Controlled Contrast Transcranial Doppler and Arterial Blood Gas Analysis to Quantify Shunt Through Patent Foramen Ovale

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Background and Purpose—A right-to-left shunt can be identified by contrast transcranial Doppler ultrasonography (c-TCD) at rest and/or after a Valsalva maneuver (VM) or by arterial blood gas (ABG) measurement. We assessed the influence of controlled strain pressures and durations during VM on the right-to-left passage of microbubbles, on which depends the shunt classification by c-TCD, and correlated it with the right-to-left shunt evaluation by ABG measurements in stroke patients with patent foramen ovale (PFO).

Methods—We evaluated 40 stroke patients with transesophageal echocardiography–documented PFO. The microbubbles were recorded with TCD at rest and after 4 different VM conditions with controlled duration and target strain pressures (duration in seconds and pressure in cm H₂O, respectively): V5-20, V10-20, V5-40, and V10-40. The ABG analysis was performed after pure oxygen breathing in 34 patients, and the shunt was calculated as percentage of cardiac output.

Results—Among all VM conditions, V5-40 and V10-40 yielded the greatest median number of microbubbles (84 and 95, respectively; \( P < 0.01 \)). A significantly larger number of microbubbles were detected in V5-40 than in V5-20 \( (P < 0.001) \) and in V10-40 than in V10-20 \( (P < 0.01) \). ABG was not sensitive enough to detect a shunt in 31 patients.

Conclusions—The increase of VM expiratory pressure magnifies the number of microbubbles irrespective of the strain duration. Because the right-to-left shunt classification in PFO is based on the number of microbubbles, a controlled VM pressure is advised for a reproducible shunt assessment. The ABG measurement is not sensitive enough for shunt assessment in stroke patients with PFO. (Stroke. 2004;35:859-863.)

Key Words: foramen ovale, patent oxygen ultrasonography, Doppler, transcranial Valsalva maneuver

The patent foramen ovale (PFO) with or without coexistent atrial septal aneurysm is generally considered to be associated with brain disorders, including first-ever ischemic stroke in young patients,1,2 cryptogenic stroke,3,4 migraine,3–6 and cerebral decompression sickness in scuba divers.7,8 Some authors do not confirm the association between isolated PFO and increased risk of ischemic stroke9 or recurrent stroke.4,10 The size of PFO and the degree of right-to-left cardiac shunt (RLS) in these disorders are debated.4,10 The presence of large PFO and high-degree RLS was demonstrated to increase the risk of cryptogenic stroke,10–13 recurrent stroke,14–16 the number of silent ischemic brain lesions in divers,16 migraine with aura,5,6,18 and cerebral decompression sickness.19 Other studies show that either percutaneous or surgical closure of PFO decreases the number of recurrent ischemic strokes,20,21 improves migraine symptoms,22 and decreases the number of decompression cerebral ischemic events23 and support the positive relation between high-degree RLS and the aforementioned pathologies.

Contrast transcranial Doppler ultrasonography (c-TCD) is a complementary method to contrast-enhanced transesophageal echocardiography (c-TEE) for RLS diagnosis.11 Its sensitivity approaches 90% and specificity approaches 92% compared with c-TEE.12 c-TCD does not require sedation of the patient, thus ensuring better collaboration during the Valsalva maneuver (VM). It does not provide any information concerning either the morphology of the interatrial septum or the size of PFO.24 The degree of RLS with c-TCD is expressed in numbers of microbubbles passing through the middle cerebral arteries. The application of VM was standardized for c-TCD RLS diagnosis at an international consensus meeting26 and more recently by Droste et al.24 However, the importance of the VM duration according to strain pressure is not established for the RLS assessment. Consider-
erating the positive relationship between the RLS and the aforementioned disorders8,6,10,12–23 and taking into account that the criterion of large RLS may be used in making treatment decisions in patients with PFO,20,22 we therefore hypothesized that control of VM criteria in terms of duration and strain pressure might improve c-TCD validity. The degree of RLS can also be estimated by a totally independent method, ie, by measuring arterial blood gas (ABG) while the subject is breathing pure oxygen.25 To the best of our knowledge, there are no data in the literature comparing the degree of shunt defined by c-TCD criteria and by ABG analysis.

In the first part of the study we evaluated with c-TCD the potency of different VMs with different controlled durations and target strain pressures in patients with PFO. We assessed the influence of different VM settings on c-TCD classification of RLS. In the second part we assessed RLS with ABG and compared the results of RLS estimation with c-TCD and with ABG.

**Subjects and Methods**

**Patients**

We prospectively evaluated 40 patients (24 men, 16 women) aged 25 to 70 years (mean age, 44.6 ± 9.3 years). Patients were selected on the basis of (1) diagnosis of ischemic stroke attributed to cerebral paradoxical embolism through the PFO, (2) c-TEE–confirmed PFO without atrial septal aneurysm, and (3) good recovery of neurological function (National Institutes of Health Stroke Scale score <3). Patients who had had endovascular or surgical closure of PFO were not included in the study. The study protocol was approved by the institutional ethical committee.

**Controlled VM**

VM started 5 seconds after agitated saline injection.26 For the VM, 2 controlled strain pressures of 20 and 40 cm H2O and 2 controlled durations of 5 and 10 seconds were studied, thus producing 4 different controlled VM conditions (duration in seconds and pressure in cm H2O, respectively): (1) V5-20; (2) V10-20; (3) V5-40; and (4) V10-40. Before the c-TCD recording, patients were instructed regarding how to perform VM to keep the target strain pressure for the desired time. In all patients the c-TCD recordings were performed at the following standard sequence: (1) at rest, (2) V5-20, (3) V10-20, (4) V5-40, and (5) V10-40. Strain pressure was measured with a mouthpiece connected to a pressure transducer and was displayed on a screen as well as on paper. Time was counted with the use of a calibrated time stopper.

**Contrast Transcranial Doppler**

In each patient a bilateral TCD (Multidop-T2 device; DWL Sipplingen) with two 2-MHz probes installed on a special headset (Spencer Mark 500) was performed according to international criteria.27 We based the RLS classification on the international consensus criteria.26 We pooled the patients with >20 microbubbles and with a curtain of microbubbles and defined them as having large RLS. The rest of the patients were categorized as having no RLS (no occurrence of microbubbles) and as having minimal RLS (1 to 20 microbubbles).

**ABG Analysis**

Thirty-four patients (25 men) underwent arterial blood analysis (3 refused to participate; in 3 sampling was not feasible). Unlike TCD, ABG analysis was performed during resting breathing only, without VM. Arterial blood was drawn from the radial artery after 10 minutes of the subject breathing 100% oxygen and was analyzed immediately. RLS was estimated from ABG with the use of the following equation and was expressed in percentage of cardiac output, as follows:

\[
RLS_{-}ABG(\%) = \frac{C_{O2}_{-}ABG}{C_{O2}} \times 100
\]

where \( C_{O2}_{-}ABG \) = oxygen content of pulmonary end-capillary blood; \( C_{O2} \) = oxygen content of arterial blood; and \( C_{O2}_{-}ABG \) = oxygen content of mixed venous blood.

The \( C_{O2} \) was calculated by adding oxygen bound to hemoglobin and oxygen bound to plasma, as follows:

\[
C_{O2} = (Hb \times S_{O2} \times 1.34) + (P_{O2} \times 0.03)
\]

where \( Hb \) = hemoglobin concentration (g L⁻¹); \( S_{O2} \) = oxygen saturation of arterial blood hemoglobin; \( P_{O2} \) = oxygen tension of arterial blood (mm Hg); 1.34 = oxygen transport by hemoglobin (mL · g⁻¹); and 0.03 = oxygen solubility in plasma (mL · L⁻¹ · mm Hg⁻¹).

The \( C_{O2}_{-}ABG \) was calculated accordingly. When a person breathes 100% oxygen, the blood leaving the pulmonary capillaries is fully saturated, and its oxygen tension equals that of alveolar air, as follows:

\[
C_{O2} = (Hb \times S_{O2} \times 1.34) + [(P_{b} - P_{HAO} - P_{C02}) \times 0.03]
\]

where \( P_{b} \) = barometric pressure; \( P_{HAO} \) = pressure of water vapor in the lung (≈ 47 mm Hg); and \( P_{C02} \) = carbon dioxide tension in arterial blood.

In the absence of a central line to analyze mixed venous blood, the arteriovenous difference in oxygen content (\( C_{O2} - C_{O2}_{-}ABG \)) was assumed to be 50 mL L⁻¹. RLS-ABG ≤ 5% was considered normal.

**Statistical Analysis**

Median numbers of microbubbles were calculated for each test and compared with Friedman 2-way ANOVA. We compared the number of median microbubbles between consecutive tests with the Wilcoxon signed rank test. The percentage of RLS-ABG was correlated with the number of microbubbles with the Spearman rank correlation coefficient. The comparison between numbers of patients with different c-TCD RLS categories was done with the Fisher exact test. The comparison between the number of RLS detected by c-TCD and by ABG was done with the Fisher exact test. Statistical significance was determined at the 0.05 level.

**Results**

Among all VM conditions tested, the most potent VM parameters in terms of number of bilateral microbubbles recorded were V5-40 (maximum 432; median 84) and V10-40 (maximum 386; median 44), and V10-20 (maximum 337; median 95) (\( P < 0.01 \)). The V5-40 reached a higher rank (3.950) in the Friedman test than did V10-40 (3.738). There was no significant difference between the 2. A significant increase of number of microbubbles was detected between V5-20 (maximum 290; median 26) and V5-40, V10-20 (maximum 386; median 44), and V10-40 (\( P < 0.01 \)). However, there was no significant difference in the number of microbubbles between V5-20 and V10-20 or between V5-40 and V10-40 (Figure 1).

The results of c-TCD shunt classification are shown in Figure 2. RLS was detected at rest in 78% of patients. The greatest difference in the percentage of patients with large RLS was detected when the results at rest and after V10-40 were compared (35% versus 75%; \( P < 0.001 \)). However, the difference in the RLS classification when different VMs were compared did not reach significance.
Thirty-one (91%) of 34 patients had RLS-ABG within the normal range. Three patients (9%) had RLS-ABG of 6%, 19%, and 21%. There was no correlation between RLS-ABG and the number of bilateral microbubbles recorded with c-TCD (Spearman coefficient $r=0.0613, P=0.172$). The patient with RLS-ABG of 6% had large RLS with TCD at rest, the patient with RLS-ABG of 19% had large RLS with TCD at rest, and the patient with 21% RLS-ABG had no RLS with c-TCD at rest.

### Discussion

In the first part of our study we demonstrated the importance of standardized and strictly controlled VM pressure in c-TCD RLS detection. To the best of our knowledge, no study has compared the efficacy of controlled VM with different target strain pressures simultaneously with different time lengths of the strain in c-TCD diagnosis of RLS. A recent international consensus greatly improved the criteria of diagnosing RLS by c-TCD—standardized VM, gave recommendations, and was opened to further studies. In a recent report, a controlled target strain pressure of 50 to 60 mmHg was used, but there was no comparison with other provocational maneuvers. Others compared a nonstandardized VM with a VM controlled for strain pressure of 40 mmHg. No difference between the nonstandardized VM and controlled VM was observed. Unlike in the latter study, we used 2 different controlled strain pressures and were able to demonstrate that when the target strain pressure was increased from 20 to 40 cm H$_2$O, the median number of microbubbles recorded bilaterally rose significantly. We also showed that RLS categorization changes significantly when c-TCD recordings at rest and at V5-40 or V10-40 are compared: we observed a 4-fold decrease in number of patients with no RLS and 2-fold increase in number of patients with large RLS. However, we did not find a significant difference in RLS classification between different VMs. We believe that our findings may be explained as follows: increasing the pressure of Valsalva strain can result in increased interatrial pressure after strain release, enhancing RLS through the PFO. This explanation is consistent with the results of a recent study showing that the pressure gradient between right and left atria during provocational procedures is directly related to the level of target strain pressure. In another study a controlled positive airway pressure of 30 cm H$_2$O was compared with nonstandardized VM. The use of controlled airway pressure led to more pronounced reduction in right atrial load and was superior to VM in detecting RLS. With this method, twice as many cases of RLS were identified in comparison to nonstandardized VM. These results are consistent with our data in that a controlled strain pressure $\geq 30$ cm H$_2$O is needed to induce RLS and is better than a noncontrolled strain to identify RLS.

Different controlled durations, from 5 to 10 seconds, of VM were introduced by several authors in c-TCD diagnosis of RLS. In 1 of these studies, different timings of VM in relation to contrast agent injection and 2 different durations of VM (5 seconds and repetitive VM < 2 seconds) were compared. No difference between the 2 VM durations was demonstrated. We compared 2 VM durations of 5 and 10 seconds and concomitantly controlled the strain pressure, thus allowing for more objective assessment of the influence of VM duration on number of microbubbles recorded. The median number of bilateral microbubbles recorded after V5-20 was significantly lower than after V5-40. Similar results were achieved when V10-20 was compared with V10-40. However, there was no difference in the number of microbubbles when V5-20 was compared with V10-20 and when V5-40 was compared with V10-40. These data demonstrate that increasing the duration of VM from 5 to 10 seconds does not influence the number of bilaterally recorded microbubbles and that strain pressure is the factor responsible for the observed differences between different VM parameters (Figure 1).

To the best of our knowledge, there is no study comparing the degree of shunt defined by c-TEE and c-TCD criteria

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**Figure 1.** Median numbers of microbubbles (MB) recorded bilaterally with c-TCD in each test. Horizontal lines of the boxes indicate 25th, 50th, and 75th percentiles. Whiskers indicate minimum and maximum values. Probability values represent statistical differences (only significant results presented) between specific standardized VM parameters. V5-20, V10-20, V5-40, and V10-40 indicate VM with controlled duration and target strain pressure (expressed in seconds and cm H$_2$O, respectively).

**Figure 2.** Shunt classification in consecutive tests (at rest, V5-20, V10-20, V5-40, V10-40). Vertical bars represent 100% of studied population for each test. Numbers in bars represent number of patients with respective types of RLS. Comparisons between different tests for different RLS degrees are as follows (2-tailed $P$): no microbubbles (MB): rest vs V5-40 ($P=0.048$); <20 microbubbles: rest vs V10-40 ($P=0.013$); large RLS: rest vs V10-20 ($P=0.013$); rest vs V5-40 ($P=0.003$); rest vs V10-40 ($P=0.0006$). V5-20, V10-20, V5-40, and V10-40 indicate VM with controlled duration and target strain pressure (expressed in seconds and cm H$_2$O, respectively).
versus ABG analysis. With the use of c-TCD, RLS was detected in 78% of patients at rest. In the ABG group (n=34), RLS was detected at rest in 79% of patients with c-TCD and in 9% of patients with ABG (P<0.0001). Several factors may be involved to explain this discrepancy. First, in the absence of a central venous line, the arteriovenous oxygen content difference (CaO2−CvO2) was estimated rather than measured, which introduces a degree of uncertainty. Second, a conservative value of 5% was considered the upper limit of normal RLS-ABG, leaving the possibility of failure to detect small venous admixture in terms of oxygen content analysis. ABG analysis during pure oxygen breathing is a well-established conservative value of 5% was considered the upper limit of normal RLS-ABG, leaving the possibility of failure to detect small venous admixture in terms of oxygen content analysis. ABG analysis during pure oxygen breathing is a well-established

The data suggest that c-TCD is sensitive enough to detect RLS that induces only a minor venous admixture in terms of oxygen content analysis. ABG analysis during pure oxygen breathing is a well-established method to estimate RLS. However, this method requires several minutes of resting breathing to reach alveolar gas equilibrium and cannot be combined with transient interventions like the VM. With the use of a simple pulse oximeter, a transient desaturation is often observed after release of VM in case of PFO. However, pulse oximetry cannot quantify RLS.

The large clinical studies such as the Patent Foramen Ovale and Atrial Septal Aneurysm Study (PFO-ASA) and Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS) were based on c-TEE RLS classification without standardization for pressure and duration. However, our results clearly show that the degree of RLS assessed with c-TCD depends on these parameters. Therefore, we suggest a comparison of both c-TEE and c-TCD with standardized pressure and duration to assess the role of RLS degree in different brain disorders.

On the basis of our results, the most potent provocative procedure for RLS diagnosis with c-TCD is VM with controlled strain pressure of 40 cm H2O irrespective of the strain duration. We did not find any association between the RLS classification estimated with c-TCD and with ABG analysis during pure oxygen breathing. For RLS detection with c-TCD, we recommend VM with controlled strain of 40 cm and duration of 5 rather than 10 seconds because it may require less effort in stroke patients.

Acknowledgment

This study was supported by a European Neurological Society fellowship to Dr Piechowski-Jóźwiak.

References

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Stroke. 2004;35:859-863; originally published online February 26, 2004;
doi: 10.1161/01.STR.0000119384.28376.EB

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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