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Variability of the Activated Coagulation Time

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Since its introduction by Hattersley in 1966, the activated coagulation time (ACT) of whole blood has become a popular bedside test for assessing heparin-induced anticoagulation (1). Because of its simplicity and expediency, ACT has gained widespread use in cardiac and vascular surgical procedures and has had some use in hemodialysis. Many centers use ACT during cardiopulmonary bypass (CPB) procedures to ensure adequate heparin-induced anticoagulation before and during CPB, to predict the protamine dose needed to neutralize heparin, to confirm the adequacy of protamine neutralization, and to diagnose heparin rebound (2-7). Because small changes in the ACT often dictate clinical therapy with heparin or protamine, this study was designed to determine ACT variability in individual patients during cardiac surgical procedures.

Methods

After obtaining protocol approval from the institutional human studies committee, 46 patients undergoing cardiac surgical procedures requiring CPB (38 coronary artery bypass, 8 valve replacements) were studied. Each patient had two simultaneous ACT determinations at three different times during the procedure: 1) control: drawn before inducing anesthesia, 2) heparin: drawn 5 minutes after receiving an intravenous heparin bolus, and 3) protamine: 5 minutes after completing protamine infusion after CPB. Patients receiving intravenous or subcutaneous heparin within 12 hours of surgery were excluded.

ACT samples were drawn from the left radial artery at a site separated from the bloodstream by a three-way stopcock, a 15-cm segment of Gould high-pressure tubing, and a 5-cm, 20-gauge Angiocath (Becton Dickinson, Sandy, UT) catheter. To clear the sampling site of heparin flush solution, a 5-ml sample was withdrawn before taking two consecutive 2-ml ACT samples. This volume was selected to ensure an adequate discard volume to negate the 0.7-ml sampling dead space (8).

ACT samples were drawn into a 3-ml plastic syringe and a 2.0-ml aliquot of this was then transferred via an 18-gauge needle into an International Technidyne (Edison, NJ) vacuum-sealed Celite-activated ACT tube within 30 seconds. After vigorously shaking the tube, it was placed in one of four International Technidyne Hemochron chambers. Timing began as the blood sample entered the ACT tube. Each ACT tube then rotated automatically in a 37°C heat block chamber. Each tube contained a magnetic rod that remained in a dependent position until engaged by fibrin clot formation, at which time a sensor detected a change in magnetic attraction and automatically stopped the tube rotation and the timer. Experienced technicians placed the samples in the tubes and the tubes in the Hemochron device and tested these devices regularly to assure consistent 37°C heat block temperature and rotational speed.

Beef lung heparin (Upjohn, Kalamazoo, MI) doses (300 IU/kg) were administered as a bolus through the right atrial port of a pulmonary artery catheter before cannulating for CPB. After selecting protamine doses by a protamine titration method (HemoTec Hepcon,
Table 1. Paired ACT Results with Coefficient of Variation

|               | Mean ± sd | Range          |
|---------------|-----------|---------------|
| ACT-control (sec) | 133 ± 18  | 93.5-198.5    |
| ACT-heparin (sec) | 526 ± 123* | 292.5-887.5  |
| ACT-protamine (sec) | 122 ± 13* | 95.0-153.5    |
| CV-control (%)   | 3.9 ± 5.0  | 0-26.5        |
| CV-heparin (%)   | 7.8 ± 6.9  | 0.2-38.1      |
| CV-protamine (%) | 3.1 ± 2.7  | 0-10.4        |

*P < 0.05, compared with control ACT.

Englewood, CO), protamine was infused over 5–10 minutes into the right atrium.

For each paired sample, mean and standard deviation (sd) were derived to determine the coefficient of variation (CV = 100 × sd/mean). Means and standard deviations were also calculated for the entire study population at each of the three sampling times. The mean ACTs for the heparin and post-protamine measurements were compared with the control ACT by paired t-tests.

Results

Table 1 shows the mean, sd, and range after averaging each ACT pairing, and the mean coefficients of variation (CV) obtained from the individual pairings. Figure 1 shows the frequency distribution of the absolute value of the difference between the two ACTS at the control, heparin, and protamine measurement periods. The CV values in Table 1 show increased within-patient ACT variability after giving heparin. Between-patient variability also increases after heparin, as judged by the range of the mean heparin ACT (Table 1). Table 2 lists statistics based on mathematical differences in the paired observations. After heparin, 40 of 46 (87%) ACT pairs differed by more than 15 seconds, whereas differences that large occurred in zero protamine and three (15%) control ACT pairs.

Discussion

The CV expresses the percentage variability of observations relative to the mean. The manufacturer's technical literature about the Hemochron device reports a CV of 4%, which presumably represents the variability of ACT values in normal individuals in the absence of anticoagulants. In the present report, each reported CV mean reflects the average of 46 CVs, each of which was derived from two observations. The CV would remain constant if the standard deviation of the paired ACT differences (Table 2) increased in proportion to the heparin-induced increase in mean ACT. The CV values indicate that ACT variability doubles after heparin doses sufficient to establish CPB.

The original manual ACT method described by Hattersley (1) may demonstrate less variability than the automated Hemochron method. However, Mabry and colleagues compared these two ACT methods and showed a closer correlation between manual and automated ACT methods after heparin-induced anticoagulation than before it (9). Their heparin doses produced lower ACT values (approximately 180–300 seconds) suitable for vascular surgery, and they did not perform paired observations with each ACT technique. Timed coagulation tests display diminished reproducibility as the clotting time prolongs (10-12). One advantage to selecting the ACT to monitor anticoagulation during cardiac surgery is that other clotting time methods (e.g., activated partial thromboplastin time, thrombin time) become either incoagulable (infinite) or highly variable at heparin concentrations below those usually required for safe CPB (10,13-15). Hemodilution and hypothermia prolong the ACT, distorting the relation between ACT and heparin concentration during CPB (16-18) and potentially complicating the diagnosis of inadequate anticoagulation during CPB. Hemodilution and hypothermia might further increase ACT variability, a possibility not investigated in the present study. After giving heparin (but before the hemodilution and hypothermia induced by CPB), the median difference between paired ACTs was 47 seconds (Table 1), with 19 of 46 (41%) pairings differing by more than 50 seconds (Fig. 1).

When using the ACT to guide clinical decisions, it would be desirable to establish an ACT value that clearly warrants supplemental heparin. Young et al. (5) used the Hemochron automated ACT method to establish the clinical safety of maintaining an ACT above 400 seconds during CPB in six children. Could ACT variability influence interpretation of Young et al.'s results? If they had averaged simultaneous paired or multiple ACT measurements, quite possibly some of their maintenance ACT values (>400 seconds by design) would have been more than 100 seconds above or below the values they observed. Consequently, it appears plausible that lesser ACT values existed and provided safe CPB anticoagulation. Young et al.'s recommended minimum ACT value (400 seconds) probably incorporates a safety margin that compensates for ACT variability. Using their recommendation, some patients would likely receive heparin doses exceeding the minimum required to
prevent subclinical coagulation during CPB, but the overall effect on patient safety would be positive. Perhaps future investigations will more precisely establish a minimum safe ACT during CPB while incorporating ACT variability into this determination.

Clinicians using the CPB heparin management protocol recommended by Bull et al. (3) should be aware that post-heparin ACT variability will influence the observed ACT response to incremental heparin doses. Bull et al.'s description of the ACT vs heparin titration shows considerable variation in the obtained ACT values despite constructing a two-stage heparin dosing protocol that was mathematically designed to produce an ACT value of 480 seconds (observed ACT range, 400 to 600 seconds in 25 patients) (3). Applying the same principle to maintain an ACT between 180 and 200 seconds (or twice the control value) for vascular surgery, however, Mabry et al. (19) observed ACT values within 5% of the predicted ones. The findings in these two studies are compatible with increasing test variability as a function of mean ACT. Interpretation of the ACT response to heparin is further complicated by the possible loss of a linear dose–response relation at ACT values exceeding 600 seconds (20). The present study indicates that clinicians should expect considerable variation in single-measurement ACT responses to heparin doses even within the presumed linear portion of the dose–response relation (ACT values below 600 seconds). Routine clinical use of averaged duplicate ACT measurements would provide more consistency, but this approach seems impractical. Combining the present findings with those from previous studies (16–18,21), one might wonder whether monitoring heparin concentrations would be safer than monitoring the ACT alone. We believe that the studies of Young et al. (5) and Haddon et al. (22) validate the ACT as an independent determinant of adequate anticoagulation for CPB. The present study simply casts doubt on rigid application of minimum acceptable ACT values for CPB and precise expectations regarding ACT response to supplemental heparin doses during CPB.

ACT variability during anticoagulation could also impair the reliability of the ACT dose–response relation for determining the protamine dose for heparin neutralization. Because hemodilution and hypothermia increase the ACT for a given heparin concentration, the ACT may overestimate protamine dose requirements. Cohen (23) suggests that this CPB-induced ACT distortion diminishes over time during CPB, but his observations might have been influenced by systemic rewarming. Other investigations indicate that CPB rewarming reduces the ACT, but that the ACT prolongation at a specific heparin concentration still exceeds that observed before initiating CPB (16,22). Considering that lower protamine doses reduce postoperative bleeding (4,24), measuring blood heparin concentration (e.g., protamine titration) should predict protamine dose requirements more accurately than the ACT dose–response relation. Alternatively, averaging paired simultaneous ACT samples on resuming normothermia should
improve ACT reliability when predicting protamine doses.

When assessing the adequacy of protamine neutralization of heparin, the ACT should return to the preanesthesia control level (or less) in most instances. Average post-protamine ACT values fell significantly below preanesthesia control values (Table 1), and only 7 of 46 (15%) pairings differed by more than 10 seconds. When using the ACT to diagnose subsequent heparin rebound, an increase of 15 seconds or more would be strongly suggestive and should nearly eliminate ACT test imprecision as an explanation for the change. Factors other than heparin rebound could also contribute to an ACT increase (e.g., clotting factor deficiency, severe platelet deficit or dysfunction).

In conclusion, the ACT becomes much less reproducible in the anticoagulated state, and clinicians should allow for this when using ACT to guide therapeutic decisions. Once prolonged beyond 300 seconds, one should not expect ACT to produce pinpoint accuracy in determining heparin or protamine doses. Maintaining ACT values over 400 seconds during CPB probably constitutes safe anticoagulation. In view of ACT variability and the small number of patients investigated by Young et al. (5) and Haddon et al. (22), it appears desirable to confirm that standard with further studies.

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