Monitoring Incomplete Heparin Reversal and Heparin Rebound After Cardiac Surgery

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Objectives: **To assess the incidence of incomplete heparin reversal and heparin rebound after cardiac surgery with cardiopulmonary bypass (CPB) and the ability of the activated coagulation time (ACT) and thromboelastography (TEG) to detect these phenomena.**

Design: **Prospective single-center study.**

Setting: **University hospital.**

Participants: **Forty-one patients undergoing elective cardiac surgery with CPB and with normal preoperative TEG parameters.**

Interventions: **ACT, TEG, and plasma heparin levels were measured in all patients at 5 different times between 20 minutes and 3 hours after protamine administration. The variability of TEG reaction time (R) with and without heparinase (delta-R [DR]) was used to detect the presence of residual heparin.**

Measurements and Main Results: **Plasma heparin expressed as anti-FXa activity was detected in 180 (88%) samples. At univariate analysis, ACT, R-kaolin (R-k), and DR significantly correlated with plasma heparin concentration (respectively, $p = 0.007$, $p = 0.006$, and $p = 0.002$). At multivariate analysis, R-k and DR remained associated with plasma heparin concentration (respectively, $p = 0.014$ and $p = 0.004$). Greater quartiles of heparin were associated with higher values of R-k and DR. Combined procedures had significantly lower DR than isolated procedures ($p = 0.017$), and CPB time and heparinization time positively correlated with R-k (respectively, $p = 0.044$ and $p = 0.022$). No association was observed between heparin concentration, ACT, and TEG parameters with postoperative bleeding and need for blood and blood components transfusions.**

Conclusions: **Heparin rebound and incomplete heparin reversal are very common phenomena after cardiac surgery with CPB; ACT is not able to detect residual heparin activity, whereas TEG analysis with and without heparinase allows the diagnosis of heparin rebound.**

KEY WORDS: heparin rebound, thromboelastography, activated coagulation time, cardiopulmonary bypass, heparin, protamine

CARDIAC SURGERY with cardiopulmonary bypass (CPB) requires full systemic heparinization and close intraoperative and postoperative monitoring of coagulation to provide adequate anticoagulation during CPB, reduce the incidence of postoperative bleeding, diagnose the cause of bleeding, and establish a targeted therapy. Postoperative bleeding represents one of the main complications after cardiac surgery with CPB; nearly 20% of patients present with significant bleeding and 2% to 8% require surgical re-exploration for bleeding.[1-5] Postoperative bleeding requiring multiple transfusions, and surgical re-exploration is associated with increased operative mortality and morbidity.[2,5-6] A surgical source of bleeding is found in 50% to 70% of patients undergoing reoperation for bleeding, whereas the remaining patients exhibit microvascular bleeding due to a multifactorial coagulopathy.

Extensive surgical trauma, prolonged blood contact with the artificial surface of CPB, high doses of heparin, and hypothermia all induce the activation of the inflammatory, coagulation, and fibrinolytic systems and platelet (PLT) dysfunction, leading to postoperative coagulopathy.[7] The heparin rebound phenomenon, first described by Huin et al[8] and defined as the reappearance of hypocoagulability after adequate neutralization of heparin with protamine, also occurs in the early postoperative period and potentially can cause clinically important postoperative bleeding. Activated coagulation time (ACT), widely used to monitor the intraoperative anticoagulant effect of heparin, measures the time to clot formation, but it is not able to measure heparin concentration.[9] Thromboelastography (TEG) provides global information on the coagulation and fibrinolytic systems; it also measures the kinetics of clot formation and growth, as well as the strength and the stability of the formed clot.[10]

In this study, the authors assessed incomplete heparin reversal and heparin rebound after cardiac surgery with CPB by measuring the plasma heparin concentration expressed as anti-FXa activity over a period of 3 hours after protamine administration. The primary endpoint was to evaluate the correlation between plasma heparin levels and ACT and TEG results. Additionally, the authors evaluated the association between postoperative heparin levels and postoperative bleeding and the need for blood-derived product transfusions.

METHODS

The local ethics committee approved the study protocol. After informed consent, patients scheduled for elective cardiac surgery with CPB were enrolled prospectively in the study. The following exclusion criteria were applied: Known pre-existing coagulopathies, abnormal preoperative TEG parameters, chronic renal insufficiency requiring

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Table 1. Patients' Preoperative, Intraoperative, and Postoperative Characteristics; Data are Expressed as Mean ± SD and Frequencies (Percentages)

Preoperative Data	
No. of patients	41
Age, y	70.1 ± 10.1
Male	29 (71%)
Systemic hypertension	32 (78%)
Diabetes mellitus	6 (15%)
Hypercholesterolemia	18 (44%)
Obesity	6 (15%)
Smoking history	9 (22%)
Previous AMI	6 (15%)
Unstable angina	3 (7%)
CAVD	6 (15%)
EF, %	49.3 ± 9.7
Chronic AF	7 (17%)
CVA	1 (2%)
PVD	2 (5%)
CRF	7 (17%)
COPD	14 (34%)
Intraoperative data	
CABG	17 (42%)
AVR	18 (44%)
MVR/MV repair	14 (34%)
Aortic surgery/Bentall	11 (27%)
Combined procedures	19 (46%)
Surgery time, h	4.79 ± 1.13
CPB. min	132 ± 46
Cross-clamping, min	101 ± 45
Heparin dose, IU/patient	23659 ± 5565
Protamine dose, mg/patient	282 ± 54
Heparinization time, min	159 ± 48
Postoperative data	
Mortality	3 (7%)
Re-exploration for bleeding	1 (2%)
ICU stay, h	81 ± 149
Total stay, d	10 ± 5.9
Mechanical ventilation, h	8.5 ± 4.35
ARF	3 (8%)
AF	3 (8%)
Mediastinal blood loss, mL	388 ± 238
Pleural blood loss, mL	218 ± 209
RBC transfusions, units	1.53 ± 2.04
FFP transfusions, units	0.68 ± 1.79
PLT transfusions, units	0.15 ± 0.48

Abbreviations: AMI, acute myocardial infarction; CAVD, calcific aortic valve disease; EF, ejection fraction; AF, atrial fibrillation; CVA, cerebrovascular accident; PVD, peripheral vascular disease; CRF, chronic renal failure; COPD, chronic obstructive pulmonary disease; CABG, cardiopulmonary bypass grafting; AVR, aortic valve replacement; MVR, mitral valve replacement; ARF, acute renal failure; ICU, intensive care unit; RBC, red blood cell; FFP, fresh frozen plasma; SD, standard deviation.

hemodialysis, oral or intravenous anticoagulant treatment, aspirin treatment taken within 72 hours before the intervention, preoperative infections with temperature greater than 37.5°C and white blood cells >12,000 per μL, history of neoplasia or autoimmune disease, and surgical emergencies.

After premedication with lorazepam, anesthesia was induced with a combination of fentanyl, midazolam, and sodium thiopenthal and maintained with proprofol. The antifibrinolytic drug tranexanic acid (3 g) was administered before CPB. Heparin (300 U/kg) was given to achieve systemic heparinization. Intraoperative heparin monitoring was performed by standard ACT (HEMOCHRON Jr. ACT+ [ITC, Edison, NJ]). Additional heparin bolus (5,000 U) was given if the ACT was below 400 seconds. Protamine was administered to reverse heparin (1 mg of protamine/100 U of heparin). CPB was established with a 2-stage venous cannula and aortic return. Moderate hypothermia (34°C) was maintained during the surgery. Cardiac arrest was induced and maintained with antegrade cold blood cardioplegia. Cardiotomy suction was used in all patients. All residual post-CPB cardiotomy blood was transfused in all patients through the arterial line, adding saline solution in the pump prime before protamine administration. Cell-saving devices were used in all patients. Intraoperative and postoperative prophylactic antibiotics were administered according to institutional protocols. Blood and blood products were transfused according to the following criteria: Allogeneic packed red blood cells were transfused if the hemoglobin value was <8 g/dL or the hematocrit was <24%. Fresh frozen plasma was infused if, in the presence of significant bleeding, TEG parameters and prothrombin time international normalized ratio values after protamine administration were above normal values. PLT concentrates were transfused with PLT count <50,000 per mm^3 in the presence of significant bleeding.

Blood samples were collected at 5 different times:

- T1: 20 minutes after protamine administration;
- T2: 1 hour after protamine administration;
- T3: 1 hour and 40 minutes after protamine administration;
- T4: 2 hours and 20 minutes after protamine administration;
- T5: 3 hours after protamine administration.

Blood samples were collected by a central catheter in the jugular vein into Vacutainer tubes (Becton Dickinson, NJ) containing 3.2% sodium citrate. Blood samples were centrifuged for 30 minutes at 2,000g at 4°C and plasma was frozen at −80°C until assayed. Whole-blood samples were collected for ACT and TEG assays at the same times.

The following assays were performed at the above mentioned sample times: ACT, TEG, and plasma heparin levels. ACT was measured by the HEMOCHRON Jr. ACT+ using 15 μL of whole blood. TEG was carried out by a TEG Hemostasis Analyzer (Haemoscope Inc, IL); whole-blood samples (360 μL) were placed into 2 cuvettes containing, respectively, kaolin (k) and k with heparinase (kh) to eliminate the effect of systemic heparin. At the end of the test the whole coagulation process was described using the following parameters: R (reaction time: Time to initial fibrin formation, reference value 3-8 minutes), K (time to clot formation, reference value 1-3 minutes), α (alpha angle: rate of clot formation, reference value 55°-78°), and maximum amplitude (absolute clot strength; reference value 51-69). The difference between the R-kh and the R-k value was defined as delta-R (DR). The amount of plasma heparin was determined from the anti-FXa activity expressed by the antithrombin(AT)-heparin complex formed in plasma using a chromogenic assay (Coamatic Heparin, Chromogenix-Instrumentation Laboratory, Milan, Italy). Laboratory tests including hemoglobin, hematocrit, white blood cells, PLT, fibrinogen, activated partial thromboplastin time, troponin I, polymerase chain reaction, and creatinine also were performed preoperatively and at 1 hour and 24 hours after the end of the intervention.

The data are given as mean values ± standard deviation, and categoric variables as frequencies and percentage. The relationship among plasma heparin levels and ACT and TEG data were analyzed using a mixed-model for longitudinal data with patients fitted as random. Because of the exploratory nature of the study, sample size was not formally computed but was decided a priori to be around 40 patients. A p value of <0.05 was considered statistically significant.

Table 2. Heparin Concentration, ACT, and TEG Parameters at Each Sample Time. Values are Expressed as Mean ± SD

Sample Time	T1	T2	T3	T4	T5
Heparin, IU/mL	0.32 ± 0.29	0.24 ± 0.29	0.24 ± 0.33	0.19 ± 0.27	0.19 ± 0.25
ACT, s	133 ± 17	130 ± 17	130 ± 24	126 ± 14	126 ± 15
R-k, min	8.4 ± 2.7	7.6 ± 2.8	8.8 ± 3	8.9 ± 3.5	8.7 ± 2.8
R-kh, min	6.8 ± 1.8	6.2 ± 1.6	7.0 ± 1.8	6.8 ± 1.5	6.5 ± 1.4
DR, min	−1.52 ± 1.97	−1.42 ± 2.53	−1.94 ± 1.92	−2.15 ± 2.83	−2.14 ± 2.31

Abbreviations: ACT, activated coagulation time; R-k, R-kaolin; R-kh, heparinase; SD, standard deviation; DR, difference between the R-kh and the R-k value.

The analyses were carried out using STATA software version 12 (StataCorp, College Station, TX).

RESULTS

Forty-one patients met all the inclusion criteria including normal preoperative TEG parameters and were enrolled in the study; 4 patients were excluded according to abnormal TEG (very large R parameter). Preoperative, intraoperative, and postoperative data of the study population are summarized in Table 1. Patients were at high surgical risk and 3 of them (7%) died, respectively, of cardiac failure, postoperative bleeding, and respiratory failure. The plasma heparin concentration was evaluated in 205 blood samples obtained at 5 different times between 20 minutes and 3 hours after protamine administration. The chromogenic assay measuring anti-FXa activity expressed by the AT-heparin complex formed in plasma showed the presence of heparin in 180 (88%) samples; that is, in at least 1 blood sample of all the 41 patients enrolled in the study. All TEG parameters were evaluated in all whole-blood samples; however, only R values are illustrated in tables, as it is well established that only R-time is affected by small amounts of heparin whereas the other parameters are not (K-time, maximum amplitude, and lysis). The mean values of heparin concentration, ACT, and TEG parameters obtained at each sample time are illustrated in Table 2.

Table 3 shows mean values of ACT, R-k, R-kh, and DR according to heparin concentration quartiles. At T1, 4 patients (10%) had heparin concentration in the first quartile (≤0.060 IU/mL), 7 (17%) in the second (0.061-0.162 IU/mL), 10 (24%) in the third (0.163-0.256 IU/mL), and 20 (49%) above the fourth quartile (>0.256 IU/mL). In 8 patients, at least 1 blood sample after T1 (from T2-T5) had heparin concentration higher than those observed at T1 (2 above the first quartile, 3 above the second quartile, and 3 above the third quartile). Twenty-five patients had the maximum values of heparin concentration from T2 to T5 in the same quartile of T1 (2 in the first quartile, 4 in the second quartile, 6 in the third quartile, and 13 in the fourth quartile). Eight patients had values of heparin concentration from T2 to T5 in a quartile lower than those observed at T1 (1 in the third quartile and 7 in the fourth quartile).

Table 4 shows the regression analysis with heparin concentration as the dependent variable and ACT, R-k, and DR as predictors. At univariate analysis, ACT, R-k, and DR significantly correlated with plasma heparin concentration (respectively, $p = 0.007$, $p = 0.006$, and $p = 0.002$). At multivariate analysis, R-k and DR remained associated with plasma heparin concentration (respectively, $p = 0.014$ and $p = 0.004$) while ACT was not associated with plasma heparin concentration in both models (respectively, $p = 0.396$ and $p = 0.516$). Fig 1 shows the mean values of R-k, R-kh, and DR according to heparin concentration quartiles. Greater quartiles were associated with higher values of R-k and of the differences between R-kh and R-k (DR).

Among patients' intraoperative and postoperative characteristics (listed in Table 1), combined procedures, CPB time, and heparinization time were related significantly to TEG parameters (data not shown). Combined procedures had significantly lower DR than isolated procedures ($p = 0.017$); CPB time and heparinization time positively correlated with R-k (respectively, $p = 0.044$ and $p = 0.022$). No association was observed among heparin concentration, ACT, and TEG parameters with postoperative bleeding and need for blood and blood components transfusions.

DISCUSSION

This study showed that incomplete heparin reversal and heparin rebound were very common phenomena after cardiac surgery with CPB, as residual plasma heparin was found in 180

Table 3. Heparin Concentration, ACT, and TEG Parameters of Each Heparin Quartile for Overall Blood Samples (From T1 to T5). Values are Expressed as Mean ± SD

Quartile, IU/mL	Q1 ≤ 0.060	Q2 = 0.061-0.162	Q3 = 0.163-0.256	Q4 > 0.256
Heparin, IU/mL	0.01 ± 0.02	0.12 ± 0.03	0.21 ± 0.03	0.60 ± 0.36
ACT, s	126.6 ± 17.3	128.1 ± 18.1	129.7 ± 19.6	132.1 ± 16.1
R-k, min	7.62 ± 2.54	8.61 ± 2.73	8.85 ± 3.44	8.79 ± 3.13
R-kh, min	6.30 ± 1.32	6.97 ± 1.49	6.91 ± 1.97	6.53 ± 1.58
DR, min	−1.31 ± 2.29	−1.68 ± 1.85	−1.97 ± 2.06	−2.39 ± 2.91

Abbreviations: ACT, activated coagulation time; R-k, R-kaolin; R-kh, heparinase; SD, standard deviation; DR, difference between the R-kh and the R-k value.

Table 4. Results of Mixed Model With Patients Fitted as Random in Explaining Heparin Concentration According to ACT and TEG Parameters. Values are Expressed as Regression Coefficiet Mean ± Standard Error. Heparin Analyzed Multiplied by 1,000

	Univariate		Multivariate		Multivariate	
	Heparin	p	Heparin	p	Heparin	p
ACT, s	2.03 ± 0.75	0.007	0.635 ± 0.749	0.396	0.567 ± 87	0.516
R-k, min	10.27 ± 3.73	0.006	9.319 ± 3.801	0.014	—	—
R-kh, min	7.76 ± 8.61	0.367	—	—	—	—
DR, min	−14.23 ± 4.55	0.002	—	—	−13.27 ± 4.65	0.004

Abbreviations: ACT, activated coagulation time; R-k, R-kaolin; R-kh, heparinase; DR, difference between the R-kh and the R-k value.

(88%) samples; all patients had at least one sample with residual plasma heparin over a period between 20 minutes and 3 hours after protamine administration. Twenty patients had considerable residual heparin 20 minutes after protamine administration, and 13 of these patients still had elevated heparin levels in the subsequent observations. These data demonstrate that it is difficult to distinguish between incomplete heparin reversal and heparin rebound. From a clinical point of view, elevated plasma heparin concentrations and the associated bleeding risk, regardless of its origin, need to be monitored.

The incidence of heparin rebound varies widely in the literature and has been reported to be as high as 50%,[11] and the phenomenon can persist for up to 6 hours after protamine administration.[12] A detailed mechanism has been proposed to explain this phenomenon.[12] The anticoagulant activity of heparin is mediated by its binding through a specific pentasaccharide to AT III, which results in a marked acceleration of the rate at which AT III inactivates thrombin, factor Xa, and other serine proteases in the coagulation cascade. Heparin also binds nonspecifically to other plasma proteins and PLT-derived proteins, as well as to endothelial cells. The affinity of heparin to plasma proteins through this nonspecific binding process is much less than its affinity to AT III, but it is likely to be important because the plasma concentration of these heparin-binding proteins is much higher than that of AT III. After its administration, heparin binds to AT III and to other plasma proteins, where it is distributed in an equilibrium that is dependent on the relative affinity of these proteins for heparin binding and the concentrations of the proteins. When protamine is administered, it binds and displaces a large proportion of heparin from its plasma protein binding sites. The resulting heparin/protamine complexes are then cleared from the circulation. Heparin rebound occurs because not all of the heparin is bound to and cleared by protamine. Rather, a proportion remains nonspecifically bound to plasma proteins and provides a reservoir of heparin that dissociates over time and produces an anticoagulant effect when it binds to AT III. CPB contributes to the phenomenon because it activates the inflammatory system, resulting in increased synthesis of acute-phase plasma proteins. Teoh et al[13] demonstrated that postoperative continuous protamine infusion was able to almost abolish completely the heparin rebound, which resulted in reduced postoperative bleeding. However, excessive heparin neutralization with protamine can result in an exacerbation of the hemostatic defect due to PLT aggregation inhibition.[14]

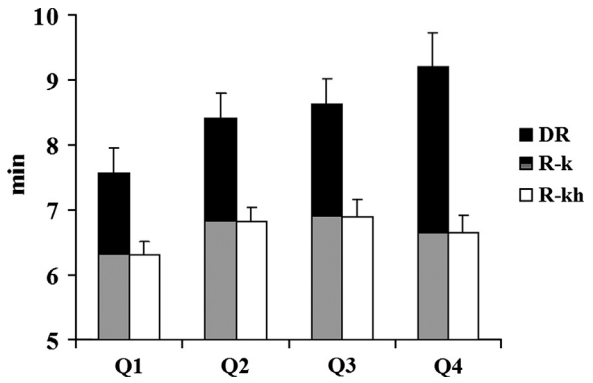

Fig 1. Mean values with standard error of R-k and R-kh according to quartiles of plasma heparin concentration. Black columns refer to the difference, defined as DR, between R-kh and R-k in each quartile.

ACT represents the main intraoperative monitoring system for anticoagulation during cardiac surgery; Despotis et al[15] showed that heparin concentration-based anticoagulation management during CPB (by means of the Hepcon HMS device) was more reliable compared to the great variability of ACT values. However, this device costs much more than standard ACT, and, therefore, in most centers it is not used in routine clinical practice. The present results showed that ACT is not useful to detect incomplete heparin reversal or the heparin rebound phenomenon. In fact, ACT values of blood samples were not correlated with plasma heparin concentration when TEG parameters (R and DR) were included in the regression model. In contrast, TEG analysis showed a significant association with plasma heparin concentration ($p = 0.014$ and $p = 0.004$, respectively, for R and the difference between the R-time value obtained with kaolin and the R-time value obtained with both kaolin and heparinase).

Heparinase is an enzyme obtained from *Flaviobacterium heparinum*, which specifically cleaves the polysaccharide portion of heparin; heparinase catalyzes an eliminase reaction directly within the AT III binding site of heparin, making it a potent reagent to eliminate the anticoagulant effect of heparin.[16] Heparinase has been shown to reverse the TEG effects of heparin, and studies in normal volunteers have demonstrated that heparinase does not affect TEG variables of whole blood not containing heparin.[17] The R-k time prolongation allows for diagnosis of coagulation factor dysfunction, but normalization of the R-kh time value suggests residual heparin activity. When patients' intraoperative and

postoperative characteristics were analyzed according to R-k and DR, TEG parameters correlated with combined procedures and CPB time. Patients undergoing combined procedures or procedures associated with longer CPB time were more likely to develop the heparin rebound phenomenon because CPB may result in increased plasma concentrations of PLT proteins that bind heparin. However, no association was observed in terms of postoperative bleeding and need for blood and blood components transfusions.

TEG analysis is a point-of-care viscoelastic measure of clot formation and clot dissolution that measures coagulation, PLT function, PLT-fibrinogen interactions, and fibrinolysis. Prior studies have documented retrospectively reduced bleeding and reoperative rates using TEG monitoring.[18] Two randomized controlled trials also have been performed.[19,20] Shore-Lesserson et al[19] compared TEG-based and conventional protocols to manage postoperative bleeding in patients undergoing cardiac surgery at moderate-to-high risk of transfusion. Although there was no significant difference in mediastinal tube drainage between the groups, blood and blood component therapy were significantly less in the TEG group than in the conventional group. Similarly, Royston and von Kier[20] demonstrated significantly less blood and blood component usage in the TEG-based group compared with the conventional group. Excessive postoperative bleeding represents a major complication after cardiac surgery, and it is caused by a combination of incomplete surgical hemostasis and an acquired hemostatic defect. CPB-induced coagulopathy is multifactorial, and one of the main causes is represented by PLT dysfunction.

The heparin rebound phenomenon has a high incidence in patients undergoing cardiac surgery with CPB. In patients involved in this study it did not affect blood loss, need for blood-derived products transfusions, or surgical re-exploration for bleeding. Teoh et al[13] demonstrated that extra protamine administration decreased postoperative bleeding, although the magnitude of the reduction was rather modest and the reduced bleeding did not translate into decreased transfusion requirements. Similarly, Martin et al[21] showed that postoperative bleeding and coagulation in patients with heparin rebound did not differ significantly from that seen in patients who did not exhibit the phenomenon. These data suggest that heparin rebound is a minor contributor to postoperative bleeding; however, based on the authors' clinical experience, it may be a cause of excessive postoperative bleeding. TEG analysis is useful in evaluating incomplete heparin reversal and heparin rebound, and it should be used in patients at high risk of bleeding, patients undergoing complex procedures, or in the presence of clinically significant postoperative bleeding.

In conclusion, heparin rebound and incomplete heparin reversal are very common phenomena after cardiac surgery with CPB and may increase the risk of postoperative bleeding. ACT is not able to detect residual heparin activity, whereas TEG analysis with and without heparinase allows the diagnosis.

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