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The RoPE Score and Right-to-Left Shunt Severity by Transcranial Doppler in the CODICIA Study

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Key Words
Cerebrovascular disease · Stroke · Doppler · Cryptogenic stroke · Patent foramen ovale · Echocardiography

Abstract
Background: For patients with cryptogenic stroke (CS) and patent foramen ovale (PFO), it is unknown whether the magnitude of right-to-left shunt (RLSh) measured by contrast transcranial Doppler (c-TCD) is correlated with the likelihood an identified PFO is related to CS as determined by the Risk of Paradoxical Embolism (RoPE) score. Additionally, for patients with CS, it is unknown whether PFO assessment by c-TCD is more sensitive for identifying RLSh compared with transesophageal echocardiography (TEE). Our aim was to determine the significance of RLSh grade by c-TCD in patients with PFO and CS. ***Methods:*** We evaluated patients with CS who had RLSh quantified by c-TCD in the Multicenter Study into RLSh in Cryptogenic Stroke (CODICIA) to determine whether there is an association between c-TCD shunt grade and the RoPE Score. For patients who underwent c-TCD and TEE, we determined whether there is agreement in identifying and grading RLSh between these two modalities. ***Results:*** The RoPE score predicted the presence versus the absence of RLSh documented by c-TCD (c-statistic = 0.66). For patients with documented RLSh by c-TCD, shunt severity was correlated with increasing RoPE score (rank correlation (r) = 0.15, p = 0.01). Among 293 patients who had both c-TCD and TEE performed, c-TCD was more sensitive (98.7%) for detecting RLSh. Of the 97 patients with no PFO identified on TEE, 28 (29%) had a large amount of RLSh seen on c-TCD. ***Conclusions:*** For patients with CS, severity of RLSh by c-TCD is positively correlated with the RoPE score, indicating that this technique for shunt grading identifies patients more likely to have pathogenic rather than incidental PFOs. c-TCD is also more sensitive in detecting RLSh than TEE. These findings suggest an important role for c-TCD in the evaluation of PFO in the setting of CS.

Introduction

Patent foramen ovale (PFO) is seen in approximately 25% of adults and generally is considered a normal anatomic variant [1]. Nonetheless, a consistent association between PFO and cryptogenic stroke (CS) has been observed [2]. However, given that PFO is common in the general population and that CS can be caused by several different occult stroke mechanisms, a PFO discovered in

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Table 1. RoPE score calculator. Clinical characteristics used to estimate the likelihood of an observed PFO is related to CS (adopted from [9])

Characteristic	Points	RoPE score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Non-smoker	1	
Cortical infarct on imaging	1	
Age, years		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥70	0	
Total score (sum of individual points)		
Maximum score[a]		10
Minimum score[b]		0

[a] Patient >30 years with no hypertension, no diabetes, no history of stroke or TIA, non-smoker, and cortical infarct. [b] Patient ≥70 years with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct.

a patient with CS may be an incidental finding unrelated to the index stroke, and not linked to the risk of recurrence [3]. Heterogeneity of stroke mechanisms among patients with PFO and CS likely explains, in part, why three recent randomized controlled trials of patients with CS and PFO showed no difference in their primary intention to treat outcomes for patients randomized to either device-based closure or medical therapy [4–7].

It has recently become clear that for patients with CS and PFO, the probability that an identified PFO is an incidental finding is related to patient-specific characteristics [8]. We reported the Risk of Paradoxical Embolism (RoPE) score (table 1), a tool that stratifies patients with CS according to the probability of finding a PFO. The score is based on the strong and consistent empirical relationship between easily obtainable clinical variables and the prevalence of a PFO in CS patients. Bayes' theorem relates the score to the PFO-attributable fraction – that is, an estimate of the probability that an observed PFO is related to an index CS rather than being an incidental finding [9]. Briefly, for patients with CS and PFO, younger patients without risk factors for atherosclerotic disease (i.e. hypertension, diabetes, smoking) or a prior stroke and with a visible superficial lesion on neuroimaging are more likely to have a PFO-attributable CS (high RoPE score). Conversely, for older patients with more traditional risk factors for ischemic stroke and without a cortical infarct on imaging, an observed PFO is more likely to be an incidental finding (low RoPE score).

While the RoPE score stratifies patients with CS based on clinical variables, it is unknown whether anatomic or physiologic features of the PFO itself are associated with the likelihood that an observed PFO is pathogenically related to CS. Several anatomic features have been proposed as identifying higher risk PFOs, including the presence of an atrial septal aneurysm [10], large shunt size [11], and the presence of a right-to-left shunt at rest [12]. Prior studies, however, have found poor interobserver agreement in identifying these features with transesophageal echocardiography (TEE) [13], long considered the gold standard for investigating PFOs [14]. Further, we recently reported that these purported 'high risk' TEE features, as measured in the component RoPE databases, do not correlate with the likelihood that an observed PFO is related to CS (as estimated by the RoPE score) [15]. These observations suggest that better tools are needed to evaluate the risk associated with PFOs.

Contrast transcranial Doppler (c-TCD) is an alternative technique for quantifying right-to-left shunt (RLSh) [16, 17]. This technique has fair concordance with TEE for detection of RLSh, and a recent meta-analysis has reported a c-TCD sensitivity of 97% and specificity of 93% for detection of RLSh [18, 19]. Although the ability and relevance of RLSh grade evaluated by c-TCD are unknown, some authors have recommended that c-TCD be the first-line screening test to detect RLSh for patients with CS [20]. In this study, we investigate whether shunt grade determined by c-TCD is correlated with RoPE score, and also whether c-TCD and TEE agree with respect to shunt identification and grading.

Methods

We analyzed patient level data from the Multicenter Study into RLSh in Cryptogenic Stroke (CODICIA) [21]. This was a prospective, multicenter, observational study that took place from 2000 to 2005 in 17 Spanish neurology departments. Patients were at least 18 years old and had a recent diagnosis of CS. c-TCD was the prespecified screening test for RLSh detection.

The c-TCD protocol used in the CODICIA database has been previously reported [21]. Briefly, the presence or absence of RLSh was investigated with a 2-MHz probe monitoring the middle cerebral artery (MCA) through the temporal window, consistent with current practice standards [22, 23]. Agitated microbubble saline solution was injected in the antecubital vein through a 20-gauge/32-mm catheter. Microbubble injection was performed 3 times at rest and 3 times during the Valsalva maneuver. The Valsalva maneuver was standardized by asking patients to blow into a manometer un-

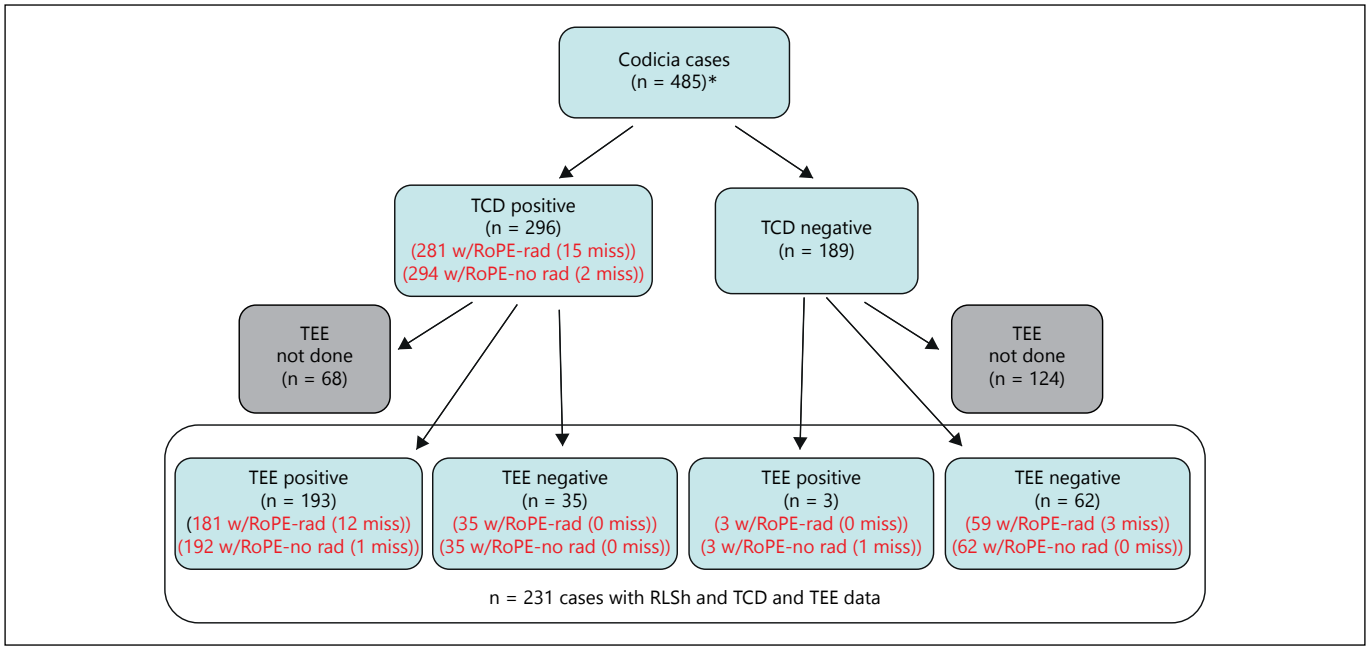

Fig. 1. Patients in the CODICIA database included in this analysis. Our primary analysis evaluated patients who had RLSh documented by c-TCD. Our secondary analyses focused on the patients with RLSh who were evaluated by both c-TCD and TEE. * Original report contains 486 patients. One patient's data was closed before the incident event and as a result not included [21].

til 50–60 mm Hg of pressure was reached and held for at least 5–7 s. Efficacy of the Valsalva maneuver was identified by a reduction of the mean velocity in the MCA by at least 25%. The magnitude of RLSh was determined by counting the number of microbubbles in the MCA in the first 7 s after bolus infusion. Patients were divided into 5 groups: 'normal' c-TCD study = no microbubbles, 'small' <10 microbubbles, 'moderate' = 10–25 microbubbles, 'shower' pattern >25 microbubbles, and 'curtain' pattern = uncountable microbubbles. As originally presented, subjects in the CODICIA database were placed into 1 of 3 groups: 'no RLSh', 'nonmassive RLSh' (≤25 microbubbles), and 'massive RLSh' (m-RLSh; corresponding to the shower and curtain patterns).

Our secondary analysis focused on participants in CODICIA who underwent both c-TCD and TEE examination either as part of the study protocol or at the discretion of the treating clinicians. Per protocol, TEE was performed when m-RLSh was detected by c-TCD [21]. As with the c-TCD exam, saline microbubbles were injected through the antecubital vein. RLSh was defined as the appearance of microbubbles in the left atrium within 3 cardiac cycles of arrival in the right atrium. The TEE protocol used in CODICIA has been previously described and is consistent with current practice standards [21, 24]. TEE derived RLSh severity was determined by the maximum microbubble count in a given frame: 'no RLSh', 'small RLSh' (1–10 bubbles), 'moderate' (11–25 bubbles), and 'large' (>25 bubbles). In this analysis, we examined the sensitivity of both techniques for detecting RLSh.

RoPE Score

The RoPE score predicts the likelihood of finding a PFO for patients with CS [9]. Through application of Bayes' theorem the RoPE score allows estimation of PFO attributable fraction from strata-specific PFO prevalence and the control rate PFO prevalence [8]. By using factors strongly and consistently associated with finding a PFO for an individual with CS across 12 different database, the RoPE Score permits a patient-specific attributable fraction to be empirically estimated by applying a patient-specific PFO prevalence rate. Namely, PFO prevalence in CS patients is increased in younger patients, without vascular risk factors (diabetes, hypertension, smoking) or a prior stroke or transient ischemic attack, and with a superficial lesion on neuroimaging. As previously reported, the 10-point RoPE score is calculated from a simple count of these factors [9].

Analysis

To explore whether the severity of RLSh determined by c-TCD is correlated with the RoPE score, we first evaluated the RoPE score to confirm that it effectively discriminates CODICIA patients based on the probability that they have a PFO. It should be noted that for this population, RLSh on c-TCD was used as a surrogate for the presence of PFO, originally described in the RoPE database as any right-to-left shunting seen either on c-TCD or TEE [25]. As previously reported, the RoPE score performed well in the original database and was able to predict the presence or absence of PFO in the RoPE database (c-statistic = 0.68) with the PFO-attributable fraction ranging from 0% (truncated lower limit for RoPE score 0–3) to 88% for high RoPE scores (9–10), assuming a 25% control PFO prevalence rate [9].

Following this, our primary analysis evaluated patients with RLSh in the CODICIA database investigated with c-TCD. Since the primary screening test was c-TCD, there were patients who had RLSh quantification with this technique who did not undergo TEE (fig. 1).

Table 2. Comparison of the RoPE score, the observed probability of identifying RLSh in CODICIA population, and the predicted PFO prevalence according to RoPE score across the entire CODICIA database studied by c-TCD

Patients studied with c-TCD	RoPE score (3 groups)		
	1–4	5–6	7–10
n for analysis	151	169	146
Observed RLSh prevalence, %	50	56	79
Predicted PFO prevalence, %	30	46	63

Table 3. Primary analysis. Comparison of characteristics of subjects who had shunt (n = 296) vs. no shunt (n = 192) based on TCD result

	Full cohort (n = 485)	Subjects with RLSh by c-TCD (n = 296)	Subjects with no RLSh by c-TCD (n = 189)	p value comparing RLSh+ vs. RLSh–
Age, years, mean ± SD	56.2±15.2 (485)	53.3±14.7 (296)	60.8±14.8 (189)	<0.0001
Men, %	59.8 (290/485)	61.8 (183/296)	56.6 (107/189)	0.2537
Hypertension, %	34.7 (168/484)	27.8 (82/295)	45.5 (86/189)	<0.0001
Diabetes mellitus, %	11.8 (57/485)	6.4 (19/296)	20.1 (38/189)	<0.0001
Coronary artery disease, %	4.9 (24/485)	3.7 (11/296)	6.9 (13/189)	0.1174
Current/recent smoker, %	31.8 (154/484)	32.9 (97/295)	30.2 (57/189)	0.5304
Migraine, %	9.9 (48/483)	11.9 (35/295)	6.9 (13/188)	0.0763
History of stroke/TIA, %	6.0 (29/485)	5.7 (17/296)	6.3 (12/189)	0.7837
Taking antiplatelets, %	6.8 (33/485)	6.8 (20/296)	6.9 (13/189)	0.9587
Incident event TIA, %	20.0 (97/485)	23.3 (69/296)	14.8 (28/189)	0.0225
Atrial septal aneurysm, %	22.2 (101/454)	34.9 (98/281)	1.7 (3/173)	<0.0001
mRS of 0–1 at discharge, %	65.4 (317/485)	72.6 (215/296)	54.0 (102/189)	<0.0001
Bilateral lesion, %	4.4 (16/363)	5.1 (11/215)	3.4 (5/148)	0.428
RoPE score, median	5.5 (466)	6 (281)	5 (185)	<0.0001

mRS = Modified Rankin score; TIA = transient ischemic attack.

We assessed whether the severity of RLSh by c-TCD correlates with the RoPE score. Our secondary analyses focused on the patients who underwent both c-TCD and TEE. We evaluated whether there is agreement between c-TCD and TEE for detection of PFO as a categorical variable (shunt vs. no shunt). We also evaluated agreement between these techniques for shunt grade represented as an ordinal variable (no shunt vs. small shunt vs. large shunt) by mapping the grading categories from each imaging technique empirically (online suppl. tables e-3 and e-4; for all online suppl. material, see www.karger.com/doi/10.1159/000430998). For both TEE and c-TCD, small shunts were defined as those with 10 microbubbles or fewer. For TEE evaluation, Valsalva was attempted during each examination though the presence or absence of effective Valsalva maneuver during the exam was not reported in the original dataset. For c-TCD exams we evaluated the presence or absence of RLSh during Valsalva maneuver, thus representing the period of presumed maximum shunting. We determined the sensitivity of both techniques of RLSh detection by using 'identification of RLSh by either technique' as the gold standard method of identifying shunts and assumed 100% specificity. For the analysis of RLSh severity and RoPE score category, we calculated Spearman's rank coefficients. We created scatter plots with smoothed lines to demonstrate this association.

Results

The RoPE score effectively stratified the CODICIA patients according to the likelihood of finding RLSh (table 2 and online suppl. table e-1). The RoPE score c-statistic for this database was 0.66 and compares favorably to that in the overall RoPE development database (c-statistic 0.68). The PFO prevalence ranged from 50% for patients with low RoPE scores (1–4) to 79% for high RoPE scores (7–10). Of the 485 patients in the CODICIA study, 296 patients were positive for RLSh by c-TCD (fig. 1). The characteristics of subjects with RLSh included in our primary analysis are shown in table 3. When compared to patients who did not have RLSh documented by c-TCD, the patients evaluated here were younger and less likely to have the traditional stroke risk factors of hypertension or diabetes. For patients with RLSh identified with c-TCD, shunt grade determined by c-TCD was correlated with the RoPE score (rank correlation (r) = 0.15 (95% confidence interval (CI): 0.038, 0.268), p = 0.01) (fig. 2).

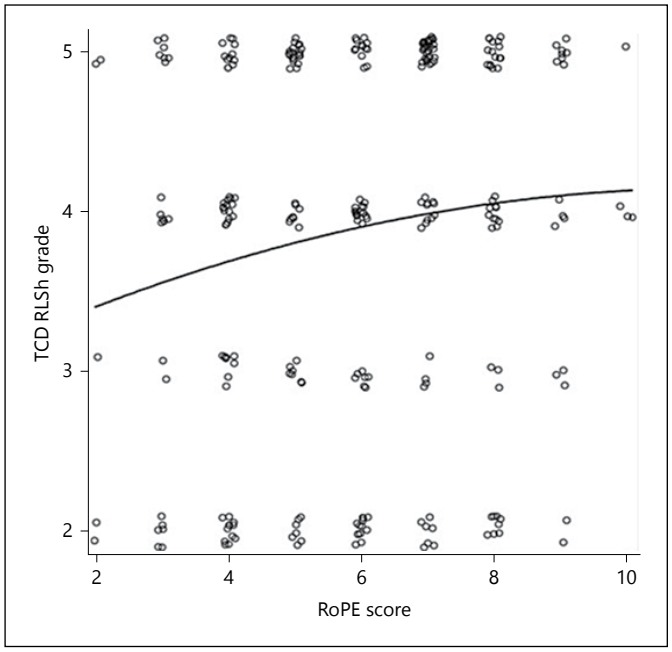

Fig. 2. Correlation between the RoPE score and shunt grade determined by c-TCD. Scatter plot with fitted penalized B-spline curve with 4 evenly spaced knots. Higher RoPE score indicates higher probability that an observed PFO is pathogenically related to CS. For c-TCD grade, microbubble count was made in the first 7 s after bolus (1 = none, 2 = 1–10 microbubbles, 3 = 11–25 microbubbles, 4 >25 microbubbles, 5 = uncountable).

Table 4. Agreement of right-to-left shunt severity determined by c-TCD and TEE

c-TCD/ Valsalva shunt	TEE shunt (worse from Valsalva or rest)			Total
	none (1)	small (2)	large (3, 4, 5)	
None (1)	62	3	0	65
Small (2)	7	16	9	32
Large (3, 4, 5)	28	33	135	196
Total	97	52	144	293

Shunt size is coded: (1) is no shunt, (2) is small shunt, (3, 4, or 5) is larger shunt size. Shunt severity is coded as worst shunt either during Valsalva or rest.

Our secondary analyses were limited to patients with c-TCD and TEE data (online suppl. table e-2). Of the 485 CODICIA patients, 228 had protocol-driven TEE and 65 patients who had TEE despite PFO-negative c-TCD. TEEs were not obtained for 68 patients despite RLSh positive c-TCD (fig. 1). Characteristics of patients (n = 293) included in this secondary analysis are shown in the online supplementary table e-5. We attempted to compare these two imaging modalities directly. RLSh was seen by c-TCD in 228 (78%) and TEE in 196 (67%) subjects, $\kappa = 0.68$ (95% CI: 0.59, 0.77) (online suppl. table e-6). There were 97 patients with no PFO identified by TEE. Of these patients, 35 (36%) had an RLSh detected by c-TCD. Twenty-eight of these shunts (80%) seen only with c-TCD were large in size. The sensitivities for identifying RLSh by c-TCD and TEE were 98.7 and 84.8%, respectively. Overall, a large shunt was identified in 144 (49%) of the cases by TEE and in 196 (67%) of the cases by c-TCD. There was moderate agreement between shunt grades identified by these two techniques, $\kappa = 0.59$ (95% CI: 0.51, 0.67) (table 4).

Discussion

Clinical decisions for patients with CS and PFO depend on whether or not an observed PFO is believed to be pathogenically related to an index CS event. We have shown previously that patient-specific factors can help us understand this relationship [9]. However, we have not found proposed 'high-risk' features determined by TEE to be associated with the RoPE score [15]. Conversely, in this analysis of patients in the CODICIA database, we demonstrated that RoPE score predicts the likelihood of finding RLSh by c-TCD and that shunt severity determined by c-TCD is correlated with the RoPE score. Our analysis of patients who had both tests done showed that there is moderate agreement between c-TCD and TEE for identifying and grading RLSh and that there are many examples where c-TCD identified RLSh where none was seen during TEE evaluation. Moreover, a significant number of the RLSh cases identified only by c-TCD showed large shunting. Our findings suggest that c-TCD evaluation and grading of RLSh are important tools for patients with CS and complement TEE characterization of PFO.

As previously reviewed, the evaluation of shunt grade by TEE in routine practice is prone to measurement error and other limitations [15]. RLSh evaluation by c-TCD overcomes some of the limitations that accompany TEE. Notably, c-TCD is noninvasive and thus better tolerated in patients with a history of stroke or swallowing difficulties. Additionally, no sedation is needed making Valsalva maneuver more effective. Further, when patients are evaluated both with and without a TEE probe in place, the presence of a TEE probe itself may reduce the probability of achieving a right > left pressure gradient during Valsalva [26]. c-TCD also permits direct detection of the

microbubbles that flow into the cerebral circulation and as compared with TEE, there is a high level of agreement in identifying embolic signals with this technique [27]. These advantages and also increased RLSh detection rate likely contribute to the higher correlation with 'pathogenicity' as determined by the RoPE score.

To our knowledge, our analysis represents the largest cohort ever reported of patients with CS investigated by both c-TCD and TEE. As previously documented [20, 28], we demonstrated moderate agreement between c-TCD and TEE for identifying and grading RLSh. While prior work has suggested that TCD may be a sensitive tool compared to TEE [17, 29–33], these prior studies were not performed on large numbers of patients with CS and there is no prior work showing that TCD might be better at distinguishing pathogenically important from less important PFOs. In this analysis, the subset of patients investigated by both techniques was not representative of the entire CODICIA database. The restricted TEE ordering pathway discussed in our methods led to a cohort that disproportionally excluded patients with a low RoPE score, and therefore, did not afford the opportunity to directly compare these techniques with respect to correlation to the RoPE score. At this time, TEE continues to be the gold standard in the cardiac study of CS, since this technique allows direct visualization of the interatrial septum and allows for the detection of other potential sources of stroke including intracardiac thrombus and aortic atheroma – an advantage over c-TCD.

There were certain limitations of our study that should be noted. RLSh identified during c-TCD study may be due to extracardiac shunting (and not related to a PFO). This may contribute to the increased sensitivity in detecting RLSh of c-TCD compared to TEE found in this and other studies [19, 33, 34]. While the RoPE Score was derived from data from multiple databases, the TEE and c-TCD data for this analysis were derived only from the CODICIA database; therefore, this is a multicentered, but not a multinational study; the applicability to other centers around the world is not known. We did not evaluate the relationship between c-TCD shunt severity and stroke recurrence though a recent report from the RoPE study group indicates that there is significant mechanistic heterogeneity for stroke recurrence for patients with CS and PFO [35]. An additional limitation of selection bias might stem from the original CODICIA study protocol. As originally described, c-TCD was the reference evaluation of RLSh. TEE was obtained only if there was massive RLSh or if requested by the treating clinician. As a result, patients with small RLSh were less often studied with TEE. This observation has the potential to affect the correlation between these techniques. Finally, as is common in routine clinical practice, microbubble injection in the CODICIA study was performed from the anticubital vein, a site that correlates less well with anatomic size [36]. This may attenuate the correlation of c-TCD shunt grade with the RoPE score under more ideal conditions.

Nevertheless, we validated the RoPE score in this population and identified a correlation between RLSh severity assessed by the c-TCD and RoPE score, suggesting that this technique is an important tool for evaluating patients with CS. There is agreement between RLSh detection and grading with TEE and c-TCD though there are important examples of substantial right-to-left shunting seen only with c-TCD. More work is needed to identify and validate reproducible techniques for assessing the risk associated with observed RLSh for patients with CS.

Disclosure Statement

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