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PEDIATRIC AND CONGENITAL HEART DISEASE

Original Studies

Sensitivity of Brachial Versus Femoral Vein Injection of Agitated Saline to Detect Right-To-Left Shunts with Transcranial Doppler

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Background: Transcranial Doppler (TCD) can detect a right-to-left shunt (RLS) with high sensitivity but has a 5% chance of a false negative study. TCD is usually performed with injection of agitated saline into an arm vein. We compared the sensitivity of TCD performed from the brachial versus femoral veins. Methods: Patients presenting to the cardiac catheterization laboratory for percutaneous closure of a patent foramen ovale (PFO) were enrolled. Power M-mode Transcranial Doppler (Terumo 150 PMD) was conducted. After injection of a mixture of 8 cc of agitated saline, 0.5 cc of air, and 1 cc of blood into the brachial vein, embolic tracks were counted over the middle cerebral arteries. The degree of RLS was evaluated by TCD at rest, and with Valsalva at 40 mmHg aided by visual feedback with a manometer device. The test was repeated using femoral venous injections. Results: Sixty five patients were enrolled, mean age 52, 43% male. TCD grades were significantly higher with femoral injections compared to brachial injections at rest ($p<0.0001$), and with the Valsalva maneuver ($p<0.0001$). The presence of a RLS was confirmed by intracardiac echocardiography (ICE) during cardiac catheterization in 62 (95.4%) patients. Conclusion: The sensitivity of TCD for detection of RLS is increased when agitated saline injections are performed through the femoral vein. In patients with a high clinical suspicion for RLS, low TCD grades obtained with traditional brachial venous access should be interpreted with caution. When possible, a repeat study using femoral venous access may be considered.

Key words: CLAS; closure; ASD/PDA/PFO; ITTE; imaging; TTE/TEE; CONA-congential heart disease; adults

INTRODUCTION

Pioneered almost 25 years ago by Dr. Merrill Spencer for detection of atheroemboli [1], Transcranial Doppler (TCD) is applied in variety of medical conditions. TCD with agitated saline injection is commonly used for diagnosing cardiac right-to-left shunting (RLS). Compared with contrast transesophageal echo (TEE), TCD has increased sensitivity, for diagnosis of RLS [2]. In addition, it is highly reproducible, has low inter-observer variability [3], is easier to perform, and is more comfortable for the patient than TEE.

The results of TCD are technique-dependent and may vary with positioning of the patient [4] and the

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Conflict of interest: Nothing to report.

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TABLE I. Spencer Logarithmic Scale for TCD Grading

Grade	Microbubbles (mB)
Grade 0	0 mB
Grade 1	1–10 mB
Grade 2	11–30 mB
Grade 3	31–100 mB
Grade 4	101–300 mB
Grade 5	>300 mB

site of contrast injection [5]. The purpose of this study was to compare the sensitivity of brachial venous access TCD with femoral venous access TCD.

METHODS

Study Population

Sixty-five consecutive patients referred for PFO closure were evaluated between March 2009 and January 2011. All 65 patients had a history of cryptogenic stroke or migraine, and were initially diagnosed with PFO by using TCD, TTE, or TEE agitated saline contrast injected from a brachial vein.

Study Procedure

Brachial access TCD was performed within 1 hr prior to the patient entering the cath lab. The brachial vein was accessed with a 20G Angiocath. Agitated saline was formed by mixing 8 cc of normal saline, 0.5 cc of room air, and 1 cc of blood to ensure production of a foam of bubbles to enhance echo contrast. The mixture of bubbles was then injected into the brachial vein. For TCD, the middle cerebral arteries (MCAs) were insonated bilaterally, and the bubble grade was measured and recorded at rest by a Terumo 150 PMD TCD machine (Spencer Technologies, Seattle, WA). The TCD study was repeated with a provocative maneuver, visually aided Valsalva strain, performed with the patient exhaling forcefully into a manometer graduated to 40 mm Hg.

A second TCD procedure was performed in the catheterization laboratory with femoral venous access. A percutaneous puncture of the right femoral vein was performed to introduce two 8-French sheaths. The agitated saline contrast mixture was injected into the right femoral vein at rest and immediately after release of the visually aided Valsalva maneuver (with the patient exhaling into the manometer to attain 40 mm Hg). The Spencer grade was used to analyze the number of microbubbles that appeared in the middle cerebral artery bilaterally during the first minute after the injection. Grade 3 and higher ($\geq$31 microbubbles equivalent) was considered as a positive result representing a significant shunt (Table I).

TABLE II. Baseline Characteristics of the Study Cohort ($n = 65$)

Baseline characteristics	Mean $\pm$ SD, or N (%)
Age (years)	52.3 $\pm$ 14.0
Male	28 (43.0%)
CVA	40 (61.5%)
Anterior circulation	19 (47.5%)
Posterior circulation	14 (35%)
Both vascular distributions	7 (17.5%)
Migraine	47 (72.3%)
CVA and migraine	32 (49.2%)
Prior TIAs	21 (32.3%)
MRI performed	53 (81.5%)
Nonspecific white matter lesions on MRI	14 (21.5%)
Pulmonary embolism	1 (1.5%)
Peripheral embolism other than stroke	6 (9.2%)
Smoking	6 (9.2%)
Hyperlipidemia	30 (46.1%)
Diabetes	5 (7.7%)
Hypercoagulable state[a]	21 (23%)
Malignancy	4 (6.1%)

[a]Hypercoagulable state includes: birth control pills/hormone replacement therapy use, pregnancy, factor V Leiden, prothrombin G20210A mutation, antiphospholipid antibodies, homocysteinemia, protein S deficiency, protein C deficiency, elevated lipoprotein A, antithrombin III deficiency, anticardiolipin AB, increased factor VIII activity, B2-glycoprotein-1 AB and thrombocytosis.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD. Dichotomous values are expressed as frequency percentage. A two-tailed t-test was used to compare the Spencer grade at rest and on Valsalva, using the brachial and femoral route of contrast injection, respectively. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Sixty five patients with a mean age of 52.3 $\pm$ 14.0 years were enrolled. Of these patients, 40 (61.5%) had a stroke and 47 (72.3%) had a diagnosis of migraine headaches. Baseline characteristics of the study population are presented in Table II.

The presence of RLS was confirmed during cardiac catheterization with intracardiac echocardiography (ICE) in 62 (95.4%) patients. Of these 62, only 56 had a PFO confirmed by the passage of a guide wire through the interatrial septum. The remaining six had a RLS present without evidence for a PFO. In these

TABLE III. TCD Grades at Rest and During Valsalva Using Brachial and Femoral Venous Access

	Mode of the injection	Mean grade ± SD	*P*-value
TCD grade at rest	Brachial	2.1 ± 1.6	<0.0001
	Femoral	3.2 ± 1.7	
TCD grade on Valsalva	Brachial	3.5 ± 1.3	<0.0001
	Femoral	4.5 ± 1.1	

cases, a 7-French Berman end-hole catheter was advanced beyond the right atrium into the main pulmonary artery and a repeat agitated saline study confirmed the positive bubble study, thus signifying the presence of intrapulmonary shunting. The timing of RLS appearance on the TCD in these six cases varied. In three of the patients, TCD demonstrated the appearance of a RLS within the first five cardiac cycles, while in the other three patients it was delayed (>7 cardiac cycles after agitated saline injection). The presence of an extracardiac source of shunting was suspected and confirmed on chest CT in three patients. The pulmonary arteriovenous malformations in these patients exceeded 15 mm in diameter.

Three patients in the study had a negative TCD, with Spencer grade not exceeding grade 2 on Valsalva. In these three cases the absence of a PFO was confirmed during cardiac catheterization, as demonstrated by the inability to pass a guide wire across the atrial septum. All three patients with negative TCDs had false-positive TEE studies.

The average tunnel length of the PFO based on TEE measurements was 11 ± 3.2 mm; the average height of the PFO was 3.2 ± 2.2 mm measured as the separation between the septum primum and the septum secundum. Right atrial (RA) pressure was measured during cardiac catheterization in 35 patients. The mean RA pressure at rest was 7.6 ± 3.1 mm Hg and increased to 27.8 ± 10.1 mm Hg during the Valsalva maneuver.

The average TCD Spencer grade at rest was 2.1 ± 1.6 obtained through the brachial access, versus 3.2 ± 1.7 with injection via femoral access ($P < 0.0001$). During the Valsalva maneuver, the average TCD grade at rest was 3.5 ± 1.3 for brachial access and 4.5 ± 1.1 for femoral access ($P < 0.0001$) (Table III).

TCD results obtained through a brachial injection demonstrated a negative study in 8 of 65 patients (12.3%). However, when repeating the study through the femoral injection, the number of negative TCD studies decreased to 3 (4.6%). Figure 1 demonstrates the mean TCD grade increment in patients with brachial vs. femoral injection of agitated saline. The average increase in the Spencer scale was 1.0 ± 1.5 at rest and 1.0 ± 1.1 after release of the Valsalva maneuver set at 40 mm Hg. All five patients whose RLS was found only with a femoral injection, had a documented PFO on cardiac catheterization.

The majority of TCD grades obtained with injection through the femoral venous access were higher than those obtained through the brachial venous access ($P < 0.0001$, both at rest and on Valsalva). Six patients had lower Spencer grades on femoral injection at rest, with an average of 1.7 ± 0.8. During the study with Valsalva strain, the mean difference did not exceed a grade of 1 and was observed only in three patients.

Of 65 patients, 6 (9%) patients were found to have an atrial septal aneurysm (ASA). In these patients, the average Spencer grade at rest was 2.8 ± 1.3 for brachial access TCD, and 4 ± 0.6 for femoral access TCD ($P = 0.06$). During the Valsalva maneuver, the average TCD grade at rest was 4.3 ± 0.8 for brachial access and 5.0 ± 0 for femoral access ($P = 0.1$). Patients with an ASA, compared with their counterparts with a PFO but no aneurysm, exhibited less variability in Spencer grades, independent of the mode of the TCD study (rest vs. Valsalva maneuver) or the route of the agitated saline injection (brachial vs. femoral venous access) (Table IV).

DISCUSSION

This study reaffirms that the site of injection of agitated saline bubbles as an echo contrast agent influences the Spencer grade recorded during TCD studies. Two other studies that have looked at differences in brachial vs. femoral contrast injection during TEE and/or TCD [5,6] found improved efficacy of contrast injections via the femoral route for detecting PFOs [5].

A number of factors could explain the observed differences between the femoral and brachial injection routes. The sheaths that are placed in the femoral vein are larger than the 20G Angiocath used for brachial intravenous infusion lines. Shorter vascular transit time and a higher concentration of bubbles in the right heart may contribute to the increased Spencer grade observed with femoral access TCD.

Another factor that may account for the higher grade of shunting seen with femoral access TCD is the "streaming" effect of contrast injection coming from the IVC, as opposed to the "angulated" flow of the blood from the SVC which is directed away from the interatrial septum [7]. The IVC and the SVC can be viewed as cylinders with the apertures turned towards the fossa ovalis (for IVC) and tricuspid valve (for SVC). Certain extracardiac events (e.g., unilateral paralysis of diaphragm, rapid weight loss, pneumothorax) produce changes in the geometry on interatrial septum, with a placement of PFO directly above the ostium of IVC. The

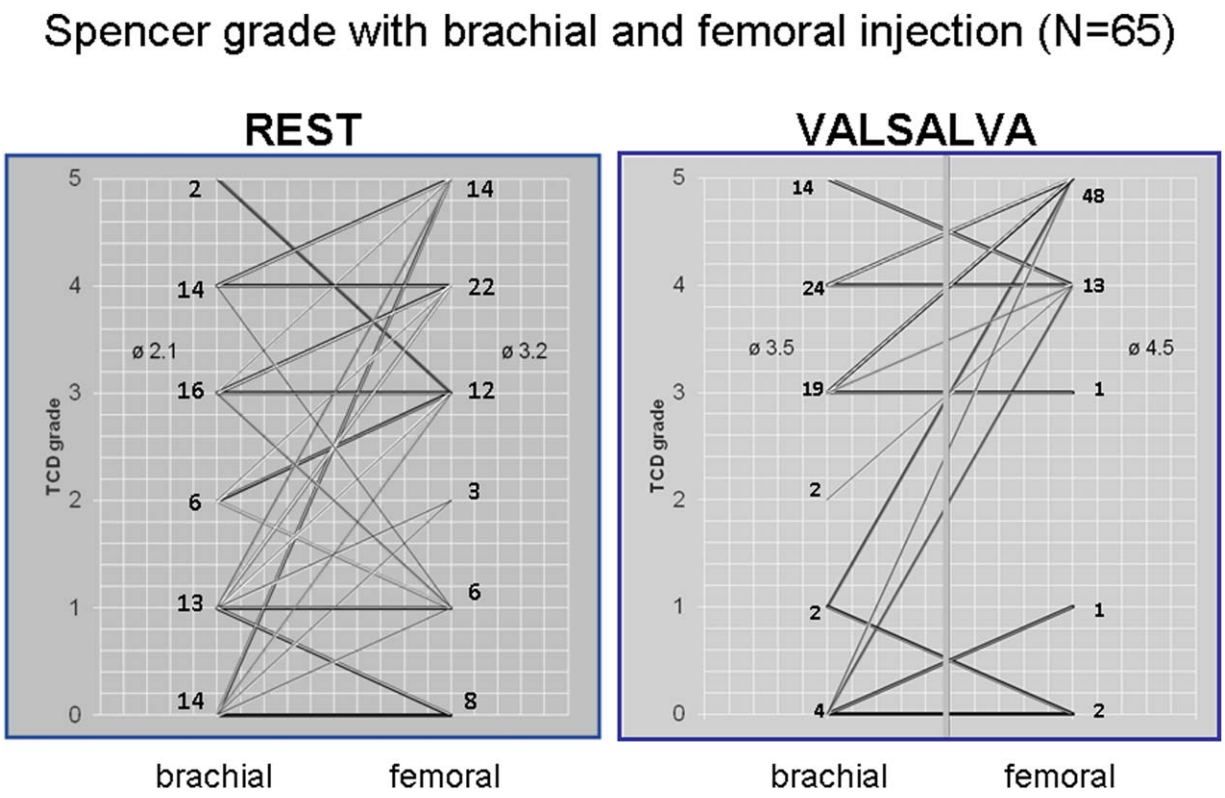

Fig. 1. TCD grade increment in patients with brachial vs. femoral injection of agitated saline. The Spencer grades obtained on TCD at rest and on Valsalva through brachial injection were compared to those with femoral injection. The observed mean Spencer grade increment was 1.1 at rest and 1 on Valsalva. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE IV. Comparison of TCD Grades in Patients with vs. without Atrial Septal Aneurysm

	Positive studies ($N = 62$)						
	Patients with ASA ($N = 6$)			Patients without ASA ($N = 56$)			
	Brachial injection	Femoral injection	Increment	Brachial injection	Femoral injection	Increment	p-value[a]
At rest	2.8 ± 1.3	4 ± 0.6	1.2 ± 1.0	2.2 ± 1.5	3.2 ± 1.6	1.0 ± 1.5	0.75
P-value	0.06			<0.0001			
On Valsalva	4.3 ± 0.8	5 ± 0	0.7± 0.8	3.6 ± 1.1	4.8 ± 0.4	1.1 ± 1.1	0.39
P-value	0.1			<0.0001			

[a]p-value for comparison of the Spencer grade increment between the groups of patients with ASA and without ASA.

TCD with bubble study performed through femoral vein in these patients demonstrates RLS of severe magnitude, whereas the study obtained through the brachial injection reveals only modest shunting at best, and can even be negative. These patients often exhibit severe orthodeoxia in the absence of clinically significant pulmonary disease—a sign indicative of significant RLS.

Anatomically, the Eustachian valve directs fetal blood from the IVC toward the foramen ovale. In adults, variations in the size of the remnant of the Eustachian valve, or the morphology of the PFO itself (longer canal, hyperdynamic excursion of the septum, more rigid canal with "gapping" appearance of the RA opening of the PFO canal) could be responsible for emphasizing the RLS during an agitated saline injection through the femoral vein. In addition, increased right atrial opacification with the femoral injection may be a contributing factor.

The diagnostic accuracy of the standard Transcranial Doppler procedure with injections via brachial access can be enhanced by several methods. Both optimizations of the IV access size (20 Gg Angiocath) and vein access site (antecubital fossa) in order to shorten the transit time of the bubbles from the entry point to the right atrium are effective ways enhance the sensitivity of TCD study [5].

The position of the patient may increase the Spencer grade detected by brachial vein access TCD. Prior studies have shown that the TCD grade increases when the subject is sitting or even standing compared with the recumbent position [4]. In our study, brachial vein access TCD procedures were performed on patients in a semireclined position. In contrast, all the femoral vein access TCD studies were obtained with the patients lying supine. Assuming that gaseous bubble buoyancy may enhance the grade of the shunt (because the foramen ovale is located in the superior aspect of the atrium), this could increase the grade of RLS obtained from the brachial venous access. This may account for the lower TCD grade at rest through the femoral injection in six patients.

In addition, during femoral access TCD, patients were under conscious sedation as a part of their closure procedure. The measurements of RA pressure demonstrate that the patients, despite the visual feedback and verbal directions from the operator, consistently generated lower than expected pressures during the Valsalva maneuver performed during femoral injections. We do not have data on RA pressure generated during TCD with brachial injections, and cannot compare it with the RA pressure findings obtained during Valsalva strain with femoral vein cannulation.

In patients with ASA, femoral injections did not produce a significant increase in Spencer grades, signifying that TCD with agitated saline injection via brachial venous access is a reliable diagnostic tool in this subset.

The observation that five patients would be categorized as having an insignificant shunt by the brachial approach, but had a positive TCD grade by a femoral vein injection, emphasizes that the diagnosis of right to left cardiac shunting is subject to procedural techniques.

LIMITATIONS

Femoral vein cannulation is a minimally invasive procedure that is impractical to perform on an outpatient basis, but may be useful in a cardiac catheterization laboratory.

CONCLUSIONS

The sensitivity of TCD for detection of RLS is increased when agitated saline injections are performed from the femoral vein as compared with the brachial vein. Anatomic factors, such as the orientation of the inferior vena cava to the foramen ovale and the Eustachian valve may contribute to this phenomenon. In patients with a high clinical suspicion for RLS, TCD grades that are insignificant when obtained with the traditional brachial venous access, have an 8% false negative rate. When feasible, a repeat study using femoral venous access can be considered.

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