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Case Reports

PFO and Paradoxical Embolism Producing Events Other Than Stroke

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Background: A patent foramen ovale (PFO) is a risk factor for cerebral events such as cryptogenic stroke, transient ischemic attacks, and migraine headaches. Far less commonly, PFO is associated with non-cerebral, paradoxical systemic embolic events such as myocardial infarction (MI), renal infarct, and limb ischemia. This report details the incidence of systemic paradoxical emboli at our institution. Methods: 416 patients were referred for evaluation of PFO related conditions from 2001 to 2009. Clinical history and medical records of the patients were reviewed for incidence of cryptogenic stroke, transient ischemic attack (TIA), migraine headache, arterial desaturation, and noncerebral systemic embolism. Results: As the primary presenting symptom, 219 patients had a diagnosis of cryptogenic stroke, 38 patients had migraine headaches, and 80 patients had transient neurologic deficits consistent with a TIA or complex headache. Twelve patients (2.9% of the total population) presented with a presumptive diagnosis of systemic embolism. Eight of these patients had acute MI diagnosed by elevated cardiac biomarkers, electrocardiogram changes, and/or imaging evidence of a left ventricular wall motion abnormality, without evidence of obstructive coronary disease on angiography. Four patients had evidence of peripheral embolism to a systemic artery, including the popliteal artery, ophthalmic artery, and brachial artery. PFO closure was performed in 197 patients (47.4% of the total population), including eight patients in the systemic embolism group. All closure procedures were successful. Conclusion: Although most paradoxical emboli travel to the brain, noncerebral paradoxical embolism is also associated with PFO. In addition to embolism of thrombus, there may be paradoxical passage of vasoactive chemicals that induce intense coronary spasm and myocardial infarction. Diagnosis is often challenging, given the lack of definitive criteria and the need to exclude other potential etiologies.

Key words: stroke; myocardial infarction; arterial embolism

INTRODUCTION

Paradoxical embolism is a potential cause of cryptogenic stroke. The presence of a patent foramen ovale (PFO) may act as a pathway for a thrombus from the peripheral veins to bypass the lungs and enter the systemic circulation. A cerebral event is the usual presenting symptom in patients with a PFO. Systemic, noncerebral, paradoxical embolisms occur with far less frequency, accounting for 5–10% of all paradoxical embolisms [1], and represent a diagnostic challenge. Although uncommon, these events have been described as a cause of acute myocardial infarction (MI), renal infarction, and limb ischemia. We report a series of patients who presented with embolic events other than stroke, which presumably were the result of embolization of thrombus

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Conflict of interest: Nothing to report.

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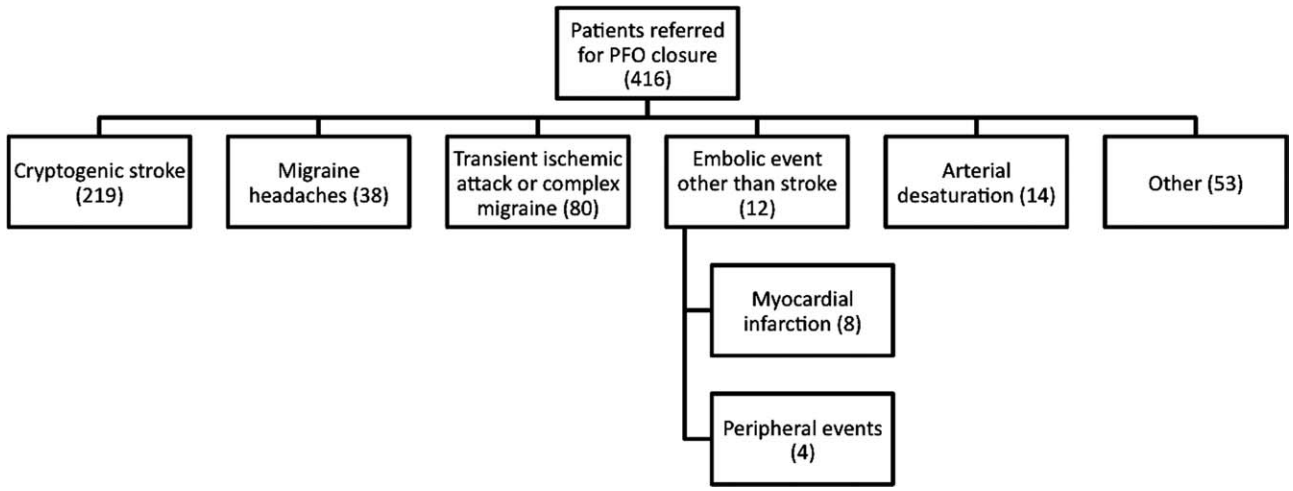

Fig. 1. Patients who were referred for evaluation of PFO at our institution.

or chemicals from right-to-left shunting through a PFO. We also examine the effect of PFO closure in these patients.

METHODS

Patient Population

From April 2001 to April 2009, 416 patients (mean age 49.0 ± 23.4 years, range 13–86) were referred for evaluation of PFO-related conditions to the Interventional Cardiology Program at the University of California, Los Angeles. Medical records including history, procedure reports, imaging, and echocardiography data were reviewed retrospectively. The primary reason for referral was a history of cryptogenic stroke ($n = 219$), initially diagnosed by a neurologist. Other primary conditions for which the patients sought treatment included migraine headaches ($n = 38$), transient neurologic deficits consistent with a transient ischemic attack (TIA) or complex migraine ($n = 80$), significant arterial desaturation due to right-to-left shunt ($n = 14$), and noncerebral paradoxical embolism ($n = 12$; Fig. 1).

PFO was diagnosed with transthoracic (TTE) or transesophageal echocardiography (TEE) with bubble study and transcranial Doppler (TCD) using the Spencer scale of grade 0–5. Atrial septal aneurysm was diagnosed with TEE as abnormally redundant interatrial septum with an excursion of $\geq$10 mm into the right or left atrium.

Procedure

PFO closure was performed without general anesthesia and on an outpatient basis after August 2001. Guidance with TEE or intracardiac echo was used during the procedure to ensure that the device was optimally placed. Implanted devices included the Amplatzer PFO occluder (AGA Medical Corporation, Golden Valley, MN), the Amplatzer Cribriform occluder (AGA Medical Corporation, Golden Valley, MN), the CardioSEAL device (Nitinol Medical Technologies, Boston, MA), and the Helex Device (W. L. Gore and Associates, Flagstaff, AZ). Patients considered for PFO closure at our institution included those who were symptomatic with a PFO-related condition, such as stroke, decompression illness, severe migraines, or orthodeoxia.

All patients who underwent the procedure had a TEE approximately 1–3 months after the procedure to confirm adequate positioning of the device and to document the absence of residual shunt or thrombus formation on the device. Clinical follow-up was performed at 6- to 12-month intervals to evaluate symptoms, persistence, and severity of migraine headaches, or the presence of recurrent thromboembolic events.

RESULTS

Successful PFO closure was performed on 197 patients (47.4% of the total population). The Amplatzer PFO occluder device was implanted in 111 patients, the Amplatzer Cribriform occluder device in 18 patients, the CardioSEAL device in 30 patients, and the Helex Device in 38 patients. Twelve patients (2.9% of the total population) presented with a diagnosis of systemic embolism. Demographic and clinical characteristics for this group are demonstrated in Table I. The mean age was 42.7 ± 14.4 years. Eight of these patients (1.9% of the total population) had acute MI diagnosed by elevated cardiac biomarkers, electrocardiogram (ECG) changes, and/or evidence of regional wall motion abnormalities on echocardiography or ventriculogram without evidence of obstructive coronary

TABLE 1. Patient Demographic and Clinical Characteristics

	Number
Age (mean)	42.6 (± 14.4) years
Gender	Female = 7 (58.3%), male = 5 (41.7%)
Hypertension	5 (51.7%)
Hyperlipidemia	7 (58.3%)
Diabetes	0
Smoking	Current = 0, former = 3 (25.0%)
Family history of CAD	3 (25.0%)
Previous CVA	6 (50.0%)
Previous TIA	2 (16.7%)
Migraine headache	9 (75.0%)
Hypercoagulable state	Heterozygous = 1 (8.3%), contraception use = 3 (25.0%)
Weight	167.9 lbs
ASA (>10 mm) on TEE or ICE	1 (8.3%)
Acute myocardial infarction	8 (66.7%)
Systemic embolism	4 (33.3%)
PFO closure	7 (58.3%)

disease on angiography. Of the eight patients with MI, four had one or more cardiac risk factor (e.g., hypertension, hyperlipidemia, diabetes mellitus, positive family history of coronary disease, or smoking history). Four patients (0.96% of the total population) had peripheral vascular embolism (location included the popliteal artery [1], ophthalmic artery [2], and brachial artery [1]). Six patients in this group had a history of previous stroke, and two patients had previous TIA. Migraine with aura was present in nine patients. Brain magnetic resonance imaging (MRI) or computed tomography (CT), revealed evidence of infarction in all six of the stroke patients. One patient had evidence of infarct on brain CT but MRI could not be performed due to the presence of a cardiac pacemaker. One patient was heterozygous for the prothrombin gene mutation and three patients reported concomitant hormone contraceptive use. Atrial septal aneurysm was present in one patient; the excursion measurement was 11.5 mm.

Transcatheter PFO closure was performed in eight patients [Amplatzer PFO ($n = 6$), Helex ($n = 2$)]. Of the four patients who were not closed, one patient died from complications of the myocardial infarction and hemorrhagic stroke before the procedure could be performed and three patients chose not to have the procedure performed. Follow-up TEE was performed in eight patients, an average of 2.5 months later. No residual shunt or recurrent cerebral or extracerebral embolism was observed in these patients during a mean follow-up of 12 months.

Three exemplary cases are described.

Case 1: Sequential Cerebral and Myocardial Infarction

A 43-year-old man was evaluated for recurrent neurological symptoms. He had suffered from migraine headaches with visual aura for over 20 years. His past medical history included several prior small cryptogenic strokes. Each event was associated with sudden onset left-sided numbness and weakness, and dysarthria or aphasia. Brain MRI demonstrated infarcts in the left Sylvian fissure and bilateral cerebellum, while MRA showed no abnormality in the intracranial or extracranial circulation. Transesophageal echocardiography demonstrated a PFO with right-to-left shunting. While the patient was deciding whether to have his PFO closed, he developed sudden onset of chest pain and was hospitalized at an outside facility. Though the patient had no cardiac risk factors, electrocardiogram showed ST segment elevation and troponin was elevated.

Two months later the patient underwent successful percutaneous PFO closure with a Helex PFO occluder. Coronary angiography revealed sluggish flow in the left anterior descending coronary artery consistent with prior MI, but otherwise there was no obstructive atherosclerotic disease. There was significant anterolateral hypokinesis on left ventriculogram and elevated left-ventricular end-diastolic pressure. He was treated with clopidogrel for 2 months and aspirin indefinitely. Four months postprocedure, his neurological symptoms had improved, with complete resolution of his migraine headaches. Transesophageal echocardiography showed that the closure device was properly in place without thrombus or evidence of residual right-to-left shunting.

Case 2: Peripheral Embolism

Three days after returning from a cross-country airline flight, a 40-year-old woman presented with acute pain and numbness of her right lower leg while jogging. She had no significant past medical history, though she reported developing weekly migraine

headaches with visual aura in the previous 3 months, which coincided with the use of a hormone-containing intravaginal ring for contraception (NuvaRing, Schering-Plough Corp, Kenilworth, NJ). Previously, she had been taking oral contraceptive pills without symptoms. Lower extremity MRA revealed popliteal artery occlusion and thrombus in the peroneal and posterior tibial trunk. No aneurysm or dissection of the arterial vasculature was noted. There was no evidence of DVT. Thrombolytic therapy with human tissue plasminogen activator was initiated, and angioplasty of the popliteal artery was successfully performed. She was placed on heparin and ultimately on warfarin. Transesophageal echocardiogram demonstrated a PFO with atrial septal aneurysm and significant right-to-left shunting. Chest MRA revealed mild ectasia of the ascending aorta, with no evidence of atherosclerosis or dissection of her great vessels or coronary arteries. A hypercoagulability work-up was negative.

The patient underwent percutaneous closure of her PFO. Warfarin was discontinued and she was treated with clopidogrel for 2 months and aspirin indefinitely. Eight-months postprocedure, she was doing well. Her headaches persisted, though they were less severe and without aura. The intravaginal ring was discontinued. Transesophageal echocardiography at 3-months post-closure demonstrated that the device was properly positioned without thrombus or evidence of residual shunting.

Case 3: PFO Migraine and Myocardial Infarction

A 49-year-old woman with a 30-year history of migraine headache presented to an outside hospital with progressive chest pain. While being evaluated in the emergency department for her symptoms, she suffered a cardiac arrest and required cardiopulmonary resuscitation and defibrillation. She immediately underwent cardiac catheterization, which showed diffuse narrowing in a large diagonal branch as well as more focal narrowing in the distal LAD (Fig. 2a and b). There was no evidence of occlusive thrombus or slow flow in the coronary arteries. Nitroglycerine was not given. Her left ventriculogram showed preserved function and was not consistent with Takostubo syndrome. There was no history of illicit drug use. She underwent balloon angioplasty of the diagonal artery with a 2-mm balloon. No stent was placed.

Four months later, she was referred to our institution for evaluation of her unusual coronary presentation. A history of migraines for many years was obtained and a TEE with agitated saline bubble study revealed the presence of a PFO. Brain MRI demonstrated multifocal white matter lesions. Her chest pain symptoms improved with nitrates and cyproheptadine, a serotonin antagonist. Six months after the cardiac arrest, successful closure of her PFO was performed. Coronary angiography obtained during the closure procedure demonstrated no evidence of atherosclerotic disease (Fig. 2c). Her initial angiograms were interpreted by us as demonstrating coronary artery spasm (Fig. 2a and b) because the narrowing in both the diagonal and LAD had resolved completely, although such a diagnosis could not be proven since intra-coronary vasodilators were not used during the initial event and intravascular ultrasound (IVUS) imaging was not obtained at the time to rule out other entities such as dissection. Intravascular ultrasound of the left anterior descending artery during the second catheterization revealed no dissection or atherosclerotic plaque (Fig. 2d).

DISCUSSION

Paradoxical embolism has been implicated as a potential cause of cryptogenic stroke, coronary embolism, peripheral arterial thromboembolism, renal, and other organ infarction, [2,3]. It is believed that these emboli originate from thrombus in the veins of the legs or pelvis and reach the systemic circulation from right-to-left shunting through the PFO when pressure in the right atrium transiently exceeds left atrial pressure. Patent foramen ovale is proposed as a possible risk factor for neurological deficits other than stroke, such as migraine headaches, dementia, and TIA [4–6]. A PFO is also associated with nonspecific white matter lesions in migraineurs, which might represent destruction of myelin fibers either due to embolic phenomenon or vasospasm of the smaller perforating arterioles in the brain [7]. In our series, the majority of patients (11 of 12, 91.6%) had a history of some type of neurological deficit. Six patients had a history of prior stroke, while two had previous TIA. Nine patients suffered from migraine headaches. Two patients had evidence of embolus to the ophthalmic artery. Although this artery is a branch of the internal carotid artery, it is not involved in cerebral circulation. Thus, an embolic event at this location is not considered a CVA.

It is not known why the overwhelming majority of paradoxical embolism associated with PFO present as strokes. Blood flow to the cerebral vessels only accounts for 15% of the cardiac output, yet of the patients in our series who had definite infarctions, 95% (219/231) had cerebral emboli. Presumably there are other emboli to different parts of the body that may be asymptomatic, such as to the kidneys or spleen. Although the cause remains unknown, it is interesting to speculate that the patient who had an embolus to the popliteal artery while running, might have prevented a cerebral event by increasing her blood flow to the

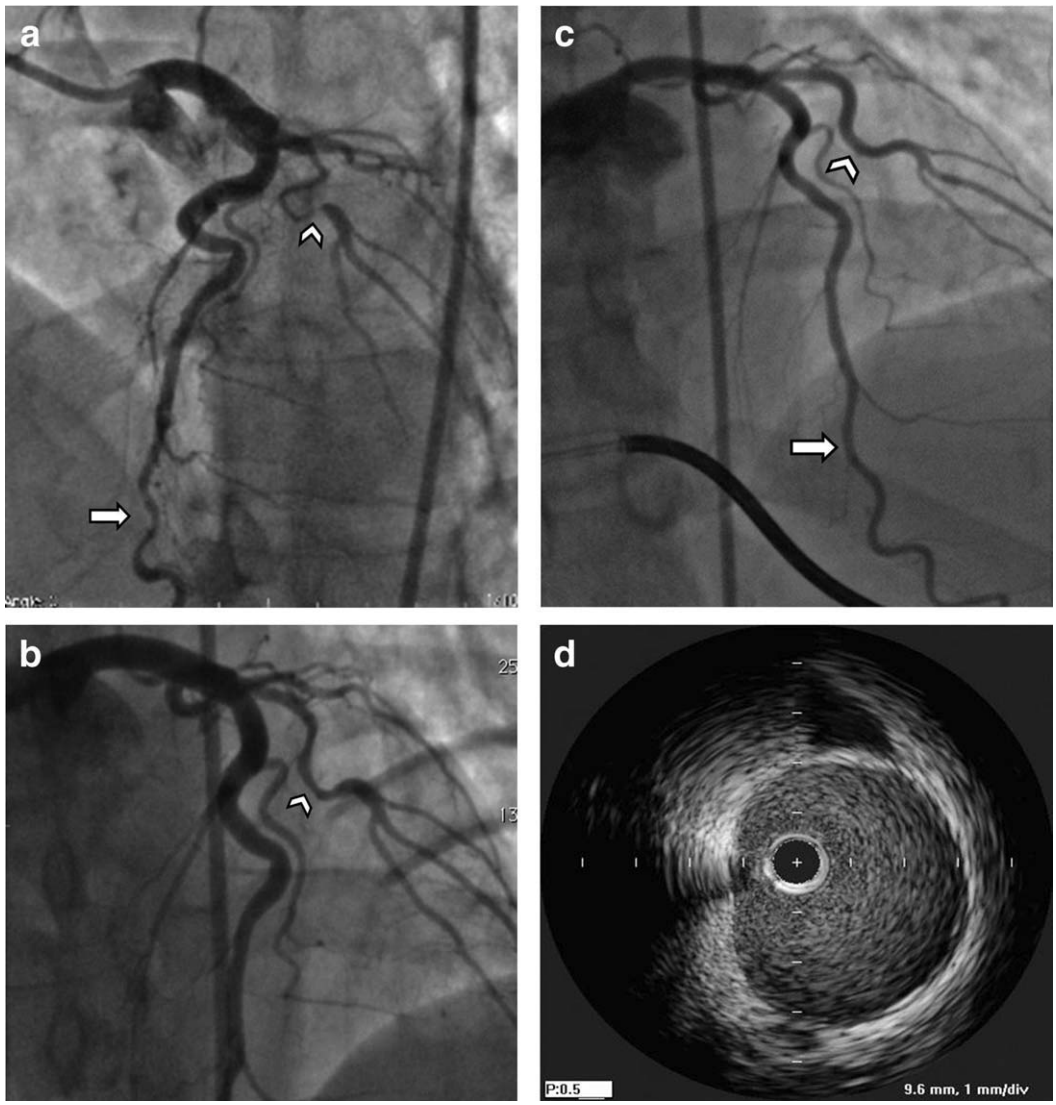

Fig. 2. a. Left coronary angiography reveals a long segment of diffuse narrowing in the diagonal branch of the LAD (arrowhead), as well as a shorter segment in the distal LAD (arrow). The other coronary arteries have no evidence of atherosclerotic disease. The diagonal artery was treated with balloon dilatation only. b. Post-balloon angioplasty image demonstrates persistent narrowing in the diagonal artery. c. Angiography repeated 6 months later demonstrates no evidence of coronary disease or spasm in the previously stenosed vessels. The patient received an implantable cardiac defibrillator for her episode of cardiac arrest (dark electrode at base of picture). d. Intravascular ultrasound reveals no evidence of coronary artery disease or atherosclerotic plaque in the LAD.

exercising muscles during the time that the venous thrombus was dislodged into the circulation.

Hypercoagulable states and hormone therapy in women are associated with an increased risk of paradoxical embolism [3,8]. In our series, three patients were taking contraceptive medications at the time of their embolic event, and one patient was heterozygous for the prothrombin gene mutation. While atrial septal aneurysm occurring in the presence of PFO has been postulated to increase the risk of paradoxical emboli [9], an atrial septal aneurysm was present in only one patient in this report.

Patients in our series who presented with acute MI were found to have extensive, regionally depressed wall motion on echocardiography or left ventriculogram, yet no evidence of obstructive epicardial coronary disease was found on angiography. These patients were relatively young (mean age 41.0 $\pm$ 12.6 years) and four of the eight (50%) had no known cardiac risk factors. One 24-year-old patient had a large filling defect in the right coronary artery on angiography (Fig. 3), which was extracted and documented to be thrombus. This patient had congenital heart disease with Ebstein's anomaly, a PFO, and clot in the right atrium

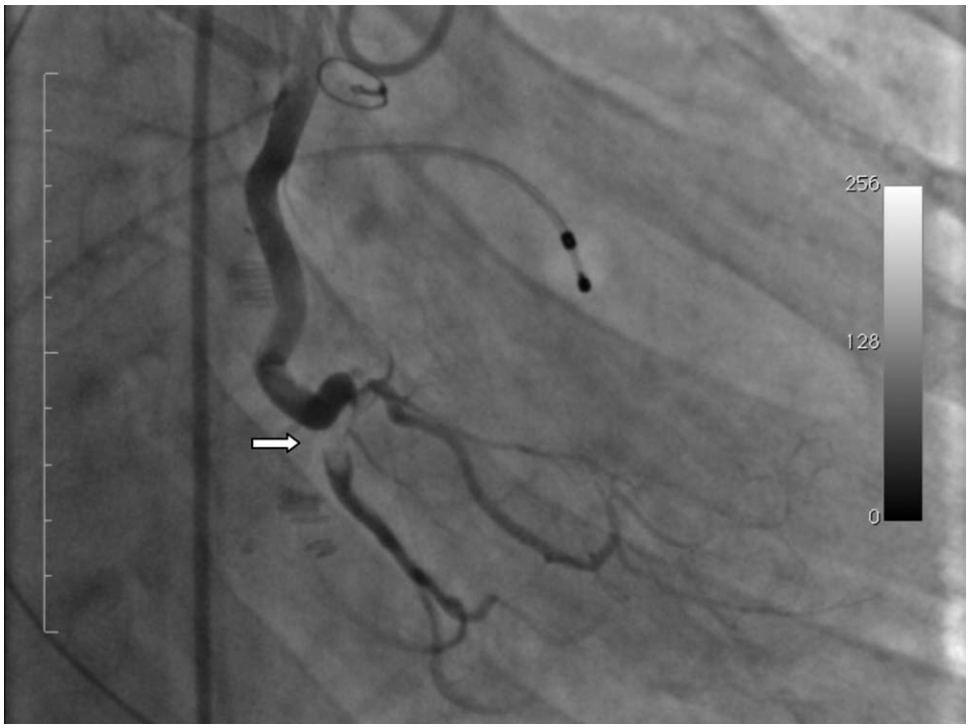

Fig. 3. Right coronary angiogram shows a large filling defect in the right coronary artery (RCA) of a 24-year-old patient with Ebstein's anomaly and a PFO. The lesion (arrow) is consistent with acute embolism, as demonstrated by a meniscus sign. It was extracted and documented to be a thrombus.

on echocardiography. He presented with a large stroke and died from complications associated with this event.

As distinguished from the mechanism of thrombotic embolism to the coronary arteries as a cause of myocardial infarction in the presence of a PFO, the presentation of case 3 is particularly noteworthy. Since there was no evidence of obstruction or thromboembolism to the coronary arteries at the time of the patient's MI, and no evidence of illicit drug use, we suspect that the event was the result of intense coronary vasospasm and not a paradoxical embolus. We hypothesize that a vasospastic substance such as serotonin, can bypass degradation in the lungs and enter the arterial system through a PFO in a higher concentration than is usual. The substance could then trigger intense arterial spasm in a coronary vessel producing an infarction, or ischemia with ventricular arrhythmia.

Myocardial infarction caused by paradoxical coronary embolism represents a diagnostic challenge. Definitive diagnostic criteria for coronary embolism have not been established [2]. It is a diagnosis of exclusion and is often difficult, if not impossible, to prove. In the absence of angiographic coronary artery disease, other possible causes for myocardial injury such as hypercoagulable states, cocaine or methamphetamine use, myocarditis, coronary dissection, or localized pericarditis should be considered in the diagnostic work-up. Cannabis causing vasospasm is also a documented cause of MI [10], however there was no evidence of such use in this case.

Secondary prevention for patients with a PFO who have had a cryptogenic stroke remains controversial [9]. These patients are often treated empirically with anti-platelet medications or anticoagulants, or referred for PFO closure with percutaneous intervention or open-heart surgical repair. Randomized clinical trials are ongoing [11,12] to determine which of these strategies is most beneficial. Similarly, appropriate treatment for patients with non-cerebral paradoxical embolic events is unclear. Given the rarity of the condition and its presumptive diagnosis, large randomized controlled-trials to determine the appropriate strategy will be difficult to perform.

CONCLUSION

Patent foramen ovale (PFO) is an important risk factor for cerebrovascular accidents occurring from paradoxical emboli to the brain. This report documents that passage of thrombus through a PFO may also be incriminated as a potential mechanism for paradoxical systemic embolism. In addition, it raises the hypothesis that some of the myocardial infarctions associated with PFO may be due to intense coronary vasospasm

possibly initiated by a vasoactive substance that ordinarily would be metabolized in the lungs.

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