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Usefulness of Transcranial Doppler for Detecting Pulmonary Arteriovenous Malformations in Hereditary Hemorrhagic Telangiectasia

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The aim of this study was to assess transcranial Doppler (TCD) as a screening test for pulmonary arteriovenous malformation (PAVM) in patients with hereditary hemorrhagic telangiectasia (HHT). This retrospective study included suspected patients with HHT who were screened for PAVM with a TCD and a chest computed tomography (CT) study. The results of TCD and CT were compared to evaluate the usefulness of TCD for detecting PAVM. A TCD Spencer grade ≥3 was defined as positive for a significant right-to-left shunt (RLS). The diameter of the pulmonary arteries feeding the PAVM was measured by calipers from the CT study. In 86 subjects from 74 families with HHT, the sensitivity of TCD for identifying a PAVM at rest was 98% and post-Valsalva was 100%. Specificity was 58% and 35%, respectively, presumably due to pulmonary shunts too small to recognize on CT. Of the patients with HHT who were referred for embolization therapy for their PAVMs, all 20 had TCD grade ≥3. In patients who were diagnosed with a PAVM by chest CT, patients with TCD grade ≥5 had a significantly larger sum of artery diameters feeding the PAVMs compared to those with grade ≤4 (5.0 ± 3.2 mm vs 2.6 ± 1.9 mm, p = 0.01). In conclusion, a TCD examination for evaluating RLS is sensitive for identifying PAVM in patients with HHT and is useful in quantitating the degree of RLS flow. The sensitivity of the TCD examination makes it a useful screening test without radiation in HHT subjects to determine which patients need to undergo CT evaluation to identify PAVMs. **(Am J Cardiol 2016;117:1180−1184)**

Hereditary hemorrhagic telangiectasia (HHT) is a genetic disorder in which control of vascular growth is abnormal and produces arteriovenous communications in the cutaneous, pulmonary, cerebral, gastrointestinal, and hepatic arterial beds.[1] Pulmonary arteriovenous malformations (PAVMs) have been reported to occur in 15% to 33% of patients with HHT.[2,3] Patients with PAVMs may experience consequences of right-to-left shunt (RLS) such as hypoxemia, transient ischemic attack, migraine, stroke, and cerebral abscess because of the passage of deoxygenated blood, aseptic, or septic emboli into the cerebral circulation. The incidence of stroke has been reported between 2.6% and 25% of patients with PAVMs, and the incidence of cerebral abscess has been reported between 5% and 9% of patients with PAVMs.[4,5] Because of the high risk for cerebrovascular events, screening for asymptomatic PAVMs is recommended for patients with HHT.[6] There have been several proposed methods for screening patients with HHT and their families for the presence of PAVMs, including chest computed tomography (CT) and transthoracic echocardiograms with agitated saline contrast.[7−10] The aim of this study was to assess the usefulness of transcranial Doppler (TCD) to screen for PAVMs in patients with HHT. This study includes the largest number to date of patients with HHT for the assessment of TCD as a screening test for detecting PAVM.

Methods

Between July 2010 and November 2015, 312 suspected patients with HHT and family members were evaluated through the HHT Center of Excellence at University of California, Los Angeles (UCLA). There were 134 subjects who required screening for a PAVM and had a TCD examination; 86 of these also had a chest CT study. Medical charts of the patients were retrospectively reviewed for history, examination findings, and laboratory results to confirm the diagnosis of HHT. The diagnosis of possible or definite HHT was made according to the Curacao criteria.[1] The Curacao criteria is a diagnostic tool that assigns a score of 0 to 4 based on the presence of epistaxis, telangiectasia, visceral lesions, and family history of HHT. The HHT diagnosis is considered definite if ≥3 criteria are present and possible if 2 criteria are present. There was no required genetic testing for the diagnosis of HHT, but there were subjects who had genetic testing performed for the diagnosis of asymptomatic family members. The study received prior approval by the UCLA Institutional Review Board for Human Research, and all patients signed informed consent.

TCD was performed using a power M-mode Terumo 150 PMD machine (Spencer Technologies, Redmond,

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See page 1183 for disclosure information.

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Washington). Ultrasonic probes were mounted on a head frame and positioned over insonation windows located on the temporal bone. Individual probes on each side were manipulated to locate the middle cerebral artery. A mixture of 8-ml normal saline solution combined with 0.5 ml of air and 1 ml of blood was agitated between 2 syringes connected by a 3-way stopcock and injected into the brachial vein; embolic tracks were then counted over the middle cerebral arteries. The addition of blood increases the number of microbubbles produced and may increase the effectiveness of microbubble contrast.[11] The degree of RLS was evaluated by TCD at rest and post-Valsalva maneuver. During Valsalva, patients were instructed to exhale at a sustained pressure of 40 mm Hg, aided by visual feedback with a manometer device; bubble injection commenced just before cessation of Valsalva. The Spencer Logarithmic Scale, which assigns a score of 0 to 5, was used to grade the results. Grade 3 or higher (≥31 microbubbles/min) was considered as a positive result representing a significant RLS.[12] Grade 4 was defined as detection of 101 to 300 microbubbles per minute, grade 5 was defined as detection of >300 microbubbles per minute and microbubbles with a shower effect (too numerous to count) was considered as grade >5. In 12 patients who showed a shunt of grade 4 or ≥5 at rest, the injection was not repeated post-Valsalva. In one 11-year-old female, the bubble study was performed only post-Valsalva to avoid repeated bubble injections. Spencer TCD grades at rest and post-Valsalva were compared with the presence of PAVM on CT. The presence or absence of PAVM on CT was used as the standard to determine the sensitivity and specificity of the TCD examination. The highest TCD grade either at rest or post-Valsalva was compared with the size of the feeding arteries of the PAVMs.

Chest CT was used as the reference for the morphologic evaluation of PAVM. There were 30 patients who brought CT studies from their referring institutions. The remaining 56 patients underwent imaging with a CT scanner at UCLA (SOMATOM Definition Flash [n = 9]; Sensation 64 [n = 41]; Sensation 16 [n = 5]; Emotion 6 [n = 1], Siemens Healthcare, Germany). The diagnosis of PAVM was based on the typical appearance of a nodular opacity of variable size with both an afferent and efferent vessel on CT. The number and the diameter of the feeding arteries for the dominant PAVMs were measured using software calipers on the CT images. Measurements were obtained by a physician blinded to the results of TCD. The sum of the diameters of the arteries feeding the PAVMs were calculated and compared with the TCD grades of RLS flow. Patients were classified in groups according to the feeding artery diameter of the main PAVM (<2 mm, 2 to 2.9 mm, and ≥3 mm).

The recommendation for embolization therapy was based on the presence of a PAVM feeding artery diameter of ≥3 mm on CT,[13] whereas <2 mm was considered to be too small for embolization. A PAVM with a feeding artery diameter between ≥2 and ≤2.9 mm received embolization therapy based on a discussion between the patient and the physician performing this therapy regarding the risks and benefits of undergoing the procedure versus watchful waiting.

Table 1
Clinical characteristics of study patients

Clinical data	Value (N = 86)
Age (years)	40 ± 19 (9-81)
Male	32 (37%)
HHT according to number of Curacao diagnostic criteria present	
4	41 (48%)
3	33 (38%)
2	10 (12%)
1	2 (2%)
Epistaxis	77 (90%)
Telangiectasia	69 (80%)
Family history of HHT	82 (95%)
Visceral arteriovenous malformations	54 (63%)
Lung (PAVM)	43 (50%)
Single vs. Multiple PAVMs	18 vs. 25
Brain	9 (10%)
Liver	12 (14%)
Gastrointestinal tract	7 (8%)
Spine	1 (1%)
Gene mutations for HHT	54 (63%)
Endoglin gene	27 (31%)
Activin A receptor type II-like 1 gene	19 (22%)
SMAD4	1 (1%)
Unknown	5 (6%)
No mutation found	2 (2%)
Not performed	32 (37%)
Referred for embolization therapy of PAVMs	20 (23%)

HHT = hereditary hemorrhagic telangiectasia; PAVM = pulmonary arteriovenous malformation.

To assess the utility of the Valsalva maneuver for distinction between PAVM and patent foramen ovale (PFO), the differences in TCD grades were compared between the patients with HHT with documented PAVM and a population of patients with PFO where TCD is routinely performed. The PFO population consisted of 140 patients who underwent a screening evaluation for an RLS with TCD at rest and post-Valsalva maneuver and had a PFO documented by a right heart catheterization.

Continuous variables were expressed as mean ± standard deviation. Statistical significance was determined using unpaired *t* tests for continuous variables. Pearson's chi-square test or Fisher's exact test were used for categorical variables; a value of $p < 0.05$ was considered significant. Data were analyzed using JMP, version 9.0 for Windows (SAS Institute, Inc., Cary, North Carolina).

Results

Baseline patient characteristics are listed in Table 1. There were 74 (86%) patients who were diagnosed with definite HHT after a complete evaluation, including CT study to identify any PAVM. Of those who were diagnosed with definite HHT, 40 (54%) patients had a PAVM on CT, whereas 3 (30%) patients diagnosed as possible HHT and 0 (0%) patients diagnosed as unlikely for HHT had a PAVM on CT. Visceral AVMs in multiple organs (lung, liver, gastrointestinal, or brain) were present in 15 (17%) patients. Genetic testing for the gene responsible for the clinical

Table 2
Sensitivity and specificity of TCD grade for PAVM

	Definition of positive RLS on TCD		
	Grade ≥3	Grade ≥4	Grade ≥5
TCD grades at rest, N = 85*			
Sensitivity	98% (41/42)	79% (33/42)	52% (22/42)
Specificity	58% (25/43)	84% (36/43)	100% (43/43)
Positive Predictive Value	69% (41/59)	83% (33/40)	100% (22/22)
Negative Predictive Value	96% (25/26)	80% (36/45)	68% (43/63)
TCD grades post-Valsalva, N = 74†			
Sensitivity	100% (31/31)	81% (25/31)	42% (13/31)
Specificity	35% (15/43)	84% (36/43)	100% (43/43)
Positive Predictive Value	53% (31/59)	78% (25/32)	100% (13/13)
Negative Predictive Value	100% (15/15)	86% (36/42)	70% (43/61)

PAVM = pulmonary arteriovenous malformation; RLS = right-to-left shunt; TCD = transcranial Doppler.

* An 11-year-old patient underwent TCD only after Valsalva to avoid repeat bubble injection.

† There were 12 patients with TCD grade 4 or 5 at rest who declined to repeat after Valsalva.

Table 3
Measurement of the PAVM feeding artery compared with TCD grade

	Highest TCD grade		p value
	Grade ≤4* (N = 19)	Grade ≥5 (N = 24)	
Sum of artery diameter feeding PAVMs, mm	2.6 ± 1.9	5.0 ± 3.2	0.01
Diameter of artery feeding the main PAVM			0.01
≥3 mm, N	3†	14	
≥2 to ≤2.9 mm, N	4	4	
<2 mm, N	12	6	
Multiple PAVMs			0.23
Single, N	10	8	
Multiple, N	9	16	
Referred for embolization therapy, N (%)	5 (26%)‡	15 (63%)	0.03

PAVM = pulmonary arteriovenous malformation; TCD = transcranial Doppler.

* Consisted of 6 patients with grade 3 and 13 patients with grade 4.

† All 3 patients had TCD grade 4.

‡ Consisted of 1 patient with grade 3 and 4 patients with grade 4.

syndrome of HHT was performed in 54 (63%) patients, and 52 were found to have a known gene mutation; these consisted of 27 patients with mutation in the endoglin gene, 19 patients with mutation in the activin A receptor type II-like 1 gene, 1 patient with mutation in the SMAD4 gene, and 5 patients who had previous positive genetic testing but the results of the specific gene mutation were not available. A PAVM was documented on CT in 17 (63%) patients with endoglin gene mutations and 4 (21%) patients with activin A receptor type II-like 1 gene mutations.

A history of ischemic stroke was present in 5 (6%) patients and 3 (3%) patients had a history of cerebral bleeding. There was 1 patient (1%) with a PAVM who had a history of cerebral abscess. A history of migraine was reported in 35 (41%) patients and an additional 5 (6%) patients had a transient neurologic deficit, which may be difficult to discern from a complex migraine. A PAVM was more common in migraineurs than nonmigraineurs (66% vs 39%, $p = 0.03$), but the Spencer grade of RLS was not statistically different between the migraineurs and nonmigraineurs (3.4 ± 1.8 vs 2.9 ± 1.6, $p = 0.23$ for rest; 3.5 ± 1.5 vs 3.0 ± 1.2, $p = 0.17$ for post-Valsalva).

The sensitivity and specificity of the TCD grade compared with CT is shown in Table 2. Defining TCD grade ≥3 as positive for RLS, the sensitivity at rest was 98% and post-Valsalva was 100%. One patient with a small PAVM with a feeding artery of 2 mm had a TCD grade 1 at rest, which increased to grade 3 post-Valsalva. The effect of using different thresholds, grade ≥4 or ≥5, for the definition of a positive TCD is also presented. As the cutoff for a positive TCD grade increases, the specificity increases at the expense of sensitivity.

Table 3 lists the measurement of the diameter of the PAVM feeding arteries by CT versus the result of the TCD studies. In 43 patients who were diagnosed with PAVMs by CT, patients with a TCD grade ≥5 had a significantly larger sum of artery diameters feeding the PAVM compared with those with grade 4 or less ($p = 0.01$). There were no patients with a grade 3 or less shunt who had a PAVM with a feeding artery diameter of ≥3 mm. Patients with TCD grade ≥5 were more frequently referred for embolization therapy compared with patients with TCD grade ≤4 ($p = 0.03$). There were 5 patients who were referred for embolization therapy with a TCD grade ≤4; these consisted of 1 patient with a TCD grade 3 with the main feeding artery diameter of 2.1 mm and 4 patients with a TCD grade 4 where the main feeding artery diameters were between 2.0 mm and 4.0 mm.

Table 4 lists the TCD grades at rest or post-Valsalva for the patients with PAVM compared with a PFO group of 140 patients who had a TCD as part of an evaluation of the severity of RLS for PFO-related conditions. Of the 43 patients with PAVM, 30 (70%) had TCD studies both at rest and post-Valsalva. Compared with patients with PFO, patients with PAVMs had a higher mean TCD grade at rest. However, there was no significant difference in TCD grade post-Valsalva. The difference between TCD grade at rest and post-Valsalva was significantly smaller in patients with a PAVM compared with those with a PFO (Δ rest vs post-Valsalva; $p < 0.001$). There were 5 patients with a PAVM who had an increase in TCD grade from rest to post-Valsalva, but fewer patients with PAVM had an increase of TCD grade compared with patients with a PFO ($p < 0.001$). A transesophageal echocardiogram was performed in 1 of these 5 cases and that patient had a large PFO, which was subsequently closed.

Discussion

Because of the high risk for cerebrovascular accidents, the current guidelines recommend that patients with HHT undergo screening for RLS due to a PAVM. The present study demonstrates that TCD is a useful screening examination, which does not require ionizing radiation for detecting PAVMs in people with suspected HHT. Using the definition of a positive RLS as Spencer grade ≥3 (≥31 microbubbles/min),[12] TCD had a sensitivity of 100% in detecting PAVMs,

Table 4
Comparison of Spencer grade of shunt at rest versus post-Valsalva between patients with PAVM or PFO

	Shunt Etiology		p value
	PAVM (N = 30)	PFO (N = 140)	
TCD grade at rest	4.0 ± 1.0	2.7 ± 1.5	< 0.001
TCD grade post-Valsalva	4.2 ± 0.8	4.2 ± 1.1	0.87
Increase in TCD grade	0.2 ± 0.6	1.5 ± 1.3	< 0.001
Increase in TCD grade, N (%)	5 (17%)	113 (81%)	< 0.001

PAVM = pulmonary arteriovenous malformation; PFO = patent foramen ovale; TCD = transcranial Doppler.

but a relatively low specificity of 58%. The high negative predictive value (100%) indicates that patients with HHT with TCD grade <3 are unlikely to have a PAVM on subsequent chest CT examination. The low specificity of TCD is caused by the presence of a positive TCD when the CT does not have a visible PAVM. This may reflect the presence of multiple microscopic pulmonary telangiectasias, which are beyond the detection limit of a CT. Alternatively, there may be an unsuspected PFO, which occurs in about 20% of adults.[14,15] The specificity of TCD increases as the threshold for a positive test is raised. Defining a positive threshold as grade ≥5 at rest, the specificity was 100%, indicating that patients with HHT with TCD grade ≥5 at rest are likely to have a PAVM on subsequent chest CT examination. The time required to perform a TCD is similar to a CT, but a TCD costs less than a CT.

A TCD examination only demonstrates an RLS by definition because the contrast bubbles are injected into the venous circulation and are visualized in the cerebral arteries. Therefore, a TCD indicates the presence of a PAVM or a PFO, but not the presence of other visceral arteriovenous malformations (cerebral, gastrointestinal, or hepatic) because visceral arteriovenous malformations represent left-to-right shunts, which cannot be assessed by a TCD examination.

Our study did not compare TCD directly with contrast transthoracic echocardiography (CTTE), which has also been demonstrated to have a high sensitivity for PAVMs in adults with HHT compared with CT and pulmonary angiography reference tests.[7,16] TCD has been reported to have higher sensitivity than CTTE for detecting RLS in patients with paradoxical cerebral embolization from a PFO.[17] One report of 12 patients showed that both TCD and CTTE had 100% sensitivity in detecting PAVMs, with specificity of 38% and 25%, respectively.[18] However, the investigators did not describe what they defined as their threshold for a positive RLS for either technique. The high sensitivity and relatively low specificity of TCD are confirmed in our present study with a larger number of patients (n = 86). In a recent study of 248 patients with HHT with a PAVM detected on CT,[19] the sensitivity of CTTE was 98% when a positive RLS was defined as grade ≥1 (≥1 microbubbles/frame). Defining a positive RLS as grade ≥2 (≥30 microbubbles/frame), the sensitivity of CTTE dropped to 87%.

Our results also indicate that the shunt grade on TCD is related to the aggregate size of the diameter of the PAVM feeding arteries, which may affect the indication for embolization therapy. No patient with a TCD grade ≤3 had a feeding artery diameter of ≥3 mm. Thus, TCD grade ≤3 has the potential to identify subjects who do not require embolization therapy.

There was a small difference between TCD grades at rest compared with post-Valsalva in patients with a PAVM. This difference was significantly smaller compared with that observed in cardiac atrial shunts because of a PFO, which might help to distinguish these 2 entities. The Valsalva maneuver leads to increased right atrial pressure that can reveal, or increase, an RLS through a PFO; however, the Valsalva maneuver does not affect a shunt due to a PAVM. There were 5 (17%) patients with PAVM who had an increase in TCD grade post-Valsalva, which is similar to the expected occurrence of a PFO in the general population. One could speculate that these patients might have a concomitant PFO to explain the increase in shunting post-Valsalva. A PFO was discovered in 1 of these 5 patients, but it is unknown whether a PFO existed in the other 4 patients.

The limitations of this study include the inability of TCD to distinguish an RLS because of a PAVM versus a cardiac shunt such as a PFO. Right-sided cardiac catheterization studies were not performed so the frequency of PFO in this population is not known. Another limitation is that the decision for transcatheter embolization therapy of PAVMs with a feeding artery size between 2 mm to 2.9 mm was arbitrarily determined by the operator. There is no longer a specific size threshold for the indication of embolization therapy.[20]

Disclosures

The authors have no conflicts of interest to disclose.

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