

## Early Anticoagulation Peak and Rapid Distribution After Intravenous Heparin

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For many years, cardiac surgical teams assumed heparin's dose-response relationship and clinical onset time. In 1975, Bull *et al.* observed that patients vary widely, both in the peak anticoagulation response to heparin and in the decay rate of the response.<sup>1,2</sup> They recommended using the activated coagulation time (ACT) to monitor heparin's action before and during cardiopulmonary bypass (CPB). Introduced by Hattersley in 1966, the ACT conceptually imitates the lengthier and more cumbersome Lee-White whole blood clotting time using a contact activant (Celite) to speed the process.<sup>3</sup> Hattersley's method was subsequently modified by International Technidyne (Edison, NJ) to a more automated one that has gained widespread use for anticoagulation monitoring during CPB.

Despite the ACT's wide acceptance, the onset time and peak anticoagulation following intravenous heparin remain ill-defined. Many centers follow Bull *et al.*'s<sup>1,2</sup> recommendation to perform an ACT 5 min after administering intravenous (iv) heparin. Upon examining ACT values following iv heparin administration to cardiac surgical patients, however, Effenev *et al.* suggest that heparin's peak action occurs at 20-30 min.<sup>4</sup> Inexplicably, they found an earlier peak (14 min) in vascular surgical patients. They recommended waiting 20-30 min after heparinization to determine the ACT. To establish the validity of the Bull *et al.*'s<sup>1,2</sup> two-step heparin dosing protocol and to expedite the onset of CPB following heparin administration, we investigated the

early time course of heparin-induced anticoagulation by selecting ACT sampling intervals different than those of Effenev *et al.*<sup>4</sup>

## MATERIALS AND METHODS

After obtaining protocol approval from our Clinical Research Practices Committee, we studied 30 consecutive patients (mean age  $58 \pm 9$  yr) undergoing coronary revascularization with a combined left internal mammary and saphenous vein graft technique. After premedication with lorazepam (50  $\mu$ g/kg po) and morphine (0.1 mg/kg im), each patient was anesthetized with a narcotic (fentanyl 30-70  $\mu$ g/kg or sufentanil 5-10  $\mu$ g/kg iv) accompanied by pancuronium (0.1 mg/kg iv). During internal mammary artery dissection, each patient received 300 International Units (IU) of beef lung heparin (Upjohn) per kilogram injected into the right atrial port of a pulmonary artery catheter. The injection site was aspirated to verify free blood return, then flushed with 1-2 ml of heparinized saline (1,000 IU heparin/500 ml 0.9% saline) after heparin administration.

ACT samples were withdrawn before beginning CPB at 2, 5, 10, 15, and 20 min after giving heparin. A control ACT was taken before anesthetic induction. Each sample was drawn from the left radial artery after clearing the continuous flush solution from the tubing by withdrawing 5 ml of blood. The sampling site was separated from the blood stream by a 2-inch 20-gauge Angiocath® catheter and a 6-inch segment of Gould high-pressure tubing. We used four Hemochron™ (International Technidyne, Edison, NJ) ACT devices, each of which was tested for consistent heat block temperature control at 37° C. The 2-ml whole blood samples were placed in the vacuum-sealed tubes within 1 min of sampling, and then placed in the continuously rotating Hemochron chamber. Each vacuum-sealed tube contained Celite, a coagulation activator, and was vigorously agitated to insure complete mixing before placement in the chamber. A magnet in the tilted, rotating tube remains in a dependent position until it is engaged by the formation of a fibrin clot, whereupon a detector senses the loss of magnetic contact, concludes the test, and sounds an alarm. Differences in ACT values over time were assessed using repeated-measures analysis of

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variance. Individual contrasts in ACT values at different sampling periods were compared using paired *t* tests with a Bonferroni correction, resulting in a *P* value significance threshold of 0.005.

RESULTS

Analysis of variance showed a highly significant variation in the ACT values over time (*P* < 0.001). All post-heparin ACT values differed significantly from the control value (*P* < 0.0001). Table 1 and figure 1 summarize the observed ACT values for the group as a whole. The 2-min ACT significantly exceeded each subsequent ACT.

Viewing the change from the control ACT ( $\Delta$ ACT) as a measure of response to heparin, the mean  $\Delta$ ACT at 2 min was  $455 \pm 172$  (SD) s, whereas it was significantly less ( $345 \pm 101$  [SD] s, *P* < 0.001) at 20 min. This yields an apparent mean difference of 110 s between the 2- and 20-min ACT values for these 30 patients, but the mean difference becomes  $117 \pm 111$  (SD) (median 78 s, range -51-447 s) when comparing the 29 patients who had ACT measurements at both 2 and 20 min.

Figure 2 shows the frequency distribution over time for the maximum post-heparin ACT value. ACT peaked at 2 min in 21 of 30 patients.

DISCUSSION

Based on previous reports suggesting that the anticoagulation peak ranges from 5 to 25 min after iv heparin, we did not expect such an early peak.<sup>4-6</sup> In the study performed by Effeney *et al.*, sampling occurred at 10-min intervals for 30 min. The discrepancy they found in peak heparin activity between peripheral vascular and cardiac surgical patients is difficult to understand. Other than the larger dose of heparin required, patients undergoing vascular surgery tend to be demographically similar to coronary artery bypass (CABG) patients, and nine of their 11 cardiac surgical patients underwent CABG. Because Effeney *et al.* did not mention the timing of CPB onset, the later anticoagulation peak may attribute to CPB-related ACT prolongation from hemodilution, hypothermia, or additional heparin in the priming solution.<sup>7,8</sup>

We assume that the ACT directly reflects plasma heparin concentrations before CPB. Previous investigations demonstrate variability in the relationship between ACT and plasma heparin concentration among different patients.<sup>7,9</sup> Before beginning CPB, however, the short-term relationship between ACT and plasma heparin concentration should remain constant and nearly linear for an individual patient.<sup>10,11</sup> Table 1 shows much larger ACT standard deviations after heparin, even when considered in relation to the higher mean

TABLE 1. Activated Coagulation Time After a 300 IU/kg Heparin Bolus

ACT Sampling Time	Mean	SD	SE	Range
Control (N = 30)	129	10.0	1.8	115-151
2 min (N = 30)	584*	171	31.0	313-1060
5 min (N = 30)	517†	130	23.6	359-974
10 min (N = 30)	499	121	22.0	308-842
15 min (N = 30)	505‡	100	18.2	324-733
20 min (N = 29)	473	100	18.6	315-728

All units are seconds. SD = standard deviation; SE = standard error of the mean.

\* *P* < 0.001, compared with 5, 10, 15, and 20 min.

† *P* < 0.001, compared with 20 min.

‡ *P* < 0.005, compared with 20 min.

ACT values (control SD < 10% of mean, post-heparin SD  $\geq$  20% of mean). This reflects interpatient variability in ACT prolongation following a fixed heparin dose and reduced precision of clotting times in anticoagulated blood.<sup>1,12</sup> The technical data accompanying the Hemochron™ device suggest a coefficient of variation ( $100 \times \text{SD}/\text{mean}$ ) of 4%; however, our unpublished observations suggest that this value rises to 8% when ACT values exceed 400 s. This test variability may explain the peak ACT occurrence at 10-15 min post-heparin in three patients (fig. 2), which might be artifactual.

Our results suggest that significant distribution or metabolism of heparin may occur quickly, the former mechanism holding more appeal. Using  $\Delta$ ACT as an index of heparin action, 25.7% of the anticoagulation response was lost between 2 and 20 min after the bolus dose. It was formerly assumed that heparin's bulk and polarity limited its distribution to the plasma compartment.<sup>13</sup> Pharmacokinetic studies using clotting time assays confirmed an apparent volume of distribution compatible with plasma volume, but the earliest sampling intervals uniformly exceeded 5 min.<sup>13,14</sup> *In vitro* studies demonstrate that heparin avidly binds to endothelium, and that considerable endothelial heparin uptake occurs.<sup>15-18</sup>

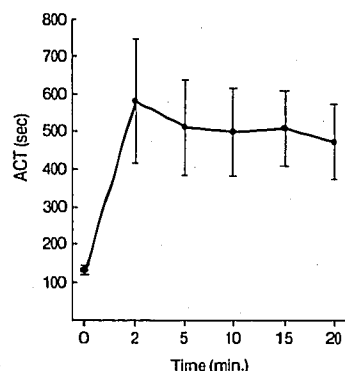


FIG. 1. ACT after a heparin bolus injection of 300 IU/kg body weight. Plotted ACT values show mean  $\pm$  1 SD (N = 30 except for 20-min value, where N = 29).

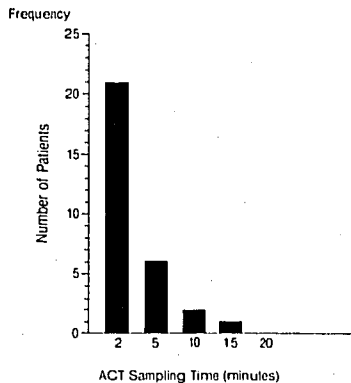


FIG. 2. Frequency distribution of the peak post-heparin ACT value.

Three clinical studies support rapid heparin distribution to some peripheral site.<sup>19-21</sup> After administering heparin 250 IU/kg intravenously to healthy volunteers, deSwart *et al.* sampled venous blood at 2, 5, 10, 15, 45, and 60 min, then at 30-min intervals until 540 min had elapsed.<sup>19</sup> Using activated partial thromboplastin time prolongation and anti-Factor Xa activity as heparin assays, their findings also suggest a rapid redistribution phase for heparin kinetics. When plotting heparin's decay curve semi-logarithmically, their study reveals initial zero-order elimination kinetics, followed by a terminal first-order elimination phase. They postulate that saturation of heparin's metabolic or excretory pathways explains the zero-order phase.

After labeling heparin with <sup>99</sup>Tc<sup>m</sup>, Decousus *et al.* measured heparin levels in six volunteers at nine unspecified intervals for 2 h after a small (160 IU) intravenous heparin bolus.<sup>20</sup> Their results best fit a traditional two-compartment model with a distribution half-life of  $9.3 \pm 1.8$  min and an elimination half-life of 162 min. Because these half-lives apparently fall before and after their sampling periods, more frequent early sampling combined with a longer total sampling period might have altered their results. Nevertheless, their data support a rapid distribution phase in heparin's pharmacokinetics, and an apparent volume of distribution (4.1 liters) exceeding estimated plasma volume by approximately 30%.

Sampling the ACT at 10-min intervals after unspecified doses, Hattersley<sup>21</sup> briefly described an atypical biphasic decay with half-lives similar to Decousus's observations.<sup>20</sup> A few of Hattersley's patients displayed a steep drop in ACT over 10-20 min, leveling into a gradual decay at 30-40 min. The majority, however, exhibited a steady monophasic decay with an elimination half-life of 73 min. His atypical patients might parallel the three patients in our study who had a post-heparin ACT peak 10 or 15 min after heparin. Only in those three patients could we have observed a biphasic

pharmacokinetic response if sampling had been delayed until 10 min after heparin dosing.

Combining our results with those from previous clinical studies, a three-phase pharmacokinetic process appears plausible after a high-dose heparin bolus: 1) rapid distribution, 2) zero-order elimination, and 3) first-order elimination. Previous studies may have missed heparin's actual peak and possible early peripheral distribution by beginning their post-heparin assay 10 or more min after intravenous heparin. Studies using longer sampling intervals and following heparin's effect for several hours have found elimination half-lives of 30-150 min, depending upon dose, body temperature, the sensitivity of the heparin assay, and patient variability.<sup>22,23</sup> Unfortunately, the 20-min span of our ACT sampling cannot adequately serve as a pharmacokinetic model. We concluded our study before CPB, because CPB distorts both heparin's elimination pharmacokinetics and the relationship between ACT and plasma heparin concentration.<sup>7,8</sup>

Based upon heparin's anticoagulation decay and upon the observation by Young *et al.* that fibrin monomers appear during CPB in monkeys having ACT values below 400 seconds,<sup>24</sup> Bull *et al.*'s recommended pre-CPB target ACT of 480 s seems reasonable.<sup>2</sup> Bull *et al.* recommended a two-stage process beginning with a heparin dose of 200 IU/kg, then extrapolating a 5-min ACT to 480 s, assuming a linear dose-response relationship. What is the most appropriate ACT sampling interval following heparin administration? We cannot pinpoint heparin's peak action, but 2 min is adequate for full anticoagulation under most clinical circumstances. Whereas Effeney *et al.*<sup>4</sup> suggest that Bull *et al.*'s<sup>2</sup> 5-min ACT sampling method precedes heparin's peak action, our study shows that the 5-min interval usually follows peak anticoagulation. For testing anticoagulation adequacy before CPB, we suggest focusing on the steady-state heparin level rather than on the pre-distribution peak. Because the 5-, 10-, and 15-min ACT values were practically identical, the 5-min interval appears most expeditious; thus, we agree with the 5-min sampling interval recommended by Bull *et al.*

In summary, we have shown that peak anticoagulation after intravenous heparin usually occurs within 2 min. As a result of probable heparin distribution into capillary endothelium, anticoagulation diminishes significantly between 2 and 20 min, with the greatest decrease occurring between 2 and 5 min after heparin administration. A 5-min interval after heparin appears optimal for ACT sampling. Should CPB begin more than 20 min following heparinization, the level of anticoagulation may have already diminished enough to warrant additional heparin.

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## Sufentanil Analgesia Following Cesarean Section: Epidural Versus Intravenous Administration

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Administration of epidural opioids for the relief of postoperative pain has become a common practice in the management of cesarean section patients.<sup>1</sup> Although morphine and other long-acting agents have been used commonly for this purpose, the risk of delayed respiratory depression from cephalad spread of the opiate in the cerebrospinal fluid remains a disadvantage for patients who are not normally intensively monitored.<sup>1-3</sup> Another disadvantage of epidural morphine relates to its low lipid solubility and slow onset of action. Theoretically, these drawbacks should be less