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## CLINICAL CASE OF THE MONTH

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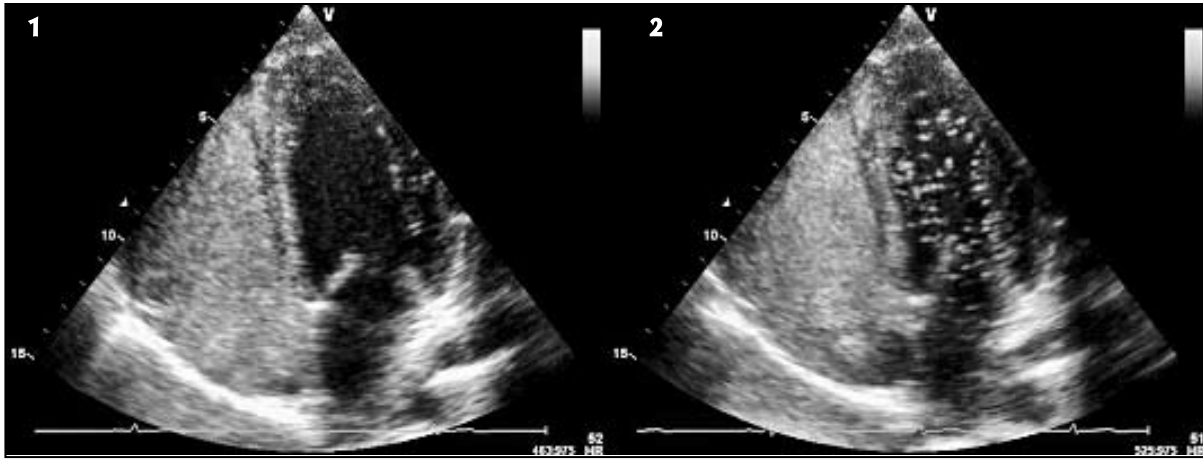
# A 29-Year-Old Man With Acute Onset Blurry Vision, Weakness, and Gait Abnormality

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A 29-year-old man, with no significant past medical history, was in his usual state of health until the afternoon of admission. The patient was seated at work eating lunch when he suddenly noticed that his vision became blurry. He covered his right eye and had no visual difficulty but noted blurry vision upon covering his left eye. At this point, the patient tried to stand up, but had difficulty walking and noticed he was “falling toward his left.” Facial asymmetry when smiling was also appreciated. The patient denied any alteration in mental status, confusion, antecedent or current headaches, aura, chest pains, or shortness of breath. He was not taking any prescribed medications and had no known allergies. The patient denied any prior hospitalization or surgery. He denied use of tobacco, alcohol, or illicit drugs, and worked as a maintenance worker in a hotel. His family history is remarkable for his father who died of pancreatic cancer in his 50s and his mother who died of an unknown heart condition in her late 40s.

Vital signs on presentation to the emergency department included temperature of 97.6°F; respiratory rate of 18 per minute; pulse of 68 per minute; blood pressure of 124/84 mmHg; pulse oximetry of 99% on ambient air. His body mass index was 24 and he was complaining of no pain. The patient had no carotid bruits and no significant jugular venous distention. Cardiovascular exam revealed a regular rate and rhythm with no murmurs. Neurological exam revealed left-sided facial weakness, dysarthria, and preserved visual fields. He was able to furrow his brow. Gait deviation to the left was present, and Romberg sign was negative. Deep tendon reflexes were 2+ throughout, and no other focal neurological deficit was present.

The patient was admitted to the hospital with a diagnosis of stroke. Electrocardiogram, fasting lipid profile, computed tomography (CT) scan of head, magnetic resonance imaging (MRI) of head and neck, and transthoracic echo with bubble study were ordered. The initial head CT did not reveal bleeding. He was started on aspirin (ASA). On the second hospital day, the symptoms improved with resolution of dysarthria. His ataxia had also improved. Fasting lipid profile revealed mildly elevated low-density lipoprotein and total cholesterol. His head MRI revealed an acute right thalamic stroke. Echocardiography was significant only for a patent foramen ovale (PFO) with transit of agitated saline “bubbles” from right atrium to left heart within three cardiac cycles (Figure). Doppler ultrasound of extremities revealed no evidence of deep venous thrombosis. A complete resolution of symptoms occurred by the third hospital day. The patient was discharged on full dose aspirin and a statin and was referred for consideration of enrollment in a PFO closure versus medical management trial.



**Figure.** Opacification of the right atrium with agitated saline “bubbles” (panel 1) and visualization of the “bubbles” in the left atrium and ventricle within three cardiac cycles (panel 2) confirms the presence of an intracardiac right-to-left shunt.

## INTRODUCTION

Stroke is the third leading cause of death in adults in the United States.<sup>1</sup> A large portion of first-time ischemic strokes have no known source. With no obvious source, a more extensive workup must be performed to rule out paradoxical embolization as a cause for stroke. In a subset of cases, a patent foramen ovale (PFO) is subsequently diagnosed. The diagnosis is made *in vivo* by echocardiography using contrast bubbles. If the bubbles are transmitted between the atria within three to four cardiac cycles, an intracardiac shunt such as a PFO is present.

## EPIDEMIOLOGY

Approximately 40% of ischemic strokes have no known etiology and are termed “cryptogenic” stroke(s). Patent foramen ovale is present in approximately 25% of the general population when looked for at autopsy. It is linked to a variety of clinical conditions including ischemic stroke,<sup>2</sup> myocardial infarction,<sup>3</sup> migraines, and decompression sickness.<sup>4</sup> Studies show a 40% prevalence of PFO in patients with ischemic stroke as compared to 10% in controls.<sup>5</sup> A PFO can be difficult to detect as there are few clinical manifestations; however, certain clues should raise suspicion for this condition (see below).

## PATHOPHYSIOLOGY

The foramen ovale is patent during fetal development. This allows blood from the inferior vena cava to pass primarily from the right-to-left circulation while in utero. This shunting allows oxygenated maternal blood to bypass the pulmonary circuit ascend ductus arteriosus and enter into the fetal systemic circulation supplying the head and upper extremities. At birth, there is a marked decrease in pulmonary vascular resistance as arterioles dilate in response to filling the alveoli. Right heart pressures decrease, and

left-sided pressures increase as a consequence of increased pulmonary venous return. This change in pressure creates a left-to-right force which causes the septum secundum to contact the valve of the foramen ovale (previously the septum primum), resulting in a gradual fusion which is complete in 75% of individuals by age two years;<sup>6</sup> the remaining ~25% have a residual PFO. The causes of patency are still ill defined; however, some speculate that it relates to multifactorial inheritance patterns.

To understand fully the mechanism behind a PFO, it is important to be familiar with its embryologic development. As reported by Hara et al,<sup>7</sup> the primordial heart consists of a single-chambered atrium at four weeks of gestation. During this time, a crescent shaped structure begins to form at the roof of the atrium and grows toward the endocardial cushions. The opening present between the septum primum and endocardial cushions is termed the foramen primum. As the septum primum grows, several perforations (due to predetermined apoptosis) join to form a central opening which is known as the foramen secundum. The foramen secundum is antecedent to the foramen ovale. At the time the foramen secundum is formed, the foramen primum is closed as the caudal portion of the septum primum contacts the endocardial cushion. Now, a second septal structure begins to form just to the right of the ventrocranial portion of the septum primum. This second septal structure is termed the septum secundum. The septum secundum grows from the cranial portion of the septum toward the endocardial cushions just as the septum primum had previously. At this point, the atrium is separated into left and right atria by the septum primum from below (which is seated on the endocardial cushion) and the septum secundum from above (which is based on the roof of the atrium).<sup>7</sup> As the two structures grow and eventually articulate, they form a valve-like structure. This flap valve can allow blood to flow from right to left when right atrial pressure exceeds left atrial pressure, such as during cough or other Valsalva maneuver.<sup>13</sup>

## CLINICAL PRESENTATION

Patent foramen ovale can be an associated cause of transient ischemic attack, cryptogenic stroke, myocardial infarction, or decompression sickness in divers. Evidence also exists that a certain subset of migraine headaches is associated with the presence of a PFO. However, PFO is usually diagnosed incidentally. Typically no murmur or other physical finding is associated with PFO. There is no evidence of cyanosis, significant left-to-right shunting, or activity restriction. Suspicion of PFO should be prompted when a young person without significant risk factors (hypertension, hyperlipidemia, diabetes, smoking history, or hypercoagulability) presents with sudden onset of neurologic or cardiovascular compromise. In the case of stroke, aphasia, paresthesias, ataxia, visual disturbance, or headache can be present.

A patient with decompression sickness (DCS) and atrial septal defect (ASD) was first described in 1986.<sup>8</sup> Type 1 DCS involves localized joint pain, musculoskeletal pain and skin rash and is not commonly associated with PFO or ASD. Type 2 DCS is more likely associated with PFO. The symptoms of type 2 DCS more closely resemble those of stroke: paresthesia, severe headache, confusion, paraplegia, and loss of consciousness. An association between PFO and migraine also exists. In a study assessing the prevalence of PFO in persons with migraine, it was found that 48% of persons with migraine had PFO, compared to 23% with no migraine.<sup>9</sup>

## DIAGNOSTIC WORKUP

As there are no typical physical exam findings, the suspicion for PFO should be prompted by history. Secondary workup, such as a fasting lipid profile, glucose readings (glycosylated hemoglobin in cases of diabetes), and hypercoagulable workup for treatable causes of thrombosis, should be performed to determine the presence of additional risk factors. Sources for potential deep vein thrombosis should be evaluated by venous ultrasonography of lower and/or upper extremities and ultrasound of the carotid arteries should be performed to look for a source of embolization. In cases of cryptogenic stroke in persons aged 18-60 years, venous MRI studies revealed an increased prevalence of pelvic deep vein thrombosis (20% vs 4% in controls).<sup>10</sup> Echocardiography is essential in providing or excluding the diagnosis of PFO. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are options; of the two, TEE has proven to be the more sensitive modality in PFO detection.<sup>11</sup> The diagnosis of PFO can be made if inter-atrial communication of agitated saline bubbles occurs within three to four cycles after right atrial opacification on TTE. The study can be enhanced by the use of a Valsalva maneuver to increase right heart pressures and precipitate right-to-left flow of blood across an inter-atrial communication. Transit

of agitated saline bubbles from right-to-left heart that occurs after three to four cardiac cycles is more suggestive of an intrapulmonary shunt. An additional modality, transcranial ultrasound, can detect embolic events in the cerebral circulation but has been shown to miss smaller PFOs (<2mm) which remain otherwise detectable by TEE.<sup>11</sup>

## TREATMENT

The first treatment for patients presenting with ischemic stroke, transient ischemic attacks, or myocardial infarction is to treat the presenting diagnosis. Once the acute phase is completed, there is no clear standard of care established for long-term management of patent foramen ovale. The American Heart Association (AHA) and American Stroke Association (ASA) guidelines do not provide recommendations for PFO closure in the event of first stroke. There is a IIb recommendation (level of evidence: C) for PFO closure in recurrent cryptogenic stroke while on optimal medical management.<sup>14</sup> Three principal methods of treatment exist: medical management, percutaneous closure, and surgical closure.

In medical management, the AHA/ASA<sup>14</sup> and American College of Chest Physicians<sup>15</sup> guidelines for transient ischemic attack (TIA) in a person with PFO recommend antiplatelet therapy unless otherwise contraindicated. The Warfarin-Aspirin Recurrent Stroke Study incorporated 2,206 patients with prior stroke in a prospective study to evaluate recurrence of stroke and/or death over two years between the respective drugs. The study found no significant differences between aspirin (325mg/day) and warfarin (titrated to an international normalized ratio of 1.4-2.8) during the two-year period in patients with cryptogenic stroke. This evidence is further supported by the PFO in Cryptogenic Stroke Study.

Percutaneous transcatheter techniques have shown an efficacy for closing PFOs ranging from 86% to 100%, and the procedure is widely considered safe and effective.<sup>18</sup> There are a variety of closure devices available for PFOs and ASDs. At this time, no specific device for PFO closure after cryptogenic stroke has been approved by the US Food and Drug Administration (FDA).<sup>18</sup> Historically, the Amplatzer device (AGA Medical Corporation) has been shown to have the least thrombus formation; however, changes in post-procedure management have lead to improved functionality in a variety of devices.<sup>19</sup> Additionally increased anticoagulation and hematological screening for coagulopathies have improved overall outcomes. Separately, patients with migraine showed significant improvement and/or complete resolution of symptoms in many cases after PFO closure.<sup>20</sup>

Surgical closure is no longer a common procedure. This trend is likely attributable to the success of percutaneous closure and patient preference. There is no strong evidence to support better outcomes in open thoracotomy versus percutaneous closure.<sup>21</sup>

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## CONCLUSION

A young patient with few risk factors for cerebrovascular disease who presents with stroke-like symptoms should warrant diagnostic workup including echocardiography with an agitated saline "bubble" study. Further workup should include ultrasonography to evaluate for thrombosis in the upper and lower extremities, as well as carotid ultrasonography to assess for a source of emboli. If absent, a pelvic MRI should be considered to evaluate for pelvic deep vein thrombosis. Taking into account symptoms and patient preference, both medical and interventional management can be discussed as treatment options. Medical therapy should consist of at least a full dose aspirin daily. Percutaneous PFO closure may present another viable option for management. Closure may result in improvement of symptoms for those suffering with migraine headaches as well, although these data remain controversial. Studies on long-term outcomes have not been published; however, several trials for PFO closure in cryptogenic stroke are nearing completion at this time.

## REFERENCES

- Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics-2008 update: report from the American Heart Association Statistics Subcommittee. *Circulation* 2008;117:e5-146.
- Cohnheim J. A general pathologic lecture. In: *Thrombosis and Embolism*. Berlin:Marzhouzer; 1877:134-137.
- Agostoni P, Gasparini G, Destro G. Acute myocardial infarction probably caused by paradoxical embolus in a pregnant woman. *Heart* 2004;90:e12.
- Cartoni D, DeCastro S, Valente G, et al. Identification of professional scuba divers with patent foramen ovale at risk for decompression illness. *Am J Cardiol* 2004;94:270-273.
- Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med* 1988;318:1148-1152.
- Clark EB. Pathogenetic mechanisms of congenital cardiovascular malformations revisited. *Semin Perinatol* 1996;20:465-472.
- Hara H, Virmani R, Ladich E, et al. Patent foramen ovale: current pathology, pathophysiology, and clinical status. *J Am Coll Cardiol* 2005;46:1768-1776.
- Wilhmurth PT, Ellis BG, Jenkins BS. Paradoxical gas embolism in a scuba diver with an atrial septal defect. *Br Med J (Clin Res Ed)* 1986;293:1277.
- Anzola GP, Magoni M, Guindani M, et al. Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. *Neurology* 1999;52:1622-1225.
- Cramer SC, Rordorf G, Maki JH, et al. Increased pelvic vein thrombi in cryptogenic stroke: results of the Paradoxical Emboli from Large Veins in Ischemic Stroke (PELVIS) study. *Stroke* 2004; 35:46-50.
- Di Tullio M, Sacco RL, Venketasubramanian N, et al. Comparison of diagnostic techniques for the detection of patent foramen ovale in stroke patients. *Stroke* 1993; 24:1020-1024.
- Attaran RR, Ata I, Kudithipudi V, et al. Protocol for optimal detection and exclusion of patent foramen ovale using transthoracic echo with agitated saline microbubbles. *Echocardiography* 2006;23:612-622.
- Lynch JJ, Schuchard GH, Gross CM, et al. Prevalence of right-to-left atrial shunting in a healthy population: detection by Valsalva maneuver contrast echocardiography. *Am J Cardiol* 1984; 53:1478-1480.
- Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention. *Circulation* 2006;113:e409-449.
- Salem DN, O'Gara PT, Madias C, et al. Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133:593S-629S.
- Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;345:1444-1451.
- Homma S, Sacco RL, Di Tullio MR, et al. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation* 2002;105:2625-2631.
- Pearson AC, Labovitz AJ, Tatineni S, et al. Superiority of tranesophageal echocardiography in detecting cardiac source of embolism in patients with cerebral ischemia of uncertain etiology. *J Am Coll Cardiol* 1991;17:66-72.
- Anzai H, Child J, Natterson B, et al. Incidence of thrombus formation on the CardioSeal and the Amplatzer interarterial closure devices. *Am J Cardiol* 2004;93:426-431.
- Reisman M, Christofferson RD, Jesurum J, et al. Migraine headache relief after transcatheter closure. *J Am Coll Cardiol* 2005;45:493-495.
- Homma S, Di Tullio MR, Sacco RL, et al. Surgical closure of patent foramen ovale in cryptogenic stroke patients. *Stroke* 1997;28:2376-2381.

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