Thrombosis Research 176 (2019) 95–100

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Role of spleen and liver for enhanced hemostatic competence following administration of adrenaline to humans

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ARTICLE INFO

Keywords:
Adrenaline
Coagulation competence
Hemostasis
Multiplate
Thrombelastography

ABSTRACT

This study evaluated by thrombelastography® (TEG) and Multiplate® analyses the role of the spleen and the liver for adrenaline-induced enhanced hemostatic competence. Eight splenectomized subjects and eight matched healthy control subjects were exposed to one-hour infusion of adrenaline (6 μg/kg/h). Administration of adrenaline to the healthy subjects reduced time to TEG-detected initial fibrin formation (by 22%) and increased rate of clot development (by 10%), maximal amplitude (by 8%), platelet count (by 30%), and Multiplate evaluated Ristocetin-induced platelet aggregation (by 21%) (all $p \leq 0.05$), but infusion of adrenaline did not result in significant arterial to liver vein differences for plasma markers of coagulation. In the splenectomized subjects, adrenaline reduced the TEG-determined time to initial fibrin formation (by 17%; $p = 0.005$) whereas rate of clot development and maximum amplitude were unaffected. Also, 6 patients undergoing liver transplantation were exposed to infusion of adrenaline (4.8 μg/kg/h) during the anhepatic phase of the operation and that increased TEG-determined rate of clot formation (by 10%; $p < 0.05$), maximal amplitude (by 9%; $p = 0.002$) and tended to reduce time to initial fibrin formation ($p = 0.1$). In conclusion, adrenaline enhances hemostasis as evaluated by TEG in both healthy subjects and in anhepatic patients during liver transplantation and Ristocetin-induced aggregation in control subjects. In contrast, infusion of adrenaline reduces only time to initial fibrin formation in splenectomized subjects. These findings suggest that mobilization of platelets from the spleen dominates the adrenaline-induced enhanced hemostatic competence.

1. Introduction

Failing hemostatic competence increases perioperative bleeding [1], but administration of adrenaline enhances hemostatic competence as demonstrated early in the 20th century. Von den Velden et al. [2] reported infusion of adrenaline to reduce whole blood coagulation time in humans as confirmed by Forwell & Ingram [3]. Sympathetic activity enhances coagulation competence [4] illustrated by infusion of adrenaline or noradrenaline to humans affecting blood coagulation markers (prothrombin [5], thrombin-antithrombin III complexes [6], and von Willebrand factor [7]) along with an increase in platelets and coagulation factor 8 released from the spleen [8,9]. Thus both the spleen and the liver seem important for adrenergic-induced enhanced hemostatic competence [10,11].

Hemostasis includes three phases: Initiation, amplification/propagation and fibrinolysis [12]. The initiation phase is driven mainly by coagulations factors, and when evaluating hemostasis using thrombelastography (TEG®) represented by the reaction time, i.e. time to until initial fibrin formation (R-time). For the amplification/propagation phase, platelets are important along with coagulation factors [12,13] and the role of platelets and coagulation factor 8 during low-dose adrenaline infusion is demonstrated by TEG [8,14,15]. Using TEG the

Abbreviations: α-angle, rate of clot formation; ADP, adenosine diphosphate-induced activation; aPTT, activated partial thromboplastin time; ASPI, arachidonic acid cyclooxygenase-dependent activation; AUC, area under the curve; BPM, beats per minute; CO, cardiac output; DBP, diastolic blood pressure; h, hour; HR, heart rate; INR, international normalized ratio; LY30, thrombosis at 30 min; LTx, liver transplantation; MA, maximal amplitude; MAP, mean arterial pressure; RISTO, Ristocetin-induced aggregation; R-time, initial fibrin formation; SBP, systolic blood pressure; SD, standard deviation; SV, stroke volume; TEG, thrombelastography; TPR, total peripheral resistance; TRAP, thrombin receptor-activation peptide thrombin receptor PAR-1 activation

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https://doi.org/10.1016/j.thromres.2019.02.018
Received 13 September 2018; Received in revised form 17 January 2019; Accepted 15 February 2019
Available online 16 February 2019
0049-3848/

Table 1
Characteristics for splenectomized and control subjects.

	Splenectomized (n = 8)	Controls (n = 8)
Age (years)	28.3 ± 7.3	27.8 ± 7.0
Height (cm)	173.5 ± 7.8	175.8 ± 7.1
Weight (kg)	72.3 ± 15.4	73.7 ± 16.8
Sex (n = male/female)	2/6	2/6

Values are mean ± SD; n = number.

amplification/propagation phase is evaluated by the rate of clot formation (α-angle) and maximal amplitude (MA) reflecting clot strength. Fibrinolysis is evaluated using TEG by LY30 that represents the percentage decrease in MA after 30 min.

We evaluated the effect of low-dose adrenaline infusion on hemostatic competence as assessed by TEG and Multiplate in subjects who had undergone splenectomy. Furthermore, in healthy subjects the release of coagulations factors, activated partial thromboplastin time, and fibrinogen from the liver in response to administration of adrenaline was determined. Lastly, the effect of adrenaline on hemostatic competence was assessed by TEG during the anhepatic phase of orthotropic liver transplantation (LTx). We hypothesized that the effect of adrenaline on hemostatic competence would be dominated by the spleen rather than by coagulation factors released from the liver.

2. Methods

The study was approved by the Scientific Ethics Committee of the Capital Region of Denmark (H-2-2012-082) and conducted in accordance with the Declaration of Helsinki including oral and written informed consent obtained before the study. The effect of adrenaline on hemostatic competence during LTx was carried out while administration of adrenaline aimed to reduce perioperative bleeding and attenuate increase in plasma potassium during reperfusion of the donated liver. Observations reported were in accordance with guidelines provided by The National Committee on Health Research and approved by the Local Ethical Committee (H-2-2014-FSP27) who waived the need for patient consent.

2.1. Splenectomized and healthy subjects

Eight subjects who had undergone splenectomy and eight age, sex, weight, and height matched healthy subjects were included in the study (Table 1). The subjects had been splenectomized for various reasons (spherocytosis, trauma, immune thrombocytopenia, autoimmune hemolytic anemia, or malformation) and were cured or had been symptom free for at least two years at the time of the study. All control subjects were healthy, non-smokers, not pregnant, and free of medication at the time of the study.

With the subjects supine a 20 G catheter was placed in the brachial artery of the non-dominate arm for blood sampling and for monitoring arterial pressure, heart rate (HR), cardiac output (CO), and total peripheral resistance (TPR) using a modified Finometer™ system (Finapres Medical System BV, Holland) [16]. For adrenaline infusion a catheter (20 G Cavafix, Braun, Melsungen, Germany) was placed in a vein on the non-dominant arm and advanced to the axillary vein and after a 30-min rest period, adrenaline (6 μg/kg/h) was administrated for 1 h. Arterial blood samples were collected before infusion, after 30 and 60 min of infusion, and 30 min thereafter. In seven of the healthy subjects, a liver venous catheter was introduced, guided by x-ray, through a sheet in the femoral vein under cover of local anesthesia (2% lidocaine). Liver venous blood samples were collected simultaneously with those from the artery to obtain arterial-liver venous differences.

2.2. Liver transplantation

The effect of adrenaline (4.8 μg/kg/h) on hemostatic competence was also assessed in 6 patients during the dissection and anhepatic phase of LTx representing clamping of the hepatic artery, the portal and inferior caval vein until reperfusion of the grafted liver and a veno-venous bypass was used to secure venous return from the lower body [17].

2.3. Whole blood coagulation analysis

Whole blood was collected in citrate tubes (9NC, BD Vacutainer; 6 × 3 mL) for TEG and analyzed within 30 min. 340 μL of Kaolin-activated blood was added to the cup of the TEG apparatus along with 20 μL 0.2 M calcium chloride and analyzed at 37 °C.

2.4. Platelet aggregation analysis

Blood samples were drawn in heparin tubes (LH, BD Vacutainer; 2 × 4 mL) for whole blood impedance aggregometry using the Multiplate® assay (Roche) and analyzed 30 min after sampling. Adenosine diphosphate (6.5 μmol/L) was used to evaluated ADP-induced activation (ADPtest), arachidonic acid (0.5 mmol/L) evaluate cyclooxygenase-dependent activation (ASPItest), and thrombin receptor-activation peptide-6 (32 μmol/L) evaluated thrombin receptor PAR-1 activation (TRAPtest). Furthermore, Ristocetin-induced aggregation by von Willebrand factor (vWF; RISTOhigh (0.77 mg/mL) and RISTOlow (0.2 mg/mL)) was determined. Values are reported as

Table 2
Hemodynamic variables in response to adrenaline administration in splenectomized and control subjects.

	Group	0 min	30 min	60 min	30 min after
SBP (mm Hg)	Splenectomized	133 ± 10	140 ± 14	136 ± 13	126 ± 8
	Controls	123 ± 17	136 ± 20	129 ± 15	120 ± 9
DBP (mm Hg)	Splenectomized	66 ± 8	57 ± 4	57 ± 4	65 ± 5
	Controls	63 ± 9	56 ± 7	54 ± 5	63 ± 5
MAP (mm Hg)	Splenectomized	89 ± 8	84 ± 7	83 ± 7	85 ± 6
	Controls	83 ± 11	82 ± 10	79 ± 7	82 ± 6
HR (BPM)	Splenectomized	62 ± 6	85 ± 8	86 ± 11	78 ± 10
	Controls	64 ± 6	86 ± 11	89 ± 10	79 ± 14
SV (mL)	Splenectomized	86 ± 16	108 ± 21	102 ± 16	77 ± 10
	Controls	91 ± 19	117 ± 27	112 ± 26	89 ± 18
CO (L/min)	Splenectomized	5.4 ± 1.3	9.1 ± 1.6	8.7 ± 1.7	6.0 ± 0.9
	Controls	5.9 ± 1.6	10.1 ± 3.0	10.0 ± 2.8	7.1 ± 1.7
TRP (mm Hg/mL/min)	Splenectomized	1402 ± 321	745 ± 147	753 ± 136	1157 ± 171
	Controls	1185 ± 266	679 ± 154	647 ± 146	953 ± 274

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; BPM, beats per minute; SV, stroke volume; CO, cardiac output; TRP, total peripheral resistance. Values are mean ± SD.

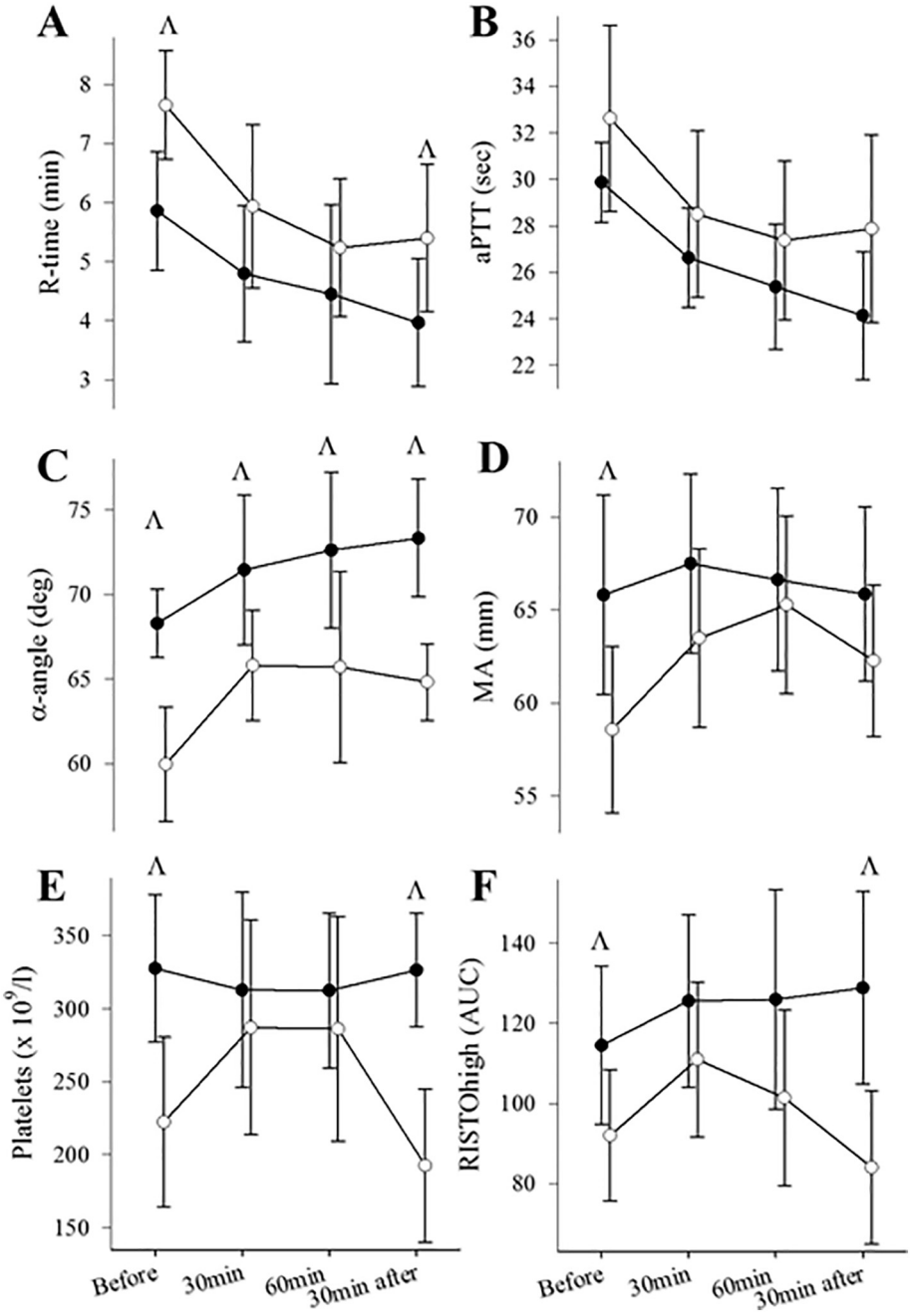

Fig. 1. Coagulation competence before, during and after adrenaline infusion in control subjects (n = 8, open circle) and splenectomized subjects (n = 8, black circle). R-time, reaction time; α-angle, rate of clot formation; deg., degrees; MA, maximal amplitude; aPTT, activated partial thromboplastin time; sec, seconds; RISTOhigh, Ristocetin-induced aggregation with von Willebrand factor; AUC, area under the curve. Values are mean ± SD. $^{\Lambda}p < 0.05$ between groups at the same time point.

area under the curve (AUC).

2.5. Plasma and cell count analysis

For plasma analysis blood samples were collected in citrate tubes (9NC, BD Vacutainer; 6 × 3 mL) and centrifuged for 10 min (3000*g*) at 5 °C with plasma stored at −80 °C. Plasma was analyzed for fibrinogen, activated partial thromboplastin time (aPTT), coagulation factor 2 + 7 + 10, and international normalized ratio (INR). aPTT was measured using IL APTT-SP liquid (ILS) and 2 + 7 + 10 and INR using Owren's PT (MediRox) both automated on an ACL TOP (ILS). Additionally, blood was sampled in EDTA tubes (K2E, BD Vacutainer; 2 × 3 mL) for determination of platelet count (XE-2100; Sysmex Corporation, Kobe, Japan) and hemoglobin.

2.6. Statistics

SPSS 23 (IBM, Armonk, NY USA) was used for analysis. Data were evaluated for normality by the Shapiro-Wilk test, Q-Q plots and box-plots. For normally distributed data a linear-mixed model was applied. For model selection, the maximum likelihood value determined the model chosen. Covariance structure was heterogeneous compound symmetry. For post hoc analysis, pairwise comparison was performed using the EMMEANS-command. *p*-Values were adjusted by Bonferroni correction to account for multiple comparisons. Presented values are mean ± SD and a *p*-value < 0.05 was taken to represent a statistically significance.

Table 3
Hemostatic variables in response to administration of adrenaline in splenectomized and controls.

	Group	0 min	30 min	60 min	30 min after
R-time (min)	Splenectomized	5.9 ± 1.0†	4.8 ± 1.1*	4.5 ± 1.4 *	4 ± 1.1 *†
	Controls	7.7 ± 0.9 †	5.9 ± 1.4 *	5.2 ± 1.2 *	5.4 ± 1.3 *†
α-Angle (deg)	Splenectomized	68.3 ± 4.9 †	71.5 ± 4.1 †	72.6 ± 4.3 †	73.3 ± 3.5 †
	Controls	60.0 ± 3.4 †	65.8 ± 3.3 †*	65.7 ± 5.6 †*	64.8 ± 2.3 †*
MA (mm)	Splenectomized	65.8 ± 5 †	67.5 ± 4.5	66.6 ± 5	65.9 ± 4.7
	Controls	58.6 ± 4.5 †	63.5 ± 4.8 *	65.3 ± 4.8 *	62.3 ± 4.1 *
LY30 (%)	Splenectomized	2 ± 2.1	1 ± 1.1	1 ± 1	2.5 ± 2.1
	Controls	0.5 ± 0.5	1 ± 2.2	0.3 ± 0.3	0.7 ± 0.6
ADP (AUC)	Splenectomized	100 ± 15	108 ± 21	103 ± 22	112 ± 26
	Controls	85 ± 17	93 ± 15	92 ± 16	83 ± 20
ASPI (AUC)	Splenectomized	108 ± 16	108 ± 24	109 ± 26	130 ± 28
	Controls	90 ± 23	105 ± 19	106 ± 22	90 ± 25
TRAP (AUC)	Splenectomized	127 ± 24	123 ± 19	127 ± 19	140 ± 27
	Controls	126 ± 17	138 ± 14	140 ± 18	147 ± 23
RISTOhigh (AUC)	Splenectomized	115 ± 20 †	126 ± 21	126 ± 27	122 ± 24†
	Controls	92 ± 16 †	111 ± 19 *	101 ± 22 *	84 ± 19 †
RISTOlow (AUC)	Splenectomized	39 ± 8	33 ± 13	34 ± 5	43 ± 13
	Controls	26 ± 14	27 ± 7	24 ± 7	25 ± 6
Platelets ($\times 10^9$/L)	Splenectomized	327 ± 50 †	313 ± 67	313 ± 53	327 ± 39 †
	Controls	222 ± 58 †	287 ± 74 *	286 ± 77 *	193 ± 52 †*
aPTT (sec)	Splenectomized	30 ± 1.8	27 ± 2.0 *	25 ± 2.5 *	25 ± 2.8 *
	Controls	33 ± 4.0	29 ± 3.6 *	27 ± 3.4 *	28 ± 4.1 *
CF 2 + 7 + 10 (arb. unit)	Splenectomized	0.8 ± 0.1	0.8 ± 0.2	0.8 ± 0.1	0.7 ± 0.1 *
	Controls	0.8 ± 0.1	0.7 ± 0.1	0.7 ± 0.1 *	0.7 ± 0.1 *
Fibrinogen (μmol/l)	Splenectomized	8.1 ± 1.3	8.3 ± 1.3	8.3 ± 1.4	7.8 ± 1.7
	Controls	7.3 ± 1.8	7.1 ± 2.0	7.2 ± 1.7	7.0 ± 1.3

R-time, reaction time; α-angle, rate of clot formation; deg., degrees; MA, maximal amplitude; LY30, percentage decrease in amplitude 30 min post-MA; ADP, adenosine diphosphate-induced activation; ASPI, cyclooxygenase-dependent activation; TRAP, thrombin receptor PAR-1 activation; RISTOhigh and RISTOlow, Ristocetin aggregation with von Willebrand factor; aPTT, activated partial thromboplastin time; sec, seconds; CF 2 + 7 + 10, coagulation factor 2 + 7 + 10; arb. unit., arbitrary unit; Values are mean ≠ SD, *$p < 0.05$ compared to baseline, †$p < 0.05$ between groups at same time point.

3. Results

No significant differences were observed between the splenectomized and control subjects in regard to hemodynamic changes during administration of adrenaline (Table 2).

3.1. Healthy controls

After 30 min of adrenaline infusion R-time was reduced by ~22% ($p < 0.001$) (Fig. 1A) and aPTT by ~11% ($p < 0.001$) (Fig. 1B) and both remained low. The α-angle increased by ~10% ($p < 0.04$) (Fig. 1C), MA by ~8% ($p = 0.001$) (Fig. 1D), platelets by ~30% ($p < 0.001$) (Fig. 1E) and RISTOhigh-value by ~21% ($p = 0.004$) (Fig. 1F). After 60 min of infusion coagulation factor 2 + 7 + 10 decreased by ~6% ($p = 0.033$) and reached a ~14% decrease 30 min thereafter compared with baseline ($p < 0.001$). After 60 min of infusion RISTOhigh decreased to a value ~9% below baseline ($p < 0.001$) as did platelets by ~13% ($p < 0.002$) (Fig. 1E). In contrast fibrinogen, LY30, ADP, ASPI, RISTOlow, and TRAP were not affected by adrenaline (Table 3). There were no significant arterial-to-liver venous differences for plasma markers of coagulation in response to administration of adrenaline (aPTT: $p = 0.977$; fibrinogen: $p = 0.972$; coagulation factor 2 + 7 + 10: $p = 0.875$; INR: $p = 0.829$) (data not shown).

3.2. Splenectomized subjects

At baseline R-time was ~30% lower in the splenectomized subjects than in the controls ($p = 0.005$) (Fig. 1A), while both platelets (~20%; $p = 0.028$) (Fig. 1E) and RISTOhigh (~32%; $p < 0.002$) were higher (Fig. 1F). After thirty minutes infusion of adrenaline R-time decreased by ~17% ($p = 0.05$), aPTT by ~11% ($p < 0.001$) (Fig. 1B) and both remained low, and coagulation factor 2 + 7 + 10 decreased by ~7% 30 min after end of the infusion ($p < 0.013$) (Table 3). Also, after end of the infusion R-time was ~40% lower than in the controls ($p = 0.019$), while higher values were seen for RISTOhigh (~40%; $p = 0.003$) and platelets (~30%; $p = 0.003$). Administration of adrenaline had no effect on α-angle (Fig. 1C), MA (Fig. 1D), LY30 (Table 3), platelet count (Fig. 1E), RISTOhigh (Fig. 1F), RISTOlow, ADP, ASPI, TRAP, or Fibrinogen (Table 3).

3.3. Anhepatic subjects

During the anhepatic phase of LTx, administration of adrenaline resulted in a trend towards reduced R-time (from 5.4 ± 1.0 to 4.8 ± 1.5 min, $p = 0.10$), whereas α-Angle increased by ~10% (from 58 ± 9 to 64 ± 8, $p < 0.05$) and MA by ~9% (from 53 ± 12 to 58 ± 12 mm, $p = 0.002$) (Fig. 2A–C). No significant effect of adrenaline on LY30 was detected (0 ± 0%) (data not shown).

4. Discussion

This study examined the influence of the spleen and the liver for the enhanced hemostatic competence following low-dose adrenaline infusion. The main finding was that the adrenaline-mediated effect on hemostatic competences is derived primarily from the spleen. We confirmed that low-dose infusion of adrenaline induces a hypercoagulable state and Ristocetin-induced platelet aggregation increased. Vischer et al. [18] found von Willebrand factor to increase during administration of adrenaline, and Ristocetin induces platelet aggregation through von Willebrand factor. The increase in von Willebrand factor during adrenaline infusion might be due to release from the Weibel-Palade bodies [19].

Furthermore, adrenaline increased platelet count in the control group, but not in the splenectomized subjects. The spleen encompasses approximately 30% of the platelet pool [20], and functions as a reservoir that empties during adrenergic stimulation [8,10]. The high baseline platelet count in the splenectomized subjects may reflect the missing reservoir for platelets and seems of clinical relevance as splenectomized subjects demonstrate increased risk of cardiovascular events and the elevated platelet count may be important in that regard

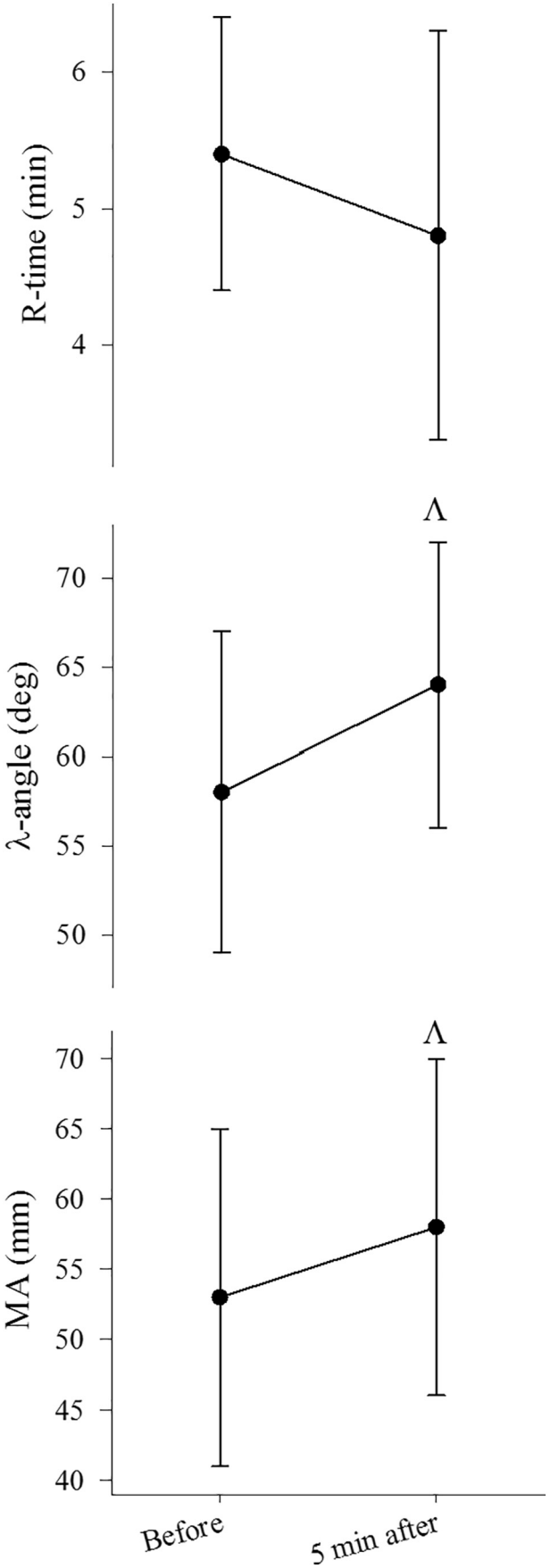

Fig. 2. Adrenaline infusion and coagulation competence before and 5 min after a 15-min period of adrenaline infusion during the anhepatic phase of liver transplantation in 6 patients. R-time, reaction time; α-angle, rate of clot formation; deg., degrees; MA, maximal amplitude. Black circle, patients. Values are mean ± SD. $^{\Lambda}p < 0.05$ compared to baseline.

[21–23].

The TEG analysis showed reduced R-time, increased α-angle and MA for the controls during infusion of adrenaline, i.e. adrenaline affected clot initiation and amplification/propagation. The splenectomized subjects were at baseline hypercoagulable as evaluated by TEG and demonstrated a decrease in R-time during the infusion suggesting that adrenaline had an effect on the coagulation factor driven initiation phase of hemostasis. The amplification/propagation phase, represented by α-angle and MA values, was unaffected in splenectomized subject probably due to lack of recruitment of platelets.

This study demonstrated a trend towards an effect of adrenaline on R-time in the anhepatic phase of LTx and a significant effect on both α-angle and MA. The trend towards a reduced R-time during infusion of adrenaline suggests that the sample size was too small because coagulation factors produced in the liver are important for the initiation of clot formation [12]. We found no arterial to liver venous concentration differences for plasma markers of coagulation in response to administration of adrenaline in healthy controls. Coagulation factor 8 has a peak response 15 min after administration of adrenaline and the first blood sample was collected only after 30 min of infusion and that might explain the lack of difference in plasma markers across the arterial to liver venous samples [4].

We acknowledge limitations to this study. First, the diagnosis leading to splenectomy might influence results, although we find it unlikely because the patients were diverse in regard to their diagnosis. Second, the coagulation results obtained in anhepatic patients are not directly comparable to results from healthy subjects since they were obtained during LTx for routine evaluation of coagulation and a Multiplate analysis was not applied. Thirdly, the sample size was small, and the few time points may have affected the results.

In conclusion, adrenaline enhances hemostatic competence as evaluated by TEG and Ristocetin-induced aggregation in healthy subjects, and as evaluated by TEG in anhepatic patients during LTx. Patients who had undergone splenectomy demonstrated also enhanced hemostasis during adrenaline infusion expressed as reduced R-time and aPTT. Due to a missing platelet reservoir, no changes manifested for α-Angle and MA. Accordingly, splenic storage of platelets seems important for the effect of adrenaline on hemostatic competence, while the liver may contribute to initiation of clot formation.

Declaration of interest

None.

Acknowledgements

We thank Karen Dyremose and Pär I. Johansson, Department of Clinical Immunology, Rigshospitalet for analyzes of TEG and Multiplate.

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