Inhibition of Repetitive Thrombus Formation in the Stenosed Canine Coronary Artery by Enoxaparin, But Not by Unfractionated Heparin

Robert J. Leadley, Jr, Charles J. Kasiewski, Jeffrey S. Bostwick, Ross Bentley, Christopher T. Dunwiddie, Mark H. Perrone

Abstract—Experiments were designed to compare the antithrombotic efficacy of enoxaparin and unfractionated heparin (UH) in a model of platelet-dependent cyclic flow reductions (CFRs) in the stenosed canine circumflex coronary artery. Low-molecular-weight heparins (LMWHs) are safe and effective in the prevention and treatment of venous thromboembolism. The present experiments were designed to evaluate the potential use of LMWHs in arterial thrombotic indications by comparing the antithrombotic effect of an LMWH with that of UH in an animal model of unstable angina. After establishment of consistent CFRs by experimentally induced vascular stenosis and damage, vehicle (saline), enoxaparin, or UH was administered intravenously as a loading dose plus a continuous infusion for 1 hour. The inhibition of CFRs was taken as an indicator of antithrombotic efficacy. Enoxaparin inhibited repetitive platelet thrombus formation in a dose-dependent manner, with significant inhibition of CFRs achieved at 0.5 mg/kg for 1 hour. This dose of enoxaparin resulted in anti-Xa levels of 0.9 to 1.0 IU/mL, anti-IIa levels of 0.2 to 0.3 IU/mL, activated partial thromboplastin time (APTT) of 1.3-fold over baseline, and a 1.4-fold increase (NS) in template bleeding time. Near-complete abolishment of CFRs was achieved with enoxaparin at 1.0 mg/kg for 1 hour. This dose of enoxaparin produced anti-Xa levels of 2 to 2.2 IU/mL, anti-IIa levels of 0.5 to 0.6 IU/mL, an increase in APTT of 1.4- to 1.5-fold over baseline, and a 1.9-fold increase (P<0.05) in template bleeding time. In contrast, UH had no significant effect on CFRs at a dose (100 U/kg for 1 hour) that resulted in anti-Xa levels of 1.2 to 1.6 IU/mL, anti-IIa levels of 1.8 to 2.4 IU/mL, an increase in APTT greater than 10-fold over baseline, and a 2.5-fold increase (P<0.05) in template bleeding time. Compared with the vehicle group, circulating platelet count and hematocrit were not changed significantly by any dose of enoxaparin or UH tested. Enoxaparin, unlike UH, prevented repetitive platelet-dependent thrombus formation in the dog, thereby supporting the potential use of enoxaparin as a replacement for heparin in the treatment of arterial thrombotic disorders such as unstable angina. (Arterioscler Thromb Vasc Biol. 1998;18:908-914.)

Key Words: low-molecular-weight heparin | heparin | thrombosis | unstable angina | antithrombotics

Heparin has long been considered standard therapy for arterial thrombotic indications and has been proven to have a positive effect in the treatment of unstable angina and other coronary artery syndromes, particularly when administered along with aspirin. However, there are several limitations to the use and efficacy of heparin in treating coronary artery disease. The pharmacodynamic limitations include substantial plasma protein binding, neutralization by platelet factor 4, and an inconsistent level of anticoagulation requiring continuous monitoring and dose adjustment. Pharmacokinetically, heparin has limited bioavailability after nonintravenous administration. Consequently, heparin is usually given intravenously, thereby limiting its use to within the hospital. Heparin also has a relatively short half-life, requiring multiple subcutaneous or intravenous doses each day or a continuous intravenous infusion. Furthermore, complications of heparin treatment include bleeding diatheses and heparin-induced thrombocytopenia.

Depolymerization of heparin results in fractionated LMWHs that are not as prone to the limitations described above for UH. LMWHs have a number of pharmacodynamic and pharmacokinetic advantages over UH that would favor the use of LMWH instead of heparin for arterial indications. For example, LMWHs are more resistant than heparin to neutralization by platelet factor 4, which is released from activated platelets present at the site of arterial thrombus formation. In addition, reliable anticoagulation can be achieved with LMWHs by subcutaneous dosing without monitoring, thereby providing convenient antithrombotic therapy that can be easily maintained for a prolonged time.

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Compared with heparin, LMWHs have a high bioavailability after subcutaneous administration, a relatively long half-life, and appear to offer an improved safety profile.4,10

LMWHs have been used increasingly over the past few years, primarily for the prevention and treatment of venous thromboembolism.11 However, recent evidence indicates that LMWHs are safe and effective antithrombotic agents for arterial thrombotic diseases.2 For example, preclinical studies have demonstrated that LMWHs improve reflow after thrombolysis in canine models of thrombosis.12,13 Clinically, a small trial provided evidence to support the potential use of enoxaparin instead of heparin as adjunctive therapy during thrombolysis with streptokinase.14 In addition, prolonged treatment (35 to 45 days) with the LMWH dalteparin reduced the incidence of death or new myocardial infarction at 6 and 40 days in patients with unstable coronary artery disease.15 More recently, the ESSENCE trial (Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events) demonstrated that, compared with intravenous heparin, subcutaneous administration of enoxaparin significantly reduced the 14- and 30-day combined incidence of death, myocardial infarction, and recurrent angina in patients with non–Q-wave coronary events.16

A previous preclinical study examining the efficacy of heparin in a model of arterial stenosis and vascular damage demonstrated that thrombin may be an important mediator of platelet-dependent thrombus formation in this model, particularly within the first 30 minutes after establishment of repetitive thrombus formation.17 However, the antithrombotic effect of heparin was not demonstrated in 33% of the dogs in that study and was reversed over time in almost all of the dogs tested. In addition, heparin lost its antithrombotic effect when it was administered 3 hours after establishment of repetitive thrombus formation.18 Another study using the same model demonstrated that heparin (200 U/mL, IV bolus) abolished cyclic flow variations in only 2 of 13 dogs tested.18 The model used in that study and in the present study is characterized by vascular stenosis, vascular damage, and platelet-dependent repetitive thrombus formation, conditions that are believed to be present in patients with unstable angina.19 Considering the limited effect of heparin in this model and the potential advantages of LMWHs over UH described above, it is possible that LMWHs may be more effective than heparin in this experimental model of unstable angina.

Therefore, the purpose of this study was to compare the relative antithrombotic effects of UH and the LMWH enoxaparin in a well-established model of repetitive thrombus formation in the stenosed canine coronary artery.

**Methods**

All procedures in this study were performed in compliance with the Animal Welfare Act Regulations and with the Guide for the Care and Use of Laboratory Animals (DHEW publication No. NIH 85–23, 1985).

Mongrel dogs of either sex (15 to 21 kg) were anesthetized with sodium pentobarbital (30 mg/kg IV, with supplements given as needed), intubated, and ventilated using a Harvard respirator (Harvard Apparatus). A trilumen catheter (SAFEDWELLplus, Becton Dickinson) was placed in the right femoral vein for the administration of test agents and supplemental anesthesia. The right femoral artery was cannulated for measurement of arterial blood pressure and for obtaining blood samples.

A left thoracotomy was performed at the fifth intercostal space and the heart was suspended in a pericardial cradle. The left circumflex coronary artery was isolated and dissected for a distance of 2 cm, ligating side branches when necessary. An electromagnetic flow probe (Carolina Medical Electronics, 501D) was placed on the vessel to monitor coronary blood flow, and a snare ligature was placed on the distal portion of the vessel to produce a temporary mechanical occlusion, which was used to adjust the degree of stenosis and to aid in validating zero-flow measurements.

Distal to the flow probe, a Lexan occluder was positioned for the purpose of creating a critical stenosis, which was confirmed by abolishment of the hyperemic response to a 10-second mechanical occlusion of the vessel. The endothelial and vascular smooth muscle cells were damaged by compressing the vessel with a vascular clamp. These conditions result in platelet adhesion and aggregation at the damaged area, thus producing a gradual decrease in coronary blood flow. When flow reached zero, the occluder was moved back and forth over the damaged area to mechanically dislodge the platelet-rich thrombus, thus restoring blood flow. This repetitive pattern of decreasing blood flow that is restored by mechanical disruption of the platelet thrombus is referred to as CFR. The antithrombotic effect of the test agents was quantified by comparing the number of CFRs that occurred during a 20-minute control period with the number of CFRs per 20 minutes for three consecutive 20-minute periods after drug administration. A significant reduction in the number of CFRs was taken to represent an antithrombotic effect.

Throughout the protocol, continuous recordings of lead II ECG, arterial pressure, heart rate, and mean and phasic coronary artery blood flow were obtained by using Gould signal conditioners and recorders (6600 series, Gould Instrument Systems) connected to a computerized data recording system (DataFlow, Crystal Biotech).

**Experimental Treatments**

Thirty dogs were assigned to one of six treatment groups: (1) vehicle (saline), (2) enoxaparin at 0.5 mg/kg + 5 μg/kg per minute, (3) enoxaparin at 0.6 mg/kg + 6 μg/kg per minute, (4) enoxaparin at 1 mg/kg + 10 μg/kg per minute, (5) heparin at 60 U/kg + 0.7 U/kg per minute, and (6) heparin at 100 U/kg + 1 U/kg per minute. All compounds were diluted in saline, bolus injections were made using a volume of 5 mL, and constant infusions were administered for 1 hour using a volume of 22 mL. After a 20-minute control period of reproducible CFRs, agents were administered as bolus intravenous injections followed immediately by a continuous infusion for 60 minutes. Enoxaparin was prepared at Rhône-Poulenc Rorer, and heparin was obtained from Elkins-Sinn, Inc.

**Platelet Aggregation**

Blood samples were collected during the control period and at 5, 10, 30, and 60 minutes after initiation of drug administration. The samples were obtained via the femoral arteries within the femoral artery catheter and drawn into plastic syringes containing trisodium citrate (1 mL 3.8% sodium citrate to 9 mL of blood). Platelet-rich plasma was prepared by centrifugation of the whole blood at 150g for 10 minutes. After removal of the supernatant containing platelet-rich plasma, platelet-poor plasma was prepared by centrifugation of the remaining sample at 1000g for 10 minutes. Platelet count was determined with a Coulter ZM or Coulter ZBI particle counter (Coulter Instruments). When necessary, platelet count was adjusted to 3 × 10^10 platelets per milliliter using autologous platelet-poor plasma. Platelet-rich plasma (250 μL) was incubated at 37°C while being stirred at 1200 rpm.

**Selected Abbreviations and Acronyms**

- APTT = activated partial thromboplastin time
- CFR = cyclic flow reduction
- LMWH = low-molecular-weight heparin
- PT = prothrombin time
- UH = unfractionated heparin
After preincubation with epinephrine for 1 minute (1 μmol/L, Chrono-par 393, Chrono-log Corp), platelet aggregation was induced by thrombin (4 U/mL, Enzyme Research Institute; plus Gly-Pro-Arg-Pro, a fibrin polymerization inhibitor, 2 mmol/L, Sigma Chemical Company), ADP (10 μmol/L, Chrono-par 384, Chrono-log Corp), collagen (equine tendon, 10 μg/mL, Chrono-par 385, Chrono-log Corp), or arachidonic acid (1 mmol/L, Biodata Corp). Platelet aggregation was monitored spectrophotometrically with a PAP-4C platelet aggregometer (Bio Data Corp). Results are expressed as the percent inhibition of the rate of aggregation compared with the predrug aggregation response.

Coagulation Time and Template Bleeding Time
Platelet-poor plasma was used for determination of APTT and PT, which were measured using a Microsample Coagulation Analyzer (MCA210, Bio Data Corp) and Dade reagents (Thromboplastin-C Plus and Actin FS Activated PTT reagent, Baxter Diagnostics, Inc).

Template bleeding time measurements were obtained at the same time points as for the blood samples, as mentioned previously. Template bleeding time measurements were made after a uniform incision was made on the mucous membrane of the inner upper lip with a Surgicutt automated incision device (ITC). Blood was blotted with Surgicutt bleeding time blotting paper every 30 seconds, with care taken not to disturb the incision site. Template bleeding time was measured from the moment of the incision until the blood no longer stained the blotting paper. Bleeding times of 10 minutes were taken to be maximal.

Anti-Xa and Anti-IIa Activity
Additional blood samples (4.5 mL) were collected in chilled syringes containing 0.5 mL trisodium citrate for analysis of anti-Xa and anti-IIa activity. These samples were centrifuged at 1500g for 10 minutes at 4°C. The plasma was removed and stored at −70°C until assayed. Anti-Xa and anti-IIa activity were analyzed by chromogenic methods using kits supplied by American Diagnostica (Actichrome Heparin and Actichrome Heparin Anti-IIa). Optical density measurements (405 nm) were made using a SPECTRAmax microtiter plate spectrophotometer and Softmax Pro software (Molecular Devices Corp). The 1st International LMWH Standard and the 4th International Standard for Unfractionated Heparin (National Institute for Biological Standards and Control, London) were used to construct standard curves for measuring the ex vivo activity of enoxaparin and heparin (respectively). The curves were constructed using a four-parameter curve-fitting model (Softmax Pro, Molecular Devices). Values for anti-Xa and anti-IIa activity of heparin and enoxaparin are reported in international units.

Statistics
Data were analyzed by two-way repeated-measures analysis of variance. Posthoc multiple comparisons of means to control values within treatment groups were performed using the least significant difference test. A value of $P < 0.05$ was considered significant.

Results
Figure 1 shows a representative tracing from two experiments in which enoxaparin or heparin was administered to separate dogs. CFRs were not altered by heparin (100 U/kg + 1 U/kg per minute) but were completely abolished by enoxaparin. Enoxaparin dose dependently inhibited CFRs in the stenosed canine coronary artery (Figure 2). Significant inhibition was achieved at the lowest dose of enoxaparin tested, 0.5 mg/kg + 5 μg/kg per minute, which resulted in a decrease in CFRs from 5.5±0.3 during the control period to approximately 3 per 20 minutes during enoxaparin administration. The highest dose of enoxaparin tested (1.0 mg/kg + 10 μg/kg per minute) resulted in near-complete inhibition of CFRs; the number of CFRs was reduced from 4.3±0.2 during the control period to 0.8±0.8 during enoxaparin administration. Although both doses of heparin tended to decrease CFRs, this effect was modest and not significant.

Both enoxaparin and heparin produced dose-dependent increases in APTT (Figure 3) and PT. During enoxaparin administration, the maximal increases in APTT and PT were 1.5±0.1-
fold and 1.1±0.1-fold greater than baseline, respectively. The low dose of heparin (60 U/kg + 0.7 U/kg per minute) increased APTT and PT by 2.3±0.2-fold and 1.1±0.1-fold over baseline, respectively. The high dose of heparin (100 U/kg + 1.0 U/kg per minute) produced a >10-fold increase in APTT and a maximal 1.3±0.1-fold increase in PT.

Enoxaparin administration produced stable anti-Xa levels that ranged from 0.9±0.1 IU/mL at the lowest dose to 2.2±0.3 IU/mL at the highest dose tested; anti-IIa levels ranged from 0.3±0.1 to 0.6±0.1 IU/mL at these doses (Figure 4). The low dose of heparin resulted in anti-Xa and anti-IIa levels of 0.9±0.2 and 0.6±0.1 IU/mL, respectively. The high dose of heparin, targeted to provide anti-Xa levels comparable to that achieved with the higher doses of enoxaparin, resulted in anti-Xa and anti-IIa levels of approximately 1.5 and 2 IU/mL, respectively.

Template bleeding times were increased significantly by both doses of heparin and by the two higher doses of enoxaparin (Figure 5). However, the maximal increases in template bleeding time achieved with heparin and enoxaparin were only 2.5-fold and 1.9-fold over baseline, respectively. Enoxaparin and heparin significantly inhibited ex vivo thrombin-induced platelet aggregation (Table). The low dose of enoxaparin inhibited platelet aggregation by 20% to 54% and the middle dose of enoxaparin inhibited platelet aggregation by 69% to 85%. The high dose of enoxaparin and both doses of heparin inhibited platelet aggregation by 85% to 91%. Platelet aggregation induced by ADP, collagen, or arachidonic acid was not inhibited by enoxaparin or heparin at the doses tested (data not shown).

There were no significant changes in mean arterial blood pressure in any treatment group over the course of the experiment. Heart rate decreased modestly (6 to 11 beats per minute) in all groups, but these changes were not significantly different than in the vehicle group, in which heart rate decreased approximately 9 beats per minute over the course of the experiment.

Figure 2. Effect of enoxaparin and heparin on CFRs in the stenosed canine circumflex coronary artery. CFRs were quantified by counting the number of times blood flow decreased to 0 mL/min during four consecutive 20-minute periods (a 20-minute control period and three 20-minute treatment periods; n=5 per treatment group). *P<0.05 vs control.

Figure 3. Effect of enoxaparin and heparin on APTT. Data are presented as fold-changes from control samples (0'). Mean control APTTs ranged from 10.3 to 12.6 seconds (n=5 per treatment group). *P<0.05 vs control.
Discussion

These experiments have demonstrated that enoxaparin dose dependently inhibits repetitive thrombus formation in the stenosed canine coronary artery. UH, however, did not inhibit repetitive thrombus formation in this model at doses that produced comparable anti-Xa and anti-IIa plasma levels to those achieved with enoxaparin.

The ability of heparin to prevent repetitive platelet-dependent thrombus formation in this model has not been consistently demonstrated. However, several studies suggested that heparin has a positive, although unimpressive, antithrombotic effect in this model. In a study by Eidt et al, heparin administration 30 minutes after the establishment of CFRs abolished CFRs in only 12 of 18 dogs. Furthermore, in 6 of the 12 dogs monitored for 4 hours, CFRs returned approximately 3 hours later, despite continuous heparin treatment. Also, when heparin was administered 3 hours after establishment of CFRs, it did not inhibit CFRs. In the current study, enoxaparin or heparin was administered 20 minutes after establishing consistent CFRs, and plasma levels of heparin and enoxaparin were maintained by continuous infusion for 1 hour. Another potential difference between the present study and other studies is the difference in the degree of vascular stenosis and damage. For example, Eidt et al used a stimulus (stenosis and damage) for platelet adhesion and aggregation that was relatively mild and allowed for the spontaneous dislodgment of platelet aggregates. Likewise, a similar study using this approach found that heparin significantly attenuated CFRs by approximately 50% but completely abolished CFRs in only 2 of 13 dogs tested. Under the experimental conditions used in those studies (ie, spontaneous restoration of flow), CFRs can be eliminated more readily than in the current implementation of the model, which incorporates greater vascular damage and a consistent pattern of CFRs in the control period. This difference may explain the discrepancy between the relatively positive effect of heparin in those studies compared with the lack of effect of heparin in the present study. In the current study, in which consistent CFRs were maintained by mechanical dislodgment of the occlusive thrombus, there was no significant effect of heparin on CFRs at either the low dose or the high dose. Although the clinical relevance of the different degrees of vascular stenosis and
damage is debatable, the present results indicate that even supratherapeutic doses of heparin do not prevent repetitive thrombus formation in this model when a reproducible pattern of CFRs is produced by vascular stenosis and a relatively high degree of vascular damage.

In contrast, enoxaparin dose dependently inhibited repetitive thrombus formation in this model at doses that are therapeutically relevant. Clinically, enoxaparin has been shown to be safe and effective when plasma anti-Xa levels of up to at least 0.9 U/mL are achieved. In the present study, significant inhibition of CFRs was achieved at a dose of enoxaparin that resulted in anti-Xa levels of 0.9 IU/mL and no significant increase in template bleeding time, demonstrating the effectiveness of enoxaparin at relatively low, and presumably safe, doses. Higher doses of enoxaparin were able to completely abolish CFRs in the present study without substantially prolonging template bleeding time (less than a twofold increase from baseline). It should be noted, however, that a recent clinical dose-ranging trial of enoxaparin for unstable angina indicated that when peak anti-Xa levels approached 2 IU/mL, the incidence of major hemorrhage increased. The high dose used in the current study (1 mg/kg + 10 µg/kg per minute) produced anti-Xa levels of approximately 2 IU/mL, suggesting that this dose may represent the maximum tolerable dose of enoxaparin in humans. However, the significant antithrombotic effect of the lower doses in the present study is achieved at anti-Xa levels (0.9 to 1.4 IU/mL) that fall within the tolerable range for humans.

Unfortunately, none of the individual parameters measured in the present study can provide an adequate explanation for the greater efficacy of enoxaparin compared with heparin in this model. Similar levels of anti-Xa and anti-IIa were achieved for both agents at the various doses, and yet enoxaparin inhibited CFRs but heparin did not. Likewise, both agents inhibited thrombin-induced platelet aggregation to a similar extent at various doses. In addition, APTT and PT were markedly higher during high-dose heparin treatment than during any dose of enoxaparin. All of these data suggest that both agents were systemically available and that other unique actions of enoxaparin were responsible for its antithrombotic efficacy in this model.

Many possible mechanisms may have contributed to the greater antithrombotic effect of enoxaparin compared with heparin in this model. First, enoxaparin, compared with heparin, is relatively resistant to the neutralizing effects of platelet factor 4, especially for anti-Xa activity. Platelet factor 4 is released from platelets in conditions that favor platelet activation (high shear stress and vascular endothelial damage), such as those present in the model used for these experiments, and thus may play an important role in vivo by neutralizing heparin locally. Second, heparin has been shown to be a more potent stimulator of platelet aggregation in vitro than enoxaparin. Therefore, the inhibition of thrombus formation by heparin may be counteracted by heparin’s platelet-activating action. Third, a preliminary report suggests that enoxaparin may interfere with P-selectin-mediated cell adhesion to a greater degree than heparin.

**Effect of Enoxaparin and Heparin on Thrombin-Induced Platelet Aggregation**

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<th>30 Minutes (%)</th>
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<td>60 U/kg + 0.7 U/kg/min</td>
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Data presented are mean±SEM. Enoxaparin or heparin were administered as intravenous loading doses plus constant infusions for 1 hour. Ex vivo platelet aggregation was determined spectrophotometrically after addition of α-thrombin to platelet-rich plasma (4 U/mL, thrombin with 2 mmol/L Gly-Pro-Arg-Pro). Data are presented as the percent inhibition of the rate of change of light transmission compared with control samples obtained prior to drug administration.

*P<0.05 vs control period.

**Figure 5.** Effect of enoxaparin and heparin on template bleeding time. Data are presented as fold-changes from control samples (0'). Mean control template bleeding times ranged from 73 to 101 seconds (n=5 per treatment group). *P<0.05 vs control.
P-selectin is expressed on activated platelets and endothelial cells and plays a role in heterotypic cell adhesion. Inhibition of P-selectin in this model may prevent the formation of an occlusive thrombus. Fourth, as the most potent physiological agonist of platelet activation, thrombin formed at the damaged site may be important in thrombus formation, as evidenced by the positive antithrombotic effect of direct thrombin inhibitors in models similar to that used in the present study. Consequently, inhibition of thrombin or the production of thrombin may play an important role in the antithrombotic effect of enoxaparin in this study. Recent data suggest that enoxaparin inhibits coagulation factor VIIa generation in vitro to a greater extent than does heparin. The vascular damage and the presumed release of tissue factor would result in the local activation of factor VIIa–tissue factor pathway of coagulation. Consequently, relatively greater inhibition of this pathway by enoxaparin would provide an additional advantage over heparin. Further studies will be required to determine the exact mechanisms that endow enoxaparin with greater antithrombotic efficacy than heparin in this model.

In summary, enoxaparin significantly inhibited repetitive thrombus formation in the stenosed canine coronary artery at doses considered clinically safe and effective. On the other hand, supratherapeutic doses of heparin were unable to inhibit CFRs in this model. The antithrombotic efficacy of enoxaparin was demonstrated clinically in the recent ESSENCE trial, in which enoxaparin was shown to be superior to heparin in the treatment of unstable angina. Taken together, these data are consistent with the notion that enoxaparin has features, some of which have yet to be identified, that make it an appropriate replacement for UH in the treatment of coronary artery disease.

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References


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