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STEMI and CVA in Hypercoagulable State with Ostium Secundum Defect

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Abstract Atrial septal defect (ASD) is a risk factor for multiple vascular thrombotic events, which can occur either sequentially or simultaneously. In this report we present a case of ST-elevation myocardial infarction (STEMI) and cerebrovascular accident (CVA). The severity of adverse cardiovascular or cerebrovascular events can be increased by the presence of specific type of ASD, such as a patent foramen ovale (PFO) or osteum secundum defect. This case report discusses a unique presentation of a 48-year old male on warfarin therapy for a history of cerebral venous thrombosis (CVT) who subsequently presented with simultaneous STEMI with CVA, and who was incidentally found to have an ostium secundum defect on echocardiography. He was emergently taken for cardiac catheterization, which revealed significant proximal LAD occlusion. There has been a long standing debate within the international scientific communities regarding the therapeutic benefit of PFO closure for long-term secondary prevention of recurrence CVA. We discuss the different points of view regarding PFO closure for secondary prevention of CVA with a review of the literature on this rather controversial topic.

Keywords: *hypercoagulability, atrial septal defect, myocardial infarction, cerebrovascular accident*

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1. Introduction

Patent Foramina Ovale (PFO) has a prevalence of 25-30% within the population and has important implications in the occurrence of cryptogenic strokes, which account for one-fourth of all ischemic strokes. [1] The pathophysiological mechanism is entry of an embolized clot into the systemic arterial circulation via the PFO. [2] Furthermore, the risk of these events is accentuated by the presence of a hypercoagulable state, such as protein S deficiency or autoimmune disease such as lupus. Both venous and arterial circulations are at risk of thrombosis in these contexts. We discuss the case of a patient who fits the paradigm of clotting in both venous and arterial circulation due to the following constellation of underlying predisposing factors: septum secundum defect, protein S deficiency, and lupus anticoagualnt. In patients undergoing echocardiography to evaluate for complications of MI, such as wall motion abnormalities, other defects can be discovered incidentally, such as an atrial septal defect, which although is unrelated to cerebral venous thrombosis, further increases the patient's risk of arterial cerebrovascular thromboembolic events. In addition to hereditary predisposition to hypercoagulability, there are environmental risk factors such as hypertension, diabetes, hypercholesterolemia, smoking history, and premature family history of coronary artery disease (CAD). We present the case of a patient who experienced a myocardial infarction and cerebrovascular accident (CVA) who was on warfarin therapy for a prior history of cerebral venous thrombosis, and who was incidentally found to have an ostium secundum defect on echocardiography. Although the patient may have benefited from genetic testing of hypercoagulable disorders, our focus will be on the manifestations of vascular thrombotic events in more than one site of the body as well as present the literary evidence in favor of atrial septal defect closure to maximize risk reduction of recurrence of these events.

2. Case Presentation

A 48 year-old male with a past medical history of cerebrovascular accident (CVA) in Barbados; records from Barbados is showing evidence of cerebral venous thrombosis complicated by left frontal infarction, hemorrhagic conversion and seizures. On initial imaging at that time, patient was noted to have a prior cerebellar

infarct. Patient was started on warfarin then. The patient presented to our facility with substernal chest pain radiated to his left shoulder and associated with diaphoresis. He stated that he was adherent on warfarin and denied any illicit drugs. His EKG showed new RBBB and ST-segment elevation in lead V1-V2 (Figure 1). His troponin I peaked to 0.38 ng/L [Normal <0.01]. He was started on Aspirin, clopidogrel, sublingual nitroglycerin, heparin and morphine. STEMI Code was initiated for primary percutaneous coronary intervention (PCI). He underwent urgent cardiac catheterization which revealed anterolateral and apical hypokinesis with Global left ventricular function moderately depressed. Ejection fraction (EF) by contrast ventriculography was 37 %. Coronary circulation revealed proximal left anterior descending (LAD) artery 100 % occlusion with completely normal rest of coronary circulation which may indicate embolic lesion. He was treated with drug-eluting stent in LAD with 1 % residual stenosis (Figure 2). During procedure, patient developed ventricular tachycardia. Electrical cardioversion was performed and lidocaine drip was initiated and continued for 24 hours. His transthoracic echocardiography at the day of PCI revealed EF of 30-35%, severe hypokinesis of the anterior, mid-distal, anteroseptal, and apical wall(s), and systolic and diastolic flattening of ventricular septum which may indicate right ventricular (RV) volume and/ pressure overload. RV was moderately to markedly dilated and atrial septum showed prominent Doppler flow noted at the mid-upper septum suggestive of an atrial septal defect (Figure 3).

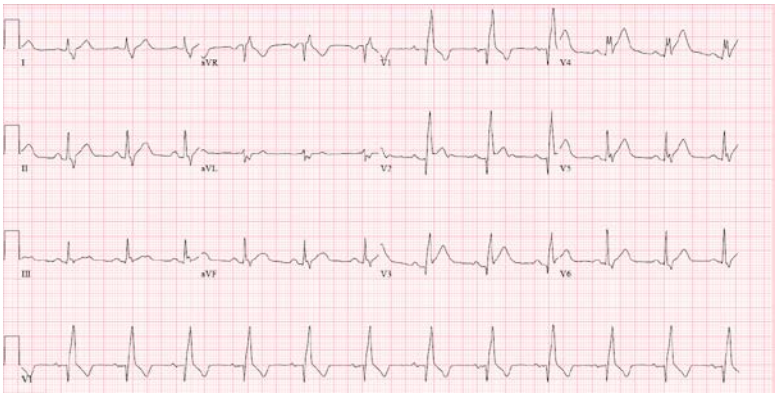

Figure 1. EKG showed new RBBB and ST-segment elevation in leads V1-V2

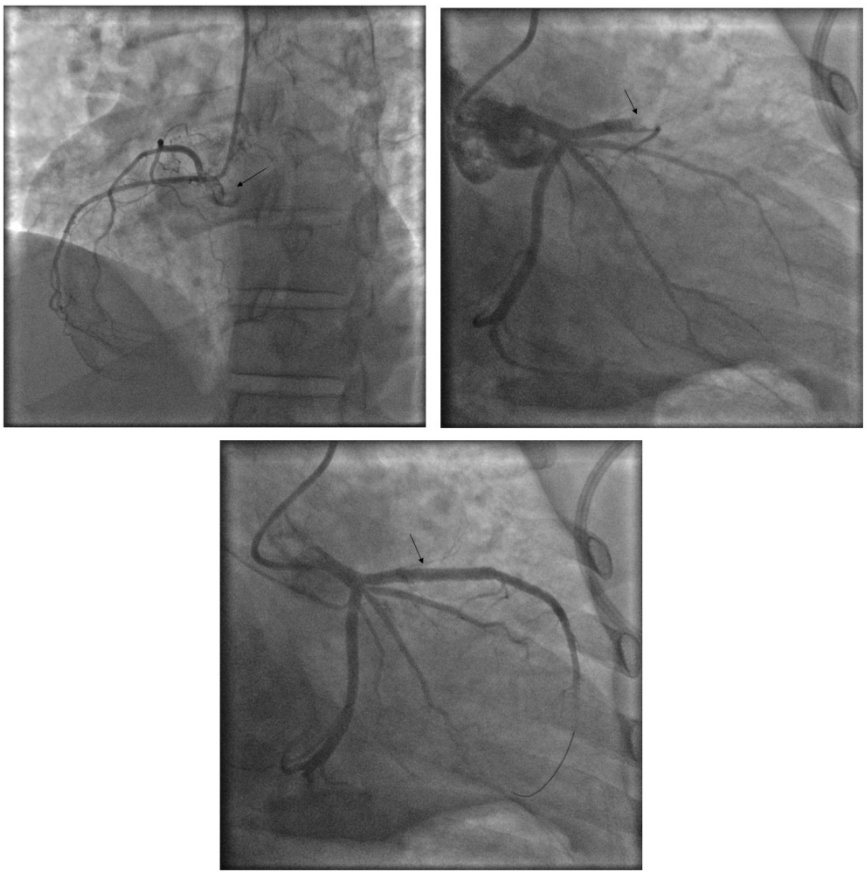

Figure 2. Cardiac catheterization which revealed anterolateral and apical hypokinesis with Global left ventricular function moderately depressed. Ejection fraction (EF) by contrast ventriculography was 37 %. Coronary circulation revealed proximal left anterior descending (LAD) artery 100 % occlusion with completely normal rest of coronary circulation which may indicate embolic lesion. He was treated with drug-eluting stent in LAD with 1 % residual stenosis

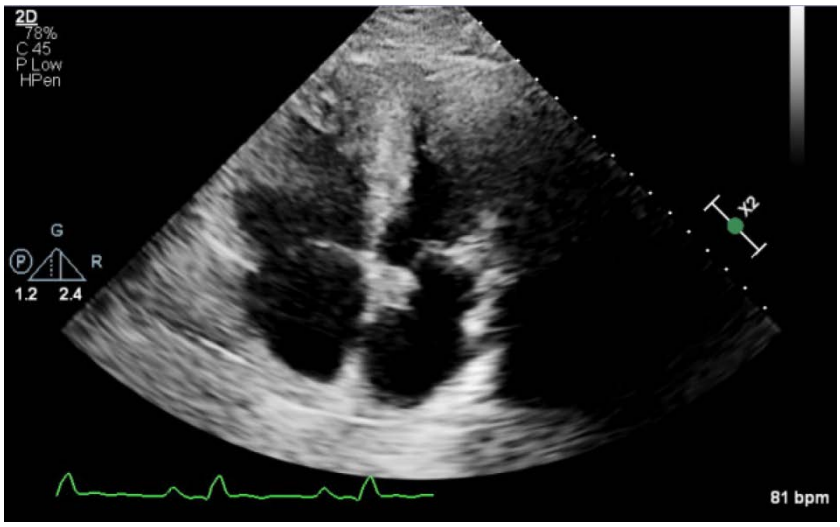

Figure 3. Transthoracic echocardiography at the day of PCI revealed EF of 30-35%, severe hypokinesis of the anterior, mid-distal, anteroseptal, and apical wall(s), and systolic and diastolic flattening of ventricular septum which may indicate right ventricular (RV) volume and/ pressure overload. RV was moderately to markedly dilated and atrial septum showed prominent Doppler flow noted at the mid-upper septum suggestive of an atrial septal defect

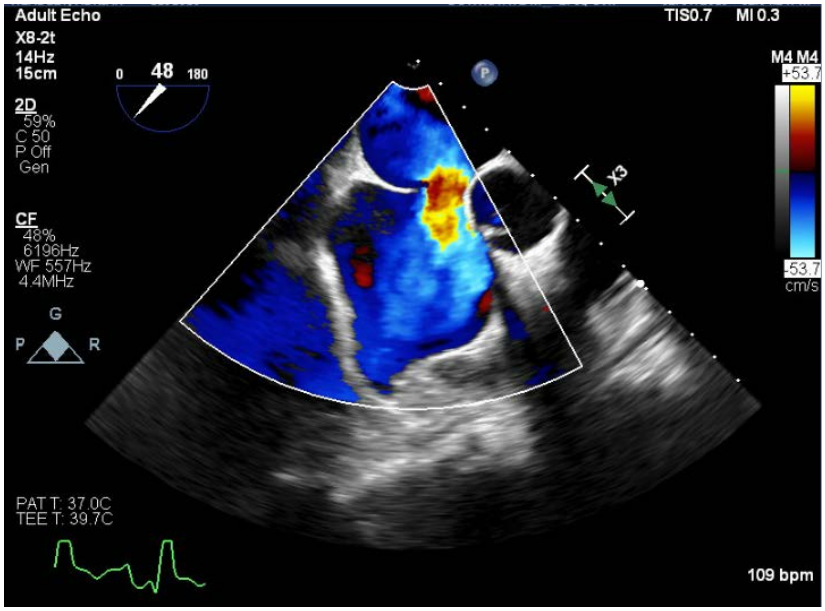

Figure 4. Transesophageal echocardiography which revealed large secundum septal defect measuring 20 mm with left to right flow

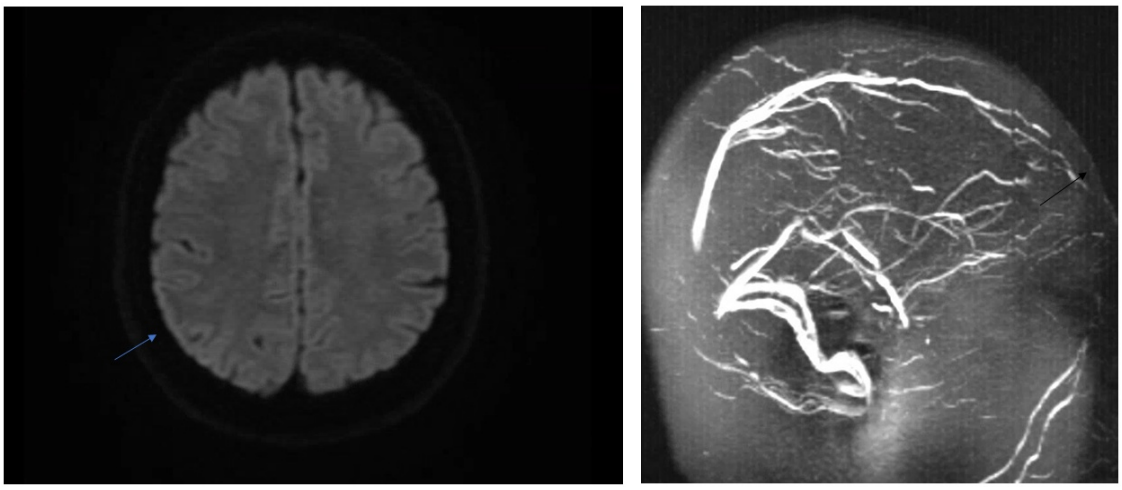

Figure 5. MRI brain revealed tiny focus of restricted diffusion left posterior parietal lobe on the Diffusion-weighted magnetic resonance imaging (DWI) series, which may represent a small area of acute or subacute ischemia; and anterior portion of superior sagittal sinus appears thinned and irregular, which may represent partial thrombosis

His INR was 1.1 despite patient's report of adherence to warfarin. MI was suspected to be secondary to hypercoagulability given subtherapeutic INR and prior history of CVA. He underwent transesophageal echocardiography which revealed large secundum septal defect measuring 20 mm with left to right flow (Figure 4). He was sent for hypercoagulable studies which revealed low protein S, which can be explained by the use of warfarin, and positive anti lupus antibodies. Lower extremity Duplex showed no evidence of deep venous thrombosis. MRI brain revealed a tiny focus of restricted diffusion in the left posterior parietal lobe on the Diffusion-weighted magnetic resonance imaging (DWI) series, which may represent a small area of acute or subacute ischemia and anterior portion of superior sagittal sinus appears thinned and irregular, which may represent partial thrombosis (Figure 5).

The patient was discharged on enoxaparin, dual antiplatelet therapy, metoprolol succinate, warfarin and rosuvastatin. He was referred for outpatient ASD closure.

3. Discussion

With our patient who had a preceding CVA, he presented with simultaneous CVA and MI, and the pathogenesis was deemed to be most likely an embolic event from an unknown, unidentified thrombotic source. The biggest factor that contributed to his presentation was the presence of septum secundum defect, which although has not been studied thoroughly in the literature, is the equivalent of a PFO, which has abundant published data. The decision to close PFO has been the subject of decades-long controversy, with older studies showing no benefit and newer studies demonstrating superiority of PFO closure over antiplatelet/anticoagulant therapy as a secondary preventive measure. Backtracking to primary prevention, our patient would have benefited from pre-emptive septal defect closure because the defect was large enough to permit recurrent thrombus passage into the arterial circulation. This finding is supported by the study by *Trabattoni et al. (2011),* demonstrated that 10.8% of patients with PFO after a first cerebral ischemic event had subclinical MI in cardiac MRI [3]. This is relevant to our patient, who had a CVA preceding the onset of his co-occurring STEMI and second CVA. According to *Favilla et al.*, there is a robust association between PFO and cryptogenic stroke. [4] Although the protein S deficiency and lupus anticoagulant confounded the patient's predisposition to hypercoagulability while he was on warfarin, it did not alter the likelihood of paradoxical embolization because the structural defect, ASD, was the strongest determinant of his CVA with concomitant MI.

Favilla et al. reported that the difference between medical therapy and surgical intervention was not statistically significant, suggesting the need to evaluate cryptogenic stroke on a case-by-case basis. Even though the p-value was not less than 0.05, the difference in recurrent stroke rate between closure vs. medical therapy was clinically significant at 4 years, where there was a 0.5% recurrence after closure and 2.4% with medical therapy (HR, 0.20; 95% CI, 0.02–1.72; P=0.14). Per-protocol analysis yielded statistically significant results, whereas intention-to-treat analysis failed to show a difference. [4] The 2.5-year recurrent stroke rate was 1.8% after closure and 3.3% with medical therapy (HR, 0.49; 95% CI, 0.22–1.11; P=0.08), but a significant difference was identified in the per-protocol analysis, 1.3% versus 3.0% (HR, 0.37; 95% CI, 0.14–0.96; P=0.03). [4]

Although the source of embolization was never found in our case, the co-occurrence of CVA and MI had a common underlying pathophysiology of paradoxical embolization, given the presence of the inter-atrial connection. Studies performed in 2013 (RESPECT, PC) concluded that there was no statistically significant difference between PFO closure and antiplatelet/anticoagulant therapy. [5,6] *Carroll et al.* (2013) showed in RESPECT trial that there was no advantage with PFO closure inpatients who experienced cryptogenic stroke; [5] however the per-protocol and as-treated analyses of that trial demonstrated superiority of closure over medical therapy. Similarly, the PC trial showed that in secondary prevention efforts, PFO closure did not significantly reduce the risk of embolic recurrence when compared to pharmacologic therapy. [6] However, the CLOSE trial (2017) demonstrated superiority in outcomes among 663 young patients with cryptogenic stroke, where no strokes were detected in 238 patients after closure and 14 strokes were reported in 235 patients treated with antiplatelet (P<0.001). [7] The trial also showed that in patients who experienced PFO-mediated cryptogenic stroke in the setting of atrial septal aneurysm or large interatrial shunt are at lower rate of recurrent stroke in combined PFO closure with antiplatelet therapy. [7] *Furlan et al* (2012) in CLOSURE I trial showed that device closure of PFO failed to provide a more effective prevention of recurrent cerebrovascular events than stand-alone medical therapy. [8]

Furthermore, during extended follow-up in the RESPECT trial, *Saver et al* (2017) reported that PFO was associated with a lower rate of recurrent ischemic strokes than medical therapy alone. [9] Studies conducted in 2017 (CLOSE, subsequent RESPECT) managed to show that PFO closure had more favorable outcomes. [8,9]

Anantha-Narayanan et al. conducted a meta-analysis five randomized controlled trials (CLOSE [7], CLOSURE I[8], PC, [5] REDUCE, [6] RESPECT [9]) and reported 41% reduction in incidence of recurrent strokes in PFO closure compared to medical therapy alone in patients with cryptogenic stroke [risk ratio (RR): 0.59, 95%CI: 0.40-0.87, P = 0.008]; and no difference was found in major bleeding, overall mortality, or adverse events. [10] However, there was a remarkable increase in incidence of atrial fibrillation in the closure device group, but this outcome tended to occur in the immediate post-operative period. *Collado et al* proposed changing the name from cryptogenic stroke to PFO-mediated stroke since we know that the PFO has a central role in the pathogenesis of paradoxical embolization/ischemic stroke. [11]

On the other hand, *Ali et al* shed light on the importance of evaluating MI patients who have unknown risk factors. [12] A study by *Hakim et al* (2014) highlighted the importance of having high index of suspicion for

paradoxical embolism in patients who have myocardial infarction in the absence of traditional cardiovascular risk factors. [13] This perspective is applicable to our patient despite his presumed genetic predisposition to hypercoagulability. The study asserted that 10-15% of all paradoxical emboli are responsible for paradoxical coronary embolism. [13]

Moreover, meta-analysis by *Kottoor and Arora* supported the finding that PFO closure is an appropriate therapeutic strategy in patients with anticoagulant contraindications, such as non-adherence or bleeding diathesis. [14]

The most recent randomized trial, Gore REDUCE trial (2017) by *Sondergaard et al*, concluded that patients who underwent combination of PFO closure with antiplatelet therapy had a lower risk of recurrent ischemic CVA compared to patients who received only antiplatelet therapy. [15] However, atrial fibrillation was common after device implantation.

The evidence base in support of PFO closure continues to grow, increasing the chance that PFO closure may eventually become a standard prophylactic therapeutic measure against vascular thromboembolic events. However, the guidelines have not been updated to reflect these findings, thereby perpetuating the controversy over whether to perform PFO closure on all affected patients.

4. Conclusion

In summary, recent trials have shown superior outcome when undergoing PFO closure rather than medical therapy alone for secondary prevention of CVA, which is in contrast to preceding trials that showed no statistically significant difference.

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