

## Activated thrombelastogram in neonates and infants with complex congenital heart disease in comparison with healthy children

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**Background.** The goal of the study was to determine activated thrombelastographic (TEG<sup>®</sup>) parameters with the rotational TEG<sup>®</sup> (ROTEG or ROTEM) device (Pentapharm GmbH, Munich, Germany) in neonates and infants <1 yr with complex congenital heart disease (CCHD) and to compare them with those of healthy children.

**Methods.** A total of 59 children were included: Group I (Gr I) 24 children, ASA I, scheduled for minor surgery; and Group II (Gr II) 35 children with CCHD, ASA III–IV, scheduled for cardiac surgery. Each group was subdivided into four age groups. Blood samples were obtained before the surgical procedure.

**Results.** Statistically significant differences (two-way ANOVA analysis) between Gr I and Gr II [mean (SD); *P*-value] were found in INTEG-CT [Gr I 175(19), Gr II 271(162); *P*=0.049], EXTEG-MCF [Gr I 63(8), Gr II 56(8); *P*=0.013], EXTEG-MCE [Gr I 186(65), Gr II 137(41); *P*=0.003], FIBTEG-MCF [Gr I 24(7), Gr II 19(5); *P*=0.012], FIBTEG-MCE [Gr I 32(13), Gr II 24(8); *P*=0.012] and EXTEG-MCE–FIBTEG-MCE [Gr I 155(55), Gr II 113(37); *P*=0.003]. Clotting time via contact activation was prolonged in Gr II and varied widely, mainly in the age group 0–1 month and to a lesser extent in 1–3 months, and maximum clot firmness was reduced in the same age groups. In comparison with Gr II, the healthy children showed relatively homogenous TEG values with a tendency to hypercoagulability; the maximum was found in age group 1–3 months, decreasing towards adult values in the course of the first year of life.

**Conclusions.** These preliminary TEG results indicate that the coagulation-fibrinolytic system in CCHD patients <1 yr is functionally intact and balanced but at a lower level than in healthy children. This could be interpreted as a reduction in the haemostatic potential with less reserve.

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Precise management of blood coagulation is of critical importance during repair or palliation of complex congenital heart disease (CCHD) in neonates and infants. It is essential to diagnose perioperative haemostatic disturbances quickly and precisely to administer the adequate amount of blood products, if indicated, and to avoid their unnecessary usage with possible adverse consequences.<sup>1,2</sup> Conventional laboratory coagulation tests are time-consuming and describe only parts of the whole coagulation process.<sup>3</sup> In contrast, whole blood coagulation tests such as thrombelastographic

(TEG<sup>®</sup>) tests may provide quick and timely useful information and may help to decide when and how to intervene in managing perioperative coagulopathies. The eventual usefulness of TEG<sup>®</sup> has been investigated in several studies in paediatric and adult patients, respectively.<sup>4–6</sup> In addition, a blood sparing effect has been documented by using the TEG<sup>®</sup> during open heart surgery in adults.<sup>7,8</sup>

One of the newly developed point-of-care instruments for whole blood coagulation analysis based on the conventional TEG<sup>®</sup> is the rotational TEG<sup>®</sup> (ROTEG, recently

re-named rotational thromboelastometry, ROTEM; Pentapharm GmbH, Munich, Germany), producing a computerized, multi-channel, activated thrombelastogram. Until now paediatric studies have not been conducted with this specific device, and normal values are only available for the adult population. To avoid incorrect interpretations and application of extrapolated data to children, it is a precondition to know the device-specific and activation-specific baseline TEG<sup>®</sup> parameters and age-related differences.<sup>9–11</sup>

The goal of our study was to obtain and analyse preoperative thrombelastograms provided by the ROTEG device in healthy neonates and infants and to compare them with those of CCHD patients of the same age.

## Methods

After approval of the local Ethics Committee and parents' written informed consent, patients less than 1 yr of age were included in a prospective study: in Group I (Gr I) were children with ASA status I, scheduled for minor surgery or diagnostic procedures (i.e. herniotomia, circumcision, rectoscopy) and in Group II (Gr II) children with CCHD, ASA status III–IV, scheduled for cardiac surgery with cardiopulmonary bypass. Each group was subdivided into four age groups: 0–1, 1–3, 3–6 and 6–12 months. Exclusion criteria for both groups were the application of drugs known to interfere with coagulation [with the only exception of prostaglandin E1 (PGE1)-infusion in the subgroup 0–1 month of the CCHD patients] and the receipt of blood products within 1 month before surgery.

In all children blood samples for ROTEG, coagulation profile and whole blood count were collected after induction of anaesthesia, but still before surgery. Induction of anaesthesia was at the discretion of the anesthesiologist in both groups, but no drugs or fluids with known effect on coagulation were applied during the period of induction and sample collection.

The conventional coagulation parameters and whole blood count were analysed at the institutional laboratory according to their standards: prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen concentration (fibrinogen), thrombin time (TT), antithrombin III (AT III), platelets, haematocrit (hct), haemoglobin (hb).

Blood for the ROTEG tests was collected in a citrate-containing tube (S-Monovette; Sarstedt, Nümbrecht, Germany). The activated TEG<sup>®</sup>s were performed with the ROTEG device (now re-named ROTEM; Pentapharm, Munich, Germany). Four channels were available for simultaneous measurements. Each test required 300 µl of citrate-anticoagulated whole blood. The blood was re-calcified with 20 µl of calcium chloride (ProTEG STARTTEST; Probe&go Labordiagnostica, Eendingen, Germany; calcium chloride 0.2 mol litre<sup>-1</sup> in HEPES buffer) and activation of coagulation was performed with different agents:

EXTEG: tissue factor pathway activation of the coagulation with 20 µl of tissue factor (TF, tissue thromboplastin

from rabbit brain extract, ProTEG EXTEST; Probe&go Labordiagnostica, Eendingen, Germany).

INTEG: contact pathway activation of the coagulation with 20 µl of contact activator (partial thromboplastin-phospholipid from rabbit brain extract and Ellagic-acid, ProTEG INTEST; Probe&go Labordiagnostica, Eendingen, Germany).

FIBTEG: TF plus inhibition of GPIIb/IIIa receptors on platelets with 10 µl of Fab-fragment abciximab c7E3 (Reo-Pro, Centocor B.V., Leiden, The Netherlands; 2 mg ml<sup>-1</sup>).

HEPTEG: contact activator plus inhibition of heparin effect with 20 µl of heparinase, a heparin processing enzyme (ProTEG HepTest; ProDia GmbH, Eendingen, Germany; heparinase 2 u ml<sup>-1</sup>).

The TEG tracings were automatically started after injection of the blood sample with an automatic pipette and were calculated by the integrated computer of the device.

The following standard variables were determined at 37°C (Fig. 1): clotting time (CT=*R*, s), clot formation time (CFT=*k*, s), angle (alpha, degrees), maximum clot firmness (MCF=MA, mm), maximum clot elasticity (MCE, 100\*MCF/100–MCF), clot lysis index (LI60, % of MCF 60 min after CT).<sup>3 12</sup>

For comparison, Table 7 shows the reference ranges of healthy adults, published by the manufacturer of the ROTEG device.

All ROTEG samples were analysed with the same device and the same production number of the reagents. Controls were run regularly with standard human-based controls according to the manufacturer's instructions (RO-TROL N; Pentapharm, Munich, Germany). All ROTEG samples were analysed within 30–90 min of sample collection.<sup>13 14</sup>

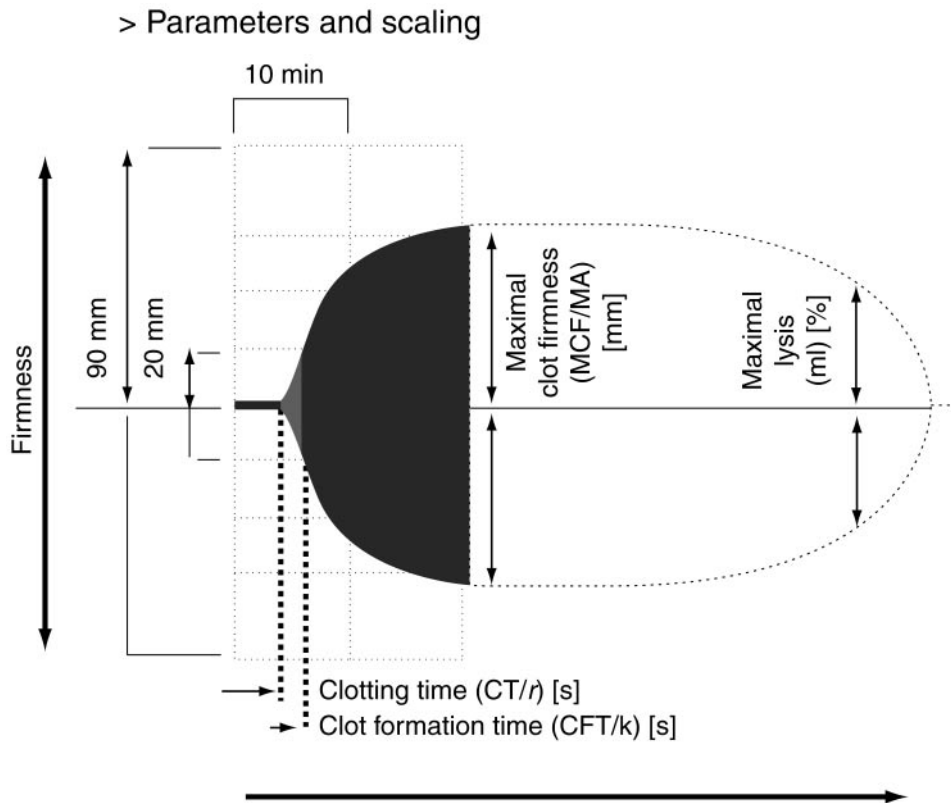
Two-way ANOVA and Pearson's coefficient of correlation were used for statistics: Group comparisons were performed by using two-way ANOVA with the factors 'group' and 'age group'. A *P*-value of less than 0.05 was considered significant. Correlations between variables were analysed by Pearson's coefficient of correlation (*r*). An *r*-value of 0.7 or more was considered meaningful. All data are given as means (SD) with the exception of the values in Table 7 (minimum–maximum).

## Results

A total of 59 consecutive patients were enrolled in the study: 24 in Gr I and 35 in Gr II. The age subgroups 0–1, 1–3, 3–6 and 6–12 months comprised 6, 6, 6 and 6 patients in Gr I and 17 (4 without PGE1 and 13 with PGE1), 6, 6 and 6 patients in Gr II, respectively.

There were statistically significant differences between Gr I and Gr II concerning age, body weight and size, mainly in the youngest age subgroup (Table 1).

The indication for surgical or diagnostic procedures in both groups are listed in Table 2; the majority of Gr II



**Fig 1** Depicting the ROTEG—tests performed and the parameters obtained. ROTEG=rotational thrombelastogram; INTEG=contact activated TEG: CT, CFT, alpha, MCF, MCE, LI60; EXTEG=tissue factor activated TEG: CT, CFT, alpha, MCF, MCE, LI60; FIBTEG=tissue factor activated TEG+abciximab: MCF, MCE; EXTEG-MCE–FIBTEG-MCE=platelet component of the clot; HEPTEG=contact activated TEG+heparinase: CT, CFT, alpha, MCF, MCE, LI60.

**Table 1** Demographic variables. Values expressed as mean (SD)

Group	Age group (months)	Age (days)	Sex (m/f)	Body weight (kg)	Size (cm)
Gr I	0–1	29.0 (1.5)	3/3	4.7 (0.6)	55.4 (1.1)
	1–3	65.0 (8.6)	5/1	4.8 (0.8)	56.5 (3.9)
	3–6	125.5 (28.6)	3/3	6.6 (0.9)	62.6 (3.6)
	6–12	275.8 (74.1)	3/3	8.9 (1.5)	71.6 (8.1)
Gr II	0–1	8.4 (4.7)	15/2	3.3 (0.3)	50.5 (3.3)
	1–3	62.3 (18.0)	4/2	4.4 (0.7)	55.7 (3.4)
	3–6	120.0 (26.0)	3/3	5.5 (1.2)	57.8 (6.4)
	6–12	238.5 (42.9)	0/6	7.0 (1.3)	67.5 (2.9)
<i>P</i> -value Gr I vs Gr II		0.044	—	<0.001	0.005
<i>P</i> -value age groups		<0.001	—	<0.001	<0.001

patients had cyanotic congenital heart disease (30 of 35 patients; 85.7%), the remaining patients were acyanotic; most Gr I patients had to undergo minor surgical procedures (22 of 24; 91.7%), only 2 patients diagnostic procedures; all of the Gr I patients were otherwise healthy (ASA status I).

Complete TEG's were obtained from all patients and there were no drop-outs. All ROTEG parameters are summarized in Table 3; from all the measured values the following showed statistically significant intergroup differences: INTEG-CT was significantly prolonged in Gr II

compared with Gr I; EXTEG-MCF and EXTEG-MCE, respectively, were significantly reduced in Gr II compared with Gr I; all three above mentioned parameters mainly concerned age groups 0–1 and 1–3 months; FIBTEG-MCF and FIBTEG-MCE, respectively, were significantly reduced in Gr II compared with Gr I (mainly concerning age groups 0–1, 1–3 and 3–6 months), HEPTEG-alpha was less steep in Gr II vs Gr I (also mainly in age group 0–1 and 1–3 months). INTEG-, EXTEG- and HEPTEG-LI60% showed significantly lower values in Gr I compared with Gr II, but none of the values was below 85%. The calculated parameters with statistically significant differences were the following: EXTEG-MCE–FIBTEG-MCE, was significantly lower in Gr II vs Gr I (mainly concerning age groups 0–1, 1–3 and 3–6 months). There were no statistically significant differences between the age groups.

Some of the conventional coagulation parameters were statistically significantly different, but still in the lower range of normal (Table 4): PT, aPTT and AT III; the same was true for platelet counts and haemoglobin (also Table 4).

ROTEG data subanalysis of age group 0–1 month of the Gr II patients is depicted in Table 5. The reason for this differentiation was that most of the patients in this

**Table 2** Indications for surgical or diagnostic procedures. tga, transposition of great arteries; dorv, double-outlet right ventricle; vsd, ventricular septal defect; tof, tetralogy of Fallot; hlhs, hypoplastic left heart syndrome; iaa, interrupted aortic arch; pda, patent ductus arteriosus; ta, tricuspid atresia; ps, pulmonary stenosis; asd, atrial septal defect; av-canal, atrio-ventricular canal; tapvc, total anomalous pulmonary venous connection; papvc, partial anomalous pulmonary venous connection; pht, pulmonary hypertension

	0–1 months	1–3 months	3–6 months	6–12 months
<b>Gr I</b>				
Anal atresia+st.p.anal atresia operation	2		1	
Colon polyp	1			
Hemangioma regio scapulae dexter	1		2	
Granuloma umbilicalis	1			
Hernia inguinalis	1	5	1	
Hydrocele testis		1	1	
Sacral sinus			1	
Craniosynostosis				1
Obstipation (diagnostic procedure)				2
Atheroma of the ear				2
Cervical cystis				1
<b>Gr II</b>				
tga	6			
dorv, tga, vsd	1		1	
tof		4		
truncus arteriosus	1			
hlhs	6			
hlhs, st.p.norwood stage I			3	
iaa, vsd, pda	1			
ta, ps, asd II, vsd				2
Malalignment vsd, aortic coarctation	1			
vsd, Williams syndrome				1
Subaortic vsd, double chamber right ventricle, ps			1	
Complete av-canal		1	1	
Partial av-canal, restrictive vsd, Down syndrome				1
tapvc, asd	1			
papvc, pht, vsd		1		
Subaortic stenosis, st.p.complete av-canal repair				1
Aneurysm of left ventricular outflow tract				1

group received PGE1. Because of the small number of children not receiving PGE1, a statistical evaluation was not appropriate.

Correlation coefficients ( $r$ ) between ROTEG parameters and conventional laboratory parameters of both groups are shown in Table 6 (only parameters with an  $r > 0.7$  were considered meaningful). There were differences between Gr I and Gr II concerning the  $r$ -values: there were statistically significant correlations between some ROTEG parameters (INTEG-CT, -CFT, -alpha, -MCF, EXTEG-CT, -CFT, -alpha, HEPTEG-CFT, -alpha) and the conventional laboratory parameters aPTT and TT in Gr II, but not in Gr I. On the other hand, there were significant correlations between some ROTEG parameters (INTEG-MCE, EXTEG-MCF, -MCE, FIBTEG-MCF, -MCE, HEPTEG-MCE) and fibrinogen in Gr I, but not in Gr II.

All Gr II patients received packed red blood cells and most of them also platelets, fibrinogen and coagulation factor concentrates during operation or in the immediate postoperative period, respectively. Mean blood loss (SD) in Gr II was 144.7 ml (90.7 ml) during the first 24 h postoperatively. None of the Gr II patients had to undergo reoperation for bleeding or any other reason. Concerning Gr I, only the patient undergoing craniosynostosis operation received packed red blood cells and fresh frozen plasma during the surgical procedure because of blood loss; all

other Gr I patients received no blood products throughout the perioperative period. Postoperative blood loss in Gr I patients was minimal and an exact amount cannot be presented.

## Discussion

The major finding was that the preoperatively obtained activated TEG<sup>®</sup> data indicated a functional mature haemostatic system in healthy children less than 1 yr of age and an at least balanced one in CCHD patients of the same age. This observation is in agreement with the results of other investigators using another TEG<sup>®</sup> device.<sup>9</sup> Additionally, the TEG<sup>®</sup> values observed in this healthy paediatric group differed only slightly from the published reference ranges of healthy adults provided by the manufacturer (Table 7).

We observed some tendencies and statistically significant differences between Gr I and Gr II: healthy children at the age of 1–3 months have a seemingly increased procoagulatory potential—a finding also described by others.<sup>9</sup> The rates of clot formation via TF activation were increased (less via contact activation). The same was true for build-up of clots and maximum clot firmness. This ‘hypercoagulable state’ decreased to adult values in the course of the first year of life.<sup>9,10</sup>

**Table 3** Activated ROTEG parameters and *P*-values. Values expressed as mean (SD). ROTEG, rotational thrombelastogram; INTEG, contact activated TEG; EXTEG, tissue factor activated TEG; FIBTEG, tissue factor activated TEG+abciximab; EXTEG-MCE–FIBTEG-MCE, platelet component of the clot; HEPTEG, contact activated TEG+heparinase; CT, clotting time (s); CFT, clot formation time (s); Alpha, angle (degree); MCF, maximum clot firmness (mm); MCE, maximum clot elasticity (100\*MCF/100–MCF), dimensionless value; \**P*-value <0.05; *N*, number of patients

ROTEG parameter	Age group										<i>P</i> -value	
	0–1 months		1–3 months		3–6 months		6–12 months		Total		Gr I vs Gr II	Age groups
	Gr I	Gr II	Gr I	Gr II	Gr I	Gr II	Gr I	Gr II	Gr I	Gr II		
<i>N</i>	6	17	6	6	6	6	6	6	24	35		
<b>INTEG</b>												
CT	179 (17)	332 (207)	166 (25)	257 (95)	183 (22)	187 (29)	172 (11)	196 (55)	175 (19)	271 (162)	0.049*	>0.2
CFT	56 (23)	127 (184)	45 (9)	78 (47)	49 (22)	53 (11)	60 (17)	61 (11)	53 (18)	95 (132)	>0.2	>0.2
Alpha	78 (4)	71 (14)	79 (6)	75 (8)	80 (4)	79 (2)	78 (3)	77 (2)	79 (4)	74 (11)	0.181	>0.2
MCF	68 (7)	62 (10)	69 (3)	61 (6)	67 (7)	69 (4)	63 (8)	66 (3)	67 (7)	64 (8)	>0.2	>0.2
MCE	219 (58)	173 (55)	228 (31)	166 (48)	219 (62)	232 (40)	187 (74)	191 (24)	213 (57)	185 (51)	0.122	>0.2
LI60	91 (2)	93 (3)	89 (2)	91 (2)	90 (3)	94 (3)	89 (2)	92 (4)	90 (2)	93 (3)	0.001*	0.140
<b>EXTEG</b>												
CT	35 (12)	55 (62)	35 (9)	35 (7)	33 (9)	34 (15)	45 (19)	36 (11)	37 (13)	45 (44)	>0.2	>0.2
CFT	65 (31)	119 (119)	65 (12)	98 (43)	75 (33)	79 (29)	96 (39)	85 (17)	75 (31)	103 (86)	>0.2	>0.2
Alpha	78 (6)	71 (12)	77 (2)	72 (8)	78 (8)	75 (4)	72 (7)	74 (3)	76 (6)	72 (9)	>0.2	>0.2
MCF	65 (9)	54 (10)	64 (2)	54 (7)	65 (9)	63 (5)	59 (9)	58 (5)	63 (8)	56 (8)	0.013*	>0.2
MCE	209 (79)	126 (43)	178 (15)	121 (35)	203 (79)	176 (34)	155 (67)	144 (30)	186 (65)	137 (41)	0.003*	0.181
LI60	91 (2)	92 (4)	90 (4)	91 (2)	89 (3)	94 (4)	89 (2)	92 (3)	90 (3)	92 (3)	0.013*	>0.2
<b>FIBTEG</b>												
MCF	25 (10)	19 (6)	23 (4)	18 (6)	26 (6)	22 (5)	20 (8)	18 (2)	24 (7)	19 (5)	0.012*	>0.2
MCE	36 (19)	24 (9)	30 (8)	23 (8)	34 (10)	28 (8)	26 (14)	22 (4)	32 (13)	24 (8)	0.012*	>0.2
<b>HEPTEG</b>												
CT	179 (17)	236 (136)	169 (25)	232 (86)	198 (46)	178 (10)	165 (10)	198 (48)	178 (29)	219 (104)	0.162	>0.2
CFT	48 (17)	105 (96)	45 (10)	85 (45)	51 (24)	50 (8)	64 (21)	66 (12)	52 (19)	86 (72)	0.125	>0.2
Alpha	80 (4)	71 (11)	81 (2)	74 (7)	80 (5)	80 (2)	77 (4)	77 (3)	80 (4)	74 (9)	0.049*	>0.2
MCF	66 (7)	61 (10)	68 (3)	59 (6)	67 (7)	69 (3)	62 (7)	63 (2)	66 (6)	62 (8)	0.160	>0.2
MCE	209 (60)	167 (56)	217 (29)	150 (37)	217 (64)	227 (37)	176 (62)	175 (18)	205 (55)	176 (50)	0.081	0.117
LI60	92 (1)	95 (2)	92 (2)	92 (2)	91 (3)	94 (3)	89 (2)	94 (3)	91 (2)	94 (3)	0.002*	0.081
<b>EXTEG-MCE–FIBTEG-MCE</b>												
MCE	173 (68)	103 (35)	150 (18)	98 (28)	169 (69)	148 (34)	129 (54)	122 (34)	155 (55)	113 (37)	0.003*	>0.2

**Table 4** Conventional laboratory parameters. Values expressed as mean (SD). hb, haemoglobin; PT, prothrombin time; aPTT, activated partial thromboplastin time; TT, thrombin time; AT III, antithrombin III; *N*, number of patients

<i>N</i>	Months	hb (g dl <sup>-1</sup> )	Platelets (10 <sup>3</sup> μl <sup>-1</sup> )	PT (%)	APTT (s)	Fibrinogen (mg dl <sup>-1</sup> )	TT (s)	AT III (%)
<b>Gr I</b>								
6	0–1	12 (1)	396 (166)	99 (15)	37 (4)	245 (86)	16 (1)	77 (12)
6	1–3	9 (1)	421 (97)	98 (19)	35 (2)	208 (31)	16 (1)	84 (11)
6	3–6	11 (1)	439 (124)	97 (16)	33 (3)	265 (68)	15 (1)	95 (18)
6	6–12	10 (1)	375 (99)	92 (10)	32 (2)	226 (83)	15 (1)	115 (19)
<b>Gr II</b>								
17	0–1	13 (2)	284 (129)	76 (16)	55 (34)	239 (50)	26 (22)	63 (18)
6	1–3	10 (2)	237 (76)	65 (12)	51 (14)	194 (41)	18 (2)	66 (13)
6	3–6	11 (2)	408 (113)	70 (10)	42 (12)	262 (71)	21 (9)	84 (11)
6	6–12	11 (2)	269 (103)	78 (11)	35 (6)	239 (49)	18 (3)	88 (5)
<i>P</i> -value Gr I vs Gr II		0.020	0.002	<0.001	0.049	>0.2	0.115	<0.001
<i>P</i> -value age groups		<0.001	0.145	>0.2	>0.2	0.102	>0.2	<0.001

In comparison with the healthy children this tendency to ‘hypercoagulability’ was less pronounced in the CCHD children and appeared with a delay at an age of 3–6 months respectively; ROTEG parameters of the CCHD patients, especially in the youngest age group, showed a still balanced haemostatic system as already mentioned above, but at a lower level and with greater variability (Table 3).

Major mean differences in ROTEG parameters could be found in neonates and children 1–3 months, respectively: clotting time via the contact activation pathway (INTEG-CT) was significantly longer in the CCHD patients than in the comparative age group of healthy children; and parameters concerning maximum clot firmness via tissue factor activation were significantly lower; the plasmatic



**Table 5** Activated ROTEG parameters in patients Gr II, 0–1 month. Values expressed as mean (SD). ROTEG, rotational thrombelastogram; INTEG, contact activated TEG; EXTEG, tissue factor activated TEG; FIBTEG, tissue factor activated TEG+abciximab; CT, clotting time (s); CFT, clot formation time (s); Alpha, angle (degree); MCF, maximum clot firmness (mm); MCE, maximum clot elasticity ( $100 \times \text{MCF}/100 - \text{MCF}$ ), dimensionless value; LI60, clot lysis index (% of MCF 60 min after CT); PGE1, prostaglandin E1; N, number of patients

N		CT	CFT	Alpha	MCF	MCE	LI60
With PGE1							
13	INTEG	329 (227)	141 (210)	70 (16)	60 (11)	166 (59)	93 (3)
13	EXTEG	50 (61)	135 (133)	69 (13)	51 (9)	112 (36)	92 (4)
13	FIBTEG				17 (5)	22 (8)	
Without PGE1							
4	INTEG	340 (150)	82 (19)	74 (4)	66 (5)	196 (40)	92 (1)
4	EXTEG	72 (71)	68 (20)	76 (4)	63 (3)	173 (22)	92 (1)
4	FIBTEG				23 (5)	30 (8)	

**Table 6** Correlation coefficients (*r*) between ROTEG parameters and conventional laboratory parameters. ROTEG, rotational thrombelastogram; INTEG, contact activated TEG; EXTEG, tissue factor activated TEG; FIBTEG, tissue factor activated TEG+abciximab; HEPTEG, contact activated TEG+heparinase; CT, clotting time (s); CFT, clot formation time (s); Alpha, angle (degree); MCF, maximum clot firmness (mm); MCE, maximum clot elasticity ( $100 \times \text{MCF}/100 - \text{MCF}$ ), dimensionless value; PT, prothrombin time (%); aPTT, activated partial thromboplastin time (s); TT, thrombin time (s)

	Gr I	Gr II			
		Fibrinogen	Platelets	aPTT	Fibrinogen
INTEG					
CT			0.7		0.7
CFT			0.9		0.9
MCF	0.6		-0.7	0.6	-0.7
Alpha			-0.8		-0.8
MCE	0.7			0.6	
EXTEG					
CT			0.7		0.7
CFT			0.8		0.8
MCF	0.7			0.6	
Alpha	0.6		-0.7		-0.7
MCE	0.7			0.6	
FIBTEG					
MCF	0.8	0.6		0.6	
MCE	0.8	0.6		0.6	
HEPTEG					
CT			0.6		
CFT			0.8		0.8
MCF		0.6		0.6	
Alpha			-0.8		-0.7
MCE	0.7			0.6	

and platelet components of the clot were also reduced (EXTEG-MCF and FIBTEG-MCF and their calculated derivatives).

The reasons for those TEG<sup>®</sup> differences between Gr I and Gr II remain to be investigated. A major impact may have been the age difference, especially concerning the neonatal group. But there are some other possible explanations; one of them might be an increased quantitative deficiency or immaturity of the plasmatic coagulation factors in Gr II.<sup>9</sup> According to Andrew and colleagues, already in healthy newborns the vitamin K-dependent factors (II, VII, IX and X) and contact factors (XII, XI, prekallikrein and high molecular weight kininogen) and many of the coagulation inhibitors (antithrombin III, heparin cofactor II

**Table 7** Activated ROTEG reference ranges of adults (according to the manufacturer of ROTEG device). Values are expressed as minimum and maximum. ROTEG, rotational thrombelastogram; INTEG, contact activated TEG; EXTEG, tissue factor activated TEG; FIBTEG, tissue factor activated TEG+abciximab; CT, clotting time (s); CFT, clot formation time (s); Alpha, angle (degree); MCF, maximum clot firmness (mm); LI30, clot lysis index (% of MCF 30 min after CT)

	CT	CFT	Alpha	MCF	LI 30
INTEG	110–173	34–108	70–83	50–72	94–100
EXTEG	38–79	34–159	63–83	50–72	94–100
FIBTEG				8–20	

protein C and S) are decreased, whereas other factors such as fibrinogen, FV, FVIII and FXIII are similar or increased compared with adults at birth. Those authors also found that coagulation factor levels are increasing into adult ranges by 6 months of age; and they stated that in the fibrinolytic system, plasma concentrations of plasminogen are decreased at birth, whereas tissue plasminogen activator and plasminogen activator inhibitor are increased.<sup>9,15</sup> The reason for the assumed increased quantitative deficiency or immaturity of the plasmatic coagulation factors in Gr II patients could be explained the following way: impaired liver function as a result of the Qp:Qs-ratio imbalance, which is a mismatch between pulmonary and systemic flow as a result of shunts with pulmonary overcirculation and systemic hypoperfusion, or chronic hypoxia or congestive heart failure; one single factor or a combination of all of these factors could lead to the alterations of the coagulation system, which are mirrored in the TEG<sup>®</sup> profiles of the sick children.<sup>2</sup>

Also, platelets as major contributing factors in clot strength have to be taken into consideration: functional immaturity of the platelets and their receptors or platelet function abnormalities, are known phenomena in children with CCHD.<sup>2,16</sup> The proposed underlying mechanism is hypoxia in cyanotic patients.

PGE1 with its inhibitory effect on platelet aggregation might have an additional effect in the neonatal group. To find out whether PGE1 had an influence on our TEG results we divided the group of neonates with CCHD (0–1 month) in two subgroups: one group receiving PGE1 and the

other not (Table 5). The absolute MCF values were slightly higher in the group not receiving PGE1. But, because of the small sample size, it cannot be concluded from this subanalysis that the difference is statistically significant. Additionally, it is questionable whether the PGE1 influence could have been detected in the TEG<sup>®</sup>; the reason for this is that the inhibitory effect of PGE1 on platelet aggregation is dependent on the synergism with endothelial cells—and this endothelial component is not present in TEG<sup>®</sup> assay. Therefore, a significant PGE1 effect on TEG<sup>®</sup> results in the usual paediatric clinical dosage seems unlikely. Furthermore, *in vitro* studies showed that plasma concentrations of at least 0.1 ng ml<sup>-1</sup> of PGE1 are necessary to exert a platelet inhibitory effect.<sup>17</sup> However, it is unknown whether this prostaglandin level was achieved in our patient population. We were well aware of the problem of PGE1 and its possible effect on coagulation. The majority of patients undergoing cardiac surgery in the neonatal period receive PGE1 to keep the ductus arteriosus open until the operation is performed, and because survival is dependent on the patency of the duct, PGE1 could not be stopped for study reasons. Therefore it was difficult to receive data from patients in this age group without PGE1.

Although there were statistically significant differences in INTEG-, EXTEG- and HEPTEG-LI60 (Table 3), none of the values in both groups fulfilled the criteria of hyperfibrinolysis, which was defined as a reduction of maximum clot firmness of 15% and more, evaluated 60 min after clot initiation.<sup>9 18</sup>

To eliminate a possible ‘contamination-effect’ of heparin on INTEG-CT results in the cardiac patients, whose samples were obtained from arterial lines, we simultaneously performed TEG<sup>®</sup>'s adding the enzyme heparinase (HEPTEG).<sup>1 19 20</sup> The results of the two parameters showed good correlations in all groups (not shown in a table), proving that the prolongation of the INTEG-CT was not caused by heparin.

When comparing conventional coagulation and whole blood count parameters with ROTEG values, we found only weak or no correlations, respectively (Table 6: only parameters with an *r*-value >0.6 are shown in the table, and only *r*-values >0.7 were considered meaningful). This is in accordance with the findings of other investigators who documented the ‘functional integrity of coagulation (i.e. TEG<sup>®</sup>-based results) in clinically stable infants despite, in part, decreased conventional coagulation variables’.<sup>11</sup> Additionally, in our study the correlations differed between the groups. It means that a particular coagulation factor or conventional coagulation parameter is not exclusively responsible for a certain TEG variable, neither in healthy nor sick infants. This seems to be true with the only exception of an isolated critical reduction of one of the factors II, VII, X or XII below 1% activity, as Nielson showed in his experimental laboratory work.<sup>21</sup> Only in this case and only when both contact and TF-activated TEG<sup>®</sup>'s are performed, do the TEG<sup>®</sup> results show typical profiles. Owing to the fact

that we did not investigate factor activity nor platelet function, one can only speculate the reasons for the discrepancy in our study. One reason might be that the concentration of coagulation factors and number of platelets, respectively, do not necessarily reflect function or activity. Additionally, conventional tests such as fibrinogen concentration measurement do not reflect the interaction with other components of the coagulation-fibrinolytic process as exemplarily shown in FIBTEG. Last but not the least, the type of conventional laboratory test *per se* and quantity of the activator used might play a role. In our children we used the method of Clauss for determination of the fibrinogen concentration. The principle of this method is that the measured coagulation time is directly proportional to the fibrinogen concentration when a standardized amount of thrombin is added. This precondition of a precisely defined amount of thrombin is not necessarily present in the patient's blood, even if fibrinogen concentration is the same. And above all FIBTEG, similar to all other TEG<sup>®</sup> tests, is obtained from whole blood in contrast to fibrinogen, which is determined from plasma. The slight prolongation of the TT with a mean (SD) of 26 (22) s in the youngest age group of the Gr II children might be explained by a greater amount of ‘fetal fibrinogen’; according to Andrew<sup>15</sup> or Barthels and von Depka,<sup>22</sup> it is known that fetal fibrinogen can influence thrombin time test results. The TT-reference values for healthy full-term neonates are mean 23 (min 19–max 28) s on day 1, changing to 24 (18–29) s on day 30 of the neonatal period. Those values are considered physiological. Another explanation for TT prolongation could be an albumin level <2 g litre<sup>-1</sup>, but we did not investigate this parameter. A heparin effect was excluded by HEPTEG.

Limitations of the study are the small total number of patients as a result of their prospective enrolment in the study. Our aim was to get data of at least six patients in each group. An overwhelming majority of neonates with CCHD were operated on. As their preliminary data showed a great variability, we kept collecting them. There was also an age difference between Gr I and Gr II, 0–1 month. The reasons were that not enough healthy neonates were operated on during the study period and a significant number of parents refused consent. In addition, because of the small sample volume obtained, no intra-sample variability could be estimated.

In conclusion, our preliminary TEG<sup>®</sup> results showed that the haemostatic system in CCHD patients is functionally intact but in some aspects borderline and with greater variability compared with healthy children. This could be interpreted as a reduction in the procoagulatory potential in some of those partly very sick children, mainly in the age group 0–1 and to less extent in 1–3 months.

In comparison with CCHD patients, the healthy children showed relatively homogenous TEG<sup>®</sup> values with a tendency to ‘hypercoagulability’; the maximum was found in the age group 1–3 months, slowing down to adult values in the course of the first year of life.

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