

Unilateral versus Bilateral Middle Cerebral Artery Detection of Right-to-Left Shunt by Power M-Mode Transcranial Doppler

Jill T. Jesurum, PhD, Cindy J. Fuller, PhD, Mark A. Moehring, PhD, Joshua Renz, V. T., Meryl Harley, R.V.T., Merrill P. Spencer, MD*

From the Department of Cardiovascular Scientific Development, Swedish Medical Center, Seattle, Washington (JTJ, CJF); Spencer Technologies, Seattle, Washington (MAG); and Spencer Vascular, Seattle, Washington (JR, MH, MPS).

ABSTRACT

BACKGROUND AND PURPOSE

Comparison was performed between unilateral and bilateral power M-mode transcranial Doppler to detect right-to-left circulatory shunt (RLS).

METHODS

Recorded Doppler data from 87 patients with confirmed RLS referred for transcatheter closure of patent foramen ovale were reanalyzed for embolic tracks (ET) counted from left and right temporal bone windows during bubble study. Unilateral counts were obtained by multiplying each side by 2; bilateral counts were obtained by summing left and right ET. Both unilateral and bilateral ET were converted to a 6-point logarithmic grade. Sex and age group subanalyses were performed.

RESULTS

At rest, significantly more ET were detected with bilateral versus unilateral detection ($P = .01$), but not following Valsalva ($P = .13$). Unilateral and bilateral detection were equally able to detect large RLS (grades IV or V) following Valsalva ($P = 1.00$). For the group aged ≥ 55 years, the right-hand side yielded greater ET than the left-hand side (mean difference $9\% \pm 37$; 95% confidence interval -3 to 21%) at rest ($P = .01$), but not following Valsalva (mean difference $1\% \pm 25$; 95% confidence interval -7 to 9% , $P = .10$).

CONCLUSIONS

Unilateral detection of ET by power M-mode transcranial Doppler is equivalent to bilateral detection to assess RLS.

Introduction

Contrast-enhanced transcranial Doppler (TCD) detection of right-to-left circulatory shunt (RLS) is commonly performed using bilateral placement of transducers on temporal bone windows to quantify embolic tracks (ET) in the middle cerebral arteries (MCA).¹⁻³ Although an early Consensus Group recommended insonating at least 1 MCA for diagnosis of RLS,⁴ bilateral insonation may be technically challenging or impossible in some patients. Increasing age, sex, and ethnicity have been associated with adequacy of the windows.⁵⁻⁷ Reliable measurement of ET from a single temporal bone window may also be compromised by asymmetry between left and right cerebral circulations, as in carotid artery disease.^{8,9} Droste et al¹⁰ found a 12% higher number of microbubbles in the right MCA than in the left MCA after calibrated Valsalva maneuver using multi-gated TCD. This is in contrast to an earlier study using single-gated TCD,¹¹ in which no asymmetry was found between the left and right MCAs.

The purpose of this study was to determine if unilateral detection of ET with power m-mode transcranial Doppler (pmTCD)^{12,13} yields similar results to bilateral detection for assessment of RLS. For this study, unilateral ET counts were multiplied by 2 and compared to summed bilateral ET counts.

*Deceased.

Keywords: Transcranial Doppler, middle cerebral arteries, right-to-left shunt, patent foramen ovale.

Acceptance: Received July 19, 2007, and in revised form April 22, 2008. Accepted for publication May 19, 2008.

Correspondence: Address correspondence to Jill T. Jesurum, PhD, Scientific Director, Swedish Heart and Vascular Institute, Swedish Medical Center, 550 17th Avenue, Suite 6351, Seattle, WA 98122. E-mail: jill.jesurum@swedish.org.

J Neuroimaging 2009;19:235-241.
DOI: 10.1111/j.1552-6569.2008.00280.x

The primary hypothesis was that there would be no significant difference in the number of ET detected between unilateral (double left or right window) and bilateral (sum of left and right windows) evaluation. Secondary hypotheses were: (1) there would be no significant difference in the number of ET detected between left and right temporal bone windows; and (2) there would be no age or gender effects in the number of ET detected between left and right temporal bone windows.

Methods

The observational study was a single-group retrospective analysis. The primary endpoint was comparison of unilateral and bilateral ET detection of RLS. Secondary endpoints included comparison of right and left ET counts and the effects of sex and age on ET counts. The accessible population included 246 patients with confirmed RLS who underwent transcatheter patent foramen ovale (PFO) closure for prevention of recurrent paradoxical cerebral embolism at Swedish Medical Center (Seattle, WA) between April 2001 and June 2005. For the purposes of this study, ischemic stroke was defined as an acute focal neurological event with corresponding positive findings on magnetic resonance imaging, regardless of duration of clinical symptoms; transient ischemic attack was defined as a temporary, reversible focal neurological event without changes on magnetic resonance imaging. Patient data were collected in a

registry approved by the Western Institutional Review Board (IRB; Olympia, WA). Detection of RLS by pmTCD was obtained prior to PFO closure. Approval of the Swedish Medical Center IRB was obtained for this analysis. Patients who met eligibility criteria were consecutively selected from the Registry for requantitation of ET and stratified by age (< and ≥ 55 years) and gender. For the purpose of group comparisons, efforts were made to include equal numbers of males and females, and patients aged < and ≥ 55 years. If recorded data on a patient could not be located, the next consecutive patient who met eligibility criteria was included. The study targeted a sample size of 100. Selection criteria included: (1) detectible RLS on pmTCD; (2) PFO probe patency (ie, a catheter probe successfully passed across the PFO during cardiac catheterization); (3) adequate bilateral temporal bone windows, defined as stable blood flow signals with pmTCD in the full range of both left and right MCA+ACA (40-75 mm);^{13,14} and, (4) absence of significant flow-limiting internal carotid artery (ICA) stenosis (>70%).

Detection of ET was performed using the PMD100 TCD platform (Spencer Technologies, Seattle, WA) in the Swedish Medical Center cardiac catheterization laboratory. A PMD100 2 MHz ultrasound probe was mounted and stabilized over each temporal bone using the Marc 600 head frame (Spencer Technologies). Eight different sonographers performed the initial pmTCD examinations. Patients were placed in a supine position with the head raised 30° and measures were taken to avoid neck rotation or flexion. After obtaining adequate bilateral temporal bone window signals, all patients had at least 2 contrast injections during pmTCD evaluation using methods described by Spencer et al.¹³ Each contrast injection consisted of 9 mL saline, 1 mL air, and a small amount of the patient's blood manually agitated between 2 syringes for 10 seconds and injected into the antecubital vein.^{4,13} The first injection was performed during normal respiration (rest). The second injection was performed immediately prior to performance of a calibrated Valsalva maneuver. Each patient was instructed to blow into a mouthpiece attached to a manometer until 40 mmHg pressure was achieved and maintained for 10 seconds. ET for both injections were counted for 1 minute after the microbubbles reached the pulmonary artery.¹³ Unilateral (multiplied by 2) and bilateral pmTCD data were expressed as ET counts, then converted to the RLS grading scale published by Spencer et al. (grade 0 = 0 ET, grade I = 1-10 ET, grade II = 11-30 ET, grade III = 31-100 ET, grade IV = 101-300 ET, grade V >300 ET).¹³ If unilateral ET exceeded 150 or were too numerous to count (washout or curtain), 151 ET was assigned for a maximum possible bilateral total of 302 ET. A bilateral count of 302 was assigned to patient recordings with washout or curtain. Large RLS was defined as a bilateral (or unilateral multiplied by 2) ET >100 or grade IV or V following Valsalva.

Inter- and intrarater reliability analyses were performed to ensure the reliability of the data collected and to evaluate the need for sonographer retraining. A second sonographer read the first 20 patient recordings to establish interrater reliability with the primary sonographer. Both sonographers were blinded to the original ET counts, and to each other's results. After in-

terater reliability was established, 1 sonographer (JR) manually counted the number of ET from the left and right MCA/ACA for the entire sample, and calculated the sum for the bilateral measurement. Intrarater reliability was assessed by comparison of 2 readings of 10 patient recordings (1 year apart) by a single sonographer (JR).

Statistical Analysis

Descriptive statistics were performed for demographic and echocardiographic characteristics. Continuous variables were reported as mean \pm standard deviation (SD); nominal and categorical data were reported as frequencies and percentages. Interrater reliability was established with recorded continuous data from the first 20 patients. Pearson's product moment correlation coefficients and kappa statistics were computed to assess pairwise correlation among raters of ET counts and RLS grades, respectively, at rest and following Valsalva. A correlation coefficient of $r > .85$ or kappa significance of $< .05$ was established as acceptable inter-rater reliability. Intrarater reliability was established in a similar fashion on recorded continuous data from 10 patients.

To determine the temporal bone window to be used for the primary aim, Wilcoxon signed rank tests were used to compare detection of ET between left and right windows at rest and following Valsalva. To evaluate asymmetry between left and right temporal bone windows, paired-*t*-tests were performed on ET counts for males and females, and for patients aged <55 and ≥ 55 years. The *t*-tests for independent samples were used to assess sex and age differences on left and right temporal bone window ET counts at rest and following Valsalva.

For the primary aim, the paired-*t* test was used to assess if detection of RLS via unilateral ET count multiplied by 2 yielded similar results as the sum of left and right (bilateral) ET counts. The Wilcoxon signed rank test was used to assess differences in RLS grades at rest and following Valsalva between unilateral (multiplied by 2) and bilateral measurements. Pearson correlation coefficients were calculated to assess pairwise correlation among unilateral (multiplied by 2) and bilateral ET counts at rest and following Valsalva. The McNemar test was used to determine the ability of unilateral (multiplied by 2) compared to bilateral pmTCD evaluation to detect large RLS, defined as grades IV or V at rest or strain. The threshold for statistical significance for all analyses was set at $\alpha = .05$. Statistical analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL). Post hoc power calculations were performed with SamplePower 2.0 (SPSS).

Results

Study Sample

A total of 87 digital file recordings of bilateral pmTCD data were analyzed for this study. The target sample size of 100 was not attained due to inability to locate archived recorded pmTCD data or lack of preclosure carotid duplex ultrasound examination. Demographic, atrial septal, and internal carotid artery characteristics of the patients are listed in Table 1. Forty-six (53%) patients were aged <55 years, and 41 (47%) patients were aged ≥ 55 years. Twenty-one (24%) patients had coexisting atrial

Table 1. Demographic and Atrial Septal Characteristics of Patients (N = 87)

Characteristic	Frequency (%) or Mean ± Standard Deviation
Age, year	55 ± 15
Age ≥ 55 years	41 (47%)
Females	41 (47%)
Caucasian	81 (93%)
History of stroke	66 (76%)
History of transient ischemic attack	35 (40%)
Atrial septal aneurysm	21 (24%)
Atrial septal defect	1 (1%)
PFO balloon diameter, mm	12.6 ± 4.0
PFO septal tunnel length, mm	11.4 ± 3.3
Left internal carotid artery stenosis	
0–15%	72 (83%)
16–49%	9 (10%)
Right internal carotid artery stenosis	
0–15%	73 (84%)
16–49%	9 (10%)

septal aneurysm, and 1 (1%) had a coexisting atrial septal defect. Most patients had minimal ICA stenosis, defined as <15% (left ICA 83%, right ICA 84%), indicative of normal blood supply to the MCA and ACA.

Inter- and Intrarater Reliability

The first 20 pmTCD sonograms were analyzed by 2 sonographers to determine interrater reliability. The correlation coefficients for total ET counts at rest and following Valsalva were .99 and .97, respectively (both $P < .001$), indicative of an acceptable degree of interrater reliability. The kappa coefficients for bilateral RLS grades at rest and following Valsalva were .81 and 1.00, respectively (both $P < .001$). Intrarater correlation coefficients for total ET counts at rest and following Valsalva were .96 ($P < .001$) and .86 ($P = .001$), respectively. The kappa coefficient for bilateral RLS grades at rest was .87 ($P < .001$).

Unilateral Monitoring: Left versus Right ET Counts

Unilateral measurements are shown in Table 2. There was a higher mean ET count in the right temporal bone window at rest ($P = .020$); however, this was not determined to be a clinically important difference (mean difference $4 \pm 38\%$). There was no significant difference between mean left and right temporal bone window ET counts following Valsalva ($P = .12$, mean difference $1 \pm 23\%$). Based on the results of a coin toss, only the left temporal bone window ET counts (multiplied by 2) were used for comparison with bilateral ET counts.

Sex and Age Effects on Distribution of ET Counts

Subanalysis comparisons of left and right ET counts were performed by sex and age group (< or ≥55 years), to test for asymmetry between the 2 temporal bone windows. These results are shown in Figures 1 and 2, respectively. No differences were

Table 2. Comparison of Left and Right Temporal Bone Window ET at Rest and Immediately Following Calibrated (40 mmHg), Sustained (10 seconds) Valsalva

Status	Embolic Tracks		
	Left	Right	P-value
Rest	53 ± 57 (29)	57 ± 59 (28)	.020
Valsalva	113 ± 53 (151)	115 ± 52 (151)	.118

Data (N = 87) are displayed as mean ± standard deviation (median). The P value is based on Wilcoxon signed rank test. The right-hand side ET at rest were statistically significantly higher compared to the left-hand side; however, this difference was not deemed to be a clinically important difference.

found within females or for left versus right ET counts at rest or following Valsalva (rest: left 45 ± 54 vs. right 50 ± 56 , $P = .06$; Valsalva: left 111 ± 55 vs. right 113 ± 54 , $P = .19$). At rest, males had a slightly greater right ET count than left ET count (mean difference $7\% \pm 30$; 95% confidence interval -2 to 16) at rest ($P = .05$); these differences were not present following Valsalva. For the group aged ≥55 years, the right ET count was slightly greater ($9\% \pm 37$; 95% confidence interval -3 to 21%) than the left ET count at rest ($P = .01$). In comparing left and right ET counts, there were no significant differences between males and females (left: rest $P = .25$, Valsalva $P = .72$; right: rest $P = .31$, Valsalva $P = .76$) or age groups (left: rest $P = .28$, Valsalva $P = .92$; right: rest $P = .60$, Valsalva $P = .97$) at rest or following Valsalva.

Left Unilateral versus Bilateral ET Counts for Detection of RLS

Unilateral (left multiplied by 2) ET counts and bilateral ET counts are shown in Figure 3A. Following Valsalva, there were no statistically significant differences noted between unilateral and bilateral ET counts ($P = .128$); however, at rest, there was a statistically but not clinically significant difference between unilateral and bilateral ET counts (bilateral, 110 ± 115 vs. unilateral, 105 ± 114 , $P = .007$). Figure 3B shows the distribution of RLS grade at rest and following Valsalva for unilateral and bilateral measurements. There were no differences between unilateral and bilateral RLS grades at rest or following Valsalva (rest, $Z = -1.90$, $P = .06$; Valsalva, $Z = -1.73$, $P = .08$). Patients were classified on presence or absence of large-grade RLS (IV or V) based on unilateral and bilateral ET counts and the results were compared using the McNemar test. Seventy (80%) patients were classified as having a large-grade RLS following Valsalva by both methods, and 17 (20%) patients were classified as not having a large-grade RLS by both methods. There was no discrepancy in the classification of large-grade RLS based on either unilateral or bilateral ET counts (McNemar $P = 1.0$). The paired sample correlation between unilateral and bilateral ET counts following Valsalva was .997 ($P < .001$). With a sample size of 87, the study had a >99% power to yield a statistically significant result.

Gender Differences in Unilateral pmTCD Embolic Tracks

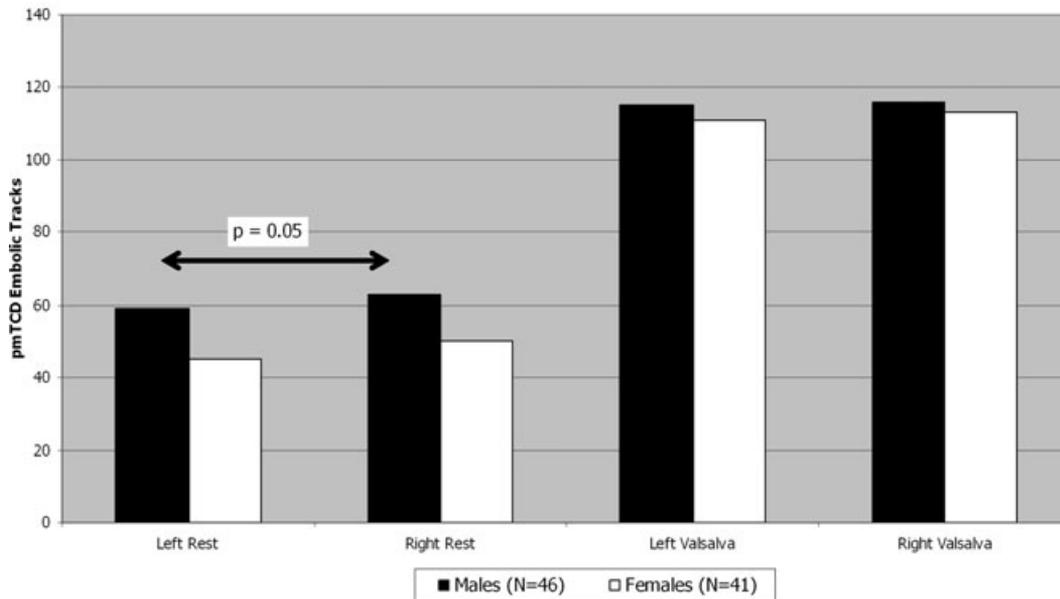


Fig 1. Left versus right temporal bone window ET, separated by sex. Males had a small increase in right versus left ET counts at rest (left 59 ± 60 vs. right 63 ± 62 , $P = .05$), but not following calibrated, sustained Valsalva (left 115 ± 52 vs. right 116 ± 50 , $P = .41$). There were no differences in left and right ET counts within females at rest or following calibrated, sustained Valsalva (rest: left 45 ± 54 vs. right 50 ± 56 , $t = -1.91$, $P = .06$; Valsalva: left 111 ± 55 vs. right 113 ± 54 , $t = -1.35$, $P = .19$). In comparing left and right temporal bone windows, there were no differences between males and females in ET counts at rest or following Valsalva.

Discussion

The results of this retrospective study show that unilateral pmTCD detection of RLS is comparable to bilateral pmTCD detection following calibrated Valsalva. Large-grade RLS was

detected equally well with unilateral and bilateral pmTCD evaluation. This is the first study to systematically compare unilateral and bilateral pmTCD to diagnose and quantify RLS in patients with documented PFO. An additional advantage of

Age Differences in Unilateral pmTCD Embolic Tracks

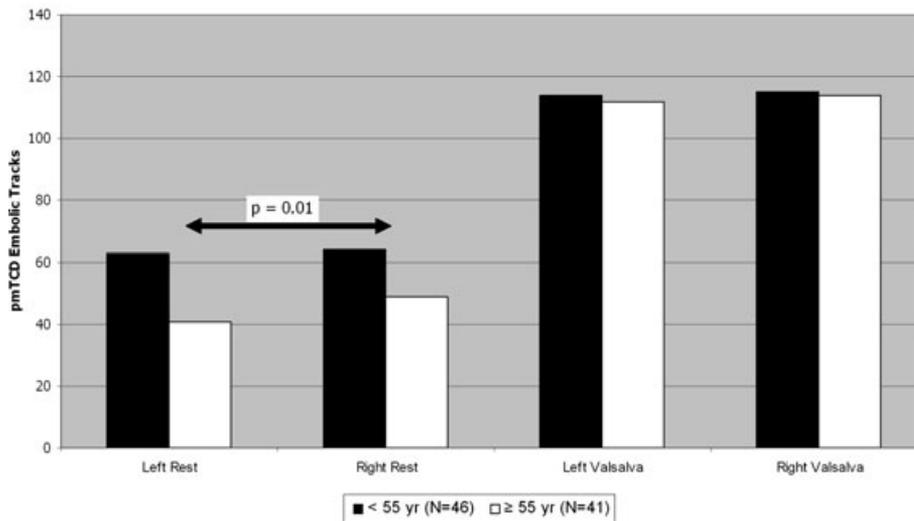


Fig 2. Left versus right temporal bone window ET, separated by age group. There were no differences in left versus right ET counts within patients aged < 55 years at rest or following Valsalva (rest: left 63 ± 64 vs. right 64 ± 65 , $t = -0.97$, $P = .34$; Valsalva: left 114 ± 52 vs. right 115 ± 51 , $t = -.593$, $P = .56$). In the group aged ≥ 55 years, the right temporal bone window had a slightly larger number of ET at rest than the left temporal bone window (left 41 ± 46 vs. right 49 ± 51 , $t = -2.65$, $P = 0.01$), but not following Valsalva (left 112 ± 55 vs. right 114 ± 53 , $t = -1.66$, $P = .11$). In comparing left and right temporal bone windows, there were no differences in left and right ET counts between the age groups at rest or following Valsalva.

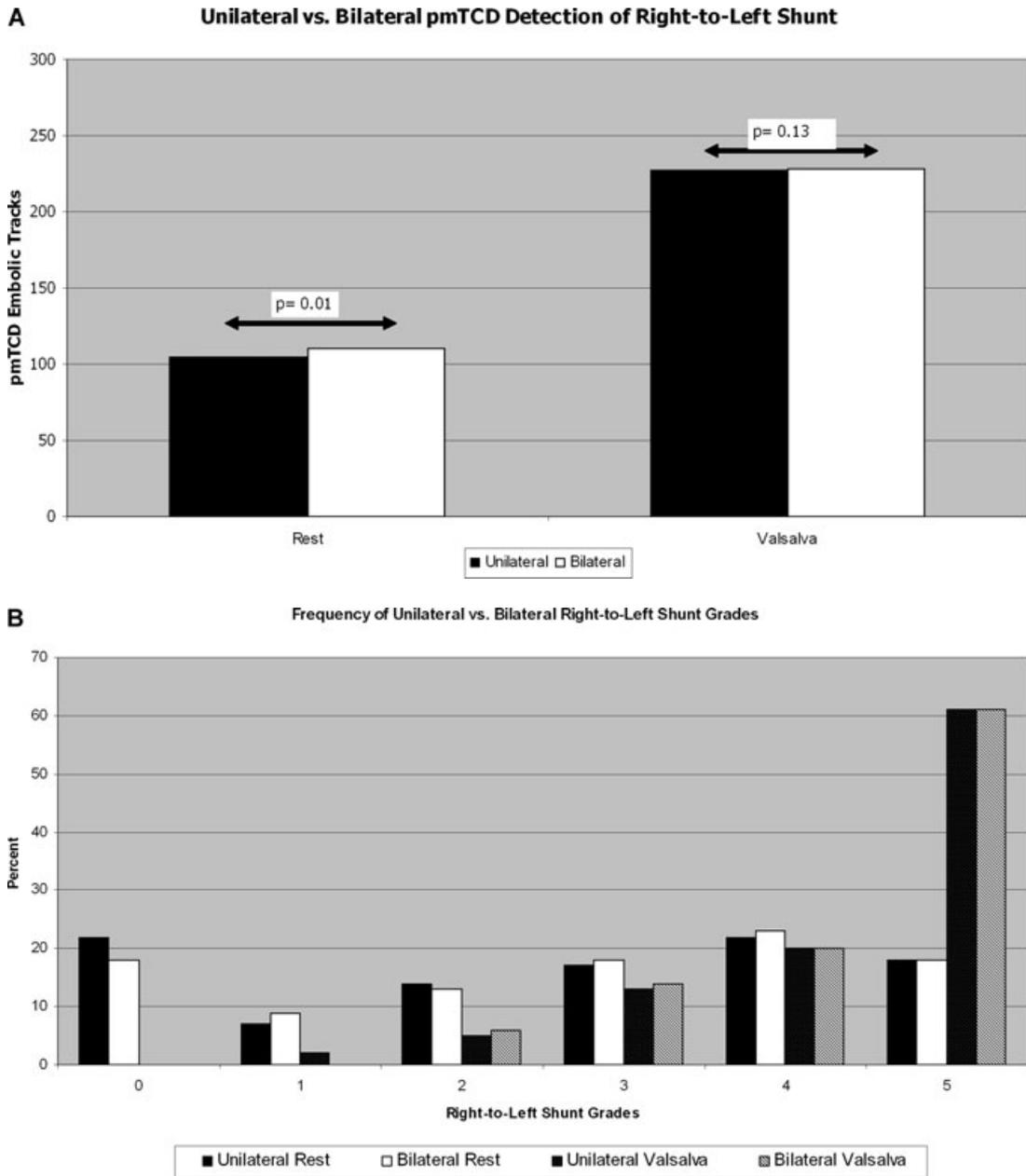


Fig 3. (A) Unilateral (left temporal bone window ET × 2) versus bilateral (sum of left and right temporal bone window ET) at rest and following calibrated Valsalva maneuver. There was a small, but statistically significant difference between unilateral and bilateral ET counts at rest (unilateral 105 ± 114 vs. bilateral 110 ± 115, $t = 2.757$, $P = .007$), but not following Valsalva (unilateral 227 ± 106 vs. bilateral 228 ± 105, $t = 1.536$, $P = .128$). (B) Frequency of right-to-left shunt grades for unilateral and bilateral pmTCD. There were no differences between unilateral and bilateral grades at rest or following Valsalva (rest, $Z = -1.897$, $P = 0.058$; Valsalva, $Z = -1.732$, $P = .083$). Unilateral and bilateral assessments were equivalent at detecting large right-to-left shunt at rest and following Valsalva (McNemar test, $P = 1.00$ for both).

this study is the measurement of inter- and intrarater reliability, which has not been reported in other TCD publications. These results support the insonation of a single temporal bone window to detect RLS with pmTCD, which may result in a more timely and efficient examination.

The validity of unilateral evaluation of RLS by TCD requires symmetry of ET counts in left and right temporal bone windows. This study found a small increase in ET counts at rest in the right temporal bone window compared to the left in the overall sample ($P = .02$), but not following Valsalva.

These small differences at rest are probably not clinically significant, because RLS grade is commonly established following Valsalva.^{2,15} Our results are in partial agreement with Droste et al. in 2004,¹⁰ who reported a 12% difference between left and right high intensity transient signals on multiple-gated TCD. Of note, these authors found the difference only following Valsalva. The authors speculated that there may be a preferential streaming pattern of contrast from the aorta into the brachiocephalic trunk, which favors flow into the right carotid artery; however, they had no evidence to support this pattern.

Asymmetry between left and right temporal bone window ET counts was not seen with single-gated TCD instrumentation by other investigators.^{11,16}

Unilateral pmTCD may not produce adequate quantification of RLS in some groups. In this study, subgroup analyses of males showed small but statistically significant increases in ET counts at rest in the right temporal bone window compared to the left. Women showed no asymmetry in ET counts at rest or following Valsalva. The results of other investigations showed that women are less likely to have adequate bilateral temporal bone windows, especially with increasing age. A 17% success rate for bilateral MCA recording was reported in Asian women aged ≥ 70 years in 1 study,⁵ whereas 74% of Asian men in the same age group had 2 adequate temporal bone windows. The authors attributed the sex differences to increased temporal bone thickness, as increasing the transducer power from 100 to 400 mW/cm² increased detection of MCA blood flow signals in women. In a study of elderly patients, 23% of temporal windows in women were impenetrable to ultrasound, whereas only 1% of the temporal bone windows in men could not be insonated.¹⁷

This study did not find differences between age groups for left or right ET at rest or following Valsalva; however, those aged ≥ 55 years had a larger right ET count than left ET count at rest. Older individuals were more likely to have inadequate temporal bone windows (odds ratio 1.05, 95% CI 1.02-1.09, $P < .01$) in a previous study.¹⁸ Four of 35 patients (11.4%), all aged > 70 years, had suboptimal or no temporal bone windows in an early study of pmTCD.¹⁴ The quality of the signal appears to depend on temporal trabecular bone thickness¹⁹ and density,¹⁸ as cortical plate thicknesses were identical in patients with adequate and inadequate temporal windows.¹⁹ Jarquin-Valdivia et al²⁰ found that temporal squama thickness ≥ 5 mm predicted a poor window for TCD. The need to assess the presence and degree of RLS with TCD in elderly persons was given additional weight by the recent finding that PFO is also associated with cryptogenic stroke in persons aged ≥ 55 years.²¹

The research is not without limitations. The study sample did not have equal numbers of men and women, nor equal numbers of patients aged $<$ or ≥ 55 years. The sample was not randomly selected due to inability to access archived recorded pmTCD data and lack of baseline carotid duplex examinations on all patients. Patients were excluded from the present investigation if they had a single temporal bone window or flow-limiting carotid artery stenosis. All of the patients in this study underwent PFO closure procedures, which may have introduced bias toward larger RLS. No attempt was made to rule out other sources of RLS, although only 1 patient in the group had a coexisting atrial septal defect. It has recently been reported that 35% of patients with PFO have a secondary source of RLS, based on balloon occlusion of the PFO tunnel during closure procedures.²² Future research should compare unilateral pmTCD sensitivity to detect degree of RLS with the current gold-standard of transesophageal echocardiography prospectively and under real-world conditions.

In conclusion, our results indicate that diagnosis and quantification of RLS using pmTCD may be confidently achieved through unilateral temporal bone window detection and yield

equivalent results as bilateral detection. Unilateral pmTCD detection may be performed without preference for left or right temporal bone approach.

This research was funded by a grant from Terumo Medical Corporation. Dr. Moehring is Vice President of Product Development at Spencer Technologies. At the time this study was performed, Terumo Medical was the international distributor of Spencer Technologies instruments.

The authors wish to thank staff members of Spencer Vascular and Spencer Technologies for their assistance in data retrieval. The authors would also like to thank Robert L. Salazar for his expertise in database management.

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