Optimizing the Technique of Contrast Transcranial Doppler Ultrasound in the Detection of Right-to-Left Shunts

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Background and Purpose—A cardiac right-to-left shunt (RLS) can be identified by transesophageal echocardiography and transcranial Doppler ultrasound (TCD) with contrast agents and a Valsalva maneuver (VM) as a provocation procedure. This article applies the modalities of these tests detailed in previous studies to a large patient cohort and compares 2 contrast agents (saline and Echovist-300).

Methods—Eighty-one patients were investigated by both transesophageal echocardiography and bilateral TCD of the middle cerebral arteries. The following protocol with injections of 10 mL agitated saline was applied in a randomized way: (1) no VM, (2) VM for 5 seconds starting 5 seconds after the beginning of contrast injection, and (3) repetition of the test with VM if the first test with VM was negative. The VM was performed for 5 seconds starting exactly 5 seconds after the beginning of saline injection. Thereafter, the same protocol was repeated with 10 mL Echovist-300 instead of saline.

Results—Thirty-one patients had a cardiac RLS. The Echovist-300 investigation disclosed all these 31 shunts, but saline disclosed only 29 of them. Twenty-two had an RLS only in at least 1 of the above TCD tests, some of them even with a considerable shunt volume.

Conclusions—Contrast TCD performed with Echovist-300 but not with saline yields a 100% sensitivity to identify transesophageal echocardiography–proven cardiac RLSs. The TCD test should be repeated if negative the first time. This article gives detailed information for the optimization of the contrast TCD technique. Extracardiac shunts detected only during contrast TCD can have a considerable shunt volume and may allow for paradoxical embolism. (Stroke. 2002;33:2211-2216.)

Key Words: cerebral embolism ■ cerebrovascular disorders ■ foramen ovale, patent ■ ultrasonography

Paradoxical embolism of thrombotic material originating from the deep leg or pelvic veins via a cardiac or extracardiac right-to-left shunt (RLS) can cause ischemic stroke.1,2 Prerequisites for the diagnosis of paradoxical brain embolism are the demonstration of such a shunt, the presence of an embolic pattern of infarction on cerebral imaging, and the absence of competing stroke origins. Other factors such as the performance of a mostly incidental Valsalva maneuver (VM) before the onset of infarction, the demonstration of remnants of the venous thrombosis during crural venous ultrasound or phlebography, concomitant pulmonary embolism, thrombophilia, and other factors predisposing to venous thrombosis additionally support the diagnosis. In very rare cases, echocardiography or autopsy discloses a thrombus trapped in the cardiac RLS and thus unequivocally proves the paradoxical embolism.3,4 About 30% of the general population show a cardiac RLS, in most cases a patent foramen ovale. Juvenile patients with otherwise not explainable stroke have a much higher cardiac RLS prevalence of 11%.5,6 This fact corroborates the importance of paradoxical embolism in stroke origin. Extracardiac shunts, mainly pulmonary ones, can also deliver a substantial shunt volume comparable to the shunt volume of cardiac shunts. These shunts occur in an additional 11% of the population and may be the pathway of paradoxical embolism.7–12

Precise disclosure of an RLS is a keystone in the diagnosis of paradoxical embolism. Contrast-enhanced transesophageal echocardiography (TEE) is thought to be the method of choice to detect intracardiac RLSs and is generally accepted as the gold standard.13–15 The performance of a VM enhances the RLS, unveils a latent RLS, or even leads to flow inversion of an otherwise left-to-right shunt.16–18 Contrast-enhanced transcranial Doppler sonography (TCD) is a complementary method to detect cardiac and extracardiac RLSs. We used contrast agents with microbubbles (MBs), which do not survive pulmonary passage. Injected into a cubital vein, these bubbles appear only in the cerebral circulation, where they can be detected by TCD, if an RLS exists. Contrast TCD is as

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sensitive as TEE in the detection of cardiac RLS; moreover, it allows the detection of extracardiac shunts, which also can be the pathway of paradoxical embolism.8–12 In a consensus meeting and in several recent publications, recommendations have been set up to optimize the TCD technique.7,19–23 A major point of discussion is whether agitated saline containing small air bubbles is as sensitive as a commercially available contrast agent (Echovist-300, Schering AG). In this study, we apply the elaborated modalities to a large patient cohort to test their usefulness and to compare both contrast agents.

**Patients and Methods**

**Patients**

Eighty-one subjects (50 men, 31 women) 20 to 78 years of age (mean, 48.7 years) were included in the study. All patients had suffered ischemic strokes, transient ischemic attacks, attacks of amaurosis fugax, or central retinal artery occlusions. Thirty-two patients had had recurrent ischemic events. Twenty-eight subjects were cigarette smokers, 3 were diabetics, 28 had arterial hypertension, and 29 suffered from hyperlipidemia. Patients with a mechanical prosthetic cardiac valve were excluded from the study.

In all 81 patients, TEE was performed to detect or rule out an intracardiac shunt. Twenty-three additional patients had been screened but were excluded from the study for the following reasons: TEE either was not available or had already been performed in an external hospital with an unknown protocol in 17 patients; the TCD recording had to be stopped because of noncompliance in 1 patient; there was no bilateral temporal window suitable for TCD in 4 patients; and 1 patient was excluded because of an implanted mechanical cardiac valve prosthesis.

**Echocardiography**

All patients underwent TEE, which was performed by cardiologists well trained in this technique. The investigators used a Hewlett Packard Sonos 2500 or 5500 imaging system and a 4- to 7-MHz wide-band multiplane transducer. After informed consent had been obtained, patients were examined in the fasting state and received an intravenous injection of 10 mL contrast agent (Echovist-300, Schering AG). In this study, the same transcranial pulsed Doppler ultrasound device (TC4040, ME/NCKey, software version 2.30) was used for all studies. The machine used a 128-point fast Fourier transform analysis and a graded color-scale to display the intensity of the Doppler signals received. In addition to online recording onto the hard disk, the Doppler audio signal was recorded by an 8-channel digital audio tape deck recorder (TA-88, TEAC Corporation) with normal speed. An experienced observer’s analysis of MB comprised listening to each of the software-recorded signals, watching each signal on the screen, and evaluating the tapes. The following definition for MB was used: typically visible and audible (click, chirp, whistle) short-duration, high-intensity signal within the Doppler flow spectrum with a time delay in the 2 channels of each side.24 Single MBs within clusters were discriminated by reducing the amplification during offline analysis. The test was considered positive when at least 1 MB was present within 40 seconds of the injection.20

The following protocol of contrast agent injection (10 mL each) was applied in a randomized way: (1) saline without VM, (2) saline with VM for 5 seconds starting 5 seconds after the beginning of contrast injection, (3) repetition of test 2 if it was negative. Afterward, independently from the previous results, the procedures were repeated following the same scheme but with Echovist-300 instead of saline. Each of these tests required at least 2 minutes, with bolus injection of the contrast agent starting at 0 second, Valsalva strain for 5 seconds, and resting phase until 120 seconds. Microcaviation saline contrast was generated by agitating a mixture of 10 mL normal saline and 1 mL air between two 12-mL syringes connected by a 3-way stopcock. Once the contrast was prepared, 10 mL was immediately injected as a bolus into a right cubital vein, which had previously been cannulated with a 21-gauge in-dwelling intravenous catheter. Echovist-300 was prepared following the instructions of the manufacturer. About 10 mL Echovist-300 was injected accordingly. The VM started with deep inspiration, followed by pressing against the closed glottis and expiration 5 seconds later. Before the procedure, the patients were meticulously trained to perform the VM correctly.

Occasionally, MB could still be detected 80 to 120 seconds after the injection. In these cases, the resting time preceding the next test was prolonged until an MB-free period at least 40 seconds long was documented. In each test, only the first 40 seconds after injection was used for MB analysis. Data from the right and left MCA were pooled.

**Vascular Ultrasound Investigations**

All subjects underwent a full color duplex investigation of their neck arteries (Sonos 2500, Hewlett Packard) and a continuous-wave Doppler investigation of the periorbital arteries. Subjects were also examined by TCD, including the intracranial segments of the internal carotid arteries, middle cerebral arteries (MCAs), and anterior and posterior cerebral arteries. Three patients had an extracranial internal carotid artery occlusion, and 1 patient had a high-grade internal carotid artery stenosis. No further high-grade stenoses or occlusions were detected in the anterior circulation.

For TCD embolus detection, the MCA was insonated bilaterally through the temporal bone windows. Two 2-MHz transducers were mounted on the temporal planes and secured with a head ribbon. A small sample volume of 8 mm in length and a low gain provided a setting optimal for embolus discrimination from the background spectrum. The bigate technique was used, placing 2 sample volumes a distance of 10 mm into each MCA main stem. The patients were lying comfortably on a stretcher. The investigations were well tolerated by the subjects without major side effects.

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**Statistical Analysis**

Patients were divided into 3 groups: (1) patients with a RLS in at least 1 TCD investigation but without demonstration of a shunt on TEE; (2) patients with a shunt on TEE only after VM, but not spontaneously, and with an RLS in at least 1 TCD investigation; and (3) patients with an RLS on TEE without VM, ie, with a spontaneous shunt, and with an RLS proven in at least 1 TCD investigation. With TEE used as the gold standard to detect intracardiac RLS, the sensitivity of TCD was calculated as follows: percentage of true
Segments of TCD recordings representing a provisional, arbitrary categorization into 4 categories of MB [absolute number (1) without and (2) with VM (sum from the right and the left MCA)]: a, no MB; b, 1 to 20 MB; c, >20 MB but no shower (temporarily single MB cannot be differentiated from each other); and d, MB shower (from Droste et al, with permission).21 Number of MB refers to a time 40 seconds after the beginning of contrast injection. Quantification is done once without and once with the performance of a VM.

Results

Thirty-one patients had a cardiac RLS, 14 of them without performing a VM (spontaneous RLS). All 31 cardiac RLSs were also found in at least 1 TCD investigation. The Echovist-300 investigation disclosed all 31 shunts; in contrast, only 29 were disclosed by means of agitated saline. Twenty-two had an RLS only in at least 1 of the above series of TCD examinations. The remaining 28 patients did not show any shunt at all. The sensitivity to detect TEE-proven shunts was 100% with Echovist-300 but 94% with saline.

Table 1 gives the detailed numbers of MBs detected during all tests and their spread, as well as their allocation to the 4 categories. Taking all the patients together, the mean number of MBs was 82.6 with Echovist-300 without VM, 30.1 with Echovist-300 without VM, 15.0 with saline with VM, and 9.8 with saline without VM. In the 1-way ANOVA with post hoc multiple comparisons (Duncan’s multiple range test), there were more MBs detected during the TCD test with Echovist-300 with VM compared with each of the other 3 tests. In general, most MBs were detected by TCD in patients with a spontaneously open cardiac RLS, less MBs in those patients with a cardiac shunt patent only during VM, and only a few MBs in patients without a cardiac shunt. However, there was a considerable overlap of MB numbers, and in single cases, there were large amounts of bubbles also in the group of patients without an RLS during TEE (cf the maximum of 235 in a particular patient with Echovist-300 during VM in Table 1).

Discussion

The present study demonstrates that contrast TCD detects TEE-proven RLSs with a sensitivity of 100%. The use of Echovist-300 is strongly recommended because there were 2 false negatives with the use of agitated saline. A smaller study had already shown a lower number of MBs with saline, but in this previous trial, sensitivity had been equal with agitated saline and Echovist-300.7 Our present finding is partially in contrast to a recent consensus statement in which saline was recommended.22 The irrefutable advantage of agitated saline is its low cost and broad availability in underfunded health systems. The present results prove that despite the repetition of the procedure if negative during the first performance, there was only a 94% sensitivity with saline. The economic advantage of using saline has to be weighed carefully against its diagnostic limitations.

Our findings are in concordance with 3 previous studies and with the majority of recommendations of a consensus meeting, which emphasized the need to perform the tests with a provocation maneuver twice, when the first test was negative.7,19,20,22 The performance of a VM for 5 s starting 5 s after the beginning of the injection using Echovist®-300 is advisable.

TCD cannot replace TEE because there are other possible cardiac embolic sources detectable only on TEE, such as left atrial thrombus or severe atherothrombosis of the aortic arch. Furthermore, TCD can give additional information on RLSs not noted during TEE. Possible causes of these discrepancies are poor VM, loss of the right plane of insonation during and because of the VM, or the presence of pulmonary shunts. Similar to intracardiac shunts, pulmonary shunts can produce a considerable transit of contrast bubbles. There is evidence that these RLSs can also allow for paradoxical embolism and stroke.8–12 Those patients with a shunt detected only during TCD warrant further interest in future trials concerning stroke origin. This may include an extended TEE investigation with the assessment of pulsatility in the pulmonary arteries and thoracic CT scans to possibly detect pulmonary shunts. Therefore, both techniques must not be seen as exchangeable but as complementary.

The fact that 1 MB was found during TCD in a patient with a cardiac RLS patent on TEE only during VM is in concordance with a previous report in which the threshold for a positive TCD examination was set at 1 MB.20 Shunt quantification remains a problem. The differentiation into shunts patent only under VM and those spontaneously patent is not dichotomous because under physiological breathing different cardiac right-to-left pressure gradients do occur. The findings of TEE and TCD are not congruent (Table 1): a patient with a shunt on TEE only under VM may have a spontaneously patent shunt in the TCD investigation and vice versa. The
following TCD categorization should be used: (1) RLS patent only under VM and (2) RLS spontaneously open, although there is an overlap when the tests are repeated and these categories are not distinct. It is also worth performing the test with VM when the test without VM has already been positive to better evaluate the increase in shunting induced by VM.

For the echocardiographer, quantification of a patent foramen ovale is not easy. The 2 septa of the foramen ovale separate from each other inconsistently, they overlap with a larger or smaller surface, and the pressure gradients differ independently from the size of the defect. Eventually, both the echocardiographers using TEE and the neurologists using TCD quantify the shunt by the number of MBs that trespassed. Stratifying the size of a RLS size makes sense as long as it indicates different paradoxical embolic risk and as long as it results in specific medical or interventional treatment. So far, only a few reports in the literature address the size of the RLS in relation to the risk of first or recurring embolic stroke. The evidence for stratified therapeutic consequences is even more scarce. The above 4 categories of MB quantity cover quite evenly the quantity range of MBs found in a typical cohort of interest. Moreover, they give a rough

**TABLE 1. Detailed Numbers of MBs in All Subgroups and Tests**

<table>
<thead>
<tr>
<th>Category</th>
<th>No Cardiac RLS (n=50)</th>
<th>Cardiac RLS only With VM (n=17)</th>
<th>Spontaneous Cardiac RLS (n=14)</th>
<th>Any Cardiac Shunt (n=31)</th>
<th>Shunt Not Noted During TEE (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline without VM</td>
<td>Mean±SD: 1.8±8.6</td>
<td>6.4±9.9</td>
<td>42.4±72.0</td>
<td>22.6±51.3</td>
<td>4±12.8</td>
</tr>
<tr>
<td>Median: 0</td>
<td>2</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Range: 0–59</td>
<td>0–37</td>
<td>0–227</td>
<td>0–227</td>
<td>0–59</td>
<td>0</td>
</tr>
<tr>
<td>Categories</td>
<td>0 MBs: 44</td>
<td>6</td>
<td>4</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>1–20 MBs: 5</td>
<td>9</td>
<td>5</td>
<td>14</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>&gt;20 MBs: 1</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Shower: 0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Echovist-300 without VM</td>
<td>Mean±SD: 2.0±5.8</td>
<td>11.7±21.0</td>
<td>65.8±106.1</td>
<td>36.2±76.6</td>
<td>4.4±8.2</td>
</tr>
<tr>
<td>Median: 0</td>
<td>0</td>
<td>20</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Range: 0–36</td>
<td>0–83</td>
<td>0–353</td>
<td>0–353</td>
<td>0–36</td>
<td>0–36</td>
</tr>
<tr>
<td>Categories</td>
<td>0 MBs: 35</td>
<td>6</td>
<td>2</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>1–20 MBs: 14</td>
<td>9</td>
<td>5</td>
<td>14</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>&gt;20 MBs: 1</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Shower: 0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Saline with VM</td>
<td>Mean±SD: 3.1±11.2</td>
<td>41.4±73.4</td>
<td>112.7±149.0</td>
<td>73.6±117.5</td>
<td>7.0±16.2</td>
</tr>
<tr>
<td>Median: 0</td>
<td>6</td>
<td>36</td>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Range: 0–56</td>
<td>0–265</td>
<td>0–456</td>
<td>0–456</td>
<td>0–56</td>
<td>0–56</td>
</tr>
<tr>
<td>Categories</td>
<td>0 MBs: 42</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>1–20 MBs: 6</td>
<td>10</td>
<td>3</td>
<td>13</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>&gt;20 MBs: 2</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Shower: 0</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Echovist-300 with VM</td>
<td>Mean±SD: 9.4±35.2</td>
<td>117.3±0.2</td>
<td>302.1±471.2</td>
<td>200.8±352.5</td>
<td>21.4±51.1</td>
</tr>
<tr>
<td>Median: 0</td>
<td>53</td>
<td>85</td>
<td>74</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Range: 0–235</td>
<td>1–802</td>
<td>2–1682</td>
<td>1–1682</td>
<td>0–235</td>
<td>0–235</td>
</tr>
<tr>
<td>Categories</td>
<td>0 MBs: 30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>1–20 MBs: 17 (2 only 1 MB)</td>
<td>6 (1 only 1 MB)</td>
<td>1 (0 only 1 MB)</td>
<td>7 (1 only 1 MB)</td>
<td>17 (2 only 1 MB)</td>
<td></td>
</tr>
<tr>
<td>&gt;20 MBs: 2</td>
<td>5</td>
<td>6</td>
<td>11</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Shower: 1</td>
<td>6</td>
<td>7</td>
<td>13</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Because the test with Echovist and VM turned out to be the most sensitive, we give the number of patients presenting with only 1 MB during the different procedures for this particular test as well.*
TABLE 2. Recommendations for the TCD Detection of RLS*

<table>
<thead>
<tr>
<th>Modality</th>
<th>Recommendation</th>
<th>Explanation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient position</td>
<td>Supine position leads to a higher sensitivity than sitting position</td>
<td>Gravity induced stronger than venous and thus contrast agent backstream when the injection arm is placed horizontally</td>
<td>23</td>
</tr>
<tr>
<td>Bilateral or unilateral MCA monitoring</td>
<td>Bilateral monitoring leads to a higher sensitivity than unilateral monitoring</td>
<td>Double amount of signals detected</td>
<td>7</td>
</tr>
<tr>
<td>Contrast agent</td>
<td>Echovist-300 possibly superior to Echovist-200; both lead to a higher sensitivity than saline</td>
<td>Higher bubble number in Echovist, falsely negative findings with saline in proven cardiac shunts</td>
<td>7, 19, 21</td>
</tr>
<tr>
<td>Contrast agent volume</td>
<td>10 mL superior to 5 mL superior to 2.5 mL</td>
<td>More bubbles injected</td>
<td>23</td>
</tr>
<tr>
<td>Injection mode</td>
<td>Bolus injection via a 21-gauge (“green”) butterfly catheter into a cubital vein</td>
<td>Needle diameter and site of injection relevant for contrast agent backstream to the heart; needle size used allows rapid injection without making the vein burst; standardization of the method; also larger needles (18–20 gauge) are recommended but in our experience can make the vein burst</td>
<td>7, 19–22, 32</td>
</tr>
<tr>
<td>Provocation maneuver</td>
<td>Conventional VM superior to coughing, superior to a standardized VM; the VM needs to be trained with patients before test</td>
<td>Technically simple performance; improved patient cooperation</td>
<td>19</td>
</tr>
<tr>
<td>Time of the VM</td>
<td>For 5 s starting 5 s after the beginning of injection</td>
<td>VM for 10 s, which also is discussed, could not be performed in a large number of our patients, namely elderly stroke patients</td>
<td>7, 19–22, 33</td>
</tr>
<tr>
<td>Threshold of MB numbers</td>
<td>Detection of 1 MB sufficient for the diagnosis</td>
<td>Several cases of only 1 MB in the cerebral circulation and a cardiac RLS patent spontaneously or under VM</td>
<td>7, 19, 20, 33–42</td>
</tr>
<tr>
<td>Time window for MB appearance</td>
<td>Up to 40 s after the beginning of injection</td>
<td>Higher MB number using a longer window</td>
<td>19–22</td>
</tr>
<tr>
<td>Number of tests</td>
<td>(1) Without VM, (2) with VM; if the test with VM was negative, the test with VM should be repeated</td>
<td>In several cases of a TEE-proven patent foramen ovale, negative first TCD test with VM but positive second TCD test with VM; also in the case of a positive test without VM, performance of a test with VM makes sense to obtain an idea of the dynamics of shunting; only when there is an MB shower already without VM can the performance of the test with VM be omitted</td>
<td>Present study, 7, 21</td>
</tr>
<tr>
<td>RLS quantification</td>
<td>Absolute number without and with VM (sum from the right and left MCAs); provisional, arbitrary categorization: a = no MBs, b = 1–20 MBs, c = &gt;20 MBs but no shower (temporarily single MB cannot be differentiated from each other); d = shower of MB</td>
<td>Categories must be defined post hoc and are meaningful only if they entail different diagnostic and therapeutic consequences</td>
<td></td>
</tr>
<tr>
<td>Differentiation of cardiac and extracardiac RLSs</td>
<td>In single cases not possible using TCD; latency to first bubble appearance and total bubble number not helpful</td>
<td>A fast transition of large numbers of MBs via an extracardiac shunt is possible</td>
<td>7, 19–21, 35, 43</td>
</tr>
</tbody>
</table>

*With this technique, all cardiac RLSs were disclosed in this study.

estimate of the severity of the shunt. For TCD, we currently recommend it to indicate the absolute number of MBs in addition to the arbitrary categories as suggested in the literature.23 Furthermore, test modalities used should be indicated precisely because the number of MBs differs considerably with the methods used.7,19,20 This approach allows post hoc analysis once clinically useful categories are established. Table 2 summarizes recommendations based on this article and the current literature2,7,19–23,31–43 on how to optimize RLS detection by TCD.

In conclusion, TEE and properly performed contrast TCD are complementary diagnostic procedures that are helpful in the assessment of stroke and stroke-prone patients.

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