INTRODUCTION
Patent foramen ovale (PFO) is a common abnormality of fetal origin causing right-to-left shunts which are associated with a variety of severe pathological processes like cryptogenic stroke, vein-to-artery gas embolism associated with decompression sickness in divers and even systemic hypoxemia1.

Diagnosis of PFO is achieved mainly with echocardiographic techniques like TransThoracic Echocardiography (TTE) and TransEsophageal Echocardiography (TEE), while TransCranial Doppler (TCD) is another method commonly used. Among them TTE is of limited diagnostic power, while TEE is considered the golden standard for detection of PFO2. Unfortunately, TEE is a semi-invasive, unpleasant procedure for a patient that requires mild sedation1. On the contrary, TCD is an easy-to-perform, non-invasive technique4, simple and friendly to the patient. Moreover there is an ongoing effort to associate the findings on TCD, with the presence and size of PFO. Generally, TCD is considered a reliable technique for diagnosis of PFO5-8, even though there are some objections on its accuracy9 and is therefore of limited use10. Yet, there is only a small number of studies investigating the association between microembolic (HITS) signals on TCD and the size of PFO11-13 with controversial results.

This study was designed to investigate the correlation between the presence and size of PFO with the findings of TCD in healthy volunteers and patients with ischemic stroke or other pathological conditions associated with right-to-left shunt.

Original Article

PFO size estimation using TCD: Are the measurements gender related?

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ABSTRACT: There is an ongoing interest in using the findings of Transcranial Doppler (TCD) as a diagnostic technique for patent foramen ovale (PFO) determination. The aim of this study was to investigate the sensitivity of TCD for detection of PFO presence and the correlation of PFO size with the detected microbubble signals. The study group comprised of 103 individuals, healthy volunteers and patients with ischemic stroke or other cerebrovascular diseases. TCD was performed on all subjects, while the presence and size of PFO was estimated with Transesophageal Echocardiography (TEE). PFO diagnosis with TCD had a 92.68% sensibility, 89.47% specificity, 86.65% positive predictive value and 94.44% negative predictive value. PFO size was moderately correlated with the number of microembolic signals detected (r = 0.404, p = 0.026). Further analysis for gender shown a strong correlation for men (r = 0.781, p = 0.003), but no correlation for women (p = 0.92). Our results show that TCD is a good predictor of PFO in terms of sensibility and specificity. The correlation between the size of PFO on TEE and the number of microembolic signals detected on TCD is gender biased. Further anatomic and physiological studies are required to identify the reasons for this phenomenon.

Key Words: PFO, Transcranial Doppler, Gender.

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PATIENTS AND METHODS

Patients
The study group was comprised of 103 individuals, 61 males and 42 females (age 15 to 81 years), healthy volunteers (60), and patients with ischemic stroke or other cerebrovascular diseases (43), with or without a history of PFO. In all subjects TCD was performed as part of the diagnostic process. The presence of PFO as well as its size were recorded from the medical history of the patient or evaluated with TEE after the TCD examination if possible. Patients with microemboli detected on TCD and PFO were classified according to age into two groups (<45 years and ≥ 45 years).

The study was approved by the Bioethics and Deontology Committee of the Medicine School of Aristotle University of Thessaloniki, Greece.

TCD
TCD was performed with the patient in a supine position. The equipment used was a Multi-Dop T (DWL, Germany) device with 2 MHz probes. Bilateral middle cerebral arteries (MCA) were insonated through the temporal window at a depth of 50 to 60 mm. Contrast consisted of 10 ml air-mixed saline solution, (9 ml of normal saline solution and 1 ml of air), injected as a bolus twice into a large right antecubital vein, while resting and before Valsalva maneuver (VM). The VM was performed five seconds after intravenous contrast injection. A right-to-left shunt was considered positive when at least one High Intensity Transient Signal (HITS) was recorded between 5 and 20 seconds after the injection of contrast. Only HITS of amplitude ≥ 12dB were recorded for both MCAs. For each patient the time required for the first HITS to appear, the number of HITS, and the mean HITS amplitude were estimated after the examination from the record file using monitor software MF (DWL Elektronisch Systeme GmbH) ver. 8.27.

TEE
TEE was performed under local anesthesia. A Philips iE33 xMATRIX Echocardiography System, 3D/2D (Philips Healthcare, Hamburg, Germany) was used. The size of PFO was measured by 2D TEE mode as maximal diameter of PFO defect.

STATISTICAL ANALYSIS
The relationship between the size of PFO on TEE and the various parameters recorded on TCD were evaluated with Spearman’s correlation coefficient ($r_s$). All statistical tests were two-tailed and level of significance was set at $p < 0.05$. Student’s t-test was applied for means comparison. Data were analyzed using SPSS ver.18 for windows.

RESULTS
Transcranial Doppler examination revealed the presence of HITS in 47 of 103 subjects. Only 3 patients with diagnosed PFO were not identified with TCD. In 4 patients without PFO, as shown in TEE, a relatively small number of HITS (7-14) were recorded only after VM. Finally in 5 patients with HITS on TCD it was not possible to identify the presence of PFO due to lack of TEE data. The comparison of TCD versus TEE results are indicated in Table 1. PFO diagnosis as presence of HITS on TCD had a 92.68% sensitivity, 89.47% specificity, 86.65% positive predictive value and 94.44% negative predictive value.

<table>
<thead>
<tr>
<th>TCD+</th>
<th>TEE-</th>
<th>Total</th>
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<tbody>
<tr>
<td>38</td>
<td>6</td>
<td>44</td>
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<tr>
<td>3</td>
<td>51</td>
<td>54</td>
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<tr>
<td>Total</td>
<td>41</td>
<td>57</td>
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Among the 38 individuals with PFO and HITS on TCD, 22 gave HITS without VM, while in 16 the performance of VM was necessary for HITS to appear. The size of PFO was evenly distributed between the two groups (Kolmogorov-Smirnov Test, $p > 0.751$).

The maximum diameter of PFO was measured with TEE to 31 individuals (15 males and 16 females). There was a statistically significant moderate correlation between the maximum diameter of PFO and the number of HITS after the Valsalva maneuver ($r_s = 0.404$, $p = 0.026$) while there was no correlation between the maximum diameter of PFO and gender ($p = 0.428$), age ($p = 0.795$), first HITS time ($p = 0.693$) or mean amplitude of HITS ($p = 0.121$).
Further analysis for gender (Figure 1) showed that there was no correlation between the maximum diameter of PFO and the number of HITS in women \( (p = 0.920) \), while there was a strong correlation in men \( (r_s = 0.781, \ p = 0.003) \). Only in men, the number of HITS was also correlated moderately with the time of first HITS \( (r_s = -0.565, \ p = 0.013) \). Another difference between genders observed, was that the average time for the first HITS is shorter for women \( (t = 2.114, \ p = 0.041) \). This difference was more clear for young patients \( (age < 45) \) \( (p = 0.009) \) while there was no difference in patients older than 45 years \( (p = 0.685) \).

The group of healthy volunteers, consisted of 60 individuals. None of these subjects had a history of PFO, but 4 of them (5%) presented HITS on TCD. A TEE was performed for 1 of these subjects and it was positive for PFO, but no TEE was available or possible to perform on the remainder 3 of them in order to reach a definite diagnosis. In total, 47 subjects out of the 103 (45.63%), 22 males and 25 females, were found positive for HITS on TCD; of them 38 (80.85%) had a positive diagnosis of a PFO, 4 (8.5%) were found negative for PFO on TEE, 2 (4.25%) had other heart defects producing a right-to-left shunt, while on 3 individuals (6.12%) there was no information on the presence or absence of PFO or other related disorders.

**DISCUSSION**

In our study 41 individuals out of a sample of 103 subjects (39.8%) presented with a PFO, a percentage which appears to be higher than the incidence of PFO in the general population (27%)\(^1\). This can be attributed to the fact that a high percentage of our sample (43 subjects – 41.7%) were patients suffering from cerebrovascular disease, given the theory that PFO could contribute to this condition.

Our results indicated that TCD is a good predictor of PFO both in terms of sensibility and specificity. A recent retrospective study of 45 patients for PFO screening\(^{14}\) gave very similar percentages of sensibility (92.84%) and specificity (82.35%) between TEE and TCD, while the general accepted values\(^{15}\) are between 90% and 95% although it can vary\(^{16}\). Other transcranial sonographic methods gave similar results\(^{17}\).

Although in the literature the diagnosis of PFO with TCD is considered a generally accepted method\(^{18-19}\), the data on the correlation between the microembolic signals on TCD and the size of PFO are very limited\(^11\). In our study a significant correlation was found between PFO size measured by 2D TEE and the number of HITS detected on TCD but this correlation is gender biased as female patients shown no
correlation between the size of PFO and the number of HITS counted.

Telma et al.\textsuperscript{11}, also found a significant correlation between the size of PFO on TEE and the number of microembolic signals detected on TCD. One limitation in their work was the semi-quantitative nature of their data (the exact size of PFO was not known in all patients); a problem absent in our study. Telman\textsuperscript{12} in his response to the criticism of Sharma\textsuperscript{13} implies that gender may be a critical factor in PFO studies, with no further elaboration. Other studies\textsuperscript{20} noticed the effect of gender on the association of PFO with embolic signals on TCD, revealing the need for additional research on the reasons behind these gender related differences.

Transcranial Doppler studies\textsuperscript{21-22} have shown a sex-depended hemispheric difference in mean flow velocity in the left middle cerebral artery, and changes of cerebrovascular reactivity associated with menopause and the protective role of oestrogens on the vascular system. In any case no clear aetiology is given up to date and therefore further anatom-o-physiological studies are required.

List of abbreviations

PFO: Patent Foramen Ovale
TEE: TransEsophageal Echocardiography
TCD: TransCranial Doppler
HITS: High Intensity Transient Signal

Εκτίμηση ανοικτού ωοειδούς τρήματος με τη χρήση του ενδοκρανίου Doppler.

Υπάρχει συσχέτιση με το φύλο του εξεταζομένου;

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ΠΕΡΙΛΗΨΗ: Το ενδιαφέρον για τη χρήση των ευρημάτων του διακρανιακού Doppler (TCD) ως μιας διαγνωστικής τεχνικής για την καθορισμό της παρουσίας ανοικτού ωοειδούς τρήματος (PFO) είναι συνεχώς αυξανόμενο. Σκοπός αυτής της μελέτης είναι η διερεύνηση της ευαισθησίας του TCD για την ανίχνευση της παρουσίας PFO και η συσχέτιση του μεγέθους του PFO με τα μικροέμβολα που ανιχνεύονται. Η ομάδα μελέτης περιελάμβανε 103 άτομα, υγιείς εθελοντές και ασθενείς με ισχαιμικά εγκεφαλικά επεισόδια ή άλλες αγγειακές εγκεφαλικές νόσους. Σε όλα τα άτομα πραγματοποιήθηκε TCD, ενώ η παρουσία και το μέγεθος του PFO εκτιμήθηκαν με διοισοφάγειο υπερηχογράφημα (ΤΤΕ). Η διάγνωση του PFO από τα δεδομένα του TCD παρουσίασε 92,68% ευαισθησία, 89,47% ειδικότητα, 86,65% θετική διαγνωστική αξία και 94,44% αρνητική διαγνωστική αξία. Το μέγεθος του PFO συσχετίστηκε μετριά με τον αριθμό των μικροεμβόλων που ανιχνεύονται (r = 0.404, p = 0.026). Η συσχέτιση των αποτελεσμάτων με το φύλο εδάφει μια σημαντική συσχέτιση για τους άντρες (r = 0.781, p = 0.003) και έλλειψη συσχέτισης για τις γυναίκες (p = 0.92). Τα αποτελέσματα υποδηλώνουν ότι το TCD έχει καλή προγνωστική αξία για την παρουσία PFO. Η συσχέτιση του μεγέθους του PFO, όπως καταγράφεται με TCD, και του αριθμού των μικροεμβόλων που ανιχνεύονται με TCD επηρεάζεται από το φύλο. Η κατανόηση αυτής της διαφοροποίησης απαιτεί επιπρόσθετες ανατομικο-φυσιολογικές μελέτες.
REFERENCES


