Antiphospholipid Syndrome and Cardiac Bypass: The Careful Balance between Clotting and Bleeding

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Abstract: Antiphospholipid syndrome (APS) is an acquired autoimmune condition characterized by the presence of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibody, and anti-β2 glycoprotein-I antibody) which leads to clinical thrombosis via a multifactorial mechanism of action. Despite the propensity to form clot in vivo, these antibodies interfere with the assembly of the prothrombinase complex on phospholipids in in vitro assays, leading to prolongation of activated clotting time and activated partial thromboplastin time. This disconnect between what occurs in vivo and in vitro makes monitoring anticoagulation during cardiac surgery particularly complex. We present a patient with APS undergoing coronary artery bypass grafting with cardiopulmonary bypass. We delineate our strategy for managing anticoagulation in the presence of this syndrome using the Hepcon Hemostasis Management System Plus (Medtronic, Inc. Minneapolis, MN) device by targeting whole blood heparin concentration to monitor anticoagulation. Keywords: antiphospholipid syndrome, anticardiolipin antibodies, lupus anticoagulant, anticoagulation, Hepcon hemostasis management system plus. J Extra Corpor Technol. 2021;53:46–9

Dr. Graham Hughes first described antiphospholipid syndrome (APS) in 1983 as a condition that included “recurrent arterial and venous thromboses, fetal losses, and thrombocytopenia in the presence of autoantibodies, the so-called antiphospholipid antibodies” (1). Since then, medical researchers have come to understand the condition as the cause of thromboembolic symptoms in vivo, whereas paradoxically presenting with prolonged coagulation in vitro (2). It is important to note that the presence of antiphospholipid antibodies alone does not confirm the diagnosis of APS because these antibodies can be present in otherwise healthy patients. APS is diagnosed using the Sapporo classification criteria, which require the patient to meet at least one of the clinical criteria and at least one of the laboratory criteria (3) (see Table 1).

Several theories exist for how antiphospholipid antibodies interact with the cellular and molecular environments to promote hypercoagulability. One theory describes that antiphospholipid antibodies interact with β2 glycoprotein-I bound to endothelial cells and cause activation of these cells. This leads to increased expression of adhesion molecules and the secretion of cytokines while also suppressing the activity of tissue factor pathway inhibitor, protein C, and protein S (4,5,6). Another theory states that antiphospholipid antibodies interact with specifically anticardiolipin (aCL) antibodies, cross-react with oxidized low-density lipoprotein (LDL). Oxidized LDL is then taken up by macrophages, which activate and damage endothelial cells (7,8). Platelets may also have a role to play in the interactions between antiphospholipid antibodies and endothelial cells (6).

Given that coagulation is often measured with either an activated partial thromboplastin time (aPTT) or activated...
clotting time (ACT), both of which calculate timing of the coagulation cascade via the common and intrinsic pathways, both are also inaccurate measurements of coagulability for patients with APS and are not corrected by the addition of normal plasma (9).

Frequently, anticoagulation for cardiopulmonary bypass (CPB) is accomplished by administering a weight-based bolus dose of heparin to reach a target ACT (typically 400–480 seconds). The ACT is then checked periodically while on CPB, and heparin is re-dosed as appropriate to maintain the target. An alternative monitoring technique for anticoagulation is to assess the amount of circulating heparin. The concentration of circulating heparin can be measured via protamine assay, which is how the Hepcon Hemostasis Management System Plus (HMS+) device (Medtronic, Inc.) functions (10). This method of measurement and maintenance of heparin, by using calculations of heparin concentration, may be more reliable than administering heparin to reach a target ACT in patients with APS because of the inaccuracies of the ACT measurement.

CASE DESCRIPTION

An 80-year-old man (height 183 cm; weight 83 kg) with a medical history of APS and coronary artery disease presented to the hospital for a three-vessel coronary artery bypass grafting. His other medical histories included osteoporosis, hypothyroidism, paroxysmal atrial fibrillation, venous insufficiency of both lower extremities, deep venous thrombosis (DVT), and facet arthritis of the cervical region. He met the Sapporo criteria for APS classification, given his history of two DVTs of the lower right extremity following surgery in 1997 and 2007 and repeated positive lupus anticoagulant antibodies confirmed by increased hexagonal phospholipid antibodies test in 2011. His outpatient medications included acetaminophen–codeine, alendronate, aspirin, clopidogrel, warfarin, duloxetine, finasteride, gabapentin, isosorbide mononitrate, levothyroxine, methocarbamol, nitroglycerin, omeprazole, pravastatin, and trazodone. He was admitted 2 days before surgery. His warfarin and clopidogrel were stopped on the morning of surgery, his preoperative laboratory values were as follows: an international normalized ratio (INR) of 1.1 (ref, .8–1.2), a prothrombin time of 11.2 seconds (ref, 9.0–12.5 seconds), an aPTT of 37.1 second (ref, 21–32 seconds), a platelet count of 179K, and a hematocrit of 43.2%.

The patient was taken to the operating room and had an uneventful induction of general anesthesia. An arterial catheter and central venous catheter were placed under sterile conditions. Shortly after induction, a blood sample was obtained from his arterial line and tested using the HMS+ system heparin dose response cartridge. His baseline ACT was measured as 180 seconds. The slope of the sample, a measurement of heparin responsiveness, was 205 sec/unit/mL (normal value: 80–100 sec/unit/mL). Hepcon testing prescribed a bolus dose of 10,186 units of heparin (123 units/kg) to reach the institutional target ACT of 480 seconds. However, given the patient’s history of APS and the likelihood that this dose would be insufficient, the clinical decision was made to use weight-based heparin dosing, and the patient was given a dose of 25,000 units of heparin to target a heparin concentration of 300 units/kg. The ACT measurement after this bolus dose was 903 seconds, yet the heparin concentration, measured via a tan heparin assay cartridge with a range of 1.5–3 mg/kg, was only 250 units/kg. The perfusionist elected to administer an additional 10,000 units of heparin because of the low heparin concentration. Repeat ACT was >999 seconds, and the heparin concentration measured again with a tan cartridge increased to >300 units/kg, which is the upper limit of the cartridge assay. CPB was initiated, and during bypass, the heparin concentration was measured every 20 minutes. An additional 5,000 units of heparin was given at the discretion of the perfusionist during CPB to maintain a heparin concentration >300 units/kg. All ACT measurements during CPB were >999 seconds. Total CPB time was

<table>
<thead>
<tr>
<th>Clinical Criteria</th>
<th>Laboratory Criteria</th>
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<tbody>
<tr>
<td>Vascular thrombosis</td>
<td>Lupus anticoagulant present in plasma</td>
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<tr>
<td>Pregnancy morbidity</td>
<td>aCL antibody of immunoglobulin (Ig) G or IgM isotype</td>
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<td>Unexplained death beyond 10th week of gestation, premature birth before 34th week of gestation due to eclampsia or placental insufficiency, spontaneous abortions before the 10th week of gestation with maternal anatomic or hormonal and paternal chromosomal abnormalities excluded</td>
<td>in serum or plasma measured by enzyme-linked immunosorbent assay (ELISA) on 2 or more occasions at least 12 weeks apart</td>
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<tr>
<td>Lupus anticoagulant antibodies confirmed by increased hexagonal phospholipid antibodies test in 2011</td>
<td>Anti-β₂ glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma measured by ELISA on 2 or more occasions at least 12 weeks apart</td>
</tr>
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Adapted from Miyakis et al. (3). Antiphospholipid syndrome is present if at least one clinical and one laboratory criteria are met.
92 minutes, and total cross-clamp time was 66 minutes. At the conclusion of CPB, 240 mg of protamine was administered based on heparin–protamine titration assay, and the patient’s resulting measurement showed an ACT of 153 seconds, which was below his baseline. No residual circulating heparin was detected.

Intraoperatively, the surgeon reported that the patient was “oozy,” especially from the saphenous vein graft harvest site which necessitated drain placement. The patient received 1 unit of packed red blood cells during the procedure, and his hematocrit immediately on arrival to the intensive care unit (ICU) was 29.2%. He was admitted to the ICU post-procedure and received 1 additional unit of blood on postoperative day 1 because of ongoing bleeding from his chest tubes which totaled 1,230 mL during the first 24 hours. His clopidogrel was restarted on postoperative day 1. His Coumadin (3 mg) was resumed on postoperative day 2 along with an unfractionated heparin infusion until his INR reached therapeutic range of 2.0–3.0. A standard institutional normogram was chosen by the postoperative critical care team for heparin monitoring with goal aPTT of 60–80 seconds. His INR reached goal on postoperative day 6, and the heparin infusion was discontinued. He was discharged to cardiac rehabilitation on postoperative day 10 and continues to do well.

COMMENT

Approximately two patients per 10,000 are diagnosed with APS every year, and the prevalence of the condition is approximately 50 per 10,000 population (11). Although the condition is uncommon, it is important to recognize the unique challenges these patients present regarding anticoagulation monitoring and to plan accordingly. Although a multidisciplinary committee released a set of guidelines for managing APS and cardiac disease in 2003, no such agreed-on set of published recommendations exists for patients with the syndrome undergoing surgery using CPB (12). During CPB, thrombin is generated, which leads to activation of the patient’s coagulation system. This risk is compounded in patients with APS because they are hypercoagulable at baseline. Accurate measurement of coagulability is essential during these cases as the risk of thrombotic complications must be weighed against the risks of excessive bleeding.

This case highlights that average ACT readings are unreliable for patients with APS. The patient’s baseline ACT was elevated before administration of the heparin bolus. The ACT measurements after the heparin bolus were continually >999 seconds. Despite the prolonged ACT, the patient’s heparin concentration, as measured by the HMS+ device, indicated a more desirable level of circulating heparin at >300 units/kg. To review, the HMS+ device uses a system of multichannel cartridges containing known and differing concentrations of protamine and a known amount of thromboplastin to measure whole blood heparin concentration (WBHC) using heparin/protamine titration. A known volume of blood is pipetted into each channel of the cartridge via an automated syringe. Each channel contains a daisy-shaped plunger which is lifted and dropped through the sample/reagent mixture. The change in fall rate due to clot formation is detected by the instrument, and the channel to clot first is determined to represent optimum heparin neutralization. The heparin concentration is then determined using the known protamine concentration in that chamber (10). One caveat is that the actual heparin concentration must remain within the boundaries of the highest protamine concentration for the selected cartridge. For example, if none of the channels clot, the heparin concentration of the blood may be higher than the range of the cartridge and a different cartridge should be used.

Another way in which we could have accurately measured coagulation for this APS patient would have been thrombin time. Thrombin time uses thrombin as an activating agent to measure the sequence “fibrinogen to fibrin monomer to initial clot,” which bypasses measurement of coagulation affected by antiphospholipid antibodies. To run this test, a standard dilution of buffered thrombin is added to a patient’s citrated plasma, and clotting time is compared with normal control plasma and the same standardized dilution of plasma (13). Although thrombin time correlates best with predicted heparin concentrations and is unaffected by APS, it still would not have been appropriate to use for our patient undergoing CPB because of the amount of time it takes to run the test.

We were fortunate to have access to the HMS+ system and realize that many institutions faced with this dilemma may not have this equipment available. A 2019 survey of North American institutions demonstrated that only 24.5% of respondents use a Hepcon HMS+ system and only 13% of respondents target a heparin concentration in addition to ACT (14). For institutions without the HMS+ system, other methodologies have been described to manage anticoagulation using ACT. These vary from making no changes in the ACT goal to setting an ACT that is double the baseline measurement (15).

The HMS+ device was also useful for calculating the appropriate protamine dose for anticoagulation reversal. The device determines the protamine dose needed to neutralize the circulating heparin based on the patient’s estimated blood volume (calculated by inputting the patient’s gender, height, and weight). We chose to fully reverse the patient’s heparin with protamine sulfate, after which the ACT result was less than the baseline ACT; however, the optimal management for heparin reversal in APS patients undergoing surgery is not well known. Incomplete heparin reversal has been reported with mixed results (9).
In conclusion, patients with APS require unique consideration when presenting for cardiac surgery. Using ACT alone to determine the adequacy of anticoagulation with heparin is insufficient and can lead to underdosing. The use of the HMS+ to target a WBHC was beneficial for evaluating circulating heparin levels and for calculating the needed protamine dose for heparin reversal.

REFERENCES