BRIEF COMMUNICATIONS

RECOMBINANT HIRUDIN AS A NEW ANTICOAGULANT DURING CARDIAC OPERATIONS INSTEAD OF HEPARIN: SUCCESSFUL FOR AORTIC VALVE REPLACEMENT IN MAN

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Natural hirudin was isolated from the medicinal leech in the 1950s and characterized as a potent and specific thrombin inhibitor. Ever since recombinant hirudin (r-hirudin) was produced in sufficient quantities, the efficacy of this cofactor-independent anticoagulant has been shown in several studies and clinical investigations.[1] Recent experiments in the dog and pig model have demonstrated that r-hirudin is a safe and efficient anticoagulant for cardiac operations in which cardiopulmonary bypass (CPB) is used.[2, 3] Furthermore, r-hirudin has already been effectively used as an anticoagulant during CPB in a patient with chronic pulmonary embolism.[4] As a result of the positive results gained from previous animal and clinical studies, the Behringwerke, Marburg, Germany, is conducting an investigation in which patients with a heparin-induced thrombocytopenia may be treated with r-hirudin. We report about one patient involved in this study, in whom r-hirudin was used as an anticoagulant during CPB.

A 72-year-old woman weighing 52 kg was admitted after cardiac decompensation resulting from valvular aortic stenosis (Δ pressure 71 mm Hg, aortic valve opening area 0.4 cm^2). Left ventricular function was compromised (ejection fraction 37%) and pulmonary vascular resistance was increased to 296 $dyne \cdot sec \cdot cm^{-5}$. After the diagnostic cardiac catheterization, while the standard heparin anticoagulation regimen was still being administered, deep pelvic vein thrombosis developed along with a decrease in platelet count from 343,000 to $14{,}000 \times 10^9$/L. The suspected heparin-induced thrombocytopenia type II was confirmed by means of the heparin-induced platelet activation test. The only anticoagulant suitable for use during extracorporeal circulation proved to be r-hirudin HBW 023 (Behringwerke, Marburg, Germany), because all heparins and heparinoids caused platelet aggregation. The patient was transferred to our department for aortic valve replacement with r-hirudin used as the anticoagulant instead of heparin during CPB.

Anticoagulation with phenprocoumon (Marcumar) because of pelvic vein thrombosis was discontinued 3 days before the operation, and r-hirudin was simultaneously substituted. An initial bolus of 0.2 mg/kg body weight was administered intravenously followed by an infusion regimen with 0.1 mg/kg body weight per hour intravenously until the time of the operation to achieve a prolonged activated partial thromboplastin time (aPTT) within the range of 60 to 80 seconds. The resultant plasma concentration of r-hirudin was 1 to 1.5 μg/ml. Anesthesia was maintained with intravenous infusions of propofol and pancuronium bromide along with intermittent doses of fentanyl (up to 25 μg/kg body weight). The patient received a bolus of 9 mg of r-hirudin intravenously 10 minutes before the start of CPB. The heart-lung machine contained a capillary membrane oxygenator and was primed with 2000 ml of lactated Ringer's solution, 100 ml of mannitol solution (Osmofundin 15%), 50 ml of sodium bicarbonate, 750 ml of packed erythrocytes, and 5 mg of r-hirudin. The perfusion flow rate during normothermia was 3.9 L/min. The perfusion time was 83 minutes and the aortic crossclamp time, 60 minutes. Aortic valve replacement with a bioprosthesis was conducted with mild hypothermia up to 33° C. To monitor the anticoagulation during CPB, we measured the ecarin clotting time (ECT)[5] along with the aPTT in 10-minute intervals (Fig. 1). The aPTT was between 90 and 130 seconds and the ECT remained between 300 and 456 seconds. The plasma concentration of r-hirudin was kept within a range of 2.5 to 3.2 μg/ml throughout CPB. Four separate doses of r-hirudin (5, 5, 2.5, and 2.5 mg) were necessary to remain within this level. The half-life of r-hirudin depends on normal renal function. Therefore our patient showed a rapid fall of the r-hirudin concentration (documented by means of aPTT and ECT) toward the end of CPB. Throughout the CPB time the entire system remained free of clots. The pressure proximal to the oxygenator was constant during CPB. Bleeding and thromboembolic complications were not observed at any time during the operation or in the postoperative period. The total fluids from the chest drainage amounted to 240 ml. The entire postoperative course remained without sequel.

Platelet function was measured by means of adenosine diphosphate–induced and collagen-induced platelet aggregation (Fig. 2). After the injection of r-hirudin the platelet function remained normal and then continued to diminish as a result of the CPB-mediated trauma. Within 60 minutes after CPB the adenosine diphosphate–induced and collagen-induced platelet aggregations were 40% and 60% of the baseline values, respectively. At the end of the operation platelet function was almost fully restored. The

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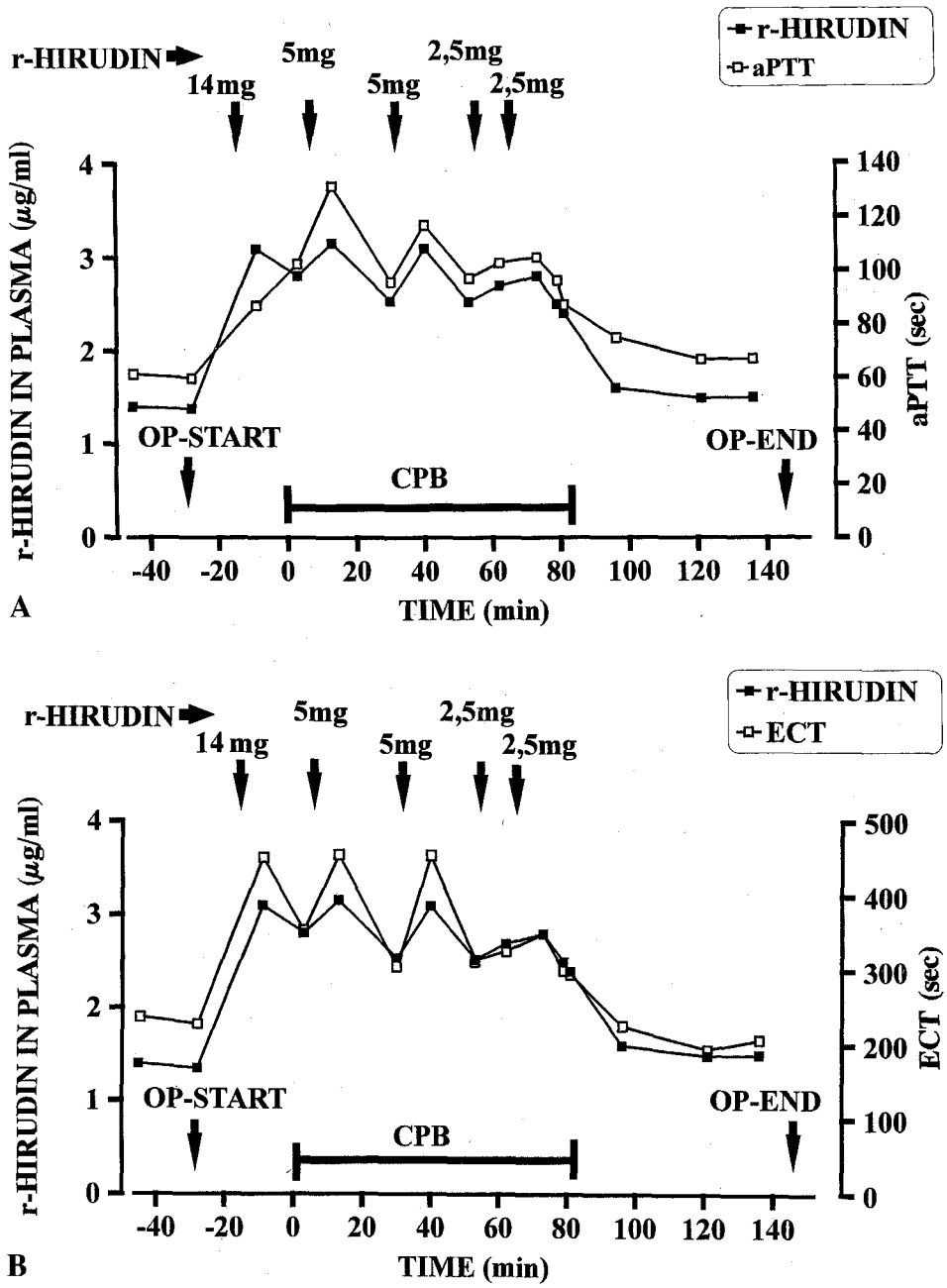

Fig. 1. Anticoagulation monitoring: Change of ECT **(A)** and aPPT **(B)** in correlation with r-hirudin plasma concentration before, during and after CPB.

anticoagulation regimen with intravenous r-hirudin infusions (0.1 mg/kg body weight per hour) was continued for 7 days during the postoperative period and led to aPTTs between 57 and 73 seconds. On the third postoperative day we again started simultaneous phenprocoumon (Marcumar) therapy. The patient was able to be discharged in good health on the twelfth postoperative day.

These data show that it is possible to perform cardiac operations in human beings with r-hirudin used as an anticoagulant for CPB without any problems. Furthermore, ECT and aPTT are suitable parameters to monitor the plasma concentration and anticoagulation of r-hirudin. As a result of the intact kidney function and the short half-life of r-hirudin, the plasma concentration decreases rapidly at the end of CPB so that it was unnecessary to reverse any residual effects. In the case of an overdose or during renal failure, it is possible to lower the r-hirudin plasma level quickly and effectively by means of hemofiltration. This was demonstrated in previous studies on nephrectomized pigs (unpublished data) and during CPB

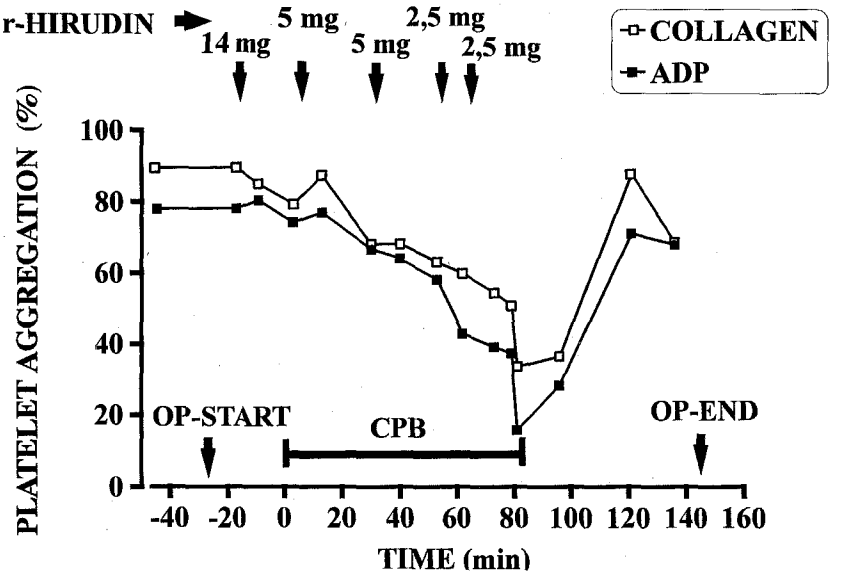

Fig. 2. Platelet function: Platelet aggregation induced by adenosine diphosphate *(ADP)* and by collagen before, during, and after CPB. Platelet counts were adjusted by dilution or centrifugation to 100,000 platelets μl^{-1} and aggregation was induced by addition of adenosine diphosphate (10 mmol/L) or collagen (4 μg/ml).

in human beings.[4] The stable platelet function as manifested by the low bleeding tendency is an especially good reason to surmise that r-hirudin is a better anticoagulant than heparin for CPB.

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A NEW STAGED OPERATION FOR EXTENSIVE AORTIC ANEURYSM BY MEANS OF THE MODIFIED "ELEPHANT TRUNK" TECHNIQUE

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A new first-stage operation through a median sternotomy for extensive aortic aneurysm involving the ascending aorta, the aortic arch, and the descending aorta is presented.

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Operative procedures. Minimum dissection of the ascending aorta and the proximal aortic arch is done through a median sternotomy. Cardiopulmonary bypass is established by femoral and bicaval venous cannulations. The patient is cooled to a nasopharyngeal temperature of 18° C. Then circulatory arrest is obtained with continuous retrograde cerebral perfusion (CRCP).[1] Myocardial protection is obtained by retrograde cardioplegia with crystalloid solution and blood. A longitudinal incision is made on the ascending aortic aneurysm and is extended minimally to the aortic arch.