Methodological Parameters Influence the Detection of Right-to-Left Shunts by Contrast Transcranial Doppler Ultrasonography

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Background and Purpose—Contrast transcranial Doppler ultrasonography is a new method to detect intracardiac right-to-left shunts, such as the patent foramen ovale. However, the methodology of the procedure varies considerably among investigators. This study was undertaken to assess the influence of methodological parameters on the results of the contrast transcranial Doppler examination in the detection of right-to-left shunts.

Methods—A total of 72 patients (mean age, 58.2 ± 14.7 years) had a contrast transcranial Doppler ultrasonography examination. To study the influence of methodological factors, patients with evidence of a right-to-left shunt underwent repeated examinations with modified procedures. Parameters under investigation were the timing of the Valsalva maneuver, the dose of the contrast medium, and the patient’s posture during the examination.

Results—The median contrast signal count was 58.5 and 48.0 (P < 0.001) and the median latency of the first intracranially detected contrast signal was 12.5 and 8.5 seconds (P < 0.05) when the Valsalva maneuver was performed 5 and 0 seconds after the start of the injection, respectively. Reducing the contrast medium dose from 10 to 5, 2.5, and 1.2 mL resulted in a decline of the median signal count from 54.5 to 28.5, 20.5, and 12.0 (P < 0.01), respectively, while the latency of the first contrast signal increased from 13.3 to 14.0, 14.6, and 15.0 seconds (P < 0.05). The sitting position also produced a lower signal count than the supine position (P < 0.02).

Conclusions—This study demonstrates that several essential methodological parameters influence the results of the contrast transcranial Doppler ultrasonography examination. Therefore, it is necessary to standardize the procedure to permit comparable quantitative assessments of the shunt volume. The findings of the present study suggest that 10 mL of contrast medium be injected with the patient in the supine position and that the Valsalva maneuver be performed 5 seconds after the start of the injection. (Stroke. 1999;30:1234-1239.)

Key Words: contrast media, paradoxical embolism, foramen ovale, patent heart septal defects, ultrasonography, Doppler, transcranial

Paradoxical embolism through right-to-left (R/L) shunts, such as the patent foramen ovale (PFO), is widely accepted as a potential cause of cerebral ischemia.\(^1\)–\(^4\) Contrast transesophageal echocardiography (contrast TEE) is currently viewed as the gold standard in the detection of such R/L communications.\(^5\)–\(^9\) However, because of its semi-invasive nature, this method has some limitations, especially in elderly patients with acute strokes. It has been shown that complications during contrast TEE examinations are more common among the elderly, although overall they are relatively infrequent.\(^10\)–\(^12\) In addition, a Valsalva maneuver (VS), which is frequently necessary to elicit R/L shunting, may not be feasible during contrast TEE examinations because patients often require sedation.\(^11\),\(^13\)

More recently, transcranial Doppler ultrasonography during an injection of a nontranspulmonary ultrasonic contrast medium (contrast TCD) has been proposed as an alternative method in the detection of such R/L shunts.\(^14\)–\(^22\) A number of studies proved the contrast TCD method to be highly sensitive and specific compared with contrast TEE.\(^15\),\(^17\)–\(^21\) However, the methodology of the contrast TCD examination differs considerably among investigators. Two of the main discrepancies in the methodology are the timing of the VS and the dose of the ultrasonic contrast medium (CM). In some studies, patients performed the VS simultaneously with the CM injection,\(^20\),\(^22\),\(^23\) while in others the VS was performed with a delay of 3 to 5 seconds.\(^17\),\(^18\) In addition, the amount of CM differs notably, since some investigators inject 5 mL of CM,\(^17\),\(^20\),\(^22\),\(^24\) while others inject up to 10 mL.\(^18\),\(^19\),\(^23\),\(^25\) Only little is known about the influence of these external factors on the results of the examination.\(^26\)

Since a PFO may be found in a substantial number (17% to 32%) of healthy individuals,\(^27\)–\(^29\) of whom only a small

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fraction will sustain an embolic stroke (and a paradoxical embolism will be considered the probable cause in an even smaller fraction), it has been suggested that some characteristics of the PFO itself, such as size and shunt volume, may determine the clinical relevance of a PFO. Only quantitative data on shunt volume can provide the information that is required to assess the clinical relevance of the R/L shunt and to allow therapeutic decisions to be made. To obtain quantitative data on shunt volume, the method that generates the data must be standardized, ie, factors that influence the results of the contrast TCD method must be known and controlled for. Therefore, this study does not intend to validate the contrast TCD method by comparing it with contrast TEE but intends to investigate the influence of some essential methodological variations, such as the timing of the VS, the CM dose, and the patient’s posture during the examination, on the results of the contrast TCD.

Subjects and Methods

Patients
A total of 72 patients (40 [55.6%] men and 32 [44.4%] women; mean age, 58.2 ± 14.7 years) who presented with symptoms consistent with a cerebrovascular accident were enrolled in this study. In 7 patients the neurological deficit was attributed to small-vessel disease, in 6 to large-vessel disease, and in 18 to cardiogenic embolism. Twenty-six patients were classified as having cryptogenic cerebral ischemia, since no obvious cause could be identified. In 15 cases the diagnostic evaluation revealed underlying pathologies other than cerebral ischemia. To ensure that pertinent R/L shunts were studied, patients were only included if >12 high-intensity transient signals caused by CM (CM-HITS) were detected during the initial contrast TCD examination, which comprised an injection of 10 mL of CM with the patients resting in the supine position and a VS performed 5 seconds after the start of the injection (see Study Parameters). All patients gave informed consent to participate in this study.

TCD Studies
A 2-MHz pulsed transcranial Doppler (TCD) device (Multi-Dop X4, DWL) with 2 simultaneously insonating probes was used. In all patients, 1 middle cerebral artery and the contralateral posterior cerebral artery were monitored simultaneously. The TCD examination was performed according to previously described methods. The TCD device was equipped with a software program that permitted the online detection of HITS, which were all saved on hard disk. All HITS were retrospectively analyzed to eliminate artifacts and to count the CM-HITS. Accepted signals appeared after the CM injection, were unidirectional from the baseline, and occurred randomly throughout the cardiac cycle. They lasted 10 to 50 milliseconds, had an intensity of ≥9 dB higher than that of surrounding blood, and were associated with a characteristic audio output.

Contrast Medium
A commercially available prefabricated suspension of galactose particles with adherent gas microbubbles (Echovist 300, Schering) was used as CM. The intravenously injected CM is usually confined to the right heart and the venous branch of the vasculature and does not survive transpulmonary passage. Therefore, the CM cannot be detected in intracranial arteries by TCD unless a R/L shunt is present. A bolus injection of CM into an antecubital vein was followed by a flush injection of 5 mL of normal saline. To increase the sensitivity of this method, the patients performed a VS during the contrast TCD examination. For standardization purposes, the VS was monitored by means of a pressure gauge, which was connected to a flexible tube with a snorkel mouthpiece. The patients were asked to maintain a pressure of 40 mbar for 5 seconds.

TEE Studies
As part of their routine evaluation, the patients of our study population underwent a contrast TEE examination. During the examination, patients were in the left lateral decubitus position, 10 mL of CM was injected, and all patients were asked to “bear down” when the CM appeared in the right atrium. The contrast TEE examination was considered positive if >3 CM signals were detected in the left atrium within 3 heart cycles after the appearance of the CM in the right atrium.

Study Parameters

Valsalva Maneuver
In 16 patients (8 men and 8 women; mean age, 57.4 ± 11.7 years), the timing of the VS was modified. During the first examination, the patient performed the VS 5 seconds after the start of the injection (VS5). During the second examination, the patient built up the pressure simultaneously with the start of the CM injection (VS0). In another 26 patients (mean age, 58.4 ± 11.7 years), the first injection was also performed 5 seconds after the start of the injection (VS5), but the second injection was performed 25 seconds after the start of the injection (VS25).

Amount of Contrast Agent
In 30 patients (23 men and 7 women; mean age, 54.6 ± 12.3 years), 4 successive doses of CM (10, 5, 2.5, and 1.2 mL) were administered during 1 examination. The CM was administered at a fixed sequence, beginning with the highest dose of 10 mL followed by decreasing amounts of CM.

Posture
In 13 patients (8 men and 5 women; mean age, 53.6 ± 13.3 years), 1.2 mL was first administered with the patients in a supine position and then in a sitting position. These 13 patients were a subgroup of the 30 patients to whom different CM doses were administered.

All Tests
During each subset of tests, only 1 methodological parameter was modified at a time, while all other parameters remained unchanged. Between injections, a CM-HITS–free interval of ≥3 minutes, including 2 repeated VS, was required. According to the current literature, patients were thought to have evidence of a R/L shunt if ≥5 CM-HITS were detected ≥20 seconds after the start of the injection. Patients fulfilling these criteria were considered positive; all others were considered negative. These criteria were verified before this study by a good correlation with the results of the contrast TEE examinations at our institution.

Latency was defined as the time interval between the start of the CM injection and the detection of the first CM-HITS. The total CM-HITS count consisted of all CM-HITS detected during a time interval of 20 seconds after the appearance of the first CM-HITS. It is our policy that the maximum dose of CM applied to a patient during 1 examination shall not exceed 20 mL, which is well below the manufacturer’s recommendation for the maximum dose.

Statistical Analysis
Data were tested for normal distribution with the Kolmogorov-Smirnov test. Normally distributed data values were given as mean ± 1 SD. Data that were not normally distributed were given as median. The application of the mean or median was specifically labeled within the text. Nonparametric data were tested for statistical significance with the use of a paired Kruskal-Wallis ANOVA test for repeated measures to compare the total CM-HITS count at different doses. The unpaired version of the Kruskal-Wallis ANOVA test was chosen for the comparison of the latencies of the same subset of tests because data were missing in cases in which the CM-HITS count was 0. The different Valsalva timings and body positions were compared with the use of the Wilcoxon signed rank test for the total CM-HITS count and the Mann-Whitney U test for the latencies. Normally distributed data were analyzed with the Student’s t test. Statistical significance was accepted at P<0.05.
Results

Valsalva Maneuver

The median latency of the first CM-HITS declined from 13.1 seconds during the VS5 examination to 8.7 seconds during the VS0 examination (P<0.05) (Figure 1). There was, however, a substantial difference between 2 subgroups of this study population. In patients 6 to 16, whose individual VS5 latency was >10 seconds, the median latency declined from 13.6 at VS5 to 10.1 seconds at VS0 (P<0.02), while in patients 1 to 5, whose individual VS5 latency was <10 seconds, the median latency increased from 7.4 (VS5) to 8.4 seconds (VS0) (P=NS). When the individual latency changes were calculated, it was found that the median individual latency change of patients 1 to 5 (−0.9 seconds) was significantly lower than the median individual latency change of patients 6 to 16 (+3.9 seconds) (P<0.02).

In addition, it was found that the median CM-HITS count declined significantly (P<0.001) from 58.5 at VS5 to 48.0 at VS0 (Figure 1). Again, there was a difference between the same 2 subgroups. In patients 1 to 5 the median CM-HITS count decreased from 131 to 104, while in patients 6 to 16 it declined from 39 to 27 (P<0.005). The decline in patients 1 to 5 did not quite reach the significance level, with P=0.06, but indicated a strong trend. The median relative decline of the CM-HITS count was similar in both groups (24.5% in patients 1 to 5 and 32.5% in patients 6 to 16) (P=NS). However, the absolute median CM-HITS counts were clearly different: 131.0 (patients 1 to 5) versus 39.0 (patients 6 to 16) at VS5 (P<0.002) and 104.0 (patients 1 to 5) versus 27 (patients 6 to 16) at VS0 (P<0.004). On contrast TEE examination, 2 of the 16 patients (14 and 15) did not have evidence for a R/L shunt according to the above criteria.

In the second group of patients (n=26), the effects of a very late VS performance (25 seconds after the start of the injection) were evaluated. Since under this condition 25 seconds elapsed without a VS, this condition also permitted an assessment of the contrast TCD examination without a VS. The interval between the injection and the performance of the VS after 25 seconds was labeled VSnone. Eleven (42%) of the 26 patients tested positive under the VS5 condition did not have evidence for a R/L shunt during VSnone. Seven of the 11 patients had evidence for a R/L shunt when the VS was performed 25 seconds after the start of the injection. The remaining 4 patients, representing 15% of the entire group of 26 patients, still did not have evidence of a R/L shunt. Moreover, there is a significant difference in the number of CM-HITS when VS5 is compared with VSnone and VS25 (Figure 2.). The median CM-HITS counts at VS5, VSnone, and VS25 were 41.0, 11.5, and 7.5, respectively. In 1 of the 11 cases who did not have evidence for a R/L shunt under the VSnone condition, a PFO was not detected on contrast TEE examination. In 1 of the 3 cases, 2 CM-HITS were detected during the VS25 condition, and the other 2 had no CM-HITS except under the VS5 condition.

Figure 1. Total CM-HITS count (left y axis) and latency of the first CM-HITS (right y axis) at different timings of the VS of the 16 patients investigated. The bars depict the median CM-HITS count with the VS performed 5 seconds after the start of the injection of the contrast medium (VS5) and the shaded bars the CM-HITS count with the VS performed simultaneously with the injection (VS0). The latencies of the first CM-HITS are depicted as a line graph.

Figure 2. CM-HITS count of patients performing VS 5 seconds (VS 5) and 25 seconds (VS 25) after the start of the injection. VS none indicates the CM-HITS count during the time that elapsed between the injection and the late performance of the VS (25 seconds). The parameters of the boxes indicate the 25th and the 75th percentiles of the data. The lines inside the boxes mark the value of the 50th percentile, and the vertical lines above and below the boxes indicate the 10th and 90th percentiles, respectively.

Figure 3. CM-HITS count with patients receiving varying doses of contrast medium. The parameters of the boxes indicate the 25th and the 75th percentiles of the data. The lines inside the boxes mark the value of the 50th percentile, and the vertical lines above and below the boxes indicate the 10th and 90th percentiles, respectively.
Importance of a VS in the Detection of a R/L Shunt, which has not have evidence for a R/L shunt. This underscores the importance of a VS in the detection of a R/L shunt, which has been previously reported by others.6,15,17,26 The considerably greater CM-HITS count at VS5 compared with VS0. Interestingly, this delay of the first CM-HITS at VS5 in patients 6 to 16 (Figure 1) may be substantially larger than in patients 1 to 5. On the other hand, the decreased venous return during the strain phase may have an accumulating effect on the CM, increasing the bolus dynamics of the CM injection, which may be responsible for the greater CM-HITS count at VS5 compared with VS0. Interestingly, this delay of the first CM-HITS is not observed in patients with a latency <10 seconds during the VS5 examination. It may be postulated that in these cases the CM has already passed through the interatrial shunt before the VS was started, ie, a VS may not have been required to allow R/L shunting. This was not tested in this group of patients to limit the total amount of CM per examination and individual to 20 mL. The fact that these patients also have a significantly greater CM-HITS count than those with a VS5 latency of >10 seconds suggests that the shunt volume in patients 1 to 5 (Figure 1) may be substantially larger than in patients 6 to 16. Therefore, a short latency and a large number of CM-HITS may both be used as evidence for large shunts. This, in turn, has been shown to be of great clinical relevance, since patients with cryptogenic infarcts have significantly larger shunts than patients with probable causes of their infarcts.5,30,31

When the patients did not perform a VS (VSnone), 42% of the patients who tested positive under the VS5 condition did not have evidence for a R/L shunt. This underscores the importance of a VS in the detection of a R/L shunt, which has been previously reported by others.6,15,17,26 The considerably lower CM-HITS count during VSnone suggests that even if CM
traverses the interatrial septum and the R/L shunt is demonstrated, its size may be underestimated in a substantial number of cases if the examination is performed without VS. Since the size of a PFO appears to determine its clinical relevance,\textsuperscript{4,30,31} it seems reasonable to choose the procedure with the highest yield of contrast signals to quantitatively evaluate the contrast TCD examination, which is, according to the present study, the VS5 condition. Similarly, all but 1 case had a lower CM-HITS count after the delayed performance of the VS (VS25). Even if the contrast signals that appeared before the VS were added to the ones that appeared after the VS25, the total CM-HITS count was lower than the one at VS5. This again underscores the significance of the correct timing of the VS, particularly if a quantitative assessment is desired.

Our findings are consistent with those published by Zanette et al.\textsuperscript{26} Despite the different contrast media used (agitated normal saline by Zanette et al and galactose-based microbubbles in the present study), the observed effects of different timings of the VS are quite similar in that both studies demonstrated a decline in CM-HITS count and latency when VS5 was compared with VS0. This confirms the reliability of the results of both studies and may therefore be used as guideline for other, less commonly used contrast media such as gelatin.\textsuperscript{19}

### Amount of Contrast Agent

With decreasing CM doses, the total CM-HITS count declined and the latency increased. This may be due to the hemodynamics associated with a R/L shunt. The short period of time during which the right atrial pressure exceeds the left atrial pressure has probably been consistent throughout successive injections of different CM doses, since all other parameters remained unchanged. Therefore, during a given period when the pressure gradient reverses, the more CM will pass through the PFO, the more CM is available in the right atrium. If only small amounts of CM reach the left atrium per 1 heartbeat, it is conceivable that it takes \( \approx 2 \) heartbeats to propel a sufficient amount of CM into the arterial branch of the vasculature so that detectable amounts of CM reach the intracranial arteries, accounting for a “delay” of the first CM-HITS at small CM doses.

### Body Position

Changing the patient’s body position during the examination from supine to sitting resulted in a reduction of the median CM-HITS count. These findings are consistent with those of others who performed contrast TEE examinations in supine and sitting positions.\textsuperscript{34,35} Brown et al\textsuperscript{34} reported that they detected fewer PFOs with patients in the sitting than in the supine position. This effect may be caused by the diminished venous return in the sitting position.

Two recent studies have demonstrated that a femoral injection of CM is superior to an injection into the antecubital vein with regard to the CM-HITS count and the sensitivity of the procedure.\textsuperscript{36,37} The anatomic situation in the right atrium is such that blood flow coming from the inferior vena cava is directed at the fossa ovalis, while the blood flow from the superior vena cava is directed at the tricuspid valve. This anatomic situation favors the transition of oxygenated blood originating from the inferior vena cava into the left atrium during fetal life. The eustachian valve at the interior portion of the right atrium, of which there may be remnants during adult life, fosters the aforementioned intra-atrial hemodynamics. Although the procedure seems to be more sensitive if the CM is injected into a femoral vein, the potential hazards due to accidental arterial puncture or unnoticed paravascular CM injection are too grave to use this method routinely.

It is conceivable that other factors, such as heart rate, stroke volume, and the existence of heart failure, may influence the results of the contrast TCD examination. Jauss et al\textsuperscript{17} described a patient with heart failure who had a substantially increased latency. It is conceivable that the CM-HITS count is much lower in such patients than in patients with normal hearts. There was no patient with significant heart failure in our population; hence, the influence of this factor could not be evaluated. These investigations were confined to some essential methodological parameters to develop guidelines for the methodology of the procedure. This does not mean that other factors such as the aforementioned factors are of no importance; rather, they may warrant a separate study.

In conclusion, the results of the present study demonstrate that the timing of the VS, the amount of CM injected, and the patient’s posture during the examination influence the total CM-HITS count and the latency of the first CM-HITS. Therefore, the authors suggest that 10 mL of CM be injected with the patient in the supine position and that the VS be performed 5 seconds after the start of the injection, since this procedure appears to be most sensitive.

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