Thrombophilia and Cardiac Thrombi

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ABSTRACT

Thrombotic episodes of under 40-50 years of age is rare without a thrombophilia and thrombus formation in the cardiac chambers is extremely rare compared to arterial and venous thrombosis. Selected cases from recent literature demonstrate how thrombophilia results in life threatening thrombus formation, manifestations and management.

Keywords
Cardiac Thrombi, Thrombus formation, Thrombophilia, Protein S deficiency.

Introduction
Thrombotic episodes for persons under 50 years of age is rare without a thrombophilia. Nevertheless, thrombus formation in the cardiac chambers is extremely rare compared to arterial and venous thrombosis elsewhere. Most intracardiac thrombi reported were in association with high altitude, reduced left ventricular function (LV) and cardiomegaly [1]. Reportedly, heritable thrombophilias are the leading causes for developing cardiac thrombi [2]. Inherited thrombophilias are classified in to two groups based on the deficiency of natural anticoagulants or deficiency of coagulation factor Inhibitor (CFI).

Group I Thrombophilia is the deficiency of natural anticoagulant proteins such as Protein C (PC), Protein S (PS) and Antithrombin III deficiency. Group II Thrombophilias result from an increased level and or function of coagulation factors. Examples of Group II Thrombophilias are factor V Leiden or prothrombin 20210A, elevated levels of coagulation proteins, Antiphospholipid antibody syndrome, Hyperhomocysteinemia, and Activated Protein C Resistance [3-5]. In this manuscript the focus is on PS and or PC deficiency which is a Group I thrombophilia.

There are a few episodes of cardiac thrombi resulting in thrombophilia such as PS and PC deficiencies reported in recent literature. The six selected cases presented here will illustrate how PS and PC deficiencies were manifested and diagnosed as cardiac thrombi. The common signs and symptoms among these cases were large cardiac thrombi at different sites such as left ventricle, pulmonary artery, hepatic vein and inferior venacava, right atrium and aorta. However, stent thrombosis was the most reported problem resulting from thrombophilia. PS was found to be deficient in 11 of 13 patients (84.6%) patients presented with stent thrombosis while PC was found deficient only in 2 of 13 patients (16.7%). Low PS levels were strongly associated with stent thrombosis also [6].

Case # 1
A 33-year-old woman with dyspnea and chest pain came in with no previous history of thromboembolic events. With a four-chamber view echocardiography, a rounded mass-a mural thrombus was detected attached to the anterior wall of the left ventricle. Transesophageal echocardiography (TEE) also showed large thrombus in LV. It is unusual for intraventricular thrombus to form in LV when the heart is structurally and functionally normal. In laboratory exam, PC-S deficiency was confirmed; however, other related test of thrombophilia was negative. The PC level was 30% (normal: >70) and protein S level was 50% (normal: > 65%).

There were no abnormal values of antithrombin III, lupus anticoagulant, and anticardiolipin antibodies. HLA-B5, HLA-B27, anti-nuclear antibody and rheumatoid factor were negative. This patient underwent cardiopulmonary bypass with thrombosis extraction, her cardio-respiratory sign and symptoms disappeared after the surgery and she recovered uneventfully. At 4-month
follow-up, an echocardiogram showed no evidence of recurrent clot in the patient’s LV. PC -S levels had not been normalized at that time; therefore, the warfarin was continued [7].

Case # 2
A 29-year-old male came in with tachycardia and palpitation for three days and cardiac etiology was ruled out. His BP was 90/60, pulse 120/minute, and all other routine lab and EKG were normal however contrast enhanced computer tomography (CECT) revealed thrombi in the main pulmonary artery, hepatic vein and inferior venacava reaching up to the renal vein. Patient was managed with Teflectaplace for 2 minutes, Unfractionated Heparin (UH) for 48 hours, Low Molecular Weight Heparin (LMWH) for 5 days. Warfarin from the second day restored perfusion and eliminated symptoms. Coagulation studies revealed underlying PS deficiency with a value 30% [8].

Case # 3
43-year-old woman with recurrent stent thrombosis (ST) presented with prolonged chest pain that developed while playing a mobile game at home. Coronary risk factors were dyslipidemia and current smoking. EKG showed 1-mm ST segment elevation in the precordial leads V1–V4 and reciprocal 1-mm ST segment depression in leads I and aVL, with abnormal Q waves in V1–V3. Bare metal stent in the proximal left anterior descending (plAD) artery 3 years earlier. An intravascular ultrasound study showed an in-stent fibrous thrombus in the pLAD artery. After each aspiration of the thrombus with a special catheter, a large, red thrombus reappeared, requiring 10 consecutive aspirations over 45 minutes. The concentration of PS was 35 % (normal = 60–150 %). Total PS antigen was 56 % (normal = 65–135 %). Free PS antigen was 50 % (normal = 60–150 %). Therefore, Type 1 PS deficiency was confirmed. A thrombus was found in the in-stent segment of the proximal left anterior descending artery. Administration of thrombolytics and argatroban, followed by repeated balloon dilatations, ended the formation of new thrombi [6].

Case # 4
A 58-year-old female had a case of bilateral segmental pulmonary embolism, also had a transient right radial artery occlusion. Her initial contrast-enhanced transthoracic echocardiography confirmed a presence of a 42 × 10mm thrombus arising from the lateral wall of the ventricles and extending into the left ventricular outflow tract. There was popliteal and superficial femoral vein thrombosis and evidence of multiple arterial and venous clots. The presence of the large cardiac thrombus raised the suspicion for inherited thrombophilia. Laboratory investigation showed positive signs for PC and PS deficiency with activity of 26% (normal range: 84–171) and 18% (normal range: 54–132%) for females) for proteins C and S, respectively. The patient underwent a surgical cardiac thrombectomy to prevent further systemic embolization. Patients with mural pedunculated thrombi are at increased risk for both systemic embolization and recurrent embolism despite anticoagulation therapy. Surgical thrombectomy appears to be clinically effective in cases with mobile pedunculated thrombi [1].

Case # 6
A 40-year-old Asian man with a history of heavy cigarette smoking had sudden onset of abdominal and lumbar pain, history of stroke for 2 years presented with progressively increasing shortness of breath with exertion for two weeks without any other symptoms The clinical exam showed increased right atrial pressure – (RAP) 109 mm Hg (Normal 2-6 mmHg) dilated right atrium and ventricle, hypokinesia ventricular wall, Grade 3 Systolic murmur in Tricuspid area, negative cardiac enzymes, MRI-bilateral showed pulmonary artery thrombosis, complete occlusion of the descending branch of the right pulmonary artery, popliteal and posterior tibial veins. Mobile intra-aortic thrombus is very rare but sometimes occurs mainly due to thrombi in the left side of the heart. PS level was 28%. Immediate thrombolysis with streptokinase, enoxaparin 1mg/Kg twice a day for 7 days, overlapped by warfarin 5 mg once day along with Aspirin 150 mg once a day were the primary management strategies. Symptoms relief, RAP reduced to 34 mm. PC and PS deficiency should be considered in the differential diagnosis in patients presenting with intracardiac and systemic thrombosis. Advanced cardiovascular imaging is useful in determining the need for surgical thrombectomy. Systemic anticoagulation therapy is the most appropriate therapeutic option in patients with intracardiac and systemic thrombosis [9].

The cardiac thrombi formation can result from combined genetic and environmental factors. The interaction between inherited hypercoagulable defects such as PS and PC and acquired factors such as age or acute illness, can result in an increased “thrombosis potential”. This thrombosis potential, upon reaching a “thrombosis threshold,” can result in symptomatic thromboembolism causing either bleeding (hemophilia) or clotting tendencies (thrombophilia). Underlying inherited and acquired thrombophilia factors may be triggered by adverse environmental conditions such age, trauma, cancer, pregnancy, liver diseases and immobilization. Oral Contraceptives (OC) estrogen, or combined with progestin in OCs is a well-documented risk factor for venous thrombosis [10-15].

Discussion
PS and PC deficiency
PS and PC deficiency detected in 1984 are uncommon genetic thrombophilic disorders that can cause both arterial and venous thrombosis in unusual sites [1]. PS is produced by hepatocytes, endothelial cells, and megakaryocytes and serves as a cofactor for activated PC (APC), which in turn, inactivates procoagulant factors Va and VIIIa. PS is found in two forms: free and bound to a complement protein. The free form comprises 30-40 % of PS and has a cofactor activity with PC. PC produced by the liver binds to the endothelial cell surface protein thrombomodulin and is converted to activated protein C (APC) by thrombin. Combined deficiency of these two factors produce hypercoagulable conditions. However, the clinical outcome of a single deficiency or double deficiencies remains the same [1,16]. FVL mutation renders factor V (both the activated and inactive forms) insensitive to the actions of activated protein C, a natural anticoagulant. In essence, deficiency of these natural anticoagulant or mutation leads to thrombosis.
Individuals with deficiencies in natural coagulants such as PS and PC, manifest in less than 1% of the population. Yet, these deficiencies are highly prothrombotic, with 30% to 50% of carriers having a symptomatic thrombotic event before they reach 60 years of age. For example, the prevalence of PS deficiency among Caucasians is 0.03-0.13% whereas it is 1-2% in the Asian population. Among Asians, the Japanese have a higher incidence related to a special gene mutation called PS Tokushima manifested as a qualitative PS deficiency [14,17,18]. PS deficiency has 2-11-fold increase risk of these episodes compared to others such as acquired disorders. PC in milder form is seen 1/250-300 general population, severe 1 in 500,000-750,000 [8].

If there are recurrent VTE, younger age (< 50), and clots in unusual sites; inherited or acquired hypercoagulability should be ruled out. Abnormal thrombosis can also result from an imbalance between procoagulant and anticoagulant factors [3].

There are differences between a blood clot and a thrombus. A blood clot contains only blood clotting system; whereas as a thrombus has formed elements of blood, platelets and fibrin deposits around platelets. In normal blood vessel, endothelium is resistant to thrombosis, yet, trauma, infections, or cancer invading the blood vessels exposes the thrombogenic subendothelium to fibrin and platelet adhesions. Congestive heart failure, varicose veins and immobilization can cause venous flow to slow down, and turbulence promotes platelet adhesion to the walls. Hypercoagulable stages such as liver diseases and anticoagulant deficiency aggravates thrombophilia. The best clue for hypercoagulability is family history.

Cardiac thrombi could be of arterial, venous, capillary and lymphatic in origin. Thrombus may be located in the valves (valvular thrombus) or in the cavities (mural thrombus). Lateral thrombus is confined to one side of the blood vessel, occluding thrombi occupies the entire circumference, a saddle thrombus is located at the bifurcation of a blood vessel completely occluding the blood supply. When new blood channels run through a clot that will be canalized thrombi. A white thrombus has only platelets in that and a red thrombus has fibrin attached to platelets. However, the most common type is mixed type, when the white and red seen in layers, it appears as laminated. Thrombus causes diminished perfusion or complete obstruction in the vessels.

**Diagnostic studies**

When and whether to test for thrombophilia is controversial. Hematologists focus on management than the investigation of the underlying anomaly by coagulation testing. The testing is indicated if the results influence patient management. There is no absolute indication for coagulopathy testing [4,10,19,20]. The current practice of relative testing for thrombophilia is limited to family members of known cases, high risk cases for thrombosis, pregnancy, recurrent thrombosis, thrombosis in early age, and certain chemotherapy. However, testing should not be done during an acute phase or pregnancy because “natural anticoagulants and procoagulant plasma proteins are acute phase reactants” [21]. Consequently, PC, PS, and antithrombin level could be reduced during this phase. Testing can be done after childbirth or 6 weeks after the acute thrombotic phase. (Table 1. for lab values).

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Normal PC values</td>
<td>40 IU/dL Average</td>
</tr>
<tr>
<td>Mild PC deficiency</td>
<td>Below 40 IU/dL</td>
</tr>
<tr>
<td>Moderate severe deficiencies</td>
<td>1 and 20 IU/dL</td>
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<tr>
<td>Severe deficiencies</td>
<td>IU/dL undetectable</td>
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<tr>
<td>Normal PS values –Total</td>
<td>65-135%</td>
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<tr>
<td>Free PS</td>
<td>65-150%</td>
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<tr>
<td>PS Activity</td>
<td>65-150%</td>
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**Management**

The immediate focus of such thrombosis management is to restore hemostasis by reestablishing perfusion. Patients with acute inherited or acquired thrombophilia are treated in existing standards of practice with UH infusion, LMWH, whereas patients with persistent risk factors need prolonged anticoagulation [21,22]. Secondary prophylaxis may be needed for patients with high risk for life threatening recurrent VTE. The diagnosis of the inherent thrombophilia’s should take place after this initial restoration of perfusion [23].

Anticoagulation by unfractionated heparin (UFH), or low molecular weight heparin (LMWH), overlapped with warfarin is the conventional treatment to reestablish blood flow. If warfarin is to be prescribed, it should be initiated simultaneously, until the goal International Normalized Ratio (INR) is reached. Warfarin works by inhibiting Vit-K dependent procoagulants such as II, VII, IX, and X. While working to impede this procoagulant factors warfarin hinders the Vit-K dependent anticoagulants PS and PC also. Therefore, warfarin may further aggravate clotting or generate new clots in certain cases. In addition, PS deficiency can cause warfarin -induced skin necrosis during warfarin therapy. Heparin and low molecular weight heparin do not influence PS deficiency test results. Indefinite anticoagulation is recommended for many patients with an unprovoked thromboembolism event especially with a strong family history of VTE. 3-6 months’ anticoagulation.

Vitamin K antagonist (VKA) was the only anticoagulants for decades and the management and patient safety was challenging. Patients on anticoagulants require regular testing of their prothrombin time (PT) and international normalized ratio (INR) to maintain safe serum drug levels. Nurses were in front line of VKA monitoring and teaching through in-patient follow-up and special coagulation clinics. Side effects of VKA is a major public health problem. Pre-discharge teaching of patients getting anticoagulants has reduced readmission and complications. To facilitate better education, Garcia and others [24] developed a tool to assess the knowledge of oral anticoagulant therapy. Ben Jeddou et al. [25] conducted a study to find out the focus educational needs of the patients; Patients under VKA therapy reported needs for information on both the disease pathology and their anticoagulant
Direct oral anticoagulants (DOA) are also effectively used for the management lately. These DOAs act by suppressing thrombin or factor Xa. Examples of DOAs are apixaban (Eliquis), edoxaban (Savaysa), dabigatran (Pradaxa), rivaroxaban (Xarelto) and they can affect the functional assays for PS. Using these drug rest in two reasons: 1. DOAs do not reduce PS and PC levels. 2. It has less drug–drug, drug-food interactions compared to warfarin. However, false Protein S elevation is seen during Rivaroxaban therapy [28,29].

Thrombophilias and their management are still in infancy. PS deficiencies and associated problems were identified in 1984 and FVL mutation and related issues were identified around 1993. Direct acting oral anticoagulants and their place in thrombophilia are relatively new to practice and there is much to learn about the possible drug–drug interactions. For example, there are reports about adverse complication from DOAs such as a major gastrointestinal bleed in a 76-year old male on Megestrol acetate reports about adverse complication from DOAs such as a major gastrointestinal bleed in a 76-year old male on Megestrol acetate (Megace) for geriatric failure to thrive (GFTT) also received a DOA (Savaysa), dabigatran (Pradaxa), rivaroxaban (Xarelto) and they can affect the functional assays for PS. Using these drug rest in two reasons: 1. DOAs do not reduce PS and PC levels. 2. It has less drug–drug, drug-food interactions compared to warfarin. However, false Protein S elevation is seen during Rivaroxaban therapy [28,29].

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