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CLINICAL INVESTIGATIVE STUDY

Estimation of patent foramen ovale size using transcranial Doppler ultrasound in patients with ischemic stroke

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Abstract

Background and Purpose: Patent foramen ovale (PFO)is associated with cryptogenic stroke, especially in young adults. Transcranial Doppler (TCD) ultrasound is used as a screening tool before transesophageal echocardiography (TEE). However, the use of Valsalva maneuver (VM) to identify a right-to-left-shunt underlies interindividual variability. Here, we aimed to assess whether a pressure-controlled standardization of VM is useful to estimate PFO size.

Methods: We included patients aged 18–80 years with a PFO according to TEE. Subjects underwent TCD with microembolic signals (MES) counted under four pressure conditions (i.e., at rest, 15 mbar, 40 mbar, and maximum expiratory pressure). Findings were correlated with TEE-based PFO size. The predictive value of TCD at rest and VM-based TCD for PFO size estimation was assessed by stepwise multivariate linear regression models and multiple cross-tab-analyses.

Results: We screened 203 subjects after a cerebrovascular event, of which 78 (48 males [61.5%], median age 55 years [22–80]) with PFO were included. We found an association between MES count and expiratory pressure ($p < .001$). Predefined MES count categories at TCD pressure conditions correlated significantly with PFO size measured by TEE. We propose a PFO size estimation model based on TCD at rest and under VM, which classified PFO size correctly in 64.1% with the highest accuracy for small PFOs.

Conclusion: Our data provide evidence that TCD with step-wise barometric standardization allows an estimation of PFO size with good accuracy. Though TCD will not replace TEE in future, this might be of clinical value in circumstances where TEE cannot be easily performed.

KEYWORDS
barometric control, patent foramen ovale, stroke, transcranial Doppler ultrasound, transesophageal echocardiography, Valsalva maneuver

INTRODUCTION

Patent foramen ovale (PFO) is a congenital remnant of the fetal circulation, representing the major pathway between the venous and the arterial system, which may persist into adulthood in approximately 25% of the general population.[1] Although asymptomatic in the vast majority of individuals, PFO is significantly associated with ischemic stroke due to paradoxical embolism, especially in young adults with no additional cardiovascular risk factors (i.e., cryptogenic stroke).[2]

In clinical practice, the Risk of Paradoxical Embolism (RoPE) score, considering patient age, stroke localization, and concomitant cardiovascular risk factors, is frequently used to assess a causal relationship between a PFO and ischemic stroke.[3] Moreover, PFO size represents an independent risk factor of stroke occurrence and recurrence.[4] Hence, a thorough risk assessment based on RoPE score and morphological PFO features seems particularly important, as recent evidence derived from three randomized-controlled trials consistently demonstrated a therapeutic benefit of PFO closure for patients below 60 years with cryptogenic stroke.[5–7]

In view of the abovementioned treatment implications, screening for PFO plays an increasingly relevant role in the diagnostic work-up of patients with ischemic stroke. While a PFO may be detected by transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) remains the current gold standard and allows to precisely assess its morphology and size.[1,8] Yet, its routine application is often bedeviled by the reduced compliance of patients with neurological deficits or by the medication-induced sedation that may be necessary to capture anatomical details by TEE.

Complementarily, the hemodynamic significance and the severity of a potential right-to-left shunt (RLS) can be assessed indirectly by the less invasive transcranial Doppler (TCD) ultrasound, which is a well-established and highly sensitive screening tool.[9,10] To this end, agitated saline is injected into a peripheral vein and in case of RLS, microembolic signals (MES) can be detected by transcranial ultrasound of the middle cerebral artery (MCA). This procedure is usually performed in resting state (i.e., without forced expiration) and during Valsalva maneuver (VM) with maximal achievable expiratory pressure (EP). Depending on the number of observed MES, the following four categories have been proposed: (1) 0 MES (negative); (2) 1–10 MES; (3) >10 MES and no curtain; and (4) curtain (meaning a shower of MES with no single bubble being identified).[11]

One previous study indicated that the size of a PFO measured by TEE significantly correlates with the amount of MES observed by TCD.[12] A concordance between the two methods was also found when they were performed simultaneously.[13] However, maximum EP is likely to show marked interindividual variability, thus limiting generalizable conclusions regarding PFO size and RLS classification. Another group used controlled strain pressures and showed a correlation between pressure values and the count of MES, suggesting that a barometrically controlled VM may be useful for a reproducible shunt assessment.[14] It has also been shown that a pressure- and time-controlled modified VM may yield a higher rate of RLS detection when compared to coughing alone.[15,16]

To the best of our knowledge, no previous study has evaluated whether the size of a PFO (measured by the current gold standard TEE) can be reliably predicted by TCD, when standardized EPs are used during VM. To fill this gap in the literature and to facilitate the diagnostic work-up of PFO in a clinical real-life setting, we performed a prospective study to investigate the diagnostic value of indirect PFO size estimation using TCD with a standardized barometric control.

METHODS

Subjects

Patients were recruited between October 2014 and February 2016 via the Stroke Unit and the outpatient clinic of the Department of Neurology of the Medical University of Vienna. We screened patients aged 18–80 years after a recent transient ischemic attack (TIA) or ischemic stroke without atrial fibrillation, recent cardiac surgery, endocarditis, or high-grade carotid stenosis. All patients with a PFO detected by TEE were eventually analyzed.

The study was approved by the local ethics committee of the Medical University of Vienna on 14th of August 2014 (EC number 1442/2014).

Demographic and clinical details, including patient history, neurological examination, and imaging (MRI or CT) findings, were documented for all included patients. Patients underwent a TCD at the Department of Neurology and subsequently a TEE at the Division of Cardiology (Department of Medicine II) of the Vienna General Hospital (Medical University of Vienna).

Transcranial Doppler ultrasound

TCD was performed using a GE LOGIQ P9 ultrasound system. Patients were examined lying in supine position. A 2 MHz ultrasound probe was put over the MCA via the temporal window. Based on the routine protocol used at our department, agitated saline, that is a mixture of 4.5 ml gelofusine (succinylated gelatine), 4.5 ml sodium chloride, and 1 ml air, was injected in a peripheral vein (preferentially right antecubital vein) over a period of 2–3 s. MES were observed by TCD as a sign for RLS at different pressures while performing VM. Patients were asked to exhale, and the resulting pressure was measured by PARI-PEP® (PARI-Positive Expiratory Pressure), allowing for barometric standardization.

Agitated saline was injected four times per patient with MES being counted at rest (without exhaling) and then at three predefined EPs of 15 and 40 mbar as well as the maximally achievable EP, each lasting for 10 s. The occurrence of MES within 10 s after injection was considered to be suggestive of a PFO. According to previous suggestions, MES count was categorized as follows: (1) 0 MES (negative); (2) 1–10

MES; (3) >10 MES and no curtain; and (4) curtain (meaning a shower of MES with no single MES being identified).[11]

Transesophageal echocardiography

TEE was performed using a Siemens ACUSON SC2000 ultrasound system. During the procedure, mild sedation was used, and patients were lying in lateral position. The ultrasound probe was placed inside the esophagus until the atrial septum appeared at the level of the fossa ovalis, the potential source of cardiogenic embolism, followed by an intravenous injection of contrast agent. TEE was performed during a state of rest and during maximally achievable VM. The size of PFO was defined as the maximal separation of septum primum and septum secundum in mm. In line with previous studies, PFO was defined as small (≤1.9 mm), moderate (2–3.9 mm), and large (≥4 mm).[12,17,18]

Statistical analysis

Statistical analysis was performed using SPSS 25.0 (SPSS Inc, Chicago, IL, USA). Univariate comparisons were done by chi-square-test, Mann–Whitney U test, or independent *t*-test (with Welch's correction in case of unequal standard deviations between the groups) as appropriate based on whether visual inspection of the data and Kolmogorov–Smirnov test indicated normal distribution. A two-sided *p*-value <.05 was considered statistically significant.

First, to verify the basic assumption of an association between increasing VM pressure and increasing TCD MES count, we used Friedman's Test with post-hoc pairwise comparisons by Wilcoxon signed-rank test.

Nonparametric Spearman's rank correlation analysis was performed between the four TCD measures (TCD at rest and VM with 15 mbar, 40 mbar, and the maximal achievable mbar) with the gold standard TEE-based PFO size.

Then, we compared accordance rate between size estimation by TCD measures and TEE-based PFO size by cross-tab-analyses and chi-square tests. To determine the contribution of resting state and Valsalva TCD measures to PFO size estimation, we calculated stepwise linear regression models with TEE PFO size as the dependent variable and TCD measures as independent variables adjusted for age and sex. *R*-squared was used to assess contribution of each variable to explanation of variance in PFO size estimation within the overall model.

We tested all variables in regression models for collinearity by variance inflation factor (VIF) and excluded variables from the regression analysis if the VIF was >2.0, corresponding to an R^2 of 0.60.

RESULTS

Demographic and clinical baseline characteristics

A total of 203 patients fulfilled our abovementioned screening criteria. Of these patients, in which a TCD was performed, 156 (77%) also underwent a TEE. Twenty-three of these 156 patients (14.7%) had a TCD with evidence of a PFO, but subsequent TEE was negative.

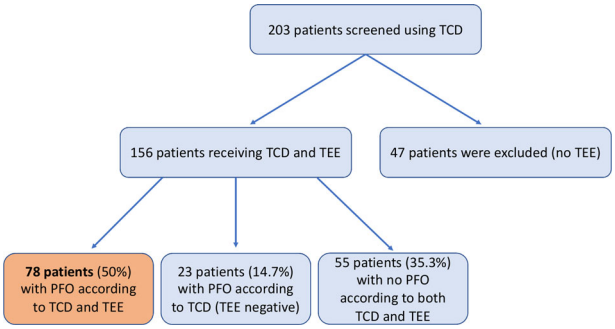

FIGURE 1 Recruitment of patients. Flowchart illustrating patient selection from all 203 patients screened with transcranial Doppler (TCD) ultrasound toward the final inclusion of 78 patients with evidence for patent foramen ovale according to both TCD and transesophageal echocardiography. Abbreviations: PFO, patent foramen ovale; TEE, transesophageal echocardiography

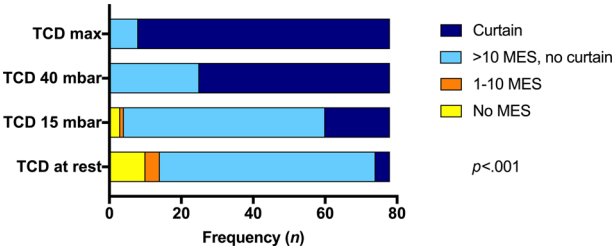

FIGURE 2 Change of transcranial Doppler measures with increasing Valsalva pressure. Abbreviations: Max., maximum pressure; mbar, millibar; MES, microembolic signals; *n*, number of individuals; TCD, transcranial Doppler ultrasound

In total, 78 subjects (48 males and 30 females) with a median age of 55 years (total range: 22–80 years) and a diagnosis of PFO according to TEE were included in the study (Figure 1).

The majority suffered a first stroke (82%). Most included individuals had a minor stroke with National Institutes of Health Stroke Scale (NIHSS) ≤4 (53%), followed by TIA (36%) and major stroke with NIHSS >4 (11%). Embolic stroke of undetermined source criteria[19] were fulfilled in 42% of cases. More strokes were located in the anterior territory (49%). The most frequently observed cardiovascular risk factors were hypertension (54%), hyperlipidemia (51%), and smoking (32%) (Table 1).

TCD measures change with increasing EP

For all four pressure levels used in TCD (i.e., at rest, 15 mbar, 40 mbar, and maximum pressure), the distribution of MES categories is depicted in Figure 2. The amount of MES was significantly associated with EP ($p < .001$). In resting state, all MB categories could be noticed in TCD, whereas with increasing pressure levels (i.e., 15 mbar, 40 mbar, and maximum pressure), significantly more MES were detected, showing

TABLE 1 Baseline characteristics of all 78 patients with evidence for a PFO according to both TCD and TEE

Characteristics	
Sex	
Male	*n* = 48 (62%)
Female	*n* = 30 (38%)
Age at recruitment, years	55 (median), 22–80 (total range)
Type of stroke	
TIA	*n* = 28 (36%)
Minor stroke	*n* = 41 (53%)
Major stroke	*n* = 9 (11%)
Lesion site	
Left hemisphere	*n* = 33 (42%)
Right hemisphere	*n* = 28 (36%)
Bilateral	*n* = 6 (8%)
MRI-negative	*n* = 11 (14%)
ESUS criteria fulfilled	
Yes	*n* = 33 (42%)
No	*n* = 45 (58%)
Cerebral vascular territories	
Anterior	*n* = 38 (49%)
Posterior	*n* = 22 (29%)
Multilocular	*n* = 7 (9%)
Cardiovascular risk factors	
Hypertension	*n* = 42 (54%)
Hyperlipidemia	*n* = 40 (51%)
Smoking	*n* = 25 (32%)
Diabetes	*n* = 7 (9%)
Coronary heart disease	*n* = 3 (4%)
Oral contraception	*n* = 1 (1%)
No risk factors	*n* = 15 (19%)
History of previous stroke	
First stroke	*n* = 64 (82%)
Recurrent stroke	*n* = 14 (18%)

Abbreviations: ESUS, embolic stroke of undetermined source; *n*, number of individuals; TIA, transient ischemic attack.

a curtain with 40 mbar and maximal achievable pressure in almost all patients. A statistically significant difference was noted between all four pressure levels (at rest vs. 15 mbar: $p < .001$; 15 vs. 40 mbar: $p < .001$; 40 mbar vs. maximum pressure: $p < .001$). Median maximal achievable pressure was 70 mbar (total range 45–100 mbar).

Correlation between MES and PFO size

TCD pressure categories were significantly associated with PFO size, as measured by TEE. As shown in Table 2, this was the case for both continuous (mm) and categorical (i.e., PFO size categories) data, with TCD at 15 mbar showing the strongest correlation (Spearman rho = 0.425 and 0.449, respectively, $p < .001$ for both).

Estimation of PFO size by TCD

In the multivariate regression model, 32.3% of PFO size variance was explained by the sum of all TCD measures. Resting state TCD and 15 mbar contributed the most to PFO size estimation (explaining 14.9% and 16.3% of variance, respectively), while 40 mbar contributed to a lesser extent (1.1%, not significant) and maximal EP not at all (Table 3).

By multiple-cross-tab-analysis, we developed a PFO size estimation model based on the combination of TCD measures (Table 4). This TCD classification system was able to correctly classify PFO size in 64.1% of cases. The estimation was most accurate for small PFOs, in which all pressure levels up to 40 mbar contributed to size estimation. In medium and large PFOs, the size estimation model performed less accurately and the application of TCD at 40 mbar did not provide an additional benefit (Table 4).

DISCUSSION

In this prospective study, we demonstrate that barometrically standardized pressure levels in TCD correlate significantly with the PFO size measured by TEE. Furthermore, we implement a PFO size estimation model based on pressure-controlled TCD findings with an overall accuracy of 64%, showing the highest diagnostic accuracy for small-sized PFOs.

In general, studies investigating diagnostic approaches for PFO are currently warranted, as multiple randomized-controlled trials convincingly demonstrated a therapeutic benefit of PFO closure, especially in young patients with cryptogenic stroke.[5–7] According to the current guidelines of the American Heart Association, closure is particularly recommended in cases with high-risk anatomical features, such as large shunt size and atrial septal aneurysm, while its therapeutic benefit is less clear in PFOs without these characteristics.[20]

While TEE represents the diagnostic gold standard for PFO diagnosis, noninvasive TCD is often used beforehand as an easily accessible screening tool.[21,22] In TCD, VM is used in addition to resting state examination to detect RLS but underlies interindividual variability.

We hypothesized that barometric standardization may mitigate this interindividual variability, thus increasing the diagnostic accuracy of TCD for estimating PFO size. Moreover, this is of clinical relevance, as PFO size represents an independent risk factor for cryptogenic ischemic stroke.[4]

Herein, we finally analyzed subjects with both TCD and TEE indicating the presence of a PFO for comparative analyses. However, during our screening procedure, around 15% of patients undergoing both procedures had a positive TCD (thus indicating RLS), but no structural abnormalities according to TEE and could, therefore, not be included. Of note, no case with a PFO detected by TEE was missed by TCD-based screening. This is in line with previous data that show a higher sensitiv-

TABLE 2 Correlation between TCD measures with increasing Valsalva pressure and TEE-based PFO size

	TEE size (mm)	*p*-value[a]	TEE size (ordinal)	*p*-value[a]
TCD at rest	0.278	.014	0.263	.020
15 mbar TCD	0.425	<.001	0.449	<.001
40 mbar TCD	0.322	.004	0.361	.001
Max pressure TCD	0.326	.004	0.379	.001

[a]Calculated by Spearman-Rank correlation.
Abbreviations: Max., maximum pressure; mbar, millibar; TCD, transcranial Doppler ultrasound; TEE, transesophageal echocardiography.

TABLE 3 Contribution of TCD measures at different pressures to estimation of PFO size

	B (regression coefficient)	95% CI	*p*-value	Change in R^2 (overall R^2)
TCD at rest	0.565	0.023–1.420	.048	0.149 (0.149)
15 mbar TCD	1.367	0.310–2.773	.042	0.163 (0.312)
40 mbar TCD	0.576	−0.927 to 2.079	.448	0.011 (0.323)
Max pressure TCD	0.044	−2.673 to 2.550	.973	0.000 (0.323)

Abbreviations: CI, confidence interval; Max., maximum pressure; mbar, millibar; PFO, patent foramen ovale; TCD, transcranial Doppler ultrasound.
Note: Whole model: $p<.001$ (omnibus-test of fit) calculated by a stepwise linear multivariable regression model with TEE separation (mm) as the dependent variable adjusted for age and sex. Positive regression coefficients indicate a positive association with PFO size.

ity but lower specificity of TCD compared to TTE.[23] Some authors suggest that TCD might even be more sensitive than TEE for the detection of RLS.[24] It is also noteworthy that a positive TCD only points toward an RLS without differentiating between a cardiac and an extracardiac shunt origin.[25] As a result, TEE should definitely be performed in case of a positive TCD indicating RLS. On the other hand, given the high sensitivity, one may argue that a negative TCD may be sufficient to exclude a clinically relevant RLS.

TABLE 4 Classification of PFO size depending on TCD at rest, 15 mbar TCD, and 40 mbar TCD

TCD at rest	15 mbar TCD	40 mbar TCD	Expected PFO size	Frequency of correct classification
No MES	No MES	No MES	No PFO	NA
		Any MES	Small PFO	100% (3/3)
	1–10 MB	1–10 MES	Small PFO	100% (1/1)
		>10 MES, no curtain or curtain	NA	NA
	>10 MES, no curtain or curtain MES	>10 MES, no curtain or curtain MES	Medium PFO	50% (3/6)
1–10 MES	1–10 MES	>10 MES, no curtain or curtain	Medium PFO	75% (3/4)
	>10 MES, no curtain or curtain	NA	NA	NA
>10 MES, no curtain	>10 MES, no curtain	>10 MES, no curtain or curtain	Medium PFO	65.2% (30/46)
	Curtain MES	NA	Large PFO	50% (7/14)
Curtain MES	NA	NA	Large PFO	75% (3/4)
Whole cohort				64.1% (50/78); *p*-value <.001[a]

[a]Calculated by chi-square test.
Abbreviations: mbar, millibar; MES, microembolic signals; NA, not applicable; PFO, patent foramen ovale; TCD, transcranial Doppler ultrasound.
Note: Some pressure levels were not fulfilled with one of the four categories (no MES; 1–10 MES; >10 MES, no curtain; curtain), explained by NA. Since the maximal achievable expiratory pressure did not provide additional information, it was removed from the classification algorithm.

As one would expect, the amount of MES observed by TCD in our study continuously increased from resting state to maximum EP in all study participants. Comparable findings have been reported by Devuyst et al.[14] Other studies revealed that the use of a pressure- and time-controlled VM may enhance the RLS detection rate.[15,16] These findings along with our results argue in favor of controlled EPs for a reproducible shunt assessment in clinical practice.

As mentioned above, the size of a PFO plays an increasingly appreciated role in association with stroke risk.[4,26] While it has been suggested that the amount of MES seen by TCD may correlate with PFO size,[12] to our knowledge, no previous study has sought to investigate this relationship by applying a barometric standardization. Hence, we could demonstrate for the first time that MES counts at standardized TCD pressure conditions are significantly associated with PFO size, with lower pressure levels (mainly 15 mbar) contributing to the greatest extent. By contrast, the maximum achievable pressure, which is commonly used in clinical routine, did not contribute to size estimation at all. This again strongly supports a change toward pressure control in the standard diagnostic assessment of PFO.

To translate the aforementioned findings into clinical practice, we applied an estimation model with the aim to correctly estimate PFO size prior to TEE examination. In the long run, this could help to prioritize patients at higher risk for a prompt and more detailed cardiological assessment. In our study, we were able to provide a correct estimation of PFO size in almost two thirds of all included subjects. The estimation was most accurate for small PFOs in which all pressure levels up to 40 mbar contributed. Since the accuracy of size estimation was only moderate in medium and large PFOs and TCD at 40 mbar did not result in additional information, a subtler pressure grading, for instance 30 mbar, may even enhance accuracy. This is an important direction for future studies.

The major strength of our study is the prospective and systematic use of barometric standardization, which may allow a more objective assessment in TCD-based PFO screening. In view of the potential therapeutic consequences in case of a PFO diagnosis, our research question also addresses a clinically meaningful question. Since the study was performed in one single tertiary care center, it was possible to standardize the diagnostic procedures regarding both technical and personal aspects. Additionally, all included individuals have recently experienced an acute cerebrovascular disease and can, therefore, be considered a representative cohort in which PFO diagnostics may, indeed, play a relevant role in a real-life clinical setting.

Our study also has some limitations. First, the sample size of 78 eventually analyzed patients is still comparably small, and future studies using similar approaches in larger patient populations are necessary to replicate our findings. Another drawback of our study is the lack of a control cohort with PFO but without a history of stroke. It is also worthy of note that only subtle inaccuracies of the TEE-measured PFO size may have resulted in different predefined categories (small, moderate, and large PFO). Nonetheless, we believe that this drawback could be minimized by our monocentric study design. Moreover, TCD has some inherent limitations, as it fails to depict important morphological features other than PFO size (e.g., atrial septal aneurysm). Further, its use may also be restricted due to anatomical circumstances, such as an insufficient temporal bone window.[27]

Taken together, our study provides evidence that TCD with stepwise barometric standardization allows an estimation of PFO size with comparably good accuracy prior to TEE. Although TCD is a clinically useful and highly sensitive screening tool, TEE justifiably represents the current gold standard for PFO diagnosis. In view of the more detailed anatomical assessment, TEE can be expected to remain the method of choice in the future.

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