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

Time Window and Threshold in Microbubble Numbers

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Background and Purpose—Cardiac right-to-left shunts can be identified by transesophageal echocardiography (TEE) and by transcranial Doppler ultrasound (TCD) with the use of contrast agents and a Valsalva maneuver (VM) as provocation procedure. Currently, data on the appropriate timing of the VM, the use of a diagnostic time window, and a threshold in contrast agent microbubbles detected are insufficient.

Methods—Fifty-eight patients were investigated by both TEE and bilateral TCD of the middle cerebral artery. The following protocol with injections of 10 mL of the commercial galactose-based contrast agent Echovist was applied in a randomized way: (1) no VM, (2) VM for 5 seconds starting 2 seconds after the beginning of contrast injection, (3) VM for 5 seconds starting 5 seconds after the beginning of contrast injection, (4) VM for 5 seconds starting 8 seconds after the beginning of contrast injection, and (5) repetitive short VMs in between 2 and 13 seconds after the beginning of contrast injection. In addition to the single tests, we also tested the sensitivity and specificity of combined results of the tests with VM.

Results—In 21 patients, a right-to-left shunt was demonstrated by TEE and contrast TCD (shunt positive). Twenty-one patients were negative in both investigations, no patient was positive on TEE and negative on TCD, and 16 patients were only positive on at least 1 TCD investigation but negative during TEE. Test 3 was the most appropriate test when combined with the results of 1 of the other tests with VM. The highest sensitivities were achieved with a diagnostic time window of 40 seconds and when the presence of a single microbubble was sufficient for the diagnosis of a shunt.

Conclusions—TCD performed twice with 2 provocation maneuvers with Echovist is a sensitive method to identify TEE-proven cardiac right-to-left shunts. The VM should be performed for 5 seconds starting at 5 seconds after the beginning of contrast injection. (Stroke. 2000;31:1640-1645.)

Key Words: cerebral embolism ■ cerebrovascular disorders ■ foramen ovale, patent ■ ultrasonography
after injection, the time delay between injection and VM was frequently not clearly specified in relation to the start or the end of injection. In the studies with a clear specification, the time from the beginning of injection to the beginning of the VM ranged between 0 and 5 seconds.\textsuperscript{2,11,12,15} (2) Several authors use a threshold for the number of MES detected in the TCD recording; most authors, however, qualify the test as positive when at least 1 MES can be identified. Thresholds proposed for the number of MES are $\geq 4,\textsuperscript{21} \geq 6,\textsuperscript{18}$ and $\geq 11,\textsuperscript{22}$ Furthermore, the question of whether the use of a diagnostic time window for MES appearance increases the specificity of the test without necessarily decreasing sensitivity is not yet resolved.\textsuperscript{14,23,24} Time windows proposed between the intravenous injection of the contrast medium and its appearance in the MCAs are 6 heartbeats,\textsuperscript{20} 10 seconds,\textsuperscript{20,21} 15 seconds,\textsuperscript{13} 20 seconds,\textsuperscript{22} 22 seconds,\textsuperscript{15} and 25 seconds.\textsuperscript{11,14} A recent study described the necessity of including MES at least 20 to 25 seconds after the start of injection to achieve a high sensitivity; it may also be possible that no time window is necessary.\textsuperscript{12} In the present study we (1) investigated the effect of different temporal relationships between injection of the contrast agent and the VM on the sensitivity and specificity of contrast TCD compared with TEE as the gold standard and (2) evaluated whether the use of a threshold in number of MES and the use of a diagnostic window influenced sensitivity and specificity.

Subjects and Methods

Patients

Fifty-eight subjects (30 males, 28 females) aged 15 to 83 years (mean age, 51 years) were included in the study. All except for 1 patient had suffered strokes, transient ischemic attacks, attacks of amaurosis fugax, or central retinal artery occlusions. Twenty-four patients had had recurrent events. One patient was asymptomatic but had a strong family history of strokes in young and middle age and asked for a full risk factor profile. Nineteen subjects were cigarette smokers, 6 were diabetics, 24 had arterial hypertension, and 36 suffered from hyperlipidemia. No patient had a mechanical prosthetic cardiac valve.

In all 58 patients, TEE was performed to detect or rule out an intracardiac shunt. Apart from these 58 patients, 48 additional patients had been screened but had been excluded from the study for the following reasons: in 34 of them no TEE could be obtained or the TEE was performed in an external hospital with an unknown protocol. In 2 patients the TEE had to be stopped prematurely because of discomfort and was not repeated. In 3 patients the TCD recording had to be stopped because of noncompliance. One patient was pregnant. In 7 patients there was no bilateral temporal window suitable for TCD, and in 1 patient no venous catheter could be placed because of anatomic reasons.

Echocardiography

All patients underwent TEE, which was performed by trained echocardiographers from the Department of Cardiology of our hospital. The investigators used a Hewlett Packard Sonos 2500 or 5500 imaging system and a 4- to 7-MHz multiplane probe. After informed consent had been obtained, patients were examined in the fasting state and received local pharyngeal anesthesia with 10% topical lidocaine. Additional intravenous sedation (midazolam) was given if the probe was not well tolerated. For the diagnosis of an interatrial shunt, 10 mL of contrast agent (Echovist) was injected as a bolus into a large antecubital vein during 2-dimensional TEE. The presence of an interatrial shunt was assumed when microbubble transit from the right to the left atrium occurred spontaneously or during subsequent VM within 3 heartbeats. The VM was trained with the patients before the procedure. The effectiveness of the VM was verified by a reduction in ventricular and atrial size and by bulging of the interatrial septum into the left atrium. Intrapulmonary shunts were not systematically investigated in this study.

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, the MCAs, and the anterior and posterior cerebral arteries. One patient had an extracranial internal carotid artery occlusion and a high-grade stenosis on the contralateral side, 1 patient had an unilateral high-grade carotid artery stenosis, and an additional patient had a high-grade carotid siphon 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, in which 2 sample volumes were placed at a distance of 1 cm 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.

The same transcranial pulsed Doliultrasound device (TC4040, EME/Nicolet, software version 2.30) was used for all studies. The machine employed a 128-point fast Fourier transform analysis and used a graded color scale to display the intensity of the Doppler signals received. In addition to on-line recording onto the hard disk, the Doppler audio signal was recorded by an 8-channel digital audiotape deck recorder (TA-88, TEAC Corporation) with normal speed. An experienced observer’s analysis of MES comprised listening to each of the software-recorded signals, watching each signal on the screen, and evaluating the tapes. The following definition of MES was used: typical 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.\textsuperscript{10} Single MES within clusters were discriminated by reducing the amplification during off-line analysis.

The following protocol with injections of 10 mL of the contrast agent Echovist was applied in a randomized way: (1) no VM, (2) VM for 5 seconds starting 2 seconds after the beginning of contrast injection, (3) VM for 5 seconds starting 5 seconds after the beginning of contrast injection, (4) VM for 5 seconds starting 8 seconds after the beginning of contrast injection, (5) and repetitive short (<2 seconds) VMs in between 2 and 13 seconds after the beginning of contrast injection. Each of these tests lasted at least 2 minutes, with bolus injection of the contrast agent starting at 0 seconds, Valsalva strain, and resting phase until 120 seconds. Echovist was prepared following the instructions of the manufacturer; 10 mL was immediately injected as a bolus into a right cubital vein, which had previously been cannulated with a 21-gauge indwelling intravenous catheter. The VM started with deep inspiration, followed by pressing against the closed glottis and expiration. The patients were meticulously trained before the procedure.

Occasionally, MES 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 MES-free period of at least 40 seconds’ duration was documented. In each test, only the first 40 seconds after injection were used for MES analysis. Data from the right and left MCAs were pooled.

Statistical Analysis

With TEE used as the gold standard, the sensitivity and specificity of TCD were calculated as follows. Sensitivity was calculated as the percentage of true positives (RLS confirmed by both methods) in comparison to true positives plus false-negatives (TCD negatives and
Thresholds and different diagnostic time windows taken into account, are given in Table 2. A configuration with a high sensitivity entailed a lower specificity.

The 2 patient groups with concordant shunt identification in both investigations (n=21) and with shunt demonstration only in the TCD investigation (n=16) were compared concerning the total number of MES in all 5 TCD tests. There was a significant difference indicating more MES in the group of 21 patients with concordant shunt identification (P=0.0002; Mann-Whitney U test). Although in general there were fewer MES in the patient group with a shunt only in the TCD investigation compared with the group with concordant shunt identification, introducing a threshold in number of MES could not reliably discriminate between the 2 groups. The total numbers of MES in the individual patients within 40 seconds after the injection were 1, 1, 1, 1, 1, 2, 3, 4, 4, 8, 10, 10, 12, 33, and 52 (mean 9, median 3.5; shunt only in the TCD recording), and 1, 3, 6, 7, 7, 18, 38, 40, 45, 49, 51, 57, 96, 100, 146, 162, 173, 330, 450, 484, and 890 (mean 150, median 51; concordant shunt identification).

Discussion

Our study demonstrates that contrast TCD detects TEE-proven RLS with a sensitivity of 90% to 100% and a specificity of 70% to 76% when the results of 2 tests with the VM performed after the injection of Echovist are combined. This is in concordance with 2 previous studies, which emphasized the need to perform the tests with a provocation maneuver at least twice when the first test was negative.11,12 The performance of a VM for 5 seconds starting 5 seconds after the beginning of the injection and combinations of the results of this test with the results of the other tests, in which the VM was performed at different time intervals in relation to the injection, reached the highest ranks in an ANOVA, indicating that this test was the most appropriate. Table 3 gives an overview of the studies comparing the results of contrast TCD and TEE and the modalities of the provocation maneuver used.

Our values for sensitivity and specificity are comparable to those described in the literature. Comparisons are difficult, however, since (1) some studies used unilateral and other studies bilateral recordings, (2) different diagnostic time windows were used, and (3) in some studies, the tests were repeated if the first test was negative. The duration of the VM was not specified in the earlier studies; in the most recent studies, a duration of at least 5 seconds was used. A Valsalva strain of 5 seconds can be performed by most patients and therefore seems to be a good compromise between the need to allow as many bubbles as possible to trespass the shunt and the patient’s tolerance of the procedure. The temporal relationships between the injection of the contrast medium and the VM differ considerably. In our experience, bolus injection of 10 mL takes approximately 2 to 3 seconds. The contrast agent needs a mean time of 5.1±1.4 seconds to reach the right atrium. Therefore, performance of the VM before injection does not make sense. In most studies, VM was performed after injection. Zanette et al15 were the first to systematically investigate the most appropriate timing for the performance of the VM. They also found the highest sensitivity when the

### Results

Twenty-one patients had no RLS on TEE and did not show MES in any of the tests within 40 seconds after the beginning of the injection. Twenty-one patients had a RLS on both tests, the TEE, and within 40 seconds after the beginning of the injection in at least 1 TCD procedure. In all these 21 patients, a patent foramen ovale was found during TEE. Sixteen patients had MES in at least 1 TCD investigation but no RLS on TEE. No patient had a RLS on TEE but failed to have one in the TCD investigation.

Table 1 summarizes the results of the individual tests and of the combination of the results of 2 tests with the highest numbers of MES. The values for the combination of the results of 2 tests were calculated as follows: the numbers of MES from the 2 tests at each second after the injection were added to form a new series of numbers. Eventually sensitivity and specificity were calculated as previously described. The highest ranks in a Friedman 2-way ANOVA were achieved in the tests with the performance of the VM starting 5 and 8 seconds after the beginning of the injection as well as the test including repetitive short VMs. This held true in the combination of the results of 2 tests with the provocation maneuver. When we combined the results of the 2 tests with the VM performed 5 and 8 seconds after the start of injection, respectively, all TEE-proven shunts were reliably identified.

The values for sensitivity and specificity of the single tests and of the combined results of tests with VM, with different thresholds and different diagnostic time windows taken into

### Table 1. Results of Individual Tests and Combination of 2 Tests With Highest Number of MES

<table>
<thead>
<tr>
<th>Test</th>
<th>Total No. of MES</th>
<th>Rank</th>
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<tbody>
<tr>
<td>No VM</td>
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<tr>
<td>VM 2 s</td>
<td>726</td>
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</tr>
<tr>
<td>Repetitive VM</td>
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<td>VM 8 s</td>
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<tr>
<td>VM 5 s</td>
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<td>5.23</td>
</tr>
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<td>6.75</td>
</tr>
<tr>
<td>VM 2 s and VM 5 s</td>
<td>1615</td>
<td>6.87</td>
</tr>
<tr>
<td>VM 8 s and repetitive VM</td>
<td>1454</td>
<td>6.92</td>
</tr>
<tr>
<td>VM 5 s and repetitive VM</td>
<td>1862</td>
<td>6.99</td>
</tr>
<tr>
<td>VM 5 s and VM 8 s</td>
<td>1370</td>
<td>7.18</td>
</tr>
</tbody>
</table>

# References

1. Zanette et al15 were the first to systematically investigate the most appropriate timing for the performance of the VM. They also found the highest sensitivity when the...
VM was performed after injection compared with its performance before or during the injection.

It is a well-known phenomenon that more patients are identified as having a RLS when investigated by contrast TCD compared with TEE (compare the specificities in Tables 2 and 3). In these cases, the lungs are the most likely location of venous-arterial shunts, allowing the contrast material to bypass the pulmonary capillaries and to slip into the cerebral arteries. Another option would be that these shunts correspond to very small intracardiac shunts not noted during TEE. In our study smaller amounts of bubbles passed these shunts compared with the shunts also demonstrated on TEE. Despite training and control, the Valsalva maneuver may occasionally not have been as effective during TEE as during the TCD investigation because of the TEE tube in the esophagus and sedation. Some authors believe that a high number of MES and their early occurrence may help to discriminate cardiac from noncardiac shunts or clinically relevant from irrelevant shunts.18,19,21,22 Our results, however, show that in individual cases, discrimination based only on the number of MES or their occurrence is not feasible. Additionally, shunts not noted on TEE can allow considerable and early transit of microbubbles. On the other hand, TEE-proven cardiac RLS can lead to small amounts of MES occurring late after contrast medium injection. Sensitivities of contrast TCD of 100% could, except for 1, only be achieved when the time window was expanded to 40 seconds and when the occurrence of a single MES was regarded as indication of a shunt. Thus far, contrast TCD is a screening procedure before TEE, since closure of a cardiac RLS by open heart surgery or the endovascular approach relies on TEE to prove the target lesion.26–28 Thus, sensitivity of contrast TCD prevails over

### TABLE 2. Sensitivity and Specificity of Single Tests and Combined Results of Tests With VM

<table>
<thead>
<tr>
<th>Threshold, s</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<td></td>
<td>≥1 ≥2 ≥3 ≥4 ≥6 ≥11</td>
<td>≥1 ≥2 ≥3 ≥4 ≥6 ≥11</td>
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<tr>
<td>No VM</td>
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<td></td>
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<tr>
<td>40</td>
<td>71 62 48 48 33 19</td>
<td>81 92 92 95 90 100</td>
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<tr>
<td>25</td>
<td>67 62 48 43 33 19</td>
<td>86 95 95 95 97 100</td>
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<tr>
<td>20</td>
<td>62 48 43 38 29 19</td>
<td>86 95 97 97 100 100</td>
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<tr>
<td>VM 2–7 s</td>
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<td>86 86 76 71 67 48</td>
<td>84 95 97 100 100 100</td>
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<tr>
<td>25</td>
<td>81 81 76 71 67 62</td>
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<tr>
<td>20</td>
<td>81 71 67 62 57 43</td>
<td>92 97 97 100 100 100</td>
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<tr>
<td>VM 5–10 s</td>
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<tr>
<td>40</td>
<td>86 86 76 76 71 57</td>
<td>76 86 92 95 95 95</td>
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<tr>
<td>25</td>
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<td>78 89 92 95 97 97</td>
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<td>76 76 71 71 67 52</td>
<td>81 92 97 97 97 97</td>
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<tr>
<td>VM 8–13 s</td>
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<td>40</td>
<td>86 76 76 62 62 57</td>
<td>78 84 92 97 97 97</td>
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<td>25</td>
<td>81 76 71 57 57 43</td>
<td>78 89 95 97 97 100</td>
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<td>20</td>
<td>71 67 57 57 52 33</td>
<td>86 92 97 97 100 100</td>
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<td>Continuous VM</td>
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<td>84 89 92 92 95 97</td>
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<td>86 76 71 62 52 43</td>
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<tr>
<td>20</td>
<td>81 76 71 62 52 38</td>
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<td>95 90 86 86 76 62</td>
<td>76 89 92 92 97 97</td>
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<td>VM 2–7 s and VM 5–10 s</td>
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<td>90 90 86 86 76 71</td>
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<td>VM 8–13 s and continuous VM</td>
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<td>70 78 86 89 92 97</td>
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specificity. Given these premises, our study demonstrates that (1) double performance, (2) the use of a time window of 40 seconds, and (3) no threshold in MES numbers yields the best results. Long-term follow-up of patients having suffered a stroke by paradoxical embolism and treated by shunt closure is scarce and inconclusive.27,28 The role of shunts demonstrated only during TCD for clinically manifest paradoxical embolism is unknown and requires further research. Anticoagulation would minimize thrombus formation and thus embolization through cardiac and noncardiac shunts. Once conclusive recommendations on the treatment of RLS patients are available, the importance of contrast TCD may

<table>
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<tr>
<th>Author/Special Modalities</th>
<th>Year</th>
<th>Provocation Maneuver</th>
<th>Duration of Provocation Maneuver</th>
<th>Temporal Relationship of Injection to Provocation Maneuver</th>
<th>MES Threshold for Positive TCD Result</th>
<th>Sensitivity of TCD, %</th>
<th>Specificity of TCD, %</th>
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<td>NS</td>
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<td>67</td>
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<td>NS</td>
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<td>VM</td>
<td>5 s</td>
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<td>Injection end just before VM</td>
<td>≥1</td>
<td>97</td>
<td>70</td>
</tr>
<tr>
<td>Devuyst et al21</td>
<td>1997</td>
<td>VM</td>
<td>NS</td>
<td>Injection during VM</td>
<td>≥4</td>
<td>100</td>
<td>62 and 100, respectively</td>
</tr>
<tr>
<td>Albert et al33</td>
<td>1997</td>
<td>VM</td>
<td>NS</td>
<td>VM started before injection and discontinued shortly after injection</td>
<td>≥10</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Hamann et al22</td>
<td>1998</td>
<td>VM</td>
<td>2 s</td>
<td>VM when contrast filled right atrium (simultaneous performance of TCD and TEE)</td>
<td>≥11</td>
<td>75 and 100, respectively</td>
<td></td>
</tr>
<tr>
<td>Stendel et al9</td>
<td>1998</td>
<td>VM</td>
<td>NS</td>
<td>Injection before VM</td>
<td>≥1</td>
<td>85</td>
<td>100</td>
</tr>
<tr>
<td>Droste et al11</td>
<td>1999</td>
<td>VM</td>
<td>5 s</td>
<td>Injection 5 s before provocation</td>
<td>≥1</td>
<td>95</td>
<td>83</td>
</tr>
<tr>
<td>Schwarze et al17; only RLS patients studied, based on TCD</td>
<td>1999</td>
<td>VM controlled by manometer</td>
<td>5 s</td>
<td>Injection 5 s before provocation Simultaneously</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VM controlled by manometer</td>
<td>5 s</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Droste et al12</td>
<td>1999</td>
<td>VM</td>
<td>5 s</td>
<td>Injection 5 s before provocation</td>
<td>≥1</td>
<td>90</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VM controlled by manometer</td>
<td>5 s</td>
<td>Injection 5 s before provocation</td>
<td>≥1</td>
<td>80</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Injection 5 s before provocation</td>
<td>≥1</td>
<td>85</td>
<td>69</td>
</tr>
<tr>
<td>Heckmann et al18</td>
<td>1999</td>
<td>VM</td>
<td>NS</td>
<td>Injection immediately before VM</td>
<td>≥6</td>
<td>85</td>
<td>100</td>
</tr>
</tbody>
</table>

NS indicates not specified; NA, not applicable.
further increase (1) because of its ability to detect RLS not noted during TEE and (2) because of the possibility of quantifying shunts by the number of MES detected.29

References
Contrast Transcranial Doppler Ultrasound in the Detection of Right-to-Left Shunts: Time Window and Threshold in Microbubble Numbers
Dirk W. Droste, Karen Silling, Jörg Stypmann, Matthias Grude, Vendel Kemény, Thomas Wichter, Karsten Kühne and E. Bernd Ringelstein

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