Perioperative management of a patient with an autosomal dominant hypercoagulation disorder scheduled for off-pump coronary artery bypass surgery

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Factor V Leiden (FVL) is the most common known inherited cause of thrombophilia; it is present in ~5% of the Caucasian population. This results from mutation of the factor V protein, which is found to have normal procoagulant function in vitro but is resistant to inactivation by activated protein C. We describe the case of a 61-year-old male heterozygote for FVL with diagnosed coronary artery disease scheduled for off-pump coronary artery bypass grafting. Avoidance of antifibrinolytics completely, early administration of antiplatelet agents, heparin infusion 6 h after surgery or starting low molecular weight heparin, early extubation, active limb physiotherapy, use of pneumatic compression pumps, and most important of all early mobilization holds the key for successful outcomes of these patients. A comprehensive care team comprising an anesthesiologist, surgeons, and a hematologist should manage individuals with FVL.

Keywords:
activated protein C, deep vein thrombosis, Factor V Leiden, off-pump coronary artery bypass grafting

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Introduction

Factor V Leiden (FVL), an autosomal dominant condition, is the most common hereditary hypercoagulability disorder with an estimated incidence of about 5% in Caucasians. In this disorder, activated protein C (aPC) cannot inactivate the Leiden variant of factor V. These patients have a very high incidence of postoperative deep vein thrombosis (DVT) and pulmonary thromboembolism along with high incidence of occlusion of venous graft after coronary artery bypass grafting (CABG) [1].

After taking written consent for submission of clinical case report for potential publication, we reporting a case of a 61-year-old man with diagnosed FVL mutation with coronary artery disease scheduled for off-pump CABG.

Case report

After taking consent a 61-year-old man weighing 70 kg with diagnosed coronary artery disease is scheduled for off-pump CABG. His coexisting diseases included type 2 diabetes mellitus, long-existing hypertension, and heterozygote for FVL, diagnosed 2 years ago. His daughter had a history of recurrent DVT during two subsequent pregnancies, investigated and found to possess heterozygote mutation for FVL. Later on, both her parents were investigated and the father was discovered to be heterozygote for FVL. The patient had no history suggestive of DVT. He was taking oral aspirin 150 mg/day for last 2 years but no anticoagulants. Preoperative hemoglobin was 13.3 g, with a platelet count of 131 000 cm^3, prothrombin time 13.5 s, international normalized ratio of 1.02, and activated partial thromboplastin time of 32 s. Echocardiography showed normal left ventricular function and type I diastolic dysfunction. Coronary angiography was suggestive of triple vessel disease and CABG was planned under general anesthesia.

The patient was premedicated with oral lorazepam 2 mg and pantoprazole sodium 40 mg the night before surgery and aspirin was continued on the day of the surgery. His baseline activated coagulation time (ACT) was 151 s. Anesthesia was induced with intravenous midazolam, fentanyl citrate, and rocuronium bromide and maintained with intermittent doses of fentanyl citrate, rocuronium bromide, and isoflurane in 50% oxygen in air. Intraoperative monitoring included electrocardiogram with ST segment analysis, oxygen saturation, end-tidal carbon dioxide, temperature, urine output, invasive arterial pressure, pulmonary artery and central venous pressures, cardiac output, arterial blood gas analysis, and ACT. Heparin 200 IU/kg was administered after dissection of the left internal mammary artery and 100 IU/kg was

administered every hour after initial dose to maintain an ACT greater than 300 s. His grafts and conduits included left internal mammary artery to left anterior descending artery and saphenous vein grafts to posterior descending artery and obtuse marginal artery. Anatomical lesions, the possibility of competitive flow and the existence of collateral circulation guided the choice of conduits. Heparin was partially reversed with protamine in a 0.5 : 1 ratio at the end of the grafting. ACT which was measured hourly after partial heparin reversal was 200 s [2].

The intraoperative period remained uneventful with a blood loss of 700 ml and postoperative hemoglobin of the patient was 10.8 g. Ringer's lactate 1500 ml and 1000 ml of hydroxyethyl starch were given but no blood transfusion was done perioperatively. The patient was transferred to the recovery room and the trachea was extubated after 8 h of ventilation. Anticoagulation in the form of heparin 1000 U/h intravenously and aspirin 75 mg was administered through an orogastric tube at 6 h postoperatively, after assessing the chest tube drainage (total 400 ml). Activated partial thromboplastin time maintained at 1.5 times the control value. Postoperative pain relief was achieved with intermittent doses of tramadol hydrochloride (1.5 mg/kg) and injection paracetamol 1 g intravenously every 8 h. Postoperatively, coagulation parameters remained within normal limits. Pneumatic compression pump applied in the left lower limb from which saphenous graft was not harvested. On postoperative day (POD) 1, heparin infusion was stopped, active limb physiotherapy was done, and early patient mobilization started. Injection fondaparinux 2.5 mg subcutaneously was started and continued until POD 7 when full mobilization is achieved. Clopidogrel 75 mg was started and continued along with routine cardiac medications for the next review and the patient was discharged from the hospital on POD 8. Oral anticoagulant therapy was not started, as the patient had no features and radiological evidence of any DVT.

Discussion

The excessive clotting that occurs in FVL is usually restricted to the veins, where the clotting may cause DVT and pulmonary embolism along with high incidence of occlusion of venous graft after CABG. Inheriting one copy of the mutation increases the chance of developing a clot by fourfold to eightfold, whereas people inheriting two copies of the mutation (homozygous), from each parent, may have up to 80 times the usual risk of developing this type of blood clot [3].

The presence of acquired risk factors for venous thrombosis such as smoking, use of estrogen-containing hormonal contraception, and recent surgery further increases the chance that an individual with the FVL mutation will develop DVT. It is extremely rare for this disorder to cause the formation of clots in arteries that can lead to stroke or myocardial infarction, though transient ischemic attack is known to occur. Women with this disorder have an increased risk of miscarriage and still birth [4].

Cardiac surgery, especially CABG, is a particularly relevant situation for clarifying genetic coagulation disorders as postoperative thrombosis can be disastrous. The clinical outcome of the patient after bypass surgery is further dependent on the extent of native disease, the type and quality of conduits used for grafting, surgical expertise, compliance with post-surgery drug regimen, and adherence to strict lifestyle modifications [5].

The perioperative management of the patient with FVL prerequisites avoidance of any intervention which predisposes the patient to a hypercoagulable state. Antifibrinolytic therapy is routinely used in a cardiac surgery setup for decreasing the hemorrhagic risk in both off-pump and on-pump settings. However, controversy has surrounded these drugs because of their possible prothrombotic risks [6,7]. Aprotinin, a known inhibitor of aPC, induces resistance to aPC in normal plasma and exacerbates aPC resistance further in the plasma from FVL heterozygotes. This doubly impaired the anticoagulant function of aPC in the presence of FVL, which may account for the thrombosis observed in some clinical studies involving aprotinin [8,9]. However, aprotinin is no longer FDA approved for use in the USA, and is available for use in uncomplicated, primary CABG in Canada. The authors described two lethal massive thrombotic events occurring after protamine administration in patients undergoing cardiac surgery with ε-aminocaproic acid [10]. We routinely administer one dose of ε-aminocaproic acid to our CABG patients prior to sternotomy, however, considering the presence of FVL, antifibrinolytic therapy should be withheld.

Donahue *et al.* [11] in their study on FVL patients undergoing cardiac surgery concluded that FVL carriers had an average of 30% less blood loss and

the magnitude of blood sparing was nearly the same as that provided by antifibrinolytic drugs. Furthermore, the chance of not receiving any blood product transfusion during hospitalization was 46% among FVL patients, compared with 28% for noncarriers.

The role of point care tests (POC) like thromboelastography and ROTEM is immense perioperatively to determine the degree of hypercoagulability. The α-angle, maximum amplitude, shear elastic modulus, and clot strength determines the level of hypercoagulability. As our institution did not have thromboelastography, it was not done.

Sometimes a situation arises in which grafting is done under cardiopulmonary bypass. According to our institution protocol, we administer 350 IU/kg heparin to achieve an ACT of greater than 480 s. If target ACT is not reached, heparin up to 700 IU/kg is administered. Even after this, if ACT is not attained antithrombin III is transfused. For a safe level to undergo cardiac surgery under cardiopulmonary bypass, ACT greater than 480 s is mandatory in normal cases as well as in patients with hypercoagulable states.

The possible association of FVL with graft occlusion has been addressed by Moor *et al*. [12] by performing coronary angiography on a population of 100 men 3 months after elective CABG. They reported graft occlusion in 45% of FVL carriers (5 of 11) and in only 20% (18 of 89) of the noncarriers, borderline statistical significance (P=0.06) was found.

Of note, all patients in this trial received postoperative aspirin therapy beginning on the day after surgery. These findings are mirrored by a case report describing complete graft and some native coronary artery occlusion, 1 month after surgery in a patient with FVL and additional prothrombotic gene allele [13].

There is high risk of coronary bypass graft occlusion within the first few months after surgery in FVL patients. There is no evidence documenting the benefits of any targeted postoperative therapy to maintain graft patency in patients with FVL [1]. Prescribing both antiplatelet and anticoagulants in elderly patients may put them at undue risk of bleeding. Adherence to established guidelines [14] for maintaining graft patency including the use of arterial conduits, postoperative antiplatelet therapy, antilipid therapy, lifestyle modifications, cardiac rehabilitation, and regular medical follow-up have the greatest benefits in these higher-risk group of patients. The use of long-term anticoagulation without a history of DVT in these patients is still unclear. One should keep a high degree of suspicion of short-term and long-term thrombotic complications in these patients.Our patient continues to be on a regular follow-up and is strictly following his regime of antiplatelet agents, statins, and active lifestyle. He was completely asymptomatic on his last follow-up.

It is worth mentioning here that FVL heterozygosity differs considerably from a 50% factor V deficiency. In heterozygous FVL, half of the factor V is resistant to aPC and is sufficient to continue thrombin formation. This caused an increased thrombin formation with FVL, whereas in factor V deficiency, all circulating factor V still remains sensitive to inactivation by aPC and thus there is no thrombin formation [15].

The complexity of this hematological problem warrants a detailed evaluation of these patients by a team of hematologists, anesthesiologist, and surgeons. The patients need to be explained about hypercoagulability and the risk of venous thrombosis, pulmonary embolism, and occlusion of venous graft post-CABG. Avoidance of intraoperative antifibrinolytics, early administration of antiplatelet agents and heparin would safeguard against any prothrombotic predisposition in the immediate postoperative period. Early extubation, active limb physiotherapy, use of pneumatic compression pumps, and most important of all early mobilization holds the key for successful outcomes in these patients.

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Conflicts of interest
There are no conflicts of interest.

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