Use of A Direct Antithrombin, Hirulog, in Place of Heparin During Coronary Angioplasty

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Background. Since the inception of coronary angioplasty, heparin with or without aspirin has been routinely given intraprocedurally to avoid coronary thrombotic complications. Recently, the direct thrombin inhibitor hirulog has been demonstrated to inactivate clot-bound thrombin. The present study was a multicenter dose escalation of hirulog to determine its appropriate dose and feasibility as the sole anticoagulant during coronary angioplasty.

Methods and Results. At 11 participating centers, 291 patients undergoing elective coronary angioplasty and pretreated with 325 mg aspirin daily were enrolled in sequential groups of intravenously administered hirulog instead of heparin as follows: group 1: bolus, 0.15 mg/kg; infusion, 0.6 mg·kg⁻¹·hr⁻¹ (54 patients); group 2: bolus, 0.25 mg/kg; infusion, 1.0 mg·kg⁻¹·hr⁻¹ (53 patients); group 3: bolus, 0.35 mg/kg; infusion, 1.4 mg·kg⁻¹·hr⁻¹ (44 patients); group 4: bolus, 0.45 mg/kg; infusion, 1.8 mg·kg⁻¹·hr⁻¹ (74 patients); and group 5: bolus, 0.55 mg/kg; infusion, 2.2 mg·kg⁻¹·hr⁻¹ (54 patients). The hirulog infusion was maintained for 4 hours; the primary end point was abrupt vessel closure within 24 hours of the initiation of the procedure. Activated clotting times (ACT) and activated partial thromboplastin times (aPTT) were serially monitored. Abrupt vessel closure occurred in 18 patients (6.2%). By intention to treat, the abrupt closure event rate for groups 1–3 was 11.3% compared with 3.9% in groups 4 and 5 (p = 0.052). There were no significant bleeding complications except for one patient in group 1, who received a two-unit transfusion. A dose–response curve of both ACTs and aPTTs was noted; no coronary thrombotic closures occurred in the small number of patients with ACT >300 seconds.

Conclusions. The present study documents for the first time that it is possible to perform coronary angioplasty with an anticoagulant other than heparin in aspirin-pretreated patients. Hirulog was associated with a rapid onset, dose-dependent anticoagulant effect, minimal bleeding complications, and at doses of 1.8–2.2 mg/kg, a rate of 3.9% for abrupt vessel closure. (Circulation 1993;87:1622–1629)

Key Words • anticoagulation • angioplasty • thrombin • coronary artery disease

Heparin has been used in coronary angioplasty procedures since this nonsurgical revascularization technique was first introduced in 1977.¹ Intraprocedural use of anticoagulation was empirically deemed necessary because of the direct introduction of thrombogenic wire and catheter equipment into the diseased coronary artery as well as the local activation of coagulation factors and platelets as a consequence of balloon dilatation, plaque compression, and subintimal exposure. Despite the conventional use of intravenous heparin during coronary angioplasty, there is a 6–8% reported rate of abrupt vessel closure²–⁴ occurring either intraprocedurally or within 24 hours of balloon dilatation, which accounts for most of the initial mortality, emergency coronary bypass surgery, and morbidity of the procedure.⁵ At least half of these acute closure events are due to coronary artery thrombosis, whereas many may be related to vessel wall laceration or to a combination of both factors.² Recent retrospective analyses indicate that the rate of thrombotic closure may be diminished by higher doses of heparin with intraprocedural monitoring of its anticoagulant effect.⁶,⁷

The major theoretical limitations of heparin are that it cannot inactivate clot-bound thrombin, which proteolytically activates platelets and cleaves fibrinogen, relies on the presence of anti-thrombin III at adequate levels, and is neutralized by components of the platelet release reaction such as platelet factor 4 and heparinase. This results in considerably reduced efficacy of heparin in inhibiting thrombin-induced cyclic flow alterations caused by platelet aggregation and dislodgment.
at sites of endothelial injury and coronary artery stenosis in experimental models. Each of these limitations is potentially overcome by a novel synthetic, bivalent, direct thrombin inhibitor known as hirulog. These peptides were designed from hirudin, the most potent natural and specific inhibitor of thrombin. In the present multicenter dose escalation study, our objective was to determine the appropriate dose and feasibility of using hirulog as the sole anticoagulant during coronary angioplasty.

**Methods**

**Patient Population**

Patients undergoing coronary angioplasty procedures were considered for inclusion into the study if they were between ages 18 and 76 years, had a ≥ 70% stenosis, had normal baseline hematologic laboratory values, including a normal activated partial thromboplastin time (aPTT), and no history of systemic, gastrointestinal, or intracerebral hemorrhage or stroke. Patients provided informed consent, and the protocol was approved by the institutional review boards at all 11 participating sites. Patients were enrolled between February 26, 1991, and May 15, 1992.

**Pharmacological Protocol**

Hirulog (BG8967), a 20–amino acid peptide with the chemical structure of \([\alpha\text{-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu}]\), was supplied by Biogen (Cambridge, Mass.) as 25-mg vials. On a daily basis for a week before angioplasty and at a minimum of 24 hours before the angioplasty procedure, patients received 325 mg aspirin. The procedure was performed transfemorally using standard angioplasty access sheaths, guides, wire, guiding catheters, and balloon dilatation catheters. An intravenous bolus of hirulog was given as soon as the guiding catheter was coaxially engaged with the target coronary artery before balloon dilatation. An infusion of hirulog was initiated immediately after the bolus and was continued for a total of 4 hours. For each dose level, the bolus was 25% of the continuous infusion hourly dose. The infusion could be maintained at 0.2 mg·kg⁻¹·h⁻¹ for an additional 20 hours (maximum total infusion duration, 24 hours) if there was angiographic evidence of intraluminal thrombus, haziness, dissection, or clinical signs of ischemia that had occurred in the periprocedural phase. No heparin was administered unless the patient developed abrupt vessel closure or had completed the 4-hour continuous infusion and the investigator chose heparin rather than hirulog because of either angiographic or clinical instability. Thrombolytic therapy was not given unless abrupt vessel closure or new, partially occlusive intraluminal thrombus occurred during the procedure.

The protocol plan consisted of sequential enrollment of approximately 50 patients at each of five dosing regimens as follows: group 1: intravenous bolus of 0.15 mg/kg, infusion of 0.6 mg·kg⁻¹·h⁻¹; group 2: 0.25 mg/kg bolus, 1.0 mg·kg⁻¹·h⁻¹ infusion; group 3: 0.35 mg/kg bolus, 1.4 mg·kg⁻¹·h⁻¹ infusion; group 4: 0.45 mg/kg bolus, 1.8 mg·kg⁻¹·h⁻¹ infusion; and group 5: 0.55 mg/kg bolus, 2.2 mg·kg⁻¹·h⁻¹ infusion.

Prospectively, a dose level was considered ineffective if thrombotic abrupt vessel closure occurred at a frequency of two in 25 patients or three in 50 patients. Abrupt vessel closure was defined as cessation of flow as defined by angiography during the procedure or within 24 hours after the angioplasty procedure, lasting more than 10 minutes, not relieved by intravenous, intracoronary, or sublingual nitroglycerin, and associated with ischemic pain and ECG changes. Abrupt closure was accompanied by myocardial infarction if the postprocedural total serum creatine kinase was more than twice upper limits of the normal laboratory standard and myocardial band isoenzyme absolute values exceeded normal parameters. Abrupt closure was deemed related to thrombosis if filling defects suggestive of intraluminal clot were discernible by coronary angiography. Auto-perfusion balloon angioplasty, stents (whenever available), or emergency coronary bypass surgery were used as necessary to treat abrupt closure events.

**Monitoring of Anticoagulation Status**

Coagulation variables, including aPTTs and activated clotting times (ACT), were measured serially beginning before angioplasty, 10 minutes after the hirulog bolus was administered, at least every 30 minutes during the procedure, and at least once after the procedure but before termination of the 4-hour hirulog infusion. Both bedside unit and central laboratory values were obtained whenever possible. aPTTs were measured in the cardiac catheterization laboratory and at the patient’s bedside using whole blood droplets with the CIBA-Corning 512 Monitor (CIBA-Corning, Obertlin, Ohio) and in the central laboratory on citrated blood specimens using an MLA (Medical Laboratory Automation, Inc.) 750 or 1000 coagulation instrument with CaCl₂ and Dade actin (American Dade, Miami, Fla.) or platelet factor III (Organon Teknika, Oklahoma City, Okla.) aPTT reagents. ACTs were determined in the catheterization laboratory using the Hemochron (International Technidyne Corporation, Edison, N.J.). The Hemochron unit uses 2 mL of whole blood placed in a test tube containing 12 mg of celite and a cylindrical bar magnet. The test tube was vigorously shaken 10 times and was placed in the instrument’s incubated test well, which has a magnet detector at its base. The temperature was maintained at 37°C by the incubator. The timer was activated by an audible tone when a fibrin mass formed, causing the magnet to rotate with the tube; the digital readouts were in seconds and were recorded. Because of the variability of sources of measurement at the 11 participating sites and different methods at individual sites (bedside versus central laboratory), the maximum value during the 4-hour infusion (however it was measured) was used for the analysis. aPTT ratios were calculated using the patient’s baseline value as the control. For adverse events, the aPTT or ACT value that was measured at the time of the event or the one most closely approximating the time of the event was used.

**Bleeding Complications**

Hemoglobin was measured at baseline, 24 hours after the procedure, and serially with any bleeding event or noticeable decline (>2 g/dL) in hemoglobin. Bleeding events were recorded by the investigators as mild, moderate, or severe and classified into seven types or sites (groin, gastrointestinal, gingival or oral cavity,
nasal, retroperitoneal, urinary tract, menstrual). Mild bleeding was defined as <250 mL observed blood loss and ≤1 g/dL decline in hemoglobin; moderate bleeding signified >250 mL observed blood loss and >2 g/dL fall in hemoglobin; severe bleeding was defined as requiring transfusion, resulting in hemodynamic instability, or intracranial hemorrhage.

**Pharmacokinetics**

For determination of plasma levels of hirulog, blood samples were drawn at baseline, when the angioplasty was complete, at the end of dosing, 2 hours after the end of dosing, and at 24 hours. Because the duration of angioplasty varied from patient to patient, for purposes of analysis, hirulog serum level data have been grouped at the median duration at 0.5 hours. Hirulog was quantitated by an inhibitory enzyme immunoassay that detects the peptide via its ability to inhibit the binding of a highly specific murine antihirulog antibody. A minimum of three individual values were used to calculate the mean concentration of hirulog for each sample; the assay was sensitive to hirulog concentrations as low as 66 ng/mL.

**Data Quality Assurance and Analysis**

Data were entered in case report forms and subsequently verified with source medical records, including the cardiac catheterization reports, by study monitors.

Data are expressed as mean±1 SD unless otherwise stipulated. Data for aPTTs and ACTs were expressed as medians and means, and the results are shown in box-and-whisker plots. The rate of abrupt vessel closure was compared by grouping the lower-dose groups (1–3) and the higher-dose groups (4 and 5) using a two-sided Fisher's exact test. The probability values were based on the Mantel-Haenszel test, which takes into account differences between centers. The analysis of abrupt closure events was based on intention to treat with angioplasty and hirulog as well as evaluable patients in whom an angioplasty was performed and the dose of study drug was administered.

**Results**

**Baseline Characteristics**

A total of 291 patients, of whom 279 were dosed with hirulog, were enrolled into the study. The angioplasty procedure was not performed in 12 patients (4%) and was unsuccessful without complication in 21 patients (7%). The baseline features for the five groups of patients were similar (Table 1). There were no important differences in features associated with procedural risk including age, sex, prior myocardial infarction, unstable angina defined as rest ischemic pain, prior bypass surgery or angioplasty, diabetes mellitus, multivessel coronary disease, or multivessel angioplasty performed during the index study drug administration.

**Anticoagulant Effects**

aPTT ratios of maximum values to baseline values during the 4-hour infusion are shown in Figure 1. These data indicate a gradual increase in aPTT median values with increasing doses of hirulog. Similarly, in Figure 2, ACT data are plotted and demonstrate increased anticoagulant effects with higher doses. The plasma hirulog data are shown in Figure 3 for dose groups 2–5; plasma samples for dose group 1 were not collected.

**Abrupt Vessel Closure and Clinical Events**

Abrupt closure occurred in 18 patients (6.2%). The event was accompanied by myocardial infarction in six patients (2.0%) and death in one patient (0.3%). Management included medical therapy in nine patients, repeat angioplasty in six patients, emergency bypass surgery in two patients, and stenting in one patient. The patients with abrupt vessel closure are presented in Table 2 by dose group, clinical event, angiographic diagnosis, time of closure relative to initiation of hirulog, aPTT and ACT values at the time of the event, and whether the patient had received the optional extended 20-hour hirulog infusion. There was no statistically significant threshold value of ACT or aPTT that was associated with avoidance of abrupt closure. However, the ACTs were >300 seconds in only three of the 12 patients who experienced abrupt closure in whom this

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of Patients by Hirulog Dose Group</th>
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</thead>
<tbody>
<tr>
<td><strong>Hirulog dose</strong></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
</tr>
<tr>
<td>Sex (% men)</td>
</tr>
<tr>
<td>Target vessel (%)</td>
</tr>
<tr>
<td>Left anterior descending</td>
</tr>
<tr>
<td>Right coronary artery</td>
</tr>
<tr>
<td>Left circumflex</td>
</tr>
<tr>
<td>Saphenous vein graft</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Unstable angina</td>
</tr>
<tr>
<td>Prior CABG or PTCA</td>
</tr>
<tr>
<td>Multivessel PTCA</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass surgery; PTCA, percutaneous transluminal coronary angioplasty.
FIGURE 1. Box-and-whisker plot of activated partial thromboplastin time (APTT) ratios for the five dose groups. In each box, the horizontal line corresponds to the median, the top of the box represents the 75th percentile, and the bottom indicates the 25th percentile. The top and bottom of the vertical lines represent the 10th and 90th percentiles, respectively.

A laboratory variable was assessed; none of these three patients had primarily thrombotic occlusions. There were two deaths in the study. Both occurred in the 1.0 mg·kg⁻¹·hr⁻¹ dose group (group 2). One patient did not have a successful angioplasty because the guide wire could not be passed across the stenosis, which was totally occluded. Hirulog was discontinued 1.25 hours later, and the patient was maintained on heparin. On the following morning, the patient suffered a myocardial infarction, later developed bradycardia and asystole, and died. The other death occurred after a two-vessel angioplasty procedure complicated by thrombus in one vessel and dissection in the other. The patient developed a myocardial infarction, ventricular tachyarrhythmias, and died 1 hour after discontinuation of the study drug. This death was attributed to an abrupt vessel closure.

In Table 3, the results of abrupt vessel closure are compared for the different dose groups. By intention to treat, the events for dose groups 1–3 were 11.3% compared with 3.9% for groups 4 and 5 (p=0.052). By analyzing only patients who actually underwent balloon dilatation, the rate of abrupt closure for low-dose compared with high-dose hirulog was 10.2% and 3.3%, respectively (p=0.032).

Bleeding Events

Only one patient enrolled in the first dose group (0.6 mg·kg⁻¹·hr⁻¹) received a transfusion of two units of packed red blood cells in the study. A fall of hemoglobin of ≥2 g/dL occurred at the following rates per dose group: group 1, 25%; group 2, 25%; group 3, 37%; group 4, 17%; and group 5, 18%. Periaccess site bleeding of more than 250 mL not accompanied by transfusion was noted in two patients, one each in groups 3 and 4. Mild bleeding from the oral or nasal cavity occurred in six patients. No patient had a severe, life-threatening, or intracranial bleeding event. Although there were few events and these were of minimal severity, there was no relation apparent between dose of hirulog and bleeding events.

Discussion

Our findings indicate that intravenous hirulog may be useful as sole anticoagulant therapy during coronary angioplasty and that at doses of 1.8–2.2 mg·kg⁻¹·hr⁻¹ abrupt vessel closure occurred in <4% of patients. Furthermore, there was a rapid, dose-dependent increase in anticoagulation variables. Of note, this synthetic antithrombin peptide was not associated with significant side effects or serious bleeding complications; only one patient required transfusion. This is the first report of coronary angioplasty performed without the use of heparin, and it suggests at the very least that this anticoagulant agent warrants further development for periprocedural inhibition of arterial thrombosis.

The significant dose response for hirulog, with the absence of coronary artery thrombosis at the optimized dose, provides the first direct clinical evidence that thrombin is a major factor in the arterial thrombotic
process associated with angioplasty in humans. This evidence is supported by thrombin's potent, catalytic action toward platelets by data from experimental models. Accordingly, at least in association with arterial injury caused by balloon angioplasty, the arterial thrombotic process can be described in two steps: first, generation of thrombin resulting in platelet activation and second, platelet recruitment via exposure of fibrinogen receptors on the platelet surface. Primary antithrombotic therapy with direct thrombin inhibitors may be sufficient to attenuate arterial thrombosis.

Previous Studies With Coronary Angioplasty

Until recently, intraprocedural monitoring of anticoagulation status was not routinely performed in most clinical laboratories. Prior studies during coronary bypass surgery suggested that with an ACT of <300 seconds, microemboli formed in the cardiopulmonary bypass machine. The availability of portable ACT and aPTT machines facilitated the measurement of these variables during angioplasty. Ogilby and associates found that 11% of patients had ACTs <300 seconds if the standard heparin dosing regimen of a 10,000-unit bolus was used. Gabliani and colleagues pointed out that 73% of the abrupt vessel closures at their institution were associated with inadequate anticoagulation using the criteria of ACT <300 seconds. In a study by McGarry et al of intravenous heparin during coronary angioplasty, patients with aPTTs less than three times control values had a four- to fivefold increased risk of abrupt vessel closure compared with patients with higher aPTT values. Using ACT values during angioplasty, Dougherty and associates showed an important relation between ACT values <250 seconds and the major in-hospital events of death and emergency bypass surgery. Using thrombin-anti-thrombin III complex measurements during angioplasty, Gulba and coinvestigators showed that two thirds of patients had no suppression of thrombin generation despite administration of intravenous heparin.

Intravenous heparin during and after angioplasty has been associated with excess bleeding events. In a randomized trial of anticoagulation after coronary angioplasty, a 12-24-hour prolonged intravenous heparin infusion compared with no further heparin was associated with higher bleeding complications and no clinical ben-
TABLE 2. Characterization of Abrupt Vessel Closure Events in Individual Patients

<table>
<thead>
<tr>
<th>Dose (mg · kg⁻¹ · hr⁻¹)</th>
<th>Event</th>
<th>Diagnosis</th>
<th>At time of event</th>
<th>Prolonged infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>aPTT (seconds)</td>
<td>ACT (seconds)</td>
</tr>
<tr>
<td>0.6</td>
<td>Non-Q MI</td>
<td>Thrombus + dissection</td>
<td>2:55</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>Abrupt closure → repeat PTCA</td>
<td>Unclear etiology</td>
<td>0:53</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>Abrupt closure → MI</td>
<td>Thrombus</td>
<td>0:55</td>
<td>67</td>
</tr>
<tr>
<td>1.0</td>
<td>Abrupt closure</td>
<td>Dissection</td>
<td>5:22</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Abrupt closure</td>
<td>Unclear etiology</td>
<td>0:44</td>
<td>OOR</td>
</tr>
<tr>
<td></td>
<td>Cardiac arrest → death</td>
<td>Dissection</td>
<td>1:07</td>
<td>OOR</td>
</tr>
<tr>
<td></td>
<td>Abrupt closure → repeat PTCA</td>
<td>Thrombus</td>
<td>6:59</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Abrupt closure → repeat PTCA</td>
<td>Thrombus</td>
<td>N/A</td>
<td>141</td>
</tr>
<tr>
<td>1.4</td>
<td>Abrupt closure + MI → repeat PTCA</td>
<td>Dissection</td>
<td>1:00</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Abrupt closure + non-Q MI</td>
<td>Dissection</td>
<td>5:22</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td>Thrombus</td>
<td>0:36</td>
<td>126</td>
</tr>
<tr>
<td></td>
<td>Abrupt closure → repeat PTCA</td>
<td>Dissection</td>
<td>1:30</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>Abrupt closure</td>
<td>Unclear etiology</td>
<td>0:30</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Acute coronary artery thrombosis</td>
<td>Thrombus</td>
<td>0:56</td>
<td>N/A</td>
</tr>
<tr>
<td>1.8</td>
<td>Abrupt closure → coronary stent</td>
<td>Dissection</td>
<td>1:01</td>
<td>146</td>
</tr>
<tr>
<td></td>
<td>Impending abrupt closure → CABG</td>
<td>Unclear etiology</td>
<td>0:36</td>
<td>275</td>
</tr>
<tr>
<td></td>
<td>Abrupt closure → repeat PTCA</td>
<td>Dissection</td>
<td>1:00</td>
<td>OOR</td>
</tr>
<tr>
<td>2.2</td>
<td>Abrupt closure → MI</td>
<td>Thrombus</td>
<td>0:55</td>
<td>138</td>
</tr>
</tbody>
</table>

aPTT, activated partial thromboplastin time; ACT, activated clotting time; non-Q, non-Q wave; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass surgery; N/A, not available; OOR, out of range.

*Time in hours/minutes of event relative to start of dosing.

Although there is a correlation of ACT with aPTT values, ACT levels measured during percutaneous transluminal coronary angioplasty may provide a better index of anticoagulation than aPTT because the clotting time responds linearly, this test responds to a wider range of heparin concentration, the patient’s own platelet factor 3 is being used, calcium variations are kept to a minimum, and sample handling is reduced.19,20

It is unclear whether some prolongation of the aPTT or ACT in response to hirulog or heparin also represents the same level of anticoagulation and antithrombotic protection. Of note, however, the current study suggests that only when the median ACT values approach or exceed 300 seconds is there a marked reduction in the incidence of abrupt closure.

Previous Work With Hirulog

Using hirudin as a model, Maraganore et al10 designed the novel class of dodecapetides known as hirulogs. Hirulog is bivalent; it combines the d-Phe-Pro-Arg catalytic site antithrombin and the C-terminal portion of hirudin (residues 53–64) that binds the anion exosite of thrombin with a polyglycyl linker. Previous studies have demonstrated the high in vitro potency of hirulog.10 Hirulog has been shown to be effective in inactivating clot-bound thrombin, which is resistant to heparin.21 In vivo, the bifunctional antithrombin peptide markedly attenuated thrombus formation onto segments of endarterectomized aorta in a baboon experimental model.22 In phase 1 studies with normal volunteers, hirulog at a dose of 0.3 mg · kg⁻¹ · hr⁻¹ prolonged the aPTT more than twice baseline values, was unaffected by aspirin, and was not associated with

TABLE 3. Abrupt Closure Events by Dose of Hirulog

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Combined groups (0.6+1.0+1.4 mg · kg⁻¹ · hr⁻¹)</th>
<th>Combined groups (1.8+2.2 mg · kg⁻¹ · hr⁻¹)</th>
<th>Combined groups (1.0+1.4 mg · kg⁻¹ · hr⁻¹)</th>
<th>Combined groups (1.8+2.2 mg · kg⁻¹ · hr⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention to treat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. events/No. patients dosed</td>
<td>17/151</td>
<td>5/128</td>
<td>14/97</td>
<td>5/128</td>
</tr>
<tr>
<td>Rate</td>
<td>11.3%</td>
<td>3.9%</td>
<td>14.4%</td>
<td>3.9%</td>
</tr>
<tr>
<td>p*</td>
<td>p=0.052</td>
<td>p=0.033</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By evaluable†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. events/No. patients with balloon inflations</td>
<td>14/137</td>
<td>4/121</td>
<td>11/87</td>
<td>4/121</td>
</tr>
<tr>
<td>Rate</td>
<td>10.2%</td>
<td>3.3%</td>
<td>12.6%</td>
<td>3.3%</td>
</tr>
<tr>
<td>p*</td>
<td>p=0.032</td>
<td>p=0.032</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on Mantel-Haenszel test (controlling for center).
†Patients who actually received hirulog and underwent a coronary angioplasty procedure.
any significant side effects. The current study represents the first large clinical experience of hirulog in patients with a need for antithrombotic therapy.

**Mechanistic and Experimental Model Advantage**

During coronary angioplasty, there is a significant predisposition toward coronary thrombosis on the basis of several factors. These include the equipment itself, release of tissue factor by compression of the plaque and vessel wall, the exposure of subintimal collagen and deep arterial injury, adhesion and aggregation of platelets, and formation of fibrin-bound thrombin, all of which tend to autoamplify the likelihood of endoluminal or mural thrombus. Angiography after routine angioplasty has provided direct visual confirmation of the presence of thrombus in most angioplasty procedures. In certain patients with preexisting intraluminal thrombus or clinical presentation with unstable angina, the risk of abrupt vessel closure after angioplasty is exceptionally high and, in some cases, prohibitive.

Heparin requires the plasma protein antithrombin III to function as an inhibitor of thrombin and thus, by itself, is a very weak anticoagulant. By virtue of intracoronary platelet activation, release of such components as platelet factor 4 or heparinase can, at least mechanistically, effectively neutralize the actions of heparin. Moreover, heparin is a weak inhibitor of clot-bound thrombin, which is the form in which thrombin accumulates after arterial injury and may represent the paramount intervention required to prevent clot accumulation and to permit vessel pasification. Direct thrombin antagonists, which bind the catalytic and substrate recognition site, such as hirudin and hirulog, have considerable theoretical potential to provide more complete and potent antithrombotic action in this setting, possibly at a lower anticoagulation level than required for the same antithrombotic effect of heparin. In several experimental models of deep arterial injury that closely simulate the clinical situation of angioplasty, direct thrombin inhibitors have been demonstrated to be far superior to even high doses of heparin for preventing arterial thrombus formation.

**Study Limitations**

The present study is limited by having no control group of heparin-treated patients for a more meaningful comparison of abrupt closure events. However, the dose escalation study was necessary to determine what level of hirulog dosing was necessary to inhibit coronary thrombotic events and whether the drug would be tolerated in this setting of invasive vascular sheaths, concomitant use of aspirin, and the possibility of requiring emergency coronary bypass surgery. Historical controls from multiple recent series indicate that even with intravenous heparin, there is an appreciable (6–8%) and clinically important rate of abrupt vessel closure. Whether this can be significantly reduced using very-high-dose heparin and in-laboratory anticoagulation ACT monitoring or with the newer direct thrombin inhibitors remains to be determined in larger, controlled studies.

In the study, we did not have standardized laboratory determinations of aPTT's throughout the 11-site network. While this would have lessened the variability in the anticoagulation parameter, this problem is representative of the field, i.e., there are a number of methods to assess the status of anticoagulation and, unfortunately, no uniform standards or recommendations have been established during coronary angioplasty. On the other hand, the method for determining ACTs in the trial was fixed throughout the multicenter network and there was concordance in the hirulog dose response between aPTT and ACT (Figures 1 and 2). Below hirulog dose levels of 1.0 mg·kg⁻¹·hr⁻¹, there was a poor correlation between aPTT and ACT.

**Conclusions**

The present study documents for the first time that it is possible to perform coronary angioplasty in patients pretreated with aspirin using an anticoagulant other than heparin. The use of hirulog was associated with a rapid-onset, dose-dependent anticoagulant effect, minimal bleeding complications, and at doses of 1.8–2.2 mg/kg, a significant reduction of abrupt vessel closure to <4%. With only historical controls from other studies of abrupt vessel closure, it is difficult to assess the significance of this absolute frequency of closure events. Our findings suggest that a large-scale randomized trial comparing the direct thrombin inhibitor hirulog with heparin is warranted.

**Appendix**

**Clinical Centers and Investigators**

Cleveland Clinic Foundation, Cleveland, Ohio. Principal investigator: Eric J. Topol, MD; co-investigators: Russell Raymond, DO; Irving Franco, MD; Stephen G. Ellis, MD; Conrad Simpfendorfer, MD; Patrick Whitlow, MD; Colleen Rouse, RN; Michele Webb, RN; Sue De Luca, RN; Ed Jones, PharmD; Dorothea Odar.

University of Michigan, Ann Arbor. Principal investigator: Eric J. Topol, MD; co-investigators: Stephen G. Ellis, MD; Eric R. Bates, MD; David W.M. Muller, MBBS; Joseph Walton, MD; Anita Galeana, RN.

Montreal Heart Institute, Montreal, Canada. Principal investigator: Dr. Raoul Bonan; co-investigators: Drs. Gilles Cote, Jacques de Crepeau, Pierre de Guise, Gilbert Gosselin, Michel Joyal, Joanne Lavoignat; Denis Bois, RPh; Madeline Parisiel, RN; Michel Marcell.

King's College Hospital, Royal Brompton National Heart and Lung Hospital, and Thrombosis Research Institute, London. Principal investigator: Professor Vijay V. Kakkar; co-investigators: Mr. David Jewitt, Valerie Ward, Dr. Nigel Buller, Ulrich Sigwart, MD.

London Chest Hospital. Principal investigator: Dr. Martin Rothman; co-investigator: Melanie Preston.

University of Leicester, Leicester, UK. Principal investigator: Professor David de Bono, MD; co-investigator: M. McCants.

St. Luke's Episcopal Hospital/Texas Heart Institute, Houston, Tex. Principal investigator: James T. Willerson, MD; co-investigators: James J. Ferguson, MD; Ali Massumi, MD; Jorge Garcia, MD; Virendra Mathur, MD; D. Richard Leachman, MD; George Christy, MD; Bernardo Treistman, MD; Patrick Hogan, MD; Mary Harlan, RN; Sharon Tinson, RN; Sharon Chapin-Wise, RN.

Medical College of Virginia, Richmond. Principal investigator: John Strongy, MD; co-investigators: Anthony Minisi, MD; Kelly Manor, PA; Cindy Bagly; Liz Hanners.

Brigham and Women's Hospital, Boston. Principal investigator: Peter Ganz, MD; co-investigators: Drs. A. Selwyn, J. Bittl, J. Kirshenbaum, T. Ryan, A. Yeung, T. Meredith, T. Anderson, J. Keany, M. Landsberg, T. Andrews; Karen Eddings, RN.
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St. Francis Hospital Center, Beech Grove, Ind. Principal investigator: Mark D. Cohen, MD; co-investigators: H.O. Hickman, MD; S.H. Kliman, MD; William Berg, MD; Brandon Roger, MSW; David Manley; Karen Baumgartner, PharmD; Paula Cross, RN.

Biogen, Inc., Cambridge, Mass. Irving Fox, MD; John Maraganore, PhD; Burt Adelman, MD; Elizabeth Levin, Robert Growth, Arthur McCullister.

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