

## 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 ( $r_s = 0.404$ ,  $p = 0.026$ ). Further analysis for gender shown a strong correlation for men ( $r_s = 0.781$ ,  $p = 0.003$ ), 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.

### 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 hypoxemia<sup>1</sup>.

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 PFO<sup>2</sup>. Unfortunately, TEE is a semi-invasive, unpleasant procedure for a patient that requires mild sedation<sup>3</sup>. On the con-

trary, TCD is an easy-to-perform, non-invasive technique<sup>4</sup>, simple and friendly to the patient. Moreover there is an ongoing effort to associate the findings on TCD, with the presence and the size of PFO. Generally, TCD is considered a reliable technique for diagnosis of PFO<sup>5-8</sup>, even though there are some objections on its accuracy<sup>9</sup> and is therefore of limited use<sup>10</sup>. Yet, there is only a small number of studies investigating the association between microembolic (HITS) signals on TCD and the size of PFO<sup>11-13</sup> 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.

## 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 (< 45years and  $\geq$  45years).

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  $\geq$  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% sensibility, 89.47% specificity, 86.65% positive predictive value and 94.44% negative predictive value.

**Table 1.** TCD versus TEE for PFO identification. (+: presence of PFO, -: absence of PFO).

	TEE+	TEE-	Total
TCD+	38	6	44
TCD-	3	51	54
Total	41	57	98

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 ( $p = 0.121$ ).



correlation between the size of PFO and the number of HITS counted.

Telma et al.<sup>11</sup>, 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<sup>12</sup> in his response to the criticism of Sharma<sup>13</sup> implies that gender may be a critical factor in PFO studies, with no further elaboration. Other studies<sup>20</sup> 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<sup>21-22</sup> have shown a sex-dependent 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 ενδοκράνιου 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 τον 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 διωσοφάγειο υπερηχοκαδιογράφημα (TTE). 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 μετρία με τον αριθμό των μικροεμβόλων που ανιχνεύονται ( $r_s = 0.404$ ,  $p = 0.026$ ). Η συσχέτιση των αποτελεσμάτων με το φύλο έδειξε μια ισχυρή συσχέτιση για τους άντρες ( $r_s = 0.781$ ,  $p = 0.003$ ) 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 TTE, και του αριθμού των μικροεμβόλων που ανιχνεύονται με TCD επηρεάζεται από το φύλο. Η κατανόηση αυτής της διαφοροποίησης απαιτεί επιπρόσθετες ανατομικο-φυσιολογικές μελέτες.

*Λέξεις Κλειδιά:* Ανοικτό ωοειδές τρήμα, Ενδοκράνιο, Ενδοκρανιακό, υπερηχογράφημα, Υπερηχογραφία, Doppler.

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