3. Williams DO, Vanecko RM, Glassroth J: Endobronchial polyposis following smoke inhalation. Chest 1983; 84:774–6

4. Park T, DiBenedetto R, Morgan K, Colmers R, Sherman E: Diffuse endobronchial polyposis following a titanium tetrachloride inhalation injury. Am Rev Respir Dis 1984; 130:315–7

5. Arguelles M, Blanco I: Inflammatory bronchial polyp associated with asthma. Arch Intern Med 1983; 143:570–1

6. Shale DJ, Lane DJ, Fisher CWS, Dunnill MS: Endobronchial polyp in an asthmatic subject. Thorax 1983; 38:75–6

7. Yamagishi M, Harada H, Kurihara M, Shijubo N, Satoh M, Kumagai M, Abe S: Inflammatory endotracheal polyp resolved after antibiotic treatment. Respiration 1993; 60:193–6

8. Spencer H, Dail DH, Arneaud J: Non-invasive bronchial epithelial papillary tumors. Cancer 1980; 45:1486–97

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Heparinase and Thromboelastography in Liver Transplantation for a Patient with von Willebrand's Disease

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THE role of heparin in impaired hemostasis during orthotopic liver transplantation (OLT), either exogenously derived from prior administration to the donor or endogenously derived from the donor liver, is controversial.[1,2] A report of improved clinical and laboratory indexes of bleeding after postreperfusion administration of protamine was not accompanied by objective evidence of the presence of heparin,[3] although Kang has promoted comparison of the untreated and protamine-treated thromboelastograph.[4]

Because the use of bacterial derived heparinase has been reported in cardiac surgery with the activated clotting time (ACT)[5] and thromboelastography,[6] heparinase was used to assess potential heparin effect with the thromboelastograph during OLT in a patient with type IIA von Willebrand's disease (vWD), when potential difficulty was expected in the diagnosis of heparin effect after reperfusion.

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Case Report

A 46-yr-old woman (weight 53.5 kg, height 1.5 m) with primary biliary cirrhosis presented for OLT. She had portal hypertension that required previous sclerotherapy for bleeding esophageal varices and a transjugular intrahepatic portosystemic shunt (TIPS) procedure. She had vWD type IIA, the diagnosis having been made on the basis of normal von Willebrand factor (vWF) antigen level, low ristocetin cofactor activity indicative of low vWF function, and no platelet aggregation in response to low concentrations of ristocetin.[7]

At preoperative assessment, apart from the stigmata of end-stage liver disease, the patient had poor dentition, with slight bleeding from the base of the left upper premolar tooth without other sites of hemorrhage, and no evidence of cardiorespiratory disease. The patient had received one-deamino-8-D-argininevasopressin (DDAVP) for oral bleeding some years previously but had not reported bleeding complication with the TIPS procedure. Laboratory results included prothrombin time (PT) 11.7 s (normal range 11.1–13.1 s), partial thromboplastin time (PTT) 40.3 s (25–34 s), platelet count 110×10^3 mm^{-3}, hematocrit 31.6%, and normal serum electrolytes.

Prophylactic DDAVP (20 μg, intravenous) was administered before anesthetic induction because of the anticipated bleeding and the previous reported use. Standard anesthetic agents, adjuvants (sodium thiopental, fentanyl, pancuronium, and isoflurane), and monitoring were used.

Thromboelastographs were recorded concurrently with and without heparinase (4 IU tube^{-1}). A 1-ml blood sample was introduced into the heparinase tube, mixed by inversion, incubated for 3 min, and 0.36 ml withdrawn for insertion into the thromboelastography cuvette. No heparin was used in the flush solution for invasive monitors or during venoveno bypass, and the donor liver was flushed with 500 ml albumin (5%) before portal vein anastomosis. Perioperative hematologic variables are presented in table 1.

Table 1. Perioperative Hematologic Values

	PT (s)	PTT (s)	TT (patient/control, s)	Fibrinogen (mg/dl)	Platelets ($\times 10^3/mm^{-3}$)
Dissection	11.9	36.6	20.5/21	259	69
Anhepatic	11.8	36.3	24/21	198	51
Postreperfusion	13	41.4	23.5/20	190	39
Normal	11.1–13.1	25–34	18–22	170–410	133–333

PT = prothrombin time; PTT = partial thromboplastin time; TT = thrombin time.

Thromboelastography traces with heparinase before the anhepatic phase were unchanged from native blood, and the preanhepatic PTT prolongation was compatible with vWD. However, immediately after reperfusion, the essentially straight-line native thromboelastograph (fig. 1A) suggested heparinlike effect that was corrected in the heparinase trace (fig. 1B). Administration of protamine (50 mg, intravenous) restored the native thromboelastography trace (fig. 1C) to that of the heparinase-treated sample.

Estimated blood loss was 7,000 ml, and blood product administration was guided by clinical inspection, thromboelastography, and standard laboratory coagulation parameters. Fifteen units of packed erythrocytes and 14 "jumbo" units of fresh-frozen plasma (volume 600–650 ml) were used. Two six-pack units of platelets and one six-pack unit of cryoprecipitate were administered toward the end of surgery for persistent thrombocytopenia and oozing. One six-pack of cryoprecipitate had been given prophylactically before incision.

Postoperatively, additional platelets and cryoprecipitate were administered in the intensive care unit to correct thrombocytopenia and the prolonged PTT. An episode of suspected organ rejection was treated with plasmapheresis in addition to immunosuppression; the patient improved slowly and was discharged on postoperative day 30.

Discussion

This report documents the use of heparinase-guided thromboelastography during OLT. Heparinase, derived from *Flavobacterium heparinum,* has been shown to cleave the alpha glycosidic linkages in heparin with loss of associated anticoagulant effect.[8] Use of heparinase has been reported as an aid to coagulation monitoring in cardiac surgery, with potential implications for protamine dosage. Heparinase added to the ACT[5] and whole blood PT and activated PTT[9] has been used to determine effective baseline coagulation parameters during bypass, and a heparinase-modified thromboelastograph was used to define coagulation indexes.[6] Tuman *et al.* concluded that the heparinase effectively removed small quantities of heparin associated with contamination without completely normalizing the thromboelastography R time in the presence of larger heparin doses used for anticoagulation during bypass.[6] However, Despotis *et al.* found heparinase to be effective in reversing large amounts of heparin in plasma from cardiac surgical patients, as measured by PT and PTT.[9]

The presence of heparin after reperfusion of the donor liver during OLT has been suggested using the PTT and thrombin time (TT).[10] A possible source is heparin sequestered in the liver after administration to the donor before organ procurement, although release of endogenous heparin or heparinlike substances from the donor liver endothelium has been hypothesized.[1,11] A report documented correction of postreperfusion bleeding and thromboelastography abnormalities in two patients with 50 mg protamine.[3] Although the ACT is insensitive to low concentrations of heparin, and laboratory measures such as the PTT and TT are subject to delay, the heparinase-guided thromboelastograph offers the advantage of clinically relevant information within minutes.

The risk of heparin contamination in this patient was eliminated by excluding heparin from the invasive cannulae flush tubing, by drawing arterial blood gas samples (heparin-containing syringe) after thromboelastography samples, and by flushing the donor liver before portal vein anastomosis to remove exogenously derived heparin. The absence of any difference in the native and heparinase thromboelastography parameters during the preanhepatic and initial anhepatic phases supports the absence of measurable heparin effect. The marginal PTT prolongation present before induction did not change significantly and was accompanied by stable TTs, also suggesting heparin absence. However, a significant effect compatible with heparin was demonstrated in the postreperfusion thromboelastography studies with further PTT and marginal TT prolongation. The heparinase-treated thromboelastograph showed no

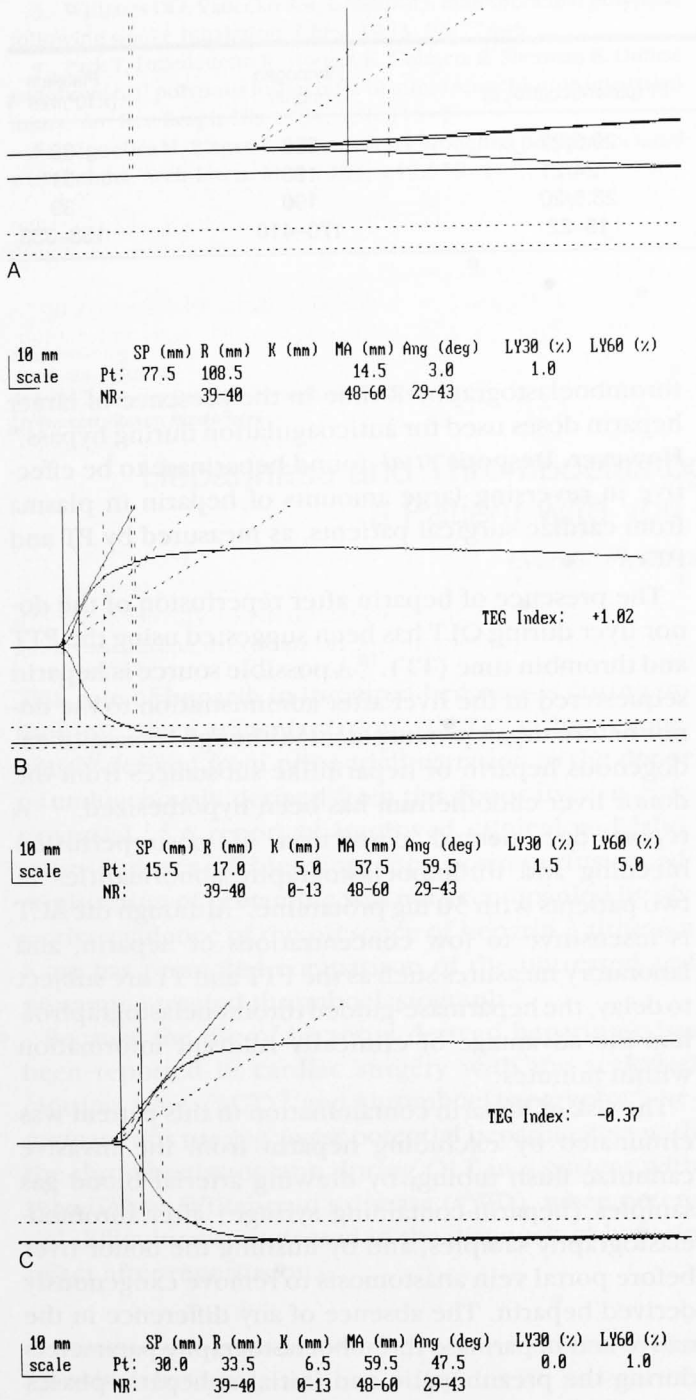

Fig. 1. (*A*) Native blood thromboelastography trace immediately after reperfusion. Patient values (top row) and normal ranges (bottom row) below (each figure). LY 30 and LY 60 are percent fibrinolysis at 0.5 and 1 h, respectively. (*B*) Heparinase thromboelastography trace immediately after reperfusion. Patient values and normal ranges below. Thromboelastography index is the mathematically derived index of R, K times, angle (Ang), and maximum amplitude (MA). (*C*) Native blood thromboelastography trace immediately after systemic protamine administration.

sign of coagulation factor or platelet dysfunction, whereas the native thromboelastography trace demonstrated negligible clot formation. Protamine (50 mg, intravenous) was administered as soon as the heparinase trace was seen, with dramatic resolution of native thromboelastography parameters and surgical oozing. In a patient with altered baseline coagulation parameters, objective evidence of heparin-like effect and thromboelastography-guided protamine therapy allowed rapid correction of one of the factors complicating postreperfusion bleeding. Although cryoprecipitate and platelet transfusions were required toward the end of surgery, the heparinase-thromboelastography prevented inappropriate blood product exposure for the immediate postreperfusion straight-line thromboelastography trace.

Although the perioperative management of von Willebrand's disease has been reviewed,[7] recent developments are of interest to anesthesiologists. Routine use of DDAVP is not recommended in the absence of individual patient testing for DDAVP response.[12] Its use is controversial in type IIB disease and of no value in type III.[12,13] DDAVP may be effective in some type-IIA patients[12] and was administered initially in this case on the basis of previous use by the patient. Thromboelastography traces were not performed before and after DDAVP administration.

Although cryoprecipitate contains sufficient factor VIII/vWF to be an effective treatment, concern about viral transmission has led to the use of factor VIII:C concentrates for vWD. Reports document the successful use of both Humate-P[14] (a pasteurized product) and Koate-HP[15] (containing a solvent and detergent to inactivate viruses), even though there is a relative lack of high molecular weight von Willebrand factor multimers in the latter product. Both products have normalized laboratory measures of platelet and vWF activity and decreased bleeding, and both have been used prophylactically in vWD patients undergoing surgery. Perioperative cryoprecipitate was used in this case instead of factor VIII products because of unawareness of these developments.

This case of OLT in a patient with vWD is an initial report of the successful use of the heparinase-treated thromboelastograph in assessment of coagulation in liver transplantation. Further study will be required to reproduce the effects of the heparinase-treated thromboelastograph, compare results with traditional tests for heparin presence (ACT, PTT, heparin concentra-

tions), and assess the impact on transfusion requirements and other indexes of outcome in OLT.

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References

1. Stremple JF, Hussey CV, Ellisson EH: Study of clotting factors in liver homotransplantation. Am J Surg 1966; 111:862–9

2. Hickman R, Bracher M, Pienaar BH, Terblanche J: Heparin as the cause of coagulopathy which may complicate grafting of the liver. Surg Gynecol Obstet 1991; 172:197–206

3. Bayly PJM, Thick M: Reversal of post reperfusion coagulopathy by protein sulphate in orthotopic liver transplantation. Br J Anaesth 1994; 73:840–2

4. Kang Y: Coagulation and liver transplantation. Transplant Proceed 1993; 25:2001–5

5. Baugh RF, Deemar KA, Zimmermann JJ: Heparinase in the activated clotting time assay: Monitoring heparin-independent alterations in coagulation function. Anesth Analg 1992; 74:201–5

6. Tuman KJ, McCarthy RJ, Djuric M, Rizzo V, Ivankovich AD: Evaluation of coagulation during cardiopulmonary bypass with a heparinase-modified thromboelastographic assay. J Cardiothorac Vasc Anesth 1994; 8:144–9

7. Cameron CB, Kobrinsky N: Perioperative management of patients with von Willebrands disease. Can J Anaesth 1990; 37:341–7

8. Klein MD, Drongowski RA, Linhardt RJ, Cooney CL, Langer RS: Heparinase: In vivo activity and immunogenicity in rabbits. J Lab Clin Med 1983; 102:828–37

9. Despotis GJ, Summerfield AL, Joist JH, Goodnough LT, Santoo SA, Zimmermann JJ, Lappas DG: In vitro reversal of heparin effect with heparinase: Evaluation with whole blood prothrombin time and activated thromboplastin time in cardiac surgical patients. Anesth Analg 1994; 79:670–4

10. Bellani KG, Estrin JA, Ascher NL, Najarian JS, Bushman J, Buckley JJ: Reperfusion coagulopathy during human liver transplantation. Transplant Proc 1987; 19(suppl 3):71–2

11. Bakker CM, Stibbe J, Gomes MJ, Groenland ThN, Metselaar HJ, Hesselink EJ, Schalm SJ, Terpstra OT: The appearance of donor heparin in the recipient after reperfusion of a liver graft. Transplantation 1993; 56:327–9

12. Logan LJ: Treatment of von Willebrands disease. Hematol Oncol Clin North Am 1992; 6:1079–94

13. Mannucci PN: A nontransfusional form of treatment for congenital acquired bleeding disorders. Blood 1988; 72:1449–55

14. Slaughter TF, Mody EA, Oldham HM, Reves JG, O'Connor CM: Management of a patient with type IIC von Willebrand disease during coronary artery bypass surgery. ANESTHESIOLOGY 1993; 78:195–7

15. Hanna WT, Bona RD, Zimmerman CE, Carta CA, Hebert GZ, Rickles FR: The use of intermediate and high purity factor VIII products in the treatment of von Willebrand's disease. Thromb Haemost 1994; 71:173–9

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Cervical Dural Puncture in a Neonate: A Rare Complication of Internal Jugular Venipuncture

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CENTRAL venous catheterization *via* the internal jugular vein (IJV) is used widely for pressure monitoring and drug therapy. Although various complications of IJV catheterization have been described, dural puncture has not been reported. We describe dural puncture during internal jugular venipuncture in a neonate undergoing cardiac surgery.

Case Report

A 16-day-old male with a diagnosis of corrected transposition of the great arteries and left-sided atrioventricular valve atresia was