Diagnostic Accuracy of Carotid Doppler Ultrasound for the Detection of Right-to-Left Cardiac Shunt

Anna Marenghi, Elisa Ceriani1, Elisa Maria Fiorelli, Mattia Bonzi2, Nicola Montano, Federico Annoni3

Department of Internal Medicine, Allergology and Immunology, Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico, 1Department of Internal Medicine, L. Sacco Hospital, University of Milan, 2Emergency Department and Emergency Medicine Unit, Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico, 3Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

Abstract

Background: Right-to-left cardiac shunt is a condition anatomically related to patent foramen ovale (PFO) and potentially related to cryptogenic cerebrovascular events. As recent studies demonstrated a reduction of recurrent stroke in patients undergoing percutaneous PFO closure after a cryptogenic cerebrovascular event, it is now of pivotal importance to screen these patients for Right-to-left shunt (RLS) presence. At this regard, transcranial color Doppler (TCCD) with contrast has a good sensitivity (97%) and specificity (93%) compared to transesophageal echocardiography and became the test of choice to assess RLS presence, thanks to its noninvasive nature. However, temporal bone window is not accessible in 6%–20% patients. Several approaches have been explored to overcome this limitation with encouraging but not definitive results for extracranial internal carotid artery (ICA) approach, proposed in previous pivotal studies. Aims of this study were to further assess the diagnostic accuracy of ICA Doppler ultrasound with contrast for RLS detection compared to TCCD, with the two tests performed simultaneously. Materials and Methods: Sixty-four patients underwent simultaneously to TCCD and ICA Doppler ultrasound, both performed at rest and after Valsalva maneuver. Diagnosis of RLS was made, both for TCCD and ICA ultrasound, if ≥1 microembolic signals (MES) were detected during the examination (either at rest or after Valsalva maneuver). Results: ICA Doppler ultrasound sensitivity and specificity resulted respectively of 97% (confidence interval [CI] 95%) and 100% ([CI] 95%), while negative likelihood ratio was 0.03 (CI 95%). Conclusions: ICA Doppler ultrasound represents a valid alternative to TCCD for RLS screening in patients without adequate transcranial acoustic window.

Keywords: Cryptogenic stroke, internal carotid artery Doppler ultrasound, patent foramen ovale, right to left shunt, transcranial color Doppler

Introduction

Patent foramen ovale (PFO) is a common condition in the general population, with a prevalence around 25%;1,2 however, only a small portion of patients has clinical sequelae such as refractory hypoxia, migraine and paradoxical embolism with consequent stroke.2 PFO has been associated with cryptogenic stroke (CS) and it is matter of debate whether PFO closure may reduce stroke recurrence. Although previous trials did not show any benefit from PFO closure over medical therapy in patients with CS,3,4 recent trials show a reduction of recurrent stroke and transient ischemic attack (TIA) in patient undergoing percutaneous PFO closure.5,6 Giving this new evidence, it is now of pivotal importance to screen patients with CS for PFO presence.

Transesophageal echocardiography (TEE) is considered the gold standard for the detection of PFO,7–9 but giving its invasive and time-consuming nature, other methods are used to diagnose PFO. At this regard transcranial color Doppler (TCCD) with microbubbles injection was found to have good sensitivity (97%) and specificity (93%) to detect PFO and became the test of choice to indirect assess the presence of PFO in patients with CS. A right-left cardiac shunt is diagnosed with TCCD in the presence of ≥1 microembolic signals (MESs) after microbubbles injection. Although TCCD has a high achievability and low cost, it is not feasible

Address for correspondence: Dr. Anna Marenghi, Department of Internal Medicine, Allergology and Immunology, Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy. E-mail: anna.marenghi94@gmail.com

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in 6%–20% of patients, due to the absence of an adequate transcranial window.\textsuperscript{[10-14]} Several other approaches have been explored to overcome this limitation. Draganski \textit{et al.} proposed an optional method for right-to-left shunt (RLS) detection based on visualization of single microbubbles in the common carotid artery (CCA) by harmonic imaging; however, the study had a limited number of patients and no clinical conclusion.\textsuperscript{[15]} In a study by Perren \textit{et al.}, TCCD was compared to Doppler ultrasound of the cervical arteries (extracranial internal carotid artery [ICA] and vertebral artery) for RLS detection, finding encouraging results for ICA approach (sensitivity of 100% and specificity of 96%). Vertebral approach showed a lower sensitivity (71.4%).\textsuperscript{[11]} However, during the examination, the two techniques were not performed simultaneously. The study by Censori \textit{et al.} compared the bubble test to detect RLSs employing TCCD of the right middle cerebral artery (MCA) to the second harmonic imaging duplex of the right CCA. A 95.3% sensitivity of duplex of CCA using the Valsalva maneuver was found while specificity was 100%. Censori \textit{et al.} conclude that second harmonic imaging duplex of the CCA may substitute TCCD approach when an adequate cranial bone window is not available.\textsuperscript{[10]} Topçuoglu \textit{et al.} demonstrated that contrast Doppler ultrasound of cervical ICA is at least as sensitive and specific as the traditional MCA method in detecting RLSs; furthermore, they found that this method seems to be more sensitive for low-volume RLSs.\textsuperscript{[17]} Although the literature shows encouraging results for ICA approach in detecting RLS, it is not yet performed routinely.

The aim of the present study is to detect the sensitivity and specificity of ICA Doppler ultrasound for RLS detection, using TCCD as reference standard.

**Materials and Methods**

Patients with clinical suspicion for RLS (age $>$18 years) who were addressed to our echo-Doppler laboratory were enrolled consecutively. Pregnant patients and patients without temporal window were excluded from the study. The number of Doppler examinations performed in our echo Doppler laboratory by the reference operator (F. A.) is 2500 examinations per year.

Two-blinded independent operators simultaneously performed TCCD and ICA Doppler ultrasound. TCCD was performed with a sector probe (3.5–5 MHz) with insonation of MCA through a temporal bone window. If the right MCA visualization resulted scanty, the left was preferred. Carotid Doppler ultrasound of the homolateral extracranial ICA was performed with a linear probe (7.5–13 MHz).

According to guidelines and previous literature,\textsuperscript{[18-20]} the presence of RLS was assessed through the detection of MESs in the explored artery, after the injection of agitated saline solution into an antecubital vein access. Agitated saline was created by using 9 ml of saline, 1 ml of the patient’s blood and 1 ml of air. The solution was rapidly mixed between two 10 ml syringes linked through a 3-way stopcock that was connected to the antecubital vein access. The agitated saline produced a foam of microbubbles that was later injected into the antecubital vein. The MES were defined as typical, visible, short-duration, high-intensity signals in the Doppler spectrum. The presence and shunt size were graded in four levels according to the number of microbubbles: grade 1: no microbubbles; Grade 2: 1–10 microbubbles; Grade 3: $>$10 microbubbles but no curtain effect; Grade 4: curtain effect, defined as shower of microbubbles that does not allow to distinguish and count them. The final diagnosis of RLS in the single patient was made if $\geq$1 MES was detected in at least one examination between rest and Valsalva tests. To avoid pulmonary shunts inclusion, a maximum delay of 20 s was considered between microbubble injection and the eventual visualization of MES. Examples of TCCD and ICA Doppler are depicted in Figure 1.

Both ICA and TCCD ultrasound were performed at rest and after a Valsalva maneuver. The Valsalva maneuver started 5 s after agitated saline injection and lasted 10 s. A reduction during the Valsalva maneuver of at least 30% of the mean blood flow velocities in the MCA was considered appropriate. The difficulty to perform the examinations, ICA and TCCD Doppler, was evaluated both at rest and during the Valsalva maneuver, and graded according to the operator perception.

The primary end point of the study was to evaluate the diagnostic accuracy of the index test (ICA Doppler ultrasound) in comparison to the reference standard (TCCD) for the diagnosis of RLS. The secondary end point was to evaluate ICA Doppler diagnostic accuracy considering different cut offs (MES $>$5 and MES $\geq$10 for RLS presence).

**Statistical analysis**

Diagnostic accuracy of detecting RLS by ICA Doppler Ultrasound was calculated with a 2 × 2 table using TCCD finding as reference standard and was expressed as sensitivity, specificity and negative likelihood ratios (LRs). Continuous
variables were expressed as mean ± standard deviation or median and interquartile range, accordingly. Two-tailed tests with a level of significance at \( P < 0.05 \) were used.

This study was approved by the local ethics committee, and informed consent was obtained before examination.

**RESULTS**

During the enrolment period, 64 patients were considered eligible for the study. Five patients were excluded: three of them did not have an adequate temporal window (neither right nor left) while for the remaining two, the carotid examination was impossible to perform due to a high difficulty in sampling the ICA during Valsalva maneuver. Thus, a total of 59 patients were ultimately enrolled in the study. The mean age was 49 years old, with 39 (66.1%) woman and 20 (33.9%) men. Each patient was submitted both to the TCCD and the ICA Doppler exam and evaluated in basal condition and during Valsalva, resulting in a total of 118 examinations. Thirteen (22%) patients were addressed to the eco Doppler laboratory after a TIA while 18 (30.5%) after a stroke. Table 1 shows the subjects baseline characteristics in detail.

The reference standard test (TCCD) resulted positive for RLS in 38 (64.4%) out of 59 patients. The test resulted positive in 28 (47.5%) tests at rest and in 10 (17.0%) tests after the Valsalva maneuver. The ICA Doppler ultrasound resulted positive for RLS in 36 (61.0%) out of 59 patients. Twenty-six (44.1%) tests were positive at rest and 10 (17.0%) tests became positive after Valsalva maneuver. In relation to the primary end point of the study, ICA Doppler sensibility and specificity were, respectively 97% (confidence interval [CI] 95%) and 100% (CI 95%), while negative LR was 0.03 (CI 95%), as illustrated in Table 2.

As planned in the secondary end point, the diagnostic accuracy of the ICA Doppler ultrasound in comparison to the TCCD was assessed using different cut offs [Table 3]. The best TCCD and ICA Doppler concordance was obtained using the > 5 MES cut off for both examinations, with sensitivity and specificity of 100%.

Considering the shunt gravity, the number of severe RLS found using TCCD was 22 (18.6%) while using ICA Doppler ultrasound was 20 (16.9%). Figure 2 shows the concordance of shunt severity assessed with TCCD and ICA Doppler ultrasound. There is a total concordance of 86%, which increases up to 99% when 1 Grade of discordance is tolerated.

Regarding the perceived difficulty to perform the examination, ICA Doppler ultrasound was easier compared to TCCD when carry out at rest, but it seemed more difficult during the Valsalva maneuver, due to the sliding of the carotid artery caused by sternocleidomastoid muscle contraction.

**DISCUSSION**

Our data show an adequate ICA Doppler ultrasound diagnostic accuracy for the diagnosis of RLS. In particular, we observed that ICA Doppler Ultrasound’s sensibility and specificity are respectively 97% and 100%, while negative LR is 0.03. Our study seems to confirm encouraging results provided by Perren et al. Although previous studies suggested an encouraging role of ICA Doppler ultrasound in detecting

Table 1: Baseline characteristics of the study population

| Characteristic       | mean(%)     |
|----------------------|-------------|
| Men, \( n \) (%)     | 20 (33.9)   |
| Women, \( n \) (%)   | 39 (66.1)   |
| Age (average) (SD)   | 49 (±14.48) |
| Ethnicities          |             |
| Caucasians, \( n \) (%) | 51 (86.4) |
| Afro-Americans, \( n \) (%) | 2 (3.4)   |
| Asians, \( n \) (%)  | 3 (5.1)     |
| Hispanics, \( n \) (%)| 3 (5.1)     |
| Exam’s reasons       |             |
| TIA, \( n \) (%)     | 13 (22.0)   |
| Strokes, \( n \) (%) | 18 (30.5)   |
| Sickle cell anaemia, \( n \) (%) | 2 (3.4)   |
| Thalassemia, \( n \) (%) | 4 (6.8)    |
| Peripheral ischemia, \( n \) (%) | 2 (3.4)   |
| Headache, \( n \) (%) | 6 (10.2)   |
| Others, \( n \) (%)  | 14 (23.7)   |

**Table 2: 2×2 table showing the results of transcranial color Doppler and Internal carotid artery Doppler ultrasound: Each number refers to the diagnosis of right-left shunt in the single patients**

| RLS diagnosis | TCCD+ | TCCD− | Total |
|---------------|-------|-------|-------|
| ICA Doppler+  | 36    | 0     | 36    |
| ICA Doppler−  | 1     | 22    | 23    |
| Total         | 37    | 22    | 59    |

TCCD+/−: Positive or negative TCCD. ICA Doppler+/−: Positive or negative ICA Doppler ultrasound. RLS=Right-left shunt, ICA=Internal carotid artery, TCCD=Transcranial color Doppler
RLS, the use of this technique in clinical practice is not yet routinely performed, even when TCCD window is not feasible. Two possible explanations may be hypothesized: the clinical evidence to support this diagnostic test is considered inadequate and the technical interpretation of the test is not sufficiently standardized. In relation to the former reasoning, our study supports the evidence of a good diagnostic accuracy of ICA Doppler in RLS diagnosis, demonstrated in a different laboratory in terms of country and clinical context compared to other studies. As for the technical aspect, we analyzed different cut offs for both examinations, estimating the diagnostic accuracy for each cut off. No guidelines formally identify a MES cut off for the diagnosis of RLS, even for the TCCD ultrasound. In order to maximize sensitivity, we decided to use the less restrictive cut off (≥1 MES) as TCCD/ICA Doppler tests are most often used as first level tests or screening tests. Moreover, we carried out both tests, TCCD and ICA Doppler ultrasound, simultaneously on each patient, to minimize the measurement error.

Deepening the purely clinical aspect of the discussion, considering the test indication and the characteristics of the individual patient is pivotal, because these data are going to influence the pretest probability and thus the posttest probability. Indeed, diagnosis is the result of a Bayesian process that combines the pretest clinical probability of a disease with the results and the diagnostic accuracy of a test. The higher the pretest probability, the lower should the test’s negative LR be to exclude the diagnosis. Hypothesizing a patient with a low pretest probability (i.e., <20%), a negative ICA Doppler Ultrasound examination is going to result in a posttest probability of RLS presence under 1%. In these patients, a negative ICA Doppler ultrasound can exclude with a high grade of certainty the RLS presence. On the contrary, for patients with high pretest probability (i.e., >50%), a negative ICA Doppler Ultrasound examination is not sensitive enough to exclude the diagnosis of RLS, because the postest probability of RLS in this population is still >20%, even in the presence of a negative ICA ultrasound. In this context, if the transcranial window is not available, performing a TEE instead is considered more appropriate.

From a practical point of view, we found ICA Doppler Ultrasound executions less difficult compared to TCCD at basal time [Table 4]. However, performing ICA ultrasound was more frequently difficult during Valsalva compared to TCCD. For this, it is preferable to employ the ICA Doppler ultrasound only when the transcranial window is not optimal.

One of the limitations of our study depends on considering TCCD as gold standard instead of TEE, for the identification of the RLS. Indeed, TCCD does not evaluate directly the interatrial septum, and does not differentiate between intracardiac shunts and extracardiac shunts; even though TCCD has a high diagnostic accuracy for the identification of the PFO, it is not completely comparable to TEE. On the other hand, since TCCD is now considered the elected first level test for the diagnosis of the RLS in clinical practice, it would not be ethically correct to use TEE as reference standard in our study.

Conclusions

Our study confirms that ICA Doppler Ultrasound is sufficiently accurate for the detection of RLSs and can be taken into consideration for patients with poor ultrasonic temporal windows. We suggest continuing to use TCCD to detect the RLS in clinical practice, because its diagnostic accuracy is supported by studies that compare TCCD to ETE, considered the gold standard to detect RLS. In those patients where the transcranial window is not available, we suggest using ICA Doppler Ultrasound to detect RLS, whenever the patient’s pretest probability is low.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Homma S, Sacco RL. Patent foramen ovale and stroke. Circulation 2005;112:1063-72.
2. Hara H, Virmani R, Ladich E, Mackey-Bojack S, Titus J, Reisman M, et al. Patent foramen ovale: Current pathology, pathophysiology, and clinical status. J Am Coll Cardiol 2005;46:1768-76.
3. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med 2012;366:991-9.
4. Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med 2013;368:1092-100.
5. Meier B, Kalesan B, Mattle HP, Khattab AA, Hillick-Smith D, Dudek D, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med 2013;368:1083-91.
6. Fiorelli EM, Carandini T, Gagliardi D, Bozzano V, Bonzi M, Tobaldini E, et al. Secondary prevention of cryptogenic stroke in patients with patent foramen ovale: A systematic review and meta-analysis. Intern Emerg Med 2018;13:1287-303.
7. Jauss M, Kaps M, Keberle M, Haberbosch W, Dorndorf W. A comparison of transesophageal echocardiography and transcranial Doppler sonography with contrast medium for detection of patent foramen ovale. Stroke 1994;25:1265-7.
8. Nemec JJ, Marwick TH, Khatib AJ, Davison MB, Chimowitz MI, Litowitz H, et al. Comparison of transcranial Doppler ultrasound and transesophageal contrast echocardiography in the detection of interatrial right-to-left shunts. Am J Cardiol 1991;68:1498-502.
9. Katsanos AH, Psaltopoulou T, Sergentanis TN, Frogoudaki A, Vrettou AR, Ikonomidou I, et al. Transcranial Doppler versus transthoracic echocardiography for the detection of patent foramen ovale in patients with cryptogenic cerebral ischemia: A systematic review and diagnostic test accuracy meta-analysis. Ann Neurol 2016;79:625-35.
10. Bogdahn U, Becker G, Winkler J, Greiner K, Perez J, Meurers B. Transcranial color-coded real-time sonography in adults. Stroke 1990;21:1680-8.
11. Perren F, Kremer C, Iwanovski P, Savva E, Landis T. Detection of right-to-left cardiac shunt in the absence of transcranial acoustic bone. J Neuroimaging 2016;26:269-72.
12. Seidel G, Kaps M, Gerriets T. Potential and limitations of transcranial color-coded sonography in stroke patients. Stroke 1995;26:2061-6.
13. Saedon M, Dilshad A, Tivas C, Virdee D, Hutchinson CE, Singer DR, et al. Prospective validation study of transorbital Doppler ultrasound imaging for the detection of transient cerebral microemboli. Br J Surg 2014;101:1551-5.
14. Nygren AT, Jogestrand T. Detection of patent foramen ovale by transcranial Doppler and carotid duplex ultrasonography: A comparison with transesophageal echocardiography. Clin Physiol 1998;18:327-30.
15. Draganski B, Blesch W, Holmer S, Koch H, May A, Bogdahn U, et al. Detection of cardiac right-to-left shunts by contrast-enhanced harmonic carotid duplex sonography. J Ultrasound Med 2005;24:1071-6.
16. Censori B, Partizguian T, Poloni M. Common carotid artery duplex for the bubble test to detect right-to-left shunt. Ultrasound Med Biol 2010;36:566-70.
17. Topcuoglu MA, Palacios IF, Buonanno FS. Contrast M-mode power Doppler ultrasonic in the detection of right-to-left shunts: Utility of submandibular internal carotid artery recording. J Neuroimaging 2003;13:315-23.
18. Mojadidi MK, Zhang L, Chugh Y, Eshtehardi P, Hovn nians N, Gevorgyan R, et al. Transcranial doppler: Does addition of blood to agitated saline affect sensitivity for detecting cardiac right-to-left shunt? Echocardiography 2016;33:1219-27.
19. Alexandrov AV, Sloan MA, Wong LK, Douville C, Razumovsky AY, Koroshetz WJ, et al. Practice standards for transcranial Doppler ultrasound: Part I-test performance. J Neuroimaging 2007;17:11-8.
20. American College of Radiology (ACR), Society for Pediatric Radiology (SPR), Society of Radiologists in Ultrasound (SRU). AIUM practice guideline for the performance of a transcranial Doppler ultrasound examination for adults and children. J Ultrasound Med 2012;31:1489-500.