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Assessment of the Resonance Thromboelastograph CS-3 for Differentiation of Coagulation Disorders: A Pilot in vitro Investigation of Simulated Post-Cardiopulmonary Bypass Coagulopathies

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Abstract: Resonance thromboelastography (RTG), a further development of the thromboelastogram (TEG), has been designed for improved differentiation of the effect of the plasmatic coagulation factors (increasing F-leg) and platelets (decreasing P-leg) on clot formation. It is based on the effect of clot elasticity on the resonance of a swinging wire. We assessed the RTG for its ability to differentiate coagulation disorders that frequently occur after cardiac surgery.

The RTG was performed with a CS-3 Analyzer. Samples from 10 healthy volunteers were investigated after the following preparations: (1) baseline values, (2) dilution to a hematocrit of 30% and 20% with either hydroxyl ethyl starch (HES) 10% or plasma; (3) addition of 0.25, 0.5, and 1.0 IU/mL porcine heparin with and without heparinase; and (4) addition of 1.0, 3.0, 4.0, and 5.0 μg/mL of the antiplatelet agent abciximab (ReoPro™). Increasing concentrations of abciximab led to a slower decrease or in the case of higher concentrations, to a persistent elevation of the platelet leg of the RTG. Dilution of the hematocrit with plasma had no effect on the fibrin and platelet leg; whereas, dilution with HES 10% led to an inhibition of the fibrin and platelet leg. Dilution of the plasmatic coagulation factors resulted in an inhibition of both the fibrin and the platelet leg. The addition of 0.25 and 0.5 IU/mL of heparin led to an increased coagulation time and inhibition of the fibrin and platelet legs. These effects were eliminated by the addition of heparinase. The RTG enables the evaluation of platelet function under the condition of a nonimpaired plasma coagulation system. Depletion of plasma coagulation factors and the administration of small amounts of heparin do not enable the distinction between residual effects of an anticoagulant, coagulation factor deficiency, or impaired platelet function. However, the heparin effects can be eliminated by the addition of heparinase. Further improvement may be achieved using a modified RTG by adding plasma coagulation factors in one channel for an improved evaluation of platelet function, even under the condition of a loss of procoagulants. **Keywords:** cardiopulmonary bypass, thromboelastography, coagulation. *JECT. 2001;33:159–166*

The large artificial surfaces of cardiopulmonary bypass (CPB) necessitate high-dose anticoagulation to avoid thrombosis of the system. However, during CPB, the plasmatic coagulation factors and platelets are diluted by the priming solution and are increasingly consumed by contact with the large artificial surfaces and fibrinolysis (1, 2). Mechanical alteration of the platelet shape leads to transient impairment of platelet function. Persistent anticoagulation after CPB caused by residual heparin, heparin-rebound, or incomplete reversal by protamine after extracorporeal circulation contribute further to impaired hemostasis.

Postoperative bleeding, caused by impaired restoration of coagulation, not only influences the outcome of the patients, but also effectively contributes to costs because of transfusion requirements or the necessity for surgical re-exploration. Therefore, immediate therapy based on a rapid point-of-care diagnosis of the complex coagulation disorder is a central goal in cardiac anesthesia.

Sophisticated laboratory tests of the plasmatic coagulation system and platelet aggregation require time-consuming pre-analytical preparation and are unsuitable for use in the operating room, where therapeutic decisions must be made rapidly. However, global whole blood point-of-care coagulation tests, such as the activated clotting time (ACT) or activated thromboplastin time (aPTT), do not permit differentiation of the causes of post-CPB bleeding. Point-of-care qualification or even quantification of residual heparin may be achieved by the use of the heparinase ACT (3) or by protamine titration methods (Hepcon HMS Medtronic, Parker, CO, USA) (1, 2). Mod-

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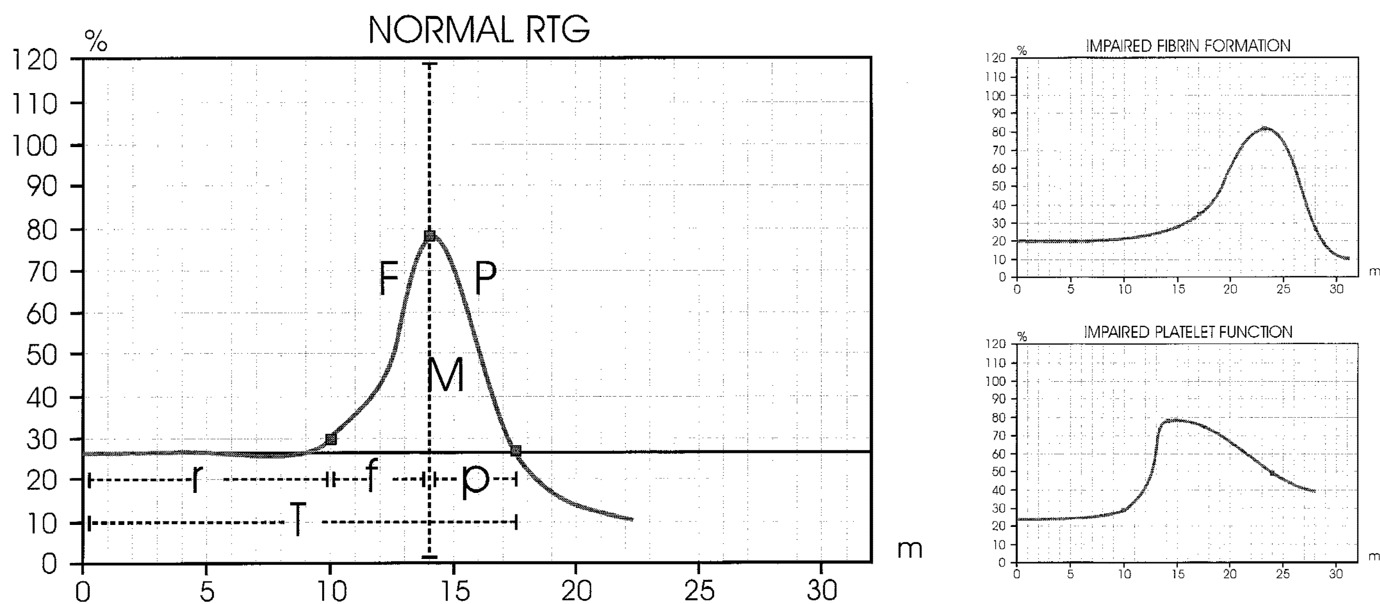
ern point-of-care platelet function tests have been demonstrated to be an effective guide for therapy, for example with desmopressin (4). However, these tests only evaluate parts of the coagulation system. In contrast, viscoelastic tests, in particular thromboelastography (TEG), reflect the more complex process of coagulation. A number of investigations have demonstrated the effectiveness of TEG for the prediction of bleeding diathesis (5, 6), the differentiation between bleeding attributable to surgical reasons or coagulation disorders (7) and as a guide for rational transfusion concepts (8). Nevertheless, the key parameters of TEG, the r-time (coagulation time), and the maximum amplitude (fibrinogen–platelet interaction), do not permit the discrimination of disturbances of the plasmatic coagulation system and platelet function.

Hartert, the developer of TEG, in order to provide better insight into the coagulation system than the conventional TEG, and particularly to differentiate the effects of the plasmatic and platelet systems, has introduced resonance thrombography (RTG). Although the technique of RTG has been known for years, there are only a limited number of investigations that address this subject (9–11).

Similar to thromboelastography in the RTG, a bar, connected to a stand by a short steel wire, is positioned in a cup where the blood sample is placed. In contrast to conventional thromboelastography (12), the cup is fixed, and the rod, which has a self-frequency of 45 Hz if touched, is driven with a frequency of 53 Hz in an orbital movement by an overlying electromagnetic field (Figure1a). With the ongoing process of coagulation, fibrin fibers bind to the end of the bar and add their elasticity to that of the steel wire. Therefore, the self-frequency of the rod rises from 45 Hz upward. The nearer the self-frequency becomes to the driving frequency, the resonance effect takes place and widens the radius of the orbital movement. The maximum resonance effect; that is, the maximum amplitude, is achieved at a coincidence frequency of 53 Hz. Because the rod serves as a sensor of the coagulation process, the frequency of 53 Hz was calculated and assessed in preliminary experiments (dependent on the material and geometry of the rod and the cuvette and blood volume), in order to achieve a maximum amplitude (sensitivity) of the RTG by minimum influence of the coagulation process itself and an optimum separation of the coagulation phases. With ongoing retraction of the clot by the platelet–fibrinogen interaction, the self-frequency of the clot is further increased by up to over 100 Hz, and the resonance effect becomes lost with a consequent reduction of the orbital movement.

In the RTG, the radius of the orbital movement is vi-



RESULTS:

r = 8:38min MFS = 12.00%/min
f = 3:30min MPF = 17.90%/min
M = 42.10% AF = 19.70%
p = 2:21min t = 18:42min

Figure 1. Simulation of RTG changes caused by impaired fibrin formation and impaired platelet aggregation. R-time = coagulation time, F-time = fibrin formation time, P-time = platelet retraction time, M = maximum amplitude, MFS = mean gradient of the fibrin leg, MPS = mean gradient of the P-leg, AF = asymmetry factor of the F, and P-legs, T = total coagulation time.

sualized in a curve (amplitude over time). The initial phase with no coagulation and uninfluenced orbital movement is called the R-time (coagulation time). With ongoing fibrin formation, the radius increases (F-time: the increasing gradient of the fibrin leg) to the point of maximum resonance (M). The clot-retraction by the platelet-fibrinogen interaction leads to a decrease of the orbital movement because of loss of the resonance effect, which is visualized in the P-time (decreasing platelet leg, Figure1b).

In the present investigation, we assessed the ability of RTG to differentiate the coagulopathies that frequently occur after CPB: the effect of hemodilution with plasma or HES 10%; the depletion of coagulation factors; the effect of low concentrations of heparin (0.25–1.0 IU/mL, with and without heparin) as observed in cases of heparin-rebound or incomplete reversal by protamine; and the effect of impaired platelet aggregation simulated by the addition of increasing quantities of the platelet GP IIb/IIIa receptor inhibitor abciximab (ReoPro™). Because of the complexity of CPB-related disturbances of the coagulation system, the study was performed using an in vitro protocol, which allowed more selective control and more specific investigation of the effects of the variables.

METHODS

The RTG was performed on the CS-3 Analyzer (Amelung, Lemgo, Germany). For measurement, 250 μL of a citrated whole blood sample was transferred into the cup and 150 μL of $CaCl_2$ were added and mixed with the blood sample. Then the measurement was started. Computerized analysis provided on-line visualization of the RTG curve and automatic calculation of the F and P time and maximum amplitude M. The maximum amplitude was expressed in percentage of amplitude of 60 μm, which was defined as the maximum orbital movement of the device. MFS [%] represents the mean gradient of the F-leg, and MPS [%] represents the mean gradient of the P-leg. The asymmetric rise of the F and P-legs was calculated in the asymmetry factor AF, and the whole process of coagulation was measured in the T-time [min].

Patients and Methods

After approval by the local ethics committee and informed consent, citrated whole blood samples were collected from 10 healthy volunteers (age 25–28 years, five female, five male), and RTG measurements were performed after preparation according to the following conditions:

1. unprepared citrated whole blood sample for measurement of baseline values;
2. variation in hematocrit (20% and 30%) obtained by centrifugation and adjustment of the plasma fraction with either hydroxyl ethyl starch (HES) 10% or plasma. The latter to differentiate whether possible dilution effects could be adequately attributed to plasma factor deficiency or platelet count or function;
3. dilution of procoagulants (50%, 30%, and 10% of the initial value), obtained via substitution of platelet-poor plasma with corresponding volumes of a 5% solution of albumin;
4. addition of 0.25, 0.5, and 1.0 IU/mL of unfractionated heparin (Liquemin, Roche, Germany), which represent concentrations as observed during high-dose thrombosis prophylaxis or residual heparin after protamine administration following CPB;
5. addition of 0.25, 0.5, and 1.0 IU/mL of unfractionated heparin (Liquemin, Roche, Germany), and 20 μL heparinase (Hepzyme, Dade Behring, Marburg, Germany); and
6. addition of 1, 3, 5, 10 μg/mL abciximab (ReoPro,™, Lilly, Bad Homburg, Germany), whereby the concen tration of 5 μg/mL should correspond with the initial concentration after the bolus administration 0.25 mg/kg BW abciximab as commonly used in the catheter laboratory.

All measurements were performed in duplicate in the two channels of the device and automatically interrupted after a period of 60 min.

Platelet Aggregation

Monitoring of platelet function was performed with the ADP (20 μmol/L) stimulated platelet aggregometry (Mölab, Bio-Data Corporation, Philadelphia, USA) in platelet-rich plasma. Platelet-rich plasma was prepared by centrifugation at 800 r/min for 15 min, adjusted to a platelet count of approximately 200,000/μL and aggregation measured at a stir rate of 900 r/min at room temperature.

Statistical Analysis

The statistical analysis was performed using analysis of variance (ANOVA) with the Scheffé test. A p-value <.01 was determined as significant.

RESULTS

The results, expressed in mean values and standard deviation, are given in Table 1. In 34 out of 158 parameters, no values were obtained because of incomplete coagulation within the period of 60 min.

1. Hemodilution

The hemodilution with HES to a hct of 30% (baseline 40.5 ± 4.1% SD) significantly increased the F, P, M, and AF values. Hemodilution to 30% by the use of plasma significantly increased the AF value and decreased the T time. The hemodilution with HES 10% to a hct of 20% led to a significant increase of the F and a decrease of the MFS

Table 1. Resonance thromboelastograph CS-3 values under different coagulation conditions.

	R (min)	F (min)	p (min)	M (%)	MFS (%)	MPS (%)	AF (%)	T (min)	Platelet count (μL)	ADP (*20 μmol/L) Platelet Aggregation (%)
Baseline	8.3 ± 1.1	3.1 ± 0.9	3.3 ± 0.8	36.9 ± 4.1	11.5 ± 2.1	12.2 ± 2.5	2.4 ± 0.4	34.7 ± 4.7	167 ± 32	97 ± 5.5
Hct 30% HES	9.5 ± 1.7	6.2* ± 1.5	5.2* ± 1.2	56.3* ± 7.4	8.8 ± 1.7	10.4 ± 2.1	8.2* ± 2.1	34.4 ± 6.7	143 ± 17	89 ± 4.1
Hct 20% HES	9.3 ± 3.4	13.3* ± 4.3	n.v.	39.9 ± 10.4	2.9* ± 0.5	n.v.	n.v.	n.v.	134 ± 32	94 ± 5.1
Hct 30% plasma	8.4 ± 1.1	3.2 ± 0.4	2.5 ± 0.3	44.0 ± 4.1	13.3 ± 2.1	15.3 ± 2.1	7.0* ± 2.1	17.3* ± 3.1	137 ± 21	95 ± 4.9
Hct 20% plasma	8.1 ± 0.7	2.3 ± 0.7	2.6 ± 0.6	40.1 ± 5.1	14.1 ± 3.1	13.6 ± 2.7	8.3* ± 3.1	16.5* ± 2.1	119 ± 21	89 ± 5.4
Coagulation factor 50%	10.2 ± 3.1	7.5* ± 2.1	5.6* ± 1.4	48.3 ± 7.8	6.4* ± 2.1	8.5* ± 1.7	13.8* ± 3.7	26.5 ± 6.8	161 ± 27	86 ± 3.9
Coagulation factor 30%	11.0 ± 3.1	9.1* ± 2.7	10.6* ± 2.9	47.7 ± 9.1	5.2* ± 1.7	4.7* ± 1.5	4.8* ± 1.2	33.4 ± 5.2	155 ± 31	87 ± 4.1
Coagulation factor 20%	11.5 ± 2.7	32.5* ± 7.1	n.v.	43.3 ± 5.8	1.3* ± 0.3	n.v.	n.v.	n.v.	171 ± 27	93 ± 4.1
0.25 IU/mL UFH	32.1* ± 6.1	17.3* ± 4.1	n.v.	27.9* ± 6.5	1.6* ± 0.4	n.v.	n.v.	n.v.	165 ± 27	92 ± 4.7
0.5 IU/mL UFH	37.5* ± 9.1	14.1* ± 6.1	n.v.	44.7 ± 7.9	3.1* ± 0.7	n.v.	n.v.	n.v.	175 ± 32	89 ± 4.5
1.0 IU/mL UFH	n.v.	n.v.	n.v.	n.v.	n.v.	n.v.	n.v.	n.v.	153 ± 27	94 ± 5.9
0.25 IU/mL UFH + Heparinase	9.5 ± 1.1	4.0 ± 0.7	4.1 ± 0.9	40.2 ± 6.4	12.8 ± 3.4	13.7 ± 2.6	2.8 ± 0.7	39.9 ± 5.7	172 ± 21	89 ± 6.1
0.5 IU/ml UFH + Heparinse	10.6 ± 1.7	4.2 ± 1.1	3.9 ± 1.0	42.7 ± 6.4	11.9 ± 3.7	13.6 ± 1.9	2.9 ± 1.1	36.4 ± 4.9	185 ± 39	93 ± 4.1
1.0 IU/ml UFH + Heparinase	9.9 ± 1.2	3.9 ± 1.1	4.0 ± 1.1	43.3 ± 7.9	14.6 ± 4.7	14.8 ± 3.1	3.1 ± 1.1	37.3 ± 3.9	161 ± 25	85 ± 6.5
1 μg/ml abciximab	11.4 ± 2.1	3.5 ± 0.4	3.2 ± 0.5	46.4 ± 6.1	12.1 ± 2.1	13.7 ± 2.8	6.2* ± 1.7	26.4 ± 3.4	159 ± 29	89 ± 7.5
3 μg/ml abciximab	11.6 ± 3.1	10.4* ± 3.2	n.v.	64.8* ± 10.5	6.1* ± 1.6	n.v.	n.v.	n.v.	167 ± 25	23* ± 9.1
4 μg/ml abciximab	10.8 ± 2.1	23.1* ± 4.2	n.v.	67.3* ± 9.2	5.2* ± 1.5	n.v.	n.v.	n.v.	172 ± 21	4.2* ± 3.1
5 μg/ml abciximab	9.4 ± 2.5	23.5* ± 2.7	n.v.	65.0* ± 10.3	4.7* ± 1.3	n.v.	n.v.	n.v.	156 ± 19	2.0* ± 2.5

n.v. = no value (no final coagulation after 60 min); *significant difference ($p < .01$) to corresponding baseline value.

values. No values could be attributed to P, MPS, AF, and T because of a persistent elevation of the P-leg. Hemodilution to 20% by the use of plasma had no significant influence on the RTG parameters obtained, apart from a significant decrease of the T time (Figure 2).

2. Dilution of Plasmatic Coagulation Factors

There was a significant prolongation of the F and P values and a significant decrease in MFS and MPS at a dilution of procoagulants to 50% and 30%. A dilution to 20% resulted in a significant increase of the F and AF values and a decrease of the MFS value. No values could be obtained for P, MPS, AF, and T because of incomplete coagulation over 60 min (Figure 3).

3. Unfractionated Heparins and Heparinase

The administration of 0.25 and 0.5 IU/mL UFH led to a significant increase of the R and F times and a significant decrease of the M and MFS values. No values could be attributed to P, MPS, AF, and T because of incomplete coagulation over 60 min. No coagulation was observed within the period of 60 min after the administration of 1.0 IU/mL UFH (Figure 4). These effects were reversed by the addition of heparinase.

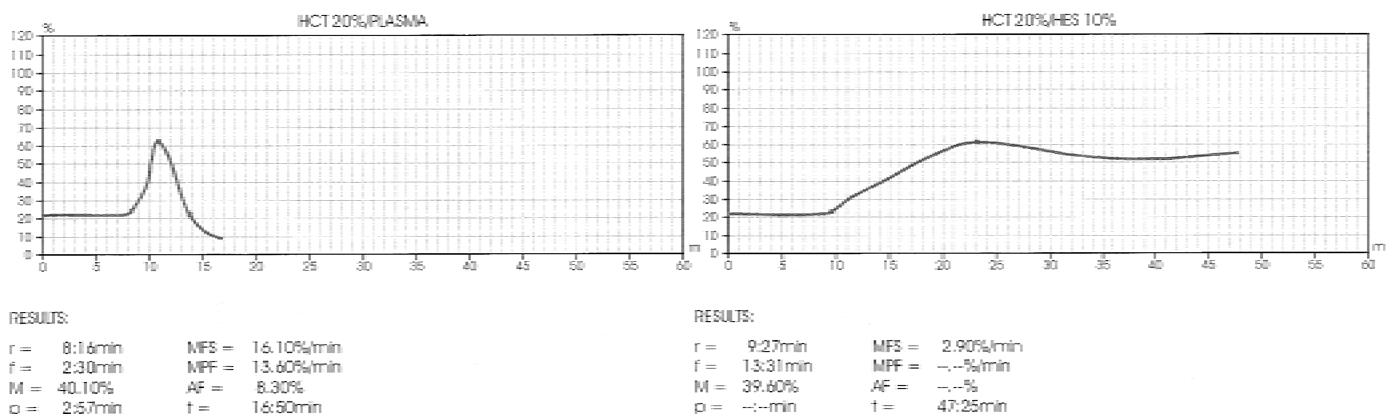


Figure 2. Influence of dilution with either plasma or HES 10% on the RTG.

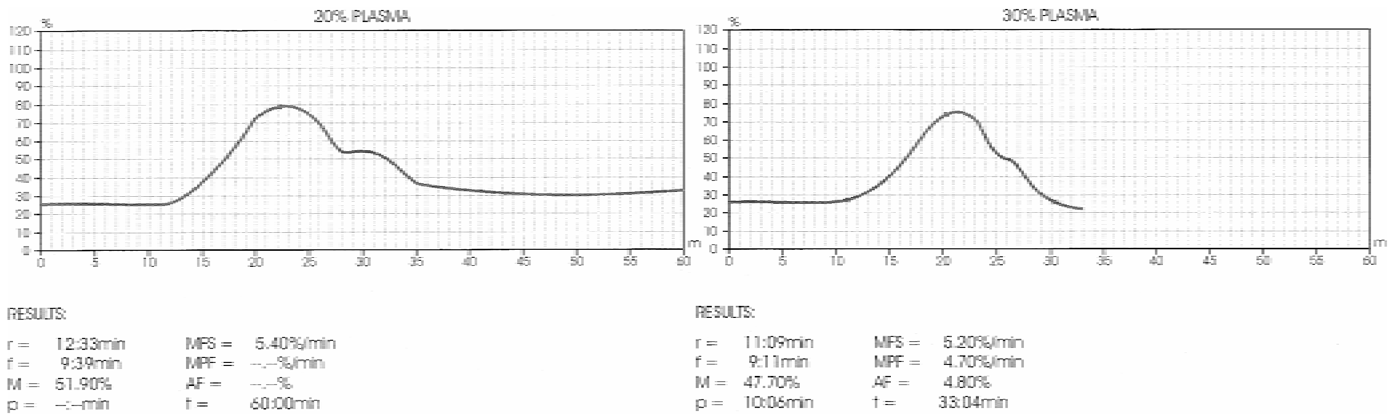


Figure 3. Influence of the dilution of plasmatic coagulation factors on RTG.

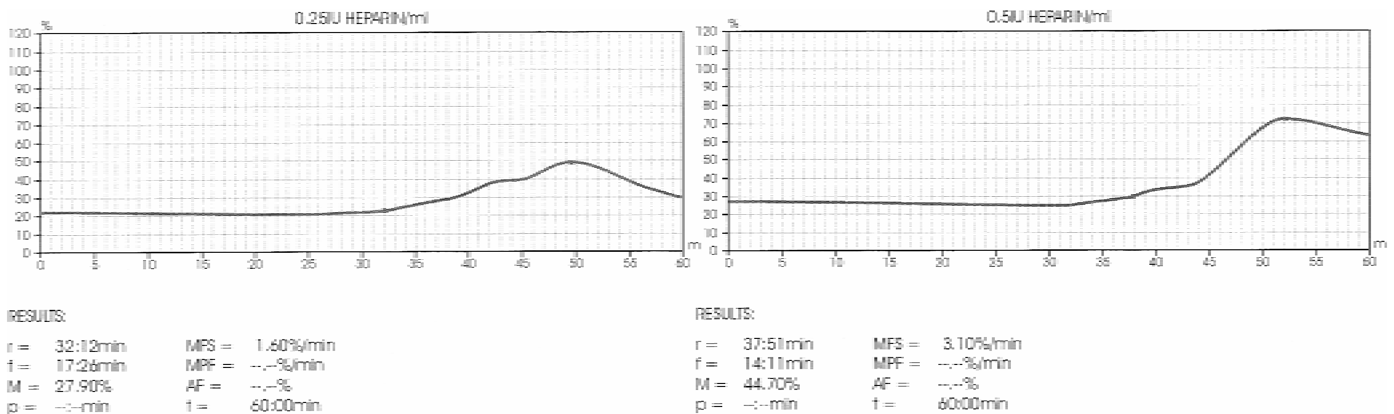


Figure 4. Influence of unfractionated heparin on the RTG.

4. Administration of Abciximab

The administration of 1.0 μg/mL abciximab had no significant effect on the RTG values obtained. The administration of 3, 4, and 5 μg/mL resulted in a significant increase of the F and M values and a decrease of the MFS value. Because the P line remained elevated, there were no values for P, MPS, AF, and T during the 60-min period (Figure 5). The ADP stimulated platelet aggregation was significantly inhibited at concentrations of abciximab of 3–5 μg/mL.

DISCUSSION

The RTG enables the evaluation of platelet function under the condition of a nonimpaired plasma coagulation system. Depletion of plasma coagulation factors and the administration of small amounts of heparin do not permit the distinction between residual effects of an anticoagulant, coagulation factor deficiency, or impaired platelet function. However, the heparin effects can be eliminated by the addition of heparinase to the sample.

Viscoelastic assays, such as TEG and Sonoclot,™ provide an insight into the whole process of clot formation. The TEG reflects the shear elasticity of the forming thrombus, but the key parameter of the maximum amplitude (MA) does not permit differentiation between the influence of the plasma coagulation factors and the platelet function on coagulation. Therefore, modified TEG is performed with platelet glycoprotein IIb/IIIa receptor inhibitors such as abciximab to unmask the effect of platelet function on the TEG graph (13). Moreover, various stimulators of coagulation and heparinase have been added to hasten the process of coagulation and to achieve results more rapidly (14, 15).

The Sonoclot™ system evaluates the change of impedance of the clot during fibrin formation and the subsequent retraction by the platelet–fibrinogen interaction. Therefore, different phases of the Sonoclot™ curve can be attributed to the plasma coagulation system and the platelet effect (16). Large intra/interindividual coefficients of variation of the Sonoclot™ graph limit the value of this device (17), and improvement by the use of different stimulators of coagulation has been suggested (18).

The RTG was designed for improved differentiation between platelet and procoagulant effects on the forming

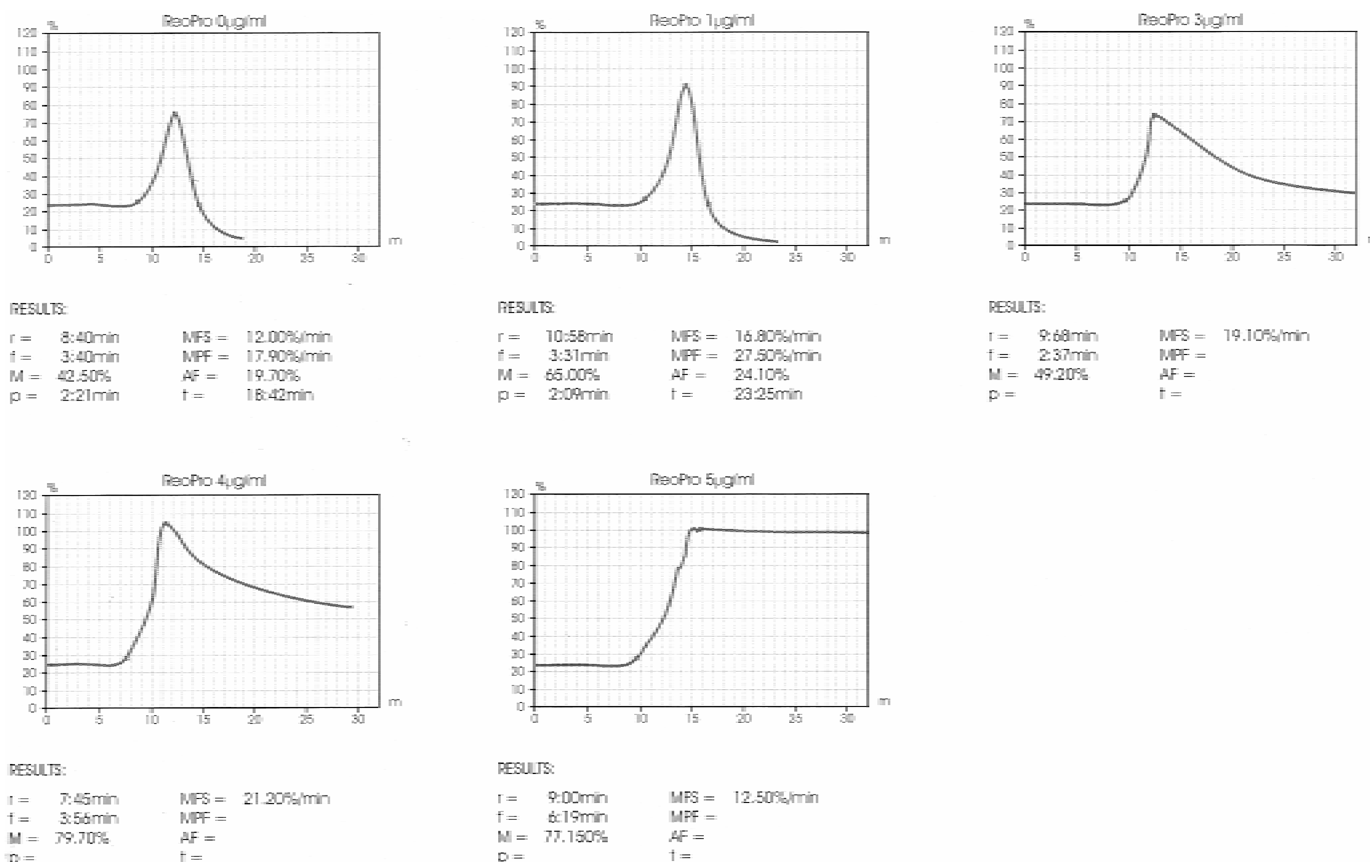


Figure 5. Influence of increasing concentrations of abciximab on the RTG.

thrombus because of the effect of clot elasticity on the resonance of a swinging wire (9–11).

In the current investigation, the RTG, following the addition of abciximab, enabled precise differentiation between an unimpaired plasma coagulation system and a potent inhibition of platelet aggregation as seen by the rapidly ascending F-leg and a dose-dependent inhibition of the decrease of the P-leg. These results correlate with the inhibition of 20 μmol/L of ADP-stimulated platelet aggregation, which is significantly reduced at abciximab concentrations between 3 and 5 μg/mL (which correspond with the calculated concentration achieved after a bolus of 0.25 mg/kg during interventions in cardiology).

The dilution with plasma had no effect on the F-leg or the P-leg. The hemodilution with HES 10% resulted in a decreased rise of the F-leg and a slowed decrease or persistent elevation of the P-leg. This, particularly in view of unimpaired coagulation after dilution within the plasma, has to be regarded as an inhibition of the plasma coagulation system attributable to dilution and inhibited platelet-induced clot retraction, which is possibly caused by HES-associated platelet coating. The dilution of plasmatic coagulation factors resulted in an inhibition of both the F and P-legs. Low UFH concentrations of 0.25 IU/mL, even though they were expected to influence only the r-time, also had a detrimental influence on the F and P-legs and, as a consequence, prevented any further interpretation of the graph. However, these effects could be eliminated by the addition of heparinase to the sample.

In summary, an assessment of platelet function by the use of RTG is possible. Nevertheless, because the RTG mainly evaluates platelet function by platelet-induced retraction of the forming thrombus, a previous formation of a fibrin clot must be a prerequisite for the evaluation of platelet function. Therefore, platelet function can only be ascertained under the condition of sufficient plasma coagulation factors. Consequently, the inhibition of fibrin formation by such anticoagulants as heparin does not permit further differentiation of a coagulopathy with RTG either.

However, because more selective and more rational therapy is the key therapeutic goal of monitoring, the complex changes of coagulation in the cardiac operating room require a distinction between the causes of bleeding. Even if the RTG provides differentiation of disturbances of hemostasis in patients with a selective deficiency of defined parts of the coagulation system, improvement of the method for use in the cardiac operation room is nec-

essary. This, similar to the modern use of TEG, may easily be achieved by the use of different antidotes or stimulators of coagulation. At first, in view of the detrimental effects of smaller amounts of heparin, the general use of heparinase cartridges, which are already employed for the standard TEG, seems to be mandatory (14, 15). Second, because the device provides the option of in parallel measurement in two channels, plasma coagulation factors (FFP, standard human plasma) may be added to one channel. This provides high levels of procoagulants for an improved isolated evaluation of the platelet leg. The synoptic evaluation of the channel with and without added procoagulants should then allow better differentiation between a coagulopathy attributable to the loss of plasmatic coagulation factors or inhibition of the platelet function. However, further investigations are necessary to warrant this assumption.

In addition to the problems associated with the use of the RTG under the special conditions of complex coagulation disorders, the interpretation of the RTG remains problematic. Although computerized calculation of key parameters, such as the time for fibrin polymerization (F) and platelet retraction (P), and the gradients of the curves of the F (MFS) and P (MPS) legs, the interpretation of the RTG findings is essentially guided by the evaluation of the graph. Incomplete coagulation after 60 min (presently observed in 20% of the obtained measurements) can be attributable to a prolonged r-time or slowly increasing F and decreasing P-legs that reveal a global coagulopathy or persistent anticoagulation, but can also be attributed to a rapidly ascending F-leg, which reveals rapid fibrin formation and a persistent elevation of the P-leg, which signals an isolated defect in platelet aggregation. This, however, requires experience and limits standardization. Therefore, similar to other devices, automated calculation of the function of the plasmatic coagulation system or platelets, as a percentage of normal, would be helpful. Moreover, the long period of time required for complete clot formation (minimum of 35 min) limits the value of the test as a point-of-care device. The use of stimulators of coagulation such as celite, kaolin, or tissue factor is desirable but may be associated with a decrease of the sensitivity of the test. Further investigations to address this subject are necessary.

We conclude that the RTG is an interesting assay for coagulation monitoring, which reflects the complex process of coagulation by the evaluation of the viscoelasticity of the forming whole blood clot. The selective changes in the platelet leg, following the administration of the platelet glycoprotein IIb/IIIa antagonist abciximab, suggest that the RTG is a valuable functional assay for the differentiation of plasmatic and platelet function related coagulation disorders and probably for functional monitoring of the efficiency of GP IIb/IIIa platelet receptor inhibitors. However, the fact that small amounts of heparin significantly limit the value of the RTG, and the fact that platelet function obviously can only be adequately evaluated by providing high levels of procoagulants, limit its value particularly in the cardiac operating room where often complex coagulopathies are observed.

Improvements may be easily achieved by the general use of stimulators of coagulation, such as heparinase, and a modified RTG with plasmatic coagulation factors added in one channel for selective evaluation of platelet function, even in cases of the loss of procoagulants. This should contribute to further progress of the method, but requires evaluation in larger clinical investigations.

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