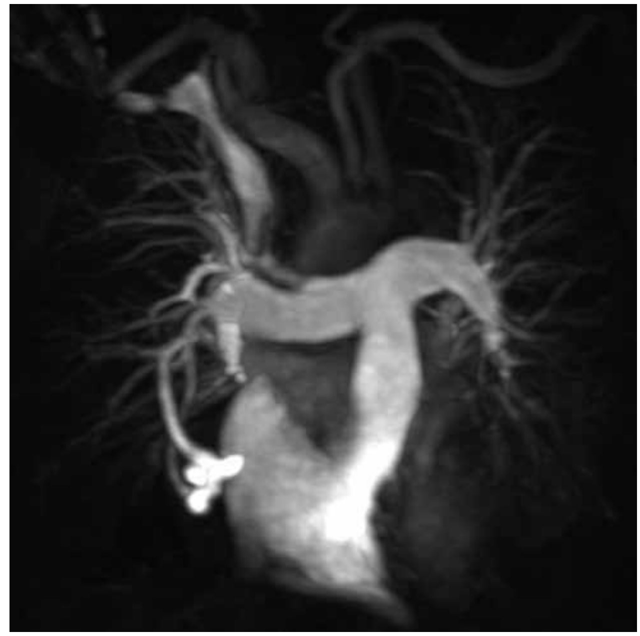

Figure 2: Pulmonary arteriovenous malformation on CE-MRA

The CE-MRA scan shows a typical simple PAVM in the middle lobe. The diameter of the feeding pulmonary artery is 4 mm.

PAVMs = pulmonary arterio-venous malformations, TAE = telangiectasia, GI-TAE = gastro-intestinal telangiectasia, CVMs = cerebral vascular malformations, HVMs = hepatic vascular malformations

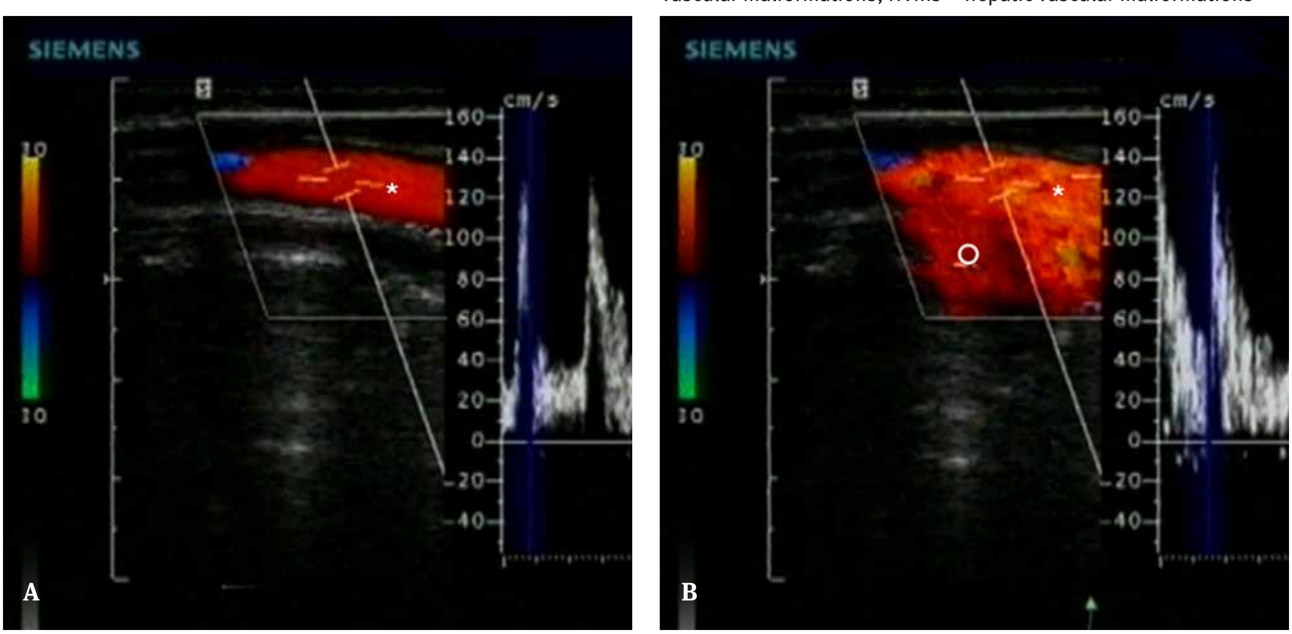

Figure 1 a-b: Pulmonary arteriovenous malformation on CE-US

B-mode, color flow and pulsed-waved Doppler of the left common carotid artery (circle) of a patient with a PAVM is demonstrated before (a) and after (b) contrast injection.

The figure illustrates the perivascular opacification color blooming artifact (asterisk) and an increased peak velocity on spectral Doppler after application of a contrast agent.

study is based on data generated between January 1998 and April 2006.

According to the study protocol, data was collected anonymously. Informed consent for the clinical tests has been obtained from all individuals included in this study. The research complies with all relevant national regulations and institutional policies, is in accordance with the principles of the Helsinki Declaration, and has furthermore been approved by the authors' institutional review board. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CE-US was performed and interpreted by one physician who was blinded to the results of CE-MRA. The CE-MRA scans were interpreted by two experienced radiologists who were not made aware of the results of CE-US. Patients with technically accessible PAVMS on CE-MRA were referred to PA. Four experienced radiologists performed and analyzed the examinations. Patients were followed-up depending on PAVM-size. In patients with confirmed PAVM-diameter < 5 mm, CE-MRA was recommended after one year. Catheter angiography was repeated after reexamination and relevant progression of PAVM. PAVMs with a diameter ≥ 5 mm were treated, even if the feeding artery was < 3 mm. In the present study, the PAVMs treated had minimal feeding artery diameters measuring between 1 and 2 mm. PAVMs with more than 1 feeding artery were defined as complex PAVMs.

2.2 Examination Protocol

Contrast-enhanced ultrasound of the common carotid artery (CE-US)

CE-US of the common carotid artery was performed using a Sonoline Elegra (Siemens Medical Systems, Issaqua, Washington) with a 7.5 MHz linear array transducer. Patients were positioned in a 30-degree upright position. After 30 seconds of displaying a baseline signal, a bolus of 10 ml D-galactose microparticulate (Echovist(R)-300; Schering, Germany), a contrast agent not crossing the pulmonary capillary bed, was injected over 10 seconds into an intravenous catheter placed in the median cubital vein of the right arm. If that was not possible, Echovist(R) was injected into an intravenous catheter in the left arm. In a few cases, only one of the carotid arteries was accessible. In the presence of shunting, the injected contrast agent leads to an increase of echo reflex, characteristically presenting as acoustic crackles. Shunt classification was based on the quantity of crackles counted, by the increase of opacification of the common carotid artery, and by the broadening of the spectral curve (Fig. 1). In the case of shunting, color flow shows the so-called blooming artifact outside the vessel, typically occurring when using contrast medium. This is caused by an increase of the Doppler signal intensity and can be avoided by reducing the color gain. After application of the contrast agent, a higher peak velocity was observed on spectral Doppler. Microbubble destruction may furthermore cause an accumulation of high-intensity spikes.

Up to 10 acoustic events were counted. For larger numbers, the amount of crackles was estimated. In ambiguous cases, a video recording was used to re-evaluate questionable results at a later time. The period of latency between giving Echovist(R) and its appearance in the carotid artery was not documented. The cut-off time of two minutes was sufficient to document the arrival of contrast material. A positive finding on CE-US was defined as contrast agent reaching the common carotid arteries, causing an optical increase in contrast and multiple (> 10) crackles. An uncertain result was characterized by an indefinite increase in signal amplification, while 1-10 crackles were audible. If crackles were not audible and an increase in signal intensity was not noticed, the result was defined as negative. Subsequently, indefinite and positive results were combined as "positive results" and compared with negative results, presuming that microscopic PAVMs may account for an unknown number of indefinite results. All examinations were video recorded.

Among the positive findings, an estimation of shunt-size was attempted by the number of crackles.

2.3 Thoracic contrast-enhanced magnetic resonance angiography (CE-MRA)

All patients underwent unenhanced and dual-phase thoracic CE-MRA (gadobenate dimeglumine 0.1 mmol/kg body weight) on a 1.5 T scanner (Magnetom Vision or Magnetom Sonata; Siemens Medical, Germany) under breath-hold, using a 3D gradient-echo sequence (repetition time 4.6 ms, echo time 1.8 ms; flip angle 30°; matrix 160-180 × 512; field of view 320 × 450-500 mm in coronal orientation; slab thickness 120-160 mm; reconstructed slice thickness 1.8-2.2 mm) with asymmetric k-space acquisition in which the center of k-space was acquired during the first third of the sequence.

2.4 Pulmonary catheter angiography (PA)

PA was performed in 25 patients with positive findings on CE-MRA and who required treatment of PAVMs on an Axiom Artis (Siemens Medical Systems, Erlangen, Germany) angiography system using iomeprol (Iomeron(R); Bracco Imaging SpA, Milan, Italy) as a contrast agent. Embolizations were performed with nester(R) platinum embolization coils (Cook Medical, Mönchengladbach, Germany – Cook Ireland Ltd. Europe, Limerick, Ireland).

2.5 Statistical analysis

The data comparing CE-US, CE-MRA and PA were presented descriptively (Table 1). The results of CE-US and CE-MRA were compared using a contingency table (Table 2). CE-MRA was used as the reference method to calculate sensitivity, specificity, positive and negative predictive values for CE-US with a 95% confidence interval (Table 3). Using McNemar's and McNemar-Bowker's test, the estimated shunt-sizes on CE-US and the number or diameter of shunts on CE-MRA were correlated (data not provided). The presence of PAVMs was correlated with age and gender, using Chi-square test.

3 Results

Results on CE-US and CE-MRA correlated in 112 of the 124 patients screened (Table 2). Twelve of the 124 patients had positive findings on CE-US but a negative result on CE-MRA. Table 3 gives values for sensitivity, specificity, positive and negative predictive values for CE-US with a 95% confidence interval. As illustrated by Tables 2 and 3, CE-US predicts PAVMs with high probability of success. A statistical association between the estimated shunt-sizes on CE-US and the number or diameter of shunts on CE-MRA could be determined.

Global (n = 21) or selective (n = 4) PA was performed in 25 of 124 patients who required treatment of PAVMs. CE-US was positive in all 25 cases (Table 1). Due to performing selective angiography of only one lung in 4 patients, 15 PAVMs in the contralateral lung were not in the field of view, leaving 66 of 81 PAVMs shown on CE-MRA for direct comparison between CE-MRA and PA. Sixteen of these 66 PAVMs (24%) between 3 and 12 mm were not identified by PA.

Table 4 shows the distribution of age, gender, other HHT-related manifestations and positive family history. There were no statistical associations between age and presence of PAVMs or gender and presence of PAVMs.

Table 2: Comparison of findings on CE-MRA with findings on CE-US

		CE-MRA		
		Positive	**Negative**	**Total**
CE-US	**Positive**	31 (25%)	12 (10%)	43 (35%)
	Negative	0 (0%)	81 (65 %)	81 (65%)
	Total	31 (25%)	93 (75%)	124 (100%)

Footnote: n = number; CE-US = contrast-enhanced ultrasound of the common carotid artery; CE-MRA = thoracic contrast-enhanced magnetic resonance angiography

Table 1: Comparison of estimated PAVM-size on CE-US with PAVM-number on CE-MRA and PA

Estimated shunt-size on CE-US	Matching number of PAVMs on CE-MRA and PA		Number of Patients undergoing CE-US, CE-MRA and PA	Number of PAVMs	
	Yes	**No**	**Total**	**CE-MRA**	**PA**
Small	1	1	2	3	2
Moderate	3	5	8	20	14
Large	8	5	13	33	26
Uncertain	1	1	2	10	8
Total	13	12	25	66	50

Caption: PAVMs were diagnosed according to CE-US in all 25 patients. Comparing CE-MRA with PA, 16 out of 63 PAVMs were not identified on PA in 12 patients. In 13 patients, results on CE-MRA and PA corresponded. Shunt classification was based on the quantity of crackles counted. Estimation of shunt-size was not possible in 2 patients.
Footnote: CE-US = Contrast-enhanced ultrasound of the common carotid artery, CE-MRA = thoracic contrast-enhanced magnetic resonance angiography, PA = pulmonary catheter angiography, PAVMs = pulmonary arterio-venous malformations.

Table 3: Diagnostic test evaluation of CE-US using CE-MRA as basis for the calculations.

Test characteristics	Value [%]	95% confidence interval [%]
Sensitivity	100.0	88.7 to 100.0
Specificity	87.1	78.5 to 93.1
Positive predictive value	72.1	56.3 to 84.7
Negative predictive value	100.0	95.5 to 100.0

Footnote: CE-US = contrast-enhanced ultrasound of the common carotid artery; CE-MRA = thoracic contrast-enhanced magnetic resonance angiography

Table 4: Age, gender, other manifestations and positive family history

CE-MRA	Age [years]			Gender		Recurrent epistaxis	TAE	GI-TAE	CVMs	HVMs	Positive family history
	< 40	≥ 40 and < 55	≥ 55	female	male						
No PAVMs	26 21%	32 26%	35 28%	53 43%	40 32%	82 74%	83 73%	15 56%	1 33%	16 84%	56 72%
PAVMs	7 6%	15 12%	9 7%	15 12%	16 13%	29 26%	30 27%	12 44%	2 67%	3 16%	22 28%
Total	33 27%	47 38%	44 35%	68 55%	56 45%	111 100%	113 100%	27 100%	3 100%	19 100%	78 100%

Footnote: CE-MRA = thoracic contrast-enhanced magnetic resonance angiography,

4 Discussion

PAVMs can result in serious neurological complications when left untreated [2, 12]. Screening for PAVMs in HHT-patients has been undisputed [1]. Only with the introduction of the international guidelines for the diagnosis and management of HHT [1], a gold standard was defined. At the outset of our data collection, only limited data on the sensitivity of different methods were available. PA was among the methods with the highest sensitivity for the diagnosis of PAVMs but because of its invasiveness, only performed when treatment was required [12, 18].

An adequate screening tool ought to be easily available, broadly applicable, inexpensive and simple. In the present investigation, Doppler ultrasound of the common carotid artery with Echovist(R) was chosen as an initial screening tool based on those criteria. It is a simple, widely available examination that can be performed within 10-15 minutes. By using the common carotid arteries as easily accessible target vessels, better reproducibility was expected than by contrast-enhanced ultrasound, using transcranial Doppler, transesophageal or transthoracic echocardiography. Echovist(R) was selected as a well-tolerated contrast medium with few side effects. Reactions occur in less than 5%, mainly paresthesia at the injection site, dysgeusia and vasovagal reactions (Echovist(R)-300 [package insert]; Berlin, Germany: Schering: 1999). Agitated saline can be used as an alternative contrast agent. However, bubble size is not predictable, and paradoxical embolism may occur. Furthermore, a lower sensitivity of transcranial Doppler for detecting right-to-left shunts is reported when using agitated saline [19]. Paradoxical air embolism is unlikely when using Echovist(R), as the size of microbubbles remains consistent [20].

Analogous to the 3-cardiac cycle rule on transthoracic echocardiography, which suggests an extracardiac shunt when microbubbles appear in the left atrium after 3 beats from opacification of the right atrium [21], contrast medium is also expected to reach the carotid arteries after a latency period. Distinction between cardiac or pulmonary shunts, using CE-US, was not routinely attempted. Interestingly, the timing of left heart contrast entry during transthoracic echocardiography, used to distinguish intracardiac from pulmonary shunts, has been shown to be unreliable [22]. In contrast to transthoracic echocardiography, obesity, emphysema, chest deformities or post-radiation therapy do not adversely affect the quality of examination results [23]. A sufficient acoustic bone window, as required for the performance of transcranial Doppler is not necessary. Sedation is not required. Hence, an effective Valsalva maneuver can easily be performed, but may lead to artifacts, due to laryngeal movements.

Accessibility of the common carotid arteries should pose no difficulty. The common carotid artery which allowed a better visibility was chosen for examination. No striking difference was noticed between the two sides, and therefore this parameter is not included. In accordance, Draganski et al. [24] report that in the detection of cardiac right-to-left shunts, no significant differences between high-intensity transient signal counts in the right and left middle cerebral arteries were found.

Patients' movements during the examination do have an impact on the clinician's ability to interpret result. Positioning in a 30-degree upright position seems to be favorable. In an upright position, perfusion to the lungs' bases improves, whereas in the supine position the bases where the majority of PAVMs are located [13] are less well perfused. Sensitivity on CE-US may consequently be improved by scanning the patient upright [25, 26].

As confirmatory tests we chose CE-MRA and PA. There is no reference arm against CT but considering the cumulative effects of life-time radiation exposure in HHT patients, CE-MRA was preferred. We aimed to avoid ionizing radiation and potentially nephrotoxic iodinated contrast media, especially with regard to children, women of child-bearing age, and renally impaired persons. For the same reasons, negative results on CE-US and CE-MRA were not routinely controlled by PA. Only 25 of 31 patients with positive results on CE-MRA and CE-US, who required therapy, were physically able and willing to undergo PA. In 25 patients, PA confirmed positive results on CE-US but 24% of PAVMs were not detected on PA. Subsequently, diagnostic accuracy may not have been fully determined by this investigation. Additionally, the findings of Schneider et al. [27] suggest that CE-MRA is a technique superior to PA because it permits the detection of significantly more PAVMs. On these grounds, CE-MRA was used as the reference test for CE-US, and the data comparing CE-US, CE-MRA and PA were presented descriptively (Table 1).

The results of the present study demonstrate that CE-US is a sensitive screening method for the detection of PAVMs. CE-US correlated with CE-MRA in 112 of 124 cases (Table 2). No PAVMs identified by CE-MRA were failed to be diagnosed by CE-US. Shunts were classified by estimated size on CE-US, based on a study presented by Pilcher et al. [25], who found a strong correlation between the microbubble-count on CE-US with the radionuclide shunt result. Our data comparing the estimated shunt-sizes on CE-US with the number and diameters of PAVMs on CE-MRA support these findings. Recent studies report that small shunts on transthoracic echocardiography may be without clinical relevance [28, 29]. Contrary to this, our findings indicated that shunts classified small on CE-US had therapeutic implication. Positive and indefinite results on CE-US require immediate further testing and possibly treatment. Negative findings were negative on all confirmatory tests. In these cases, regular long-term follow-up is sufficient. As expected, CE-US showed more positive findings than CE-MRA. In 12 cases results on CE-US were positive while CE-MRA was negative. The 12 patients with discrepant results were contacted to arrange for follow-up examinations. However, due to a large geographical recruitment area, these patients could not consistently be followed up at our institution. Nine of the 12 patients were classified indefinite on CE-US: on reflection, seven patients with indefinite results probably should have been classified negative due to likely artifacts. The remaining two patients who were classified indefinite were suspected to have cardiac shunting. As a precaution, all cases with indefinite result were counted as positives. Three of the 12 patients with discrepant results were categorized positive on CE-US: on the first patient, transcatheter embolotherapy had been performed several times at another institution prior to our screening with CE-MRA and CE-US. After completion of the study, the patient underwent a partial lung resection at another institution which showed diffuse PAVMs of microscopic size. After the intervention, the patient's main symptom, lung hemorrhage, ceased. Since then the patient has had no further follow-up. The discrepant result in the above mentioned patient with the diffuse PAVM suggests that his positive result on CE-US may have been due to remaining diffuse PAVMs of microscopic size. The second patient showed no symptoms. Although transesophageal echocardiography showed extracardiac shunting, the patient declined further follow-up examinations for PAVMs. The third patient with a positive result on CE-US had valvular transplants and suffered from dyspnea due to cardiac insufficiency. He was recommended further tests to rule out PAVMs, but because of his poor health, he decided against follow-up. He was under medical treatment at another institution that had no experience with HHT.

Discrepant results may be caused by several phenomena. If cardiac shunting is ruled out, positive findings on ultrasound-based examinations may represent microscopic PAVMs [11, 12, 14, 30, 31] or may even be physiological [30, 32]. Spontaneous regression of PAVMs has been described [33]. The Euler-Liljestrand mechanism or the absence of a Valsalva maneuver may also have contributed to discrepant results. Among the patients contacted for follow-up, one patient with a shunt graded as indefinite on CE-US and negative result on CE-MRA showed development of a PAVM on CT within 6 years of the initial examinations. This may indicate that during CE-US and CE-MRA, a microscopic PAVM may already have been present. Therefore, patients with negative CE-MRA and positive CE-US should be recommended controls at close intervals by an imaging method and an antibiotic prophylaxis for procedures with potential bacteremia. These precautions are not necessary for patients whose examination results are negative in both methods.

Despite the high negative predictive value for transthoracic echocardiography, which is today considered the gold standard for primary, non-invasive screening for PAVMs, false-negative cases in the detection of right-to-left shunts have been described [12, 30, 34]. This implies that optimization of all ultrasound-based examinations, including CE-US, may be necessary and that regular follow-up is essential, regardless of the initial outcome. To increase sensitivity, complementary screening by imaging methods remains indispensable until prospective studies with a larger number of cases have been performed.

Ethical considerations and the initial absence of a generally accepted gold standard restricted the selection of reference methods. One major limitation is that the results on CE-US were not routinely compared with CT or CT angiography. PA was only performed in subjects who required embolization based on positive PAVM findings on CE-MRA. Subsequently, true values of sensitivity and specificity could not be evaluated. CE-US was not compared to transthoracic echocardiography. Patients with intracardiac shunts were not excluded prior to conducting the study. Cardiac shunts present in the screened population may have influenced the results on CE-US. A Valsalva maneuver was not performed routinely after a negative CE-US result. Interpretation of CE-US was subjective; automated bubble-count may have allowed for more objectivity. Examination of the common carotid arteries was not performed completely uniformly, and documentation could have been extended. Tests on the reproducibility of the method, including positioning of the patient, speed of the injection, the localization of the injection site, the exact position of the ultrasound transducer, and the timing of the first appearance of bubbles were not performed. Assessment of blood flow velocity as established in other disease patterns [35, 36] was not performed, but may have contributed to the estimation of shunt-volume. Management and reproducibility of the examination need to be optimized, especially with regard to long-term follow-up of discrepant results.

In conclusion, several ultrasound-based screening methods are available for the detection of PAVMs. Among them, transthoracic echocardiography is the best established and is considered the most sensitive. In comparison, CE-US is a simple, widely available examination with easy access to the target vessels. A further advantage is the option to increase reproducibility by adding computerized quantification of the bubble-count. False-positive results due to cardiac and physiological shunts or microscopic PAVMs are possible. Indefinite results ought to be followed-up closely. For further studies, rigorous examination protocol needs to be developed, potentially including the performance of a Valsalva maneuver after initially negative result on CE-US. At present, CE-US cannot replace transthoracic echocardiography but may be helpful as a simple alternative in the assessment of PAVMs in HHT-patients when transthoracic echocardiography is not readily available.

Acknowledgments: The authors wish to thank Dr. sc. hum. J. König (Institute for Biostatistical support, Mainz, Germany), Mei-Fang Ong D.Sc. (Homburg / Saar, Germany) and K.M. Schardt (Frankfurt / Main, Germany) for their additional statistical support. For the proofreading of the English language and editing we thank Ms. A. Thiemann MA (Pirmasens, Germany), Mr. H. Thiemann E. E. (Perkasie, PA), Prof. J. Philips (University of Kentucky), Mr. B. F. Killeen BA and Ms E. Bayerköhler (Hammersmith Hospital, London, UK). The publication of this study was made possible by a non-specific grant of “Shake your world” (www.shakeyourworld.it) to U.G.

Conflict of interest: Authors state no conflict of interest

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