Screening for Right-to-Left Shunts With Contrast Transcranial Doppler in Hereditary Hemorrhagic Telangiectasia

Dulka Manawadu, MRCP; Dilini Vethanayagam, FRCP; Maher Saqqur, FRCP; Carol Derksen, RVT; Jonathan Choy, FRCP; Khurshid Khan, FRCP

Background and Purpose—Contrast transthoracic echocardiography (TTCE) is used to screen hereditary hemorrhagic telangiectasia (HHT) patients for right-to-left shunts (RLS) associated with increased stroke risk. We hypothesized that contrast transcranial Doppler (TCDc), shown to be highly sensitive for detecting RLS in patent foramen ovale, will be as comparable to TTCE for screening HHT patients.

Methods—We compared TTCE and TCDc for detecting RLS in 12 patients with HHT who also underwent CT pulmonary studies to determine pulmonary arteriovenous malformation (PAVM) presence. The sensitivity and specificity of TTCE and TCDc in detecting PAVM were determined and the agreement between TTCE and TCDc in detecting RLS was assessed.

Results—Both TTCE and TCDc had 100% sensitivity in detecting underlying PAVM; the specificity was 25% and 38%, respectively. The agreement in detecting RLS between TTCE and TCD was high (κ=0.76). TCD was well-tolerated with no immediate adverse or embolic events over the next 3 months.

Conclusions—TCDc offers a simple office-based alternative to TTCE for screening RLS associated with PAVM in HHT patients. (Stroke. 2011;42:1473-1474.)

Key Words: arteriovenous malformations ▪ hemorrhagic ▪ hereditary ▪ telangiectasia ▪ transcranial Doppler ultrasonography

Stoke and neurological deficits occur in 15% patients with hereditary hemorrhagic telangiectasia (HHT), mainly because of significant right-to-left shunt (RLS) secondary to underlying pulmonary arteriovenous malformations (PAVM). Because of the high stroke risk, HHT patients are screened for asymptomatic PAVM using contrast transthoracic echocardiography (TTCE) plus anteroposterior chest radiograph, which has 100% sensitivity for PAVM detection. It has been shown that contrast transcranial Doppler (TCDc) has equivalent sensitivity to TTCE in detecting RLS in patients with patent foramen ovale. We hypothesize that TCDc studies have equal sensitivity to and agreement with TTCE in detecting the presence of PAVM in patients with HHT.

Subjects and Methods

We recruited 12 patients with definite or possible HHT according to established criteria between January and September 2008. Informed consent was obtained and TTCE was undertaken by an experienced echocardiologist who also graded shunt severity. TCDc was performed by a trained physician (D.M.) or technician (C.D.), either at the time of TTCE performance (n=4) or separately if patients had already undergone recent TTCE examination (n=8). TCDc was undertaken using a Spencer PMD 150 TCD machine (Spencer Technologies) with patient head frame to allow simultaneous sonation of the right and left middle cerebral arteries. Patients lay supine at 45 degrees and agitated saline (0.5 mL of air plus 0.5 mL of blood plus 9.0 mL of normal saline) was injected through the antecubital vein. A Valsalva maneuver was performed if no microembolic signals (MES) were initially detected. The number of cardiac cycles from the end of injection of agitated saline to first MES (M-Mode and spectrography) detection and volume of MES were recorded. TCDc recordings were analyzed by 2 physicians (M.S. and K.K.) blinded to presence of PAVM and the result of TTCE. Sensitivity and specificity of both TCDc and TTCE in detecting PAVM-related RLS was calculated. The agreement between TCDc and TTCE in detecting the presence of a RLS was assessed using kappa statistic.

Patients’ medical charts were reviewed for history, examination findings, and results of investigations to confirm a definitive diagnosis of PAVM. All patients were followed-up for complications of the TCD procedure (D.M.). This study was approved by the local Health Research Ethics Board.

Results

Of the 12 patients (7 male, 5 female; median age, 42 years), 10 had definite and 2 had possible HHT. Their clinical features are described in the Table.
Table. Disease Characteristics of Study Patients (n=12)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>Gastrointestinal involvement</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>Ischemic stroke or TIA</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0</td>
</tr>
<tr>
<td>Family history of HHT</td>
<td>11 (92%)</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>11 (92%)</td>
</tr>
<tr>
<td>Abnormal chest radiograph</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>PAVM on chest CT/CT angiography</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td>CAVM on brain imaging</td>
<td>0 (1 previous excision)</td>
</tr>
</tbody>
</table>

Two patients did not have chest CT/CT angiogram.

CAVM indicates cerebral arteriovenous malformations; CT, computed tomography; HHT, hereditary hemorrhagic telangiectasia; PAVM, pulmonary arteriovenous malformations; TIA, transient ischemic attack.

TTCE showed RLS in 10 of the 12 patients. The RLS was considered extracardiac in 6 patients because bubbles were detected in the left side of the heart after >3 cardiac cycles after right atrial opacification or because bubbles entered in a direction not suggestive of interatrial crossing. All 4 patients with PAVM on CT chest studies had detectable RLS; RLS on TTCE was also present in 3 patients without proven PAVM or patent foramen ovale. TTCE had 100% sensitivity and 25% specificity in detecting PAVM.

TCDC showed a RLS in 9 of 12 patients and RLS was detected in all 4 patients with definite PAVM. Early MES (<5 cardiac cycles) on TCDC were seen in 3 patients, suggestive of a cardiac source (all patients had patent foramen ovale). Late MES (>7 cardiac cycles) were seen on TCDC of 2 patients without proven PAVM. The volume of MES detected was greatest for those with grade 3 shunts on TTCE. TCDC had 100% sensitivity and 37.5% specificity in detecting PAVM. The likelihood ratio for a positive TCD shunt test was 6.9. The agreement for detecting RLS between TTCE and TCD was 92% ($\kappa = 0.76$).

There were no immediate complications with use of TCDC and all 12 patients found the TCDC head frame tolerable. At 90 days, no new embolic adverse events had occurred.

**Discussion**

These findings suggest TCDC may be comparable with TTCE (existing best practice) in screening for RLS associated with PAVM in HHT patients. In this small series, TCDC had a sensitivity of 100% in detecting RLS and agreed 92% ($\kappa = 0.76$) with TTCE. These findings are consistent with a previous report showing that carotid artery ultrasound had 95% sensitivity and 85% specificity of shunt detection in patients with PAVM. In addition, TCDC is easy to use, portable, and can be kept within a clinic or office setting to screen for shunts at the time of patient contact. Furthermore, TCDC, unlike TTCE, does not require extensive technical expertise. TCDC may be particularly helpful in screening during pregnancy because of the higher risk of PAVM enlargement and rupture, when TTCE may prove cumbersome because of posture and access.

Our study has limitations, the main one being a small sample size because of the rarity of HHT. The study is open to statistical bias and caution is needed in interpreting findings. The air volume used was 0.5 mL, which was commensurate with local practice but may have compromised sensitivity in shunt detection. This is unlikely because, even with low air volumes, TCDC had 100% sensitivity in detecting RLS. It is possible that, unlike TTCE, TCDC may not be able to distinguish between intracardiac and extracardiac shunts. Our data showed that MES were detected early (within 5 cardiac cycles) in all patients with known patent foramen ovales. This suggests that it may be possible to discriminate between intracardiac and extracardiac RLS with TCDC, but this needs confirmation in future studies. TTCE is the recommended gold standard tool for screening RLS associated with PAVM.

TCDC offers a simple office-based alternative when TTCE may not be easily available or logistically difficult to perform.

**Disclosures**

None.

**References**

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