Undervalued Significance of Moderate Enzyme Elevation in Paradoxical Coronary Embolism Secondary to Deep Vein Thrombosis: Short Review

Abstract
Myocardial infarctions (MI) are relatively common in people with deep vein thrombosis (DVT). In fact, the rate of myocardial infarction has been reported to be greater in adults with DVT as compared to those without DVT and recent studies have shown interest in quantifying the relationship with MI and DVT. However, cryptogenic nature of MI in these individuals is underestimated. Approximately one-fourth of the US populations are estimated to have a patent foramen ovale (PFO). Of note, since MI being the single largest cause of mortality, a large number of these patients have a PFO. The high percentage of myocardial infarction in patients with a PFO has not been addressed in the literature appropriately before and might have been overlooked because most of the patients with infarctions had an uncomplicated course and only moderate enzyme elevation.

Keywords: Cardiac enzymes; Paradoxical embolism; Myocardial infarction

Introduction
Patent foramen ovale (PFO) is a condition where an opening that exists between the left and right atria of the heart. This hole is present in everyone before birth, but most often the hole closes shortly after birth. As a result, shunting is seen which may be either right-left, left-right or both [1]. PFO with intracardiac shunting is associated with cryptogenic myocardial infarction (MI) in both young and elderly [2]. Many of them are found to have subclinical enzyme levels [3]. In individuals with a PFO, there are transient episodes of right-to-left intracardiac shunting associated with increased right atrial pressures that occur with Valsalva-like maneuvers, including coughing, forced expiration, or bowel movements. MI in this setting are thought to occur when a venous thromboembolism travels to the coronary arterial system after avoiding filtration in the lungs during right-to-left shunting through the PFO, an event called a paradoxical coronary embolism (PCE) which was first described in 1877 [4].

Previous studies with improved imaging technology indicate that the subclinical myocardial infarctions determined in cardiac magnetic resonance imaging were observed as many as 10.8% of patients with PFO after a first cryptogenic cerebral ischemic event [5]. It is known that a MI can potentially disclose presence of PFO [6]. In addition, reports of silent myocardial infarct without overt cardiac symptoms, presumably related to patent foramen ovale have also been described [7]. The role of PFO closure in reducing silent cerebral ischemic events is well known [8]. However, not all PFOs may require treatment. Risk factors for PCE with PFO include previous or current pulmonary emboli, pregnancy, factor Leiden deficiency, ischemic stroke and various genetic mutations [9-12]. Nonetheless, treatment options for PFO remain controversial due to the risks associated with both transcatheter and surgical procedures.

An autopsy series of 1050 patients with myocardial infarctions by Prizel et al. did not find a single case of PCE among the 55 patients identified with coronary embolism [13]. The Navigator study estimated the prevalence of venous thromboembolism in patients with established cardiovascular disease or cardiovascular risk factors to be only 1.4% and the patients with venous thromboembolism had higher 5-year event rates...
for the composite of death, myocardial infarction, and stroke, as compared with patients without venous thromboembolism (10.7% vs. 5.9%) [14].

Deep vein thrombosis (DVT) is associated with pathologic changes and physiologic adaptations that can lead to cryptogenic myocardial infarction in the setting of a PFO. For example, erythrocyte adhesion, endothelial damage, and platelet and coagulation activation in DVT result in a hypercoagulable state and increased susceptibility to venous thrombosis. Recently, coronary microvascular dysfunction has been linked to conditions that predispose to venous thrombosis such as myeloproliferative neoplasms (PV), and there is growing evidence that more and more venous hypercoagulable states increase the risk of myocardial infarction [15]. In the presence of PFO, the underlying hypercoagulability could lead to PCE as per our literature review (Table 1). Loscalzo et al. has noted 9% of paradoxical emboli go to coronaries [16]. In addition, the presence of “thrombus in transit” in patients with DVT, either at baseline or during an episode of acute chest syndrome, could further increase the risk of PCE [17,18]. Indeed, till date, more than 100 cases of thrombus in transit have been described in literature. Most of the investigators concluded that further studies are warranted to determine if PFO is an independent risk factor for MI with DVT. Another study found that PFOs may be underestimated as possible causes of coronary embolic events even without venous hypercoagulabilities [19].

Based on literature review of six isolated cases, we found out a large number of PCE can coexist or co-present with pulmonary embolism (PE) in patients with underlying DVT with varying cardiac enzyme values [17-23]. However, in few patients, MI can present independently without PE. In one of the cases, non-surgical closure of PFO was performed [19]. There are also studies which indicate coronary heart disease is a risk factor for PE in absence of clinically diagnosed DVT [24].

Future studies are needed to investigate the benefit and outcomes of nonsurgical PFO closure in patients with DVT and MI. It will also be important to examine the relationship between DVT and PFO in both young adults and elderly. Unfortunately, current approaches to MI prevention for elderly with DVT have been limited to secondary prevention because of the lack of methods for identifying patients at increased risk for developing their first MI. PCE prevention is especially important in young adults given the impact on physical function. For young adults, DVT and MI can lead to disability, morbidity and mortality. The devastating outcomes of acute MI in patients with DVT demand further study, not only to define additional risk factors, but also to identify successful interventions. Although further research is needed, the positive outcome of our patients with DVT suggests that identifying PFOs and closing them non-surgically could be beneficial in selected patients.

**Conclusion**

Similar to cryptogenic stroke secondary to deep vein thrombosis (DVT), patients with DVT associated cryptogenic myocardial infarction are at higher risk for recurrent paradoxical embolism and they should be considered for PFO closure. Presence of moderate enzyme elevation should not be a ground for denial for closure.

**Table 1 Hypercoagulability and patent foramen ovale leading to paradoxical coronary embolism.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Age/Sex</th>
<th>Associated Emboli</th>
<th>Risk Factor</th>
<th>Closure</th>
<th>Stent</th>
<th>Deep Vein Thrombosis</th>
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<tr>
<td>Farhang P</td>
<td>43/M</td>
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<tr>
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<td>Smoking</td>
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<td>IVC Filter</td>
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<td>Murthy A</td>
<td>29/F</td>
<td>Presumed PE</td>
<td>Pregnancy</td>
<td>Yes</td>
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<td>IVC Filter</td>
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<td>Edibam C</td>
<td>30/F</td>
<td>PE, Cerebral and Splenic emboli</td>
<td>Delayed Hip Fracture Reduction, Prothrombin 20210 Mutation</td>
<td>No</td>
<td>Aspiration Alone</td>
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<tr>
<td>de Swiet J</td>
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<td>Oral Contractive pills</td>
<td>-</td>
<td>-</td>
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References


