

## CASE CONFERENCE

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### CASE 5—1996 Thrombosis After the Use of a Heparin-Coated Cardiopulmonary Bypass Circuit in a Patient With Heparin-Induced Thrombocytopenia

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#### Case Presentation

A 64-year-old, 165-cm, 58-kg woman was admitted to the hospital with an inferior myocardial infarction. She underwent an emergent percutaneous transluminal coronary angioplasty (PTCA) complicated by an early reocclusion necessitating a second PTCA. The second PTCA complicated itself by the dissection of the right coronary artery (RCA), necessitating the placement of four stents in the RCA. The patient was then treated with porcine heparin (H) for 7 days. Warfarin was progressively titrated to a prothrombin time of 23% (international normalized ratio = 3.8), and heparin was then stopped. After 3 days of effective warfarin treatment, she suddenly developed cardiogenic shock with third-degree atrioventricular block, necessitating resuscitation maneuvers, intubation, placement of an intra-aortic balloon pump, and a pacemaker. After this resuscitation, she recovered well except for a right hemiparesis that was attributed to a prolonged hypotensive state. Coronary angiography disclosed a reocclusion of the RCA. Fibrinolytic therapy was then administered, and a continuous infusion of heparin was reintroduced. Forty-eight hours after her ischemic event, a cerebral computed tomography (CT) scan was normal, and she had no neurologic sequelae. Nine days later, despite receiving a continuous infusion of heparin, she became ischemic in the right coronary artery territory, and an emergent coronary revascularization was planned.

While evaluating the patient's files, the attending anesthesiologist found that the platelet level was below 35,000/mm<sup>3</sup> from the beginning of the second heparin administration 10 days earlier (Fig 1), and he suspected a syndrome of heparin-induced thrombocytopenia (HIT). Because of the presence of four stents in the patient's RCA and owing to her history of the repetitive coronary occlusions, the cardiologists refused to stop the heparin infusion. This infusion was therefore stopped in the operating room. A central venous catheter was already in place, a radial arterial catheter was then placed under local anesthesia, and both were flushed with 0.9% saline without heparin. Anesthesia was induced with etomidate and sufentanil, and muscle paralysis achieved with pancuronium. Anesthesia was maintained with midazolam, and a continuous infusion of sufentanil, 2 µg/kg/hr.

Iloprost is not available in Belgium; neither are the

heparin substitutes proposed in the literature. The anesthesiologist had no experience with the use of low-molecular-weight heparin (LMWH) during bypass. Therefore, he elected to use a heparin-coated cardiopulmonary bypass (CPB) circuit (HC-CPB) (Durafluo II; Bentley [Englewood, CO], because of its theoretical advantages of biocompatibility and protection of platelets against activation caused by contact with the artificial surfaces. Only 50 IU/kg of porcine heparin were administered in place of the usual 300 IU/kg. Two saphenous grafts were sutured on the RCA. The procedure was performed under normothermia and intermittent antegrade warm blood cardioplegia. Aortic cross-clamp time was 34 minutes, and CPB lasted 55 minutes. No pharmacologic support was needed to come off bypass.

The platelet level was 34,000/mm<sup>3</sup> before surgery and 39,000/mm<sup>3</sup> after 50 IU/kg of H. It decreased to 22,000/mm<sup>3</sup> after 7 minutes of CPB, possibly because of hemodilution, and returned to 39,000/mm<sup>3</sup> after discontinuation of CPB. Activated coagulation times with kaolin (ACT) (Hemotec; Medtronic [Uden, The Netherlands]) were 151 seconds before heparin administration, 231 seconds after 50 IU/kg of H, 445 and 443 seconds during CPB, and 295 seconds after CPB. Only 10 mg (2,000 IU) of protamine were then administered, and ACT returned to 148 seconds (Fig 2).

After administration of another 1,000 IU of protamine, the ACT was 82 seconds. Despite this, the patient was still bleeding actively. It was then judged that no more heparin was circulating at that time, and it was decided that it would

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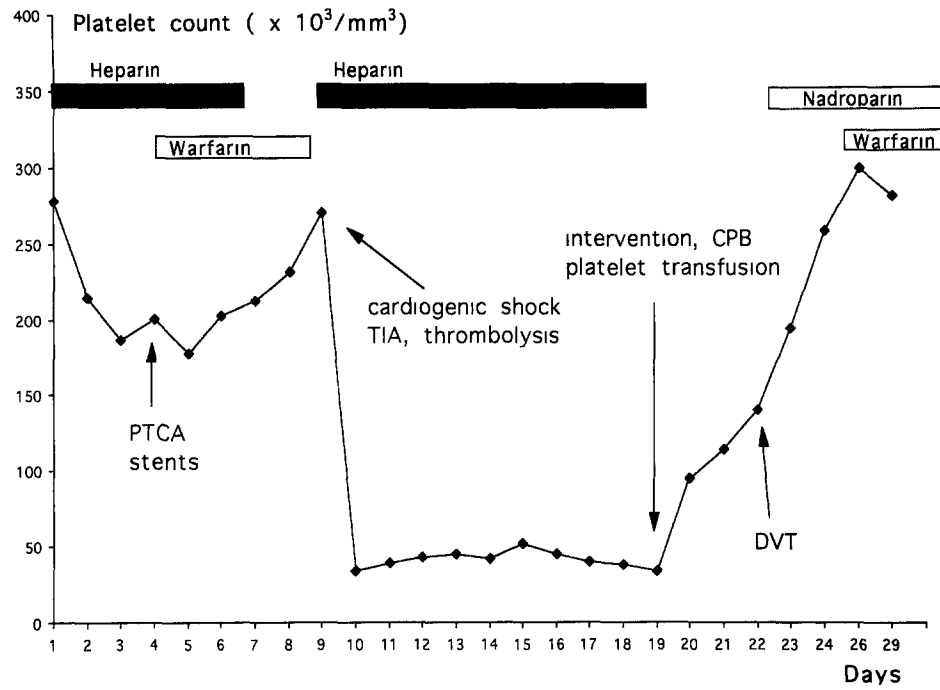


Fig 1. Course of the platelet count versus hospital stay. PTCA, percutaneous transluminal coronary angioplasty; TIA, transient cerebral ischemic attack, CPB, cardiopulmonary bypass; DVT, deep venous thrombosis.

be safe to administer 6 units of platelet concentrate. All the blood lost during the procedure was processed (Cobe-IBM 2991, Lakewood, CO) and readministered to the patient: It constituted a volume of 650 mL of erythrocytes concentrate.

The patient was admitted to the intensive care unit (ICU) and there, because of continuous bleeding, received 6 more units of platelet concentrate. This administration stopped the bleeding, and the platelet count at that time was 83,000/mm<sup>3</sup>. Judged empirically as being safe, nadoparin and aspirin therapy were begun on the second postoperative day. The patient left the ICU on the second postoperative day, and from that moment her platelet count continuously improved up to normal values (Fig 1). Unfortunately, on the third postoperative day, the patient developed swelling of both inferior limbs. A pelvic CT scan disclosed an extensive thrombosis of her two iliac veins and the inferior vena cava up to the renal veins. Despite addition of warfarin to the therapy, only a partial resolution was obtained 25 days later.

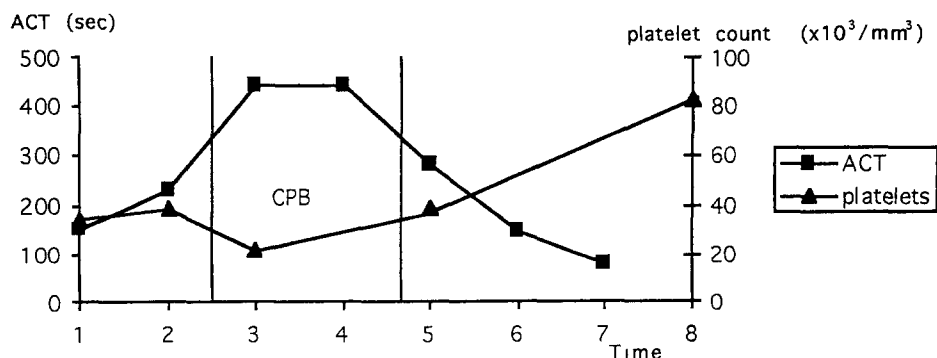
She left the hospital on the 30th postoperative day, 49

days after her admission, under effective warfarin anticoagulation and without neurologic deficit.

DISCUSSION

HIT is a syndrome in which thrombocytopenia, sometimes accompanied by thrombosis, develops after 5 or more days of heparin therapy. Although type I is a direct aggregating effect of heparin on platelets, type-II HIT is an immunologic reaction, involving immunoglobulin G (IgG). These antibodies bind to the antigenic complex formed by heparin and platelet factor-4 (H/PF4), and, in turn, activate the platelets through their Fc receptors.<sup>1-4</sup> This syndrome is a challenge for the cardiac anesthesiologist because it can be precipitated by the heparin used during CPB.<sup>5-7</sup> It can also occur after surgery,<sup>8,9</sup> and in 20% of the cases is associated with arterial or venous thrombosis leading to severe morbidity. Several strategies to prevent or minimize its occurrence have been proposed including the following: blockade of platelet activation by aspirin, dipyridamole, or iloprost before heparin administration<sup>7,10-12;</sup>

Fig 2 Evolution of the intraoperative ACT and platelet count 1, before CPB; 2, after heparin, 3,000 IU, 3, 10 minutes CPB, 4, 35 minutes CPB, 5, after CPB, 6, after protamine, 2,000 IU; 7, after protamine, 1,000 IU; 8, after 12 units of platelets



plasmapheresis before surgery<sup>13</sup>; substitution of anicrod,<sup>14,15</sup> hirudin,<sup>16</sup> or heparinoids<sup>17</sup> for heparin; or use of LMWH.<sup>18,19</sup>

HC-CPB prevents blood from clotting when it contacts the artificial surfaces and can reduce the degree of parenteral anticoagulation required for CPB, reduce complement activation, and simultaneously protect platelets from deterioration.<sup>20-22</sup>

Recent progress has been made in the understanding and management of the HIT syndrome.<sup>1-4</sup> This entity has been divided into two types: Type I, the most frequent, is mild, of early onset, and reversible despite continuation of heparin. It is not associated with thrombosis and appears related to a direct pro-aggregant effect of heparin binding on platelets. Type II affects 0.1% to 3% of patients on heparin, is caused by an immunologic mechanism, and is often associated with severe venous or arterial thrombosis.<sup>23</sup> IgG binds to the antigenic complex formed by heparin and H/PF4, and, in turn, activates the platelets through their Fc receptors.<sup>1-4</sup> Thrombocytopenia occurs within 5 to 15 days of heparin therapy and can occur earlier if sensitization with heparin already exists (Table 1). The antibodies could also react with endothelial cells and possibly provoke an immunologic vascular injury that could predispose the patient to thrombosis.<sup>1,23</sup>

Some tests have been described to confirm the diagnosis of HIT.<sup>6</sup> The platelet aggregation test is highly specific but poorly sensitive with a high incidence of false-positive tests.<sup>24</sup> <sup>14</sup>C-Serotonin release assays are both sensitive and specific but difficult to perform.<sup>25</sup> Only an enzyme-linked immunosorbent assay (ELISA) test with heparin and PF4 reacting with IgG from the serum of susceptible patients could confirm the diagnosis, but ELISA is not performed by all laboratories.<sup>4</sup>

This patient appears to have first presented a type-I HIT with a transient decrease of her platelet count from 278,000 to 177,000/mm<sup>3</sup> (Fig 1). Then, after a 3-day interruption of treatment, the reintroduction of heparin immediately provoked a catastrophic decrease of her platelet level to 34,000/mm<sup>3</sup>, evocative of a type-II HIT. She thereafter presented with postoperative thrombosis of her inferior vena cava and iliac and femoral veins. The transient cerebral ischemic attack that she sustained may not have been a thrombotic complication of HIT. At that time, she had not yet resumed receiving heparin, and thrombocytopenia was not present. Owing to its emergent nature, this case raises some important concerns.

**Table 1. Characteristics of Type I and Type II HIT**

| Type I                                       | Type II  |
|--|--|
| Frequent                                     | Rare   |
| Mild (> 100,000 platelets)                   | Severe (< 35,000 platelets)                        |
| Early (< 5 days)                             | 5-15 days  |
| Without thrombosis                           | Associated with thrombosis                         |
| Reversible during heparin administration     | Reversible with heparin discontinuation            |
| Pro-aggregant effect of heparin on platelets | Immunologic reaction, IgG binding to H/PF4 complex |

Abbreviations: IgG, immunoglobulin G; H/PF4, heparin/platelet factor 4

1. Heparin should have been stopped as soon as the diagnosis was suspected.<sup>6</sup> The cardiologists refused to make this decision because of the expected risk of right coronary artery thrombosis at the level of the intraluminal stents. The heparin infusion was stopped in the operating room, and no heparin was added to the arterial flush. A single bolus dose of 50 IU/kg administered before the CPB was the only heparin source.

2. Plasmapheresis could have been performed preoperatively. This therapy could reduce or remove the offending antibodies from circulation<sup>13</sup> but requires daily apheresis for at least 2 to 3 days preoperatively to obtain normalization of the platelet count.

3. The heparin-coated CPB circuit should not have been used. Thrombocytopenia has been described, associated with the use of heparin-coated catheters.<sup>26,27</sup> Such catheters are coated with a heparin-benzalkonium chloride complex.<sup>5</sup> Elution of heparin from these catheters has been demonstrated.<sup>27</sup> Even this slow release of heparin could be sufficient to cause thrombocytopenia in patients with anti-H/PF4 antibodies.<sup>27</sup> This patient had a triple-lumen catheter in place (Arrow [Reading, PA]) that was not heparin-coated. No pulmonary artery catheter was inserted.

HC-CPBs have some advantages over conventional uncoated circuits, all of them accounting for an increased biocompatibility. The artificial surfaces are less thrombogenic; the inflammatory response to CPB is reduced; and the platelets undergo less activation and functional deterioration.<sup>20-22</sup> Two main types of HC-CPB circuits are manufactured: Duraflo II (Bentley) and Carmeda CBAS (Medtronic). In the first type of circuit, the tubing is coated with unfractionated porcine heparin, whereas in the second, it is coated with a fractionated heparin. The mode of binding of heparin in these circuits is different from the heparin-benzalkonium complex used on the pulmonary artery catheters and is also different in each of the two circuits. An ionic binding is used in the Duraflo II, and a covalent end-point attachment is used in the CBAS. The latter appears to account for a more stable heparin attachment<sup>5</sup> with less release and more available active binding sites for antithrombin III. The CBAS circuit could therefore be the better choice and has been successfully used, along with LMWH, in one case of HIT.<sup>28</sup> Because of the emergency nature of the case and the availability of the circuits, the authors' choice was limited to a conventional circuit with full-dose (300 IU/kg) heparin or a Duraflo II circuit. They relied on a Duraflo circuit, and used low-dose porcine heparin (50 IU/kg). von Segesser<sup>29</sup> showed that when HC-CPB is conducted without systemic heparinization, clotting could occur in the zones of stagnation of blood and during the phases of low pump flow. Because this patient received 3,000 IU of heparin (50 IU/kg) and some heparin could have been released from the tubings during the bypass, this small amount may have been sufficient to aggravate the immunologic reaction, and hence the thrombocytopenia and the development of the postoperative deep venous thrombosis.

4. A heparin substitute should have been used. Some molecules are under clinical trial: dermatan sulfate, Orga-

ran (Nourypharma, The Netherlands), ancrod, and hirudin (Table 2). Recombinant-hirudin is a potent thrombin inhibitor and has been used as the anticoagulant for cardiac operations<sup>16,30</sup> and as a treatment for deep venous thrombosis.<sup>31</sup> It has a short half-life in patients with normal renal function, and its effect could be monitored by means of activated partial thromboplastin time (aPTT) and ACT. However, r-hirudin has been found less effective than heparin in suppressing thrombin formation and fibrinopeptide-A production.<sup>32</sup> No antagonist is available.

Ancrod is a defibrinogenating enzyme purified from viper's venom. It selectively cleaves fibrinopeptide A and has been used as an alternate method of anticoagulation during CPB in HIT patients.<sup>14,15</sup> Its infusion should be begun 12 hours preoperatively, and fibrinogen levels should be measured repetitively. Cryoprecipitates can be administered at the end of the surgery to reverse the effects of ancrod.

Heparinoids like dermatan<sup>33</sup> and Orgaran (danaparoid sodium)<sup>17</sup> could be promising in such cases. Both of them have been used during CPB instead of heparin. Orgaran is said to have good antithrombotic activity with only minimal bleeding-enhancing activity and no effect on platelet function.

5. Use of LMWH during CPB has been proposed<sup>18,19</sup> and also used as an alternative to unfractionated heparin for urgent surgery.<sup>34-38</sup> However, even if patients receiving LMWH appear to have a lower incidence of thrombocytopenia, thrombosis, and antibody formation than those receiving standard heparin,<sup>39</sup> some cases of HIT have been described with the use of LMWH, possibly caused by some cross-reactivity with the heparin-dependent antibodies.<sup>5,6</sup> Moreover, biologic tests are insufficient to guide the therapeutics, and protamine has only a slight antagonistic effect. The authors relied on nadroparin (Fraxiparin [Sanofi-Winthrop, Bondeville, France] 0.6 mL BID) for the treatment of the postoperative thrombosis in the present patient. This, along with concomitant warfarin therapy and heparin discontinuation, allowed restoration of the platelet count to normal values in 3 days (Fig 1). In retrospect, it would have been judicious to test the absence of cross-reactivity by aggregation tests before its administration.

6. The platelets should have been protected with iloprost, aspirin, or dipyridamole<sup>7</sup> before conventional CPB under a full dose of unfractionated heparin. This patient had not received aspirin for the last 10 preoperative days, and therefore a protective effect could not be expected. Successful use of the prostacyclin analog iloprost has often

been described,<sup>10,11</sup> but this drug was not available. Prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) does not seem to be as effective as iloprost in contrast to prostaglandin E<sub>2</sub> that has been used as a substitute.<sup>12</sup> However, these three drugs cause profound hypotension necessitating the concomitant infusion of vasopressors.

7. Platelets should not have been administered after protamine administration: They could have acted like "oil on the fire" and have been responsible for the observed postoperative thrombosis. However, their administration was deemed necessary because of continuing bleeding after protamine administration despite normalization of the ACT. Moreover, they were administered only after complete heparin reversal with protamine; therefore, no more heparin was circulating to form an immune complex able to react with the patient's IgG. Recently, Boshkov et al found a strong association between venous thrombosis and recent surgery of any type.<sup>23</sup> They considered HIT syndrome as a procoagulant disorder able to provoke thrombosis at sites of preexisting vascular pathology. The observed venous thrombosis can be either the consequence of the surgery or a complication of a low output state with venous stasis, as well as the consequence of the platelet infusion itself.

8. Immunoglobulins should have been administered postoperatively. Their administration has been described in HIT, along with platelet transfusion, based on their efficacy in restoring platelet count in immune thrombocytopenic purpura.<sup>40</sup> In these two syndromes, immunoglobulin possibly works by blocking the Fc receptor.

#### COMMENTARY\*

The case presented illustrates many of the typical management problems associated with patients diagnosed with HIT who are undergoing surgery requiring heparinization.

First, the question of how the diagnosis of HIT was made and in fact whether the patient has HIT should be ascertained. The diagnosis of HIT may be obscured by the presence of other medical conditions or medications that may cause thrombocytopenia. Often, as presented in this case, laboratory tests such as <sup>14</sup>C-serotonin release assay and heparin/PF4-IgG ELISA are simply not available, and clinical presentation is the sole basis for diagnosis. Either a decrease in platelet count of 30% of preheparin level or an unexpected thromboembolic event in a patient receiving heparin warrants consideration of the diagnosis of HIT.

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Table 2. Comparison of Heparin Substitutes for Use as Anticoagulants During CPB

|                    | LMWH             | Hirudin      | Ancrod  | Dermatan                            |
|--------------------|------------------|--------------|---|-------------------------------------|
| Availability       | (+)              | (-)          | (-)   | (-)                                 |
| Onset              | Immediate        | Immediate    | 12 h  | Immediate                           |
| Tests of efficacy  | Anti Xa activity | TT, PT, APTT | Plasma fibrinogen concentration<br>ACT ?-APTT | Anti-IIa activity, anti-Xa activity |
| Antidote           | (Protamine)      | (-)          | Cryoprecipitate                               | (-)                                 |
| Duration of action | 24 h             | 30 min       |   | 40 min                              |

Abbreviations: LMWH, low-molecular-weight heparin; ACT, activated coagulation time; APTT, activated partial thromboplastin time; PT, prothrombin time, TT, thrombin time

Sheridan et al<sup>25</sup> have classified the likelihood of HIT based on the clinical setting. If thrombocytopenia develops in a patient receiving heparin and other causes are excluded, if thrombocytopenia recurs on challenge with heparin, or if acute arterial thrombosis occurs in the absence of other thrombotic factors, a diagnosis of "definite" HIT is made. The likelihood is designated "probable" if thrombocytopenia occurs in a patient receiving heparin and other causes are excluded; "possible" if these two criteria are present but the thrombocytopenia either resolves with continued heparin administration or fails to recur with a heparin challenge; or "unlikely" if another cause of thrombocytopenia is found or it fails to resolve on discontinuing the heparin.

Criteria that may also be present when the diagnosis of HIT is made are shown in Table 3. However, these criteria are not necessarily all met before the diagnosis is made. An abrupt decline in platelet concentration on reexposure to heparin as occurred in this case strongly supports the diagnosis of HIT. However, it should be noted that HIT can occur in the absence of a decrease in platelet count,<sup>41</sup> and occasionally, an unexpected thromboembolic event in a patient receiving heparin may be the first sign of HIT. In light of this, it is tempting to speculate that the cause of the patient's ischemia may have been heparin-induced platelet aggregation in the right coronary artery distribution.

Once the diagnosis has been established, choosing an appropriate management plan can be a challenge. As in many immune-mediated diseases, the presence of even trace amounts of antigen or antigen/hapten may be capable of inducing immunoglobulin-mediated reactions. Therefore, all heparin administration should be discontinued including the use of subcutaneous heparin. Saline should be substituted for heparin in pressure monitoring tubing and intravenous flush solutions, and heparin-bonded catheters should be removed.

If surgery requiring the use of heparin is not urgent, it should be postponed. Discontinuing heparin will result in a decrease in heparin-dependent antiplatelet antibodies over several weeks. Unfortunately, it is not possible to reliably predict how long antiplatelet antibodies will remain in the circulation. Patients rechallenged with heparin up to 2 months after recovery have become thrombocytopenic.<sup>42</sup> Interestingly, although plasma heparin-dependent IgG diminishes rapidly over 2 months after cessation of heparin exposure, platelets of sensitized patients are still capable of activation and aggregation, suggesting a major portion of the heparin-dependent antibody may be membrane bound.<sup>42</sup>

**Table 3. Criteria That Are Usually Present When a Diagnosis of HIT Is Made**

|   |   |
|---|---|
| 1 | The patient was not thrombocytopenic before heparin administration  |
| 2 | A platelet count of less than 150,000/ $\mu$ L is determined on two separate occasions 24 hours apart during heparin therapy  |
| 3 | Other causes of thrombocytopenia are excluded   |
| 4 | A thrombotic event (venous or arterial) distinct from that for which the heparin was administered occurs 2 or more days after initiation of heparin administration. |

In vitro tests of heparin-induced platelet aggregation and activation should follow and will gradually become negative.<sup>43</sup> Several patients in whom surgery was delayed until platelet aggregation studies were negative underwent uneventful heparinization and CPB.<sup>43</sup>

When surgery cannot be postponed as in this case, the choice of management is between the use of heparin with concomitant administration of agents that prevent heparin-induced platelet activation (for example iloprost, a PGI<sub>2</sub> analog, or PGE<sub>1</sub>), LMWH preparations, ancrod, or other nonheparin anticoagulation agents

The authors' use of a heparin-bonded CPB circuit is a novel approach, and they are to be congratulated on their creativity in a desperate circumstance. However, it also raises important concerns. Although the use of heparin-bonded CPB circuits has been shown to produce better platelet preservation,<sup>44</sup> the presence of a heparin-dependent IgG in patients with HIT complicates the scenario. The Duraflo II CPB circuit is manufactured by a process called "universal bonding" whereby unfractionated heparin molecules are modified and attached to the circuit using a proprietary formulation.<sup>45</sup> Although the stability of the heparin bonding on the Duraflo II circuit is superior to other heparin-bonded circuits, leaching of bound heparin from the circuit into the circulation still occurs<sup>45</sup> and could precipitate platelet activation and aggregation in patients with HIT. It is also likely that heparin that is bound on the circuit can interact with PF4 to form the reactive antigen on the platelet surface. The presence of a heparin-dependent IgG in patients with HIT would allow binding of this complex with subsequent activation of platelets. Perhaps even more important, systemic heparin administration is still required when using a heparin-bonded CPB circuit. Fifty IU heparin/kg is very likely to precipitate HIT in susceptible patients with specific IgG.

The early postoperative bleeding and extensive thrombosis that occurred in the patient presented is not an unexpected outcome in patients with HIT who are exposed to heparin without the concomitant use of agents that prevent platelet activation. This unfortunate outcome might have been prevented by the concomitant use of prostaglandin E<sub>1</sub> from immediately after induction of anesthesia through heparin neutralization and chest closure. PGE<sub>1</sub>, like PGI<sub>2</sub>, inhibits platelet activation and aggregation by increasing intracellular concentrations of platelet cyclic adenosine monophosphate.<sup>46</sup> Hypotension associated with the use of prostaglandins can be prevented by simultaneous infusion of vasopressors such as phenylephrine.

Alternatively, the use of other management pathways such as ancrod, LMWHs, antiplatelet agents, or hirudin can be considered. Unfortunately, some of these agents may be unavailable (hirudin), are of limited efficacy (LMWH, antiplatelet agents), or are associated with severe adverse side effects (ancrod). The small number of patients presenting with HIT has also contributed to the lack of controlled trials in this area. In fact, iloprost, one of the most promising agents for managing patients with HIT, was

denied approval by the Food and Drug Administration citing lack of control trials (personal communication, Berlex Laboratories, Wayne, NJ).

Argatroban, a small molecular direct thrombin inhibitor

that rapidly, selectively, and reversibly binds the catalytic site of thrombin, is currently undergoing clinical trials and may be available soon for the management of patients with HIT.<sup>47</sup>

#### REFERENCES

1. Aster RH: Heparin-induced thrombocytopenia and thrombosis. *N Engl J Med* 332:1374-1376, 1995 (editorial)
2. Kelton JG, Smith JW, Warkentin TE, et al: Immunoglobulin G from patients with heparin-induced thrombocytopenia binds to a complex of heparin and platelet factor 4. *Blood* 83:3232-3239, 1994
3. Gremacher A, Potzsch B, Amiral J, et al: Heparin-associated thrombocytopenia. Isolation of the antibody and characterization of a multimolecular PF4-heparin complex as the major antigen. *Thromb Haemost* 71:247-251, 1994
4. Amiral J, Bridey F, Wolf M, et al: Antibodies to macromolecular platelet factor 4-heparin complexes in heparin-induced thrombocytopenia. A study of 44 cases. *Thromb Haemost* 73:21-28, 1995
5. Gravlee GP: Anticoagulation for cardiopulmonary bypass. In Gravlee GP, Davis RF, Utley JR (eds): *Cardiopulmonary Bypass. Principles, and Practice*. Baltimore, Williams & Wilkins, 1993, pp 364-369
6. Singer RL, Mannion JD, Bauer TL, et al: Complications from heparin-induced thrombocytopenia in patients undergoing cardiopulmonary bypass. *Chest* 104:1436-1440, 1993
7. Palmer Smith J, Walls JT, Muscato MS, et al: Extracorporeal circulation in a patient with heparin-induced thrombocytopenia. *Anesthesiology* 62:363-365, 1985
8. Munver R, Schulman IC, Wolf DJ, et al: Heparin-induced thrombocytopenia and thrombosis: presentation after cardiopulmonary bypass. *Ann Thorac Surg* 58:1764-1766, 1994
9. Kalangos A, Relland JY, Massonet-Castel S, et al: Heparin-induced thrombocytopenia and thrombosis following open heart surgery. *Eur J Cardiothorac Surg* 8:199-203, 1994
10. Kraenzler EJ, Starr NJ: Heparin-associated thrombocytopenia: Management of patients for open heart surgery. Case reports describing the use of iloprost. *Anesthesiology* 69:964-967, 1988
11. Corbeau JJ, Jacob JP, Moreau X, et al: Iloprost (Ilomedine) et circulation extracorporelle avec héparinisation conventionnelle chez un patient ayant une thrombocytopenie à l'héparine. *Ann Fr Anesth Réanim* 12:55-59, 1993
12. Shorten G, Comunale ME, Johnson RG: Management of cardiopulmonary bypass in a patient with heparin-induced thrombocytopenia using prostaglandin E1 and aspirin. *J Cardiothorac Vasc Anesth* 8:556-558, 1994
13. Brady J, Riccio JA, Yumen OH, et al: Plasmapheresis: A therapeutic option in the management of heparin-associated thrombocytopenia with thrombosis. *Am J Clin Pathol* 96:394-397, 1991
14. O Yurvatn AH, Laub GW, Southgate TJ, et al: Heparinless cardiopulmonary bypass with anicord. *Ann Thorac Surg* 57:1656-1658, 1994
15. Spiekermann BF, Lake CL, Rich GF, et al: Normal activated clotting time despite adequate anticoagulation with anicord in a patient with heparin-associated thrombocytopenia and thrombosis undergoing cardiopulmonary bypass. *Anesthesiology* 80:686-688, 1994
16. Riess FC, Lower C, Seelg C, et al: Recombinant hirudin as a new anticoagulant during cardiac operations instead of heparin. Successful for aortic valve replacement in man. *J Thorac Cardiovasc Surg* 110:265-267, 1995
17. Chong BH, Mangnani HN: Orgaran in heparin-induced thrombocytopenia. *Haemostasis* 22:85-91, 1992
18. Robitaille D, Leclerc JR, Laberge R, et al: Cardiopulmonary bypass with a low-molecular-weight heparin fraction (enoxaparin) in a patient with a history of heparin-associated thrombocytopenia. *J Thorac Cardiovasc Surg* 103:597-599, 1992
19. Altés A, Martino R, Garí M, et al: Heparin-induced thrombocytopenia and heart operation. Management with tedelparin. *Ann Thorac Surg* 59:509-511, 1995
20. Videm V, Mollnes TE, Garred P, et al: Biocompatibility of extracorporeal circulation. In vitro comparison of heparin-coated and uncoated oxygenator circuits. *J Thorac Cardiovasc Surg* 101:654-660, 1991
21. Fosse E, Moen O, Johnson E, et al: Reduced complement and granulocyte activation with heparin-coated cardiopulmonary bypass. *Ann Thorac Surg* 58:472-477, 1994
22. Svennevig JL, Geiran OR, Karlsten H, et al: Complement activation during extracorporeal circulation. In vitro comparison of Duraflo II heparin-coated and uncoated oxygenator circuits. *J Thorac Cardiovasc Surg* 106:466-472, 1993
23. Boshkov LK, Warkentin TE, Hayward CP, et al: Heparin-induced thrombocytopenia and thrombosis: Clinical and laboratory studies. *Br J Haematol* 84:322-328, 1993
24. Kelton JG, Sheridan D, Brain H, et al: Clinical usefulness of testing for a heparin-dependent platelet-aggregating factor in patients with suspected heparin-associated thrombocytopenia. *J Lab Clin Med* 103:606-612, 1984
25. Sheridan D, Carter C, Kelton JG: A diagnostic test for heparin-induced thrombocytopenia. *Blood* 67:27-30, 1986
26. Moberg PQ, Geary VM, Sheikh FM: Heparin-induced thrombocytopenia: A possible complication of heparin-coated pulmonary artery catheters. *J Cardiothorac Anesth* 4:226-228, 1990
27. Laster J, Silver D: Heparin-coated catheters and heparin-induced thrombocytopenia. *J Vasc Surg* 7:667-672, 1988
28. Couyant MA, Beemer GH, Tatoulis J, et al: A proposed protocol for the management of cardiopulmonary bypass for patients with heparin-induced thrombocytopenia syndrome. *Austras Perfusion Soc J* 1:33-36, 1992
29. von Segesser LK, Weiss BM, Pasic M, et al: Risk and benefit of low systemic heparinization during open heart operations. *Ann Thorac Surg* 58:391-398, 1994
30. Walenga JM, Bakhos M, Messmore HL, et al: Potential use of recombinant Hirudin as anticoagulation in a cardiopulmonary bypass model. *Ann Thorac Surg* 51:271-277, 1991
31. Nand S: Hirudin therapy for heparin-associated thrombocytopenia and deep venous thrombosis. *Am J Hematol* 43:310-311, 1993
32. Edmunds LH Jr: HIT, HITT, and desulfatohirudin. Look before you leap. *J Thorac Cardiovasc Surg* 110:1-3, 1995 (editorial)
33. Brister SJ, Buchanan MR: Heparinless cardiopulmonary bypass revisited: A newer strategy to avoid heparin-related bleeding using dermatan sulfate. *J Cardiothorac Vasc Anesth* 9:317-321, 1995
34. Gouault-Heilmann M, Huet Y, Contant G, et al: Cardiopulmonary bypass with a low-molecular-weight heparin fraction. *Lancet* II 1374, 1983 (letter)
35. Massonet-Castel S, Pelissier E, Dreyfus G, et al: Low-molecular-weight heparin in extracorporeal circulation. *Lancet* I 1182-1183, 1984 (letter)
36. Roussi JH, Houbouyan LL, Goguel AF: Use of low-molecular-weight heparin in heparin-induced thrombocytopenia with thrombotic complications. *Lancet* I.1183, 1984 (letter)

37. Dreyfus G, Massonnet-Castel S, Pélissier E, et al. Etude d'une héparine de bas poids moléculaire au cours des circulations extracorporelles. Premières applications cliniques. *Arch Mal Coeur* 13:1851-1857, 1986
38. Drakos P, Uziely B, Nagler A, et al: Successful administration of low molecular weight heparin in a patient with heparin-induced thrombocytopenia and coumarin-induced skin necrosis. *Haemostasis* 23:259-262, 1993
39. Warkentin TE, Levine MN, Hirsh J, et al: Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 332:1330-1335, 1995
40. Frame JN, Mulvey KP, Phares JC, et al: Correction of severe heparin-associated thrombocytopenia with intravenous immunoglobulin. *Ann Intern Med* 111 946-947, 1989
41. Kappa JR, Fisher CA, Berkowitz HD, et al: Heparin-induced platelet activation in sixteen surgical patients: Diagnosis and management. *J Vasc Surg* 5 101-109, 1987
42. Kapsch DN, Adelstein EH, Rhodes GR, et al: Heparin-induced thrombocytopenia, thrombosis, and hemorrhage. *Surgery* 86:148-155, 1979
43. Olinger GN, Hussey CV, Olive JA: Cardiopulmonary bypass for patients with previously documented heparin-induced platelet aggregation. *J Thorac Cardiovasc Surg* 87:673-677, 1984
44. Thelin S, Bagge L, Hultman J, et al: Heparin-coated cardiopulmonary bypass circuits reduce blood cell trauma. Experiments in the pig. *Eur J Cardiothorac Surg* 5:486-491, 1991
45. Hsu L-C: Heparin coating of bypass circuits. Principles of heparin-coating techniques. *Perfusion* 6:209-219, 1991
46. Gorman RR, Bunting S, Miller OV: Modulation of human platelet adenylate cyclase by prostacyclin (PGX). *Prostaglandins* 13:377-388, 1977
47. Schwarz RP, Becker JC, Brooks RL, et al: The preclinical and clinical pharmacology of NOVASTAN (Argatroban). A small-molecule, direct thrombin inhibitor. *J Clin Appl Thromb Hemo* (accepted for publication)