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TRANSCRANIAL DOPPLER FOR PATENT FORAMEN OVALE SCREENING

Is there a good correlation with transesophageal echocardiography?

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Abstract – Right-to-left shunt (RLS) can be identified by contrast-enhanced transcranial Doppler (cTCD) in patent foramen ovale (PFO) patients. **Aim:** To evaluate cTCD for PFO screening comparing it to cTEE. **Method:** 45 previous cTCD performed for PFO diagnosis and correlated its findings with cTEE. Patients were submitted to a cTCD standardized technique and were divided in two groups according to RLS: Group 1, patients with a positive RLS and Group 2 when RLS was negative. **Results:** 29 (65%) patients were included in group 1 and 16 (35%) in group 2. PFO confirmation by cTEE was performed in 28 (62%) patients. cTCD had a 92.85% sensitivity, 82.35% specificity, 89.65% positive predictive value and 87.5% negative predictive value when compared to cTEE for PFO diagnosis. **Conclusion:** Standardized technique cTCD allows for RLS visualization in PFO patients with a good correlation with cTEE and can be used as a screening test before cTEE.

KEY WORDS: patent foramen ovale, transesophageal echocardiography, transcranial Doppler, ultrasonography.

Doppler transcraniano contrastado para triagem de forame oval patente: existe boa correlação com ecocardiograma transesofágico?

Resumo – A comunicação direita-esquerda (CDE) pode ser identificada por Doppler transcraniano contrastado (DTCc) em pacientes com forame oval patente (FOP). **Objetivos:** Analisar o DTCc para triagem de FOP comparado a ecocardiografia transesofágica (ETEc). **Método:** Realizamos 45 exames de DTCc para diagnóstico de FOP e correlacionamos com os achados do ETEc. Os pacientes foram submetidos a técnica padronizada e divididos em dois grupos conforme a positividade do exame. **Resultados:** 29 (65%) pacientes foram incluídos no grupo 1 (CDE positiva) e 16 (35%) no grupo 2 (CDE negativa). A confirmação do FOP pelo ETEc ocorreu em 28 (62%) pacientes. O DTCc apresentou sensibilidade de 92,85%, especificidade de 82,35%, valor preditivo positivo de 89,65% e valor preditivo negativo de 87,5% comparado ao ETEc para o diagnóstico de FOP. **Conclusão:** A técnica padronizada de DTCc possibilita a visualização de CDE em pacientes com FOP com boa correlação com o ETEc.

PALAVRAS-CHAVE: forame oval patente, ecocardiograma transesofágico, Doppler transcraniano, ultrasonografia.

Patent foramen ovale (PFO) is a congenital heart disease characterized by an opening between the right and left atria resulting from incomplete closure of the *ostium secundum* by the *septum secundum*[1]. Recent studies have found an increase prevalence of PFO in women with migraine with aura and young adults (less than 55 years old) with so-called "cryptogenic" ischemic stroke[2-6]. Emboli from the venous system can cross the PFO reaching the arterial circulation through a right-to-left shunt (RLS) and thus leading to a stroke. PFO diagnosis is done by using a contrast-enhanced technique (by injecting saline solution in a peripheral vein) while performing a transesophageal echocardiography (cTEE) and, when positive, it shows a high correlation with necropsy studies[7]. In spite of both high sensibility and specificity, cTEE have some limitations, such as expensiveness, patient's low tolerability and imperfect intra and inter-observer correlation, due to the fact that it is an operator-dependent method[8]. A great ad-

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vantage of this method is the direct visualization of interatrial septum and atrial septal aneurysm (ASA) identification. ASA is an abnormally redundant *septum primum* flap that extends across the atria[9]. When ASA is associated with PFO, this combined pathology leads to an increase in the risk factor for recurrence of embolic "cryptogenic" stroke[6].

On the other hand, contrast-enhanced transcranial Doppler (cTCD) is a low cost, non-invasive method, which is easy to perform and to interpret as a screening method for PFO diagnosis. Even though cTCD is known as a diagnostic tool with high sensibility, techniques for performing TCD vary according to some authors[2,5,10-12].

The primary aim of this study was to standardize cTCD technique for RLS as a screening method for PFO. Secondarily we tried to establish the sensibility and sensitivity of this method when compared with cTEE.

METHOD

We retrospectively analyzed 45 cTCD and cTEE studies for PFO investigation from April 2005 to May 2007. All studies were done after a thorough clinical and neurological evaluation and all patients gave their written, informed consent. Clinical indication for RLS investigation was stroke on 41 patients and migraine on the remaining four.

Contrast-enhanced transcranial Doppler ultrasound

All cTCD studies were performed with the patient in a supine position in a controlled temperature environment (24 to 28ºC) by a trained neurologist (Doctors MCL, VFZ, JAM). The equipments used were a RIMED – Smart Lite or a DWL – Doppler Box, both with two 2-MHz transducers. Bilateral middle cerebral arteries (MCA) were insonated through the temporal window at a depth of 50 to 60 mm and fixed with a helmet, as described elsewhere[13]. Contrast consisted of 10 mL air-mixed saline solution (9 mL of normal saline solution + 1 mL of air) injected as a bolus into a large right antecubital vein while resting (resting phase) and before Valsalva maneuver (VM). The Valsalva maneuver was performed five seconds after intravenous contrast injection and its effectiveness was monitored by a 25% decrease of MCA flow velocity. Both studies (resting phase and VM phase) were repeated three times, with each test lasting one minute. A right-to-left shunt (RLS) was considered positive (Group 1) when at least one air microbubble was detected on the spectral display of at least one of the monitored MCA. Conversely, RLS was negative (Group 2) when during the next 60 seconds following contrast injection there was no identified microbubble in either MCA. Patients with a positive test were classified in two grades: small RLS (≤ 10 bubbles) and large RLS (>10 bubbles), the latter subgroup was further labeled as a "curtain" RLS if uncountable signals passed during MCA monitoring. In addition, we separated Group 1 in two other subgroups: positive only during VM phase and positive at rest and with the VM. Finally we compared results from cTCD with cTEE.

Contrast-enhanced transesophageal echocardiography

All patients underwent cTEE, which was performed by a cardiologist trained in this technique (Dr. AMS). All exams were done with a Hewlett Packard Sonos 5500 imaging system and a 5MHz wide-band multiplane transducer. Patients were examined in the fasting state and received only local pharyngeal anesthesia (topical lidocaine spray). For the diagnosis of a RLS, contrast consisted of 10 mL air-mixed saline solution (9 mL of normal saline solution + 1 mL of air) injected as a bolus into a large antecubital vein during resting and after Valsalva maneuver. Patients were trained in performing the VM before the procedure with a five seconds' duration. The effectiveness of the VM was verified by observing the bulging of the interatrial septum into the left atrium. The presence of a PFO was assumed if at least one microbubble passed from the right to the left atrium on the first three cardiac cycles after contrast injection. An ASA was presented if interatrial septum moved more than 10 mm in either atrium side during systole.

Statistical analysis was performed with SPSS 12.0 software (SPSS Inc.). Statistical significance was assessed by t-Student test for parametric variables and Chi-Square or Mann Whitney tests were used for non-parametric variables. Correlation tests were done for etiological and risk factors with RLS grades by cTCD. Statistical significance was determined at $p<0.05$.

RESULTS

A total of 29 (65%) patients had positive RLS (Group 1): mean age was 38±14.6 years and 17 (57%) were females. The other 16 (35%) patients had a negative RLS (Group 2), with a mean age of 37±11 years. In this group 11 (68%) patients were females. There was no statistical difference between groups for demographic variables (age and gender distribution) (Table 1).

Table 1. Demographic data.

	Group 1 (positive RLS)		Group 2 (negative RLS)		p
	n (%)	Mean age±sd	n (%)	Mean age±sd	
Gender distribution					
Female	17 (58.62)	39.7±12.49	11 (68.75)	36.9±11.68	0.706*
Male	12 (41.38)	36.75±17.65	5 (31.25)	37.2±10.7	0.792*
Total	29 (64.44)	38.48±14.62	16 (35.56)	37±11.02	0.734*

RLS, right-to-left shunt; *Mann-Whitney test.

Table 2. Clinical indication for RLS investigation and stroke risk factors.

	Group 1 (n=29) n (%)	Group 2 (n=16) n (%)	EP+ × EP– p
Indication			
Ischemic stroke	26 (90)	15 (93)	0.432*
Migraine	3 (10)	1 (7)	0.616**
Stroke risk factors			
HBP	3 (10)	6 (37)	0.031*
DM	1 (3.5)	1 (6.25)	0.666*
HCh	3 (10)	1 (6.25)	0.648*
CS	4 (14)	2 (12.5)	0.904*

HBP, high blood pressure; DM, diabetes mellitus; HCh, hypercholesterolemia; CS, cigarette smoking; *Mann-Whitney test; **Chi-square test.

Table 3. Bubble findings in Group 1 (n=29).

	Total n	Rest n (%)	VM sensibilized n (%)	Rest × VM sensibilized p
Small	10	3 (30)	7 (70)	0.006*
Large	19	17 (89)	2 (11)	0.562*
Curtain	13	12 (92)	1 (8)	0.039*

Small: ≤10 bubble; large: >10 bubble; curtain- uncountable signals; rest represents patients with positive RLS study both at rest and during VM study; VM sensibilized represents patients with RLS study positive only during VM test; *Mann-Whitney test.

Clinical indication for RLS study in Group 1 was stroke in 26 (90%) patients and migraine in the remaining three (10%). For Group 2, 15 (93%) patients were evaluated for stroke and one (7%) for migraine. There was no statistical difference between the two groups (Table 2).

In Group 1 four (14%) patients were cigarette smokers, three (10%) had high blood pressure, three (10%) had hypercholesterolemia and one (3.5%) had diabetes. In Group 2 two (12.5%) patients were smokers, six (37%) had high blood pressure, one (7%) had hypercholesterolemia and one (7%) had diabetes. There was no statistical difference between groups for any of the risk factors, except for high blood pressure that was more common in Group 2 (p=0.031) (Table 2).

In relation to RLS grade in Group 1, ten (34%) patients had a small RLS and 19 (66%) had a large RLS, of the latter 13 (68%) had a "curtain" effect on cTCD (Table 3). In Group 1, 20 (69%) patients had a positive RLS during both phases (resting and VM), nine (31%) had a positive RLS only during VM phase, seven (77%) presented with a small RLS and two (22%) with a large RLS; of those, only one (11%) presented with a curtain effect (Table 3).

When VM was performed we could recognized a positive RLS increase in 45%, which was more significant in the small RLS subgroup (a 200% increase) than in the large RLS subgroup (11% increase). No patient in the study had positive test only while resting.

Table 4. Contrast-enhanced TCD versus contrast-enhanced TEE for PFO identification.

	cTEE+	cTEE–	Total
cTCD +	26	3	29
cTCD –	2	14	16
Total	28	17	45
Sensibility: 92.85%; Specificity: 82.35% Positive predictive value: 89.65%; Negative predictive value: 87.50%			

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

After comparing RLS during both the resting phase and VM *versus* RLS triage only in the VM phase we found the following results: for the small grade RLS subgroup (n=10) there is a statistical significance for VM test (p=0.006), however for the large grade subgroup (n=19) there is no statistical significance (p=0.562) between the two techniques. Also, when the "curtain" RLS subgroup was studied, we found that for those patients undergoing the combined the resting test and VM phases there was a significant finding for RLS when compared with the isolated VM phase (p=0.039).

Contrast-enhanced transesophageal echocardiography, the so-called gold-standard technique for PFO identification, was positive in 28 (62%) patients and negative on

the others 17 (38%). When we compared cTCD versus cTEE, we could identify two patients from group 2 with a positive cTEE and three from group 1 with a negative cTEE (one with a small RLS and two with a large RLS) (Table 4). Thus, cTCD for PFO diagnosis had a 92.85% sensibility, 82.35% specificity, 89.65% positive predictive value and 87.5% negative predictive value when compared to cTEE (Table 4).

In addition, three patients from group 1 had a positive ASA on cTEE, all of which had a large RLS by cTCD (two of them with a "curtain" effect). This corresponded to 15% of all large RLS grade cTCDs. Conversely, none of the patients in group 2 had ASA.

We found a good correlation between headache and "curtain" RLS (p=0.013) and stroke and large RLS (p=0.039), but not for other risk-factors as high blood pressure, diabetes, hypercholesterolemia and cigarette smoking.

DISCUSSION

Our study confirmed that cTCD can be safely performed as a screening method for suspected PFO in patients with either stroke or migraine prior to a cTEE study, with a high sensibility (92.85%) and specificity (82.35%). A standardized technique was important for these results with a VM test leading to a 45% increase the positive results.

cTCD is a non-invasive, low cost test, which also can be easily repeated and is well tolerated by the patients. Time and again cTCD was proved to be a valuable toll in the evaluation of stroke and others neurological diseases[5,14]. Our study showed similar results of cTCD when compared to cTEE for PFO evaluation as previously published in both national and international studies with a sensibility ranging from 66% to 100% and a specificity of 62% to 100%[2,5,10-12,15-19].

We highlight that the finding of positive RLS by cTCD with negative cTEE, as in three of our cases, can correspond to a cTEE false-negative. This can be due to several factors, such as an inadequate transesophageal window, negative contrast effect at right atrium and high pressure levels in the left atrium without flow inversion crossing the PFO from the right atrium to the left one[20-23]. This can also occur in the setting of an extracardiac shunt, such as a pulmonary arteriovenous fistula[24]. Using cTCD, the timing from contrast injection until identification of the first bubble on the MCA can be used to differentiate between a cardiac and an extracardiac shunt: if the first bubble is identified in up to 11 seconds after contrast injection, the RLS is considered cardiac; on the other hand, if the time until identification of the first bubble is over 14 seconds, the shunt can be considered to be extracardiac in origin. However, this remains a controversial topic in the literature and there is no consensus regarding this criterium, which we could not confirm in our study[10].

A positive cTEE with a negative cTCD for the evaluation of PFO, as found in two of our patients, can occur if the PFO is a small one, thus impairing cTCD sensitivity when it is performed by insonating only two brain vessels or if there is some kind of limitation that prevents the patient from performing the VM correctly.

VM evaluation led to an increase of 45% in RLS identification. This finding is more significant in patients with a small RLS. In order to avoid misdiagnosis, a negative resting test should be complemented by a VM test. VM increases the pressure in the right atrium causing a flow inversion across the PFO that cannot be observed in the resting phase. We cannot overstress the significance of the VM in the diagnosis of RLS, as several strokes result from embolization occurring in similar high-pressure settings such as the cuff maneuver and physical activity[25]. Incorrectly performed VM studies are due to uncooperative patients who fail to perform the maneuver properly, in ICU patients who are intubated and in assisted mechanical ventilation, if sedatives were used prior or concurrently with the cTCD and in patients with cognitive impairment.

It is also important to emphasize that the majority of patients with a positive RLS had a large RLS (66%), with a curtain pattern occurring in 68% of these patients and in 45% of all patients. Previous studies have already established the importance of quantitative evaluation related to stroke reccurrence[5].

Only three patients with PFO plus ASA were identified, all of whom had a large RLS. We hypothesize that the association of ASA and PFO has a high probability of RLS, which can be identified by cTEE in those patients with a large shunt. This dual pathology could increase RLS and recurrence of stroke as showed in previous studies[6].

Finally, we concluded that cTCD performed with a standardized technique is an excellent method for PFO identification, with both high sensibility (92.85%) and specificity (82.35%) when compared to cTEE. It is important to perform either test both while resting and under VM in order to increase these values. Availability, low cost and a less invasive technique are important features that allow the neurologist to perform a cTCD study prior to cTEE when investigating for PFO. In addition, cTCD findings can be used when performing a follow-up test after surgical or percutaneous closure of PFO.

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