

Monitoring Heparin and Protamine Therapy during Cardiopulmonary Bypass by Activated Clotting time

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Cardiopulmonary bypass depends on our ability to control the coagulation system. Heparin and protamine have been used for this purpose since the introduction of cardiopulmonary bypass. Although heparin has been used as an anticoagulant since 1935 there are still some unsolved questions as regarding its structure and metabolism.^{1,2} Many principles have been proposed for total heparinization, most of which are based upon the patient's weight or surface area. The sense of security during these procedures was heightened by the fact that serious errors in the control of heparin therapy could occur without any immediate clinical evidence.

In 1975, Brian Bull brought to our attention, that the control of heparin during and neutralization of heparin after extracorporeal circulation was not a straight forward matter which could be adequately handled by means of set protocols. Some monitoring of the therapy was needed.³⁻⁴

Although several techniques for such control are available, it is difficult to find a satisfactory one. For example the Lee-White clotting time is inaccurate and time consuming. The activated partial thromboplastin time and the thrombin time are more accurate, but require time for blood centrifugation, preparation of plasma and the help of a skilled technician.

In 1966, Hattersley⁵ described the activated coagulation time (ACT) of whole blood. A more recent modification is the *Hemochron* activated clotting time, which is estimated in an automated coagulation timer manufactured by Hemochron®, Int. Technidyne Corp., New Jersey. The technique is simple and can be performed immediately in the operating room without the use of specially trained technicians. Three ml of blood are drawn in an evacuated tube containing celite, glass beads and a small bar magnet. The test tube with blood is agitated vigorously prior to insertion in the coagulation timer. The instrument is thermostated at 37°C and rotates the tube slowly along its axis of symmetry. When fibrin forms the bar is displaced and the coagulation time is displayed in seconds.

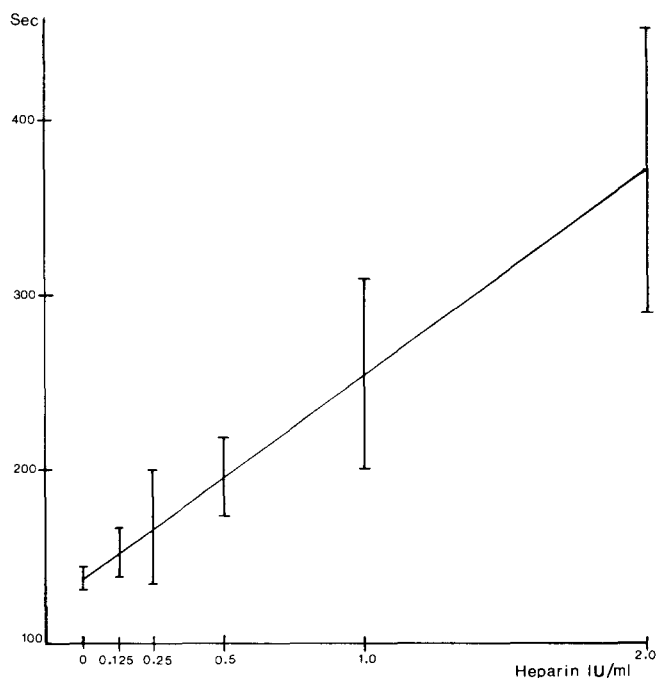


Fig. 1. *In vitro* study of relations between heparin concentration and activated clotting time. (ACT). A mean of 10 individual curves. Abscissa: Heparin IU/ml. Ordinate: ACT in seconds.

The activated whole blood clotting time has been studied *in vitro*.⁶ In healthy controls, the ACT is normally distributed with a mean of 131 seconds (SD 6).

Blood samples from 26 patients scheduled for open heart surgery showed a mean ACT of 122 seconds.

ACT was estimated in blood samples from patients with thrombocytopenia because depletion of platelets is regularly noticed during and after cardiopulmonary bypass. The mean ACT in five such patients, in which platelet counts ranged from 30 to $77 \times 10^6/l$ was 130 seconds with a range between 108 and 139 seconds.

The effect of hemodilution, which is commonly induced during cardiopulmonary bypass, was studied *in vitro*. The hematocrit was reduced to values between 20 and 24 by adding lactated Ringer's solution to the blood samples. This hemodilution failed to raise the ACT.

The effect of heparin was studied *in vitro* by adding heparin to blood samples (final concentration 0.125 to 2 units per ml). A linear relationship between the concentration of heparin and the ACT was found (Fig. 1).

A wide range of sensitivity to heparin was recorded *in vitro*. Fig. 2 shows 10 individual heparin curves, which resulted in the mean curve shown in Fig. 1. In some samples, trace amounts of heparin produced a steep rise in ACT followed by a plateau, whereas other samples proved insensitive to low heparin concentrations while higher concentrations caused a continuous prolongation of the ACT.

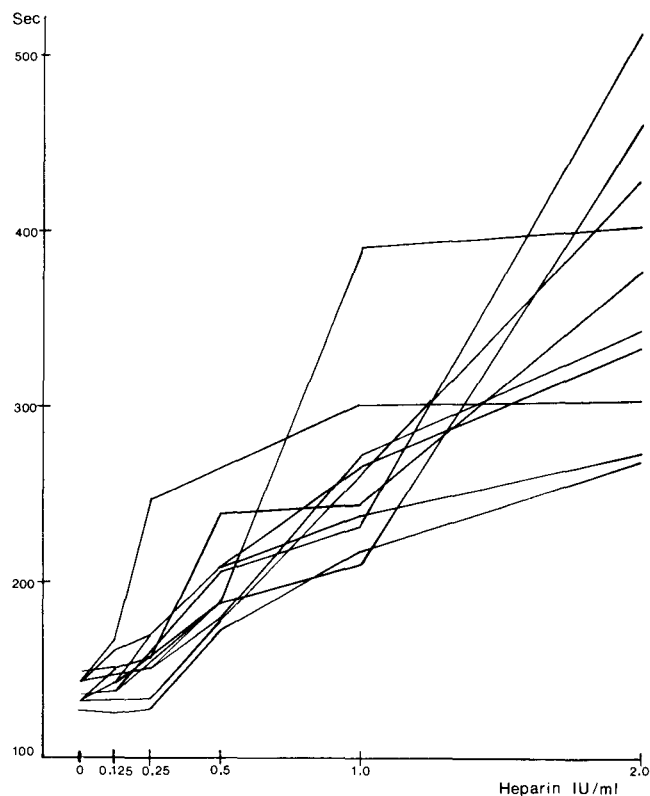


Fig. 2. Individual curves from 10 normal individuals relating the heparin concentration to the activated clotting time. Abscissa and ordinate as in Fig. 1.

The effect of hemodilution on heparinized samples was furthermore studied. In average, a hematocrit of 31 did not prolong the ACT and the dose-response curve was not altered in comparison to the nondiluted curve. (Fig. 3). A further dilution of the blood to a hematocrit of 22 gave the same result.

Based on these *in vitro* studies it was anticipated that individual dose-response curves had to be constructed in the clinical situation.

The base line ACT was determined at the start of surgery, and 200 units of heparin per kg bodyweight were then administered. Five minutes later a second ACT was determined. From these two values a dose-response curve was constructed and the amount of heparin required to prolong the ACT to 480 seconds was read from the curve and administered. At the end of bypass, heparin was neutralized with protamine chloride. The ACT was measured and the actual heparin level in units per kg bodyweight was read from the curve. The final protamine dose in mg was found by multiplying the heparin units per kg, by the patient's weight in kg and the factor 0.013. A final ACT was determined to confirm that the heparin was fully neutralized.

With this technique we found that our patients could be divided into three groups with a high, a "normal," and a low sensitivity to heparin.

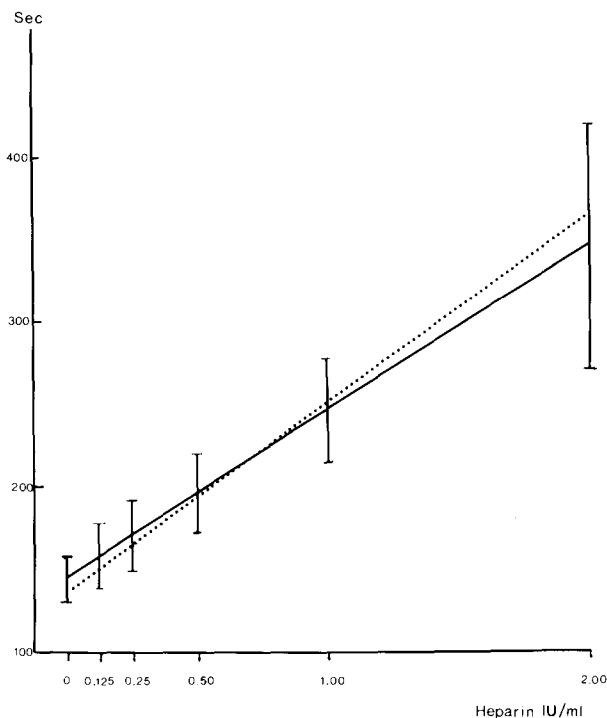


Fig. 3. *In vitro* study of the relation between heparin concentration and the activated clotting time of whole blood (solid line) and hemodiluted blood (hematocrit of 31) (dotted line). Abscissa and ordinate as in Fig. 1.

Fig. 4 is a dose-response curve from a patient who had coronary surgery and who had an average response to heparin. The basic ACT was 134 seconds. After 200 units of heparin per kg, the ACT was 355 seconds. The curve was constructed, and showed

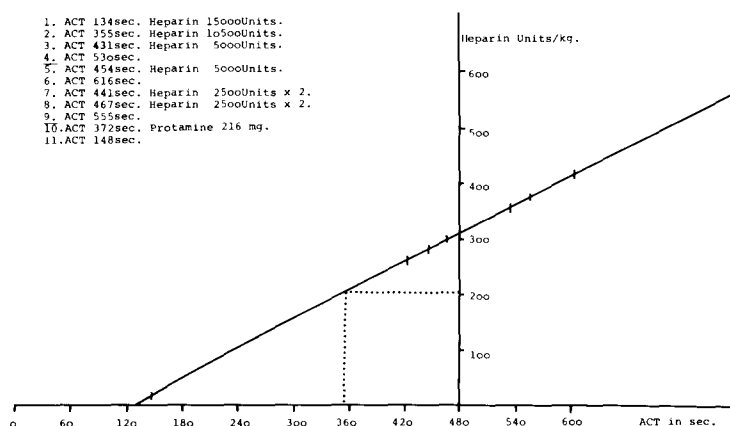


Fig. 4. Dose-response curve from 55 year old male with normal sensitivity to heparin. Weight 75.5 kg. Operation: Aorta coronary saphenous vein bypass.

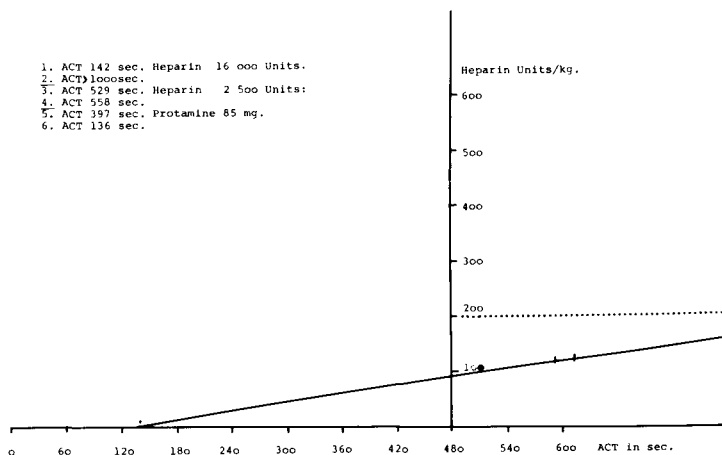


Fig. 5. Dose-response curve from a 52 year old male with a high sensitivity to heparin. Weight 80.1 kg. Operation: Mitral valve replacement.

that another 140 units of heparin should be given in order to reach an ACT of 480 seconds. Meanwhile some heparin had been metabolized and another dose of 70 units was given before the start of bypass. During bypass, the ACT was maintained around 480 seconds by administering 2.5 units of heparin for each unit of blood transfused. At the end of bypass, the heparin level was determined and neutralized by 216 mg of protamine. The final ACT showed that the heparin had been neutralized. The postoperative bleeding was 410 ml over 12 hours.

Fig. 5 is a dose-response curve obtained in a patient who had mitral valve replacement. A dose of 200 units of heparin was enough to prolong the ACT to more than 1.0 seconds. The ACT was returned to normal by 85 mg of protamine. The postoperative bleeding was 250 ml over 12 hours.

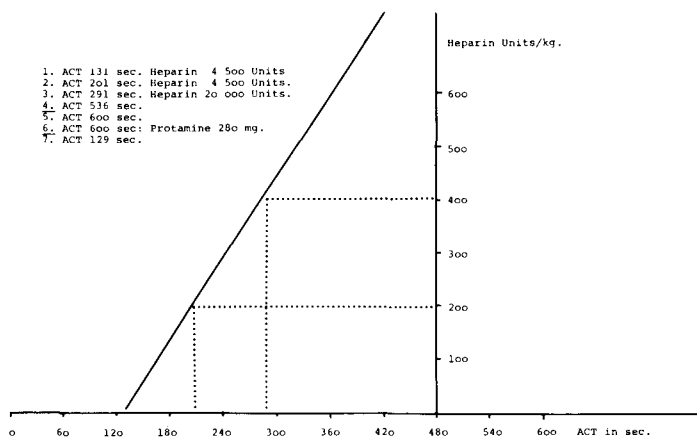


Fig. 6. Dose-response-curve from a 7 year old boy with a low sensitivity to heparin. Weight 21.9 kg. Operation: Closure of ventricular septal defect.

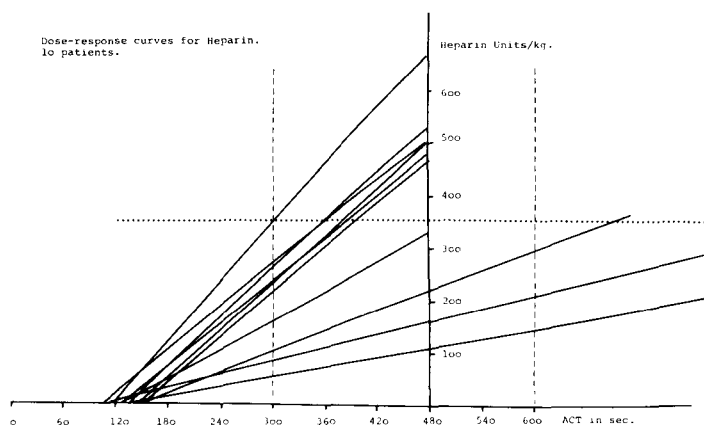


Fig. 7. Dose-response curve from 10 consecutive patients.

Fig. 6 is an example of a 7 year old boy who had a ventricular septal defect. The test dose of 200 units per kg of heparin only raised the ACT a little. Another dose of 200 units per kg was given, confirming that the patient was highly insensitive to heparin. After a dosage of 29. units of heparin (1.329 units per kg) the patient was fully heparinized with an ACT of 536 seconds. Because of the large dose of heparin, 285 mg of protamine was necessary for neutralization. The postoperative bleeding was 130 ml over 12 hours. It is evident that a regular protocol of 350 units of heparin per kg would have given the patient little protection from consumption coagulopathy during bypass.

About 35% of our clinical cases were highly sensitive to heparin, 18% could be fully heparinized on a dosage of less than 100 units per kg and 36% of the patients were insensitive to heparin and needed more than 350 units of heparin per kg in the initial dosage. 7% needed more than 1000 units per kg.

The criteria for adequate anticoagulation includes prevention of: 1) the consumption of clotting factors; 2) the formation of microscopic deposits of fibrin in the extracorporeal circuit; and 3) the appearance of thrombin-degraded fibrinogen (fibrin monomers) in the plasma.⁷ The latter substance is known to be a sensitive indicator of activation of the coagulation process. We have found no fibrin monomers at the end of bypass (Ethanol gelation test)⁸ when the ACT is sustained at 400 seconds or more. If too little heparin is given initially, the ACT will increase with the bypass time, not because of excess heparin, but because of partial consumption of clotting factors and the production of fibrin degradation products.

Fig. 7. shows dose-response curves from 10 consecutive patients who had cardiopulmonary bypass. There was a great variation in the heparin requirement and it is obvious that a fixed protocol for heparinization is far from satisfactory and leaves a significant number of patients at unsafe levels of anticoagulation. With a Hemochron test at hand, it is technically possible to determine the clotting time every 10 minutes and the construction of a dose-response curve seems a valuable adjunct to secure optimal heparinization.

Using the ACT test, a precise neutralization with protamine can easily be achieved. By this technique we have reduced the postoperative bleeding over 12 hours from an average of 600 ml to 289 ml.

In conclusion, it is impossible to predict a patient's sensitivity to heparin. Even given the patient's age, weight, surface area or blood volume, it is impossible to manage heparin therapy according to a fixed protocol. With a fixed dose of 400–500 units of heparin per kg there are about 10% of the patients who escape proper heparinization. Under these circumstances some monitoring of therapy is needed and the activated clotting time has proven to be a reliable and uncomplicated method.

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