Identification of an Intracardiac Shunt in a Patient With Recurrent Cryptogenic Strokes: Are Dextrose Solutions More Sensitive?

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INTRODUCTION

Nearly 800,000 strokes occur in the United States annually. Workup following an acute stroke attempts to identify an etiology to decrease the risk of recurrent events. Still, in 15%-30% of cases, a cause is not found, and these are labeled cryptogenic strokes. Epidemiological studies show a higher risk of stroke in those with a patent foramen ovale (PFO), which can lead to a stroke by allowing emboli to pass into arterial circulation.[1] Multiple recent trials have demonstrated a decrease in the risk of recurrent embolic stroke with PFO closure compared with antiplatelet therapy, which stresses the importance of identifying a PFO following an acute stroke.[2] Right-to-left shunting can be diagnosed on transthoracic echocardiogram (TTE), transesophageal echocardiogram (TEE), or transcranial Doppler with injection of an enhancing solution, commonly referred to as a "bubble study." Transesophageal echocardiogram is considered the gold standard for shunt identification, but TTE with an enhancing agent has reasonably high sensitivity and is less invasive, so it is often used as the initial study.[3] Agitated saline (normal saline [NS]), dextrose-containing solutions, and other commercially available options (such as Echovist, Haemacell, and Gelifundol) may be used as enhancing solutions, but evidence comparing their performance in detecting right-to-left shunting is limited.[4] We present a case of a patient with recurrent strokes with two negative bubble studies with agitated NS but a grossly positive study with the use of 50% dextrose (D50).

CASE PRESENTATION

A 73-year-old female with a medical history of rectosigmoid cancer status post resection, hyperlipidemia, type 2 diabetes, and a recent left middle cerebral artery ischemic stroke presented to the Hennepin County Medical Center Emergency Department (ED) with stroke-like symptoms. She was seen 2 months prior for a similar presentation, at which time she had a suspected embolic stroke of unknown etiology. She was in normal sinus rhythm from the time of her admission to her discharge 2 days later. Thirty-day outpatient cardiac monitoring was completed, and there was no evidence of atrial fibrillation or other cardiac arrhythmias. An echocardiogram revealed a structurally normal heart with no identifiable intracardiac embolic source. There was no evidence of a shunt at the atrial level by either color Doppler or bubble study with agitated NS at rest and after Valsalva maneuver. Her neurologic deficits resolved, and she was discharged on aspirin 325 mg daily with close neurology follow-up.

Three months later, she presented to the ED with 3 days of intermittent right hand weakness, right facial droop, and expressive aphasia. A magnetic resonance imaging/magnetic resonance angiography showed multiple new embolic strokes without any significant stenosis, occlusion, or atherosclerosis in the cervical or intracranial vasculature. Tissue plasminogen activator was not given due to the length of time since symptom onset. In the setting of her recurrent stroke, she again underwent telemetry monitoring and an echocardiogram, which was unchanged from the prior study. A bubble study with agitated NS, both at rest (Video 1 available at www.onlinejase.com) and with Valsalva maneuver (Video 2 available at www.onlinejase.com, Figure 1), and color Doppler cine loops (Video 3 available at www.onlinejase.com) were again negative for any shunt. Due to the high suspicion for a cardiac source of embolism, the bubble study was then performed with agitated D50, which showed right-to-left shunting with >1,000 microbubbles within two cardiac cycles after right heart opacification at rest (Video 4 available at www.onlinejase.com) and right-to-left shunting with dense opacification of the left ventricle within two cardiac cycles after release of Valsalva maneuver (Video 5 available at www.onlinejase.com, Figure 2). These D50 injections took place only 2 minutes after the agitated NS injection with the same cardiac sonographer, the same ultrasound machine, and no change in image settings.

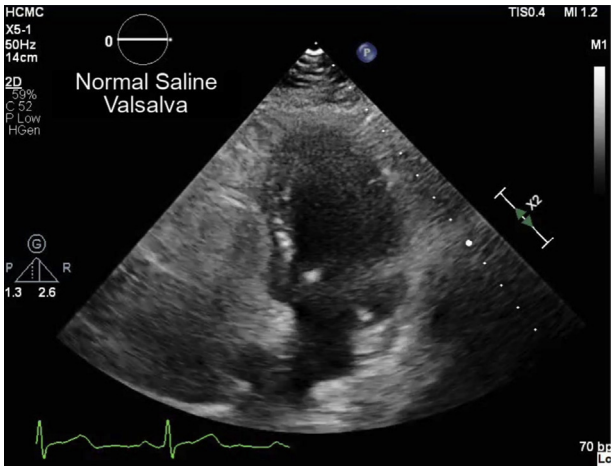

Figure 1 Negative bubble study with normal saline after release of Valsalva maneuver.

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VIDEO HIGHLIGHTS

Video 1: Bubble study with agitated normal saline at rest without evidence of right-to-left shunting.
Video 2: Bubble study with agitated normal saline after release of Valsalva maneuver without evidence of right-to-left shunting.
Video 3: Color Doppler without evidence of right-to-left shunting.
Video 4: Bubble study at rest with D50 showing right-to-left shunting with >1,000 microbubbles within two cardiac cycles after right heart opacification.
Video 5: Bubble study with D50 showing dense opacification of the left ventricle within two cardiac cycles after release of Valsalva maneuver.

View the video content online at www.cvcasejournal.com.

In light of the recurrent multi-territory infarcts, the patient was switched from antiplatelet therapy to anticoagulation with apixaban. She was discharged with the diagnosis of embolic stroke secondary to large PFO versus secundum atrial septum defect (ASD). A pulmonary source of shunting was also considered given the initial appearance of bubbles near the left pulmonary vein. However, given the temporal profile of left ventricle opacification (which occurred within three cardiac cycles), a pulmonary source was deemed unlikely, so TEE and computed tomography pulmonary angiography were not performed. In addition to follow-up with neurology, outpatient cardiology consultation in the PFO/ASD Closure Clinic was arranged to discuss the risks and benefits of interatrial shunt closure, but she was unfortunately lost to follow-up.

DISCUSSION

Given the morbidity and mortality associated with acute stroke, a thorough evaluation to identify the etiology and decrease the risk of future events is reasonable. Epidemiological studies and advances in echocardiography have identified right-to-left shunting as an essential but previously underrecognized risk factor for strokes.[5] In our patient, the initial evaluation, including a TTE and outpatient cardiac monitoring, was unremarkable. Although the bubble study with agitated NS was negative on both admissions, a study with agitated D50 performed 2 minutes after the NS injection with the same imaging and hemodynamic conditions was markedly positive for right-to-left shunting.

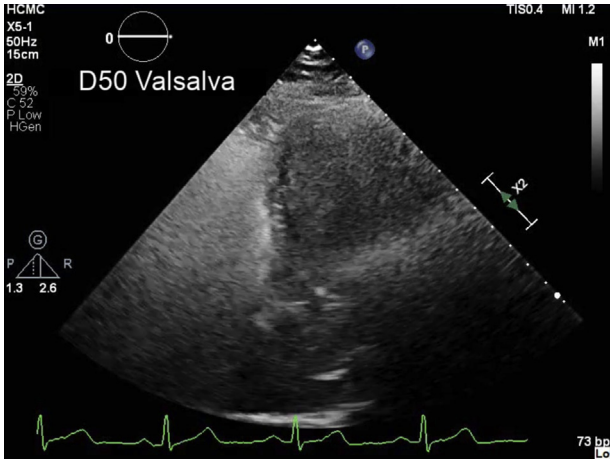

Figure 2 Bubble study with D50 showing dense opacification of the left ventricle after release of Valsalva maneuver.

There are various causes of a false-negative bubble study. In order to increase the detection of shunting during bubble studies, patients are asked to perform a Valsalva maneuver, as the release of a Valsalva maneuver can increase right-sided pressures and thereby accentuate right-to-left shunting, allowing identification on echocardiography. Patient cooperation and understanding may limit the efficacy of this maneuver and decrease the sensitivity of TTE in shunt identification. Even if a Valsalva maneuver is performed correctly, those with left-sided pathologies, such as left ventricular systolic dysfunction or mitral regurgitation, may have elevated left atrial pressures that prevent right-to-left shunting (there was no evidence of increased left atrial pressure in our patient).[6]

In this case, the key to establishing the presence of a right-to-left shunt after two negative NS bubble studies was the use of D50. Identification of right-to-left shunting by echocardiography relies on the duration and amplitude of the ultrasound signal created by microbubbles in enhancing solutions. The size of the microbubbles also plays an important role, as solutions with larger microbubbles may miss both small interatrial and interpulmonary right-to-left shunts. A study by Feinstein *et al*[7] compared in vitro characteristics of sorbitol and dextrose enhancing solutions to saline-based solutions. It found sorbitol and dextrose solutions to have smaller, more uniform microbubbles and produce a greater duration and amplitude of the ultrasound signal.[7] These characteristics of dextrose-based solutions may allow for increased detection of right-to-left shunting and can be especially helpful in uncovering small shunts. In cases where shunting is expected, an ASD or PFO may require TEE for diagnosis. In our patient, TEE or computed tomography pulmonary angiography would have been reasonable given the first appearance of bubbles near the left upper pulmonary vein. However, this was not performed due to the opacification of the LV within three cardiac cycles, making a pulmonary shunt much less likely.

There are limited data directly comparing the performance of D50 to NS for the identification of right-to-left shunting. A 2018 study by Li *et al*[8] looked at 24 patients with TEE-proven PFOs who underwent TTE echocardiography with both NS and D50. One hundred percent of PFOs were identified using D50, while only 83% were identified with NS.[8] These findings trended toward but did not reach statistical significance, perhaps due to a small sample size, suggesting that D50 may be more sensitive for identification of right-to-left shunting. This study also demonstrated that peak time and duration of microbubbles with D50 were longer than those produced by NS. Further, D50 is well tolerated, even in the presence of underlying hyperglycemia—1 mL of D50 contains 0.5 g of glucose, and only 5-10 mL are needed for an echocardiogram.[9]

At our institution, D50 has been used in the echocardiography lab for nearly 30 years. More recently, a temporary shortage of D50 triggered a change to NS. This shortage has resolved, but when there was limited D50 availability, NS was primarily used, with D50 being reserved for use if suspicion for right-to-left shunting remains high despite a negative NS study. Given the potential for increased sensitivity with D50 and its excellent safety profile, it is reasonable to use D50 either initially for all bubble studies or, if the cost is an issue, following a negative NS study if the suspicion for right-to-left shunting remains high. Transesophageal echocardiogram is a reasonable next step if suspicion for an embolic source of stroke is high—not only

will this allow for evaluation of the interatrial septum, but the left atrial appendage can also be visualized.

CONCLUSION

In cases of cryptogenic stroke and a negative bubble study with agitated NS, it is reasonable to repeat the study with D50, as this is a more affordable, less invasive study, before proceeding to TEE. Larger studies are needed to compare the efficacy of different enhancing agents in the identification of right-to-left shunts. Repair of right-to-left interatrial shunts to decrease the risk of recurrent stroke should be considered depending on patient risk factors and preferences.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.case.2020.12.001.

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