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Research Article

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Diagnostic accuracy of transcranial doppler in the detection of patent foramen ovale: can it be considered a high-sensitivity screening test?

Abstract

Introduction: Patent foramen ovale (PFO) is an interatrial embryonic remnant that results in right-to-left (RLC) circulation communication, therefore associated with paradoxical embolic events. PFO is associated with cases of stroke of undetermined origin in young people, although it is present in approximately 30% of the general population and its incidental finding in complementary exams is common. The causal relationship has been explored in many published studies, and the search for high-risk markers has been the subject of numerous meta-analyses. Transcranial contrast Doppler (cTCD) is considered the screening test of choice because it is a low-cost, non-invasive diagnostic tool with high sensitivity and specificity. The exam considered the gold standard is the transesophageal echocardiogram (TEE). Methods: The database of the Neurosonology Laboratory of a University Hospital was used, reviewing information from 901 patients from January 2015 to May 2019. From this total (901), 217 patients who had undergone cTCD and TEE were included. The functional pattern by cTCD followed criteria previously published in the Latin American Consensus. Results: The assessment of the subgroup that had the cTCD and ETE performed, we found high sensitivity and specificity of cTCD when compared to the gold standard exam. Conclusion: Comparison of diagnostic tests for RLC resulted in a sensitivity of 95.9% and a specificity of 91.3%, with a PPV of 95.9% and a NPV of 91.3%.

Keywords: transcranial doppler, screening, stroke, sensibility, transesophageal echocardiography

Volume 13 Issue 3 - 2023

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Received: April 19, 2023 | **Published:** May 09, 2023

Introduction

Patent foramen ovale (PFO) is an opening between right and left atria. This communication is present during the intrauterine life, but it is expected to close after birth by the fusion of the *septum primum* and *secundum*. When such fusion does not occur correctly, the aperture persists through adult life.[1]. When this fusion does not occur correctly, the opening persists through adult life.[1] The involvement of PFO in the etiology of some ischemic strokes has been suggested, especially in the context of young patients (younger than 60 years) with a cryptogenic event.[2] Previously published studies have demonstrated a prevalence of PFO of 44-66% in patients with cryptogenic stroke. In comparison, the prevalence in the general population is 10-27% and in patients with stroke of defined etiology, it is 21-33%.[3–6]

Both transesophageal echocardiography (TEE) and transcranial Doppler (TCD) can be used as screening exams for PFO. TEE is considered the gold standard. Among the advantages of this method are the direct visualization of the right to left shunt (RLS), the anatomy of the atrial septum, and other embolic sources, such as left atrial enlargement, complex aortic arch atheroma, extracardiac shunts, endocarditis, and atrial mass.[7] However, TEE has some limitations. Patients are usually sedated and therefore unable to perform the Valsava maneuver (VM) correctly, which may impair the sensitivity of the test.[8] In addition, the examination is uncomfortable and has risks (esophageal bleeding or perforation) and contraindications, such as esophageal varices, Barrett's esophagus, carcinoma of the pharynx, and patients at high risk of bleeding.[9] Thus, TCD, a non-invasive, low-cost, readily available and repeatable test, presents itself as an alternative for the diagnosis of PFO. Some studies have found TCD to be more sensitive than TEE, but the accuracy of the exam may vary by center, protocol, and diagnostic criteria.[10–12]

The aim of this study was to establish the sensibility and specificity of TCD in comparison to TEE in a tertiary hospital reference in neurology in the south of Brazil.

Materials and methods

We conducted a retrospective, observational study consisting of database analysis with a cross-sectional, prospective component, with a variable collection. The database used was from the Laboratory of Neurosonology of the Hospital das Clínicas, Federal University of Paraná, which comprised patients from January 2015 to May 2019. We included patients who had performed both a TCD and a TEE for PFO investigation. The study was approved by the local ethics committee (CAAE 19474013.0.0000.0096).

Data were collected using a pre-specified online form (Attachment 1). The first part of the form consisted in demographic characteristics (age, sex and race) and year of the event (in case of stroke or TIA), or year of the exam (in case of patients on investigation for migraine or other causes). Regarding clinical characteristics, the bank divided patients into those who had suffered a stroke or TIA, and those who had migraine with aura or other causes for PFO investigation.

All cTCD studies were performed by a trained neurologist in a standardized protocol following a previous publication by the same group.[13] Patients were positioned in dorsal decubitus and an agitated saline solution was injected into a large venous access. The middle cerebral arteries were insonated bilaterally using a helmet. The injected solution was composed of 8 mL of 0.9% saline + 1 mL of air + 1 mL of the patient's blood. Three resting infusions were performed, as well as three infusions seconds before performing a Valsalva maneuver for sensitization. The passage pattern was then evaluated and properly recorded. The test was considered positive for PFO when

at least one micro-bubble of air was detected in the spectral display of at least one of the monitored arteries. Sensibility, specificity, positive and negative predictive values of TCD were calculated using a 2 x 2 table, considering TEE as the gold-standard exam.

Results

The study database comprises 701 patients who underwent PFO investigation with TCD, TEE and/or TTE. Of these, both TCD and TEE were performed in 217 patients (n = 217). The baseline characteristics of the study population are shown in Table 1 (demographic data). The clinical indication for the PFO study was ischemic stroke or transient ischemic attack (TIA) in 184 (84.79%) patients and other indications, including migraine, in 33 (15.21%) patients. Regarding TEE, 146 (67.2%) tests were positive for PFO, and 69 (31.8%) tests were negative in Table 2 (TCD versus TEE). However, six patients with a negative TEE result were positive on TCD. TCD had 95.9% sensitivity, 91.3% specificity, 95.9% positive predictive value, and 91.3% negative predictive value when compared to TEE.

Table 1 Demographic data

Clinical characteristics	N (%)
< 60 years	169 (77.88%)
> 60 years	48 (22.12%)
Sex	
Male	67 (30.88%)
Female	150 (69.12%)
Clinical indications	
Ischemic stroke	156 (71.89%)
Transient ischemic attack	28 (12.9%)
Migraine	16 (7.37%)
Others	17 (7.83%)

Table 2 TCD versus TEE for PFO identification

	TEE +	TEE –	Total
TCD +	142	6	148
TCD -	6	63	69
Total	148	69	217

TEE, transesophageal echocardiography; TCD, transcranial Doppler; PFO, persistent foramen ovale

Discussion and conclusion

In our study, TCD had a high sensitivity (95.9%) and specificity (91.3%) for PFO screening when compared to the gold standard. There was no positive TEE with negative TCD. Therefore, it is reasonable to say that TCD is a satisfactory screening test for PFO, mainly because it is capable of better functional assessment and quantification of microbubble passage with the patient without sedation and with an effective Valsalva maneuver. Although it is considered to be the gold standard for achieving a more adequate anatomical and structural assessment, some authors found that TEE failed to identify some shunts.[11,14,15] Other studies demonstrated that TCD was more sensible than TEE.[10–12] Hence, there are authors who question whether TEE should remain the gold standard. The accuracy of TCD may vary according to the institution's examination protocol and tends to have progressively better results, observing the learning curve of the services. Protocols may differ on the contrast agent used, diameter of venous access, unilateral or bilateral monitoring, duration of examination, and performance of the Valsalva maneuver.[13] In a previous study comparing TCD and TEE, the sensitivity of TCD was 92.85% and its specificity was 82.35%.[16]

A meta-analysis comparing TCD and transthoracic echocardiography (TTE) with TEE for investigation of PFO in patients with cryptogenic cerebral ischemic events yielded similar results to our study regarding TCD.[17] The sensitivity and specificity of the examination were 95.9% and 91.3%, respectively. Yang et al. found that TCD and TEE showed similar performances in investigating PFO, but TEE failed to identify three shunts detected by TCD and had a propensity to underestimate the severity of shunts.[9] These results are similar to those of Van et al., where TEE did not identify PFOs confirmed by transcatheter exam,[18] and of Sastry et al., in which all 39 patients with positive TEE had positive TCD, but three large shunts on TCD weren't classified as such in TEE.[19] Due to recent studies on surgical occlusion of the PFO, a safe and effective method is essential to assess the presence of the shunt as well as the functional assessment of the passage of microbubbles to avoid unnecessary surgical procedures. A previous study from the same service evaluated 20 patients after surgical occlusion of the PFO and concluded that most of them would still have passage of a residual MES 01 year after occlusion.[20]

Some advantages of TCD include the facts that it is a non-costly, non-invasive, and repeatable examination.[21] Since it is non-invasive, the exam can be performed without sedation, which allows for patient cooperation during the Valsalva maneuver.[17] In contrast to TEE, where the performance of the Valsalva maneuver is limited, which can lead to false-negative results.[8,22] In cases of surgical occlusion, TEE monitoring often shows shunt maintenance, but TCD is able to show that a less significant shunt exists in most cases, and it is possibly a better test for post-surgical monitoring of these patients. of these patients. In addition, Palazzo et al. demonstrated that TCD is more rapidly available than TEE.[23] The authors found that the average time between symptom onset and examination was two days for the TCD and 21 days for the TEE.

The viability of TCD, however, is limited by the presence of a temporal window. Ten to fifteen percent of patients do not have a satisfactory window for examination, even more often in Asians and Afro-descendants.[24] Furthermore, TCD does not allow a reliable distinction between intra- and extracardiac shunts. The time from contrast injection until the first bleb appears in the middle cerebral artery (MCA) can be used to estimate the location of the shunt, but this technique is still controversial in the literature as it may result in false-positive results.[25–27]

In conclusion, due to its accuracy, safety, low price, feasibility and availability, TCD is considered by many authors as the test of choice for PFO screening, especially in young patients with cryptogenic ischemic stroke.[7,23,28]. Such a recommendation is supported by the results of our study. However, TEE should be performed after a positive TCD in order to differentiate intra- and extracardiac shunts. TEE is also essential in candidates for PFO closure, as the procedure cannot be safely performed without prior direct visualization of the local anatomy, adequate characterization of the PFO (diameter and length), and identification of structures such as the Eustachian valve, Chiari network, and atrial septal aneurysm.[28] Considering a controversy about the best treatment, there is a need to recognize how the variables and individualize the tools that should be employed. We suggest that each service collect and apply its own data in order to facilitate the best possible decision.

Statement of ethics

This study protocol was reviewed and approved by the Ethics Committee in Research on Human Beings of the CHC-UFPR with waiver of the use of the free and informed consent term.committee name and affiliation, approval number [CAAE 19474013.0.0000.0096].

Citation: Costa RT, Zétola VHF, Martins GCL, et al. Diagnostic accuracy of transcranial doppler in the detection of patent foramen ovale: can it be considered a high-sensitivity screening test? *J Neurol Stroke.* 2023;13(3):46–48. DOI: 10.15406/jnsk.2023.13.00543

Acknowledgments

None.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding sources

This research didn't receive grants from any funding agency in the public, commercial or not-for-profit sectors.

Author contributions

Rebeca Teixeira Costa: Database organization, data collect, analysis and interpretation of results, writing-original draft and responsible for submission, writing review and editing. Viviane de Hiroki Flumignan Zétola: Creation of database, study conceptualization, supervision, writing review and editing. Gabriela Caetano Lopes Martins: Data collect, writing review and editing. Marcos Christiano Lange: Writing review and editing.

Data availability statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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