common location of the supranumerary cusp (Fig 2), one can potentially expect an increased risk of this postoperative complication if standard valve suture techniques are used. In the case in which the valve sutures were transitioned to a supra-annular location anteriorly high within the membranous septum, no postoperative heart block was seen. The normal location of the conduction system where it traverses the lower membranous septum is between the noncoronary and the right coronary cusps, which is the most common position of the supranumerary cusp in quadricuspid aortic valves. In this situation, the annulus is displaced downward toward the muscular septum, thus increasing risk of injury to the conduction system when sutures are placed around the annulus. Valve suture placement should be transitioned to a supra-annular position at the location that corresponds to the supranumerary cusp.

Downward displacement of the annulus toward the muscular septum may also be encountered in other congenitally abnormal valves, particularly bicuspid valves fused between the right and noncoronary cusps, and similar concerns may be present.

References

Bivalirudin Anticoagulation for a Patient with Hypercoagulable Immune Syndromes Undergoing Mitral Valve Surgery
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Unfractionated heparin has been a near universal anticoagulant for cardiac surgery; however it is contraindicated in heparin-induced thrombocytopenia type II. Alternative anticoagulants such as bivalirudin (a direct thrombin inhibitor) are being utilized. Bivalirudin was successfully used in an immunologically complex patient (diagnoses of heparin-induced thrombocytopenia type II, systemic lupus erythematosus, antiphospholipid syndrome, and dialysis-dependent renal failure) requiring cardiopulmonary bypass. Thrombotic events are common in antiphospholipid syndrome patients undergoing cardiac surgery utilizing high-dose heparin. This may represent unrecognized heparin-induced thrombocytopenia type II. Our patient did not experience perioperative thrombotic or bleeding complications. The possible cross-reactivity between heparin-induced thrombocytopenia type II and antiphospholipid syndrome has not been investigated.

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Unfractionated heparin (UFH) has been a near universal anticoagulant for cardiac surgery; however it is contraindicated in patients with heparin-induced thrombocytopenia type II (HIT type II). Antibodies to platelet factor four heparin complexes (PF4-H) are present in 6% to 17% of patients prior to cardiac surgery, and 1% to 3% of all patients exhibit thrombocytopenia after administration of UFH [1]. After cardiopulmonary bypass (CPB), 30% to 50% express platelet factor four heparin complexes antibodies [1]. This immune-mediated reaction and its consequences are bringing routine use of UFH into question.

Anticoagulation strategies for patients needing CPB with HIT type II have been numerous, but none have been approved. Direct thrombin inhibitors act directly without antithrombin III. Hirudin (a leech protein) is a parent compound for this drug class. Bivalirudin (an analog of hirudin) is approved for primary anticoagula-
tion in percutaneous angioplasty interventions [2]. It is presently undergoing Food and Drug Administration trials for patients with HIT type II undergoing heart surgery. We present a successful case using bivalirudin anticoagulation for a woman requiring mitral valve surgery with HIT type II, past thromboses, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), and dialysis-dependent renal failure.

A 25-year-old black female with systemic lupus erythematosus presented to cardiac surgery with worsening congestive heart failure. For dialysis she had been receiving UFH with unexplained episodes of sudden and prolonged thrombocytopenia. She was on chronic warfarin therapy as was the TEG MA at baseline. The decreased TEG MA post-CPB is consistent with the lowered platelet count.

An enzyme-linked immunoassay for platelet factor four heparin complexes antibodies was performed, which was negative. A transesophageal echocardiogram demonstrated severe mitral regurgitation, severe pulmonary hypertension, and an ejection fraction of 40% to 45%. Mitral valve surgery was recommended.

Prior to surgery her platelet count was 106,000/mm³, and she received UFH per dialysis protocol. The next morning her platelet count was 47,000/mm³. Surgery was postponed and an enzyme-linked immunoassay for platelet factor four heparin complexes antibodies was positive. Within a week her platelets increased to 98,000/mm³ and it was decided to proceed with surgery. Bivalirudin was chosen for anticoagulation. Unknown to us, UFH was placed in her dialysis catheter overnight. After induction of anesthesia and the start of surgery, pre-bypass coagulation testing revealed a platelet count of 65,000/mm³. Surgery continued, and as planned, no further heparin would be administered.

A bolus of 1.0 mg/kg and an infusion of 2.5 mg/kg/h of bivalirudin were utilized, and 50 mg was added to the pump prime. A baseline activated clotting time (ACT) was elevated (337 seconds), which was probably due to residual warfarin that had been discontinued 4 days before surgery or due to the APS antibodies. After bolusing bivalirudin, the ACT was 507 seconds (Table 1).

Cardiopulmonary bypass was without complication and the mitral valve was successfully repaired. The post-bypass platelet count was 50,000/mm³ and 4 units of random donor pooled platelets were given. Chest tube drainage totals at 4, 8, and 24 hours, respectively, were 360 mm³, 431 mm³, and 580 mm³. She was transfused with 1 unit of packed red blood cells on postoperative days 1 and 5 when her hemoglobin was 6.6 gm/dL and 6.8 gm/dL, respectively. On postoperative day 6 she was discharged with a hemoglobin of 7.7 gm/dL and a platelet count of 94,000/mm³ (Table 2).

### Comment

There is no consensus as to the best anticoagulation for HIT Type II patients needing CPB. Several agents have been utilized, some successfully and others with bleeding or thrombosis reported. Unfractionated heparin in conjunction with tirofiban (glycoprotein IIb/IIIa inhibitor) to hinder

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<table>
<thead>
<tr>
<th>Table 1. Bivalirudin Dosing Schedule</th>
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<tr>
<td><strong>Bivalirudin Dosing Schedule</strong></td>
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<tr>
<td>Baseline</td>
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<tr>
<td>After bolus (1.0 mg/kg) and starting infusion (2.5 mg/kg/hr)</td>
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<tr>
<td>Continuous infusion during CPB</td>
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<tr>
<td>Infusion reduced to half (40 min prior to weaning from CPB)</td>
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<tr>
<td>Infusion discontinued (15 min prior to weaning from CPB)</td>
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<tr>
<td>30 min post-infusion</td>
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<td>60 min post-infusion</td>
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</tbody>
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**CPB** = cardiopulmonary bypass.

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<table>
<thead>
<tr>
<th>Table 2. Perioperative Coagulation Data*</th>
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<tr>
<td><strong>Coagulation Data</strong></td>
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<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Admission</td>
</tr>
<tr>
<td>Prior to CPB (unknown use of unfractionated heparin to flush dialysis catheter after admission and before surgery)</td>
</tr>
<tr>
<td>Post-CPB</td>
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<tr>
<td>Discharge</td>
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*Note that the activated clotting time was elevated prior to administration of bivalirudin, and even though it was elevated, the TEG R value was normal as was the TEG MA at baseline. The decreased TEG MA post-CPB is consistent with the lowered platelet count.

*aPTT* = activated partial thromboplastin time; **CPB** = cardiopulmonary bypass; **K** = speed of clot formation; **MA** = the ultimate strength of the clot which is dependent on number and function of platelets and its interaction with fibrin; **PT** = prothrombin time; **R** = time to initial clot formation; **TEG** = thromboelastography; **TEG R** = thromboelastography R; **TEG MA** = thromboelastography maximum amplitude.
the secondary thrombin generation from overt platelet activation has been used [3]. Argatroban (an arginine-derived direct thrombin inhibitor) has also been utilized [1], which has been approved by the Food and Drug Administration for use in patients with HIT type II, but not specifically for CPB. Both of these agents have had cases of severe bleeding post-CBP. Hirudin or recombinant-hirudin (lepirudin), another direct thrombin inhibitor, has also been utilized for CPB in the face of HIT type II, but it is completely dependent on renal clearance. Severe bleeding after CPB has been noted with hirudin anticoagulation.

Bivalirudin utilizes the amino acid sequences of the two active sites of hirudin connected with a tetra-glycine spacer [1, 4]. With the shortest half-life (ie, 25 minutes), it is cleaved directly by thrombin (80%) and has no known antidote. Bivalirudin is dialyzable and can be removed post-bypass via hemofiltration [5]. In renal failure there is modest prolongation of its half-life [2].

Bivalirudin has been utilized in large percutaneous angioplasty intervention studies with improved outcome compared with heparin and protamine or heparin and protamine plus IIb/IIIa blocking agents [2]. In a trial comparing bivalirudin with heparin and protamine for off-pump CABG, the bivalirudin group showed no difference in overall outcome or bleeding [6].

Antiphospholipid syndrome is an autoimmune disorder often associated with systemic lupus erythematosus [7]. It is the most common of the hypercoagulability syndromes [7]. The APS antibodies compete with anticoagulant proteins (ie, protein C, S, tissue plasminogen activator, and annexin V) for platelet binding activation sites, creating a prothrombotic state [7]. Unfractionated heparin or heparan assists in the binding of annexin V to platelets; however, no cross-reactivity to HIT type II has been described [7, 8]. The APS antibody increases the endothelial expression and creation of tissue factor, a leading cause of thrombin generation during CPB [7].

Antiphospholipid syndrome has been studied in cardiac surgery with several series reported [7]. Thrombotic events were common, and in one series of 19 patients, 16 had major postoperative complications [7]. Twelve of the 19 patients died. Heparin was used in all of these patients and the possibility of HIT type II was never examined.

With APS, the ACT is elevated at baseline because the antibody interferes with sample activation. Patients who have APS requiring cardiac surgery are often managed with high-dose heparin to maintain elevated ACTs. However, there remains a high incidence of thrombotic events and anticoagulants, such as direct thrombin inhibitors may be indicated. Our patient had an elevated baseline ACT. After receiving bivalirudin, the ACT behaved as expected for patients without APS, yet never normalized after stopping the infusion. The chest was closed with minimal bleeding and there was no subsequent hemorrhage. The APS antibodies may have been responsible for the prolonged ACT post-CPB.

Unfractionated heparin markedly increases expression of PF4 and the platelet factor four heparin complex is highly antigenic. Our patient received UFH regularly, producing repeated antigenic challenges, perhaps with increased platelet factor four heparin complex antibodies. The high incidences of thrombotic complications in patients with APS who receive UFH for CPB may represent unrecognized HIT type II. No investigation exists in the literature of increased risk of HIT type II in patients with APS.

Our patient did not have thrombotic or bleeding complications. We cannot claim these results were solely due to bivalirudin, but with the question unexplored regarding cross-reactivity between HIT type II and APS, it seems possible. The only recommendation regarding APS patients undergoing heart surgery has been to give large doses of UFH, which have often been catastrophic. Bivalirudin worked well in this complex case. We believe that patients undergoing cardiac surgery with APS should be tested for HIT type II and administered an alternative to UFH.

References


Anterior Mitral Leaflet Reconstruction With Pericardium in a 1.9 kg Infant With Endocarditis

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A premature twin of 1.9 kg had mitral valve endocarditis develop during neonatal intensive care. Vegetation involving the entire anterior mitral valve leaflet was identi-