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Heparin Dose Response Is Independent of Preoperative Antithrombin Activity in Patients Undergoing Coronary Artery Bypass Graft Surgery Using Low Heparin Concentrations

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Abstract

BACKGROUND—Unfractionated heparin's primary mechanism of action is to enhance the enzymatic activity of antithrombin (AT). We hypothesized that there would be a direct association between preoperative AT activity and both heparin dose response (HDR) and heparin sensitivity index (HSI) in patients undergoing coronary artery bypass graft surgery.

METHODS—Demographic and perioperative data were collected from 304 patients undergoing primary coronary artery bypass graft surgery. AT activity was measured after induction of general anesthesia using a colorimetric method (Siemens Healthcare Diagnostics, Tarrytown, NY). Activated coagulation time (ACT), HDR, and HSI were measured using the Hepcon HMS Plus system (Medtronic, Minneapolis, MN). Heparin dose was calculated for a target ACT using measured HDR by the same system. Multivariate linear regression was performed to identify independent predictors of HDR. Subgroup analysis of patients with low AT activity (<80% normal; <0.813 U/mL) who may be at risk for heparin resistance was also performed.

RESULTS—Mean baseline ACT was 135 ± 18 seconds. Mean calculated HDR was 98 ± 21 s/U/mL. Mean baseline AT activity was 0.93 ± 0.13 U/mL. Baseline AT activity was not significantly associated with baseline or postheparin ACT, HDR, or HSI. Addition of AT activity to multivariable linear regression models of both HDR and HSI did not significantly improve model performance. Subgroup analysis of 49 patients with baseline AT <80% of normal levels did not reveal a relationship between low AT activity and HDR or HSI. Preoperative AT activity, HDR, and HSI were not associated with cardiac troponin I levels on the first postoperative day, intensive care unit duration, or hospital length of stay.

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DISCLOSURE

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CONCLUSION—Although enhancing AT activity is the primary mechanism by which heparin facilitates cardiopulmonary bypass anticoagulation, low preoperative AT activity is not associated with impaired response to heparin or to clinical outcomes when using target ACTs of 300 to 350 seconds.

More than 50 years after heparin's discovery,¹ Rosenberg and Damus^{2,3} identified its primary mechanism of action as enhancement of the enzymatic activity of antithrombin (AT). AT binds and inactivates serine proteases' contact activation and common pathways, principally factors IIa, Xa, IXa, and VIIa, by decreasing their binding efficiency for substrate. AT's inhibition of serine protease activity is increased several orders of magnitude by heparin as a result of a conformational change induced by binding of a specific pentasaccharide unit of heparin with high affinity for AT.⁴

Heparin resistance has been reported in 4% to 22% of patients undergoing cardiopulmonary bypass (CPB).^{5–10} Potential risk factors include age older than 65 years, platelet count $>300,000$ cells/mm³, recent heparin exposure, and AT deficiency.⁹ Preoperative AT activity of $<80\%$ of normal has been associated with reduced heparin response in adults undergoing cardiac surgery.¹¹ Postoperative AT deficiency has also been associated with worsened clinical outcomes, including increased intensive care unit (ICU) length of stay, risk of reexploration for bleeding, and thromboembolic events.¹²

Because the primary mechanism of action of heparin is to facilitate the enzymatic activity of AT, we surmised that reduced AT activity would be associated with heparin response. Little evidence is available to support this hypothesis, with most data regarding AT activity and heparin dose response (HDR) reported from studies examining restoration of heparin responsiveness in cardiac surgical patients by administration of recombinant AT concentrate, usually without measurement of the patient's AT level.^{5–8,13,14} We aimed to assess the relationship between preoperative AT activity and heparin sensitivity in a cohort of primary coronary artery bypass graft (CABG) patients and additionally assess this association in a subgroup of subjects with low preoperative AT activity. We further examined whether AT activity or measures of heparin sensitivity were associated with severity of myocardial injury or duration of ICU and hospital stays, as surrogates of severity of illness.

METHODS

With IRB approval and individual patient consent, 346 patients undergoing primary CABG using CPB from February 2005 to December 2006 were enrolled into a parent study called the CABG Genomics Program with the aim of determining genetic risks for adverse perioperative outcomes. Patients were excluded from the parent study if they were younger than 20 years of age; underwent repeat or off-pump CABG, planned concomitant valve, or other cardiac surgery; had a preoperative hematocrit $<25\%$; or if they had received leukocyte-rich blood products within 30 days before surgery. For this secondary analysis, detailed demographic data, preoperative laboratory values, operative data, heparin bolus dose, anticoagulation data including activated coagulation time (ACT) values, and measured heparin concentrations were collected from hospital records. Patients with missing laboratory or demographic data ($n = 27$) and those receiving warfarin ($n = 15$) were further excluded from analysis, yielding 304 analyzable patients. ICU length of stay until first discharge was recorded in hours. Hospital length of stay was recorded in days, with the surgical day and last hospital day included as whole days.

Baseline blood samples for ACT, HDR, AT, and other assays were obtained after induction of anesthesia but before surgical incision (described as preoperative hereafter). Free

unbound AT activity was measured with a colorimetric method (Modular Analytics biochemistry analyzer, Siemens Healthcare Diagnostics, Tarrytown, NY) performed by Charles River Laboratory (Montreal, Canada). The assay limit of quantitation was 21.6%. To report human plasma AT activity results in IU/mL, the National Institute for Biological Standards and Control Second International Reference Standard was used to determine a conversion factor of activity in IU/mL = AT activity in % $\times$ 0.0102. AT content was measured using an immunonephelometric method using a BN-100 Prospeg nephelometer (Dade Behring Diagnostics, Marburg, Germany). Coefficient of variation for AT measurement was <5% within assay and <10% across assays. The assay limit of quantitation was 0.00672 mg/mL. To report human plasma AT content results in IU/mL, National Institute for Biological Standards and Control Second International Reference Standard was used to determine a conversion factor of content in IU/mL = content in g/L $\times$ 3.64. Both assays measure free AT, rather than AT complexed with heparin. Plasminogen-activator inhibitor-1, tissue factor, D-dimer, protein C, and cardiac troponin I (cTnI) were measured using a sandwich immunoassay on a triage platform using monoclonal and polyclonal antibodies (Biosite, San Diego, CA). Hemoglobin, platelet, and white blood counts, along with prothrombin time, partial thromboplastin time, and international normalized ratio were measured by a central hematology laboratory according to institutional protocols. Complete blood counts were performed using the Advia 2120 Hematology System (Siemens Healthcare Diagnostics, Deerfield, IL), and coagulation studies were performed on STA-R Evolution (Diagnostica Stago, Parsippany, NJ).

For anticoagulation management, the Hepcon HMS Plus system (Medtronic, Minneapolis, MN) was used according to the manufacturer's recommendations.¹⁵ The estimated blood volume for each patient was calculated using the manufacturer's instructions,¹⁵ according to the method described by Allen et al.¹⁶ After induction of anesthesia, baseline kaolin ACT, predicted HDR, predicted heparin concentration, and heparin bolus calculations were performed according to the manufacturer's instructions, using heparin-protamine titration cartridges encompassing whole blood heparin concentration ranging from 0.7 to 3.4 U/mL and kaolin as the activator. The recommended Hepcon HMS Plus CPB prime heparin dose based on a 750- or 1000-mL prime volume was added to the calculated heparin bolus and administered via a central venous catheter. Heparin was not added to the CPB pump prime. Throughout the entire study period, an ACT of >350 seconds was used in patients undergoing surgery where cardiomy suction was to be used. Patients undergoing primary CABG surgery without the use of cardiomy suction were anti-coagulated using a protocol that prescribed a minimal ACT of 300 seconds before the institution of CPB. Three minutes after USP porcine heparin (APP Pharmaceuticals, Schaumburg, IL) administration, heparin concentration and ACT were remeasured. This heparin management protocol including use of heparin-coated circuits was adopted in a comprehensive institutional program to reduce the rate of reoperation for bleeding. All patients received an ϵ -aminocaproic acid initial loading dose of 7.5 to 10 g over 1 hour, after the initial blood draw for AT level and baseline ACT, but before heparin administration and blood sampling for measurement of postheparin ACT.

HDR was measured as the difference in ACT between target and baseline ACT measurements, divided by target heparin level estimated from the Hepcon HMS Plus system. Because the Hepcon HMS Plus system has a limited fidelity in reporting whole blood heparin concentrations, in that it provides values with discrete categories (i.e., 0.7, 1.4, 2.0, 2.7, and 3.4 U/mL) rather than a continuous variable, the heparin sensitivity index (HSI) was also calculated from change in ACT between before and after heparin administration, divided by heparin dose, per kilogram of body weight.¹¹ The same calculation was performed using heparin dose per liter of estimated blood volume without significantly changing the results; therefore, body weight was used.

We estimated the accessible effect size for HDR, using the available sample size ($n = 319$), a 20% rate of heparin resistance based on prior studies, a mean HDR of 99 s/U/mL and an sd of 22 s/U/mL, a type I error rate of 5% and a type II error rate of 20%. We estimated that we would be able to observe differences in HDR of 9 s/U/mL, which we thought would be more sensitive than a clinically important difference.

Data are presented as mean $\pm$ sd when normally distributed, or median and 5th and 95th percentiles when not normally distributed. Data that were nonnormally distributed were compared using the Wilcoxon ranked sum test. The Student t test was used to compare means of normally distributed data. Subgroup analysis of patients with low AT activity (<80% of laboratory normal; AT activity <0.813 U/mL) who might be at risk for heparin resistance was performed. Multivariable linear regression modeling was performed to examine for clinical and laboratory predictors of HDR and HSI; variables with univariate P values <0.2 were entered into a combined forward/backward stepwise linear regression model, with an exit P value of 0.05. A 2-sided $P < 0.05$ was considered as showing statistical significance. Statistical analyses were performed using SAS version 9.1.3 and JMP 7.03 (SAS Institute, Cary, NC).

RESULTS

Baseline demographics and perioperative data for 304 patients are summarized in Table 1. Thirty-two patients (10.5%) required additional heparin administration before the institution of CPB for failing to achieve their respective target ACT with administration of the heparin dose estimated by the HepCon HMS Plus system. No patient received >300 U/kg heparin. No patients were given fresh frozen plasma or AT supplementation to reach target ACT values.

AT activity and content were highly correlated ($r^2 = 0.801$), therefore AT activity is reported. Higher AT levels ($P < 0.05$) were observed in females, younger individuals, current smokers, hypercholesterolemia, and individuals who had not had a myocardial infarction within the previous 2 weeks. No association was observed between baseline AT activity and baseline ACT ($r^2 < 0.001$; $P = 0.10$) or with HDR ($r^2 < 0.001$; $P = 0.59$) (Fig. 1), HSI ($r^2 < 0.001$; $P = 0.73$), or platelet count ($r^2 = 0.004$; $P = 0.24$). Those patients with recent preoperative heparin exposure had significantly lower AT activity (0.87 vs 0.96 U/mL; $P < 0.001$) but did not show a significant difference in heparin requirements or heparin responsiveness by any measure including HDR or HSI.

Individuals with AT activity <80% normal (<0.813 U/mL) had higher partial thromboplastin time and were more likely to have received heparin during the current admission before surgery, but otherwise showed no differences in coagulation testing or management (Table 1). No relationship between AT activity and HDR was observed in these patients ($r^2 < 0.001$). Furthermore, there was no evidence of diminished heparin responsiveness in this group, because 94.1% (48 of 51) achieved the target ACT after administration of the calculated heparin bolus dose. Neither HDR nor HSI was significantly related to AT activity in univariate relationship (Fig. 1), or after accounting for other covariates using multivariable linear regression (Tables 2 and 3).

Preoperative AT activity, HDR, and HSI were not associated with cTnI levels on the first postoperative day (all $r^2 < 0.002$; $P > 0.5$), ICU duration, or hospital length of stay.

DISCUSSION

We observed no relationship between preoperative AT activity and response to heparin, measured using either HDR or HSI, in these 304 patients undergoing primary CABG

surgery. Additional subgroup analysis in patients with baseline AT activity <80% failed to identify AT activity as a predictor of HDR or HSI. However, no patient exhibited a requirement for a heparin dose >300 U/kg to achieve target ACTs of either 300 or 350 seconds.

Acquired AT deficiency is common in patients with previous heparin administration,¹⁷ critical illness, severe hepatic dysfunction, and after major cardiovascular surgery.¹⁸⁻¹⁹ After cardiac surgery, lower levels of AT have been independently associated with prolonged ICU stay and a higher incidence of neurologic and thromboembolic events.¹² In this cohort of patients, we observed associations between clinical markers of anticoagulation (prothrombin time and ACT) and factors that may relate to the severity of illness including white blood cell count and hematocrit, and HDR. However, neither AT activity nor heparin sensitivity was associated with severity of myocardial injury, ICU length of stay, or hospital length of stay, as surrogates of severity of illness.

Administration of unfractionated heparin remains the mainstay of anticoagulation management for patients undergoing cardiac surgery requiring CPB, with the goal of maintaining therapeutic anticoagulation, thereby preventing thromboembolic complications. Its unique properties of rapidly providing systemic anticoagulation that can be maintained for the duration of CPB and rapid complete reversal with subsequent administration of protamine make heparin the anticoagulant of choice for CPB. Interindividual variability in heparin response is well described,²⁰ and contributing to this variation may be previously observed risk factors for diminished heparin responsiveness that include low AT levels, platelet count >300,000 cells/mm³, and heparin pretreatment.⁹ Although we observed substantial variability in heparin responsiveness, our data failed to show any relationship between heparin response and AT activity or heparin pretreatment.

AT is critical for maintenance of anticoagulation during CPB and is consumed during the process.²¹ Despotis et al.¹⁴ demonstrated a strong association between in vitro AT and heparin responsiveness measured by ACT slope over the range of AT levels of 0.2 to 1 U/mL. At AT levels above 1 U/mL, there was no further increase in heparin responsiveness. However, there was much weaker association in 31 patients undergoing cardiac surgery with CPB.¹⁴ Similarly, Dietrich et al.¹¹ observed a diminished HSI in adult patients with preoperative AT activity <80% of normal, whereas no relationship was found in patients with normal AT levels. Our data contrast with this, in that we observed no relationship between AT activity and heparin responsiveness in either group.

The ACT response to heparin is complex and affected by different factors as previously noted. Although AT enhancement is a primary mechanism of heparin's action, other factors may influence HDR including tissue factor pathway inhibitor levels in vivo but not in vitro, extravascular sequestration of heparin, plasma protein binding, leukocyte lactoferrin, and activated platelets.^{7,14,22} Tissue factor pathway inhibitor is an endothelium-derived endogenous serine protease inhibitor with enhanced expression after heparin administration²³ that may enhance anticoagulation in vivo.²⁴ Other endogenous mechanisms may further modify the activity of heparin in vivo. Higher molecular weight heparin (>13 kDa) is sequestered and deactivated by endothelial endocytosis and depolymerization.²⁵ In addition, neutrophil-derived lactoferrin can neutralize heparin by ionic binding.²² Heparin has shown to be similarly neutralized by histidine-rich glycoproteins such as vitronectin, fibronectin, and kininogen.⁷ Platelet factor 4 is a potent heparin binding agent released from activated platelets that reverses the ACT,^{26,27} potentially contributing to heparin resistance. These endogenous mechanisms may be important in modifying heparin's anticoagulant activity in vivo, but difficult to quantify in vitro.

This study has important limitations. Our study did not identify patients with severe heparin resistance, with only 10.5% of patients failing to reach the target ACT, and none required fresh frozen plasma or AT to initiate CPB. Perhaps the relatively low ACT target contributed to the lack of identification of heparin-resistant patients. Historically, CPB has been initiated with higher ACTs to give a margin of safety²⁸ and in many studies, a large number of patients diagnosed as heparin resistant had target ACTs >400 seconds.^{5–8,13,14} Definitions of heparin resistance based on a dose of heparin to achieve a specific target ACT such as requiring >500 IU/kg to achieve a target ACT of 480 seconds assume linearity of the HDR.¹⁰ Although Despotis et al.²⁹ observed a strong linear relationship between ACT and heparin concentration observed over a range of heparin concentrations, to assume that our results could be extrapolated to higher target ACTs would not be appropriate. Furthermore, we did not measure circulating concentrations of several important members of the coagulation pathway that may have affected these results.

In conclusion, we found that heparin responses were independent of preoperative plasma AT activity in patients undergoing primary CABG using target ACTs of 300 to 350 seconds. Preoperative heparin exposure was associated with diminished AT activity, but no change in HDR was observed. Perioperative AT activity, HDR, or HSI were not associated with cTnI levels on the first postoperative day, ICU duration, or hospital length of stay.

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Figure 1.

Preoperative antithrombin (AT) activity versus heparin dose response (HDR) ($r^2 < 0.001$; $P = 0.59$). Confidence interval of HDR for a single measurement of AT activity is shaded.

HDR slope (s/U/mL) = $94.3 + 5.31 \times \text{AT activity (U/mL)}$.

Table 1

Demographics and Perioperative Data of Patients with Low Antithrombin (AT) Activity (<80% of Normal; Defined as AT Activity <0.813 U/mL) and Normal AT Activity

	Study cohort (N = 304)	AT activity <80% of normal ^a (N = 49)	AT activity ≥80% of normal ^a (N = 255)	P
Age	65 ± 9	70 ± 9	64 ± 9	<0.0001
Male gender	247 (81.3%)	42 (85.7%)	205 (80.4%)	0.43
Race (Caucasian)	272 (89.5%)	44 (89.8%)	228 (89.4%)	1.0
Height (cm)	173 ± 9	174 ± 9	173 ± 9	0.56
Weight (kg)	88.3 ± 18.6	87.0 ± 16.6	88.4 ± 19.0	0.62
Medical history				
Previous myocardial infarction	130 (42.7%)	27 (55.1%)	103 (40.4%)	0.06
Myocardial infarction within prior 2 wk	56 (18.4%)	16 (32.7%)	40 (15.7%)	0.008
Hypertension	224 (73.7%)	30 (61.2%)	194 (76.1%)	0.03
Hypercholesterolemia	236 (77.6%)	33 (67.4%)	203 (79.6%)	0.06
Insulin-dependent diabetes	31 (10.2%)	9 (18.4%)	22 (8.6%)	0.07
Renal insufficiency (creatinine ≥2.0 mg/dL)	8 (2.6%)	2 (4.1%)	6 (2.4%)	0.62
Liver failure	0 (0%)	0 (0%)	0 (0%)	—
Preoperative medications				
Aspirin	256 (84.2%)	38 (77.6%)	218 (85.4%)	0.20
Platelet inhibitor (excluding aspirin)	71 (23.3%)	14 (28.6%)	57 (22.4%)	0.36
Intravenous heparin in current admission	88 (28.9%)	33 (67.4%)	55 (21.6%)	<0.0001
Any statin	252 (82.8%)	41 (83.7%)	211 (82.8%)	1.0
Preoperative laboratory values				
Hematocrit (%)	39.9 ± 4.5	39.5 ± 5.3	40.0 ± 4.3	0.52
Platelet count (10 ⁹ /mL)	237 (169–322)	245 (170–339)	236 (167–317)	0.55
White cell count (10 ³ /mL)	8.0 (5.5–11.2)	8.6 (5.4–11.8)	7.8 (5.5–11.1)	0.27
INR	1.0 (1.0–1.1)	1.0 (1.0–1.2)	1.0 (1.0–1.1)	0.02
INR > 1.4	0 (0%)	0 (0%)	0 (0%)	—
Partial thromboplastin time (s)	30.2 (26.5–63.2)	39 (28–94)	30 (26–40)	<0.0001
Antithrombin content (U/mL)	0.862 ± 0.123	0.703 (0.582–0.790)	0.881 (0.772–1.04)	
Antithrombin content (mg/mL)	0.23 (0.196–0.282)	0.193 (0.160–0.217)	0.242 (0.212–0.286)	
Antithrombin activity (U/mL)	0.933 ± 0.126	0.761 (0.649–0.811)	0.961 (0.855–1.11)	
Antithrombin activity (%)	91.1 (76.3–107.2)	74.8 (63.6–79.5)	93.8 (83.7–108.7)	
Protein C (μg/mL)	5.01 (2.27–6.98)	4.75 (3.32–6.63)	5.07 (3.53–6.96)	0.10
Plasminogen activator inhibitor-1 (ng/mL)	1.53 (0.0–20.2)	1.18 (0.23–3.88)	1.58 (0.06–6.92)	0.16
D-dimer (ng/mL)	183.3 (0.0–2569)	142.8 (6.8–1084)	186.6 (7.2–1381)	0.52
Tissue factor (pg/mL)	16.4 (0.03–495.6)	12.6 (0.04–73.3)	16.5 (0.04–118.8)	0.49
Heparin administration				
Baseline ACT (s)	135 ± 18	138 (114–163)	136 (114–156)	0.12
Target ACT				
300 s	257 (84.5%)	41 (16.0%)	216 (84.0%)	

	Study cohort (N = 304)	AT activity <80% of normal ^a (N = 49)	AT activity ≥80% of normal ^a (N = 255)	P
350 s	47 (15.5%)	8 (17.0%)	42 (83.0%)	0.86
Heparin dose (U/kg)	150 (86–246)	154 (112–198)	150 (111–211)	0.75
Heparin dose >200 U/kg	59 (19.4%)	8 (16.3%)	51 (20.0%)	0.69
ACT after heparin administration				
300 s	366 (300–456)	357 (300–469)	366 (300–456)	0.53
350 s	389 (324–460)	395 (366–425)	389 (319–470)	0.81
Calculated HDR slope (s/U/mL)	98 ± 21	96 ± 20	98 ± 21	0.50
Heparin sensitivity index (s/U/kg)	1.59 ± 0.41	1.58 ± 0.40	1.60 ± 0.41	0.68
Clinical outcomes				
Cardiac troponin I on POD 1 (μg/L)	0.99 (0.13–7.72)	1.17 (0.31–3.21)	0.97 (0.32–3.89)	0.48
ICU duration (h)	45 (21–94)	48 (24–116)	44 (21–90)	0.13
Postsurgical hospital stay (d)	6 (4–10)	6 (4–11)	6 (4–10)	0.17

Data presented as mean ± SD or median (10th–90th percent confidence intervals).

INR = International Normalized Ratio; ACT = activated clotting time; POD 1 = postoperative day 1; HDR = heparin dose response; ICU = intensive care unit.

^aDefined as 100% of the laboratory normal for AT activity, not corrected for the National Institute for Biological Standards and Control Second International Reference Standard (see Methods).

Table 2

Multivariable Predictors of Heparin-Dose Response (HDR)

Heparin dose response (s/U/mL)	Without AT activity		With AT activity	
	$r^2 = 0.138$		$r^2 = 0.140$	
	Estimate	P	Estimate	P
Female gender	-1.82 ± 1.66	0.27	-2.02 ± 1.67	0.23
Age (y)	0.16 ± 0.13	0.23	0.176 ± 0.131	0.18
Caucasian race	-3.81 ± 1.87	0.042	-3.69 ± 1.87	0.049
Hypercholesterolemia	5.61 ± 1.39	<0.0001	5.52 ± 1.40	<0.0001
Hematocrit	0.71 ± 0.29	0.016	0.70 ± 0.29	0.016
Prothrombin time (s)	5.57 ± 1.82	0.002	5.83 ± 1.84	0.002
White cell count ($\times 10^6$ /mL)	-1.52 ± 0.51	0.003	-1.50 ± 0.51	0.004
AT activity (U/mL)			8.32 ± 9.64	0.39

AT = antithrombin.

Table 3

Multivariable Predictors of Heparin Sensitivity Index (HSI)

Heparin sensitivity index (s/U/kg)	Without AT activity		With AT activity	
	$r^2 = 0.136$		$r^2 = 0.137$	
	Estimate	P	Estimate	P
Female gender	0.070 ± 0.032	0.029	0.068 ± 0.032	0.037
Age (y)	0.001 ± 0.003	0.79	0.001 ± 0.003	0.72
Caucasian race	0.019 ± 0.037	0.61	0.021 ± 0.037	0.58
Platelet count ($\times 10^9/\text{mL}$)	-0.0007 ± 0.0003	0.013	-0.0007 ± 0.0003	0.013
PT (s)	0.10 ± 0.04	0.006	0.10 ± 0.04	0.005
White cell count ($\times 10^6/\text{mL}$)	-0.022 ± 0.011	0.048	-0.022 ± 0.011	0.048
PAI-1 level (ng/mL)	0.032 ± 0.009	0.0005	0.031 ± 0.009	0.0007
Tissue factor level (pg/mL)	-0.0008 ± 0.0003	0.015	-0.0008 ± 0.0003	0.016
AT activity (U/mL)			0.121 ± 0.198	0.54

PAI-1 = plasminogen activator inhibitor level-1; AT = antithrombin; PT = prothrombin time.