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Evaluation of Post-Cardiopulmonary Bypass Coagulation Disorders by Differential Diagnosis with a Multichannel Modified Thromboelastogram: A Pilot Investigation

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Abstract: We assessed a modified multichannel thromboelastogram for differentiation of the causes of coagulopathy after cardiopulmonary bypass and its suitability as a therapy guide. Thirty adult patients undergoing surgery with cardiopulmonary bypass, who revealed a coagulopathy as observed by a prolonged activated clotting time of >150 sec after the application of protamine, were enrolled. Therapy was based on the results obtained by the computerized four-channel thromboelastogram with baseline, heparinase (2 IU/mL), heparinase/abciximab (5 μg/mL), and heparinase/fresh frozen plasma (25%) channels.

The mean activated clotting time before therapy was 162.2 ± 7.8 sec. Based on differential diagnosis with the modified multichannel thromboelastogram, two patients received protamine (30 mg), five desmopressin (0.4 μg/kg), 19 patients three units of fresh frozen plasma, two patients platelet transfusions, and two patients both protamine (30 mg) and three units of fresh frozen plasma. After therapy, there was a significant ($p < .01$) decrease of the activated clotting time to a mean value of 127 ± 8.3 sec. Therapy based on the synoptic modified multichannel thromboelastogram analysis provides a guide for effective therapy of coagulopathy. However, elaboration is desirable, and larger clinical trials are necessary for a final evaluation of the protocol.
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Cardiac surgery that involves cardiopulmonary bypass (CPB) is associated with a complex derangement of the coagulation system (1, 2). Important factors that contribute to post CPB coagulopathy are:

1. hemodilution by the priming volume of the CPB;
2. consumption of platelets and plasma coagulation factors on the large artificial surfaces during extracorporeal circulation;
3. mechanical alteration of platelets and passage-impaired platelet function; and
4. residual heparin in the case of an incomplete reversal by protamine.

Postoperative bleeding, caused by impaired restoration of coagulation, not only influences the surgical outcome, but also contributes to the costs because of increased transfusion requirements or the necessity for surgical re-exploration. Therefore, optimal restoration of coagulation after CPB is a major goal.

The activated clotting time (ACT), as a global coagulation assay, does not enable the differentiation of the causes of coagulopathy. Such other assays as point-of-care assays of platelet function or heparinase ACT only evaluate parts of the coagulation system. Viscoelastic tests, in particular thromboelastography (TEG), reflect more the complex process of coagulation. A number of investigations have demonstrated the effectiveness of TEG for the prediction of bleeding diathesis, differentiation between bleeding attributable to surgical causes or coagulation disorders and as a guide for transfusion decisions (2–6). However, the key parameters of TEG, the r-time and the maximum amplitude (MA), do not permit the discrimination of disturbances of the plasmatic coagulation system and platelet function or residual heparin. The r-time/coagulation time represents the period up to the beginning

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Table 1. Coagulation and TEG parameters before and after therapy.

Before Therapy		R-time (s)				MA [mm]					After Therapy
Acts (s)	Platelet Count [100,000/μL]	Baseline	Heparinase	Abciximab	FFP	Baseline	Heparinase	Abciximab	FFP	Therapy	ACT (s)
155	120	1680	903	950	850	41	43	21	43	Protamine	125
161	143	1590	895	945	870	43	45	15	46		116
158	98	1132	1080	1150	920	33	34	9	41	Desmorpressin	124
152	81	978	985	1020	930	35	37	11	42		134
161	125	1054	1010	990	870	34	33	10	43		141
159	75	1143	1134	1201	987	33	35	12	44		117
163	134	1214	1154	1242	1110	31	34	9	42		126
165	202	1245	1232	1343	890	35	37	14	45	FFP	108
167	243	1324	1301	1440	934	34	35	9	46		127
153	143	1012	989	1056	897	33	35	12	41		133
157	167	1133	1098	1234	768	28	34	13	51		137
162	303	1019	1078	1076	799	33	37	17	45		119
162	165	1045	1000	1154	660	29	32	9	42		123
167	167	1243	1189	1205	845	32	31	12	44		134
154	147	1078	1023	1089	670	33	32	13	43		123
156	201	1056	987	1201	756	25	30	9	41		128
163	123	1098	1056	1145	752	27	29	20	40		109
161	145	1123	1099	1165	790	32	35	14	49		123
164	203	1067	987	1079	799	28	33	16	47		134
157	176	1059	1123	1067	699	29	32	17	43		132
154	198	1023	1078	1099	694	31	33	12	42		127
156	181	1076	1089	1101	720	26	32	19	42		124
165	121	1189	1087	1099	801	25	35	12	45		134
164	134	1146	1043	1201	809	28	29	14	39		123
154	143	1079	1071	1077	793	28	31	17	51		129
172	154	1342	1299	1289	934	31	32	9	43		121
167	41	1401	1455	1543	1311	25	25	9	32	RDP	134
169	31	1478	1411	1567	1266	20	22	11	29		139
183	121	1647	1256	1265	699	35	35	12	43	FFP + Prot	127
185	134	1743	1345	1490	734	36	37	15	45		139

Values obtained from 30 patients after cardiopulmonary bypass.
ACT = activated clotting time; FFP = fresh frozen plasma; RDP = random donor platelet concentrates.

of fibrin formation and is influenced by heparin and plasmatic coagulation factors. The MA reflects the elasticity/strength of the forming clot, which is basically influenced by the interaction of fibrinogen with platelets and platelet-derived clot retraction. Therefore, the MA is influenced by both the plasmatic coagulation system and platelet function.

We developed a pattern analysis, based on the results obtained by a modified four-channel TEG, for improved differentiation of coagulopathy in patients following CPB. The modified multichannel TEG was performed with a baseline, a heparinase (2 IU/mL), a heparinase/abciximab (5 μg/mL), and a heparinase/fresh frozen plasma (20%) channel. Based on synoptic analysis of the results of the modified multichannel TEG, we evaluated a protocol for differential therapy of post-CPB coagulation disorders.

MATERIALS AND METHODS

Patients

After approval of the local ethics committee and informed consent, 30 adult patients undergoing cardiovascular surgery with CPB were included in the investigation.

Surgery

Surgery included coronary artery bypass grafting (CABG, $N = 5$), aortic valve replacement (AVR, $N = 3$), mitral valve replacement (MVR, $N = 2$), AVR and CABG ($N = 6$), MVR and CABG ($N = 3$), AVR and MVR ($N = 3$), AVR and MVR and CABG ($N = 3$), implantation of a ventricular assist device (VAD, $N = 2$), repair of an aneurysm of the ascending thoracic aorta ($N = 2$), and a repair of an aneurysm of the descending thoracic aorta ($N = 1$). The mean duration of CPB was 97 ± 17 min.

Performance of the TEG

The investigation was performed with the ROTEG (Dynabyte, Munich, Germany). This device is a further development of the conventional TEG in which the clot detection system is guided by a ball bearing. The ROTEG provides parallel measurement in four channels with computerized analysis of the TEG key parameters.

In preliminary investigations using whole blood samples from 20 healthy volunteers, the concentration of the stimulator of coagulation and reference values were de-

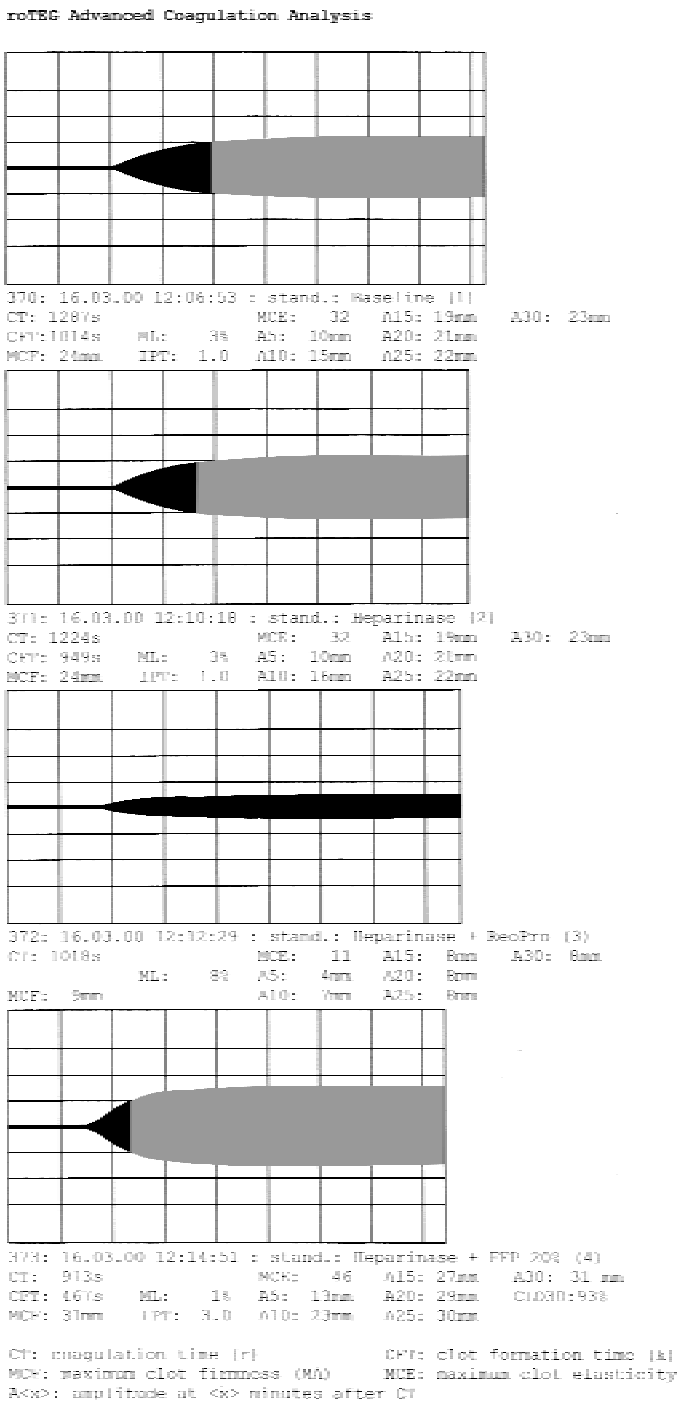

Figure 1. Scan of a modified multichannel TEG in a patient following coronary artery bypass grafting and aortic valve replacement. The ACT after protamine was 157 sec, and the patient revealed diffuse bleeding. Because of the multichannel modified TEG analysis, three units of FFP were transfused, and the ACT was decreased to 124 sec.

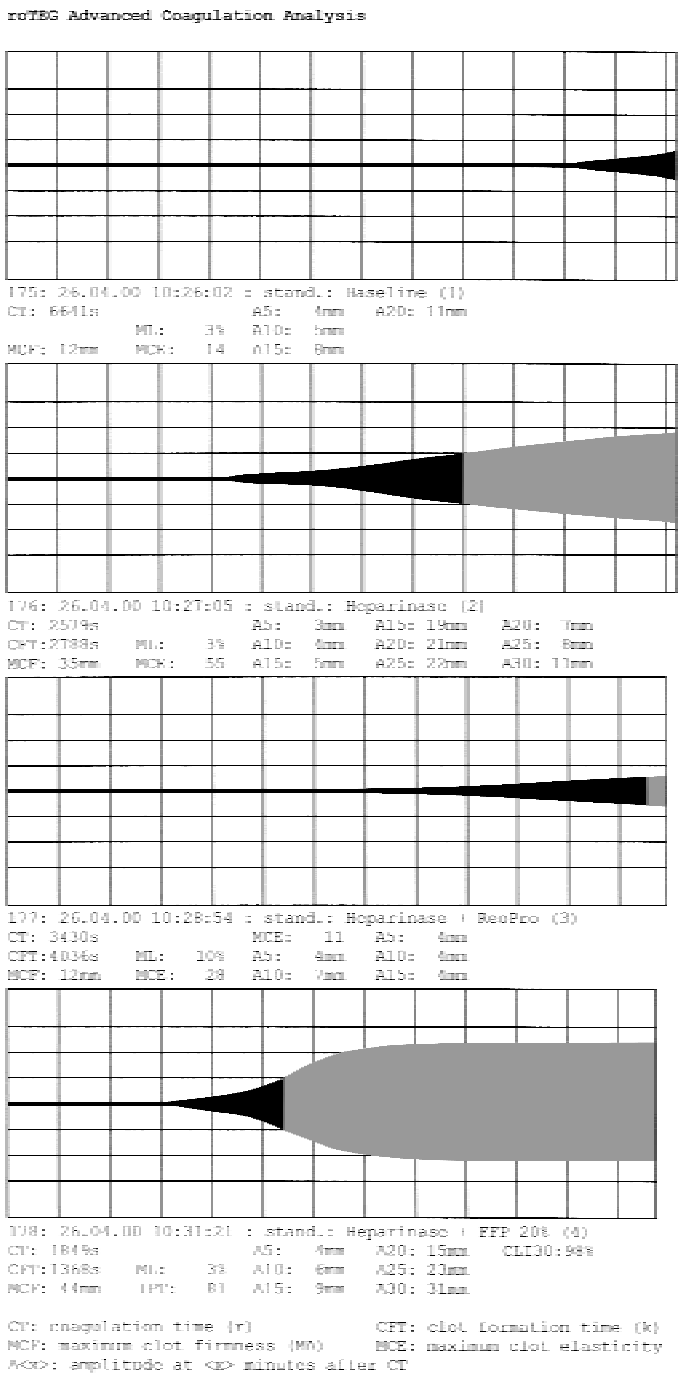

Figure 2. Scan of a modified multichannel TEG in a patient following aortic and mitral valve replacement. The ACT after protamine application was 179 sec, and the patient exhibited diffuse bleeding. Based on the multichannel modified TEG analysis 30 mg of protamine, and three units of FFP were given and the ACT decreased to 131 sec.

termined. The goal was to achieve an r-time that enabled the discrimination of the effects of small amounts of heparin (0.2–1.0 IU/mL) (compared to a heparinase channel) and quick achievement of a final result (<30 min). This was best achieved with 20 μL of kaolin reagent. Using this stimulator an r-time value of approximately 900 sec and maximum amplitude (MA) of 40–50 mm were evaluated as normal. Thereafter, the channels of the modified multichannel ROTEG were prepared according to the following:

1. *Baseline channel.* 300 μL citrated whole blood + 20 μ kaolin solution (50 mL $CaCl_2$ 0.645% + 100 μL kaolin) + 20 μL $CaCl_2$ (0.2 mol/L, buffered, Dynabite, Munich, Germany).
2. *Heparinase channel.* 300 μL citrated whole blood + 20 μ kaolin solution + 20 μL $CaCl_2$ + 20 μL heparinase (Hepzyme, Dade, Behring, Marburg, Germany), which allows for reversal of approximately 2 IU/mL heparin and discrimination between heparin or plasma coagulation factor-derived prolongation of the r-time.
3. *Abxicimab channel.* 300 μL citrated whole blood + 20 μ kaolin solution + 20 μL $CaCl_2$ + 20 μL heparinase + 35 μL abciximab (ReoPro™,Lilly, Bad Homburg, Germany), which leads to a final concentration of abciximab of 5 μg/mL, which correlates with the dose of the potent antiplatelet agent given during interventional cardiology. By isolated inhibition of platelets by abciximab, the effect of the platelets on the MA can be discriminated and, thereby, platelet function evaluated.
4. *Plasma channel.* 300 μL citrated whole blood + 20 μ kaolin solution + 20 μL $CaCl_2$ + 20 μL heparinase + 100 μL fresh frozen plasma (approximately 25%) for further improved differentiation of the contribution of the plasma coagulation factor to the r-time and MA.

Anticoagulation During CPB

Cardiopulmonary bypass was performed with nonheparin-coated lines, a membrane oxygenator, and a roller pump in moderate hypothermia of 30–32°. In all patients, Aprotinin (Antagosan, Hoechst, Frankfurt, Germany) was used with a bolus of 1×10^6 kallikrein inhibiting units (KIU) for the patient, 1×10^6 KIU into the priming solution of the CPB and a continuous infusion of 250,000 KIU/h during extracorporeal circulation. Anticoagulation was performed with unfractionated heparin (Liquemin, Roche, Grenzach-Whylen, Germany) according to the Hepcon HMS (Medtronic, Parker, CO, USA). The necessary heparin level to achieve a target kaolin ACT of >480 sec was determined by the use of the Heparin dose–response cartridge. During CPB, the heparin level was determined with the HMS cartridge and adjusted to the target level. After conclusion of CPB, the necessary dose of protamine (Protamine Sulfate, ICN, Frankfurt, Germany) was calculated depending on the measured heparin level. Fresh frozen plasma or platelet concentrates were given as a result of the clinical decision based on the preoperative platelet count, the preoperative coagulation status, the duration of CPB, and the already performed transfusions. After infusion of the entire unprocessed volume of the CPB, any remaining circulating heparin was identified using the heparin management system (HMS) low-range cartridge (range 0–1.5 IU) and the necessary protamine dose administered. Thereafter, kaolin ACT was measured. In case of a prolongation of the ACT >150 sec, patients were included into the investigation.

Protocol for the Multichannel Modified TEG-Based Therapy

Therapy was based on data obtained by the multichannel modified ROTEG in accordance with to the following protocol:

1. In the event of a shortening of the r-time in the heparinase channel, an additional 30 mg of protamine was given.
2. In the case of a shortening of the r-time and an increase of the maximum amplitude in the FFP channel, 3–6 units of FFP were transfused.
3. If there was a moderate decrease of the MA in the baseline channel (MA 30–35 mm), a major decrease in the abciximab channel (decrease >20 mm), and only a moderate increase (increase >10 mm) in the FFP channel then 0.4 μg/kg desmopressin (Minirin, Ferring, Kiel, Germany) were given for enhancement of plasmatic and platelet-derived stimulation of coagulation.
4. If there was a substantially decreased MA (<30 mm) in the baseline channel, no marked (increase <10 mm) increase of the MA in the FFP channel and no major decrease (decrease <20 mm) of the MA in the abciximab channel then platelet concentrates were transfused.

Statistical Analysis

Statistical analysis of the ACT values before and after therapy was performed by the use of the Student's-*t* test. A *p*-value <.01 was determined as significant.

RESULTS

Therapy According to Multichannel Modified TEG Analysis

In two patients an additional 30 mg of protamine was administered, and five patients received desmopressin (0.4 μg/kg). Nineteen patients received three units of FFP, and in two patients, a random donor platelet concentrate was transfused. In two patients, additional protamine (30 mg) and FFP were given.

ACT and Blood Loss After Therapy

The ACT measured before multichannel modified TEG-based therapy ranged from 152–185 sec with a mean of 162.6 ± 7.8 sec. The ACT after therapy ranged from 109–139 sec with a mean of 127 ± 8.27 sec. There was a significant difference between the preoperatively and postoperatively obtained ACT values ($p < .05$).

DISCUSSION

In a series of 30 patients, demonstrating a coagulopathy after CPB as evaluated by a prolongation of the ACT >150 sec after protamine application, therapy was based on the

information obtained by a multichannel modified TEG analysis. In all patients, therapy was effective as the ACT significantly decreased after treatment.

Important factors that contribute to post-CPB hemorrhage are residual or rebound heparin, impaired function of the platelet system, and loss of plasmatic coagulation factors. Because protamine itself reveals a strong anticoagulant effect, blind application of excessive protamine in the event of a prolonged ACT is not advisable, because it may increase the coagulopathy (7). In the multichannel modified TEG, the addition of heparinase permits the *qualification* of residual heparin by comparison of the r-time in the baseline and heparinase channel. In the current investigation, heparin in four patients contributed to the postoperatively prolonged ACT, despite a previous confirmation of complete reversal of heparin via the protamine titration assay. This imprecision of the HMS cartridge may be explained by the gaps of 0.3 IU/mL heparin between the channels. Nevertheless, in all patients, a bolus of 30 mg protamine, which in an adult patient, should antagonize approximately 0.5 IU/mL heparin, led to a considerable decrease of the ACT. However, in the case of a marked reduction of the r-time in the heparinase channel, because there is no *quantification*, titration of the ACT with small dosages of protamine seems to be advisable.

Other viscoelastic assays, such as the Sonoclot device or resonance thrombography, can discriminate between the effect of platelets and plasma factors on the forming clot (8–11). However, with the use of the platelet glycoprotein IIb/IIIa antagonist abciximab, the contribution of the platelets to the MA can be evaluated by comparison of the baseline and abciximab channel (12). A marked reduction of the MA in the abciximab channel signals satisfactory function of the platelets and provides information that discriminates between platelet and procoagulant derived coagulation disorders. In this study, only two patients who had a postoperative thrombocytopenia demonstrated a "defect of the platelets" as the reason for the coagulation disorder and platelets were transfused.

The addition of 20% FFP, which approximately correlates with the transfusion of 3 FFP in an adult patient, allows for further discrimination of the causes of coagulopathy. A decrease of the r-time and an increase of the MA in this channel signals a deficit of plasmatic coagulation factors and, in the current investigation, was identified as the cause of postoperative coagulopathy in most of the patients.

The observation that the MA, which is also influenced by platelet function, increased after administration of FFP seems to support the theory that the loss of platelet activators, particularly thrombin, contributes to the "platelet defect of CPB" (13).

There are limitations of the study that resulted in its classification as a *"pilot investigation";* namely:

1. The investigation was not performed as a clinical study with regard to clinical outcome such as postoperative blood loss or re-exploration rate and **comparison to a control group**. This calls for larger trials.
2. Only the global parameter of the ACT was used for the qualification of coagulopathy and outcome and the entry criterion of a prolongation of the ACT >150 sec seems arbitrary. However, the ACT is the most commonly used point-of-care coagulation test in cardiac surgery and immediate therapeutic decisions in clinical routine are widely based on this parameter. According to our experience, a prolongation of the ACT over 150 sec signals severe coagulopathy; whereas, a near baseline ACT of 120–130 sec rules out a coagulation disorder as a cause of hemorrhage.
3. The investigation included therapy with desmopressin, which exerts a complex influence on the coagulation system. The procoagulant effect of desmopressin is caused by an increased release of factor VIII and the von Willebrand factor (vWF). Furthermore, it reveals a stimulating effect on platelet aggregation and the platelet/endothelium interaction. Selected patients after CPB, who revealed an impaired platelet function in a platelet-activating factor (PAF) stimulated platelet function assay, responded to therapy with this agent as observed by a reduction of blood loss and transfusion requirements (14). Patients with a decreased MA in the TEG after CPB have also been shown to respond to therapy with this agent with an increase of the MA (10). Therefore, the multichannel modified TEG also seems to be a suitable assay for the discrimination of patients who will benefit from therapy with desmopressin. However, the definition of its indication in the present protocol seems to be arbitrary. Therefore, although in five patients desmopressin was an effective therapy, because of the complex influences on coagulation, more detailed elaboration of the criteria for therapy with this agent is necessary and warrants further investigations.

We conclude that the synoptic analysis of the multichannel modified TEG in a series of 30 patients enabled improved discrimination of clinically important causes for post-CPB hemorrhage and provided a guide for efficient therapy. Nevertheless, elaboration of the protocol, in particular with regard to the use of desmopressin, is desirable, and larger clinical outcome investigations are necessary for the final evaluation of this concept.

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