Haemostasis monitoring during sequential aortic valve replacement and liver transplantation

E. Sieders[1], F. De Somer[2], S. Bouchez[3], L. Szegedi[3], Y. Van Belleghem[2], I. Colle[1], R. Troisi[1].

(1) Hepato-Biliary and Liver Transplant Center ; (2) Cardiac Surgery Unit ; (3) Dept. of Anesthesiology, Ghent University Hospital Medical School, Ghent, Belgium. *E.S. is a transplant fellow from the Section of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, University of Groningen, Groningen, The Netherlands.*

Abstract

Despite advances in anaesthesiological and surgical techniques, cardiac surgery in cirrhotic patients remains hazardous. This report outlines our experience with haemostasis monitoring in two consecutive cases of sequential aortic valve replacement and liver transplantation. Clotting disturbances proved to have fatal consequences since one of these patients died following massive lung embolism. The second patient underwent successfully this combined procedure and is in good clinical state 14 months postoperatively. Evaluation and discussion of the coagulation monitoring by the Sonoclot Analyzer in both patients and related therapeutic suggestions for the prevention of thrombotic events are discussed. (Acta gastroenterol. belg., **2010**, 73, **65-68**).

Introduction

Despite advances in anaesthesiological and surgical techniques, cardiac surgery in cirrhotic patients remains hazardous. Overall morbidity and mortality in the presence of cirrhosis is high, especially in Child-Pugh class B/C or high Model of End Stage Liver Disease (MELD) score patients (1,2). Klemperer *et al.* have reported in Child B patients undergoing cardiac operations 100% major morbidity and 80% mortality rates (3). Death events were related to post-operative infectious and hemorrhagic complications culminating with hepatic and multi-system organ failure. Interestingly, in the same study Child class A cirrhotic patients had major complications in 25% of the cases but did not suffer any perioperative mortality. These data suggest that patients with advanced liver failure have poor tolerance for cardiopulmonary bypass and an unacceptable operative risk for cardiac surgery. Combined cardiac surgery and liver transplantation (LT) would be an attractive procedure to improve outcomes (4). Aortic valve stenosis with terminal liver disease requiring liver transplantation is an extremely rare setting. To our knowledge, there are only three cases of combined aortic valve replacement (AVR) and liver transplantation reported with uncertain outcome (5-7). We discuss herein haemostasis monitoring by the Sonoclot analyzer and perioperative management of two consecutive cases of sequential aortic valve replacement and liver transplantation.

Cases

Patient 1 : 55 year-old man with alcoholic liver cirrhosis and aortic valve stenosis was evaluated for combined AVR+LT in our institution in October 2006. Trans oesophageal echocardiography (TEE) showed an aorta insufficiency grade 2, a calcified aorta valve with a peak valvular gradient of 44 mmHg (mean gradient of 18 mmHg) and an aorta valve area of 1.28 cm^2. Mitral valve insufficiency grade 3/4, slightly dilated left ventricle and normal systolic function (estimated ejection fraction 50%) were also diagnosed. In July 2007 a deceased-donor liver graft became available. At that time he was Child-Pugh score C with a lab MELD of 35. Sonoclot Coagulation Analyzer was preoperatively used (8). The Sonoclot Analyzer is an *in vitro* method for analysis of the coagulation process from the start of fibrin formation, through polymerization of the fibrin monomer, platelet interaction, and eventually to clot retraction and lysis. The system measures the changes in the viscoelastic properties of whole blood during the clotting process. An open-ended plastic probe vibrates vertically immersed in a cuvette containing a 0.4 mL sample of whole blood. The curve or signature reflects the change in viscoelasticity from liquid to solid state (Fig. 1). Preoperative laboratory values of coagulation markers, platelet count and Sonoclot analysis revealed a severely compromised coagulation (Table 1, Fig. 1). From start of induction till the start of cardiopulmonary bypass (CPB), a high dose aprotinin was initiated after induction (9). Before aortic and right atrial cannulation for CPB, 300 IU/kg of unfractionated heparin were administered. In order to avoid further dilution of coagulation factors, the priming of the CPB circuit was done with fresh frozen plasma and aprotinin. Duration of the CPB was 96 minutes and total aortic cross-clamp time was 58 minutes. After aortic valve replacement, the remaining heparin was reversed with protamine sulphate. Sonoclot analysis showed a small improvement as reflected by a decreased activated clotting time (ACT) and increased clot rate, compared to the preoperative analysis (Fig. 1). Liver transplantation followed immediately after closure

Correspondence to : Roberto Troisi MD, PhD, Address: Dept. of General and Hepatobiliary Surgery, Liver Transplantation Service, Ghent University Hospital Medical School, De Pintelaan 185, 9000 Ghent, Belgium. E-mail: roberto.troisi@ugent.be

Submission date : 08/04/2009
Acceptance date : 12/12/2009

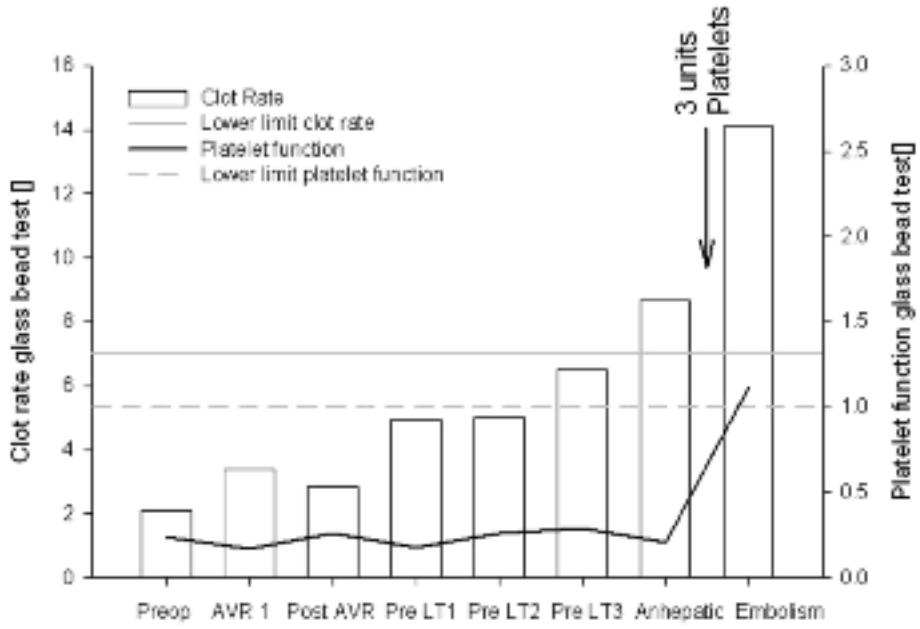

Fig. 1. — Evolution of clot rate and platelet function in patient 1.

Table 1. — **Clotting parameters in both patients**

Patient 1			*Patient 2*			
	Preop	Anhepatic		Preop	Anhepatic	End
Platelets[1]	14	-	Platelets	72	15	24
PTT[2]	30	-	PTT	43	39	45
APTT[3]	71,2	-	APTT	56.6	55.9	79.6
Fibrinogen[4]	67	-	Fibrinogen	159	133	150
AT III[5]	13	-	AT III	36	15	23
INR[6]	2,71	-	INR	1,90	2.09	1.81

[1] Platelet count in/mm 10E3/µL ; normal: 135-370 x10E3/µL
[2] Prothrombin time in percentages; normal: 70-120%
[3] Activated partial thromboplastin time in seconds; normal: 26.9-38.1 seconds
[4] Fibrinogen in mg/dL; normal: 200-400 mg/dL
[5] Antithrombin III in percentages; normal: 84-120%
[6] International normalized ratio; normal range: 2-3

of sternotomy. During hepatectomy, an old thrombus inside the portal vein was unexpectedly found. Sonoclot showed further improvement of ACT and clot rate towards normal values but no improvement in platelet function was noticed. Based on this analysis and the diffuse oozing during anhepatic phase, it was decided to administer 10 units of blood platelets. After infusion of 3 units a sudden change from a hypocoagulable to a hypercoagulable state witnessed by an ACT value below normal in combination with a supra normal clot rate and a normal platelet function was recorded (Fig. 1). The patient became hemodynamically instable and massive pulmonary thrombosis led him to death. Fresh clots were revealed in the vena cava inferior until the right atrium and ventricle. The graft still kept in cold bag was successfully implanted in another patient.

Patient 2 : A 49 year-old man suffering of compensated alcoholic liver cirrhosis and portal hypertension. Because of oesophageal bleeding a transjugular intrahepatic porto-systemic shunt was positioned in November 2005 and he was referred for LT in January 2007 (Table 1). TEE showed a severe calcified aortic valve with a severe stenosis (peak valvular gradient of 67 mmHg and mean gradient of 44 mmHg) and an aorta valve area of 1.03 cm^2. Moderate mitral insufficiency (grade 2/4), tricuspid insufficiency (grade 1 /4), normal systolic function and a mild pulmonary artery hypertension (47 mmHg of systolic pressure) were also diagnosed. When a deceased donor liver graft became available at the end of August 2007 he was Child-Pugh score C with a lab MELD of 29. The length of CPB was 67 minutes (similar protocol as patient 1): the AVR was

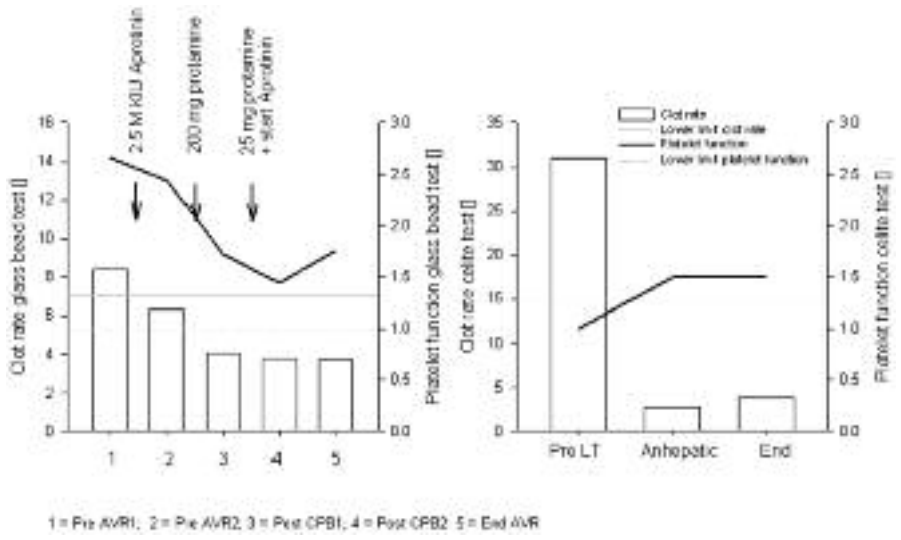

Fig. 2. — Evolution of clot rate and platelet function in patient 2.

successful and LT followed sequentially. Coagulation parameters (platelets of 40×10^{-3} and a relative high fibrinogen value) were almost normal until total hepatectomy. However, due to the low plasma level of antithrombin III (AT-III), we decided to administer 1000 IU instead of fresh frozen plasma or thrombocytes. Mild heparinization (250 IU) was also given to improve at the same time coagulation and to avoid thromboembolic phenomena. Sonoclot showed a coagulation profile slightly under the normal values during the entire LT procedure (Table 1, Fig. 2). Reperfusion was uneventful and the cardiac function remained stable during the whole LT procedure. Thereafter, coagulation was corrected by administration of 3 units of fresh frozen plasma and eight units of thrombocytes. The patient was awakened and extubated 4 hours after surgery. The hepatic and cardiac function remained good. TEE showed aortic valve prosthesis with a peak gradient of 26 mmHg and a mean gradient of 11 mmHg. After 15 days he was transferred to the ward and dismissed on postoperative day 31. The patient is alive and in good clinical conditions 19 months postoperatively.

Discussion

To date, 2 out of 3 described cases of AVR + LT have been successful (5-7). Combining AVR plus LT instead of performing deferred procedures is supported by several arguments. Liver transplantation in patients with cardiac disease may enhance the risk of myocardial ischemia, perioperative bleeding, renal dysfunction and neurological complications (10,11). On the other hand, cardiac surgery in cirrhotic patients carries a very high risk of postoperative liver failure, morbidity and mortality rates, especially in Child B and C patients (1-5). Up to date, no precise guidelines are available for surgical management during cirrhosis (12). Bleeding is one of the major risks because of thrombocytopenia, platelet dysfunction, reduced coagulation factors and fibrinolysis usually present in cirrhotic patients. Activation of cardio-pulmonary by-pass may worsen this condition (13). Ironically, cirrhotics are also at risk for thrombosis because the balance between bleeding and thrombosis becomes increasingly precarious as protein synthetic capacity is lost. Indeed, it is not infrequent to observe thrombotic events in the portal and mesenteric systems or in the lower extremities (14). Severe fibrinolysis may frequently occur in LT following graft reperfusion, mainly caused by increased levels of tissue-type plasminogen activator (t-PA). For this reason, the uses of antifibrinolytic drugs were popularized long-time ago (15). More recently, aprotinin showed significant reductions in blood loss and red-blood cell transfusions in a European multicenter study (16). However, safety of this agent has been an matter of controversy about the risks of sudden thromboembolic events contributing to its withdrawal from the clinical use in the U.S. and Europe (17,18). In our experience both patients received aprotinin but sudden massive embolism occurred in the first, although presenting with a worse clotting profile. In this case, a triggering role of aprotinin in initiating thrombotic complications seems difficult to be proven considering that aprotinin has clearly been shown in vitro and in vivo to have anticoagulant properties. In fact, that there is no evidence for increased risk of thromboembolic events associated with antifibrinolytic drugs from meta-analysis studies (19,20). Combined cardiac and liver surgery may generate high plasma levels of thrombin and t-PA, decreased clearance of activated coagulation factors during anhepatic phase and low AT-III level may result in a thrombotic condition (21-25). When surgery cannot be avoided, optimizing and monitoring of the coagulation is of paramount importance. Sonoclot device may assist the anaesthesiologist by helping to identify the causes of bleeding.

This analysis reflected a heavily disturbed coagulation in the first patient compared to the second in which most values were only slightly below normal at the beginning of surgery. In order to counteract this procoagulant state we thought to prime the CBP with fresh frozen plasma (containing also AT-III) and to use a high dose regimen of aprotinin during cardiac surgery. Although both measures were useful, it is clear that they were most likely insufficient in converting the procoagulant status to a more neutral one. When oozing was experienced in the first patient having low AT-III levels, autologous platelets were transfused. These platelets were immediately exposed to high levels of thrombin, tissue factors and ADP, which most likely led to immediate aggregation with subsequent hypercoagulability as evidenced by Sonoclot (26). This demonstrated at that time a complete recovery of plasmatic coagulation (27). In the second patient autologous platelet transfusion was not necessary due to the better preoperative coagulation profile and a higher platelet count. We could speculate that the combined effect of impaired plasmatic coagulation, thrombin inhibition by low doses of heparin and administration of AT-III most likely prevented a thrombotic event in the second patient. As proposed by De Wolf et al. when thromboelastogram or Sonoclot shows fibrinolysis, one should consider administration of AT-III concentrate and or low doses of heparin before administrating autologous platelets (25). Upon our -although very limited- experience we would advise combined AVR+LT in patients having limited clotting disturbances. Patients having a severe loss of liver synthetic function may carry prothrombotic or thrombophilic factors and should be carefully discussed for the difficulties to manage clotting factor disorders (14). Unfortunately, validation of this strategy is mainly limited by the scarcity of clinical indications.

References

1. FILSOUFI F., SALZBERG S.P., RAHMANIAN P.B., SCHIANO T.D., ELSIESY H., SQUIRE A., ADAMS D.H. Early and late outcome of cardiac surgery in patients with liver cirrhosis. *Liver Transpl*., 2007, **13** :990-5.
2. SUMAN A., BARNES D.S., ZEIN N.N., LEVINTHAL G.N., CONNOR J.T., CAREY W.D. Predicting outcome after cardiac surgery in patients with cirrhosis : a comparison of Child-Pugh and MELD scores. *Clin Gastroenterol. Hepatol.*, 2004, **2** : 719-23.
3. KLEMPERER J.D., KO W., KRIEGER K.H., CONNOLLY M., ROSENGART T.K., ALTORKI N.K., LANG S., ISOM O.W. Cardiac operations in patients with cirrhosis. *Ann. Thorac Surg.,* 1998, 65 :85-7.
4. GONZALEZ-STAWINSKI G. Early and late outcomes of cardiac surgery in patients with liver cirrhosis. *Liver Transpl.,* 2007, **13** :956.
5. ECKHOFF D.E., FRENETTE L., SELLERS M.T., MCGUIRE B.M., CONTRERAS J.L., BYNON J.S., MCGIFFIN D.C. Combined cardiac surgery and liver transplantation. *Liver Transpl.,* 2001, **7** :60-1.
6. PARKER B.M., MAYES J.T., HENDERSON J.M., SAVAGE R.M. Combined aortic valve replacement and orthotopic liver transplantation. *J. Cardiothorac Vasc. Anesth.,* 2001, **15** : 474-6.
7. HANVESAKUL R., DESHPANDE R., CARR C.S., AKBAR N. Aspergillus aortitis : a cause for aortic perforation in a patient following combined aortic valve surgery and liver transplantation. I*nteract. Cardiovasc. Thorac Surg.*, 2004, **3** : 544-6.
8. LISZKA-HACKZELL J.J., EKBACK G. Analysis of the information content in Sonoclot data and reconstruction of coagulation test variables. *J. Med. Syst.,* 2002, **26** : 1-8.
9. ROYSTON D., BIDSTRUP B.P., TAYLOR K.M., SAPSFORD R.N. Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. Lancet, 1987, **2** (8571) : 1289-91.
10. MORRIS J.J., HELLMAN C.L., GAWEY B.J., RAMSAY MA, VALEK T.R., GUNNING T.C., SWYGERT T.H., SHORE-LESSERSON L., LALEHZARIAN F., BRAYMAN K.L., Case 3-1995. Three patients requiring both coronary artery bypass surgery and orthotopic liver transplantation. *J. Cardiothorac. Vasc. Anesth.*, 1995, **9** : 322-32.
11. POLLARD R.J., SIDI A., GIBBY G.L., LOBATO E.B., GABRIELLI A. Aortic stenosis with end-stage liver disease : prioritizing surgical and anesthetic therapies. *J. Clin. Anesth*., 1998, **10** (3) : 253-61.
12. HAYASHIDA N., SHOUJIMA T., TESHIMA H., YOKOKURA Y., TAKAGI K., TOMOEDA H., AOYAGI S.. Clinical outcome after cardiac operations in patients with cirrhosis. Ann. Thorac Cardiovasc.Surg., 2004, **77** : 500-5.
13. FRANCOZ C., DURAND F.. The risk of surgery in patients with cirrhosis. *Acta Gastroenterol. Belg.*, 2008, **71** : 42-6.
14. NORTHUP P.G., SUNDARAM V., FALLON M.B., REDDY K.R., BALOGUN R.A., SANJAL A.J. et A.L. Hypercoagulation and thrombophilia in liver disease. *J. Thromb. Hemost*., 2007, **6** : 2-9.
15. KANG Y., LEWIS J.H., NAVALGUND A., RUSSELL M.W., BONTEMPO F.A., NIREN L.S., STARZL T.E. Epsilon-aminocaproic acid for treatment of fibrinolysis during liver transplantation. *Anesthesiology*, 1987, **66** : 766-73.
16. PORTE R.J., MOLENAAR I.Q., BEGLIOMINI B., GROENLAND T.H., JANUSZKIEWICZ A., LINDGREN L., PALARETI G., HERMANS J., TERPSTRA O.T. Aprotinin and transfusion requirements in orthotopic liver transplantation: a multicentre randomised double-blind study. EMSALT Study Group. *Lancet*, 2000, **355** (9212) : 1303-9.
17. BAUBILLIER E., CHERQUI D., DOMINIQUE C., KHALIL M., BONNET F., FAGNIEZ P.L., DUVALDESTIN P. A fatal thrombotic complication during liver transplantation after aprotinin administration. *Transplantation*, 1994, **57** : 1664-6.
18. LERNER A.B., SUNDAR E., MAHMOOD F., SARGE T., HANTO D.W., PANZICA P.J. Four cases of cardiopulmonary thromboembolism during liver transplantation without the use of antifibrinolytic drugs. *Anesth. Analg.* 2005, **101** : 1608-12
19. MOLENAAR I.Q., BEGLIOMINI B., GRAZI G.L., RINGERS J., TERPSTRA O.T., PORTE R.J.; EMSALT Study Group. European Multicenter Study on the Use of Aprotinin in Liver Transplantation. The effect of aprotinin on renal function in orthotopic liver transplantation. *Transplantation*. 2001, **71** : 247-52.
20. MOLENAAR I.Q., WARNAAR N., GROEN H., TENVERGERT E.M., SLOOFF M.J., PORTE R.J. Efficacy and safety of antifibrinolytic drugs in liver transplantation : a systematic review and meta-analysis. *Am. J. Transplant.,* 2007, **7** : 185-94.
21. BUTENAS S., VAN'T VEER C., MANN K.G. "Normal" thrombin generation. *Blood*, 1999, **94** : 2169-78.
22. Ranucci M., Ditta A., Boncilli A., Cotza M., Carboni G., Brozzi S., Bonifazi C., Tiezzi A. Determinants of antithrombin consumption in cardiac operations requiring cardiopulmonary bypass. *Perfusion,* 2004, **19** : 47-52.
23. BRISTER S.J., OFOSU F.A., BUCHANAN M.R. Thrombin generation during cardiac surgery : is heparin the ideal anticoagulant ? *Thromb. Haemost.*, 1993, **70** : 259-62.
24. BRISTER S.J., PELLETIER A., FEDORSHYN J., PUCHALSKI S., BUCHANAN M.R. Cardiopulmonary bypass pumps and thrombin generation: what goes around comes around. *ASAIO J*., 1998, **44** : 794-8.
25. GOLOGORSKY E., DE WOLF A.M., SCOTT V., AGGARWAL S., DISHART M., KANG Y. Intracardiac thrombus formation and pulmonary thromboembolism immediately after graft reperfusion in 7 patients undergoing liver transplantation. *Liver Transpl.*, 2001, **7** : 783-9.
26. LISZKA-HACKZELL J.J., SCHOTT U. Presentation of laboratory and sonoclot variables using principal component analysis : identification of hypo- and hypercoagulation in the HELLP syndrome. *J. Clin. Monit. Comput.,* 2004, **18** : 247-52.
27. HOFFMAN M, MONROE DM. Coagulation 2006: a modern view of hemostasis. *Hematol. Oncol. Clin. North Am.*, 2007, **21** : 1-11.