

Thromboelastographic changes in liver and pancreatic cancer surgery: hypercoagulability, hypocoagulability or normocoagulability?

Lesley De Pietri, Roberto Montalti, Bruno Begliomini, Giulia Scaglioni, Giorgia Marconi, Alexia Reggiani, Fabrizio Di Benedetto, Stefano Aiello, Alberto Pasetto, Gianluca Rompianesi and Giorgio E. Gerunda

Background and objective Despite clinical and laboratory evidence of perioperative hypercoagulability, alterations in haemostasis after potentially haemorrhagic oncologic surgery are difficult to predict. This study aims to evaluate the entity, the extent and the duration of perioperative coagulative alterations following pancreas and liver oncologic surgery, by the use of both routine tests and thromboelastogram (TEG).

Methods Fifty-six patients undergoing liver ($n = 38$) and pancreatic ($n = 18$) surgery were studied. The coagulation profile was evaluated by platelet count, prothrombin time-international normalized ratio, activated partial thromboplastin time, antithrombin III and TEG at the beginning, at the end of the operation and on postoperative days 1, 3, 5 and 10.

Results All preoperative coagulative screening and TEG traces were normal before incision. In the postoperative period of the liver and pancreas groups, despite an increase in prothrombin time-international normalized ratio, a reduction in antithrombin III and platelet count and normal activated partial thromboplastin time and fibrinogen, TEG evidenced a normocoagulability in the liver group, with a major tendency towards hypocoagulability in the pancreas group, as evidenced by a transient increase in

R-time and K-time between postoperative days 1 and 3. During the study period, four cases of pulmonary embolism, resolved with heparin infusion, were recorded, in the absence of laboratory and thromboelastographic evidence of hypercoagulability.

Conclusion Despite laboratory tests evidencing hypocoagulability in both groups, TEG traces showed a normocoagulability in liver resections, whereas a transient thromboelastographic hypocoagulability was evident in patients undergoing pancreas surgery. The discrepancy between laboratory values and thromboelastographic variables was even more evident in patients undergoing major liver resections compared with minor ones. Our study supports the role of thromboelastography, despite its limitations, as a valuable tool for the evaluation of the perioperative whole coagulation process and hypercoagulability changes and to increase patient safety through better management of antithrombotic therapy.

Eur J Anaesthesiol 2010;27:608–616

Keywords: abdominal surgery, blood coagulation, haemostatic response, surgery, thromboelastography

Received 6 May 2009 Revised 27 October 2009

Accepted 31 October 2009

Introduction

Postoperative thrombotic complications, including deep vein thrombosis or pulmonary embolism, may be the clinical evidence of hypercoagulability.¹ Major surgical procedures can induce a postoperative hypercoagulable state (also related to cancer disease) by increasing platelet activation, impairing fibrinolysis and reducing the concentration of anticoagulants (antithrombin III, ATIII).^{2,3} This acquired postoperative prothrombotic condition is often not diagnosed by standard laboratory tests such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), which cannot identify a specific factor deficiency. The accuracy of these tests is limited because of the addition of buffers, and they, therefore, remain poor assays for dynamic assessment of clot strength in whole blood. Thromboelastography, allowing

in-vitro analysis of the interactive dynamic coagulation processes, from initial clotting cascade and platelet interaction to clot strengthening and fibrinolysis, has been successfully used to detect hypercoagulable states, offering a valid alternative to standard laboratory tests.^{4,5} Haemostatic balance after liver resection or pancreatic surgery can change in an unpredictable way, and haemostatic changes after pancreatic surgery have not been evaluated in depth in the literature. The only published results describe postoperative hypercoagulability following major abdominal surgery, and hypercoagulation or early consumption of haemostatic factors during pancreatic transplant or following pancreatitis.^{6–8} Removal of a considerable hepatic mass during liver resection impairs hepatic synthesis of clotting factors. Vascular clamping and severe haemorrhage can result in a hypocoagulable state. On the other hand, hypercoagulability can result from diminished hepatic synthesis of anticoagulants, extensive tissue trauma, hyperergic acute phase response, blood loss and haemodilution.^{9–13} We planned this study to describe the perioperative coagulation changes recorded by routine coagulation tests and thromboelastogram (TEG) in patients undergoing liver and

From the Division of Anaesthesiology and Intensive Care Unit (LDP, BB, GS, GM, AR, AP), Liver and Multivisceral Transplant Centre (RM, FDB, GR, GEG), Division of Vascular Surgery (SA), Azienda Ospedaliero-Universitaria di Modena-Policlinico, Modena, Italy

Correspondence to Dr Lesley De Pietri, Division of Anaesthesiology and Intensive Care Unit, Azienda Ospedaliero-Universitaria di Modena-Policlinico, # 71 via del Pozzo, 41100 Modena, Italy
Tel: +39 059 4223669; fax: +39 059 4223765; e-mail: lesley.depietri@yahoo.it

pancreatic surgery. We also compared the routine laboratory coagulation data with values obtained by computer analysis of TEG tracings in order to find a correlation between the two methods of analysis.

Patients and methods

After ethics committee approval and informed consent, 59 consecutive patients scheduled for liver and pancreatic surgery under general anaesthesia were evaluated for this study (Table 1). Preexisting coagulation disorders, preoperative anticoagulation and use of nonsteroidal anti-inflammatory drugs or aspirin 1 week before surgery were exclusion criteria. Preoperative coagulation screening included prothrombin time-international normalized ratio (PT-INR), aPTT, fibrinogen, ATIII and D-dimer levels. Protein C and S levels, factor V Leiden mutation and lupus anticoagulant antibodies were also measured for those patients who declared an inherited coagulation disorder or some coagulation problem in their medical history. According to this protocol, one patient was excluded because of chronic anticoagulation and two patients because of chronic use of preoperative aspirin. Therefore, 56 patients out of 59 were suitable to be enrolled in the study. Ten (17.9%) patients underwent minor liver resections (unsegmentectomies and bisegmentectomies, nonanatomical resections), 28 (50%) patients had major resections of three or more segments and 18 (32.1%) patients underwent pancreatic surgery (Table 1). Data were collected prospectively from January 2007 to September 2008. Laboratory screening in all patients included haematocrit (Hct; normal range: 35–

47%), haemoglobin (Hb; normal range: 13.5–17.5 g dl⁻¹), red blood cell count (RBC; normal range: 4–5.20 × 10⁶ μl⁻¹), white blood cell count (WBC; normal range: 4.30–10.80 × 10³ μl⁻¹), platelet count (PLT; normal range: 150–400 × 10³ μl⁻¹), PT-INR (normal range: 0.84–1.25), aPTT (normal range: 0.82–1.24), fibrinogen (normal range: 200–400 mg dl⁻¹), ATIII (80–120%) and TEG (Haemoscope Corp., Skokie, Illinois, USA) traces. Laboratory tests and thromboelastographic tracings were performed at the same time after induction of anaesthesia (postinduction), at the end of surgery (EOS), and on the first, third, fifth and tenth postoperative day (POD). To obtain TEG tracings, 360 μl of blood was transferred from a 3 ml arterial sample into a disposable cup on the thromboelastograph coagulation analyser and the temperature setting was adjusted for the patient's temperature. Clot formation was triggered by contact activation. Cups containing heparinase were used from POD 1 to antagonize heparin effects resulting from the heparinized normal saline used to flush the indwelling central venous catheter. TEG variables analysed were reaction time (R-time; normal range: 12–26 min), clot formation time (K-time; normal range: 3–13 min), α-angle (normal range: 14–46°) and maximum amplitude (normal range: 42–63 mm). The normal ranges for each of these values, corresponding to native whole blood samples, were obtained from the Haemoscope Corporation. The hypercoagulable state was defined as the presence of at least two of the following: shortened R-time and/or K-time, increased α-angle and increased maximum amplitude.^{5,14} Standard routine surgical and anaesthetic care procedures were adopted. Thromboprophylaxis included lower extremity sequential pneumatic compression, during the surgical procedure and until postoperative mobilization, and a daily injection of dalteparin or enoxaparin, 5000 UI, starting the evening after surgery, according to American College of Chest Physicians Guidelines (8th edition).¹⁵ According to our surgical department policy, low molecular weight heparin (LMWH) was not administered the evening after surgery when the first postoperative laboratory data showed INR more than 1.5, PLT count less than 70 × 10³ dl⁻¹ and/or in patients who received packed RBCs during surgery. Diazepam 0.1 mg kg⁻¹ was given per os 1 h before induction of anaesthesia. Fluid infusion and haemodynamic monitoring required a peripheral 14G catheter, a 20 cm 14G central venous catheter in the right internal jugular vein, and a 20G catheter in the left radial artery. Crystalloids and hydroxyethyl starch (HES) with a low molecular substitution ratio (Voluven 6% HES 130/0.4 in 0.9% sodium chloride injection) were infused. At the placement of the epidural catheter, a preload of 10 ml kg⁻¹ Ringer's lactate was infused; after incision, a fluid protocol of 8 ml kg⁻¹ per hour of Ringer's lactate was followed both during liver resection and during pancreatic surgery. A thoracic epidural catheter (T9–T10; T10–T11) was inserted before induction in 49

Table 1 Clinical characteristics of patients

Sex (F/M)	19 (33.9%)/37 (66%)
Male	37 (66%)
Female	19 (33.9%)
Age (years)	62.6 ± 14.3
Surgical indications	
Colon cancer metastasis	17 (30.3%)
Hepatocellular carcinoma (HCC)	10 (17.9%)
Mammalian metastasis	5 (8.9%)
Colangiocarcinoma	6 (10.7%)
Pancreatic head cancer	11 (19.6%)
Pancreatic tail cancer	6 (10.7%)
Papilla di Vater cancer	1 (1.8%)
Surgical procedure	
Major liver resection	28 (50%)
Minor liver resection	10 (17.9%)
Pancreatectomy	18 (32.1%)
Surgical operations	
Right hepatectomy	21 (37.5%)
Left hepatectomy	6 (10.7%)
Bisegmentectomies	7 (12.5%)
Segmentectomies	4 (7.1%)
DCP	11 (19.6%)
TP	7 (12.5%)
Length of surgery	
Liver group (min)	376.1 ± 124
Pancreas group (min)	443.2 ± 78.5
Total amount of fluids administered	
Liver group (ml)	4227 ± 2354
Pancreas group (ml)	5366 ± 2712

DCP, duodenocephalopancreatectomy; TP, total pancreatectomy.

patients. Intraoperative hypothermia was prevented by forced air surface warming (Bair Hugger) and by warm fluids (H-275 or H-1000, Level 1 Technologies). An oesophageal temperature probe monitored core temperature in all patients. Haemonetics Cell-Saver 5 was always available. Patients were taken to the ICU for overnight observation or returned to the ward according to their preoperative condition, extent of liver resection and intraoperative events (major bleeding, cardiovascular imbalance and respiratory dysfunction).

Statistical analysis

All values are expressed as mean \pm SD. Differences between preoperative coagulation tests and TEG indexes and follow-up values were evaluated by paired *t*-test. To calculate differences between continuous data among independent groups, the *t*-test for independent samples was used. The correlations between fibrinogen and maximum amplitude, PLT count and α , INR and R, and INR and K were determined by simple linear regression analysis. Correlations between continuous data were analysed by bivariate correlation procedure, computing Pearson's correlation coefficient with their significance level. All *P* values of less than 0.05 were considered to indicate statistical significance. Statistical analysis was performed by SPSS for Windows version 15.0.

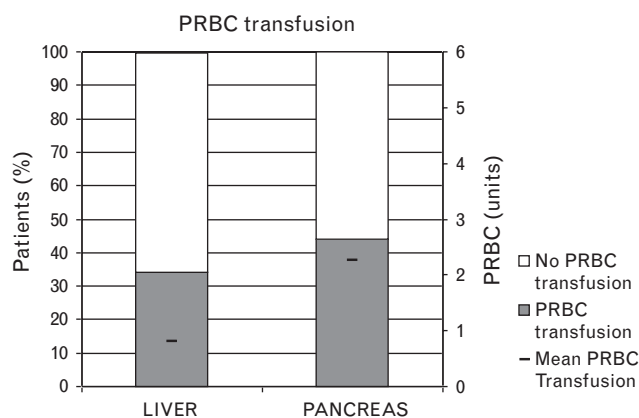
Results

All preoperative laboratory values and TEG tracings were within normal ranges. Core temperature at the EOS was $35.8^{\circ}\text{C} \pm 0.5$ (range 35–36.4). All patients were mobilized 2.2 ± 1.4 days after surgery. Fifty units of packed RBCs were transfused during the entire study in 21 patients (Fig. 1). Eight patients out of 18 (44%) undergoing pancreatic surgery received a mean of 2.25 units per patient (range 2–4 units) and 13 patients out of 38 (34.2%) undergoing liver surgery received a mean of

0.81 units per patient (range 2–4 units). In particular, two patients undergoing minor liver resection and 11 patients undergoing major liver resection were transfused, respectively, with a total amount of 4 units and 27 units. The mean Hct value in all patients in the study was $35.3 \pm 5.0\%$ and no statistically significant differences among the studied groups were registered. No PLTs, fresh frozen plasma or coagulation factors were used during the perioperative period. LMWH was not administered to 14 (25%) patients the evening after the surgical procedure. The mean length of surgery was 376.1 ± 124 and 443.2 ± 78.5 min in the liver and pancreas groups, respectively ($P = 0.04$). The total amount of fluids administered in these two groups was similar ($P = 0.11$, Table 1). Five patients had surgical complications after POD 10, but no postoperative bleeding requiring transfusion was observed. As shown in Fig. 2, a gradual increase in the mean value of INR was observed until POD 1 in both the liver and pancreas groups, followed by a gradual return to normal values by POD 5. The comparison of INR between the two groups showed consistently higher values in the liver group, mainly on POD 3 (1.28 ± 0.24 vs. 1.12 ± 0.17 , $P < 0.05$). aPTT values were within the normal range throughout the study, and patterns of changes were similar in both groups. aPTT was significantly higher in the pancreas group on POD 1 (1.25 ± 0.21 vs. 1.14 ± 0.15 , $P < 0.05$). Fibrinogen levels were normal in both groups until POD 1 (Fig. 1), then they increased and the highest values were observed on POD 3 in both groups (liver: 524 ± 166 mg dl⁻¹; pancreas: 613 ± 132 mg dl⁻¹, $P < 0.001$ in comparison with the pre-induction value). After POD 5, fibrinogen values remained above the normal range in both groups. PLT values (Fig. 2) were normal in both groups, but were also higher in the pancreas group on POD 3 (182 ± 71 vs. $143 \pm 56 \times 10^3$ dl⁻¹, $P < 0.042$), on POD 5 (241 ± 88 vs. $166 \pm 62 \times 10^3$ dl⁻¹, $P < 0.001$) and on POD 10 (355 ± 142 vs. $223 \pm 108 \times 10^3$ dl⁻¹, $P < 0.001$). ATIII levels showed a significant sharp decrease at EOS in both groups (liver group: $62 \pm 17\%$, pancreas group $64 \pm 15\%$, $P < 0.001$ in comparison with the value before induction of anaesthesia), followed by a persistent reduction in the liver group and by a progressive slight increase until POD 10 in the pancreas group (Fig. 2).

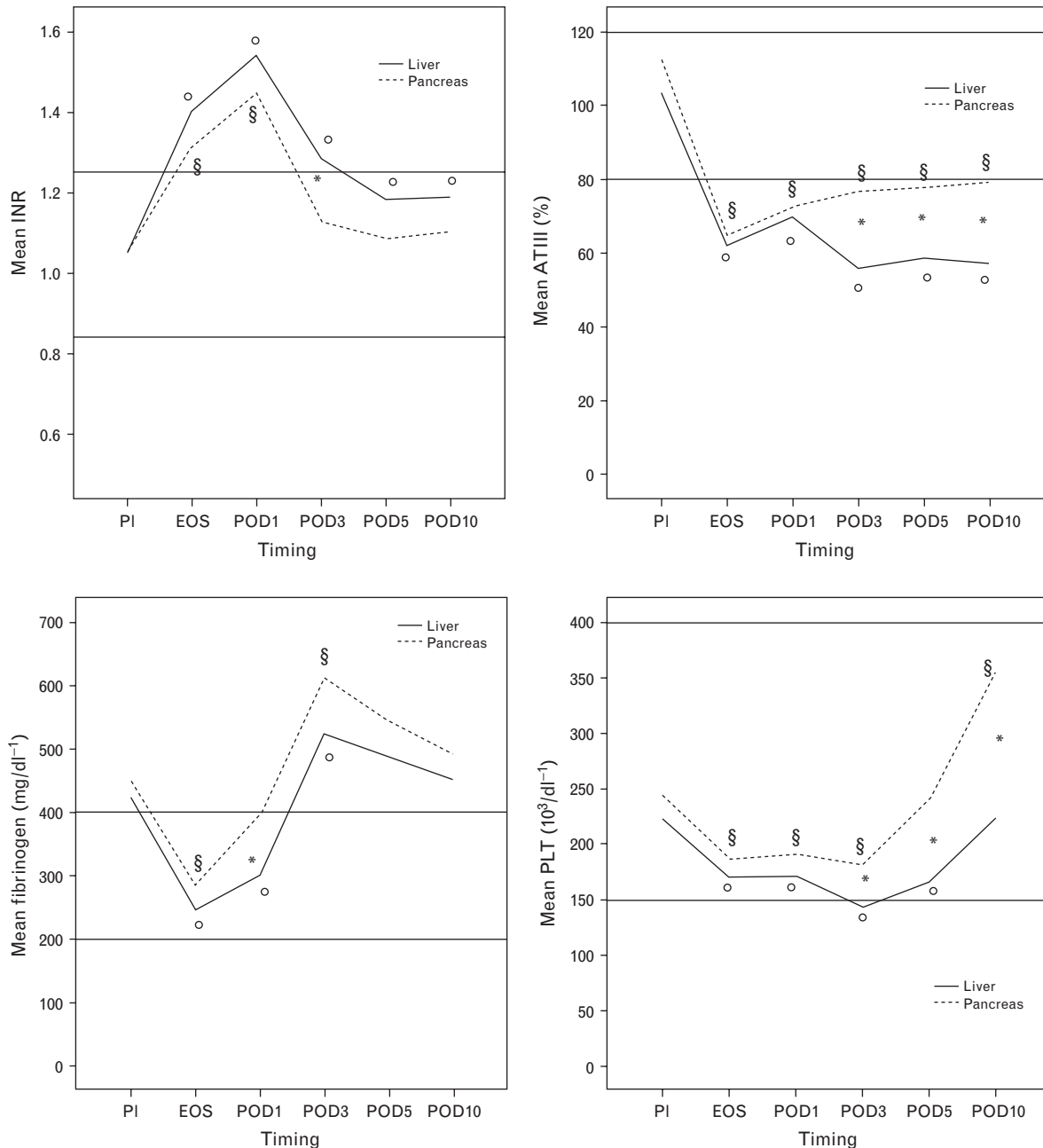
Thromboelastography variables remained consistently within the range of normality in the liver group (Fig. 3). R-time and K-time increased from the EOS until POD 3 in the pancreas group and then decreased until POD 5. α -Angle remained within the normal range in the pancreas group until POD 10 (α 42.8 ± 23), whereas maximum amplitude values (63.9 ± 9) were above the reference limits on POD 5. In both groups, strong correlations between fibrinogen and maximum amplitude, PLTs and maximum amplitude, INR and R-time, and PLTs and α -angle were observed in every sample (Table 2).

Fig. 1



Percentage of patients who received intraoperative packed red blood cell units in pancreas and liver groups and units of packed red blood cells transfused per patient. PRBC, packed red blood cells.

Fig. 2

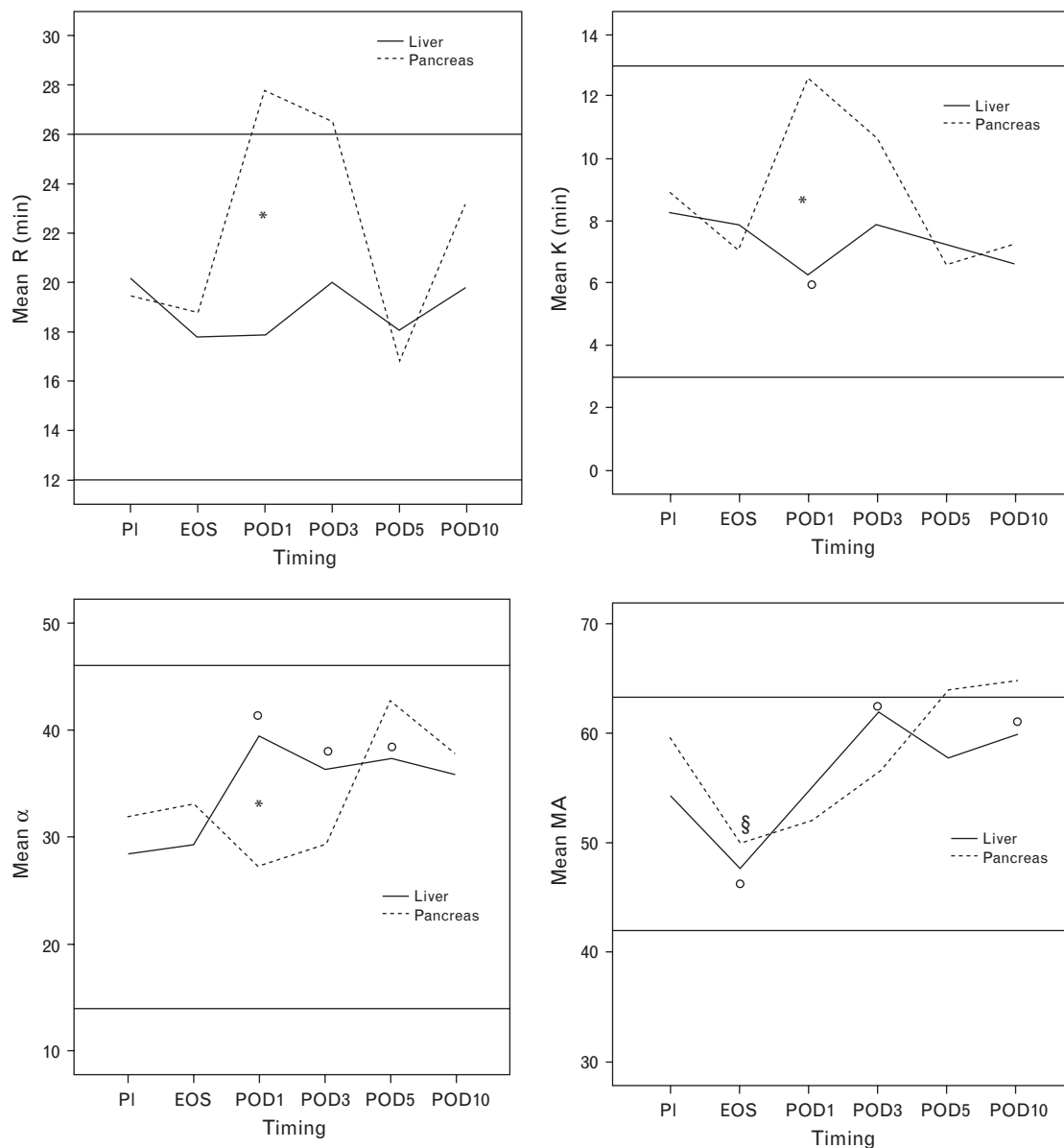


Perioperative change in laboratory variables (international normalized ratio, antithrombin III, fibrinogen, platelet count) in the liver group and the pancreas group. Data are expressed as mean and limits of normality are shown. * $P < 0.05$ between the two groups. $^{\circ}P < 0.05$ vs. PI in the liver group. $^{\S}P < 0.05$ vs. PI in the pancreas group. ATIII, antithrombin III; EOS, end of surgery; INR, international normalized ratio; PI, postinduction; PLT, platelet count; POD, postoperative day.

Patients who had major liver resections also had an INR value suggesting hypocoagulability ($P < 0.01$, in all samples excluding postinduction, compared with patients who had minor liver resections; Fig. 3). aPTT values were normal in both groups (minor and major resections), but longer times were observed in surgical procedures for major liver resections. Fibrinogen decreased at EOS and increased from POD 1 to POD

3. At this time and on POD 5, fibrinogen values were higher in minor liver resections than in major ones ($P < 0.05$; Fig. 4). PLT counts were higher in the major liver resection group in the postinduction period and progressively decreased until POD 3 (Fig. 4). ATIII levels showed a significant sharp decrease at EOS in both groups (major resection group: $64 \pm 20.4\%$; minor resection group $56 \pm 18.3\%$, $P < 0.001$ in comparison with

Fig. 3



Perioperative evolution of thromboelastogram variables (R-time, K-time, α-angle, maximum amplitude) in the liver group and the pancreas group. Data are expressed as mean and limits of normality are shown. * $P < 0.05$ between the two groups. ^o $P < 0.05$ vs. basal in the liver group. [§] $P < 0.05$ vs. basal in the pancreas group. EOS, end of surgery; PI, postinduction; POD, postoperative day; TEG, thromboelastogram.

Table 2 Correlations between variables in the liver and pancreas groups

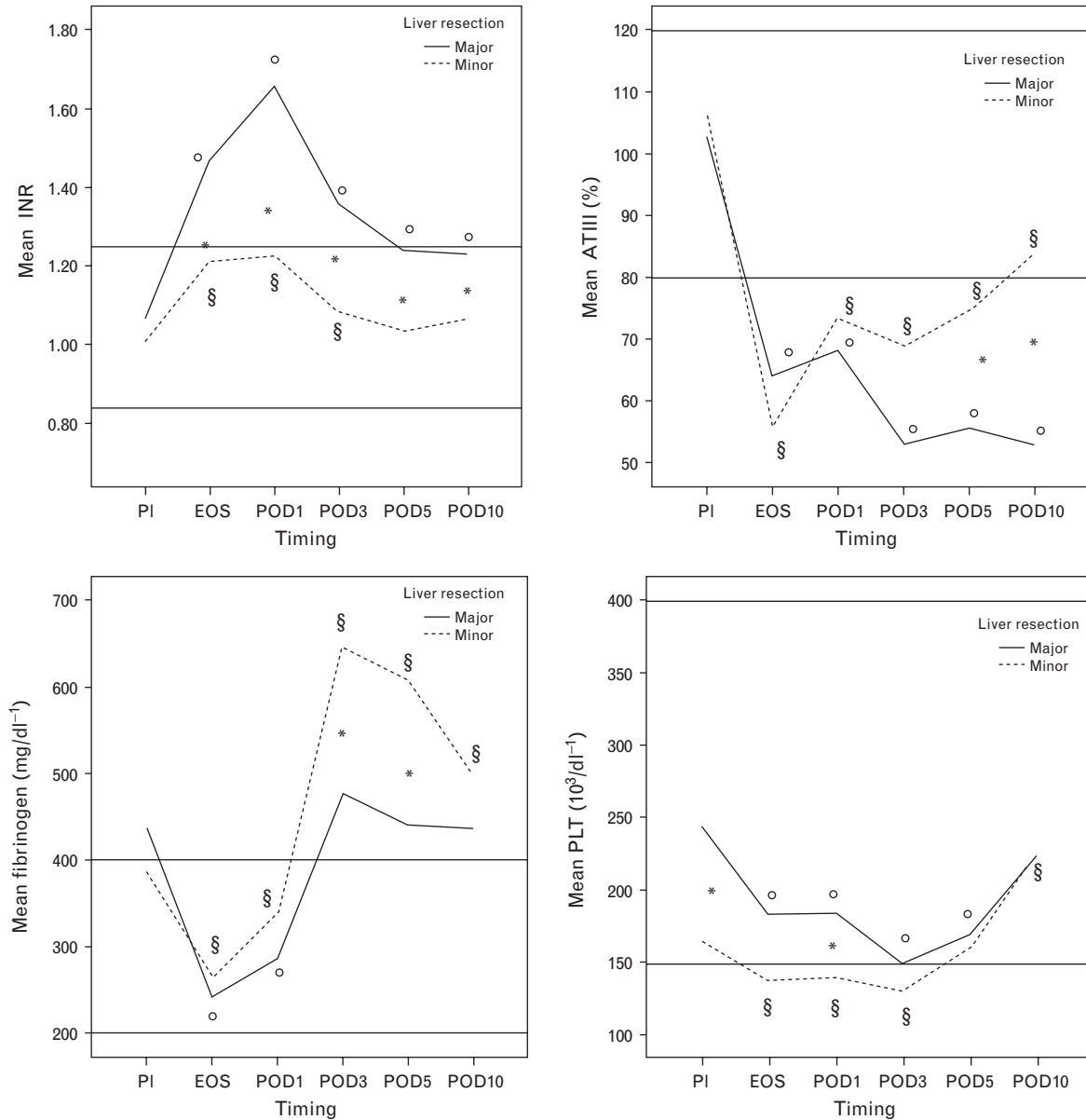
	Liver group		Pancreas group	
	r ²	P	r ²	P
INR-R	0.04	0.003	0.023	0.16
INR-K	0.012	0.16	0.011	0.334
PLT-α	0.038	0.009	0.051	0.034
PLT-MA	0.166	<0.001	0.249	<0.001
Fibrinogen-MA	0.433	<0.001	0.21	<0.001

INR, international normalized ratio; MA, maximum amplitude; PLT, platelet count.

the value before induction of anaesthesia), followed by a persistent increase in the minor resection group until POD 10, whereas in the major resection group ATIII value progressively decreased until POD 10 (Fig. 4).

The thromboelastographic tracings of patients who had liver surgery remained within the normal range throughout the study (Fig. 5). R-time and K-time were closer to the lower reference limits in patients undergoing major liver resection on POD 1 (R: 14.6 ± 6 vs. 25.8 ± 11 min, $P < 0.001$ and K: 5 ± 2 vs. 9.5 ± 5.4 min, $P < 0.001$, major

Fig. 4

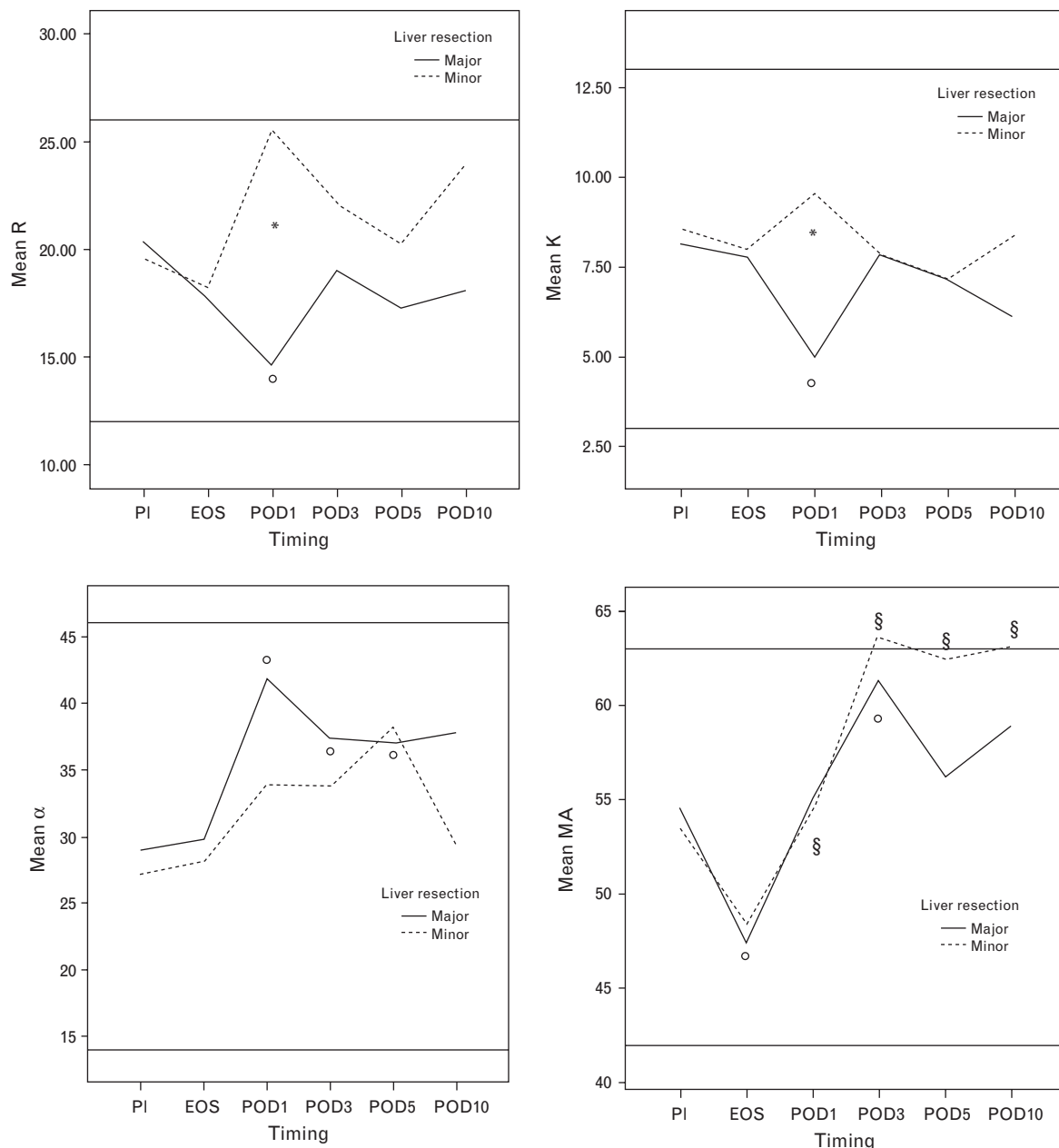


Perioperative change in laboratory variables (international normalized ratio, antithrombin III, fibrinogen, platelet count) in major and minor resection groups. Data are expressed as mean and limits of normality are shown. * $P < 0.05$ between the two groups. ° $P < 0.05$ vs. basal in the major liver resection group. § $P < 0.05$ vs. basal in the minor liver resection group. ATIII, antithrombin III; EOS, end of surgery; INR, international normalized ratio; PI, postinduction; PLT, platelet count; POD, postoperative day.

resections vs. minor resections). α -Angle values increased in both resection groups until POD 1 (Fig. 5). The highest values were observed in the group of major resections (41.8 ± 13.8 on POD 1 vs. 28.9 ± 8.8 on post-induction; $P < 0.05$). α -Angle values were higher on POD 5 in the minor resection group (38.2 ± 18 on POD 5 vs. 33.8 ± 19.6 on POD 1; $P < 0.05$). Maximum amplitude showed a quite similar behaviour, characterized by a sharp increase in both groups from EOS to POD 3. Thereafter, higher values were recorded in the group

of minor liver resections. Four patients out of 14, who did not receive LMWH the evening of surgery (two had a right hepatectomy and two a duodenocephalopancreatotomy, DCP) showed clinical signs of pulmonary embolism, diagnosed by spiral computed tomography (CT) showing lobar or segmental defects on POD 3 or POD 4. In contrast, we did not record any case of pulmonary embolism among the 42 patients who received LMWH from the evening of surgery ($P = 0.03$). Heparin intravenous treatment started after diagnosis in all these

Fig. 5



Perioperative evolution of thromboelastogram variables (R-time, K-time, α -angle, maximum amplitude) in major and minor resection groups. Data are expressed as mean and limits of normality are shown. * $P < 0.05$ between the two groups. $^{\ddagger}P < 0.05$ vs. basal in the major liver resection group. $^{\S}P < 0.05$ vs. basal in the minor liver resection group. EOS, end of surgery; PI, postinduction; POD, postoperative day; TEG, thromboelastogram.

patients, but two of them also required 1 day of mechanical ventilation. The pulmonary thromboembolism resolved within POD 14 in all patients. The thromboelastographic tracings and laboratory values of the patients who had pulmonary embolism were normal up to this event, with the exception of INR values (1.41 ± 1.18), which exceeded the upper limit in patients with or without thromboembolic complication. After the occurrence of thromboembolic episodes, no laboratory

values or thromboelastographic tracings were included in data analysis because of heparin infusion.

Discussion

Although several studies^{3,9,16} have shown substantial hypercoagulability lasting for several days after major abdominal surgery, clinical evidence of this condition has been incompletely evaluated by standard laboratory tests in oncologic liver and pancreatic surgery.

Coagulation changes after hemihepatectomy in living donors and nonmalignant hepatic tumour resection show a marked tendency to hypercoagulability, probably due to the impaired hepatic synthesis of anticoagulants (prothrombin, protein C) and reduced clearance of activated clotting factors (factor VIII or von Willebrand's factor, fibrinogen).^{9–12} Bezeaud *et al.*⁹ declared that the decrease in coagulation inhibitors, protein C and anti-thrombin, persisted longer than PT and fibrinogen deficiencies, suggesting that, after liver resection, the balance rapidly favours procoagulant rather than anti-coagulant mechanisms.

In the present study, we evaluated the coagulation behaviour of patients undergoing major and minor liver resections and pancreatic surgery for cancer in order to better understand the coagulation changes induced by surgery. We chose these surgical procedures because of their long duration, the effects on coagulation and the additional risk factor represented by cancer. We observed an early increase in INR and aPTT as well as a reduction in PLTs, fibrinogen and ATIII after surgery in all the patients studied. The preoperative values were progressively reached in the postoperative period, as previously reported by other authors.^{9,10} In agreement with the results of Cerutti *et al.*,¹⁰ our laboratory data mainly related to liver surgery showed hypocoagulability, whereas the thromboelastographic tracings outlined normocoagulability. Allowing analysis of the interactive dynamic coagulation processes, TEG has been successfully used in clinical settings to reveal hypercoagulable states related to surgical procedures^{5,17} offering a good alternative to most clotting assays (e.g. PT, INR, aPTT), which cannot identify a specific factor deficiency but only a particular pathway. The PT and aPTT tests have, in fact, proved to be limited in their ability to simulate the dynamics of clot formation. Of course, thromboelastography is an in-vitro analysis that can take place far away from the bedside, but the advantage that TEG offers in providing a comprehensive functional evaluation of overall coagulation status, rapidly at the bedside,¹⁸ has allowed it to gain more importance in everyday clinical practice. TEG has been successfully used in clinical settings to reveal hypercoagulable states related to surgical procedures,⁵ to predict thromboembolic events,¹⁹ to clinically manage haemostasis²⁰ and to guide transfusion therapy.²¹

As observed by Mahla *et al.*,⁵ we found an early decrease in the R-time and in the K-time in the liver group and an increase in clot strength, revealed by a continuous postoperative increase in maximum amplitude, in both the liver and pancreatic groups. The pattern of maximum amplitude changes was similar to the fibrinogen pattern, in both the liver and the pancreas groups, and both peaked on POD 3, as described in previously published studies.^{3,5} The discrepancy between laboratory values and thromboelastographic variables is even more evident

in patients undergoing major liver resections. In the major liver resection group, laboratory tests detected a coagulation impairment, with prolongation of INR and aPTT, from the EOS to POD 1, and a PLT and fibrinogen reduction, respectively, at the EOS and on POD 3, which was not confirmed by thromboelastographic tracings. R-time and K-time remained within the range of normality after major and minor liver resections, even if shorter in major resections on POD 1 ($P < 0.001$). This discrepancy can be explained by the greater release of factor VIII or von Willebrand's factor from the cut liver parenchyma after major resections than after minor liver resections. These factors, as described by several authors,^{9–12} are responsible for the activation of the coagulation cascade which, being an interactive dynamic process, can be detected by TEG but not by the usual laboratory tests. Cerutti *et al.*¹⁰ described a hypercoagulability state in patients undergoing major liver resections, whereas we observed normal coagulation on thromboelastography. A possible explanation can be that different patients were enrolled in the study by Cerutti *et al.*¹⁰ All these patients were healthy donors with a healthy liver and a normal coagulation profile, whereas our investigation was performed in patients with a possible liver function impairment because of neoadjuvant chemotherapy or primary liver disease (e.g. postnecrotic hepatopathy).

In contrast to patients who had liver resections, the TEG of patients undergoing pancreatic surgery showed hypocoagulability (longer R-time and K-time from POD 1 to POD 3, higher values of INR, aPTT and decreased fibrinogen values from EOS to POD 1 and POD 3). This fact could be related to a nonspecific response to injury (surgery) and to an acute pancreatitis-like reaction. The release of trypsin and other pancreatic enzymes may play a role in the pathogenesis of coagulopathies.^{6,22} The hypocoagulable profile observed in patients undergoing pancreatic surgery, apparently limited to POD 1 and POD 3, could be explained by an early intravascular consumption of coagulation factors related to circulating pancreatic enzymes, particularly trypsin.⁶

The thromboelastographic results we obtained were probably not influenced by fluids or Hct variations. The choice to administer HES with a low molecular substitution ratio within the advised range ($< 50 \text{ ml kg}^{-1}$ of body weight per day) should reduce or exclude an effect of HES on thromboelastographic variables.^{23,24} The administration of the same intraoperative fluid protocol in both surgical groups and the similar total amounts of fluids administered should have reduced the role of haemodilution in differing TEG results between hepatic and pancreatic surgery.^{25,26} In a similar way, it is difficult to presuppose an important effect of Hct on TEG variables as the mean Hct value registered in all the patients at any time of observation was $35.3 \pm 5.0\%$ and only in 8.5% of patients was it under 30%.²⁷

Two patients who had pancreatectomy and two patients who had major liver resections had nonfatal pulmonary embolism between POD 3 and POD 4 without any TEG suggestion of abnormal activation of coagulation. The TEG may have missed the changes that led to thromboembolic events because of possible inappropriate timing schedule of blood samplings (too long intervals between tracings) or because of an inherent weakness of this monitoring approach (which cannot detect regional coagulable abnormalities and local thromboembolic processes). The thromboprophylaxis we applied did not prevent the thromboembolic events, suggesting a revision of our departmental policy. The absence of postoperative bleeding even after the administration of thromboprophylaxis from the evening of surgery together with the higher incidence of thromboembolic events in patients who did not receive it recommends the administration of LMWH together with mechanical methods of prophylaxis from the day before the operation and/or the evening of the operation itself without withholding it on the basis of laboratory data.

In conclusion, although laboratory tests point to hypo-coagulability in the pancreas and liver surgical groups, TEG tracings revealed normal coagulation after liver resections, whereas a transient hypocoagulability was observed on TEG in patients undergoing pancreatic surgery. The discrepancy between laboratory values and thromboelastographic variables was even more evident in patients undergoing major liver resections compared with minor ones. Our study supports the role of thromboelastography, despite its limitations, as a valuable tool for the evaluation of the perioperative whole coagulation process and hypercoagulability changes and to increase patient safety through better management of antithrombotic therapy.

References

- Clagett GP, Anderson FA Jr, Heit J, *et al.* Prevention of venous thromboembolism. *Chest* 1995; **108** (4 Suppl):312S–334S.
- Wilson D, Cooke EA, McNally MA, *et al.* Changes in coagulability as measured by thrombelastography following surgery for proximal femoral fracture. *Injury* 2001; **32**:765–770.
- Gibbs NM, Crawford GP, Michalopoulos N. Postoperative changes in coagulant and anticoagulant factors following abdominal aortic surgery. *J Cardiothorac Vasc Anesth* 1992; **6**:680–685.
- Srinivasa V, Gilbertson LI, Bhavani-Shankar K. Thromboelastography: where is it and where is it heading? *Int Anesthesiol Clin* 2001; **39**:35–49.
- Mahla E, Lang T, Vicenzi MN, *et al.* Thromboelastography for monitoring prolonged hypercoagulability after major abdominal surgery. *Anesth Analg* 2001; **92**:572–577.
- Saif MW. DIC secondary to acute pancreatitis. *Clin Lab Haematol* 2005; **27**:278–282.
- Murphy D, Imrie CW, Davidson JF. Haematological abnormalities in acute pancreatitis. A prospective study. *Postgrad Med J* 1977; **53**:310–314.
- Salomone T, Tosi P, Palareti G, *et al.* Coagulative disorders in human acute pancreatitis: role for the D-dimer. *Pancreas* 2003; **26**:111–116.
- Bezeaud A, Denninger MH, Dondero F, *et al.* Hypercoagulability after partial liver resection. *Thromb Haemost* 2007; **98**:1252–1256.
- Cerutti E, Stratta C, Romagnoli R, *et al.* Thromboelastogram monitoring in the perioperative period of hepatectomy for adult living liver donation. *Liver Transpl* 2004; **10**:289–294.
- Dondero F, Taille C, Mal H, *et al.* Respiratory complications: a major concern after right hepatectomy in living liver donors. *Transplantation* 2006; **81**:181–186.
- Lambing A, Kuriakose P, Abouljoud MS. Hypercoagulability risks among adult living liver donors. *Transplant Proc* 2006; **38**:3579–3581.
- Shimada M, Matsumata T, Kamakura T, *et al.* Modulation of coagulation and fibrinolysis in hepatic resection: a randomized prospective control study using antithrombin III concentrates. *Thromb Res* 1994; **74**:105–114.
- Park MS, Martini WZ, Dubick MA, *et al.* Thromboelastography as a better indicator of hypercoagulable state after injury than prothrombin time or activated partial thromboplastin time. *J Trauma* 2009; **67**:266–275; discussion 75–76.
- Geerts WH, Bergqvist D, Pineo GF, *et al.* Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133** (6 Suppl):381S–453S.
- McCraith DJ, Cerboni E, Frumento RJ, *et al.* Thromboelastography maximum amplitude predicts postoperative thrombotic complications including myocardial infarction. *Anesth Analg* 2005; **100**:1576–1583.
- Traverso CI, Caprini JA, Arcelus JL. Application of thromboelastography in other medical and surgical states. *Semin Thromb Hemost* 1995; **21** (Suppl 4):50–52.
- Schreiber MA, Differding J, Thorborg P, *et al.* Hypercoagulability is most prevalent early after injury and in female patients. *J Trauma* 2005; **58**:475–480; discussion 80–81.
- Kashuk JL, Moore EE, Sabel A, *et al.* Rapid thrombelastography (r-TEG) identifies hypercoagulability and predicts thromboembolic events in surgical patients. *Surgery* 2009; **146**:764–772; discussion 72–74.
- Hobson AR, Agarwala RA, Swallow RA, *et al.* Thrombelastography: current clinical applications and its potential role in interventional cardiology. *Platelets* 2006; **17**:509–518.
- Stahel PF, Moore EE, Schreier SL, *et al.* Transfusion strategies in postinjury coagulopathy. *Curr Opin Anaesthesiol* 2009; **22**:289–298.
- Ranson JH, Lackner H, Berman IR, Schinella R. The relationship of coagulation factors to clinical complications of acute pancreatitis. *Surgery* 1977; **81**:502–511.
- Egli GA, Zollinger A, Seifert B, *et al.* Effect of progressive haemodilution with hydroxyethyl starch, gelatin and albumin on blood coagulation. *Br J Anaesth* 1997; **78**:684–689.
- Jamnicki M, Zollinger A, Seifert B, *et al.* Compromised blood coagulation: an in vitro comparison of hydroxyethyl starch 130/0.4 and hydroxyethyl starch 200/0.5 using thrombelastography. *Anesth Analg* 1998; **87**:989–993.
- de Jonge E, Levi M. Effects of different plasma substitutes on blood coagulation: a comparative review. *Crit Care Med* 2001; **29**:1261–1267.
- Langeron O, Doelberg M, Ang ET, *et al.* Voluven, a lower substituted novel hydroxyethyl starch (HES 130/0.4), causes fewer effects on coagulation in major orthopedic surgery than HES 200/0.5. *Anesth Analg* 2001; **92**:855–862.
- Iselin BM, Willmann PF, Seifert B, *et al.* Isolated reduction of haematocrit does not compromise in vitro blood coagulation. *Br J Anaesth* 2001; **87**:246–249.