

CASE REPORTS

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Emergent Cardiopulmonary Bypass in Five Patients with Heparin-induced Thrombocytopenia Type II Employing Recombinant Hirudin

Andreas Koster, M.D.,* Hermann Kuppe, M.D., Ph.D.,† Roland Hetzer, M.D., Ph.D.,‡ Ralf Sodan, M.D.,§ George J. Crystal, Ph.D.,|| Friedrich Mertzluft, M.D., Ph.D.#

HEPARIN-INDUCED thrombocytopenia (HIT) type II is a life-threatening complication of heparin therapy that most often occurs after approximately 5-10 days of exposure to heparin.^{1,2,3} Heparin-induced thrombocytopenia type II is produced by an antiheparin immunoglobulin (Ig) G in plasma that binds to repeating antigenic determinants of heparin and to the platelet surface epitopes (usually platelet factor 4 plus heparin), which reacts with the Fc receptors.³ After IgG binding, platelets aggregate and become activated, producing disseminated thrombosis and embolism and profound thrombocytopenia.^{1,2} In patients undergoing cardiac surgery, the incidence of HIT II is estimated to be 1.3%,⁴ although the appearance of antibodies (detected by the platelet factor 4 enzyme-linked immunosorbent assay) is more frequent.⁵ If HIT II develops after cardiac

surgery, thromboembolic complications are evident in 51% of patients, with a lethality of 37%.⁴ Therefore, it is advisable that heparin not be administered in any form (e.g., heparin-containing solutions and agents and heparin-bonded materials) to patients with documented or suspected HIT II. This poses a problem in patients being prepared for cardiopulmonary bypass (CPB), for which systemic anticoagulation is necessary. If the indication for CPB is not emergent, the patient may begin antiaggregative therapy, e.g., aspirin, dipyridamole, prostacyclin, and anticoagulation may be instituted intraoperatively with either a defibrogenating agent (anocrod) or, if the risk for immunologic cross-reactions with heparin-induced antibodies⁶ has been excluded, a heparinoid danaparoid sodium or a low-molecular-weight heparin. In addition, removal of plasma antibodies (e.g. plasmapheresis) may be considered.⁷ The aforementioned methods for anticoagulation are not feasible in patients with HIT II requiring emergent CPB. One alternative method is the use of the antithrombin-III-independent antithrombin, (e.g., hirudin and hirulog).^{8,9,10} Although this method has been used successfully in patients undergoing elective CPB,^{8,9,10} it remains to be evaluated in patients undergoing emergency CPB.

We report herein the management of five patients with documented HIT II coming for emergency cardiac surgery with CPB in which anticoagulation was accomplished using recombinant hirudin (r-hirudin).

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The study consisted of five patients requiring emergent CPB: three patients required coronary artery bypass grafting, one patient required aortic valve replacement plus reoperation for coronary artery bypass grafting, and the fifth patient was scheduled for aortic valve prosthesis (see table 1). In three patients (patients 1, 4, and 5 [table 1]), HIT II was indicated by (1) previous thrombocytopenia, as evidenced by a platelet count $< 100 \times 10^3/l$ or by a decrease in platelet count after exposure to heparin, and (2) a positive result in the heparin-induced platelet aggregation assay, with a minimum of three of four test chambers. In patients 1 and 4 (table 1), a positive result for the platelet factor 4 enzyme-linked immunosorbent assay

* Staff Anesthesiologist, Department of Anesthesiology, German Heart Center, Berlin, Germany.

† Professor, Chair, Department of Anesthesiology, German Heart Center, Berlin, Germany.

‡ Professor, Chair, Department of Cardiac Surgery, German Heart Center, Berlin, Germany.

§ Staff Surgeon, Department of Cardiac Surgery, German Heart Center, Berlin, Germany.

|| Director of Research, Department of Anesthesiology, Illinois Masonic Medical Center; Professor, Departments of Anesthesiology and of Physiology and Biophysics, University of Illinois College of Medicine, Chicago, Illinois.

Professor, Department of Anesthesiology and Intensive Care Medicine, University of Homburg-Saar, Homburg-Saar, Germany.

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Address reprint requests to Dr. Mertzluft: Klinik fuer Anaesthesiologie und Intensivmedizin, Universitaetskliniken des Saarlandes, D-66421 Homburg-Saar, Germany. Address electronic mail to: mertzluft@t-online.de

Key words: Antithrombin-III-independent antithrombin; ecarin clotting time; heparinoid cross-reaction; PF ELISA; platelet aggregation assay; platelet count.

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Table 1. Demographic and Clinical Data: Five Patients with Heparin-induced Thrombocytopenia Type II (HIT II) Scheduled for Emergent Cardiopulmonary Bypass; Intraoperative Systemic Anticoagulation with r-Hirudin [Accepted Range $\geq 4 \mu\text{g}$ r-Hirudin/ml Blood \equiv Ecarin Clotting Time (ECT) ≥ 400 s]

Demographic and Clinical Data, Symptoms, Operation	Conditions on Admittance, History of Present Illness	Perioperative Recording of Findings
Patient 1 F, 48 yr, 72 kg BW, 165 cm BH, NYHA IV, ASA III, 3-vessel coronary disease Unstable angina, unremitting chest pain, preinfarction: CABG (LIMA + RCA + RCX), 2nd day after admission	On admission: platelets $120 \times 10^3/\text{l}$ following 3 days of treatment with unfractionated heparin in an external hospital, no thromboembolism HIT II verified by positive HIPAA and PF 4 ELISA Blood loss = 600 ml postoperatively, no transfusions Cross-reactivity to danaparoid sodium (HIPAA)	Preop 10 mg r-hirudin bolus + infusion (aPTT ≈ 80 s) Duration of CPB = 75 min aPTT ≈ 65 s over 4 h after CPB, postop 500 mg aspirin/day, discharged uneventful after 3 days
Patient 2 M, 63 yr, 98 kg BW, 189 cm BH, NYHA IV, ASA III, 2-vessel coronary disease Unstable angina, unremitting chest pain, ST segment elevations: CABG (LAD + RCA), 1st day after admission	Known history of HIT II (6 wk earlier) verified by a positive HIPAA with cross-reaction to danaparoid sodium (external hospital) On admission: no thromboembolism, negative HIPAA, positive PF 4 ELISA, platelet count = $100 \times 10^3/\text{l}$	Preop warfarin (PT $\approx 20\%$, INR 1.5–2.5) Duration of CPB = 65 min Intraoperatively 6 units FFP Blood loss = 400 ml postop, no transfusions aPTT ≈ 87 s over 4 h after CPB, postop 500 mg aspirin/day, discharged uneventful after 3 days
Patient 3 F, 81 yr, 48 kg BW, 154 cm BH, NYHA IV, ASA III, 3-vessel coronary disease Unstable angina, unremitting chest pain, ST segment elevations: CABG (LAD + RCA), 1st day after admission	Platelets 3 wk before admission $350 \times 10^3/\text{l}$ (patient history) No history of thromboembolism On admission: platelets $130 \times 10^3/\text{l}$, HIPAA negative, PF 4 ELISA positive, no cross-reaction to danaparoid sodium (HIPAA)	No preop anticoagulation (PT $\approx 57\%$, INR ≈ 2.5) Duration of CPB = 65 min 2 units of RBC and 4 units of FFP intraop Blood loss = 200 ml postop, no further transfusions aPTT ≈ 52 s over 4 h after CPB, postop warfarin (PT $\approx 20\%$), discharged uneventful after 4 days
Patient 4 M, 74 yr, 98 kg BW, 185 cm BH, NYHA IV, ASA III, aortic stenosis (Δp 110 mmHg, EF 30%), 50% stenosis of left main coronary artery, aneurysm of the descending aorta, history of multiple vascular operations Unremaining chest pain, acute myocardial insufficiency: re-CABG (LAD + RCA) + AVR, 1st day after admission	History of HIT following left carotid thromboendarterectomy in external hospital [verified by positive HIPAA and PF 4 ELISA, proved cross-reaction to danaparoid sodium (HIPAA)] On admission: platelets = $89 \times 10^3/\text{l}$ (no former data on platelets)	Preop warfarin (PT $\approx 25\%$, INR 1.5–2.5) Duration of CPB = 113 min Intraop 2 RBC units, 8 units FFP, 8 units platelets Blood loss = 800 ml postop, no further transfusions aPTT ≈ 89 s over 4 h after CPB, postop warfarin (PT $\approx 20\%$), discharged uneventful after 7 days
Patient 5 F, 47 yr, 51 kg BW, 163 cm BH, NYHA IV, ASA IV, septic endocarditis, acute infection of the aortic valve, $\text{C}_2\text{H}_5\text{OH}$ abuse, liver cirrhosis, history of generalized oozing Acute myocardial insufficiency: AVP, 1st day after admission	Exposure to heparin 4 days earlier, platelets $240 \times 10^3/\text{l}$ (data from external hospital) On admission: platelets = $85 \times 10^3/\text{l}$, increase to $150 \times 10^3/\text{l}$ after 24 h of application of danaparoid sodium	Preop danaparoid sodium (2,500 U bolus + infusion of 150–400 U/h: anti-Xa levels ≈ 0.5 – 0.8 U/ml) Duration of CPB = 75 min Intraop 10 FFP units and 8 units of platelets Blood loss = 1,700 ml postop; 6 RBC units aPTT 60 min after CPB ≈ 185 s, then ∞ Renal failure and exitus in catecholamine refractory generalized multiple organ failure after 6 h

HIPAA = heparin-induced platelet aggregation assay; PF 4 ELISA = platelet factor 4 enzyme-linked immunosorbent assay; CABG = coronary artery bypass graft; LIMA = thoracic internal artery; RCA = right coronary artery; RCX = circumflex branch of the left coronary artery; LAD = left anterior descending; AVP = aortic valve prosthesis; AVR = aortic valve replacement; EF = ejection fraction; PT = prothrombin time (Quick's time); aPTT = activated partial thromboplastin time; INR = international normalized ratio (= prothrombin ratio^{ISI}); BW = body weight; intraop = intraoperative; Preop = preoperative; CPB = cardiopulmonary bypass; postop = postoperative; FFP = fresh frozen plasma; RBC = red blood cells.

provided further evidence for HIT II. The two other patients (patients 2 and 3 [table 1]) had recent histories of thrombocytopenia or thromboembolism after treatment with heparin approximately 3 weeks before surgery. Heparin-induced thrombocytopenia type II was confirmed by a positive result for the platelet factor 4 enzyme-linked immunosorbent assay. Although results of the heparin-induced platelet aggregation assay were negative in patients 2 and 3, this was probably because antibody concentration had decreased by the time the measurement was obtained.

After implementation of routine noninvasive monitors and establishment of adequate arterial oxygenation ($\text{PaO}_2 \geq 350$ mmHg), peripheral venous access was obtained in both forearms (14 G). Non-heparin-bonded instrumentation was used, including a left radial arterial line (20 G), a trilumen catheter with a gate (8.5 G), and a Swan-Ganz (Abbott, Wiesbaden, Germany) catheter *via* the right internal jugular vein. Induction of anesthesia was accomplished using a combination of agents: midazolam: 0.07–0.09 mg/kg; sufentanil: 0.8–1.2 $\mu\text{g}/\text{kg}$; etomidate: 0.14–0.22 mg/kg; and pancuronium bromide: 8 mg. The patients were trache-

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ally intubated (7.5–8 Ch) and a stomach tube (16 Ch), an esophageal temperature probe, and a urinary catheter (16 Ch) were placed. Anesthesia was maintained using propofol ($100 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$), sufentanil ($0.05 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$), and pancuronium bromide (supplemented on demand). Aprotinin was used according to the Hammersmith regimen, and dopamine ($2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) was administered with the onset of CPB. The operation was performed while the patient was in cardioplegic cardiac arrest with moderate systemic hypothermia (32°C). Times for CPB varied from 65–113 min (table 1).

Systemic anticoagulation during CPB was performed with r-hirudin (Refludan; Hoechst, Frankfurt, Germany). The dose for r-hirudin consisted of a 0.2-mg/kg bolus added to the prime and a 0.25-mg/kg intravenous bolus followed by a continuous infusion of 0.5 mg/min (modified Pötzsch⁸ regimen) begun 5 min before cannulation for CPB. Adequacy of anticoagulation with r-hirudin was determined using the ecarin clotting time (ECT),^{8,10} which was monitored on-line with the Thrombolytic Assessment System, (Cardiovascular Diagnostics, Raleigh, NC); an r-hirudin concentration of $\geq 4 \mu\text{g/ml}$ of citrated whole blood obtained 5 min after the r-hirudin administration was considered sufficient to start CPB.^{8,9} According to previously performed calibration curves, this concentration for r-hirudin corresponded to an ECT of approximately 400 s. If anticoagulation was not achieved initially, additional boluses of r-hirudin were administered.

During CPB, ECT was determined at 5-min intervals and maintained in the range of $\geq 4 \mu\text{g}$ r-hirudin/ml blood by adjustment of the r-hirudin infusion rate.

After CPB, forced diuresis was initiated with 200 ml mannitol (20%) and furosemide (40 mg). The blood obtained from the heart-lung machine (modified hemofiltration, maximum volume 2 l) was processed, and the derived packed erythrocytes were retransfused (C.A.T.S., Fresenius, Bad Homburg, Germany).

The decision to transfuse erythrocytes, fresh frozen plasma, and platelets intraoperatively was based on clinical demands and departmental standards. All patients recovered uneventfully after CPB. Recovery of hemostasis varied from patient to patient. The values for the activated partial thromboplastin time varied from 52–87 s over 4 h after CPB (table 1). The infusion rate for r-hirudin was augmented during the immediate post-CPB period to provide time for antiaggregative therapy (aspirin or warfarin) to take effect. Patients 1, 2, 3, and 4 (table 1) recovered completely and were discharged uneventfully within 3 to 7 days. However, septic shock (refractory to catecholamine treatment) combined with multiple organ failure and disseminated intravascular coagulation developed in patient 5 during the immediate postoperative period, and the patient died 6 h after the operation.

Discussion

The current study provides evidence that r-hirudin may be a safe and effective alternative for systemic anticoagulation in patients with documented or suspected HIT II in whom cardiac surgery is emergent. The four main advantages of this method *vis-à-vis* the other options are as follows: (1) it avoids the risk of heparin-induced HIT II; (2) it can be instituted rapidly during emergency conditions; (3) its half-life is comparably short; and (4) it can be monitored adequately.

Hirudin and hirulog are potent antithrombins that do not necessitate cofactors. Originally purified from leech saliva,

hirudin is produced as a recombinant product (r-hirudin; Refludan, Hoechst, Frankfurt, Germany). This agent is a highly specific thrombin inhibitor with little effect on other serine proteases.¹⁰ In humans, the elimination half-life is 30–60 min (provided that renal function is normal), the volume of distribution is 9–17 l, clearance is 170–2,230 ml/min, and the anticoagulant effect lasts approximately for only 40 min.^{7,8,10} Furthermore, there is no immunologic cross-reaction with heparin-induced antibodies, and a reversal agent (r-Meizothrombin) has been developed.¹¹ The anticoagulating effect of r-hirudin may be explained by inhibitory actions on platelet aggregation and on thrombus growth and organization.¹² The drug has been effectively used for low-dose anticoagulation,¹³ long-term dialysis¹⁴ in patients with HIT II, and acute anticoagulation in patients with actual heparin exposition and concomitant thrombocytopenia.¹³ Despite its advantages, and promising results in elective CPB,^{8,9} r-hirudin is not used widespread in CPB because it necessitates monitoring ECT instead of activated partial thromboplastin time and ACT.⁸ This technical capability has not been widely available until recently. If provided within or nearby the operating room, continuous ECT monitoring could allow minute-by-minute modulation of the r-hirudin dose (and thus plasma concentration), which could improve the effectiveness of the technique and maximize patient safety. This appears to be possible using point-of-care monitoring of ECT. However, such on-line monitoring of the ECT is allowed only for investigational use. The clinical application of this technique on a routine basis will necessitate additional studies, both *in vitro* and *in vivo*, confirming that it meets the same laboratory standards as the techniques associated with other Thrombolytic Assessment System parameters, (e.g., activated partial thromboplastin time).¹⁵

We conclude that r-hirudin can be used safely and effectively as an anticoagulant in patients with HIT II undergoing emergent cardiac surgery. R-hirudin has an immediate onset and a half-life of less than 1 h. Its elimination can be augmented by hemofiltration, which is particularly relevant in cases of impaired renal function. Furthermore, the level of r-hirudin plasma levels can be evaluated by the monitoring of ECT, and the infusion rate can be adjusted accordingly. Finally, r-Meizothrombin can be used as a reversal agent, which should improve the safety of high-dose r-hirudin.

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Severe Hypercapnia Induced by Acute Dissecting Aortic Aneurysm

François Lenfant, M.D.,* Marie-Laure Cittanova, M.D., Ph.D.,† Jean-Pierre Goarin, M.D.,‡ Bruno Riou, M.D., Ph.D.§

THE complications of acute dissecting aortic aneurysm include external rupture with fatal hemorrhage, aortic regurgitation, occlusion of the coronary arteries or other

major branches of the aorta, and cardiac tamponade. In very few cases, the aneurysm may induce compression of the right pulmonary artery.¹⁻⁴ In these situations, diagnosis may be difficult because the clinical picture resembles a pulmonary embolism.¹ We report the case of a patient in whom severe hypercapnia developed because of a dissecting aortic aneurysm responsible for a compression of both the right pulmonary artery and the left mainstem bronchus.

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A 42-yr-old man was admitted to hospital for acute ischemia of the right lower limb. Ten years previously, this patient underwent aortic valvular replacement for regurgitation. He was treated with acenocoumarol and flecainide. Preanesthesia clinical assessment confirmed the diagnosis of lower limb ischemia. Cardiac and pulmonary status were normal, and results of electrocardiogram were normal. Prothrombin time was less than 10% of control. Emergency surgery was begun 30 min after admission. Induction of anesthesia was performed using etomidate sufentanil, and muscular relaxation was obtained using atra-

* Assistant Professor, Department of Anesthesiology, Hôpital Général, Dijon.

† Assistant Professor, Department of Anesthesiology, Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris.

‡ Staff Anesthesiologist, Department of Anesthesiology, Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris.

§ Professor of Anesthesiology, Department of Anesthesiology, Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris.

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Address reprint requests to: Dr. Lenfant, Département d'Anesthésie-Réanimation, Hôpital Général, 3 rue du Faubourg Raines, 21033 Dijon, France. Address electronic mail to: lenfant.vaillard@hol.fr

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