Acute Coronary Syndromes

Thrombin Generation After the Abrupt Cessation of Intravenous Unfractionated Heparin Among Patients With Acute Coronary Syndromes
Potential Mechanisms for Heightened Prothrombotic Potential

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OBJECTIVES The purpose of this study was to determine the mechanistic basis for thrombin generation and increased prothrombotic potential after the abrupt cessation of intravenous (IV) unfractionated heparin among patients with acute coronary syndromes.

BACKGROUND A "rebound" increase in prothrombotic potential has been observed biochemically and clinically after the abrupt cessation of unfractionated heparin (UFH) among patients with acute coronary syndromes. Although the mechanism is unknown, tissue factor and the extrinsic coagulation cascade, both operative in atherosclerotic vascular disease and arterial thrombosis, are thought to be centrally involved.

METHODS In a single-center, pilot study, 30 patients with either unstable angina or non-ST segment elevation myocardial infarction who had received a continuous IV infusion of UFH for 48 h were randomly assigned to: 1) abrupt cessation, 2) IV weaning over 12 h or 3) subcutaneous weaning over 12 h.

RESULTS Thrombin generation (prothrombin fragment 1.2) was evident within 1 h of UFH cessation, increased progressively (by nearly two-fold) at 24 h (p = 0.002) and correlated inversely with tissue factor pathway inhibitor concentration (r = −0.61). Thrombin generation was greatest among patients randomized to abrupt cessation (1.6-fold increase at 24 h) and least in those with IV weaning.

CONCLUSIONS Thrombin generation after the abrupt cessation of UFH may represent a drug-induced impairment of physiologic vascular thromboresistance in response to locally generated tissue factor. A dosing strategy of abbreviated IV weaning attenuates but does not prevent heparin rebound among patients with acute coronary syndromes. (J Am Coll Cardiol 1999;34: 1020–7) © 1999 by the American College of Cardiology

Intravenous (IV) unfractionated heparin (UFH) is widely used in the management of patients with acute coronary syndromes, particularly those with unstable angina and non-ST segment elevation myocardial infarction (MI) (1–4) in whom atheromatous plaque disruption and intracoronary thrombosis commonly co-exist (5). Despite its proven beneficial effects as an adjunct to treatment strategies that commonly include aspirin, beta-adrenergic blocking agents, nitrates and, more recently, platelet glycoprotein IIb/IIIa antagonists, clinicians have documented and remain concerned about a resurgence of symptoms and a clustering of thrombotic events shortly after the cessation of UFH (6,7) and other thrombin antagonists (8–10).

Whether the observed clustering of thrombotic coronary arterial events shortly after UFH cessation represents a removal of suppression (of an underlying prothrombotic environment that has remained quiescent during treatment) (10,11) or true "rebound" was first investigated by Granger et al. (12). Thirty-five patients with unstable angina or acute MI who had received a continuous IV infusion of UFH for at least 48 h were studied. Thrombin generation measured in plasma increased transiently but significantly within 3 to 6 h of UFH cessation, supporting the hypothesis that a "rebound" prothrombotic state develops rapidly in patients with acute coronary syndromes when anticoagulant therapy is discontinued abruptly.

The very important questions that remain unanswered, however, are:

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Abbreviations and Acronyms
ACC     = American College of Cardiology
AHA     = American Heart Association
ANOVA   = analysis of variance
aPTT    = activated partial thromboplastin time
CAD     = coronary artery disease
ELISA   = enzyme-linked immunosorbent assay
F1.2    = prothrombin fragment 1.2
IV      = intravenous
MI      = myocardial infarction
NHLBI   = National Heart, Lung, and Blood Institute
PCI     = percutaneous coronary intervention
SC      = subcutaneous or subcutaneously
TFPI    = tissue factor pathway inhibitor
UFH     = unfractionated heparin
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1) What is the mechanistic basis for heightened thrombin generation following UFH cessation? and
2) Is it possible to prevent or attenuate the response by either gradual discontinuation (weaning) of heparin therapy or by switching from IV to subcutaneous (SC) heparin administration as suggested by the National Heart, Lung, and Blood Institute (NHLBI)-sponsored "Clinical Practice Guideline" for unstable angina (1)?

Because the extrinsic or tissue factor-mediated coagulation pathway is considered to be the predominant means for both physiologic hemostasis and pathologic arterial thrombosis (13,14), we were particularly interested in alterations of physiologic protection (vascular thromboresistance) that may occur during and after prolonged UFH administration.

METHODS

Patient population. Patients admitted to the University of Massachusetts-Memorial Medical Center between July 1, 1997 and May 1, 1998 were evaluated for entry into a single-center pilot study designed to investigate the biochemical basis and potential attenuation of heparin rebound. Thirty patients who fulfilled the following criteria were enrolled: 1) age > 18 years, 2) within 72 h of hospital admission for either unstable angina at rest with ST-segment deviation of at least 1 mm or non-ST segment elevation MI (elevated creatine kinase with CK-MB (creatine kinase MB isoenzyme) index >2.2) and 3) at least 48 h of a continuous infusion of UFH. All patients received aspirin at a dose of 160 to 325 mg daily. Patients receiving fibrinolytic therapy within the previous 96 h were excluded as were patients with refractory ischemia, moderate to severe congestive heart failure, hemodynamic instability requiring inotropic or intraaortic balloon counterpulsation support, an infusion of UFH for more than 12 h before admission to the coronary care unit and those who had undergone a percutaneous coronary intervention (PCI) within 72 h of screening. Patients with either a platelet count less than 90,000 per mm^3 (at any time) or a 30% or greater decline from baseline

during treatment were also excluded. The study was approved by the University of Massachusetts-Memorial Committee for the Protection of Human Subjects. Written informed consent was obtained from each patient before enrollment.

Study design. The overall use and duration of IV UFH therapy was at the discretion of the treating physician. All patients had their heparin titrated to a target activated partial thromboplastin time (aPTT) between 55 and 80 s according to a standardized and validated, weight-adjusted dosing nomogram. All aPTT measurements were made using a point-of-care instrument (Coaguchek Plus, Boehringer-Mannheim Corporation, Indianapolis, Indiana).

When the treating physician believed that IV UFH was no longer required (completion of therapy), randomization (using sealed envelopes) of patients to one of three dose modification strategies was performed: Group 1—the IV UFH infusion was discontinued, Group 2—the IV UFH infusion was reduced by 50% from the previous infusion rate and discontinued 12 h later (IV wean) or Group 3—the IV infusion was discontinued and UFH (12,500 U) was given SC within the subsequent 4 h followed by a repeat dose (12,500 U) 12 h later (SC wean). Staff nurses carrying out the dosing changes were blinded to the study.

Blood sampling and processing. Baseline blood samples were obtained 60 min before discontinuation of the IV UFH infusion. Additional samples were obtained at 1, 4 and 24 h after heparin cessation. Blood samples were collected for determination of heparin levels (anti-Xa), aPTT, factor VII/VIIa, tissue factor pathway inhibitor (TFPI) antigen (total), TFPI activity, protein C and prothrombin fragment 1.2 (F1.2).

All blood samples were obtained by a single trained phlebotomist through a fresh venipuncture site using a 21-gauge Vacutainer (Franklin Lakes, New Jersey) collection set. Sampling was not performed through existing venous or arterial sheaths and special care was taken to perform each phlebotomy in the contralateral arm to an existing heparin infusion. Two tubes of blood were collected at each time point: a 4.5 ml sodium citrate tube and a 5 ml tube with lyophilized (EDTA) (4.5 mM), D-Phe-Pro-Arg chloromethyl ketone (PPACK) (20 mM) and aprotinin (150 KIU/ml). The samples were immediately placed on ice, processed within 60 min of collection and stored at −20°C to −70°C.

Laboratory assays. All assays were performed in the Laboratory for Vascular Biology Research, University of Massachusetts Medical School. Test samples, standards and reference samples were measured in duplicate.

Heparin levels were measured using anti-Xa concentration (Coatest, Chromogenix AB, Sweden). Activated partial thromboplastin times (Biopool, Ventura, California) were measured using standard methods and a Mag-X Coagulation Analyzer (Organon Teknika, Durham, North Caro-

Table 1. Baseline Characteristics and Heparin Dosing for the Study Groups

	Group 1 Heparin Discontinued (n = 10)	Group 2 Intravenous Heparin Wean (n = 10)	Group 3 Subcutaneous Heparin Wean (n = 10)
Age (mean) (yr)	60	66.2	65.2
Gender (% male)	60	60	80
Weight (kg)	79.1	81.9	75.6
Admitting diagnosis			
MI	6 (60%)	6 (60%)	6 (60%)
Unstable angina	4 (40%)	4 (40%)	4 (40%)
Heparin dose (mean)	1175 U/h	1170 U/h	1190 U/h
Heparin dose per kg	14.9 U/kg/h	14.2 U/kg/h	15.7 U/kg/h
Duration of treatment (mean)	46.2 h	54 h	49 h

lina). Prothrombin activation fragment 1.2 was calculated using a two-site, enzyme-linked immunoassay (Enzygnost F1.2, Boerhinger Diagnostics Inc., Westwood, Massachusetts). Two murine monoclonal antibodies against human factors VII and VIIa (American Diagnostica Inc., Greenwich, Connecticut) were used to measure plasma factor VII antigen concentration by enzyme-linked immunosorbent assay (ELISA), while factor VIIa in the presence of recombinant soluble tissue factor was determined by plotting factor VIIa levels against a corresponding clotting time (Staclot VIIa-rTF, Diagnostica Stago, France).

Tissue factor pathway inhibitor antigen (total) was determined using an Imubind enzyme-linked immunosorbent assay (American Diagnostica Inc., Greenwich, Connecticut). Tissue factor pathway inhibitor activity was calculated using the Actichrome TFPI activity assay (American Diagnostics, Inc.) in which TFPI exhibits an inhibitory effect on the factor VIIa/tissue factor complex.

Statistical analysis. Analytical methods included simple univariate statistics, correlations and analysis of variance (ANOVA). Univariate analyses were performed on all variables of interest to examine and describe the nature of variability and to assess normality of the data. Heparin concentration and hemostatic variables were analyzed with repeated measure ANOVA for all patients and by group. Changes over the 24 h study period were calculated using the latest time point value minus the baseline value, and percent change was computed by dividing this change value by the baseline value. Pearson correlation coefficients were calculated to assess the association between measures of the change variables. Univariate and correlation analyses were carried out using SAS (Cary, North Carolina), and repeated measures ANOVA were performed using SPSS (Chicago, Illinois).

RESULTS

Patient characteristics: overall study population. A total of 30 patients was included in the pilot study. Approximately two-thirds were men with an average age of 63.8

years (range 28 to 95 years). A majority had an admitting diagnosis of MI (60%), whereas 40% had unstable angina. The duration of heparin treatment ranged from 48 to 62 h (mean 52 h, range 48 to 62 h) with an average hourly infusion rate of 1,178 U (range 600 to 2,000 U). Oral beta-blockers, nitrates, calcium channel blockers, aspirin and angiotensin converting enzyme inhibitors were administered to 63%, 80%, 33%, 100% and 33% of patients, respectively.

Coagulation measurements. The mean heparin concentration immediately before modification of the UFH infusion was 0.45 U/ml ($\pm$0.21 U/ml) with a corresponding aPTT value of 56.6 s ($\pm$29.7 s). Thrombin generation, expressed as F1.2 concentration, increased from a baseline value of 2.19 $\pm$ 0.80 nM to a maximum of 3.59 $\pm$ 1.03 nM at 24 h (p = 0.002). Although increased thrombin generation was evident within 1 h of modifying the heparin infusion (2.25 $\pm$ 0.9 nM), a more substantial increase was observed at 4 h (2.47 $\pm$ 0.8 nM, 15.3% increase from baseline). Thrombin generation persisted beyond 4 h, with an 81.5% overall increase from baseline appreciated at 24 h.

Comparison of heparin strategy groups. The baseline characteristics and heparin dosing of patients in each of the study groups are presented in Table 1. There were no significant differences in any of the measured parameters.

Changes in hematologic variables over time for each of the heparin strategy groups are shown in Tables 2–4. Thrombin generation increased in all groups by 4 h and peaked 24 h after modification of the UFH dose (Fig. 1). The percentage increase above the baseline value was greatest among patients randomized to abrupt discontinuation in whom F1.2 rose by 20.2% at 4 h and 164% at 24 h (p < 0.01). The observed changes were less striking, but still significant, in patients randomized to the SC weaning strategy (7.7% increase at 4 h, 57% increase at 24 h, p = 0.006) and those having an IV UFH wean (20.5% increase at 4 h, 44.5% increase at 24 h, p = 0.02). There were no statistically significant differences in F1.2 at any time point between the heparin strategy groups.

Table 2. Coagulation Measurements Over Time Among Patients Randomized to Immediate Discontinuation of Heparin

	Baseline		1 h		4 h		24 h		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p*
Heparin (U/ml)	0.54	0.20	0.41	0.28	0.17	0.11	0.00	0.00	0.005
Factor VII (ng/ml)	574.35	231.38	613.33	184.39	626.83	199.16	612.18	234.22	0.26
Factor VIIa (ng/ml)	1.18	0.62	0.89	0.45	2.45	1.19	1.89	0.96	0.07
TFPI (ng/ml)	132.80	28.04	93.23	31.55	74.73	24.95	86.17	29.30	0.04
TFPI activity (U/ml)	1.32	0.28	1.08	0.18	0.99	0.22	1.14	0.25	0.08
F1.2 (nM)	1.88	0.65	1.85	0.93	2.28	0.94	4.43	1.22	< 0.001

*p value was from repeated measurements ANOVA for the test of homogeneity of group means.
ANOVA = analysis of variance; F1.2 = prothrombin fragment 1.2; TFPI = tissue factor pathway inhibitor.

Changes in TFPI and factor VIIa were also evident during the study period and differed among the three heparin strategy groups. By 4 h, TFPI (total) and TFPI (activity) had declined, with the greatest proportional decreases being observed in patients having their UFH terminated abruptly (44% and 23% reduction, respectively, p = 0.03 for the change in TFPI [total]), compared with those having IV (11% and 0.3% reduction, p = 0.24) or SC (32% and 10% reduction) weaning. Factor VIIa levels increased more than two-fold in patients randomized to abrupt UFH cessation (p = 0.02) and to a lesser degree in patients having IV (74% increase, p = 0.01) or SC (35% increase, p = 0.04) weaning (Figs. 2 and 3).

By 24 h, TFPI (total) and TFPI (activity) were most notably decreased among patients randomized to SC UFH weaning (41% and 11% reduction, respectively).

Correlations. Thrombin generation at 4 h correlated directly with factor VII (r = 0.22) and factor VIIa (r = 0.17) and inversely with TFPI (total) (r = −0.61) and TFPI (activity) (r = −0.66). Changes in heparin concentration correlated inversely with F1.2 (r = −0.19) and directly with TFPI (total) (r = −0.29). Thrombin generation at 24 h correlated inversely with heparin concentration (r = −0.29), TFPI (total) (r = −0.32) and TFPI (activity) (r = −0.59). Tissue factor pathway inhibitor (total) (r = 0.35) and TFPI (activity) (r = 0.35) correlated directly with the change in heparin concentration from baseline to 24 h.

Clinical events. Recurrent angina prompting emergent coronary angiography and PCI occurred in two patients randomized to immediate UFH cessation. Both events were within 12 h of stopping the heparin infusion. Clinical events did not occur in patients randomized to either IV or SC heparin weaning.

DISCUSSION

The early management of patients with unstable angina and non-ST segment elevation MI commonly includes a strategy of antithrombotic therapy with IV UFH. A resurgence of symptoms following its abrupt cessation, however, has concerned clinicians for over a decade and, in all likelihood, compromises UFH's overall treatment effect. In our prospective, randomized pilot study, several new observations were made. First, thrombin generation was evident within 1 h of UFH cessation and increased steadily over the subsequent 24 h. Second, thrombin generation correlated inversely with heparin and TFPI concentrations, suggesting that tissue factor-mediated coagulation or impaired vascular thromboresistance are contributing factors. Third, the rapidly developing prothrombotic environment that follows UFH cessation is modifiable but not fully prevented by a strategy of IV weaning. Finally, SC weaning delays, but does not prevent, thrombin generation.

Thrombin generation in acute coronary syndromes. In vivo, thrombin serves as both the primary stimulus for thrombosis and subsequent thrombus growth on a template of activated platelets or platelet-derived procoagulant microparticles (15–17). Our group has shown that patients with clinically stable coronary artery disease (CAD) have

Table 3. Coagulation Measurements Over Time Among Patients Randomized to Intravenous Heparin Weaning

	Baseline		1 h		4 h		24 h		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p*
Heparin (U/ml)	0.40	0.21	0.21	0.18	0.21	0.23	0.00	0.00	0.11
Factor VII (ng/ml)	615.55	270.62	555.93	232.78	625.10	284.05	631.38	390.26	0.42
Factor VIIa (ng/ml)	2.31	2.31	1.78	1.95	4.02	2.70	3.07	3.37	0.05
TFPI (ng/ml)	115.52	33.77	91.20	27.06	90.63	19.98	78.00	30.59	0.32
TFPI activity (U/ml)	1.15	0.23	1.12	0.29	1.13	0.17	1.09	0.20	0.66
F1.2 (nM)	2.47	1.05	2.43	1.06	2.75	0.76	3.35	0.82	0.04

*p value was from repeated measurements ANOVA for the test of homogeneity for group means. Abbreviations as in Table 2.

Table 4. Coagulation Measurements Over Time Among Patients Randomized to Subcutaneous Heparin Weaning

| | Baseline | | 1 h | | 4 h | | 24 h | | |
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p*
Heparin (U/ml)	0.42	0.22	0.33	0.26	0.18	0.26	0.01	0.01	0.001
Factor VII (ng/ml)	379.61	120.31	419.41	166.04	407.78	103.34	431.26	130.85	0.76
Factor VIIa (ng/ml)	1.49	0.69	1.25	0.67	1.83	0.55	1.94	1.61	0.03
TFPI (ng/ml)	107.35	19.51	96.25	25.16	72.85	18.31	62.13	12.34	0.007
TFPI activity (U/ml)	1.33	0.31	1.31	0.32	1.20	0.31	1.19	0.32	0.09
F1.2 (nM)	2.16	0.71	2.36	0.83	2.36	0.90	3.29	0.87	0.05

*p value was from repeated measurements ANOVA for the test of homogeneity for group means. Abbreviations as in Table 2.

evidence of increased thrombin activity and generation (18) as do those with unstable angina (19,20) and acute MI (21) in whom the abnormality persists for weeks to months after the presenting event (22). Consistent with prior observations (23), patients in this study exhibited increased thrombin generation despite treatment with UFH (10,18,24,25). The limitations associated with UFH administration may, at least in part, be the result of its relative inaccessibility to clot-bound thrombin and an inability to effectively neutralize factor Xa-mediated procoagulant activity (26).

The thrombogenicity of atheromatous plaques and dysfunctional endothelial cells is strongly influenced by tissue factor which is considered the predominant "trigger" for pathologic arterial thrombosis. Accordingly, we focused our attention on the extrinsic coagulation pathway in general and factor VII/VIIa-tissue factor in particular (27–31). Patients with acute coronary syndromes demonstrate high concentrations of tissue factor antigen and activity within tissue specimens obtained at the time of coronary atherectomy (32,33), and it has been shown that tissue factor is released from monocytes after ischemic injury or cellular death (34). The contribution of tissue factor to intravascular thrombotic events among individuals with advanced atherosclerotic CAD suggests that natural thromboresistance pathways, particularly TFPI, are of vital importance (35–38). There is considerable evidence that TFPI contributes to the antithrombotic effect of heparin. In an original report by Sandset et al. (39), later confirmed by other investigators (40–42), TFPI was released from vascular endothelial cells into the circulation after an IV or SC injection of either unfractionated or low molecular weight heparin. Tissue factor pathway inhibitor is bound to endothelial cell surface glycosaminoglycans; however, the binding is weak and it can easily be displaced by heparin (43,44). Heparin-releasable TFPI is not bound to lipoproteins (45) and exerts a strong anticoagulant effect. Tissue factor pathway inhibitor and heparin have a synergistic inhibitory effect on tissue factor-induced coagulation in vitro (46), and it has been suggested that heparin-mediated TFPI release and mobilization is an
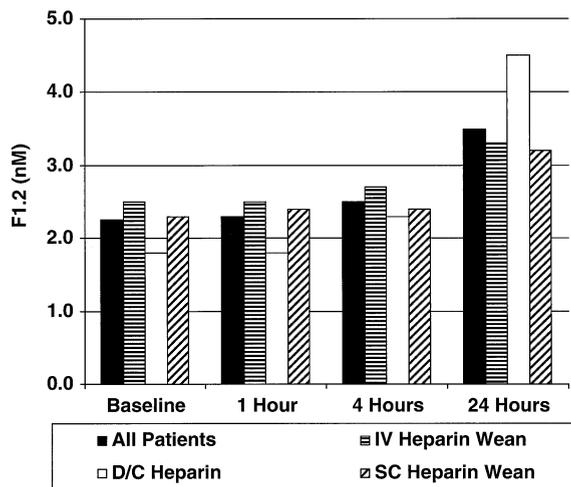

Figure 1. Thrombin generation (F1.2 concentrations) at baseline, 1 h, 4 h and 24 h for the overall patient population and patients randomized to either immediate discontinuation of heparin (D/C heparin), intravenous (IV) heparin weaning or subcutaneous (SC) heparin weaning. Thrombin generation was evident by 1 h and increased steadily over time. Thrombin generation was greatest with abrupt heparin cessation and was least with IV heparin weaning. D/C = discontinue; IV = intravenous; SC = subcutaneous.
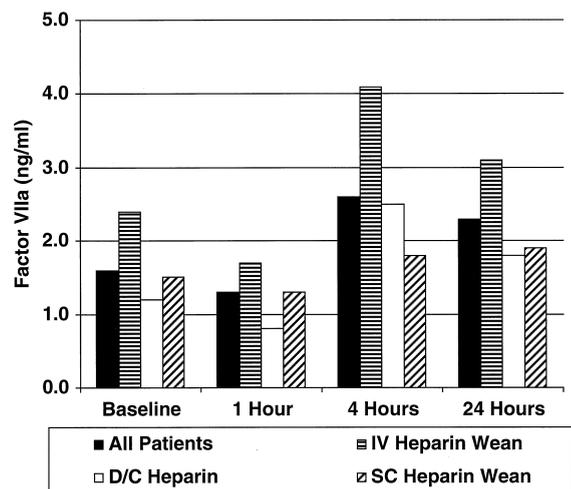

Figure 2. Factor VIIa concentration over time in the heparin strategy groups. An increase was observed in all patients; however, the greatest increase (from baseline) was observed with abrupt heparin cessation. D/C = discontinue; IV = intravenous; SC = subcutaneous.
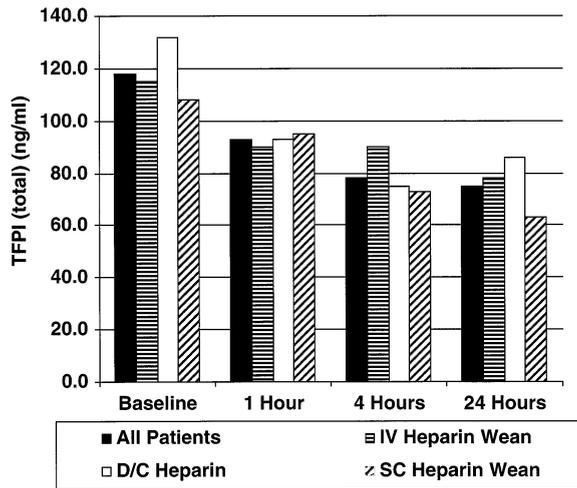
Figure 3. Tissue factor pathway inhibitor (TFPI) (total) concentration over time in the heparin strategy groups. There was a progressive increase in all patients; however, IV heparin weaning preserved TFPI levels. D/C = discontinue; IV = intravenous; SC = subcutaneous; TFPI = tissue factor pathway inhibitor.

important intrinsic means to limit thrombosis at sites of vessel wall injury when large quantities of tissue factor are exposed (41). Depletion of TFPI lowers the threshold for tissue factor-mediated coagulation (47).

In our study, TFPI declined by 30% to 40% after modification of the UFH dose with an accompanying rise in both factor VIIa and thrombin generation, suggesting either down-regulation or depletion of endothelial cell TFPI, perhaps in response to prolonged stimulation from a continuous infusion of UFH. In a study by Hanson et al. (48), repeated injections of UFH heparin at 4 h intervals caused a progressive decrease ($-45 \pm 8\%$) in heparin-releasable TFPI and a progressive shortening of the dilute prothrombin clotting time. During a 24 h continuous infusion of UFH, TFPI decreased by nearly 80% with a concomitant decrease in the contribution of TFPI to the inhibition of tissue factor-mediated coagulation by heparin. The findings suggest a depletion of intravascular pools of TFPI by continuous UFH administration and may indicate that the constitutive synthesis of TFPI is overwhelmed by its elimination under this condition. Potentially compounding the problem is the common practice and need for IV heparin bolus doses to exceed a lower threshold of anticoagulation among patients already receiving a continuous infusion (49). In our study, patients with acute coronary syndromes were required to have received a heparin infusion for at least 48 h. Fifty percent of patients were below the target range at least once and, according to a standardized weight-adjusted heparin titration nomogram, received a heparin bolus of 35 to 70 U/kg. Although we did not measure TFPI before heparin administration, the concentration immediately before randomization was comparatively low (48) and continued to decline over time.

We believe that abrupt cessation of UFH provokes a

rapid decrease in TFPI concentration impairing physiologic vascular thromboresistance and, in the presence of heightened factor Xa activity, a sudden burst of thrombin generation occurs. As long as heparin is present in the circulation, even in low concentrations, TFPI will not be cleared rapidly. A proportional decrease in TFPI accompanies a rapid clearance of heparin (39,50) and normalization of TFPI toward baseline values parallels heparin elimination. Thus, there is a declining tissue factor inhibiting capacity that occurs as the direct anticoagulant effects of heparin are dissipating. If endothelial cell stores of TFPI are depleted, a transient prothrombotic state rapidly ensues. Alternatively, it is possible that activation of the extrinsic coagulation cascade after tissue factor release from a persistently unstable atheromatosis plaque (26,35) could consume TFPI in the process of neutralizing factors VIIa and Xa (36,37). The provocation of impaired thromboresistance by UFH may also involve thrombin-thrombomodulin interactions and protein C activation (51). If this is the case, the suboptimal inhibition of factors Va, VIIa, VIIIa, Xa and tissue factor would adversely affect the balance of coagulation (thrombosis) and anticoagulation not only after but during treatment.

Strategies to prevent heparin rebound. Our pilot study was designed not only to investigate the mechanistic basis for thrombin generation after UFH cessation but to identify one or more strategies that could potentially modify the response and be used routinely in clinical practice. Within the recent American College of Cardiology (ACC)/ American Heart Association (AHA) Guidelines for the Management of Patients with Acute MI (52) a concern over heparin rebound was stated as was the possibility that a gradual reduction in dose may be preventive. The American College of Chest Physicians offered support for the SC weaning strategy (53), whereas the NHLBI-sponsored clinical practice guidelines for unstable angina (1) suggested that heparin rebound could be prevented by a gradual discontinuation or SC administration. Neither IV nor SC UFH weaning has been investigated clinically. The findings from our randomized pilot study suggest that neither strategy prevents thrombin generation; however, IV weaning attenuates the response to heparin withdrawal, perhaps by allowing endothelial cell recovery and restoration of TFPI-mediated thromboresistance (39,50). The SC weaning strategy achieved a similar result, but the possibility of delayed rebound was raised by a large proportional increase in thrombin generation between 4 and 24 h. Although the SC strategy was designed specifically to slowly lower plasma heparin concentrations, the level achieved at 4 h was similar to that observed with sudden heparin cessation. This may reflect poor or variable SC drug absorption (a recognized problem with SC UFH administration).

Study limitations. We performed a mechanistic pilot study to determine biochemical alterations associated with thrombin generation after abrupt heparin cessation. Although the patient population was small and the design was open-label,

these factors should not have influenced serial coagulation measurements. There were two clinical events—both occurred in patients admitted with unstable angina who were randomized to abrupt UFH cessation. The sample size prevents firm conclusions from being drawn; however, the findings are consistent with prior laboratory and clinical observations and support the proposed mechanism of increased tissue factor-mediated prothrombotic potential.

Conclusions. Although heightened thrombin generation and a clustering of clinical thrombotic events shortly after discontinuation of UFH have been recognized previously, contribution of the extrinsic (tissue factor-mediated) coagulation pathway in general and impairment of TFPI-mediated vascular thromboresistance in particular have not been described. An IV weaning strategy offers a means to attenuate thrombin generation; however, the modest decrease may not prevent clinical events.

The findings of our pilot study suggest that future investigation of strategies to prevent heparin rebound (currently underway) should focus primarily on tissue factor, the extrinsic coagulation pathway and anticoagulant therapy-mediated impairment of physiologic vascular thromboresistance. Potential candidates include low molecular weight heparin, particularly preparations with a high anti-Xa: IIa ratio, recombinant TFPI and platelet glycoprotein IIb/IIIa antagonists that are increasingly being recognized for their anticoagulant effects mediated by an ability to inhibit tissue factor-stimulated prothrombinase activity (and thrombin generation) on platelet aggregates and procoagulant microparticles.

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