Influence of Body Mass Index on the Activated Clotting Time Under Weight-Based Heparin Dose

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Background: Activated clotting time (ACT) has been successfully applied during percutaneous coronary intervention (PCI) to monitor the extent of thrombin inhibition and anti-coagulation from unfractionated heparin (UFH) aiming to reduce the incidence of thrombotic adverse events and hemorrhagic complications. And this investigation was to explore the influence of body mass index (BMI) on ACT in patients received weight-based dose of UFH during PCI treatment. **Methods:** 78 male patients undergoing coronary angiography or PCI treatment with a mean age of 63.86 ± 6.89 years were enrolled in this study. The patients were statistically divided into four quartiles according to their BMI. The ACT values were recorded as ACT₀, ACT₅, ACT₁₀, ACT₃₀ and ACT₆₀, respectively. Taking the preoperative ACT₀ as reference, and the differences of the other ACT values with ACT₀ was indicated as Δ ACTs. ACT values peaked at 5 min in 33.33% of the patients, 10 min in 51.33%

of the patients and 30 min in 15.34% of the patients, respectively. **Results:** In addition, significant differences were found in overall maximum post-UFH ACT values among all BMI quartiles. UFH doses per blood volume were significantly different among the BMI quartiles, showing a positive association with BMI quartiles; further evidence revealed that the areas under the Δ ACT-time curves increased gradually from quartile I to quartile IV. The proportions of ACT₆₀ > 250 s and ACT₆₀ > 300 s were found to be positively correlated with the increased BMI at 60 min after heparin loading. **Conclusions:** The results of our study have shown that a standardized dosing nomogram that uses the actual body weight to calculate the heparin doses may result in UFH overdose for patients with higher BMI compared to patients with lower BMI. J. Clin. Lab. Anal. 30:108–113, 2016. © 2014 Wiley Periodicals, Inc.

Key words: unfractionated heparin; activated clotting time; body mass index

INTRODUCTION

Unfractionated heparin (UFH) exists as a heterogeneous mixture of glycosaminoglycans involved in binding to antithrombin by pentasaccharide sequence and catalyze the inactivation of thrombin, such as factor Xa (1,2). As the widely accepted anticoagulants affecting the thrombin cascade, UFH was demonstrated to be the most commonly antithrombotic therapy to effectively suppress the thrombin generation and prevent perioperative thromboembolic events during percutaneous coronary intervention (PCI; (3–5)). However, UFH may also bind to cells and plasma proteins instead of thrombin, resulting in unpredictable pharmacokinetic and pharmacodynamic properties that limited the clinical applications (6–8). Therefore, the activated clotting time (ACT) has been successfully applied during PCI to monitor the extent of thrombin inhibition and anticoagulation

from UFH, aiming to reduce the incidence of thrombotic adverse events and hemorrhagic complications (9,10). In addition, previous studies have revealed that a weight-based dosing regimen have been widely implemented in hospitals and have become the standard administration technique for UFH (11–13); while the weight-based loading dose of UFH was increasingly challenged, especially for the overweight patients displaying the limitations of a standardized weight-based nomogram for UFH dosing (14–16). Specifically, the volume of distribution

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of UFH coincides with blood volume, adipose tissue has a smaller blood volume than lean tissue, and dosing based on actual body weight may result in excessive UFH administration in obesity patients and, consequently, increased risk of adverse events (17, 18). Recently, a growing number of evidence showed a hypothetical association between body mass index (BMI) and the ACT, which would play an important role in the UFH dosing requirements (14, 18, 19). BMI is considered as an alternative to the estimation of adipose tissue mass and the most commonly used anthropometric method to characterize obesity (20–22). Bauer et al. have attempted to assess the bleeding events and supratherapeutic activated partial thromboplastin times (aPTTs) values in patients characteristics by BMI category, and found that patients with higher BMI had higher initial aPTT values (19). Evidence also showed that UFH dosing with a weight-based nomogram will induce higher aPTT values in patients with morbidly obese, and BMI be used to help identify those patients at risk of supratherapeutic aPTTs, although they offered no dosing recommendations (14). Nevertheless, BMI is limited because it does not differentiate adipose tissue from lean muscle mass and can be influenced by age, gender, and ethnicity, therefore, has not been well studied with regard to anticoagulant agents (23–25). Therefore, this study aimed to explore the influence of BMI on the ACT in patients who received weight-based dose of UFH during PCI treatment, and provide theoretical basis for heparin loading guidance.

MATERIALS AND METHODS

Ethics Statement

The study protocol was approved by the Human Subjects Committee of The First Affiliated Hospital of Wenzhou Medical College. All patients had to sign an elaborately conceived informed consent in written form to undergo diagnostic and therapeutic procedure before study enrolment.

Subjects and Experimental Group

From November 2010 to May 2011, 78 male patients undergoing coronary angiography or PCI treatment with a mean age of 63.86 ± 6.89 years (range, 45–77 years) were enrolled in this study. Patients were excluded from the current study on the basis of the following criteria: (1) had one or more of the following diseases, including atrial fibrillation, acute cerebrovascular disease, active ulcer, congenital coagulation factor deficiencies, bleeding and clotting disorders, malignancies, severe liver and kidney dysfunction, and hypoproteinemia, (2) who received any anticoagulant drugs simultaneously (e.g., warfarin), (3) treated with low-molecular-weight heparin or UFH 12 h before

surgery, and using tirofiban hydrochloride/sodium chloride injection before or during surgery, (4) who underwent emergency PCI.

Before surgery, the height and weight of all patients were measured to calculate BMI (calculated as weight in kilograms divided by height in meters squared). The patients were statistically divided into four quartiles according to their BMI: quartile I ($15.57 \text{ kg/m}^2 \leq \text{BMI} < 23.03 \text{ kg/m}^2$, $n = 20$), quartile II ($23.03 \text{ kg/m}^2 \leq \text{BMI} < 25.35 \text{ kg/m}^2$, $n = 20$), quartile III ($25.35 \text{ kg/m}^2 \leq \text{BMI} < 27.68 \text{ kg/m}^2$, $n = 18$), and quartile IV ($\text{BMI} \geq 27.68 \text{ kg/m}^2$, $n = 20$).

Study Design and Treatment

In the analysis, 2 ml arterial blood samples were collected through arterial sheath before heparin loading and stored at -80°C and thawed to 4°C before testing. After arterial puncture, patients in the four quartiles were injected with 100 U/kg loading dose of UFH (Shanghai No. 1 Biochemical & Pharmaceutical Co., Ltd., No. 387 Shangqiu Road, Shanghai 200000, People's Republic of China), and then additional 2 ml arterial blood samples were obtained at specified time points (typically after 5, 10, 30 and 60 min, respectively). The 2 ml whole blood samples were placed in the vacuum-sealed tubes within 1 min of sampling, and then placed in the continuously rotating Hemochron chamber. All ACT measurements were performed with use of Medtronic ACT II automated coagulation timer and Hepcon ACT kit according to the instructions of the manufacturer; reagents were added when the temperature of enzyme substrate reached $37.0 \pm 0.5^\circ\text{C}$ and the ACT value was expressed as the average of the results of the two measurements. However, if the difference between two measured ACT values was higher than 12% of the average value, the patient would be excluded.

The ACT values were recorded as ACT_0 , ACT_5 , ACT_{10} , ACT_{30} , and ACT_{60} , respectively. Taking the preoperative ACT_0 as reference, and the differences between ACT_0 and ACT_5 , ACT_{10} , ACT_{30} , and ACT_{60} were recorded as ΔACT_5 , ΔACT_{10} , ΔACT_{30} , and ΔACT_{60} , respectively. The heparin dose per blood volume was calculated by the equations: $\text{inBV} = 70/\text{sqr}(\text{BMI}_P/22)$ and $\text{BMI}_P = [(\% \Delta \text{IBM}/100) \times 22] + 22$ (26). The areas under the ΔACT –time curves were calculated by MATLAB 7.0 software to reflect the UFH potency. Platelet counts on whole blood and platelet-rich plasma were determined using a Cell-Dyn 3200.

Statistical Analysis

Data are presented as mean $\pm$ standard deviation. Differences among groups were compared using ANOVA test. Further comparison of count data among the groups was performed using a chi-square test. Fisher definite probability methods was adopted when theoretical

TABLE 1. Comparison of Baseline Characteristics among Each Group

Index	Group A (n = 20)	Group B (n = 20)	Group C (n = 18)	Group D (n = 20)	P-value
Age (years)	64.65 ± 3.99	61.50 ± 7.47	66.89 ± 5.48	63.86 ± 6.89	>0.05
Height (cm)	166.90 ± 5.06	166.40 ± 6.44	167.00 ± 5.88	171.40 ± 4.68	<0.05
Weight (kg)	57.70 ± 5.72	66.90 ± 5.68	72.94 ± 5.59	88.50 ± 6.23	<0.01
BMI (kg/m ²)	57.70 ± 5.72	24.13 ± 0.65	26.12 ± 0.66	30.11 ± 1.52	<0.01
AT-III (%)	91.50 ± 12.49	92.00 ± 14.28	89.78 ± 11.83	91.60 ± 16.05	>0.05
ACT ₀ (s)	177.20 ± 14.81	179.20 ± 18.64	188.00 ± 11.83	180.90 ± 13.37	>0.05
PLT (×10 ⁹ /l)	185.25 ± 33.65	173.75 ± 49.45	184.17 ± 46.89	177.30 ± 47.29	>0.05

BMI, body mass index; AT-III, antithrombin III; ACT, activated clotting time; PLT, platelet.

frequency <1. All statistical analyses were conducted using the SPSS 16.0 software (SPSS, Inc., Chicago, IL). Differences were judged significant if $P < 0.05$.

RESULTS

Comparison of Baseline Characteristics

The comparison of baseline characteristics among all patients in each group was shown in Table 1. According to analysis of observed cases, body weight tended to increase gradually and significantly in parallel with a marked rise in BMI from quartile I to quartile IV (all $P < 0.01$); there was also difference in height in patients among the four quartiles (all $P < 0.05$). However, no statistical significance were observed in age, antithrombin III, baseline ACT level, and platelet count among the BMI quartiles (all $P > 0.05$).

Time of Peak ACT

The results showed a highly significant variation in the ACT values over time in each quartile (all $P < 0.05$). Viewing the change from the control ACT (ACT₀) as a measure of response to heparin, the mean Δ ACT at different time points (Δ ACT₅, Δ ACT₁₀, Δ ACT₃₀, and Δ ACT₆₀) were significantly different from each other in each quartile (all $P < 0.05$; Table 2). The frequency distribution over time for the maximum post-UFH ACT values in the four quartiles was summarized in Table 3. ACT values peaked at

5 min in 33.33% of the patients (24/78), 10 min in 51.33% of the patients (42/78), and 30 min in 15.34% of the patients, respectively (12/78). In addition, significant differences were found in overall maximum post-UFH ACT values among all BMI quartiles (all $P < 0.05$). There were obvious difference in the cases with an ACT peak time of 5 min; similar associations were also found in the patients with ACT peak time of 10 and 30 min (all $P < 0.05$).

Comparison of the Degree of Heparinization

Comparison of the degree of heparinization showed that the UFH doses per blood volume were significantly different among the BMI quartiles, showing a positive association with BMI quartiles; further evidence revealed that the areas under the Δ ACT–time curves increased gradually from quartile I to quartile IV (all $P < 0.01$). The proportions of ACT₆₀ > 250 s and ACT₆₀ > 300 s were found to be positively correlated with the increased BMI at 60 min after heparin loading (all $P < 0.01$; Table 4).

DISCUSSION

Clinically, adequate anticoagulation is necessary during PCI because of its significant importance to prevent clot formation or progression of both arterial and venous thromboembolic disorders (27). Currently, the guidelines have recommended that UFH is the most commonly used

TABLE 2. Comparison of the Degree of Heparin Effect among Each Group

ACT values	Quartile I	Quartile II	Quartile III	Quartile IV	P-value
ACT ₀	177.20 ± 14.81	179.20 ± 18.64	188.00 ± 11.83	180.90 ± 13.37	>0.05
ACT ₅	436.80 ± 209.77	414.00 ± 87.38	488.00 ± 222.10	510.40 ± 182.42	>0.05
ACT ₁₀	499.50 ± 245.41	555.90 ± 201.73	432.20 ± 184.40	519.30 ± 216.52	>0.05
ACT ₃₀	419.30 ± 174.94	546.20 ± 251.79	377.20 ± 72.17	405.56 ± 132.23	0.014
ACT ₆₀	261.30 ± 24.20	276.50 ± 16.58	297.70 ± 15.40	308.90 ± 25.43	0.000
Δ ACT ₅	253.10 ± 191.91	234.60 ± 74.22	301.40 ± 228.74	329.50 ± 185.45	>0.05
Δ ACT ₁₀	185.50 ± 46.42	250.10 ± 36.30	427.50 ± 126.99	653.70 ± 124.42	0.000
Δ ACT ₃₀	235.60 ± 166.31	366.80 ± 243.53	190.60 ± 77.87	224.89 ± 135.73	0.008
Δ ACT ₆₀	77.60 ± 18.62	97.10 ± 4.27	111.10 ± 12.23	132.20 ± 22.79	0.000

ACT, activated clotting time.

TABLE 3. Peak ACT Time (Cases)

Group	5 min	10 min	30 min
Group A	4	8	8
Group B	4	12	4
Group C	10	8	0
Group D	6	14	0

Min, minute; ACT, activated clotting time.

anticoagulant in patients treated with PCI (28). However, anticoagulation always carries a risk of major bleeding in patients undergoing PCI due to excessive anticoagulant activity caused by dosing errors (29). Therefore, testing ACT in patients undergoing PCI is required to monitor the intensity and effect of UFH, and moreover instruments for bedside clinical use in the PCI are supposed to be more convenient, quick, and capable to adjust the dose of UFH in time (30). Generally, the standard value of intraoperative ACT is proposed to be 250~300 s (HemoTec method) for the patients without treatment of glycoprotein inhibitors, but the proper use of UFH in patients undergoing PCI is still contradictory (13).

In the present study, our results showed that the ACT peak time after UFC loading dramatically varied among different individuals, and only a half of patients achieved peak ACT time at 10 min after UFH loading, suggesting that it is irrational to use a single time point to reflect heparin effect. Although questions pertaining to the exact mechanisms leading to various peak ACT times among individuals remain largely unanswered yet, we supposed that it may account for the unique metabolic patterns of UFH in the human body. It has been reported that the metabolic patterns of UFH include fast-elimination zero-order kinetics with which the half-life prolongs gradually as the dose increases, and consecutive slower elimination first-order kinetics with which the half-life remains unchanged as the dose increases (31). In addition, the slower elimination first-order kinetics was suspected to work after the saturation of heparin-binding and excrete UFH unchanged via the kidneys, and thereby the heparin-ACT dose-response curve may appear nonlinear (32). Taken together, the area under the curve (AUC) of Δ ACT-time might be a better way to reflect the effects of UFH load.

In general, the guidance recommended the weight-based administration of UFH, but this administration was still not confirmed in patients whose BMI is too low or too high (33). The adipose and nonadipose tissues increased significantly in obese patients as compared to the patients with the same age, gender, and height (34). However, there is only a small portion of the increased body weight in obese patients in nonadipose tissue (about 20%~40%; (35)). As a result, the proportion of nonadipose tissue per kilogram of body weight may decrease, while the proportion of adipose tissue per kilogram of body weight may increase exponentially (36). Furthermore, the distribution of heparin in the body is similar to blood volume distribution, and the blood volume in adipose tissue is obviously lower than that in nonadipose tissue (37). Therefore, the distribution of heparin is more closely correlated to the nonadipose tissue than to the body weight. Although BMI was usually used to evaluate adipose tissue, it was barely used for guidance of clinical drug doses (38). Our study evaluated the effect of BMI on the ACT in patients undergoing PCI using anticoagulation and revealed that there were significant differences among the four groups on heparin dose per blood volume and the AUC of Δ ACT-time, and BMI was positively related to the AUC of Δ ACT-time and the proportion of patients with value of intraoperative ACT being >250 s. The findings of our study implied that the UFH loading dose based on body weight might be overdosed for the obese patients. Our results were in accordance with a previous study of Barletta et al., who retrospectively analyzed 101 patients treated with UFH, and found that APTTs of the patients with BMI ≥ 40 kg/m² were obviously longer than those of the patients with BMI < 40 kg/m², suggesting BMI as an independent predictive factor of long APTT (14). Additionally, Riney et al. have found that the required heparin dose per kilogram of body weight for high BMI patients was obviously lower than that for low BMI patients to reach similar APTT values (18). Therefore, the heparin loading doses could be administered according to ideal body weight, corrected weight, or dose of heparin per blood volume of the obese patients to avoid bleeding complications that was still lack of practical clinical researches (17).

TABLE 4. Comparison of the Degree of Heparin Effect Among each Group

Index	Group A	Group B	Group C	Group D	P-value
Unit volume heparin dose (Unit/ml)	1.36 $\pm$ 0.07	1.49 $\pm$ 0.02	1.52 $\pm$ 0.39	1.64 $\pm$ 0.04	<0.01
Areas under the curve	2.3 $\times 10^6 \pm 8.9 \times 10^5$	2.7E6 $\pm$ 1.1E6	2.8 $\times 10^6 \pm 1.4 \times 10^6$	5.1 $\times 10^6 \pm 7.9 \times 10^5$	<0.01
Portion of ACT ₆₀ > 250s (%)	60.00	100.00	100.00	100.00	<0.01*
Portion of ACT ₆₀ > 300s (%)	0	0	44.44	50.00	<0.01*

ACT, activated clotting time.

*Exact probability test.

In conclusion, the results of our study have shown that a standardized dosing nomogram that uses the actual body weight to calculate the heparin doses may result in UFH overdose for patients with higher BMI compared to patients with lower BMI. However, the heparin doses would be different between male and female patients due to the physiological difference, so only male patients were enrolled for this study. Whether similar phenomenon would be observed in female patients requires a further study to confirm. Future research should focus on modeling pharmacokinetic and pharmacodynamic data to establish specific dosing recommendations.

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CONFLICT OF INTEREST

None declared.

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