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Heparin Concentration–Based Anticoagulation for Cardiac Surgery Fails to Reliably Predict Heparin Bolus Dose Requirements

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Abstract

BACKGROUND—Hemostasis management has evolved to include sophisticated point-of-care systems that provide individualized dosing through heparin concentration–based anticoagulation. The Hepcon HMS Plus system (Medtronic, Minneapolis, MN) estimates heparin dose, activated clotting time (ACT), and heparin dose response (HDR). However, the accuracy of this test has not been systematically evaluated in large cohorts.

METHODS—We examined institutional databases for all patients who underwent cardiac surgery with cardiopulmonary bypass (CPB) at our institution from February 2005 to July 2008. During this period, the Hepcon HMS Plus was used exclusively for assessment of heparin dosing and coagulation monitoring. Detailed demographic, surgical, laboratory, and heparin dosing data were recorded. ACT, calculated and measured HDR, and heparin concentrations were recorded. Performance of the Hepcon HMS Plus was assessed by comparison of actual and target ACT values and calculated and measured HDR.

RESULTS—In 3880 patients undergoing cardiac surgery, heparin bolus dosing to a target ACT resulted in wide variation in the postheparin ACT ($r^2 = 0.03$). The postheparin ACT did not reach the target ACT threshold in 7.4% (i.e., when target ACT was 300 s) and 16.9% (i.e., when target ACT was 350 s) of patients. Similarly, the target heparin level calculated from the HDR did not correlate with the postbolus heparin level, with 18.5% of samples differing by more than 2 levels of the assay. Calculated and measured HDR were not linearly related at any heparin level.

CONCLUSIONS—The Hepcon HMS Plus system poorly estimates heparin bolus requirements in the pre-CPB period. Further prospective studies are needed to elucidate what constitutes adequate anticoagulation for CPB and how clinicians can reliably and practically assess anticoagulation in the operating room.

Administration of heparin, and monitoring of whole blood activated clotting time (ACT), is still the mainstay of anticoagulation for cardiopulmonary bypass (CPB).^{1,2} Hemostasis management has evolved to include more sophisticated point-of-care systems that provide individualized dosing of heparin and protamine, through heparin concentration–based estimation of heparin dosage, and measurement of ACT.^{3,4} Individualized heparin concentration–based anticoagulation management has been reported to cause less activation of thrombin, decreased fibrinolysis, reduced blood loss, fewer transfusions, and a decreased risk of reexploration for hemorrhage,^{5–8} although there is still a lack of consensus in this area.^{9,10} Previous studies of heparin-level monitoring devices, including the Hepcon HMS Plus, had varied results, with some studies showing good agreement between whole blood heparin concentration and either ACT before CPB¹¹ or plasma anti-Xa levels before or during CPB,¹² whereas others showed a lack of significant relationship between ACT and heparin concentration¹³ or whole blood versus anti-Xa heparin concentration.¹⁴ All of these studies were limited by their small sample sizes. Importantly, there is previously observed interindividual variation in measured heparin levels for a target ACT required for CPB.

Therefore, we examined the relationship between individualized *in vitro* estimation of the heparin level for a specific target ACT, and the subsequently observed ACT and heparin level measured after bolus administration of the heparin dose response (HDR)-estimated heparin dose. We hypothesized that: 1) there would be strong correlation between calculated and measured HDR for individual patients; 2) residual variation in the predicted HDR would be due to patient factors that are accounted for in the calculation of the HDR; and 3) the HDR-estimated heparin dose would achieve the desired ACT for CPB in all patients.

METHODS

The Hepcon HMS Plus (Medtronic, Minneapolis, MN) was introduced in our institution in February 2004, in concert with a change in heparin coagulation management. Use of this system was based on a belief that adequate anticoagulation for CPB using a heparin-coated circuit could be achieved with lower ACTs as long as reasonable, albeit lower heparin levels than had been historically used were maintained. Furthermore, there was a perception that reduced heparin administration may result in reduced postoperative bleeding.

After IRB approval, we examined institutional databases for all patients who underwent CPB for cardiac surgery at our institution, from February 2005 to July 2008 ($n = 4667$). Patients with incomplete perioperative anticoagulation data were excluded from analysis ($n = 562$). The majority of patients were excluded for having a target ACT of >350 s or subsequent administration of aprotinin ($n = 157$), no record of postheparinization heparin level ($n = 144$), no record of baseline ACT ($n = 91$), or no record of height or weight ($n = 67$). Furthermore, we excluded an additional 225 patients who were not anticoagulated using the institutional protocol described below, yielding 3880 analyzed patients.

Anticoagulation Management

The Hepcon HMS Plus was used for anticoagulation management 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.¹⁴ 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 HDR cartridges encompassing whole blood heparin concentration ranging from 0.4 to 3.4 U/mL. The Hepcon HMS Plus recommended 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. Three minutes after United States Pharmacopeia porcine heparin

administration and 10 min after onset of CPB, heparin concentration and ACT were remeasured. All patients received an ϵ -aminocaproic acid load of 7.5–10 g over 1 h, after the initial blood draw for baseline ACT, but before heparin administration and blood sampling for measurement of postheparin ACT. ϵ -Aminocaproic acid was subsequently infused at a rate of 1.25–1.5 g/h.

Throughout the entire study period, an ACT of more than 350 s and a minimum heparin concentration of 2 U/mL were used in patients undergoing non-coronary artery bypass graft (CABG) procedures or CABG with the use of cardiectomy suction. Patients undergoing primary CABG surgery without the use of cardiectomy suction before March 2007 were anticoagulated using a protocol that proscribed a minimum ACT of 300 s before the institution of CPB. After February 2007, to standardize anticoagulation management, the minimum ACT before CPB was increased to 350 s with a minimum heparin concentration of 2.0 U/mL for CABG surgery. These protocols were driven by a desire to reduce heparin and protamine doses to reduce blood loss but were not supported by prior clinical evidence of efficacy.

We also observed variability in anticoagulation practice that was not proscribed by a protocol. Some perfusionists administered additional heparin when the measured heparin level was <1.4 or 2.0 U/mL, according to personal preference. These patients were excluded from analysis, as previously described.

Data Collection and Statistical Analysis

Detailed demographic data, surgical indications, preoperative laboratory values, operative data, heparin bolus dose, ACT values, and measured heparin concentrations were routinely collected into a centralized database. The calculated HDR was calculated as the target ACT – baseline ACT divided by the target heparin level and reported as $s \cdot U^{-1} \cdot mL^{-1}$. The calculated HDR differed from the method used by the Hepcon HMS Plus,¹⁵ but prospective comparison of the Hepcon HMS Plus and the above calculation in 15 patients showed excellent correlation ($r^2 = 0.991$). This calculation uses the target heparin concentration identified from the HDR slope generated by the Hepcon HMS Plus, not the protocol-driven heparin level. Thus, the calculation of the HDR slope is independent of the clinical protocol and unaffected by the heparin level desired or obtained after heparin dosing.

The measured HDR was calculated as postheparin ACT – baseline ACT divided by the measured heparin level and reported as $s \cdot U^{-1} \cdot mL^{-1}$. By using the measured postheparinization ACT and measured heparin level, the measured HDR is independent of the clinical protocol because the HDR slope has been demonstrated to be linear over the clinical range of heparin concentrations.¹¹

The Hepcon HMS Plus heparin assay has limited fidelity, reporting only 6 categorical heparin levels, with intermediate values of heparin reported to the closest level. Accordingly, we could not directly compare the calculated and measured HDR. Therefore, we report the calculated HDR for each measured postbolus heparin level. Pearson product-moment correlation was performed between calculated and measured values of HDR, and heparin concentration and ACT data. ACT data at each heparin level were compared with Wilcoxon's ranked sum test. Statistical analysis was performed with JMP version 7.02 (SAS, Cary, NC). All data are presented as mean $\pm$ SD or median and interquartile range, as appropriate. A 2-sided $P < 0.05$ was considered as showing statistical significance.

RESULTS

A total of 3880 patients were analyzed. Baseline demographics and perioperative data are summarized in Table 1. Target ACTs of 300 and 350 s were used in 23.4% and 76.6% of patients, respectively. Heparin dose, ACT, and heparin level after the heparin bolus for each target ACT are detailed in Table 2. The mean heparin dose calculated to achieve a target ACT of 300 s was 152 U/kg, and for a target ACT of 350 s was 179 U/kg. After administration of the HDR-estimated heparin dose, the target ACT was not achieved in 7.4% of patients with a target ACT of 300 s, and it was not reached in 16.9% of patients with a target ACT of 350 s (Fig. 1). Additional heparin was administered either before or immediately after initiation of CPB to 91% of patients who failed to achieve their target ACT of 300 s and to 77% of patients who failed to achieve their target ACT of 350 s.

There was wide variation among patients for the ACT seen at each heparin level (Fig. 2). Measured HDR varied substantially among patients (mean $\pm$ SD, $104.7 \pm 24.3 \text{ s} \cdot \text{U}^{-1} \cdot \text{mL}^{-1}$; median [10%–90% interquartile range], 102 [77–137]). Correlation (r^2) between the calculated and measured HDR was poor at all heparin levels ($r^2 < 0.02$; Fig. 3). To exclude an outlier effect, the analysis was repeated in a subgroup of patients within 1 SD of the mean postheparin ACT, with similar results.

The predicted heparin level expected after heparin bolus administration was compared with the heparin level measured after heparin bolus. Levels that differed by more than 0.3 U/mL differed by more than the sensitivity (1 channel) of the assay and were observed in 51.0% of samples (Fig. 4). Levels that differed by more than 0.7 U/mL differed by more than 2 channels in the assay and were observed in 18.5% of samples.

DISCUSSION

We examined the performance of the Hepcon HMS Plus to guide anticoagulation in 3880 patients undergoing cardiac surgical procedures. Data provided by the Hepcon HMS Plus were used to calculate heparin dosing throughout CPB and to direct the administration of protamine after CPB. We observed wide variability in heparin dose requirements to achieve an adequate ACT for CPB, as others have previously described.¹ We also observed poor correlation of the calculated HDR with the measured HDR. This led to ACT values that were less than the target ACT values when heparin dosing was guided by estimation of HDR, in 7.4%–16.9% of patients. The imprecision for the calculated HDR may explain the high frequency of failure to reach the target ACT.

Interpatient variability in HDR is well described, and use of a dose-response plot recommended by Bull et al.³ provides the basis of Hepcon HMS Plus calculations. Our initial hypothesis that the HDR slope calculated by the Hepcon HMS Plus would correlate with the measured HDR slope is not supported by the data. The interindividual variability in heparin response could be attributable to a number of *in vivo* factors, including error in the estimation of blood volume, effects of release of tissue factor pathway inhibitor (TFPI) by heparin *in vivo* but not *ex vivo*, extravascular sequestration of heparin, plasma protein binding, circulating antithrombin, and platelet activation.¹⁶

Estimation of blood volume is a potential source of error in heparin dose calculation. The methodology used by several previous studies^{5,6,12} is predominantly based on the method described by Allen et al.¹⁴ in 1956. The magnitude of error in estimation of blood volume in individual patients undergoing cardiac surgery has not been systematically evaluated. It is probable that the severity and nature of cardiac disease may be a substantial source of variation in blood volume estimates, thereby contributing to imprecision of point-of-care anticoagulation management instruments. Further investigation aimed at improving

estimation of blood volume in patients undergoing cardiac surgery may result in better performance of point-of-care heparin concentration–based anticoagulation systems.

Potentially contributing to the imprecision of the Hepcon HMS Plus are the effects of release of TFPI by heparin *in vivo* but not *ex vivo*. TFPI *in vivo* is bound to endothelial cell surfaces with small amounts circulating in plasma and bound to platelets.¹⁷ TFPI is an endogenous serine protease inhibitor that exerts its action primarily through neutralizing factor Xa by complexing with factor Xa and forming a TFPI-FXa complex, while also providing feedback inhibition of the factor VIIa–tissue factor complex.¹⁸ Plasma TFPI is released from endothelial surface stores by administration of unfractionated and low-molecular-weight heparins,¹⁹ increasing plasma levels during CPB.²⁰ Brodin et al.²¹ recently demonstrated significant synergy between antithrombin and TFPI in postheparin plasma with an almost equal contribution of each to the prolongation of anticoagulation in a laboratory setting. In the absence of an endothelial source of TFPI, the contribution of TFPI to heparin responsiveness may be underestimated by the initial HDR calculation performed by the Hepcon HMS Plus. This source of error in the calculated HDR would seemingly lead to increased heparin dosages and higher postheparin ACT, which is incongruous with our finding of 7.4%–16.9% of patients failing to achieve their target ACT, but congruous with the mean ACT being higher than the target ACT in our overall population. Although the exact contribution of TFPI to point-of-care measurements of heparin responsiveness has not been established, strong correlation between the TFPI-responsive Heptest (American Diagnostica, Stamford, CT) measurements of heparin level and ACT in the pre-CPB period²² has been observed, and release of TFPI correlates with the Heptest measurement of heparin response in normal volunteers receiving IV heparin.²³ These observations reinforce the importance of TFPI in heparin responsiveness and point to a likely impact on point-of-care assessments of HDR.

Earlier studies of these heparin-level monitoring devices, including the Hepcon HMS Plus, had varied results with some studies showing good agreement between whole blood heparin concentration and either ACT before CPB¹¹ or plasma anti-Xa levels,¹² whereas others showed a lack of significant relationship between ACT and heparin concentration²⁴ or whole blood versus anti-Xa heparin concentration during CPB.^{13,14} One study¹² revealed substantial interpatient variability in HDR; however, the linear relationship between heparin concentration and kaolin ACT within individual patients was generally exceptional. Our retrospective analysis demonstrated significant variability in the responsiveness of the kaolin ACT and heparin *in vivo* versus kaolin ACT and heparin *ex vivo* (i.e., after IV administration of heparin), and calculated versus measured HDR, respectively (Fig. 3). This was paralleled by the finding that the Hepcon HMS Plus–guided heparin administration failed to result in adequate anticoagulation for CPB in 16% of patients in this study when the target ACT was 350 s, even with the CPB prime heparin dose being administered as part of the initial IV bolus dose.

Early work performed by Bull et al.²⁵ and Young et al.²⁶ continues to form the basis for the ACT target used to safely institute CPB, with many centers using an ACT of more than 480 s as a target. In 1981, Jobes et al.²⁷ determined that a heparin level of 2 U/mL was associated with an ACT >300 s in >95% of patients. These data were not the basis for our use of a heparin level of 2 U/mL in the latter portion of the study period, but are in line with our observation of wide variation in ACT values at specific heparin levels. The theoretical benefit of using heparin concentration–based anticoagulation is that a stable heparin level may be achieved, thereby minimizing hemostatic activation^{7,28} and keeping the patient fully anticoagulated throughout the CPB period, which would lead to reduced blood loss and transfusion.^{5,6} We observed wide variability in ACT for any given heparin level (Fig. 2). Almost all studies using heparin concentration have used this historical reference as the

target for defining adequate anticoagulation, but establishment of a “safe heparin level” has not been systematically studied.

This study is limited by its retrospective nature. We were not able to capture all of the perioperative factors that may influence anticoagulation and an individual’s response to heparin administration. In addition, important clinical outcomes are not part of this data set, including perioperative complications that may relate to anticoagulation management, such as bleeding, transfusion, reexploration, myocardial infarction, new or worsening renal insufficiency, and cerebral vascular accident. Furthermore, our comparison of the calculated and measured HDR is limited by the imprecision of the automated protamine titration method, which measures whole blood heparin concentration using discrete cutoffs using only the 6 channels of the cartridge. Thus, we are left with 4 likely sources of disparity between calculated and measured HDR: 1) inaccurate estimate of the patient’s blood volume; 2) lack of fidelity of measured heparin concentration because only 6 categories of heparin level describe the linear range of heparin concentration; 3) inherent inaccuracy of the device; and 4) differences between the anticoagulant activity of heparin *ex vivo* compared with its several actions *in vivo*, notably upon the release of TFPI. We were unable to subset these possible causes further, but they seem to be significant.

We conclude that the Hepcon HMS Plus fails to consistently provide the therapeutic heparin bolus dose uniformly in all patients based on the wide discrepancy in calculated versus measured HDR. This can lead to inadequate heparin doses to achieve a target ACT for CPB in as much as 16.9% of patients. However, the Hepcon HMS Plus was able to identify an adequate heparin dose for the majority of the patients. Because this study, did not compare the Hepcon HMS Plus with empiric dosing regimens, we are uncertain whether empiric regimens can either under- or overperform when compared to this system. Further prospective studies are needed to elucidate what constitutes adequate anticoagulation for CPB and how clinicians can reliably and practically assess anticoagulation in the operating room.

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Figure 1. Observed activated clotting time (ACT) at each target ACT level. Box plot represents the 5th, 25th, median, 75th, and 95th percentiles of data.

Figure 2. Observed activated clotting time at each measured post-bolus heparin level. Box plot represents the 5th, 25th, median, 75th, and 95th percentiles of data.

Figure 3.

Correlation between calculated and measured heparin dose response. Each panel contains data for individuals with a specific measured heparin level after heparinization. Panel A represents a measured heparin level of 1.4 U/mL ($r^2 < 0.01$). Panel B represents a measured heparin level of 2.0 U/mL ($r^2 = 0.02$). Panel C represents a measured heparin level of 2.7 U/mL ($r^2 = 0.01$). Panel D represents a measured heparin level of 3.4 U/mL ($r^2 = 0.03$).

Figure 4. Target and measured heparin level observed after bolus heparin administration. Box plot represents the 5th, 25th, median, 75th, and 95th percentiles of data.

Table 1**Demographics and Perioperative Data**

	Study cohort (N = 3880)
Age	65.2 ± 13.4
Male gender	2538 (65.4%)
Height (cm)	171 ± 10
Weight (kg)	82.2 ± 19.0
BSA (m ²)	1.94 ± 0.24
Indication for surgery	
Coronary artery disease	2394 (63.3%)
Valve disease	1932 (53.1%)
Aortic dissection	41 (1.2%)
Medical history	
Previous myocardial infarction	989 (26.2%)
Hypertension	2550 (67.5%)
Insulin-dependent diabetes	343 (9.1%)
Renal insufficiency (creatinine ≥2.0 mg/dL)	145 (4.0%)
Preoperative medications	
Aspirin	2387 (63.1%)
Adenosine diphosphate inhibitors	182 (4.8%)
Intravenous heparin	249 (6.6%)
Warfarin	34 (0.9%)
Preoperative laboratory values	
Hematocrit (%)	38.8 ± 4.9
Platelet count (×10 ⁹ /L)	247 ± 81
INR	1.14 ± 0.30
INR >1.4	280 (7.8%)
Partial thromboplastin time (s)	36.2 ± 15.9
Partial thromboplastin time >37 s	733 (20.9%)

Data are presented as mean ± 1SD for demographics.

The upper limit of the laboratory reference range for partial thromboplastin time is 37 s.

BSA = body surface area; CABG = coronary artery bypass graft; INR = International normalized ratio.

Table 2**Intraoperative Anticoagulation Management**

	Mean $\pm$ sd	Median (10th–90th percentile)
Baseline ACT (s)	138 $\pm$ 17	137 (118–159)
Target ACT of 300 s (<i>N</i> = 908)		
Initial heparin dose (U)	12,994 $\pm$ 3909	12,000 (9000–18,000)
Heparin dose (U/kg)	152 $\pm$ 38	149 (108–203)
Postbolus ACT (s)	387 $\pm$ 73	377 (309–466)
Postbolus ACT <300 s	67 (7.4%)	
CPB + 10 min ACT (s)	340 $\pm$ 54	335 (274–409)
	Postheparin bolus	CPB + 10 min
Heparin level (U/mL)		
<1.4	16 (1.8%)	250 (27.9%)
1.4	232 (25.6%)	498 (55.5%)
2.0	460 (50.7%)	118 (13.2%)
2.7	137 (15.1%)	21 (2.3%)
3.4	60 (6.6%)	10 (1.1%)
>3.4	3 (0.3%)	0 (0%)
	Mean $\pm$ sd	Median (10th–90th percentile)
Target ACT of 350 s (<i>N</i> = 2972)		
Initial heparin dose (U)	14,313 $\pm$ 4013	14,000 (10,000–20,000)
Heparin dose (U/kg)	179 $\pm$ 42	174 (132–232)
Postbolus ACT (s)	418 $\pm$ 83	406 (332–509)
Postbolus ACT <350 s	501 (16.9%)	
CPB + 10 min ACT (s)	386 $\pm$ 73	377 (313–466)
	Postheparin bolus	CPB + 10 min
Heparin level (U/mL)		
<1.4	20 (0.7%)	278 (9.4%)
1.4	438 (14.7%)	1716 (58.2%)
2.0	1449 (48.8%)	789 (26.8%)
2.7	731 (24.6%)	125 (4.2%)
3.4	315 (10.6%)	41 (1.4%)
>3.4	19 (0.6%)	0 (0%)

ACT = activated clotting time; CPB = cardiopulmonary bypass.