
Activated Clotting Times and Cardiopulmonary Bypass I: The Effect of Hemodilution and Hypothermia upon Activated Clotting Time

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Introduction

Anticoagulation during extracorporeal circulation is achieved by a variety of protocols.^{1,2,3,4,5} Of those routinely used, the most convenient method of heparin management utilized the activated clotting time (ACT) and dose-response curve (DRC) as described by Bull.⁶ It has become apparent, however, that a number of factors other than heparin concentration influence the ACT. This study was designed to quantitate the effects of hemodilution and hypothermia on the ACT.

Methods

Twelve adult patients undergoing coronary artery bypass grafting who did not require a blood prime were included in this study. The perfusion circuit employed a Modular Pump and consisted of a membrane oxygenator, polyvinyl chloride tubing, a Pall* arterial line filter and a Bentley** Q220-F cardiotomy reservoir. The circuit was primed with 2 liters of Ringers Lactate, 500 ml. 6% hydroxyethyl starch (Colloid)*** and 1500 units beef lung heparin.**** A heparin loading dose of 300 u/kg body weight was administered to the pa-

tient immediately prior to cannulation for cardiopulmonary bypass (CPB). Patients that required the administration of either homologous blood or additional heparin during CPB were eliminated from this study. Furthermore, any patient exhibiting an abnormal blood volume as demonstrated by an indicator dilution method was excluded.

All clotting studies were performed using a heating block set at 37° C. The Hattersley ACT technique⁸ was used with the exception that the tubes were tilted every 10 seconds rather than 5 seconds. True heparin concentration was determined by protamine titration.⁹ One ml. of blood was added to each of 5 Lee-White tubes containing respectively: .005, .015, .025, .035 and .045 milligrams of protamine. After thorough mixing, the tubes were allowed to sit for two minutes in the heating block. Each tube was then tilted every 30 seconds until a solid clot was obtained in one of the tubes. Since protamine also prolongs clotting, the tube which clotted first indicated exact heparin neutralization and thus heparin concentration.

Activated clotting time and protamine titration blood samples were drawn simultaneously from a well-flushed port at the following times:

- | | |
|---------------------|--|
| 1. Baseline sample: | Prior to any major surgical trauma and heparin administration. |
| 2. Prior to CPB: | Five minutes following heparin administration to |

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* Pall Biomedical Products Corporation, Glen Cove, New York 11542

** Bentley Laboratories, Irvine, California 92714

*** Arnar-Stone Laboratories, McGaw Park, Illinois 60085

**** Upjohn Laboratories, Kalamazoo, Michigan 49001

3. On CPB sample:

establish the dose-response curve.

Five minutes after initiation of bypass and prior to the induction of hypothermia; to measure the effect of hemodilution.

4. During mild or moderate hypothermia:

To measure the effect of a decreased temperature.

5. Once rewarmed:

To measure the effect of a return to normothermia.

The activated clotting time and heparin concentration results were manipulated into an ACT/heparin concentration index by dividing the ACT by the heparin concentration to emphasize the non-heparin induced changes in the ACT. The data were analyzed with the Student's t-test.

Results

Before CPB was initiated (after heparinization), the patient's heparin concentration was determined to be 4.5 units heparin/ml. blood in every case. The pre-CPB ACT averaged 416 ± 74 seconds and the calculated ACT/heparin concentration index averaged 92 ± 17 seconds/unit heparin/ml. blood (Figures 1 and 2).

Once CPB was instituted, the ACT became prolonged in spite of the fact that heparin concentration decreased (Figure 1). Heparin concentration decreased an average of 27% once on CPB, which proved to be significant ($p < .005$). The ACT extended with hemodilution an average of 8.4% reaching levels of 451 ± 77 seconds. The combined effect of an increasing ACT together with a decreasing heparin concentration caused a significant increase in the ACT/heparin concentration index to levels of 139 ± 34 sec/u/ml. ($p < .005$) (Figure 2).

The effect of hypothermia on the ACT was apparent although less predictable. At an average temperature of $27 \pm 3^\circ \text{C}$, the average ACT was 511 ± 103 seconds, a prolongation of 13.3% in comparison with the on-CPB ACT (Figure 1). The average heparin concentration concurrent with hypothermia was 3.1 ± 0.5 u/ml., a decrease of 6%, not a significant change in comparison with the on-CPB data (Figure 1). Although the heparin concentration did not change significantly with cooling, the extension in the ACT was sufficient to cause a marked increase in the ACT/heparin concentration

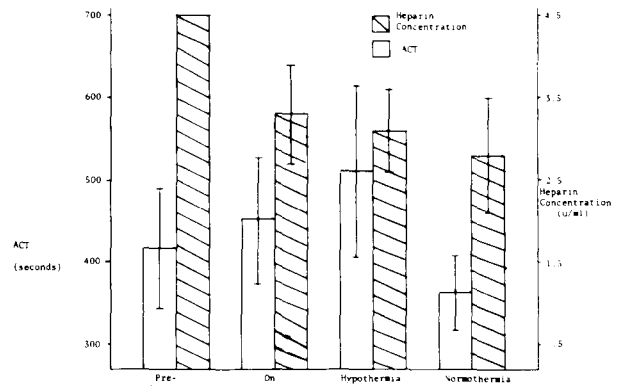


FIGURE 1. Effects of hemodilution and temperature changes on the ACT and heparin concentration.

index to levels of 173 ± 45 sec/u/ml. ($p < .050$) (Figure 2).

Prior to the termination of bypass, at an average blood temperature of $36 \pm 1^\circ \text{C}$, the ACT shortened by 29% to levels of 363 ± 44 seconds ($p < .005$) (Figure 1). In spite of a non-significant decrease in the heparin concentration at this time, the ACT/heparin concentration index became significantly shortened to levels of 135 ± 30 sec/u/ml. ($p < .025$) (Figure 2).

Discussion

This study demonstrates that the ACT is affected during several stages of CPB independent of heparin concentration. Upon the initiation of CPB, hemodilution causes a marked non-heparin induced increase in the ACT. This phenomenon was apparently due to the dilution of clotting factors occurring in spite of a decreasing heparin concentration.⁷ With hypothermia the ACT was further extended despite a concurrent decrease in heparin concentration. This extension is

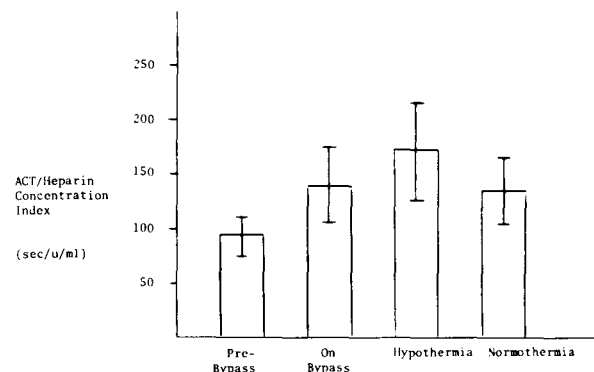


FIGURE 2. Effects of hemodilution and temperature changes on the ACT/heparin concentration index.

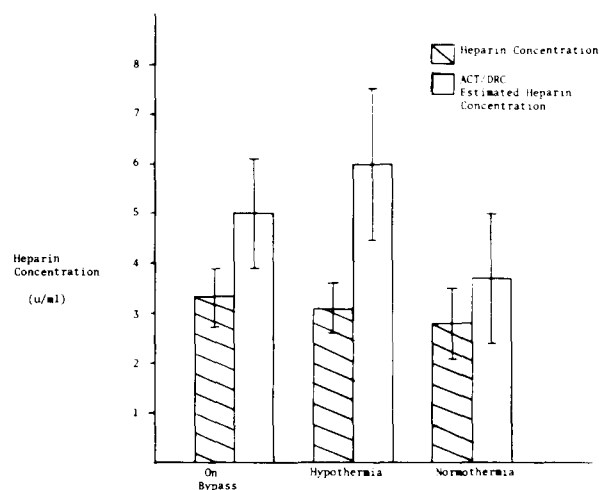


FIGURE 3. Heparin concentration estimation with the ACT/DRC during several stages of CPB.

probably due to the reduced rate of activity of enzyme systems needed for coagulation during hypothermia. Heparin concentration estimation based upon the ACT/DRC during these conditions would result in false high results (Figure 3).

Upon rewarming, the return of the ACT towards baseline may be attributed to a combination of factors. The continual loss of fluid volume from the vascular compartment either due to diuresis or translocation of priming volume to the interstitial space (third spacing) results in hemoconcentration. Furthermore, the enzyme systems are activated at normothermia. Finally, heparin is being continually degraded.³

The ACT/DRC heparin concentration data in Figure 3 were derived to exemplify the error attendant in using the ACT to predict heparin concentration during CPB. With hemodilution an average error of 51% occurred. This error was significantly extended during hypothermia reaching levels of 93% ($p < .05$). The data in Figure 3 indicate that the error associated with the normothermic ACT at the end of CPB is still large (32%) and its use as an estimation of protamine dose needs further investigation.

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