

## Bubbles in the Brain: A Rare Complication Following Transthoracic Echocardiography

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### ABSTRACT

With nearly 700,000 cases every year, ischemic stroke represents the third leading cause of death in the United States.<sup>1,2</sup> Nearly thirty percent of all ischemic strokes are due to embolism.<sup>3</sup> A standard component of every stroke work-up at most institutions, echocardiography is vital not only for diagnosis but also for prevention and treatment of cardiac sources of embolism. Visualization of right-to-left shunting is often contrast-enhanced with micro bubbles created by mixing saline with air, a so-called “bubble study.” We present a case of an 89-year-old woman who suffered cerebral air embolism and massive infarction following a routine bubble Transthoracic Echocardiogram.

**KEYWORDS:** bubble study, echocardiography, ischemic stroke, embolism, stroke

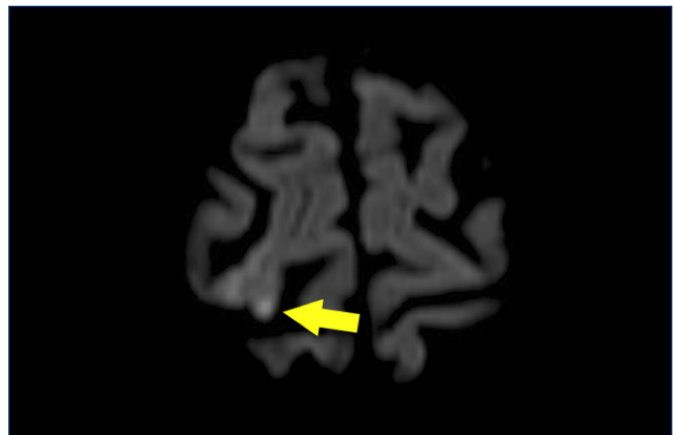
An 89-year-old woman with Peripheral Vascular Disease and Limited Scleroderma presented to the hospital with two weeks of progressively worsening burning leg pain and swelling and was admitted for cellulitis. On exam, she was found to have bilateral erythema of her lower extremities with clear drainage and was started on intravenous antibiotics. Initial laboratory workup was only significant for leukocytosis of 18,700. During the course of her hospital stay, she also became short of breath and was hypoxic with evidence of cor pulmonale. Transthoracic Echocardiogram (TTE) showed impaired left ventricular relaxation, severe right heart failure (RVDD 48mm), severe pulmonary hypertension (RVSP 92mmHg) and severe tricuspid regurgitation (TRPGmax 82mmHg).

Thirty minutes after receiving intravenous furosemide, she developed generalized left-sided weakness. The stroke team was activated although the patient’s neurological exam was unremarkable for any focal deficits, and tissue plasminogen activator was not administered due to her rapidly improving symptoms.<sup>4</sup> No acute changes were seen on an emergent head computed tomography (CT) scan. Decreased diffusion in the right precentral gyrus consistent with ischemia-induced left hemiparesis was later appreciated on Magnetic Resonance Imaging (MRI) (**Figure 1**).

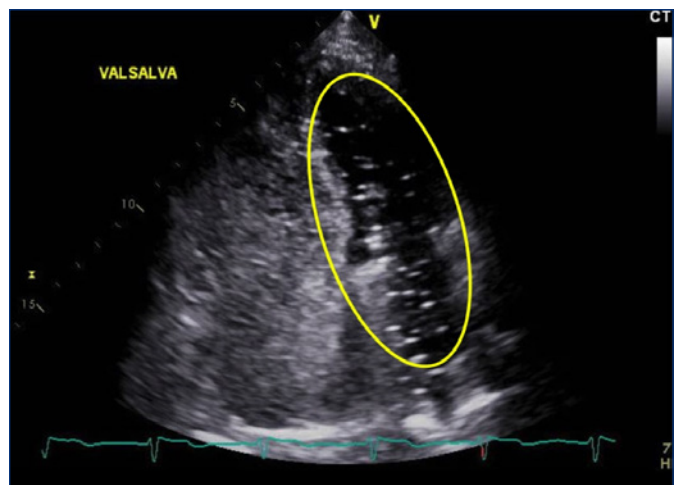
A stroke work-up was initiated with normal carotid ultrasound, lipid panel and A1c. The patient was treated

**Figure 1. Diffusion impairment on MRI**

Axial brain DWI showing right precentral diffusion impairment.



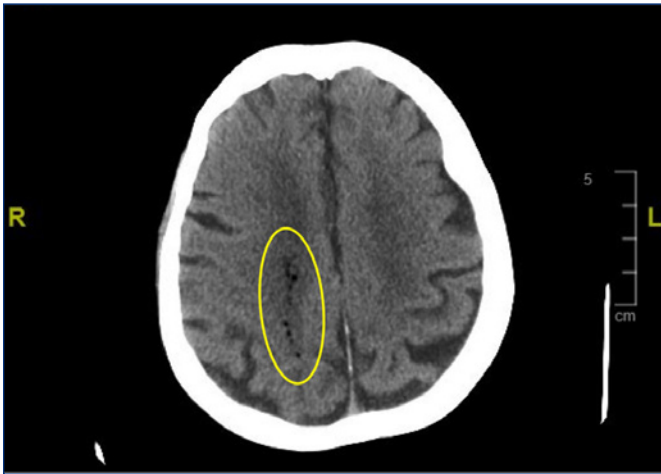
**Figure 2. Echocardiogram of Valsalva maneuver performed during bubble study showing numerous bubbles in the left heart (yellow ellipse) indicating RLS.**



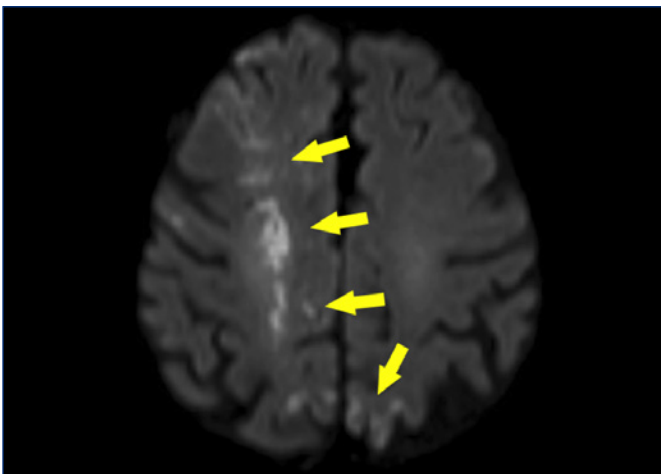
with clopidogrel, atorvastatin, and heparin throughout her hospitalization, and no arrhythmias were noted on telemetry. Three days later, a bubble TTE was performed as part of the workup that identified both an intrapulmonary right-to-left shunt (RLS) and a small patent foramen ovale (**Figure 2**). Approximately twenty minutes later, the patient was unable to move any of her limbs against gravity, had a left visual field defect, mild facial droop, and dysarthria

**Figure 3. Figure 3: Air emboli on CT**

Axial brain CT showing multiple foci of air emboli (yellow ellipse).

**Figure 4. Interval change in diffusion impairment on MRI**

Axial brain DWI showing increased diffusion impairment (yellow arrows) consistent with region of air emboli. Superior slices showed that the diffusion impairment extended bilaterally.



without aphasia or sensory deficits. Computed Tomography Angiogram revealed diffuse foci of right-sided intracerebral air embolism (**Figure 3**) with no evidence of large vessel occlusion. Tissue plasminogen activator was not administered due to the potentially increased risk of hemorrhage in recently infarcted tissue.<sup>4</sup> MRI demonstrated bilateral diffusion restriction pattern consistent with massive ischemic stroke (**Figure 4**). The patient had severe neurological damage and the family did not want to pursue any further workup. The patient was transitioned to inpatient hospice and died the subsequent day.

## DISCUSSION

The 2016 Appropriate Use Criteria by the American Society of Echocardiography recommends performing TTE or

transesophageal echocardiography (TEE) as initial tests to evaluate suspected cardiovascular sources of embolism, especially in patients for whom therapeutic management depends on the findings. Intra-cardiac shunting can be determined sometimes using color Doppler although agitated saline or bubble studies are known to yield higher results.<sup>5</sup> These tests are performed at the end of TTE when it is necessary to rule out RLS. Recent advances in medicine have enabled closure of RLS through percutaneous devices.

Alternative imaging methods include bubble transcranial doppler (TCD), which can detect a RLS by visualizing bubbles in the middle cerebral artery through the temporal bone window. Bubble TCD is limited by the absence of the temporal window in some patients and the inability to distinguish intracardiac and extracardiac sources of embolism. Paradoxical embolization with neurologic symptoms following bubble TCD in patients with RLS and congenital heart disease has been noted previously,<sup>6</sup> although the frequency has not been described.

A 2009 case series by Romero and colleagues of bubble-study-associated cerebrovascular accidents included two cases of transient ischemic attacks and three cases of ischemic stroke. All patients were female, and all experienced symptoms within five minutes of their respective bubble studies. Four of the patients had a bubble TTE and one had a bubble TCD. While protocols vary among institutions, either bubble TTE or bubble TCD can be used to detect RLS<sup>7</sup> and involve similar injection formulations.<sup>8,9</sup> In response to this series, a prospective consecutive case series was conducted in 2010 by Tsigoulis and colleagues to estimate the rate of cerebrovascular accidents in bubble TCD. Of the 508 patients who underwent bubble TCD, none had a stroke within twenty-four hours.<sup>8</sup>

In our case, bubble TTE was ordered following the recommendation of the stroke team to evaluate for intracardiac thrombus, RLS, and any structural defects. Twenty-four minutes elapsed between bubble TTE and the onset of stroke symptoms, more than the five minutes of previous cases, but well within the twenty-four hours allotted by Tsigoulis and colleagues to report these events. All twenty-four minutes can easily be accounted for by the preceding TTE as well as the transport time from the echocardiogram lab back to the patient's room during which symptoms may have been present but not appreciated.

At many institutions, TTE is the initial form of cardiac imaging for stroke work-up due to its low cost and non-invasiveness compared to TEE. In addition, TEE was not indicated in our patient as TTE already showed evidence of patent foramen ovale as well as intrapulmonary RLS and would not have changed management.<sup>5</sup> A bubble study is usually done at the end of TTE to exclude RLS.

To investigate further, we compared the procedure at our institution with those of other institutions. A TTE without bubbles is first performed. 2 mL of air is agitated with 8 mL

of normal saline. The solution-containing syringe is then connected to the patient's IV port via Luer lock and injected vertically to avoid injecting large bubbles. The study is then repeated with a Valsalva maneuver, for a total volume of injected air of 4 mL. Additional injections may be necessary if the first attempt is not definitive.

Given that bubbles are seen in the brain during bubble TCD, it should not be surprising that bubbles may also be found in the brain during bubble TTE. In general, the bubbles used in either modality are too small and short-lived to occlude cerebral vessels. While a 2 mL bolus of air is sufficient to cause an arterial embolism in a 7 kg macaque,<sup>10</sup> the volume necessary to have the same effect in a human is likely significantly greater. As all cases of bubble-study-associated cerebrovascular accident reported here have been in females, smaller size may be a risk factor.<sup>7</sup> Additionally, this patient's study was marked as "technically challenging" and may have required multiple injections. Although other institutions inject only 1 mL of air<sup>8,9</sup> compared to our hospital's 2 mL, the incidence of bubble study-associated cerebrovascular accident is so low that the relative risks of different protocols cannot be meaningfully compared. Due to this rarity, the mechanism by which cerebrovascular accident develops after bubble study is not understood. In the case of bubble TCD, previous research has hypothesized that neurologic symptoms may be related to the shunting of chemical factors other than microemboli.<sup>11</sup>

## CONCLUSION

While a previous case series has linked bubble studies to ischemic stroke temporally, our case is the first to provide direct radiographic evidence of air embolism with spatially concordant infarction. One limitation of our report is that the exact cause of death was unknown as there was no autopsy performed. Cor pulmonale and severe pulmonary hypertension could have also contributed to the patient's death in addition to the severe neurologic damage. Another limitation is that the bubble TTE was technically challenging and the patient refused further images. Hence the exact magnitude of the intrapulmonary RLS and PFO could not be ascertained. In conclusion, even though the incidence of cerebral air embolism following bubble studies is exceedingly rare, it is important for all providers to be aware of this complication and its potentially fatal consequences.

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