Cerebral Ischemic Events Associated With ‘Bubble Study’ for Identification of Right to Left Shunts

José R. Romero, MD; James L. Frey, MD; Lee H. Schwamm, MD, FAHA; Bart M. Demaerschalk, MD, MSc, FRCPC; Hari P. Chaliki, MD, FACC; Gunjan Parikh, MD; Robert F. Burke, MD; Vicken L. Babikian, MD

Background and Purpose—Detection of an intracardiac shunt is frequently sought during the evaluation of patients with cryptogenic ischemic stroke and agitated saline intravenous injection, or “bubble study” (BS), is performed in most cases. We present the first attempt to identify the clinical features in patients who had cerebral ischemic events with BS.

Methods—Using a list serve established by the American Academy of Neurology, a member posted a question regarding the safety of BS in patients with patent foramen ovale. A standardized questionnaire was used to gather data about patients with cerebral ischemic events, details of each case were reviewed, and the findings pooled.

Results—Five patients with ischemic complications of BS (all female, aged 42 to 90 years) were identified from 4 institutions, 3 ischemic strokes and 2 transient ischemic attacks. Events occurred either during or within 5 minutes of BS. Early brain MRIs confirmed acute infarction in 3, including one who had transient symptoms. MRI infarct volumes were small, and deficits were mild in those who developed stroke. Diagnostic evaluation revealed a patent foramen ovale alone in one case, a pulmonary arteriovenous malformation in one case, and a patent foramen ovale and/or pulmonary shunt in 3 cases.

Conclusions—Ischemic cerebrovascular complications can occur in patients who undergo BS and are associated with the presence of cardiac or pulmonary shunts. The true incidence and degree of disability remains unknown, and further study is indicated to assess the impact of technical differences in BS methodology. Novel methods to promote physician communication such as the use of electronic list serves may reduce barriers to reporting of drug, technique, or device complications and should be explored to identify rare complications that otherwise will likely go unappreciated. (Stroke. 2009;40:2343-2348.)

Key Words: atrial heart septal defects ■ arteriovenous fistula ■ echocardiography ■ patent foramen ovale ■ stroke ■ transcranial Doppler ultrasonography ■ transesophageal echocardiography ■ transient ischemic attack

In the United States, ischemic stroke affects approximately 678,000 individuals per year (87% of all strokes). Nearly 30% of all ischemic strokes are classified as embolic and, in young individuals, as many as 43% as cryptogenic. The search for an embolic source explaining the ischemic stroke frequently involves diagnostic testing for the presence of a patent foramen ovale (PFO) or other cardiac right to left shunts given the reported association of stroke with PFO, particularly in young patients. Different methods are available for detection of a right to left shunt, including transthoracic and transesophageal echocardiography (TTE and TEE, respectively) and transcranial Doppler ultrasound (TCD). These methods frequently involve the intravenous injection of agitated saline mixed with air (“bubble study” [BS]) and a shunt is confirmed when there is a rapid detection of the passage of microbubbles to the left side of the heart (TTE and TEE) or cerebral circulation (TCD). Although TEE is generally considered a safe procedure, there is a theoretical concern for causing paradoxical cerebral air embolism, which may result in an acute ischemic stroke or transient ischemic attack (TIA). Such embolism has been reported with procedures such as line placement, cardiac surgery, and trauma. Previous reports also suggested that this complication may occur during bubble study and when indocyanine green dye was used as a contrast agent, but available data regarding the specific features of this complication remain limited. In the present report, we present 5 patients who developed symptoms of cerebral ischemia related to the performance of a BS during evaluation of right to left shunts.
Methods
Recently, electronic and Internet-based resources have been made available to enhance communication among physicians. In the present report, we used such means to collect information regarding cerebral ischemic events related to performance of a diagnostic BS. The American Academy of Neurology established a list serve in 2006 to enhance communication among its stroke section members. The list works as a digital chat room in which members can post questions, answers, or comments. Of the 981 members in the stroke section, 739 are active members of the list serve. Using this method available online, a member posted a question regarding the safety of BS in patients with a right to left shunt. A standardized questionnaire was used to gather data about each patient and details of each case were reviewed and the findings pooled.

Results
Since January 2008, an average of 113 posts per month have been registered in the American Academy of Neurology list serve. Five neurologists with expertise in vascular neurology from 4 different institutions certified as stroke centers answered the question posted by one member and 5 cases were identified (Table). Examples of positive BS are shown during TTE (Figure 1) and during TCD (Figure 2). In 2008, there were 3314 BS performed in the 4 institutions where cases were reported, including BS done during TTE, TEE, and TCD studies.

Case 1
A 90-year-old woman developed sudden onset of horizontal diplopia and dizziness immediately after a TCD with BS performed for evaluation of acute ischemic stroke. Her examination revealed new right internuclear ophthalmoplegia. Brain MRI confirmed a new acute infarct in the right pontine tegmentum. Two days prior she was admitted after presenting with left leg paralysis and sensory loss. She was treated with intravenous tissue plasminogen activator with significant improvement in strength in the leg. Initial brain MRI revealed foci of restricted diffusion in the frontoparietal regions bilaterally; left frontal, occipital, and temporal lobes; and bilateral cerebellar hemispheres. Diagnostic evaluation included a CT angiogram showing no significant stenosis of the intra- and extracranial circulation. TTE was negative for embolic source and was considered insufficient evidence of PFO. She received treatment with antiplatelet therapy and at 4-month follow-up reported improvement in diplopia but persistent internuclear ophthalmoplegia was seen on examination.

Case 2
An 80-year-old woman underwent TTE with BS for evaluation of dyspnea and suspected right to left shunt. She had a history of hepatopulmonary syndrome related to Crohn’s disease and idiopathic cirrhosis. Within 2 minutes of BS performance, she presented sudden onset of left-sided weakness. Examination confirmed left hemiparesis. Her symptoms lasted 30 minutes and resolved completely. Head CT and MRI were negative for acute stroke or air in the intracranial circulation. The TTE and BS during the event were consistent with intracardiac shunt, but an extracardiac shunt also was suspected given the delayed large volume of microbubbles

### Table. Demographic and Clinical Characteristics of Patients and Cerebrovascular Ischemic Event Details

<table>
<thead>
<tr>
<th>Case No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>90</td>
<td>80</td>
<td>42</td>
<td>49</td>
<td>42</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Medical history</td>
<td>TIA</td>
<td>Crohn’s disease</td>
<td>Migraine</td>
<td>Migraine ischemic stroke</td>
<td>Migraine</td>
</tr>
<tr>
<td>Prior MRI findings</td>
<td>Embolic stroke</td>
<td>ND</td>
<td>Right MCA infarct</td>
<td>Chronic left frontal parietal; acute right frontal</td>
<td>None</td>
</tr>
<tr>
<td>Indication for BS</td>
<td>Acute ischemic stroke workup</td>
<td>Hepatopulmonary shunt evaluation</td>
<td>Acute ischemic stroke workup</td>
<td>Acute ischemic stroke workup</td>
<td>TIA workup</td>
</tr>
<tr>
<td>Event type/time after saline injection</td>
<td>Stroke/immediate</td>
<td>TIA/within 2 minutes</td>
<td>TIA/within 5 minutes</td>
<td>Stroke/during injection</td>
<td>Stroke/within minutes</td>
</tr>
<tr>
<td>Event symptoms</td>
<td>INO</td>
<td>Left hemiparesis</td>
<td>Left arm weakness</td>
<td>Left inferior quadrantanopia</td>
<td>Face and fingers paresthesias</td>
</tr>
<tr>
<td>Symptom duration</td>
<td>&gt;4 months</td>
<td>30 minutes</td>
<td>30 minutes</td>
<td>Persistent</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Follow-up neurologic examination</td>
<td>Partially improved</td>
<td>No residual deficit</td>
<td>No data</td>
<td>No change</td>
<td>No residual deficit</td>
</tr>
<tr>
<td>Post MRI-diffusion-weighted imaging</td>
<td>Tiny pontine focus</td>
<td>Negative</td>
<td>2 midbrain small infarcts</td>
<td>Right occipital infarct</td>
<td>Negative</td>
</tr>
<tr>
<td>Test modality</td>
<td>TCD and TEE</td>
<td>TTE and pulmonary SPECT</td>
<td>TTE and TEE</td>
<td>TTE and TEE</td>
<td>TTE</td>
</tr>
<tr>
<td>Findings</td>
<td>Possible PFO</td>
<td>PFO and pulmonary shunt</td>
<td>Pulmonary AVM</td>
<td>PFO</td>
<td>PFO and possible pulmonary shunt</td>
</tr>
</tbody>
</table>

INO indicates internuclear ophthalmoplegia; ND, not done; SPECT, single photon emission computed tomography; MCA, middle cerebral artery; AVM, arteriovenous malformation.
seen in the left atrium. Pulmonary perfusion scan confirmed an additional pulmonary right to left shunt. Examination at 1 hour after the event was normal. No additional antithrombotic therapy was used.

Case 3
A 42-year-old woman presented with a sudden onset of left upper limb paralysis approximately 5 minutes after a TEE with BS done for evaluation of acute ischemic stroke. Her symptoms began to improve within 5 minutes and by 30 minutes were completely resolved. She was admitted to the hospital 3 days prior after presenting new onset of diplopia, left-sided paresthesia, and left hemiparesis after use of methamphetamine. She had a history of 3 prior ischemic strokes, poly substance abuse (methamphetamine, cocaine, alcohol), migraine with aura, smoking, and oral contraceptive use. Her examination on admission revealed a partial third cranial nerve palsy and mild left hemiparesis. Initial brain MRI confirmed a right midbrain infarct. MR angiography of the head and neck showed normal circulation. Examination after the new symptoms after BS was unchanged. Repeat brain MRI showed additional focus of midbrain acute stroke (Figure 3). Diagnostic evaluation, including a TTE and TEE, revealed an extracardiac right to left shunt, and contrast thorax CT confirmed a pulmonary arteriovenous malformation.

Case 4
A 49-year-old woman presented new onset of vision disturbance while performing a Valsalva maneuver at the time of TTE with BS done for evaluation of recurrent migraine and isolated vision disturbance. She had a history of migraine and Raynaud’s phenomenon and takes oral contraceptives. Her examination at the time of the index event showed right lower face weakness and decreased sensation in the right V2 distribution. After the index event, she also had a left inferior quadrant anopsia. Brain MRI confirmed a sub acute right occipital infarct and showed old infarcts in the left frontal and parietal lobes and left corona radiata. Diagnostic evaluation for her strokes included a TTE suggestive of both intra- and extracardiac shunt. She underwent inferior vena cava filter placement given that iliac vein deep venous thrombosis could not be excluded. She also underwent closure of a PFO with an Amplatzer device and was treated with aspirin. She had no recurrent symptoms thereafter, and a follow-up TTE showed no evidence of residual PFO or right to left shunt.

Case 5
A 42-year-old woman presented dizziness and left face and hand paresthesias within minutes of a TTE with BS done for evaluation of recurrent migraine and isolated vision disturbance. She had a history of migraine and Raynaud’s phenomenon and takes oral contraceptives. Her examination at the time of the index event showed decreased left-sided sensation in the face and hand. Brain MRI was negative for acute infarction. TTE was consistent with a PFO and extracardiac shunt. She was treated with aspirin and her symptoms resolved completely over 2 weeks without recurrent events.

Discussion
The present study found that TIA and small strokes can occur in patients undergoing BS. Our patients experienced symptoms of brain ischemia at the time of, or immediately after, the injection of microbubbles. Both cardiac and pulmonary right to left shunts were implicated. Neurological deficits were transient or mild when persistent. Brain MRI findings in those with stroke showed a small infarct size and did not differ in appearance from infarcts caused by a mechanism other than brain air embolism.

The use of “contrast” in echocardiography has been known for almost 40 years. Various contrast agents such as saline...
mixed with air, dextrose and water, the patient’s own blood, carbon dioxide gas, hydrogen peroxide, sonicated iodinated contrast, and other commercially available agents have been used to opacify cardiac structures using echocardiography. Based on a survey of 363 physicians, the American Society of Echocardiography acknowledged that there is a risk for transient side effects (0.062%), including TIAs, but implied that the diagnostic benefits of the procedure still outweighed the risks as long as precautions were undertaken. Specifically, one should prevent the injection of visible amounts of air (ie, air that is no longer in microbubble form induced by the agitation and has collected as a large bubble at the top of the syringe), especially in patients with right to left shunt or arterial catheters.

Our case series suggests the need to re-examine the procedure and its standardization. Several possibilities may explain the potential mechanism for ischemic events. One consideration is that the anatomy or physiology of these patients predisposed them to events. The presence of an atrial septal aneurysm increases the likelihood of stroke in patients with PFO and could have been a factor in the 2 patients in our series who were studied solely without TEE. However, 3 of our patients were not reported to have aneurysm on echocardiography. Shunt size has been suggested as an anatomic feature that may predispose to paradoxical brain ischemia; however, the shunt sizes in our patients were not particularly large. In addition, a recent study has brought into question the role of shunt size in recurrent stroke. It is also possible that the operators failed to limit injection of the volume of agitated saline once an obvious moderate or large intracardiac shunt was detected using color Doppler during echocardiography.

It may be argued that cardiac disease contributes to microbubble aggregation as is thought to be the basis for the formation of circulating gaseous microbubbles in some patients with mechanical valves. If cardiac disease can predispose to spontaneous microbubbles, it may also pose a risk of aggregation and enlargement of infused microbubbles. However, significant heart disease was not identified in our patients.

Another consideration is that physiological factors may have contributed to the occurrence of brain ischemic events. All of our patients were women, and 3 had a history of migraine headaches. A strong association between PFO and migraine has been described. Both PFO and migraine are
associated with stroke. Migrainous vasospasm (without headache) provoked by microbubble transit into the brain could lead to ischemic events. Microbubbles and vasospasm would be cofactors in this scenario. Cortical spreading depression has been demonstrated in experimental studies after injection of microbubbles. The patient whose stroke deficit was the same as her migraine visual aura is of interest in this regard. Again, however, the lack of prior reports to this effect renders this unlikely. No other patient-related physiological factors were identified as contributors to the occurrence of these events.

It would appear that performance of the BS itself was the likely cause of the brain ischemic events in these patients. The ischemic events occurred either immediately or within minutes of the injection in all cases. Technical considerations of the procedure may be related to the events. One aspect of the procedure that could predispose to symptomatic embolization is the creation and perpetuation of large bubbles that aggregate and become capable of occluding small arteries in the brain. Such bubbles could be generated if the air–saline mixture was inadequately agitated through the stopcock between the 2 syringes before injection; if the needle used was too large; or if the syringe from which the final injection is made was held at an angle less than vertical to the injection site.

Larger needle size is regarded as important to deliver microbubbles rapidly, before they disintegrate. Paradoxically, larger needle size may also allow transmission of larger bubbles, which can then coalesce and become potentially occlusive.

The syringe angle may also allow larger bubbles to enter the venous system rather than be retained at its proximal end. Larger, sustainable microbubbles are less likely to reach the circulation if the injection is made with the syringe held vertical. In this position, larger bubbles will rise to the top of the syringe, and the technologist can withhold the final 0.5 to 1.0 mL of fluid to preclude these bubbles from entering the circulation.

The incidence of stroke associated with BS is unknown. In our institutions, we have found a low incidence given the frequency of BS performed per year. Our ability to ascertain the incidence, however, is compromised by uncertainty of patient reporting, sedatives used during the studies (especially TEE), and clinician unawareness of minor changes in patients with significant deficits from their recent and prior strokes.

Our cases also illustrate that BS are not just performed in young patients. Our series included 2 older patients, indicating that age is not a defining factor in eligibility for BS evaluation. Patients with strokes of uncertain etiology can occur at any age.

We are aware of only a single consensus protocol for performance of, or training in, detection of shunts using BS. This was devised for TCD only. Survey data from several physicians indicated that approaches vary significantly on how bubbles are created and used, implying the need for standardization by organizations that provide guidelines and oversight for ultrasound imaging.

The present report highlights the benefit of using electronic resources to enhance communication among physicians, which is particularly important to detect uncommon complications related to procedures such as stroke associated with BS. Unfortunately, the list serve we used functions as a digital chat room and does not afford the ability to determine the number of members viewing the question posted. This limitation leads to underreporting, because the number of nonresponding participants is unknown.

The singular weakness of our study is its small sample size, which renders discussion and conclusions speculative. However, the value of the work is that it alerts readers to an important risk of BS. Explanation of benefits and risks of BS may need to include mention of “stroke” despite suspected low but unknown true incidence.

Conclusion
Stroke risk from paradoxical microbubble embolization exists and can be clinically significant. Although the small size and ephemeral integrity of microbubbles have been presumed to render them free of risk, this apparently cannot be guaranteed.

Because we are unable to identify the precise basis for brain ischemic events in the patients reported here, our experience suggests an important quality of care opportunity, the creation of a registry whereby additional data can be gathered that may allow identification of both the incidence and mechanism of stroke associated with microbubble infusion. Such a registry could also help ascertain the yields of different protocols for bubble studies, which would be expected to facilitate development of a uniform, optimal approach to performing these procedures.

Disclosures
J.L.F. is on the speakers bureaus for Bristol Myers Squibb, EKT Pharma, Genentech, and Sanofi-Aventis. B.M.D. is the ESCAPE Trial site principal investigator sponsored by St Jude Medical and the RESPECT Trial site principal investigator sponsored by AGA. V.L.B. is a consultant for Boston Scientific and is on the speakers Bureau for Boehringer Ingelheim.

References
Cerebral Ischemic Events Associated With 'Bubble Study' for Identification of Right to Left Shunts
José R. Romero, James L. Frey, Lee H. Schwamm, Bart M. Demaerschalk, Hari P. Chaliki, Gunjan Parikh, Robert F. Burke and Viken L. Babikian

*Stroke*. 2009;40:2343-2348; originally published online June 4, 2009;
doi: 10.1161/STROKEAHA.109.549683

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/7/2343

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org/subscriptions/