Case Reports

Factor V Leiden and Cardiopulmonary Bypass

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Abstract: We present a case of a patient with factor V Leiden with an antithrombin III activity of 67%, who received a successful aortic valve replacement supported by cardiopulmonary bypass (CPB). A safe level of anticoagulation was achieved by monitoring activated clotting time (ACT) and heparin concentration ensuring adequate anticoagulation throughout the procedure. Results from ACT, heparin dose response, heparin protamine titration, and thrombelastography are given. Factor V Leiden patients can be safely anticoagulated using heparin for CPB procedures when monitored with ACT, heparin protamine titration, and thrombelastography. Postoperative chest tube losses were 360 mL, less than half our institutional average. Anticoagulation for the pre- and post-operative phase is also discussed. Keywords: cardiopulmonary bypass, anticoagulation, factor V Leiden.

Patients who present with factor V Leiden (FVL) variant pose a significant coagulation challenge during cardiopulmonary bypass (CPB). Judicious evaluation of perioperative coagulation is needed to minimize risk of thromboembolism. While Donahue et al. (1) reported a significant protective effect of FVL on post-operative blood loss and risk for blood transfusion, health-care teams need to consider that FVL poses significant coagulation risks to affected patients with regard to clotting in the CPB circuit and premature closing of new bypass grafts (2,3). This patient was successfully managed because routine determination of heparin response, concentration, and effect assured effective anticoagulation in a patient with symptomatic homozygous FVL during CPB for aortic valve replacement (AVR).

DESCRIPTION

A 74-year-old male with documented aortic stenosis presented with symptoms of chest pain, congestive heart failure, and underlying atrial fibrillation (AF). Related patient comorbidities included type II diabetes mellitus and hypertension. This patient had a history of a deep vein thrombosis (DVT) with a documented pulmonary embolus (PE). Echocardiogram demonstrated normal left ventricular end-diastolic dimensions with severe concentric remodeling, normal systolic function, mild diastolic dysfunction, and bialtrial enlargement. The patient had severe aortic stenosis with an aortic mean gradient of 58 mmHg and aortic valve area .4 cm² concurrent with mild-to-moderate regurgitation. Coronary angiogram demonstrated normal coronaries.

The patient had a significant family history of coagulation abnormalities including recurrent maternal episodes of DVT starting at age 40, paternal death at age 72 due to cerebral infarction, a sister diagnosed with “protein C deficiency,” and the patient’s daughter was found to possess a factor V Leiden (FVL) mutation. With further investigation, the patient was found to have FVL (homozygous). Laboratory analysis demonstrated a protein C level of 95% (normal 70–140%), protein S free level of 81% (normal 70–150%), and an antithrombin III (ATIII) activity of 67% (normal 80–120%). Fibrinogen was measured at .564 g/dL (normal .15–.45 g/dL). There were no other coagulation abnormalities identified with additional testing. Just prior to scheduled AVR, the patient developed a severe drug-related rash, presumably to an administered...

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angiotensin-converting enzyme inhibitor. The patient was discharged home on warfarin as treatment for DVT and PE, to be readmitted for elective AVR.

Warfarin therapy was stopped 5 days prior to surgery and bridged with enoxaparin until the day before coming to the operating room. The patient's pre-operative activated partial thromboplastin time (aPTT) was found to be 42 seconds (normal 27–39 seconds) with an international normalized ratio (INR) of 1.3 (normal .8–1.2). Patient's hemoglobin was 11.1 g/dL (normal 13.5–18.0 g/dL) and platelets were 225 × 10^9/L (normal 150–400 × 10^9/L).

The extracorporeal circuit consisted of a Sorin phosphorylcholine-coated (Sorin/Dideco, Mirandola, Modena, Italy) venous–arterial loop, a coated oxygenator with an integrated 25-μm arterial filter and an open hard-shell venous reservoir (Fusion®, Trillium®, Medtronic, Minneapolis, MN). Cardioplegia was given via an automated delivery system (Myocardial Protection System®, Quest Medical, Allen, TX). After flushing the CPB circuit with CO₂, the following priming constituents were used: plasmalyte 148 (2,000 mL), .5 g/kg of mannitol (189 mL), 50 mEq of 8.4% sodium bicarbonate (50 mL), 10,000 IU of heparin (10 mL), and 25% albumin (100 mL). After retrograde autologous priming, the remaining absolute prime was 749 mL.

Anticoagulation monitoring was achieved using activated clotting time (ACT) (ACT Plus®, Medtronic) and by heparin concentration monitoring using Hepcon Management System® (HMS) Plus (Medtronic). Coagulation maintenance was achieved throughout the operative course by assessing the patient’s heparin sensitivity and activity as well as the prediction of protamine dosing. Anesthetic management followed our standard institution protocols. Following the recommendation from the department of hematology, we elected to not give intravenous tranexamic acid to this patient, which is our standard practice. Acute normovolemic hemodilution was not used in this case.

The measured heparin dose response (HDR) slope of the HMS is designed to project a pre-bypass heparin-loading dose resulting in an ACT of 480 seconds. Department protocol is to add an additional 100 IU/kg of heparin to the calculated heparin dose concentration to ensure a heparin bolus dose that will result in an ACT greater than 480 seconds. Following heparin sensitivity analysis, the projected heparin bolus required to achieve an ACT of 480 seconds was 249 IU/kg. On the basis of our institutional protocol, the concentration was increased to 349 IU/kg and then further readjusted to 425 IU/kg. This was in an effort to ensure a circulating heparin concentration of 400 IU/kg or more would be achieved when on CPB in this patient with a known FVL variant and lower than normal ATIII activity level. This resulted in a projected heparin bolus of 39,000 units (Sandoz, Boucherville, Quebec, Canada). The patient’s resultant slope from HDR curve was 100 seconds/IU/mL. Baseline ACT was 131 seconds. After heparinization, the ACT was 699 seconds and the heparin concentration was greater than 400 IU/kg.

The patient previously had severe pericarditis necessitating partial pericardiectomy and extensive dissection of pericardial adhesions to allow cannulation and mobilization of the heart. These dense adhesions precluded the addition of planned bilateral pulmonary vein radio frequency AF ablation. A severelystenosed calcified trileaflet aortic valve was removed and replaced with a 23-mm Perimount Magna Ease bioprosthetic aortic valve (Carpentier-Edward, Irvine, CA). A bioprosthetic valve was favored over a mechanical valve in this 74-year-old patient to allow for less intensive anticoagulation post-discharge.

The initial cardiac arrest was with warm blood and 20 mEq/L of potassium chloride. Throughout the cross-clamp period, 6,242 mL of cold blood micro-cardioplegia was delivered. Before removing the cross clamp, the heart was infused with warm blood and a 2 g bolus of magnesium sulphate (4 mL).

All ACTs on CPB were greater than or equal to 763 seconds. The lowest heparin concentration obtained during CPB was 350 IU/kg. Two 10,000 IU boluses of heparin were given during CPB to maintain the heparin concentration at 400 IU/kg or greater. One unit of packed red blood cells was transfused on CPB for a hemoglobin of 7.1 g/dL and hematocrit of .22 L/L.

After completing CPB, a protamine dose of 470 mg was determined by the HMS. A post heparin–protamine titration sample showed that there was no remaining circulating heparin. Post-CPB thrombelastograph (TEG) results also confirmed no remaining circulating heparin by comparing a non-heparinase cup to a heparinase cup. The TEG results were all within normal parameters (Table 1).

Two grams of tranexamic acid mixed in 50 mL of warm (37°C) sodium chloride was applied topically on the cardiac surface prior to sternal closure as per standard institutional practice. Total CPB time was 109 minutes and the aorta was cross clamped for 85 minutes.

The patient was hemodynamically stable post-CPB. He was extubated in 7 hours and discharged from the intensive care unit (ICU) in 21 hours. Total chest tube losses were 360 mL. Intravenous unfractionated heparin was initiated 24 hours post-operatively to achieve an aPTT between 60 and 84 seconds. Warfarin was initiated on post-operative day 1. There were no post-operative complications. The patient was discharged home on post-operative day 5 with a hematocrit of .302 L/L, hemoglobin of 9.7 g/dL, and platelet count of 130 × 10^9/L. At a 2-month follow-up, the patient’s hematocrit was .360 L/L, hemoglobin was 11.3 g/dL, and platelet count was 292 × 10^9/L. Long-term
Anticoagulation included warfarin therapy adjusted to maintain an INR of 2.0–3.0.

**COMMENT**

FVL is one of a group of genetic disorders that is a risk factor for venous thrombosis and hypercoagulability through activated protein C (APC) resistance. It is the most common inherited cause of thrombophilia (4). The incidence of heterozygous FVL is 3–5% in Caucasians (1,5), whereas the incidence of homozygous FVL is less than 1%, estimated at 2 in 10,000 people (4,5). FVL occurs when there is a genetic point mutation (R506Q) of blood coagulation factor V (FV). Anticoagulant function of FV
is impaired in FVL, in that it is resistant to cleavage by activated protein C, increasing the risk of venous thrombosis (6) in affected patients. The relative risk of thrombosis is increased 7-fold in heterozygous FVL patients and can be as high as 80-fold in homozygous FVL patients (5). Zoller et al. (7) found that in families with FVL, 40% of homozygote members developed venous thromboembolism before age 33. FVL homozygotes also demonstrated a 20-fold increase for venous thromboembolism after surgery (8). This patient had DVT around the age of 54 and also had a PE indicating his relatively high risk of developing thrombus.

Venous thrombosis can significantly influence morbidity as thrombophilia can cause severe complications in cardiac surgery (3) including DVT, PE, graft occlusion, and extracorporeal circuit coagulation. Graft occlusion 3 months after coronary artery bypass grafting (CABG) in FVL patients is reported at 45% (2). Massoudy et al. (3) observed a considerable number of fatal and non-fatal thromboembolic events during the perioperative period and 32 months follow-up in 14 symptomatic patients with FVL that underwent cardiac surgery.

Pre-operatively, this patient’s TEG result showed that he was in a borderline hypercoagulable state. Angle, maximum amplitude (MA), and shear elastic modulus, clot strength (G) were all at the upper end of normal limits. This supported our decision to not administer tranexamic acid due to his history of thromboembolic events and hypercoagulable state. After CPB, the patient’s TEG results were within normal limits. A follow-up TEG sample taken from the patient on arrival to ICU showed further improvement in all TEG parameters trending toward a hypercoagulable state.

To date, our patient has not experienced any post-operative complications from warfarin requirements or any thromboembolic events post-AVR. Though no statistical conclusions can be made, three patients that underwent cardiac surgery with continuous anticoagulation of a warfarin derivative had no perioperative thromboembolic events (3). These considerations should be made for patients that undergo CABG surgery as this may not be standard practice at all institutions. Inangil et al. (9) administered two-thirds of their calculated amount of protamine for heparin reversal to keep their ACT about 200 seconds for a patient that underwent CABG. This was to provide some measure of early post-operative anticoagulation in their reported FVL patient.

Because of his history of DVTs and PE, our patient was anticoagulated with warfarin until a week pre-operatively at which time of anticoagulation was bridged with enoxaparin until the day before surgery. Surgery and anticoagulation were easily managed perioperatively because of the steps already in place within our institution ensuring adequate anticoagulation and reversal. Donahue et al. (10) found that when accounting for other known risk factors, FVL had a significant independent protective effect on post-operative blood loss and risk for blood transfusion during hospitalization. At our institution, average total chest tube losses are approximately 800 mL. This patient, in agreement with previous findings, had only 360 mL of blood loss.

Heparin’s major anticoagulant effect is accounted for by a unique pentasaccharide with a high-affinity binding sequence to ATIII that is present in only one-third of heparin molecules (11). We felt that this patient had sufficient ATIII levels (67%) to reach our anticoagulation goals, in which by providing excess heparin would theoretically provide more of the unique pentasaccharides. Considerations had been made that if a sufficient ACT of 480 seconds or greater was not reached, we would have administered ATIII as per our department protocol. Patients need to have been administered at least 700 IU/kg of heparin with a resultant ACT of less than 480 seconds in order for ATIII to be considered for administration. Interestingly, Stammers et al. (12) had an ATIII-deficient patient in which ATIII was administered. They found that the ATIII level rose only slightly and the improvement of TEG parameters were modest at best, suggesting that ATIII administration has little effect on the preservation of coagulation parameters.

Symptomatic patients appear to benefit from an anticoagulant regimen throughout their perioperative stay and patients with a familial history of coagulation disorders would benefit from the definitive diagnoses of DNA testing. Further study is required to determine if long-term anticoagulation with warfarin or other similar agents should be recommended.

REFERENCES


