Detection of Paradoxical Cerebral Echo Contrast Embolization by Transcranial Doppler Ultrasound

Steve M. Teague, MD, and Mukesh K. Sharma, MD

Contrast echocardiography has been shown to be a sensitive method for detecting patent foramen ovale in embolic stroke, implying paradoxical embolization. However, not all two-dimensional echocardiographic studies are of diagnostic quality, and direct evidence for paradoxical cerebral embolization remains lacking. We addressed these problems by simultaneously using transcranial Doppler ultrasound and contrast echocardiography to compare relative sensitivity and concordance in the detection of right-to-left vascular shunting. Forty-six patients with stroke, transient neurologic defect, or question of atrial septal defect underwent study at rest and during Valsalva strain. Two-dimensional echocardiography detected shunting in 26% at rest and 15% during Valsalva strain, whereas transcranial Doppler study returned rates of 41% and 41%, respectively. Concordance was 82% and 75%, respectively. Discordant studies almost always had evidence of paradoxical contrast embolization by transcranial Doppler and intermediate findings by two-dimensional echocardiography. Transcranial Doppler is a sensitive, unambiguous technique for the detection of anatomic substrates and target organ involvement in patients suspected to have paradoxical cerebral embolization. (Stroke 1991;22:740-745)

The etiology of stroke in more than a third of young adult patients may remain uncertain even after extensive clinical study. Paradoxical embolization via patent atrial foramen ovale has become suspect as a cause of embolic strokes or transient ischemic attacks. Contrast echocardiography with patients at rest and during provocative maneuvers has been shown to be a sensitive method for noninvasively detecting patent foramen ovale in these patients. However, not all two-dimensional echocardiographic studies are of diagnostic quality. Moreover, the technique only reveals the substrate for paradoxical embolization; the arterial delivery of emboli originating in the venous system at critical target organs is not demonstrated.

The objective of contrast echocardiography in the evaluation of interatrial shunting is the detection of microcavitation gas bubbles entering left heart chambers after intravenous injection. As an alternative to ultrasonic imaging, Doppler ultrasound has served as a sensitive detector of blood-borne gas bubbles in decompression sickness by demonstrating air bubbles in the pulmonary artery. Specially designed transcranial Doppler devices have been used to detect micro air emboli in the middle cerebral artery during surgery.

The purpose of this study was to use transcranial Doppler ultrasound as a detector of gas bubbles in the middle cerebral artery simultaneously with two-dimensional apical echocardiography as a detector of bubbles in the left atrium and ventricle so as to compare relative sensitivity and demonstrate concordance in the detection of right-to-left vascular shunting.

Subjects and Methods

We studied 46 consecutive patients referred for contrast echocardiographic examination in the evaluation of interatrial shunting. The average age was 41±7 years, and 21 (46%) were females. Twenty-six percent were referred for fixed neurologic deficit, another 26% for transient neurologic deficit, and the remaining 48% were investigated to exclude atrial septal defect.

We used a 2-MHz pulsed-wave transcranial Doppler device (TC-64e, Carolina Medical Electronics, Inc., King, N.C.) with a spherically focused transducer (sample volume depth, 45–60 mm) to sonicate the right middle cerebral artery (Figure 1). The transducer was placed between the right orbit and external
ear along the zygomatic arch, and its position was adjusted to find a transtemporal ultrasonic window allowing the best sonication of the middle cerebral artery along its proximal course. A helmet was fashioned to hold the transducer in position during the study. Fast Fourier-analyzed video displays of the returning Doppler velocity signals were mixed with two-dimensional echocardiographic video signals and a voice channel and were continuously displayed and recorded throughout the testing period.

Microcavitation contrast was generated by agitating a mixture of 0.2 ml of air, 0.5 ml of the patient's blood, and 5 ml of normal saline between two 10-ml syringes connected by a tri-port stopcock. Bubble size was measured by immediately filling a microcapillary tube with the agitated contrast mixture and measuring individual bubbles against a calibrated microscopic grid. No bubbles smaller than 24 or larger than 144 \( \mu \text{m} \) were observed (Figure 2).

The contrast medium was injected rapidly into a left antecubital vein during suspended respiration with or without Valsalva strain. Two-dimensional echocardiography was performed with the patient in the left lateral decubitus position using the apical four-chamber view. Simultaneous, continuous two-dimensional echocardiography and transcranial Doppler sonography were performed before, during, and after contrast injection. Appearance times of contrast in the left ventricle and middle cerebral artery were recorded.

We considered the two-dimensional echocardiographic study positive for interatrial shunting on unequivocal visualization of contrast microcavitations in the left atrium or ventricle (Figure 3). Appearance of microbubbles in the cerebral circulation was indicated by a "chirp" in the acoustic signals from the middle cerebral artery and a corresponding video spike. As other investigators also have observed, these signals and spikes were of much higher amplitude than the background Doppler flow signal and subjectively correlated in intensity with the quantity of bubbles shunting right-to-left on the echocardiogram (Figure 3B).

### Results

We performed resting studies on all 46 patients, 39 of whom we tested during Valsalva strain as well. Six of the seven patients not undergoing Valsalva had unequivocally positive two-dimensional echocardiograms and transcranial Doppler studies, thus obviating the need for a Valsalva strain, whereas the other patient could not perform the maneuver due to neurologic disability.

Two-dimensional echocardiography detected interatrial shunting in 12 of the 46 patients (26%) at rest and in six of the 39 patients (15%) during Valsalva strain (Table 1). Transcranial Doppler study indicated venous-injected contrast in the middle cerebral artery in 19 of the 46 patients (41%) studied at rest and in 16 of the 39 patients (41%) studied during Valsalva strain. Time to left atrial appearance was 2.6 ± 0.4 seconds at rest and 2.1 ± 0.3 seconds with Valsalva strain. Time taken for the contrast to appear in the middle cerebral artery after onset of peripheral injection was 5.9 ± 2.3 seconds at rest and 4.6 ± 2.5 seconds during Valsalva strain.

A positive transcranial Doppler study was obtained in all patients who had evidence of interatrial shunting by two-dimensional echocardiography, with concordances of 82% and 75% for resting and Valsalva studies, respectively. Discordant studies almost always had evidence of paradoxical embolization by transcranial Doppler and indeterminate findings (Figure 3C) by two-dimensional echocardiography.

### Discussion

Transcranial Doppler provided direct evidence of paradoxical cerebral echo contrast embolization in all patients who had interatrial shunting by two-dimensional echocardiography and resolved the question of shunting in those with interpretable precordial studies. The sensitivity of transcranial Doppler was particularly superior during Valsalva.
straining, during which two-dimensional echocardiography usually became uninterpretable, but large quantities of bubbles often appeared in the middle cerebral artery.

Several investigators have studied the usefulness of contrast two-dimensional echocardiography for detecting patent foramen ovale and interatrial shunting in young patients presenting with nonhemorrhagic cerebrovascular events. Lechat et al.² studied 60 stroke patients less than age 55 and found that 30% had evidence of interatrial shunting by two-dimensional echocardiography at rest and an additional 10% during Valsalva strain. Age-matched control subjects had a 10% incidence of shunting. Similarly, Webster et al.³ found that 50% of stroke patients less than 40 years of age had right-to-left shunts compared to 15% of age-matched controls. Angiographic correlation of interatrial shunting seen by two-dimensional echocardiography was provided by Harvey et al.,⁴ who studied 11 stroke patients, eight of whom had patent foramen ovale or small atrial septal defects confirmed by cardiac catheterization or surgery.

**TABLE 1. Concordance Between Echocardiographic and Doppler Studies**

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative or indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At rest (n=46)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2D Echo</td>
<td>26% (12)</td>
<td>74% (34)</td>
</tr>
<tr>
<td>TCD</td>
<td>41% (19)</td>
<td>59% (27)</td>
</tr>
<tr>
<td><strong>During Valsalva strain (n=39)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2D Echo</td>
<td>15% (6)</td>
<td>85% (30)</td>
</tr>
<tr>
<td>TCD</td>
<td>41% (16)</td>
<td>59% (23)</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate total patients in each category. 2D Echo, precordial apical four-chamber echocardiography; TCD, transcranial Doppler ultrasound.

Interatrial shunting is commonly discovered using contrast two-dimensional echocardiography in young patients who present with nonhemorrhagic cerebrovascular events.¹⁻² However, contrast echocardiography provides evidence only for material passing from the venous system to the arterial circulation. Target organ involvement is not demonstrated, and interpretation of the echocardiographic image is always difficult in patients with poor acoustic characteristics. Although this study was not designed to reexplore the prevalence of patent foramen ovale in embolic stroke, it does illustrate the difficulties en-
countered in detecting left-to-right contrast shunting in many echocardiographic studies. The clinical implication of this study is that the sensitivity for right-to-left shunt detection can be improved by Doppler monitoring of the cerebral arterial circulation after venous contrast delivery.

Passage of the small microbubbles used in this study to the cerebral circulation appeared to be well tolerated. No patient reported symptoms during or after the contrast study. These observations are concordant with a survey of contrast echocardiography safety reported by the American Society of Echocardiography.11

The air-blood interface is an excellent reflector of Doppler ultrasound, producing an acoustic amplitude many orders of magnitude greater than the reflection from flowing red blood cells. This phenomenon was first exploited by Gillis and coworkers4 for the in vivo detection of circulating gas emboli during decompression sickness in animals and later to detect air embolism during neurosurgical procedures and cardiopulmonary bypass using the transcranial Doppler Technique.8,9

Transcranial Doppler study may not be possible when the transcranial ultrasonic window or the middle cerebral artery signal cannot be located. However, a difficult window was a problem in only one subject, whereas six of the two-dimensional echocardiographic studies were of inadequate diagnostic quality. Even in those with satisfactory two-dimensional echocardiographic studies, transcranial Doppler gave less ambiguous evidence for the presence or absence of shunting.

Transesophageal two-dimensional echocardiography usually affords excellent visualization of the atrial septum and the foramen ovale.12-14 We have used this procedure to identify patent foramen ovale in patients during peripheral contrast injection. Indeed, transesophageal contrast echocardiography may become the reference standard to differentiate shunting across the atrial septum from shunting across the pulmonary vascular bed. Transesophageal echocardiography may not be appropriate for many patients with stroke syndromes, particularly those in whom Valsalva straining or sedative-induced respiratory depression might prove deleterious. We reserve transesophageal study to resolve the questions of patent foramen ovale or transpulmonic shunting to patients with uninterpretable or impossible precordial echocardiographic or transcranial echocardiographic examinations.

This study is limited by the absence of normal controls and a “reference standard.” This study was designed only as a comparison of technique, in which each patient served as his or her own control. However, cardiac catheterization appears far less sensitive to the presence of patent foramen ovale than the two ultrasonic techniques discussed here.15 Only one of the major cerebral arteries was sonicated, which may have falsely lowered the sensitivity of the transcranial Doppler.

Pulmonary shunting is unlikely to account for the positive studies. The size of microbubbles used in this study was at least four times larger than the red blood cell, making shunting through pulmonary capillaries very unlikely. Even if some unusually small microbubbles did pass through intact, the contrast effect would diminish as transit to the left atrium was prolonged by traverse of the pulmonary microvasculature. Moreover, the time taken for the appearance of contrast in the left atrium after its injection into the peripheral vein was 2.1 ± 0.4 seconds, whereas appearance after transpulmonic transit appears to be greater than 3 seconds.10 Lastly, echocardiographic shunting of microbubble contrast has been highly correlated with the presence of anatomic intratral defects, as demonstrated in an earlier study from this laboratory and by other workers.1,14

We conclude that transcranial Doppler is a sensitive, unambiguous technique for the detection of intratral shunting, anatomic substrates, and target organ involvement in patients suspected to have paradoxical embolization.

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