Automated Heparin-Delivery System to Control Activated Partial Thromboplastin Time
Evaluation in Normal Volunteers

Christopher P. Cannon, MD; Jasper Dingemanse, PhD; Cornelis H. Kleinbloesem, PhD; Thomas Jannett, PhD; Kenneth M. Curry, BS; Christian P. Valcke, PhD

Background—Unfractionated heparin is used widely; however, control of the level of anticoagulation remains its greatest problem, with fewer than 35% of patients having activated partial thromboplastin times (aPTTs) within a range of 55 to 85 seconds in recent trials.

Methods and Results—We developed and tested a prototype of an automated heparin control system (AutoHep) in which a computer-based titration algorithm adjusted the heparin infusion to reach a target aPTT. In 1 study, 12 healthy male subjects received an intravenous infusion of heparin with the rate determined by AutoHep and were randomized to receive an initial bolus or no bolus of heparin preceding the infusion. A second study evaluated the automated blood sampling system in 12 subjects. Of the 344 end-point aPTT measurements, 78% were within 6 ± 10 seconds of the target (prespecified primary end point), and 89% were within a ± 15-second range. The time to achieve a target aPTT was 93 minutes without and 150 minutes with an initial heparin bolus. The total percentage of time within the target range ± 15 seconds was 46 of 48 hours (96%). The automatic blood sampling system successfully obtained 96% of all scheduled samples.

Conclusions—These results suggest that the AutoHep system has the potential to significantly improve aPTT control of intravenous heparin compared with current clinical practice.

Key Words: heparin ■ coagulation ■ anticoagulants

Unfractionated heparin therapy is used in the care of >4 million patients annually worldwide with arterial and venous thromboembolic disease states. Numerous studies have shown that the level of systemic anticoagulation is a major determinant of clinical outcome, leading to the use of activated partial thromboplastin time (aPTT) to monitor the anticoagulant response of heparin. Because of the complex pharmacokinetics and pharmacodynamics of heparin, wide patient variability in anticoagulant response, and time delays between obtaining the blood sample and reporting aPTT results, it is difficult to establish and maintain the therapeutic level of anticoagulation for each patient. Despite numerous efforts to improve the delivery of heparin, including heparin administration nomograms, use of bedside aPTT devices, and use of weight-adjusted and computer-based algorithms, recent trials have achieved only 30% to 35% of aPTTs that were within a 30-second target range. In an attempt to improve heparin control, we developed and tested a prototype of the AutoHep system, which automatically acquires a venous blood sample, performs an aPTT measurement, and adjusts the heparin infusion rate to achieve an operator-selected aPTT target.

Methods

Heparin Control Study
After Ethics Committee approval and each subjects’ written informed consent were obtained, 12 healthy male volunteers (age, 20 to 49 years) were randomly assigned to 1 of 2 treatment groups: automated heparin system infusion after an initial bolus of 50 U/kg IV heparin (bolus group) or infusion without a loading dose of heparin (no bolus). Two intravenous catheters were placed: 1 connected to the infusion pump (IMED PC-1) for administration of the heparin solution (50 U/mL, Elkins-Sinn), and the other in the contralateral arm for collection of blood samples, with a constant saline infusion to maintain catheter patency. aPTT measurements were performed with a calibrated point-of-care instrument (Boehringer Mannheim CoaguChek Plus). Heparin infusion continued for 48 hours. The system targeted an aPTT of 1.5 times the baseline value for 40 hours and 2.0 times the baseline for the final 8 hours. Safety features of the system included audible and visible alerts or alarms for problems with either the intravenous pumps or the control algorithm (eg, air in intravenous line, intravenous catheter occlusion, or aPTT measurement outside the expected range). Heparin delivery

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continued if there were “alert” messages but was automatically
stopped by the device if an alarm occurred. The system was
programmed so that the maximum instantaneous heparin infusion
rate was <5000 U/h and maximum hourly cumulative heparin dose
was <2000 U to avoid any potential “overdosing” of heparin.

Control Algorithm

The initial infusion calculations were based on a pharmacodynamic
model relating the aPTT response to drug infusion. The aPTT
response (R) to heparin is described as
\[ R = \log aPTT - \log aPTT_{baseline} \]
which may be expressed as \( aPTT = 10^R \cdot aPTT_{baseline} \). The change in log
aPTT is proportional to the heparin concentration (H). The rate of
change in heparin concentration is as follows:
\[ \frac{dH}{dt} = \left( \lambda + \frac{V_u K_m}{K_m + H(t)} \right) H(t) + \frac{u(t)}{V_d} \]
where \( \lambda \) is the elimination rate constant, \( V_u \) and \( K_m \) are parameters
reflecting the saturable mechanism of elimination of heparin, \( u \) is the
heparin infusion rate, and \( V_d \) is the apparent volume of distribution
(approximately equal to the blood volume). Because \( R = mH \), the
time rate of change of the response may be written as follows:
\[ \frac{dR}{dt} = -\left( \lambda + \frac{VK}{K+R(t)} \right) R(t) + Su(t) \]
where \( S = m/V_d \). For the pharmacodynamic model, the parameter-
ization vector (\( \theta \)) consists of the following:
\[ \theta = (\lambda VKS \ aPTT_{baseline}) \]

The model was initialized on the basis of known data from
population analysis. As the infusion progressed and aPTT mea-
surements became available, the general model was adjusted to the
particular subject response. Adjustments were accomplished by use
of a Bayesian optimization scheme. In this method, a new parameter
estimate is calculated by weighing the confidence in the aPTT
measurement against the confidence in the current estimate of the
model parameters. Bayesian estimation is especially useful in situa-

![Figure 1: aPTT response of subject in bolus group to feedback controlled heparin. Infusion rate (lower solid line) shows adjustments during course of study. Pharmacodynamic model fit (upper solid line) is based on measured aPTT data (squares).](image)

### TABLE 1. Heparin Dose and Infusion Data

<table>
<thead>
<tr>
<th></th>
<th>Bolus (n=6)</th>
<th>Nonbolus (n=6)</th>
<th>All Subjects (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dose, U</td>
<td>43 147±16 207</td>
<td>32 722±9836</td>
<td>37 934±13 893</td>
</tr>
<tr>
<td>Mean infusion rate, U/h</td>
<td>908±340</td>
<td>693±206</td>
<td>801±290</td>
</tr>
<tr>
<td>Maximum infusion rate, U/h</td>
<td>3946±986</td>
<td>3292±580</td>
<td>3619±843</td>
</tr>
<tr>
<td>Range</td>
<td>2657–5000</td>
<td>2772–4317</td>
<td>2657–5000</td>
</tr>
<tr>
<td>Bolus dose, U</td>
<td>4154±387</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>3650–4750</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean±SD.
tions in which model parameters are estimated on the basis of sparse measurements of patient response. Furthermore, the algorithm determined the next sample time on the basis of the uncertainty in the estimated aPTT and the desired precision of control. In this prototype, the personal computer (Compaq) prompted the investigator to obtain an aPTT measurement, and the aPTT values were manually entered into the computer.

Blood samples for “end-point” aPTTs were drawn at protocol-specified intervals (0, 20, and 40 minutes; 1, 3, and 6 hours; every 3 hours thereafter, except at 27 and 33 hours; and 30 minutes and 1, 2, and 4 hours after infusion for a total of 22 samples over 52 hours) for replicate aPTT measurements to establish system performance. None of the protocol-scheduled aPTT measurements was used for feedback purposes.

**Blood Sampling Study**

After Ethics Committee approval and each subjects’ written informed consent were obtained, a second group of 12 normal volunteers (50 to 60 years of age) had a single venous catheter placed and received heparin for 60 hours with infusion rates based on a standard nomogram. In the prototype, a computer-controlled sampling pump adjusts the blood withdrawal rate on the basis of pressure measurements derived from a strain beam on the sample tubing. A pneumatic tourniquet is automatically inflated during the sample draw. Control of a saline pump allows flushing of the heparin before sample withdrawal and flushing of the blood from the sample line at the end of the sample cycle. At each of the 14 scheduled time points, replicate whole-blood aPTT measurements were obtained from these device-withdrawn samples and from manually obtained venous samples from the contralateral arm.

**End Points**

Data samples considered evaluable were those acquired during heparin infusion and after the first transition from baseline (1 hour) or washout of bolus administration (3 hours). Thus, of 525 end-point aPTTs, 181 were not included in the evaluable data set because 13 were at baseline, 72 were during the postbolus washout, and 96 were after heparin infusion. The primary performance variables were the percentage of end-point aPTT values in the target range (target level, $\pm 10$, $\pm 15$, or $\pm 20$ seconds). Performance of the blood sampling device was the percentage of successfully completed sample cycles. If a sample cycle failed, the system could retry once. Comparisons of continuous data were made with Student’s t test. Data are presented as mean±SD and as median with range.

**Results**

**Heparin Control Study**

An example of a single patient test is shown in Figure 1, which gives the measured and pharmacodynamically modeled aPTT values and the heparin infusion rate. Although total dose and mean infusion rate of heparin appeared to be lower in the nonbolus group (Table 1), no statistically significant differences were detected. For nonbolus subjects, the algorithm delivered an initial rapid infusion of heparin (average, 644 U over 20 minutes) to quickly achieve the selected target. The average number of aPTT measurements requested by the control algorithm over the 48-hour period

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**TABLE 2. Summary of aPTT Target Data**

<table>
<thead>
<tr>
<th></th>
<th>Bolus (n=6)</th>
<th>Nonbolus (n=6)</th>
<th>All Subjects (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>31</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Minimum</td>
<td>24</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Maximum</td>
<td>38</td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>Target 1, s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>46</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Minimum</td>
<td>36</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>Maximum</td>
<td>57</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td>Target 2, s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>61</td>
<td>60</td>
<td>61</td>
</tr>
<tr>
<td>Minimum</td>
<td>48</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>Maximum</td>
<td>76</td>
<td>72</td>
<td>76</td>
</tr>
</tbody>
</table>

---

**TABLE 3. Performance Evaluated by Percent aPTT Samples Within Target Range**

<table>
<thead>
<tr>
<th></th>
<th>Bolus (n=6)</th>
<th>Nonbolus (n=6)</th>
<th>All Subjects (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range $\pm 5$ s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under</td>
<td>24</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Within</td>
<td>52</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Above</td>
<td>24</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Range $\pm 10$ s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under</td>
<td>6</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Within</td>
<td>82</td>
<td>75</td>
<td>78</td>
</tr>
<tr>
<td>Above</td>
<td>11</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Range $\pm 15$ s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under</td>
<td>0</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Within</td>
<td>92</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td>Above</td>
<td>8</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>
Figure 3. Average deviation of protocol schedule aPTT measurements from selected target for bolus group (top, scale to 100 seconds) and nonbolus group (bottom, scale to 40 seconds). Shaded area indicates time interval for transition from bolus or baseline to target aPTT. Bars show mean with SD.
was \( \approx 9 \); they were evenly distributed over the infusion period.

Table 2 demonstrates that the target aPTT values of 1.5 and 2.0 times control were achieved in both the bolus and nonbolus groups. Table 3 summarizes the percent aPTT samples within \( \pm 10 \), \( \pm 15 \), and \( \pm 20 \) seconds of the selected aPTT target. For all subjects, 78% of measurements were within 10 seconds, 89% were within 15 seconds, and 94% were within 20 seconds of the target.

By use of the pharmacodynamic model–estimated aPTT trajectories, the average time to target for bolus subjects was 150 minutes (range, 93 to 275 minutes), whereas for nonbolus subjects, this interval was reduced to 93 minutes (range, 15 to 190 minutes). Thus, by the 6-hour time point, 100% of patients were within the target range (Figure 2, top). These results can be compared with the data on aPTT control in the intravenous heparin group of the ESSENCE trial (Figure 2, bottom).

The average deviation from target for all scheduled time points was usually <5 seconds and is graphically presented in Figure 3 for bolus and nonbolus subjects, respectively. During the period after the initial washout, only 9 of 326 aPTT values (3.5%) exceeded 80 seconds, and only 4 (1.2%) exceeded 90 seconds. The replicate whole-blood aPTT assays yielded very consistent results, with \( r=0.98 \) and a slope of 0.986.

### Pharmacodynamic Analysis

Table 4 shows that the initial pharmacodynamic model parameters \(^{10} \) and those for the subjects in this study were similar. The performance analysis based on the pharmacodynamic modeling showed that patients remained within a \( \pm 15 \)-second range 98% of the time (Table 5). No adverse events were reported as device related, and no bleeding events occurred.

### Blood Sampling Study

In the blood sampling study, the system successfully withdrew 161 of 168 samples (96%). All 7 of the unsuccessful sample cycles occurred when the subjects were not receiving intravenous heparin. Coefficients of variation for automatic (5.5%) and manually (5.1%) obtained aPTT measurements showed no difference \((P=0.4)\). Correlation of aPTT values \((r=0.95)\) from automatic and manual sampling methods also showed excellent agreement. One subject in this study (which evaluated the blood sampling device and used standard nomogram-titrated heparin) developed an isolated hemolytic stool.

### Discussion

Although heparin has been used for >50 years in the management of patients with acute coronary syndromes and venous thromboembolism, control of the anticoagulation level has been its greatest challenge. Numerous studies have shown that when aPTT values are above the target range, bleeding is more frequent, as are, surprisingly, recurrent infarction and mortality. \(^{1-3} \) If aPTT values are too low, recurrent thrombotic events are more common. \(^{1-3} \) Accordingly, numerous attempts to improve control of the anticoagulation level with heparin, including the use of standardized nomograms; \(^{5} \) weight-adjusted dosing; \(^{6} \) bedside aPTT monitoring; \(^{4} \) and all 3 together, \(^{9} \) have failed to make a major improvement (Figure 4). Only 30% to 35% of patients were in the target 30-second range a full 24 hours after titration of heparin in TIMI 9B\(^{7} \) and in a randomized trial of both bedside monitoring and weight-adjusted heparin dosing. \(^{8} \) We also analyzed aPTT values in 209 patients in TIMI IIIb who were found after randomization to have normal coronary arteries, thus approximating the present study population: Only 35% of aPTT values were within the 30-second target of 45 to 75 seconds.

#### Automated Heparin Control System

In this study, the prototype automated heparin control system achieved 89% of aPTT values within a 30-second range. This corresponds to subjects being within the target range for 46 hours of the 48-hour treatment period. The target aPTT was achieved in only 90 to 150 minutes both initially and when the new target was selected. This was achieved by the computerized algorithm that required on average 9 aPTT samples over the 48-hour period. The automated venous blood sampling succeeded in acquiring blood sample in 96% of the attempts overall and in 100% of attempts when the subjects were receiving heparin.

Subjects receiving an initial bolus of heparin appeared to have better aPTT control during the infusion period (Figure 3). One reason may have been that during washout of the bolus dose, with the large excursion in anticoagulant status, the aPTT values may have allowed better identification of the pharmacodynamic model in the individual subject, thus resulting in improved overall performance.

Ultimately, the AutoHep system will automatically acquire blood samples for aPTT assays and calculate the optimal heparin delivery to achieve an operator-specified target. The time required by nurses and physicians would be reduced to the initial setup and response to any alarms (which were infrequent [<5%] in this initial study). The costs of the device and cartridges are planned to be equivalent to current costs of laboratory-based

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**TABLE 4. Pharmacodynamic Model Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial Model</th>
<th>Bolus (n=6)</th>
<th>Nonbolus (n=6)</th>
<th>All Subjects (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \lambda, \text{ min}^{-1} )</td>
<td>0.16 (0.05)</td>
<td>0.15</td>
<td>0.14</td>
<td>0.15 (0.01)</td>
</tr>
<tr>
<td>( V_{\text{max}}, \text{ U} \cdot \text{L}^{-1} )</td>
<td>1.1 (0.6)</td>
<td>1.2</td>
<td>1.1</td>
<td>1.2 (0.5)</td>
</tr>
<tr>
<td>( k_{\text{on}}, \text{ U} \cdot \text{L}^{-1} )</td>
<td>0.68 (0.23)</td>
<td>0.55</td>
<td>0.52</td>
<td>0.53 (0.13)</td>
</tr>
<tr>
<td>( S, \text{ U}^{-1} \cdot \text{10}^{-4} )</td>
<td>3.0 (5.0)</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0 (0.8)</td>
</tr>
<tr>
<td>aPTT baseline, s</td>
<td>27.0</td>
<td>28.8</td>
<td>27.9 (6.0)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean values (SD).

---

**TABLE 5. Model-Estimated aPTT: Percentage of Time Within Target Range**

<table>
<thead>
<tr>
<th>Range</th>
<th>Bolus (n=6)</th>
<th>Nonbolus (n=6)</th>
<th>All Subjects (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \pm 5 ) s</td>
<td>65</td>
<td>69</td>
<td>67</td>
</tr>
<tr>
<td>( \pm 10 ) s</td>
<td>94</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>( \pm 15 ) s</td>
<td>97</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>( \pm 20 ) s</td>
<td>97</td>
<td>99</td>
<td>98</td>
</tr>
</tbody>
</table>
aPTT monitoring of unfractionated heparin or of low-molecular-weight heparin. With further refinements in the device and inclusion of patient demographic factors in the configuration of the control algorithm, the performance of the system may be improved further. Most importantly, however, a very stable anticoagulant effect from unfractionated heparin, a very inexpensive medication, can be achieved, which may translate into improved clinical outcomes. This hypothesis needs to be tested by use of an integrated version of the AutoHep system in future clinical trials.

In conclusion, this initial testing of the AutoHep system achieved nearly 90% of aPTTs within a target range of ±15 seconds, which can be compared with current clinical practice in which typically only 30% to 40% of aPTTs are within range. If these results can be duplicated with the integrated device in patients, it will represent a major advancement in the use of heparin.

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