Use of Ecarin Clotting Time (ECT) with Lepirudin Therapy in Heparin-Induced Thrombocytopenia and Cardiopulmonary Bypass

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Abstract: Heparin-induced thrombocytopenia (HIT) is described as an allergy-like adverse reaction to heparin. It is a potentially severe complication of heparin therapy that can result in serious or life-threatening venous or arterial thromboembolic events. In the United States, lepirudin (Aventis Pharma AG, Strasbourg, France) is an approved therapy for anticoagulation in patients with HIT requiring anticoagulation. Lepirudin is a recombinant form of hirudin, a leech enzyme that is a highly specific direct inhibitor of thrombin. Lepirudin monitoring during surgery can be managed with ecarin clotting time (ECT) (Cardiovascular Diagnostics, Inc., Raleigh, NC), which has recently been approved as a humanitarian device exemption (HDE) for use in the United States in the management of HIT with cardiopulmonary bypass. This case report describes a patient with HIT who was managed successfully with lepirudin and ECT during coronary artery bypass grafting. Keywords: ecarin clotting time, heparin-induced thrombocytopenia, hirudin, lepirudin, cardiopulmonary bypass, thrombolastograph. JECT. 2001;33:117–125.

Heparin-induced thrombocytopenia (HIT) can be separated into two different types based on the clinical presentation and the pathophysiological mechanism.

HIT TYPE I

HIT Type I is an early, mild form of thrombocytopenia. As the use of heparin increases, so does the potential for the occurrence of heparin-induced thrombocytopenia. Up to 20% of those who are receiving heparin will experience some degree of thrombocytopenia, usually within the first 4 days (1). Type I is characterized by a mild decrease in platelet counts (rarely below 100,000/mm³), is caused by nonimmunological mechanisms (likely mild direct platelet activation by heparin), and is not associated with any major sequelae (2). HIT I is solely a clinical diagnosis; heparin-dependent activation tests are negative. There is no specific treatment for HIT I, and the main clinical importance of HIT I is to distinguish it from the more serious HIT II (3).
Other clinical symptoms of HIT II are: (1) a drop in platelet count that occurs after 5 days of therapy or a platelet drop after only 1 day of therapy if the patient had been on heparin therapy within the previous 3 months or so; and (2) thrombocytopenia not explained by such other causes as drug-induced thrombocytopenia or such clinical conditions as sepsis, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), lupus anticoagulant syndrome, or systemic lupus. In the patient who has been re-exposed to heparin, residual circulating antibodies react upon heparin re-exposure inducing the rapid fall in platelet count (2). It is not possible to select a platelet count above which a diagnosis should not be considered nor a platelet count below normal necessary for clinical diagnoses. With at least 10% of HIT patients, thromboembolism has been associated with a fall in platelet count that does not reach less than 150,000/mm³ (6).

Pathogenesis

Most episodes of HIT II are caused by heparin-dependent antibodies, usually of the immunoglobulin G (IgG) class (less often IgA or IgM). These antibodies form several days after exposure to heparin. The IgG antibodies interact with complexes of heparin and platelet factor 4 (PF4) leading to activation of platelets via platelet receptors (6–9). This leads to platelet aggregation, thrombus formation, and thrombocytopenia caused by platelet consumption. There is further release of PF4, maintenance of the destructive cycle, and neutralization of the anticoagulant properties of heparin (2).

Laboratory Assays

Two types of assays are available to diagnose HIT: functional and antigen assays. Unfortunately, no one type of assay is 100% reliable for the diagnosis of HIT (10).

In testing for HIT, the platelet aggregation test is widely used, because it is simple and cost effective. Another functional assay used for diagnosing HIT is the ¹⁴C-Serotonin release assay (SRA). It is generally used only for confirmation of diagnosis, because it is technically challenging, uses radioactivity, and takes longer to perform than other tests (1).

The enzyme-linked immunoabsorbent assay (ELISA) is also used. This antigen test uses the heparin-PF-4 complex as the target for HIT antibodies. Because the functional and antigen assays complement each other and neither is 100% reliable, it is recommended that both types be available for the diagnosis of HIT (10).

HIT Complications

The thrombocytopenia itself rarely poses a threat. Rather, HIT type II is clinically significant because it is associated with thromboembolic disorders that can produce severe morbidity and mortality. Profound activation of the coagulation system occurs with HIT (6). Thrombin-antithrombin levels are greatly elevated in many HIT patients which suggests that in vivo thrombin generation contributes to the pathogenesis of HIT. There are at least three ways in which HIT IgG triggers procoagulant effects: (1) platelet activation with an associated platelet procoagulant response; (2) endothelial activation; and (3) heparin neutralization (6).

Failure to diagnose early and treat promptly can result in disastrous outcomes. These disorders include arterial and venous thromboses such as: deep venous thrombosis, pulmonary embolism, disseminated intravascular coagulation, cerebral thrombosis, and stroke, myocardial infarction, skin lesions, and ischemic injury to the legs or arms with possible subsequent limb amputation (11). Heparin-induced thrombosis is also known as the “white clot syndrome” because of the platelet-rich thrombus (12).

Studies have shown that risk for thrombosis is high in patients with HIT. Of patients with HIT, 29% (13) to 89% (14) of patients who develop HIT experienced thrombosis. According to Nand et al., there is a 29% fatality associated with the development of thrombosis, and another 21% of patients who require limb amputations (13). Therefore, these patients should not receive heparin in any form. Heparin–containing solutions, agents, or heparin-bonded materials, such as pulmonary catheter lines or heparin-bonded surfaces sometimes used in cardiopulmonary circuits and components should be avoided.

ANTICOAGULATION AGENTS

Because of the possibility of developing HIT antibodies and subsequent thromboembolism, heparin is contraindicated in patients with HIT. Most patients, therefore, will require treatment with an alternate anticoagulant. When systemic anticoagulation is necessary, as in cardiopulmonary bypass, this will pose a great problem (Table 1) (14–22).

Some clinicians have advocated the use of heparin with HIT and CPB with avoidance of any heparin exposure immediately postprotamine administration after CPB. The rationale to this approach is that, characteristically, platelets are activated in therapeutic heparin concentration (0.05–0.3 units/mL), but activation is inhibited at high heparin concentrations (10–100 units/mL). This is explained by displacement of PF4 away from platelet surface in the presence of very high fluid phase heparin levels preventing the PF4/heparin/platelet interaction (9). However, when the heparin levels are reduced, the fluid barrier is eliminated, and the danger of HIT antibodies and thromboembolism increases.

When agents are similar in structure to heparin, they can present with cross reactivity and should be avoided, because they can also cause HIT. Low molecular weight
Heparins present with nearly 100% cross reactivity (1). Heparinoids present with cross reactivity in the range of 10–40% (2).

LEPIRUDIN

Purified from saliva of the Hirudo medicinalis leech, hirudin was cloned and is produced as a recombinant product known as lepirudin (Aventis Pharma AG, Strasbourg, France) and marketed in the United States as Refludan®. Lepirudin is highly specific and the most potent direct thrombin inhibitor (15). It has no effect on platelets. The anticoagulation effect of lepirudin may be explained by inhibiting actions on platelet aggregation and on thrombus growth and organization. Lepirudin exerts a direct effect on both clot bound and unbound thrombin. The systemic clearance of lepirudin is proportional to the glomerular filtration rate and creatinine clearance. Dose adjustment based on creatinine clearance is recommended in patients with marked renal insufficiency (23).

Benefits of using lepirudin are: (1) immediate onset; (2) short elimination half-life; (3) no cross reaction with heparin-induced antibodies; and (4) on-line monitoring using the ecarin clotting time. However, as with other options, the actual lack of an adequate reversal agent is one of the major disadvantages (24).

Patients may also develop antihirudin antibodies. Formation of IgG antihirudin antibodies was observed in about 40% of HIT patients with lepirudin. This condition may increase the anticoagulant effect of lepirudin possibly because of delayed renal elimination of active lepirudin-antihirudin complexes (23). These antihirudin antibodies seem to cause a paradoxical increase in aPTT values (9) possibly leading to anticoagulation monitoring and management concerns.

ECARIN CLOTTING TIMES

Although lepirudin is approved in the United States for the management of HIT, there is no clinically acceptable effective method for monitoring the effect of higher doses during cardiopulmonary bypass (CPB). Lepirudin therapy for use with CPB is not widespread, because it necessitates use of Thrombolytic Assessment System (TAS) Ecarin Clotting Time (ECT) (Cardiovascular Diagnostics, Inc., Raleigh, NC), which has recently been designated as Humanitarian Device Exemption (HDE) for use in the United States. Ecarin clotting time has been used in conjunction with administration of lepirudin in some European cardiac programs as well as in the United States as investigational or emergency appeal cardiopulmonary bypass procedures. The use of ECT is not yet approved for use in therapeutic lower levels of lepirudin therapy.
Lepirudin Monitoring

Ecarin is a protein prothrombin activator from *Echis carinatus* snake venom (25). The TAS Analyzer utilizes ECT test cards to measure the clotting time of a blood sample containing lepirudin. As the in vivo concentration of antithrombin drug increases, the ECT increases in a linear dose-dependent manner. Lepirudin influences the common laboratory tests, whether coagulation is induced by the intrinsic (aPTT), extrinsic (prothrombin time [PT]) route, or directly by thrombin time (TT). A disadvantage of the ECT is its dependence on plasma levels of prothrombin. This might be problematic in patients with liver disease showing low levels of prothrombin (25).

Activated Clotting Time (ACT) and activated partial thromboplastin time (aPTT) are not specific enough measures as they lose linearity at the higher doses of lepirudin necessary for cardiopulmonary bypass. Although the aPTT is the accepted coagulation test for therapeutic lower levels of lepirudin, both the ACTs and aPTT show poor correlation with plasma lepirudin levels at the higher lepirudin levels. Potszch et al. found a linear relationship between the higher concentration of lepirudin and the prolongation of ECT values ($r = 0.94$) (26). In another study with higher levels of lepirudin, Potszch et al. found a poor relationship with lepirudin and aPTT ($r = 0.30$). With a steady concentration of 2 μg/mL of lepirudin, ACTs were scattered between 150 and 500 seconds with no stated $r$-value but revealing a poor correlation (27).

Thrombin time (TT) frequently exceeded 200 seconds even at low plasma concentrations of lepirudin, which renders this test unsuitable for routine monitoring of lepirudin therapy (28).

**Materials and Methods**

Ecarin clotting tests are performed using a specific amount of patient blood injected into a vacuum tube containing sodium citrate. A specific amount (100 μL) is “diluted” by mixing with a specific and same amount (100 μL) of Specialty Assay Reference Plasma (SARP) (Helena Labs, Beaumont, TX) or Factor Assay ConTrol (FACT) (George King Labs, Overland Parks, KS) lab reference plasma. A specific amount (30–35 μL) of that mixture is dropped onto the ECT card for testing by the analyzer.

During bypass surgery, clotting factors in the patient’s blood are diluted by fluid in the bypass circuit and depleted through activation of the clotting cascade. This dilution and depletion causes an artificial prolongation of the ECT (this effect also occurs with aPTT and ACT monitoring of r-hirudin therapy). This artificial prolongation can be corrected by “dilution” of the patient’s citrated blood sample 1:1 with pooled normal human plasma such as SARP, FACT, or other normal plasma. In our procedure, every patient sample was diluted with plasma to achieve continuity of sampling methodology and results.

**CASE REPORT**

**Clinical Condition**

A 64-year-old male arrived at our institution via air ambulance with severe dyspnea, pulmonary edema, congestive heart failure, history of tobacco use, alcohol abuse, and otherwise sketchy medical history. He required intubation and insertion of intra-aortic balloon and pulmonary artery catheters. He subsequently underwent cardiac catheterization. The catheterization revealed lesions of the left main, circumflex, and proximal right coronary arteries and a left ventricular ejection fraction of 20%.

While awaiting resolution of the congestive heart failure, and other clinical problems, it was noted that the platelet count was falling rapidly and steadily (Table 2). After consultation with hematologists, platelet aggregation and PF4 samples were sent for analysis. In the interim, the balloon pump catheter and heparin were discontinued, and the patient was placed on lepirudin therapy.

Coincidentally, the hemoglobin levels fell while waiting for the platelet aggregation and PF4 assays to be determined. The admission hemocrit of 47.4% fell during the next few days to 33.9%, leading to thoughts of possible diagnosis of thrombocytosis anemia, myelodysplastic syndrome, or lymphoma. The rapid onset of the severe thrombocytopenia did not fit the usual picture of HIT II. With the history of alcohol abuse, a diagnosis of chronic thrombocytopenia because of depressed marrow and subsequent intra-aortic balloon therapy was considered. A bone marrow biopsy was performed that revealed no clinical significance. The liver function studies revealed slightly elevated values secondary perhaps to the heavy alcohol consumption.

The lab samples of PF4 and platelet aggregation had been sent just before the weekend. Platelet counts following the cessation of heparin therapy started to rise. Activated partial thromboplastin times remained at therapeutic lepirudin levels of 1.5–2.5 times normal at 61 seconds (23). A diagnosis of HIT was made on the basis that one of the two PF4 tests was positive, while the other was negative. Aggregation tests were inconclusive. These tests are not 100% accurate and can present as false-negative. It was the combined attending clinicians’ judgement that this condition was probably HIT; clinical evidence of HIT remains the gold standard for diagnosis (3).

**Procuring Approval And Equipment**

Because the patient had operable lesions and would benefit from coronary artery bypass surgery, a decision was made to go forward with the use of lepirudin and the use of ecarin clotting time for monitoring and management of lepirudin during the CPB. After quickly obtaining hospital Internal Review Board approval via an emer-
gery appeal and Food and Drug Administration (FDA) approval, the TAS equipment and ECT cards, and quality controls were requested from the Cardiovascular Diagnostics Inc. and arrived via express shipment on the following day. Recently in the United States, an HDE status was afforded to this TAS ECT equipment, and this monitoring process may be used on any patient demonstrating HIT and requiring cardiopulmonary bypass. Because of the HDE status and the fact that the ECT cards do not have full FDA approval, certain guidelines for procuring institutional approval and the monitoring device are still in effect. With the patient consenting to the use of lepirudin and the ecarin tests, the surgery was scheduled.

**Perfusion Equipment And Considerations**

The CPB system consisted of a four roller head Cobe heart–lung machine (Sorin Cobe, Arvada, CO), Terumo 1.8 M² oxygenator, arterial filter, circuit tubing, and cardioplegia system (Terumo Sarns, Ann Arbor, MI). Prime contents of the system consisted of 1500 mL Plasmalyte-A, 25 grams of mannitol, and 10.5 mg of Refudan® based on patient weight and renal function. Cardioplegia components were the usual mixtures for induction of arrest and warm reperfusion before cross clamp removal. Mild hypothermia (34°C) was employed. Because of adequate urinary output of 450 mL during the bypass, a hemococoncentrator was not used. The cell saver was a Brat 2 (Sorin Cobe, Arvada, CO), and the anticoagulant of that system was acid-citrate-dextrose as opposed to the usual one liter of heparinized saline.

Anticoagulation monitoring consisted of ECT, aPTT, ACT by Hemochron Jr (International Technidyne, Edison, NJ), PT, derived fibrinogen, and thromboelastograph (TEG) (Haemoscope, Niles, IL), and this monitoring continued into the postoperative phase when possible.

**Anesthesia Considerations**

All heparin and heparin flushes were removed from the area, and the inserted pulmonary artery catheter was non-heparin coated. Anesthesia staff were responsible for the lepirudin maintenance infusion and the sampling for the off bypass laboratory tests and TEGs. This patient required more blood products than usual, and those products were administered by anesthesia personnel.

**Surgical Considerations**

After performing a median sternotomy, the surgeon discovered extensive intrapericardial adhesions of some unknown origin. The heart was dilated, enlarged, and severely hypokinetic. A left internal mammary artery was dissected, as was a portion of the greater saphenous vein. All surgical aspects of the procedure otherwise were performed as usual.

**Laboratory Testing**

The decision had been made to perform ECT, ACT, aPTT, PT, TEGs, and derived fibrinogen values during lepirudin therapy. A baseline TEG had demonstrated hypercoagulability. The R and K values were markedly reduced, and the α° and MA values were increased (Figs. 1–3). This may have been related to the increase of thrombin generation seen in some HIT patients.

**Lepirudin Dosing**

Suggested initial lepirudin dosing for CPB is 0.25 mg/kg as a patient loading dose, 0.20 mg/kg for the pump prime.
and a maintenance infusion of 0.075 mg/kg/h (27, 29). Originally the decision had been made to load with 75% of usual lepirudin dosing because of the compromised renal function with a creatinine clearance of 50 mL/min (23). That would yield a patient loading dose of 13 mg/kg. It was soon evident that even the manufacturer recommended routine dosing of 0.25 mg/kg would not be sufficient in this patient (Table 3). The ECT results were lower than expected, and this correlated with lower aPTTs and ACTs (for trending) as well as observation of clot in the chest. After discussion with representatives of the ECT device, incremental doses of lepirudin were administered until an ECT of 300 seconds (diluted) was surpassed. This dosing regimen required approximately 104 mg of lepirudin or 1.5 mg/kg of body weight, far exceeding the recommended dosing of 0.25 mg/kg by six times as much. This did not come as a great surprise as the baseline TEG (at 0815) had shown hypercoagulability. The serial TEGs (see Figure 3), while showing response with the increasing administration of lepirudin, showed similar trending with the ECT, aPTT, and ACT values as well. Interestingly, the derived fibrinogen levels rose as the lepirudin anticoagulation was initiated (Table 3). Because of the greatly increased lepirudin requirement, pump and intravenous dosages were adjusted accordingly.

More than 200 mg of lepirudin was required to anticoagulate this hypercoagulable patient and to maintain the ECT level above 300 seconds. Although some literature (25) suggests that ECT on bypass might be maintained between 200–300 seconds (plasma diluted), a minimum level of 300 seconds was chosen on this patient for most of the cardiopulmonary bypass. He was apparently hypercoagulable according to the TEGs and, coincidentally, clot was visualized in the chest until after the ECT exceeded 300 seconds.

**Patient Clinical Course**

In the operating room and postoperatively, the patient required significant transfusions of blood products perhaps in part because of the extensive adhesions encountered and the history of alcohol abuse. His questionable renal status also probably contributed to the slow elimination of lepirudin via the kidneys. There was a 1300 mL blood loss in the first hour in the Cardiothoracic Intensive Care Unit (Table 4).

Also complicating the immediate postoperative course was the situation of a sudden decrease of chest tube drainage along with the disappearance of the right foot pulse. A thought at the time was that the hypercoagulable situation, which had existed pre-operatively, might be complicating the situation again. However, the coagulation parameters did not support this as the ECT, aPTT, and ACT were still elevated well above baseline. Ecarin clotting time is approved for monitoring for CPB, but not at lower therapeutic lepirudin levels where aPTT monitoring is the coagulation test. The ECT and ACT were performed post-operatively for clinical information. The monitored pressures did not support the diagnosis of a cardiac tamponade. It was determined that a clot had formed at the site of the intra-aortic balloon insertion and, after a return to the operating room, a vessel repair and embolectomy were performed using dilute lepirudin in a bolus injected into the femoral artery. Although a small dose, this served to anticoagulate further. The chest was opened at the same time to evacuate clot and to explore for any bleeders, because there was some amount of blood and clot in the chest.

At that time, the patient was started on furosemide to aid in renal removal of lepirudin and to accommodate the necessary blood products since the revisit to the operating room. Although elimination of r-hirudin is fast in patients with normal renal function, high-dose application seems to cause a hirudin storage in body fluids leading to redistribution phenomena requiring hemofiltration or diuretics to aid in elimination of lepirudin (24).

The patient was maintained on dobutamine, lasix, amiodarone, and nitroglycerine because of pulmonary hypertension. The blood loss rapidly declined; the status improved. He was extubated 3 days postoperatively. He was discharged from the hospital on the fifth postoperative day with a platelet count of 109,000/mm$^3$.

**DISCUSSION**

It is our belief that patients who present with HIT and
who require anticoagulation and cardiopulmonary bypass may be treated with lepirudin, and those levels can be monitored and managed by the ECT. The patient represented in this case report was unusual in that he was confirmed via TEG with a hypercoagulable state of some type requiring a much greater than recommended dosage of lepirudin for anticoagulation. He also demonstrated suspect liver and renal function and postoperative complication requiring thrombectomy, further anticoagulation, and many blood products. Despite this, he left the hospital 5 days after surgery and continues to do well.

Our team would continue to utilize ECT, aPTT, PT, derived fibrinogen, and TEG for guidance. We would be more aggressive with the use of furosemide, mannitol, and a continuous infusion of renal dose dopamine post CPB, perhaps using those diuretics on CPB especially near separation. If the lepirudin level remained high on CPB, consideration of hemofiltration might be appropriate. The use of aprotinin (Trasylol®, Bayer Pharmaceuticals, West Haven, CT) might also be a future consideration.

It is our thought that the inclusion of TEGs in the battery of testing done with this patient proved to be quite...
valuable and may be used in the future for lepirudin dosing guidelines. Because of the hypercoagulability of some of these patients, consideration of a lepirudin maintenance drip postoperatively might be of importance, and a useful tool for that monitoring may well be TEG.

The ECT monitoring was rapid and fairly easy to use in the operating room and intensive care area. However, the equipment is not quickly available, requires a great deal of paperwork and approvals, and would be impossible to use in an emergency procedure. It is expensive to use this device with ECT cards.

This situation was only the eighth procedure performed in the United States utilizing ECT with lepirudin management and CPB yielding limited experience. This monitoring has been used more extensively in Europe and data are constantly being gathered and evaluated. More data are necessary from populations of patients in the United States.

**AUTHOR’S NOTE**

At the time of this publication, some cardiac programs have developed protocols which include construction of a reference curve for patients undergoing CPB with lepirudin.

### Table 3. Intraoperative and postoperative laboratory values

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<th>ECT</th>
<th>APTT</th>
<th>ACT</th>
<th>PT</th>
<th>Fibrinogen (Derived)</th>
<th>Lepirudin mg</th>
<th>Platelets/mm³</th>
<th>Hematocrit %</th>
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<td>Seconds</td>
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<td>Patient</td>
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<td>IV</td>
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ECT: Ecarin clotting time; aPTT: Activated partial thromboplastin time; ACT: Activated clotting time; PT: Prothrombin time.

Table 4. Blood products.

<table>
<thead>
<tr>
<th></th>
<th>Red Blood Cells (Washed Cells)</th>
<th>Fresh Frozen Plasma</th>
<th>Platelets</th>
<th>Cryoprecipitate</th>
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<td>Operating room and postoperative</td>
<td>6 Units (7 Units)</td>
<td>23 Units</td>
<td>3 Sets of 7 Units</td>
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<td>4 hours</td>
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<tr>
<td>Postoperative 6–10 hours</td>
<td>6 Units</td>
<td>3 Units</td>
<td>1 Set of 7 Units</td>
<td>2 Units</td>
</tr>
<tr>
<td>Postoperative 12–18 hours</td>
<td>2 Units</td>
<td>2 Units</td>
<td>1 Set of 7 Units</td>
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</tr>
<tr>
<td>Total</td>
<td>14 Units (7 units)</td>
<td>28 Units</td>
<td>5 Sets of 7 Units</td>
<td>3 Units</td>
</tr>
</tbody>
</table>
great effort from all involved. Of all participating. From the coronary unit through the surgical procedure requires much individual and teamwork effort on the part of anesthesia, perfusion, and nursing expertise. This type of procedure resources that are available to us along with the surgical, medical, and nursing expertise.

Weisinger states in his protocol that a lepirudin level of 3.5–4.0 μg/mL is adequate for initiation of CPB. He states that this concentration is roughly equivalent to an ECT of 350–400 seconds. (Weisinger A. Protocol for the use of Refludan (lepirudin rDNA) to provide anticoagulation in patient with heparin-induced thrombocytopenia Type II (H.I.T.) Syndrome. Heart Surgery Forum, March 2001).

ACKNOWLEDGMENT

At our institution, we are fortunate to have the vast laboratory, hematology, transfusion medicine, blood bank, and pharmacy resources that are available to us along with the surgical, anesthesia, perfusion, and nursing expertise. This type of procedure requires much individual and teamwork effort on the part of all participating. From the coronary unit through the surgical and postoperative care, this situation demanded and received great effort from all involved.

REFERENCES