A 23-year-old right-handed woman developed sudden right-sided weakness, right-sided facial droop, and aphasia. She was in her usual state of health prior and presented 70 minutes after symptom onset. Just before symptom onset she had been bearing down for a bowel movement. Recently she had undergone a 6-hour car journey. Her medical history was significant for attention deficit disorder treated with lisdexamfetamine. She does not use any insulin or oral hypoglycemic medications. On presentation she was afebrile, her blood pressure was 130/77 mm Hg, and she had a heart rate of 89 beats/min and a respiratory rate of 16 breaths/min. On assessment, she had right-sided facial drooping with mild right-sided weakness that was improving. Her National Institute of Health Stroke Scale score was 2 with facial drooping and aphasia. She had no history of migraine, recent trauma, seizures, or stroke, and no illicit drug use. A fingerstick glucose test was normal. A non-contrast computed tomography (CT) scan of the head showed no acute cortical infarction or hemorrhage. She was deemed to have suffered an acute ischemic stroke.

1. What is the next best step in the management of this patient?

a. Tissue plasminogen activator (tPA) infusion

b. Frequent neurological checks for continued improvement

c. Thrombectomy

d. Ultrasound enhanced thrombolysis

e. Tirofiban

In an acute ischemic stroke, use of tPA, such as alteplase, is first-line therapy. Patients must be 18 years or older and within 3 to 4.5 hours after symptom onset. Some of the findings that would prevent the use of tPA include evidence of intracranial hemorrhage or neoplasm, or blood pressure of 185/110 mm Hg or greater, among others.

Frequent neurological checks alone are insufficient in a patient with a clinical diagnosis of stroke when other acute stroke therapies are available for treatment.

Thrombectomy is not the first choice therapy for ischemic stroke in patients who are eligible for thrombolytic therapy. It is most often reserved for large artery occlusion in the anterior circulation.

Ultrasound enhanced thrombolysis and tirofiban are investigational therapies that are currently unproven.

This patient meets the clinical diagnosis of an acute ischemic stroke and should receive systemic tPA. She is within the 3-hour time frame from symptom onset, and there was no evidence on non-contrast CT scan such as hemorrhage or neoplasm.

She received an infusion of tPA. A magnetic resonance image (MRI) of the brain showed acute ischemic infarction in the left supramarginal gyrus, a territory of the left middle cerebral artery. Baseline laboratory testing (with reference ranges reported in brackets parenthesis) included hemoglobin 12.2 g/dL (12.0 to 15.5 g/dL), platelet count 265×10⁹/L (157 to 371×10⁹/L), sodium 141 mmol/L (135 to 145 mmol/L), creatinine 1.11 mg/dL (0.84 to 1.21 mg/dL), blood urea nitrogen 14 mg/dL (6 to 21 mg/dL), glucose 93 mg/dL (<140 mg/dL), prothrombin time 14.3 seconds (11.6 to 14.7 seconds) with international normalized ratio 1.1 (0.8 to 1.1), active partial thromboplastin time 14.3 seconds (11.6 to 14.7 seconds) with international normalized ratio 1.1 (0.8 to 1.1), active partial thromboplastin time 26.4 seconds (30 to 40 seconds), and troponin <6 ng/L (<10 ng/L). In addition, results for pregnancy testing, urine drug screen, and
electrocardiogram were negative. Further testing for workup of stroke in a young patient included a C-reactive protein $<3.0$ mg/L ($<10$ mg/L), antinuclear antibody 0.4 U ($<1.0$ U), erythrocyte sedimentation rate 9 mm/h (0 to 29 mm/h), anti-phospholipid antibody $<9.4$ GPL ($<15.0$ GPL), protein C activity 125% (70% to 150%), free protein S 81% (50% to 160%), plasma homocysteine 9 mc mol/L ($<15$ mc mol/L), and antithrombin III activity 82% (80% to 130%). Prothrombin gene mutation and factor V Leiden mutation results were negative. She did not have markers of a prothrombotic or autoimmune condition. Cardiac causes of an ischemic stroke were investigated with inpatient telemetry monitoring; this was negative for any underlying arrhythmia. Cardiac imaging was obtained to evaluate for any intracardiac thrombus, mitral stenosis, myxoma, or patent foramen ovale (PFO).

2. **What is the next most appropriate test for evaluation of a PFO in this patient?**
   a. Cardiac MRI
   b. Transthoracic echocardiogram (TTE) with agitated saline contrast
   c. Transmitral Doppler scan
   d. Intracardiac echocardiography
   e. Transesophageal echocardiogram (TEE)

Cardiac MRI would not be the first-choice test. It is expensive and not always readily available. It is less sensitive in the detection of a PFO than TTE. Transthoracic echocardiogram with agitated saline contrast (bubble study) is a standard part of testing when evaluating for a PFO. It is well tolerated by patients and does not require sedation. It has the additional benefit of allowing patients to participate in Valsalva, an important part of the bubble study. The Valsalva maneuver will transiently cause increased pressure in the right side of the heart allowing a gradient from right to left to be visualized.

A transmitral Doppler scan has good sensitivity and specificity but clinical experience is limited.

Intracardiac echocardiography will also allow direct visualization of the shunt but is more invasive and less widely available.

A TEE will allow direct visualization of a PFO and is a necessary step when evaluating for closure. However, it is invasive, the probe will interfere with the closure of the glottis, and sedation will make participation with Valsalva difficult.

The most appropriate next step for this patient is a TTE with agitated saline contrast. This is noninvasive and well tolerated, and will allow for evaluation of an intracardiac thrombus or myxoma, as well as a PFO.

The patient improved clinically over the next 24 hours with no residual neurological defects. Her TTE was significant for a PFO with no intracardiac thrombus, tumor, or valve pathology. Bilateral lower extremity venous ultrasound was negative for deep vein thrombosis. Based on her workup she was deemed to have had a cryptogenic stroke in the setting of a PFO.

3. **Which of the following interventions will be most effective in mitigating the risk of a recurrent stroke in this patient?**
   a. Antiplatelet therapy alone
   b. PFO closure
   c. Anticoagulation
   d. Lifestyle modification
   e. Inferior vena cava filter

Antiplatelet therapy will reduce the risk of stroke recurrence. However, for patients who are candidates for closure, PFO closure has been shown to result in lower recurrence in comparison (see discussion below).

For patients younger than 60 years old with a cryptogenic embolic stroke, PFO, and no other clear source of stroke, current evidence shows that PFO closure is superior to medical therapy in the prevention of recurrent ischemic stroke. The risk is reduced from 4.1% to 1.2%.

When comparing anticoagulation versus antiplatelet therapy, there has been no difference shown in reducing the risk of stroke, transient ischemic attack, or death.

Lifestyle and risk factor modification is useful in general after a stroke, but this young patient does not have the typical risk factors including hypertension, hyperlipidemia, or diabetes.
There is no indication for an inferior vena cava filter in this patient with no evidence of deep venous thrombosis and no contraindication to anticoagulation.

This patient is 23 years old and has had a cryptogenic ischemic stroke. To reduce the risk of a recurrent stroke she was advised to undergo PFO closure.

4. Which of the following complications would be most likely to occur following the planned procedure in this patient?
   a. Device migration
   b. Device thrombosis
   c. Cardiac perforation
   d. Atrial fibrillation
   e. Puncture site hematoma

Device migration and device thrombosis are both rare complications of device placement.

Cardiac perforation is a rare complication of device erosion. None of the initial studies (including Patent Formen Ovale Closure or Anticoagulation versus Antiplatelets after Stroke [CLOSE]², Patent Formen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke [REDUCE]³ and extended Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment [RESPECT]⁴) had reported adverse events of device migration or thrombosis, or cardiac perforation.

The most common complication of percutaneous PFO closure found from meta-analyses of trials was atrial fibrillation with an absolute risk increase of up to 4.1%.¹

Puncture site hematoma is a common complication but is less frequent than atrial fibrillation (0.2% vs 0.4%).⁴

This patient would be most likely to develop atrial fibrillation following PFO closure.

Risks and benefits were explained to the patient and she elected to undergo percutaneous PFO closure.

5. Five months later she had an appointment for dental cleaning. What would be the best advice regarding antibiotic prophylaxis?
   a. 2 g oral amoxicillin 30 to 60 minutes before procedure
   b. 2 g intramuscular/intravenous ampicillin 30 minutes before procedure
   c. 600 mg oral clindamycin 60 minutes before procedure
   d. Intravenous vancomycin 120 minutes before procedure
   e. No antibiotic prophylaxis required

The current recommendation for patients who have undergone PFO closure is to receive antibiotic prophylaxis for any invasive dental or respiratory procedure up to 6 months following the procedure. The most appropriate antibiotic regimen would be 2 g oral amoxicillin 30 to 60 minutes before the procedure.

The intramuscular or intravenous route is inappropriate for patients who are able to take oral medication.

Clindamycin would be appropriate prophylaxis in patients with a penicillin allergy.

Intravenous vancomycin would be appropriate for patients who are allergic to penicillin and are unable to take oral medications.

Antibiotic prophylaxis is not required if device placement was more than 6 months ago.

This patient’s procedure was only 5 months ago; therefore, she should receive bacterial endocarditis prophylaxis as above.

Her post-procedural course was uncomplicated. Results from a follow-up appointment 6 months later with TTE showed a well-positioned device with no evidence of shunting.

DISCUSSION

A PFO persists in 20% to 25% of the adult population. A PFO is found in nearly half of patients with cryptogenic stroke.⁵ During early ventricular systole and Valsalva, a transient right-to-left gradient can occur through the PFO. At these times a PFO can act as a pathway for a transit of emboli from the venous to arterial system leading to a paradoxical embolus.

A stroke cannot be termed cryptogenic until other etiologies are excluded.

A detailed history and physical exam is the cornerstone for initial evaluation. Initial
hematological testing should include a complete blood count, including a platelet count, international normalized ratio, and partial thromboplastin time. Current routine imaging of patients with an ischemic stroke includes MRI or CT. This will provide information on evidence of hemorrhage or ischemic infarct including location, volume, and multiplicity. Further imaging with ultrasound, CT, or MRI is used to assess the cerebral, neck, and thoracic arteries for dissection. Initial cardiac testing should include echocardiography for structural assessment. Transthoracic echocardiography with agitated saline contrast is preferred first as it is less invasive. If no pathology is identified, further evaluation can be performed with a TEE. A 12-lead electrocardiogram and inpatient telemetry monitoring with at least 24-hour Holter monitoring following discharge is performed for evaluation of cardiac arrhythmias; this may be extended to a 30-day mobile cardiac outpatient telemetry if no arrhythmias are detected. In the cases of young patients, the list of etiologies broadens to include autoimmune, vasculitis, hypercoagulable disorders, and congenital cardiac conditions. If no revealing cause is found after standard evaluation, then a stroke is considered cryptogenic.

If it is believed that there is a causal relationship between the PFO and ischemic stroke, the patient should undergo evaluation by both a vascular neurologist and a structural cardiologist to identify patients that are likely to benefit from device-based cardiac interventions for further stroke prevention. A scoring system was developed to aid identification of such patients. This was investigated in the Risk of Paradoxical Embolism (RoPE) study. The purpose of the RoPE score is to aid in identifying those patients without other risk factors for stroke and so will have a higher likelihood that the PFO was causative. The score includes common risk factors for ischemic stroke such as the presence of hypertension, diabetes, and previous stroke or transient ischemic attack, points will be given for not having had a history of these and a higher score will make the implication of the PFO more likely. In our case, the patient’s RoPE score was 10 of a possible 10, making it an 88% chance her stroke was due to her PFO.

Once a patient is deemed a candidate for closure of the PFO, a transesophageal echocardiography is preferred as it will allow detailed assessment of the anatomy of the atrial septum. Assessment of the atrial septum is important as it can provide information regarding suitability for device closure and can help to confirm that the shunt is due to a PFO rather than other defects of the atrial septum.

Three early randomized control trials (Closure or Medical Therapy for Cryptogenic Stroke with Patent Foramen Ovale [CLOSURE I], Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism [PC] trial, and short-term RESPECT) did not show any benefit of PFO closure for secondary stroke prevention. Further studies were done including the CLOSE and REDUCE trials, and the extended follow up of the RESPECT trial, that then showed a statistically significant decrease in stroke recurrence between patients who had undergone PFO closure and those who had been managed medically, indicating a benefit of PFO closure. The distinction appears to have mainly occurred from stricter inclusion criteria and extended follow-up. The CLOSE trial included patients up to 60 years old who had a PFO with a large intra-arterial shunt or atrial septal aneurysm. They were not considered eligible if there was small vessel disease or greater than 30% stenosis of an artery supplying the brain. The REDUCE trial included patients who were 18 to 59 years old and excluded patients who had stenosis of greater than 50% of a major vessel, lacunar stroke, or uncontrolled risk factors of ischemic stroke. When compared with the earlier studies, the stricter selection criteria likely meant that those who were included were more likely to have had a cryptogenic stroke related to their PFO rather than from large or small vessel disease.

The most common adverse effect noted across the trials was that of atrial fibrillation.
This was noted to occur often early after closure and the majority were single episodes that resolved either spontaneously, medically, or with cardioversion. Of the 4.1% of patients who developed atrial fibrillation, 80% to 90% of the cases were transient.1 This should be included in discussions in patients when planning for PFO closure. Further studies are required to assess this relationship because, although indicated for diagnosing a cryptogenic stroke, 24-hour Holter monitor was not an inclusion criteria in the studies; therefore, pre-existing paroxysmal atrial fibrillation was not excluded. Other rare risks to be discussed include hematoma at the puncture site, device migration, device embolization, and device thrombosis. In rare cases of device erosion, this could then lead to further complications of perforation with effusion, tamponade, or even creation of an atrial septal defect.

In conclusion, PFO closure can be considered in select ischemic stroke patients younger than 60 years old to reduce the risk of recurrent stroke. The patients must undergo full etiological workup, as detailed above, to exclude other plausible causes. The decision to pursue PFO closure should be collaborative between a neurologist, a cardiologist, and the patient themselves after all risks and benefits have been discussed.12

Potential Competing Interests: The authors report no potential competing interests.

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REFERENCES

Correct Answers: 1. a. 2. b. 3. b. 4. d. 5. a.