Reports of Original Investigations

Preoperative low molecular weight heparin reduces heparin responsiveness during cardiac surgery

[L'héparine de bas poids moléculaire en préopératoire réduit la réponse à l'héparine pendant la chirurgie cardiaque]

Shahar Bar-Yosef MD,* Heidi B. Cozart RPh,† Barbara Phillips-Bute PhD,* Joseph P. Mathew MD,* Hilary P. Grocott MD FRCPC*

Purpose: Cardiac surgery with cardiopulmonary bypass requires systemic anticoagulation, defined by an activated clotting time (ACT) of 400–480 sec. Patients with altered heparin responsiveness require disproportionately higher doses of heparin to achieve this target ACT. A common risk factor for heparin resistance is preoperative heparin therapy. Recently, therapy with low molecular weight heparin (LMWH) has become an acceptable substitute for prolonged heparin therapy. The current study examines the effect of preoperative LMWH therapy on subsequent heparin responsiveness during cardiac surgery.

Methods: Records of patients undergoing cardiac surgery with cardiopulmonary bypass over a period of four months were reviewed. We identified patients who, during the week preceding surgery, had received prolonged (> 24 hr) therapy with either sc LMWH (LMWH group) or continuous iv unfractionated heparin (Heparin group). A Control group consisted of patients who received neither heparin nor LMWH preoperatively. The heparin sensitivity index (calculated as the first change in ACT from baseline divided by the first intraoperative heparin dose, normalized to body weight), was compared among groups using ANOVA.

Results: One hundred and thirty-nine patients were included in the analysis. The heparin sensitivity index was 33–45% higher in the Control group ($1.6 \pm 0.7 \text{ sec} \cdot \text{IU}^{-1} \cdot \text{kg}^{-1}$; $P < 0.0001$) compared to the LMWH ($1.2 \pm 0.4 \text{ sec} \cdot \text{IU}^{-1} \cdot \text{kg}^{-1}$) and Heparin ($1.1 \pm 0.5 \text{ sec} \cdot \text{IU}^{-1} \cdot \text{kg}^{-1}$) groups. In a multivariable model, the use of preoperative LMWH remained a significant predictor of reduced intraoperative heparin responsiveness ($P = 0.002$).

Conclusion: Prolonged preoperative LMWH therapy, similar to the known effect of prolonged unfractionated heparin infusion, reduces subsequent intraoperative response to heparin.

Objectif : La chirurgie cardiaque sous circulation extra-corporelle nécessite une anti-coagulation systémique, définie par un temps de coagulation activé (TCA) de 400-480 sec. Les patients présentant une réponse modifiée à l'héparine nécessitent des doses nettement plus importantes d'héparine pour atteindre le TCA cible. Un facteur de risque commun de la résistance à l'héparine est la thérapie préopératoire à l'héparine. L'héparine à bas poids moléculaire (HBPM) est récemment devenue un substitut approprié des thérapies prolongées à l'héparine. Cette étude porte sur l'effet de thérapies préopératoires HBPM sur la réaction à l'héparine durant la chirurgie cardiaque.

Méthode : Les dossiers de patients subissant une chirurgie cardiaque sous circulation extra-corporelle sur une période de quatre mois ont été étudiés. Les patients ayant suivi une thérapie prolongée (>24 h) d'HBPM sc (groupe HBPM) ou d'héparine non fractionnée iv en continu (groupe Héparine) la semaine précédant la chirurgie ont été identifiés. Le groupe témoin était composé de patients n'ayant reçu ni héparine non fractionnée ni HBPM avant l'opération. L'indice de sensibilité à l'héparine (calculé comme l'augmentation du TCA depuis la ligne de base divisé par la première dose d'héparine intra-opératoire, normalisé à la masse corporelle), a été comparé entre les groupes à l'aide d'une ANOVA.

Résultats : Cent-trente-neuf patients ont été analysés. L'indice de sensibilité à l'héparine fut de 33-45 % plus élevé dans le groupe témoin ($1,6 \pm 0,7 \text{ sec} \cdot \text{IU}^{-1} \cdot \text{kg}^{-1}$; $P < 0,0001$) que dans les groupes HBPM ($1,2 \pm 0,4 \text{ sec} \cdot \text{IU}^{-1} \cdot \text{kg}^{-1}$) et Héparine ($1,1 \pm 0,5 \text{ sec} \cdot \text{IU}^{-1} \cdot \text{kg}^{-1}$). Dans un modèle multivarié, l'utilisation de HBPM préopératoire demeure un indice prédictif significatif de réponse diminuée à l'héparine intra-opératoire ($P=0,002$).

Conclusion : Une thérapie préopératoire prolongée à l'HBPM, comme l'effet connu d'une perfusion prolongée d'héparine non-fractionnée, réduit la réponse intra-opératoire à l'héparine.

CAN J ANESTH 2007 / 54: 2 / pp 107–113

From the Departments of Anesthesiology* and Clinical Pharmacy,† Duke University Medical Center and the VA Medical Center, Durham, North Carolina, USA.

Address correspondence to: Dr. Shahar Bar-Yosef, Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, NC 27710, USA. Phone: 919-286-0411, ext. 7152; Fax: 919-286-6853; E-mail: baryo001@mc.duke.edu

Disclosures: This work was entirely supported by departmental funds. None of the authors has any conflict of interest relative to this work.

Accepted for publication November 3, 2005.

Revision accepted October 5, 2006.

THE use of cardiopulmonary bypass (CPB) during cardiac surgery is associated with activation of the coagulation system mediated by both contact activation and endothelial injury.¹ To prevent thrombosis during CPB, high-dose heparin is used with the aim of achieving an activated clotting time (ACT) of at least 400–480 sec.¹ This can usually be achieved using *iv* heparin doses of 300–400 IU·kg⁻¹. However, considerable variability in the response to heparin is frequently observed, with some patients requiring much higher doses to achieve the target ACT, a condition known as heparin resistance,^{2–4} or altered heparin responsiveness.⁵

Some preexisting conditions described to be associated with heparin resistance during cardiac surgery are infection,^{6,7} use of an intra-aortic balloon pump (IABP),⁴ and, most frequently, preoperative therapy with heparin infusion.^{3,4,8}

The pathogenesis of reduced heparin responsiveness is ascribed mainly to a deficiency of antithrombin III (AT-III), a cofactor required for the biological activity of heparin.^{9–12} Patients with reduced heparin responsiveness necessitate either additional doses of heparin or supplementation of AT-III, given as fresh frozen plasma (FFP)¹³ or reconstituted from the purified and lyophilized product.^{10,14–16}

Preoperative treatment with a continuous infusion of heparin is common in patients undergoing cardiac surgery who have unstable angina, atrial fibrillation, or a prosthetic valve. In one study, up to 30% of patients presenting for cardiac surgery had received a heparin infusion preoperatively.¹⁴ Up to 50% of these patients may demonstrate reduced heparin responsiveness.^{4,17,18}

Recently, the use of low-molecular-weight heparin (LMWH) as a substitute for unfractionated heparin has gained popularity, with some studies demonstrating better outcome in patients with unstable angina.^{19,20} Therefore, an increasing number of patients are presenting for cardiac surgery after having been treated with LMWH in the immediate preoperative period. Both heparin and LMWH require AT-III for their activity, though LMWH has fewer binding sites for AT-III.^{1,21,22} However, no studies have examined how LMWH influences either blood AT-III levels or heparin sensitivity. Therefore, the current study sought to examine the effect of preoperative LMWH therapy on subsequent heparin responsiveness during cardiac surgery compared to patients who have received neither LMWH nor unfractionated heparin.

Methods

Patient identification

After Institutional Review Board approval, the clinical and pharmacy records of all patients in our institution having undergone cardiac surgery with CPB over a four-month period were reviewed. Patients were excluded if they had endocarditis, an IABP in place, or other cardiac assist devices. Also excluded were patients who received aprotinin intraoperatively due to its prolonging effect on the ACT response to heparin.²³ Lastly, we excluded patients who were missing documentation of either the first intraoperative heparin dose, body weight, baseline ACT or first post-heparin ACT measurement.

We identified patients who had received either therapeutic doses of LMWH (at least 40 mg twice daily of enoxaparin (Lovenox®, Aventis Pharmaceuticals Inc., Bridgewater, NJ, USA - LMWH group) or continuous *iv* unfractionated heparin (Heparin group), given for longer than 24 hr anytime during the seven days preceding surgery. The Control group consisted of patients who received neither LMWH nor unfractionated heparin (either *iv* or *sc* regardless of dose) during the week before surgery.

Anesthetic and heparin management

According to our standard anesthetic care, following sedation with midazolam (1–2 mg *iv*) and fentanyl (50–100 µg *iv*), invasive monitoring was established (radial artery and pulmonary artery lines). General anesthesia was induced with thiopental (3–5 mg·kg⁻¹ *iv*), fentanyl (7–10 µg·kg⁻¹ *iv*) and pancuronium (0.1 mg·kg⁻¹ *iv*), and maintained using isoflurane and additional doses of fentanyl and midazolam as required. Baseline celite-ACT was measured before surgical incision (Hemochron 801®, Technidyne Corporation, Edison, NJ, USA). Heparin (300–400 IU·kg⁻¹) was administered into a central venous catheter prior to the onset of CPB with a repeat celite-ACT measured three to five minutes later. If the ACT was less than 400–480 sec, a second dose of heparin, 5000–10000 IU, was given. Fresh frozen plasma transfusion or AT-III concentrate was usually given if ACT was inadequate despite two additional doses of heparin. All samples for ACT measurement were drawn from an indwelling non-heparinized arterial line. All patients received aminocaproic acid, as a 10 g loading dose over 20 min, followed by a continuous infusion at a rate of 1 g·hr⁻¹ until the end of surgery.

Statistical analysis

In order to control for varying practices regarding heparin dosing, we used a modification of the heparin

TABLE I Patient demographics and clinical characteristics

	Control group	Heparin group	LMWH group	P value
<i>n</i>	42	55	42	NA
Age (yr)	59.4 ± 14.6	65.8 ± 10.9	64.9 ± 10.0	0.02
Gender (% male)	54.7	65.5	59.5	0.56
Weight (kg)	81.3 ± 15.6	87.4 ± 22.3	86.0 ± 20.7	0.31
ASA classification (% II/III/IV)	7.7 /25.6 /66.7	3.9 /11.5 /84.6	0 /22.9 /77.1	0.18
Platelet count (× 1000 µL)	226 ± 95	208 ± 67	189 ± 51	0.12
Baseline ACT (sec)	145 ± 25	156 ± 37	144 ± 20	0.10
First heparin dose (U·kg ⁻¹ BW)	346 ± 57	348 ± 68	351 ± 64	0.95
Duration of therapy (days)	NA	3.6 ± 1.5	3.2 ± 1.3	0.20*
Cessation of therapy before surgery (days)	NA	0.02 ± 0.15	1.6 ± 1.5	< 0.0001*

LMWH = low molecular weight heparin; BW = body weight; ACT = activated clotting time. Data are presented as mean ± SD except as percents for gender and ASA classification. NA = not applicable. *This *P*-value is for the comparison between the Heparin and LMWH groups only.

sensitivity index (HSI) first described by Dietrich *et al.*¹¹ For each patient, the difference between the first post-heparin ACT and the baseline ACT was divided by the first heparin dose, normalized to body weight. The absolute values are reported in the Results and are displayed in the Figure. For the statistical analysis, these results were log-transformed to achieve a normally-distributed HSI, confirmed by the Shapiro-Wilk normality test. Comparisons between the three treatment groups (Control, Heparin and LMWH) were made using one-way ANOVA for continuous data and Chi-square test for categorical data. Tukey-Kramer HSD test was used for post hoc pair-wise comparisons. Univariate associations with HSI were tested using linear regression for continuous variables and ANOVA for categorical variables. Factors with *P* = 0.1 or less for either the univariate associations with HSI or the between-groups comparisons, were entered into a multivariable regression modeling of HSI. For this multivariable model, patients in the Heparin group were excluded to allow for testing of the primary study hypothesis regarding a difference between the Control and LMWH groups. Data is expressed as mean ± SD, unless otherwise stated. For all tests, *P* < 0.05 was considered significant. All analyses were conducted using JMP IN version 4.0.4 (SAS Institute Inc., Cary, NC, USA).

Results

One hundred and thirty-nine patients were included in the analysis, and their demographic and clinical data are presented in Table I. No significant differences between the groups were observed, apart from the Control group patients being younger. Baseline ACT tended to be slightly higher in the Heparin group, but this was not statistically significant. The

first administered heparin dose was similar in all three groups, ranging between 346–351 IU·kg⁻¹. In both the Heparin and LMWH groups, most patients had been treated for three to four days prior to surgery. While all patients but one in the Heparin group had the heparin infusion continued until the morning of surgery, LMWH was stopped an average of 1.6 ± 1.5 days before surgery (*P* < 0.0001).

The HSI was 33–45% higher in the Control group (1.6 ± 0.7 sec·IU⁻¹·kg⁻¹) compared to the LMWH and Heparin groups (1.2 ± 0.4 sec·IU⁻¹·kg⁻¹ and 1.1 ± 0.5 sec·IU⁻¹·kg⁻¹, respectively; overall ANOVA *P* < 0.0001; Figure). This difference in HSI translates to a difference in ACT response of 120–150 sec per 300 IU·kg⁻¹ of heparin. Pair-wise comparisons using Tukey-Kramer HSD test verified that both the Heparin and the LMWH groups were significantly different from the Control group, but not from each other.

Other factors found to be significantly associated with HSI include age (*P* = 0.005), platelet count (*P* = 0.0045) and heparin dose given (*P* = 0.0026); all were inversely correlated with the HSI. Factors found not to be associated with HSI include gender, ASA status and baseline ACT. Weight was borderline non-significant (*P* = 0.06). Considering the treatment groups only (i.e., the Heparin and LMWH heparin), no correlation was found between HSI and either duration of therapy or time therapy was discontinued before surgery.

A multivariable model of HSI was created, including all factors with *P* = 0.1 or less having univariate association with HSI or between-groups difference. Study group remained a significant predictor of reduced intraoperative heparin responsiveness (Table II). Age, preoperative platelet count and heparin dose also remained significant, while patient weight and baseline ACT were clearly non-significant.

FIGURE Heparin sensitivity index as function of preoperative anticoagulation therapy. The box plots show the 10th, 25th, median, 75th and 90th percentiles for each group.

TABLE II Multivariable linear regression model of heparin sensitivity index

Factor	Beta estimate	95% Confidence interval	P value
Age	-0.01	-0.02 to -0.003	0.004
Platelet count	-0.002	-0.003 to -0.001	< 0.0001
Study group [LMWH]	-0.14	-0.22 to -0.05	0.002
Heparin dose/kg BW	-0.002	-0.004 to -0.0003	0.02
Weight	-0.004	-0.01 to 0.002	0.18
Baseline ACT	-0.002	-0.005 to 0.002	0.37

LMWH = low molecular weight heparin. BW = body weight; ACT = activated clotting time. Overall model $F < 0.0001$, $R^2 = 0.42$.

The incidence of a first post-heparin ACT < 480 sec was 19% in the Control group, 24% in the LMWH group and 38% in the Heparin group ($P = 0.09$). One patient received AT-III therapy and two received FFP transfusion to correct heparin resistance, all three belonged to the Heparin group.

Discussion

While confirming the previously documented effect of prolonged preoperative heparin infusion on subsequent impaired sensitivity to heparin, our results show that preoperative LMWH therapy has a similar effect.

Heparin resistance is common during cardiac surgery, with an overall incidence described between 5–30%.^{3,4,16,24} Unfortunately, no universally accepted definition exists for this condition, and various stud-

ies have employed varying definitions for the binary classification of heparin resistance, using different heparin doses and different ACT targets.^{4,14–16,25} We have chosen to use a continuous measure of heparin responsiveness, the HSI,^{11,24} controlling for baseline ACT, heparin dose used and body weight. Advantages of this approach include avoiding definitions using arbitrary target ACT level, accommodating varying practices of heparin dosing between different practitioners (e.g., different initial heparin dosage, different threshold for FFP transfusion), and allowing for the use of more robust statistical tests. For several reasons, quantifying heparin resistance requires measuring the response to heparin before commencing CPB. First, both hypothermia and hemodilution can increase the ACT and affect the rate of heparin metabolism.¹ Second, total heparin consumption on CPB obviously depends on the length of CPB. Third, the onset of CPB itself is known to decrease AT-III levels.²⁶ Therefore, the ACT response to heparin once CPB has commenced has little to do with heparin sensitivity per se. Indeed it was shown that consumption of heparin during CPB does not correlate with the initial heparin sensitivity.⁷

Several risk factors that can decrease heparin responsiveness have been identified in previous studies, among them preoperative use of IABP,⁴ active infection (sepsis or endocarditis),^{6,7} older age,^{25,27} and increased platelet count.^{25,28} We have excluded patients with endocarditis or preoperative IABP use, and have confirmed the significance of older age and increased platelet count (Table II). Heparin binds to many proteins in the blood, including platelet factor IV,²² as well as to activated or resting platelets themselves.²⁹ Therefore, increased platelet count might decrease the amount of free heparin available for binding AT-III. Similarly, levels of factor VIII and von-Willebrand factor tend to increase with age,³⁰ and both are associated with heparin resistance;²² this may explain the effect of older age.

We have also found that the heparin dose normalized to body weight is inversely related to heparin sensitivity. While this might reflect mathematical coupling as the heparin dose is used in the calculation of heparin sensitivity, another possible interpretation is that it reflects the non-linear response of ACT to heparin at higher heparin doses, as has been described previously.³¹

The most common and significant risk factor, however, is the use of heparin preoperatively where the incidence of reduced intraoperative heparin responsiveness was found to be between 40–50%.^{4,17,18} The pathogenesis of reduced heparin sensitivity in this

setting is at least partially related to decreased blood level of AT-III, an endogenous antithrombotic factor. Normally, AT-III binds reversibly to thrombin and factor Xa and inhibits their activity. The main pharmacological effect of heparin is to accelerate these reactions; the ratio between binding of AT-III to thrombin *vs* factor Xa is related to the size of the heparin molecule.^{21,22} During the process, thrombin-antithrombin complexes are formed, and AT-III undergoes proteolysis to an inactive protein by thrombin itself; this reaction is enhanced by all heparin molecules regardless of their molecular weight.³² Patients receiving preoperative heparin infusions demonstrate on average a 20–30% reduction in AT-III activity,^{9,12} and in patients demonstrating heparin resistance during cardiac surgery, 77–85% have subnormal AT-III levels.^{14,15} Not all cases of heparin resistance, however, are reversed by administration of AT-III, hinting that additional mechanisms may be operating as well.^{16,24}

Reduced heparin responsiveness in the setting of cardiac surgery is more than just a laboratory phenomenon. Both AT-III deficiency and heparin resistance are associated with increased activation of the coagulation system during cardiac surgery,^{8,10} possibly leading to both thrombotic complications as well as a consumption coagulopathy and increased bleeding. Indeed, a catastrophic clotting of the CPB circuit has been ascribed to heparin resistance.⁷

Study limitations

As all retrospective studies, the results of the current study depend heavily on the accuracy of the original documentation. We have attempted to minimize any possible inaccuracies by cross-validating data from pharmacy records, intraoperative anesthesia and surgical charts, and patients' medical record.

We have only included patients who received therapy (either heparin or LMWH) for at least 24 hr during the last seven days before surgery. Not much is known about the kinetics of development of, or recovery from heparin resistance. One study has found that AT-III levels start to decrease after 24 hr of heparin therapy, reach a nadir after about two to four days, and return to normal levels three to four days after stopping heparin.⁹ While no similar data exist regarding LMWH, its longer half-life will probably delay the recovery of AT-III levels. As shown in Table I, therapy in our patients was continued until the day of surgery in the Heparin group and until 1.6 ± 1.5 days before surgery in the LMWH group. We therefore believe that our selection criteria created an optimal timeframe to study the effect of preoperative therapy on intraoperative heparin response.

We did not measure AT-III levels in our patients, therefore we do not know if the reduced responsiveness to LMWH was indeed related to decreased AT-III levels. However, not all studies agree that preoperative heparin therapy decreases AT-III levels,³³ or that patients who develop heparin resistance after receiving preoperative heparin infusion have indeed lower AT-III levels compared to similar patients who do not develop heparin resistance.¹⁸ One might consider that the phenomenon of reduced heparin responsiveness exists and can be demonstrated regardless of the mechanism involved. Others, though, have suggested that the problem lies in the ACT test itself, and more accurate tests, like the high-dose thrombin time, do not show the phenomenon of heparin resistance in patients receiving preoperative heparin.³⁴ It was suggested, therefore, that the term "heparin responsiveness" be used instead of "heparin resistance",⁵ as was adopted in the current study.

The difference in heparin sensitivity between the Heparin and LMWH groups was small and not statistically significant – $0.1 \text{ sec} \cdot \text{IU}^{-1} \cdot \text{kg}^{-1}$. However, given an average initial heparin dose of $350 \text{ IU} \cdot \text{kg}^{-1}$, this translates to a 35-sec greater increase in ACT in the Heparin group compared with the LMWH group. This may explain why the incidence of a first ACT < 480 sec was lower in the LMWH group. However, due to the small difference in HSI ($1.2 \text{ vs } 1.1 \text{ sec} \cdot \text{IU}^{-1} \cdot \text{kg}^{-1}$ – about 9%) and the relatively small number of patients, our study was not powered to show a difference between the Heparin and LMWH groups.

To summarize, an increasing number of cardiac surgery procedures are performed on patients with acute coronary syndromes, and the incidence of patients coming to surgery after being treated with either unfractionated heparin or LMWH is increasing.¹⁴ We have shown in the current study that both therapies are associated with a reduced responsiveness to heparin given intraoperatively. Further studies should be directed towards understanding the mechanisms and clinical significance of this phenomenon in cardiac surgery patients.

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Clayoquot Sound and Meares Island - *Tofino, British Columbia*