Heparin Resistance prior to Cardiopulmonary Bypass

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The activated clotting time (ACT) is used as a rapid means for determining anticoagulation after heparin. Using the ACT as a monitor, a case is described in which anticoagulation before cardiopulmonary bypass (CPB) was achieved only with substantial doses of heparin.

REPORT OF A CASE
A 71-yr-old female with a history of coronary artery disease, including three previous myocardial infarctions, was scheduled for coronary artery bypass grafting. Her last myocardial infarction occurred 3 weeks before surgery and was associated with ventricular fibrillation, from which she was successfully resuscitated. Because she continued to experience unstable angina after her resuscitation, the decision was made to proceed with surgery. Her past history included asthma for several years, borderline diabetes mellitus, and peptic ulcer disease. The patient was allergic to aspirin and aminophylline, which caused gastric irritation and hives, respectively. She weighed 50 kg and had been receiving a heparin infusion for 8 days before surgery that maintained her activated partial thromboplastin time (APTT) 2-2.5 times control. The heparin infusion was discontinued 22 h before the surgical procedure. The patient was also receiving procaine, quinidine, digoxin, furosemide, cimetidine, and diprydamole. Her preoperative laboratory studies included: hemoglobin 12.1 g/dl, potassium 4.5 mEq/l, creatinine 1.7 mg/dl, old inferior and anterolateral myocardial infarctions on the ECG, and the presence of moderate restrictive and obstructive defects on the pulmonary function test. The angiogram revealed the presence of severe, three-vessel coronary artery disease, while the ventriculogram noted a thrombus in the left ventricle. The left ventricle was also hypokinetic and had an ejection fraction of 27%. On the morning of surgery, the prothrombin time (PT) was 12.2 s, the APTT 26.0 s, and platelet count 450,000/mm³.

At 0545 the patient was premedicated, and at 0700 she was transported to the operating room. Multiple percutaneous lines, including a right radial arterial line and a flow-directed pulmonary artery catheter via the right internal jugular vein, were then inserted. At 0730 anesthesia was induced with diazepam, pancuronium, fentanyl, and lidocaine iv. The induction was uneventful, and, after additional fentanyl was given, the surgical incision was made at 0805. Heparin was administered sequentially with poor results in the corresponding ACT prior to CPB (table 1). At 1202, CPB was successfully terminated. Between 1210 and 1250, a total of 800 mg protamine was infused. At 1240, the ACT was 140 s, and the protamine titration (Hepcon®) demonstrated complete reversal. At 1400, bleeding was noted and was terminated by 100 mg of protamine iv during the next 30 min, resulting in an ACT of 150 s. At 1500, in the intensive care unit, the PT was 14.9 s and APTT 27.0 s. Forty-eight hours after the surgical procedure, an antithrombin III (AT III) level was 50% of normal. The patient did well postoperatively and was discharged from the hospital 8 days later.

DISCUSSION
The ACT was initially designed by Hattersley for rapid determination of coagulation disorders, exclusive of those caused by platelets and Factor VII deficiency. Hill et al. used the ACT as a means of determining proper heparin and protamine doses during CPB. Bull et al. analyzed five heparin protocols representative of about 30 protocols throughout the country in 1975. By computer simulation, the protocols failed to provide safe anticoagulation as determined by a precise protamine neutralization. Bull et al. then suggested forming individual dose–response curves from three ACT determinations to individualize the heparin and protamine dosage. This then would eliminate the problem of excessive administration of heparin and protamine and enable the physician to diagnose and treat postoperative bleeding problems much more readily. They considered the anticoagulant effect as highly questionable with ACT levels between 180 and 300 s and as inadequate at levels below 130 s. Consequently, Bull et al. recommended the ACT be kept above 300 s for CPB and designed a curve for heparin doses arriving at an ACT of 480 s. Jobes et al. proposed 300 s to be the safe minimum level for anticoagulation during CPB. Young et al., however, observed in rhesus monkeys that fibrin monomers appear during CPB at ACT levels lower than 400 s.

Although several protocols for heparin administration have been proposed, a fixed heparin dose based on body weight or surface area is commonly used. Bull et al. state that the value of the ACT is to determine not whether too much heparin is given, but too little, with a precipitation of a disseminated intravascular coagulation (DIC). They noted that in a patient population of reasonable size, patients will vary four-fold in their heparin sensitivity and three-fold in the rate at which heparin is degraded. Heparin requirements, therefore, span a twelve-fold range. Patients receiving too little heparin are the ones

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in danger. In greater than 3,000 cases using the ACT since 1973, Bull and colleagues have had no instances of a postoperative DIC.\textsuperscript{9}

Although infrequently seen in certain groups of patients, the exact cause of heparin resistance in patients undergoing CPB remains unknown.\textsuperscript{10,11} The patients' age, weight, sex, \textit{in vitro} heparin sensitivity, and heparin decay rates have had no predictive value.\textsuperscript{1} Heparin does interact with aspirin and ethacrynic acid. Although antihistamines, dextran, digitalis, nicotine, quinine, and tetracycline can interfere with the anticoagulant activity of heparin, there is no substantial literature support for such interactions.\textsuperscript{†} Many other causes of increased heparin resistance have been reported (table 2). A continuous stimulus for low-grade activation of the clotting cascade can also result in heparin resistance by consumption of AT III and release of platelet factor 4.\textsuperscript{18}

Esposito \textit{et al}.\textsuperscript{18} described two types of heparin-induced thrombocytopenia. The more common type (occurring in 30 to 40\% of patients) is seen after the administration of heparin and is secondary to transient reversible clumping, agglutination, and peripheral sequestration of platelets caused by a direct interaction with heparin. This type does not appear to be significant clinically. The second type usually occurs 7 to 10 days after treatment and is thought to be the result of heparin-induced platelet antibodies. With this type over 50\% have been associated with thromboembolism, and 38\% have been related to subsequent heparin resistance. In a patient who has received previous heparin therapy, the presence of a heparin-induced thrombocytopenia should be suspected when the patient develops increasing heparin requirements as

\begin{table}
\centering
\caption{The Patient’s Anticoagulation Profile}
\begin{tabular}{|c|c|c|c|c|}
\hline
Time & Heparin Given & Total & Heparin Dose & Other & ACT \\
 & (mg) & (mg) & (mg/kg) & (s) & \\
\hline
0630 & 150 & 150 & 5 & PT = 12.2 s & 107* \\
0830 & 50 & 200 & 4 & APTT = 26.0 s & 220 \\
0910 & 100 & 300 & 6 & platelets = 450,000/mm\textsuperscript{3} & 229 \\
0945 & 250 & 550 & 11 & 3 u FFP given & 290 \\
0950 & 300 & 850 & 17 & PT > 46 s & 430 \\
1032 & 350 & 1200 & 24 & APTT > 100 s & 602 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{*} Not measured, but derived from the equation determined by Dauchot \textit{et al}: ACT = (APTT + 15.99)/0.39\textsuperscript{6}

\begin{table}
\centering
\caption{Diseases or Situations Causing Increased Heparin Resistance\textsuperscript{2,16,17,17}}
\begin{tabular}{|c|}
\hline
1. Infective endocarditis \\
2. Intravascular balloon counterpulsation \\
3. Hypereosinophilic syndrome \\
4. Oral contraceptives \\
5. Shock \\
6. Low grade intravascular coagulation \\
7. Previous heparin therapy \\
8. Previous streptokinase \\
9. Presence of a clot within the body \\
10. Congenital antithrombin III (AT III) deficiency \\
11. Pregnancy \\
12. Neonatal respiratory distress syndrome \\
13. Increased platelet levels \\
14. Increased factor VIII levels \\
15. Secondary decrease in AT III levels \\
16. Ongoing clotting and utilization of heparin \\
\hline
\end{tabular}
\end{table}

AT III concentration is reduced to less than 10% of normal. The decrease in AT III level does not have to be very large to disturb the hemostatic balance and is thought to be the reason for marked heparin resistance during CPB. When heparin resistance is secondary to a deficiency in AT III, administration of fresh-frozen plasma to the patient is indicated and readily restores the AT III levels to normal and promotes the anticoagulant effect of heparin. In addition, this results in lower protamine-sulfate requirements for heparin reversal.

In contrast to decreasing AT III levels, heparin pretreatment does not significantly alter the levels of clotting Factors II, V, IX, and X. Indeed, heparin therapy has been associated with an enhancement of Factor VIII activity, resulting in a hypercoagulable state.

The activation of platelet factor 4 (PF4), an antiepiphanin, to the presence of circulating antiepiphanins such as the alpha-2 macroglobulins is a less common cause of heparin resistance. When heparin is used preoperatively, it can result in large increases in PF4 after subsequent intraperoperative heparin administration. Presumably, the high affinity of PF4 for heparin results in displacement of PF4 from lower affinity perivascular binding sites and the formation of circulating complexes with heparin.

Possible causes of this patient's heparin resistance include: 1) prolonged preoperative heparin infusion; 2) failure to inject all the heparin before CPB; 3) use of heparin with decreased activity; 4) presence of a thrombus in the left ventricle; 5) decreased AT III activity (normal level with decreased activity vs. normal activity with a reduced amount of protein); and 6) active clotting with ongoing heparin use.

All the heparin was injected either directly into the right atrium or into the distal port of the flow-directed pulmonary artery catheter. Multiple lots of heparin vials, including those successfully providing anticoagulation in a concurrent cardiac surgical procedure, were used. This would appear to eliminate the second and third reasons as possible causes of the heparin resistance. It is important to be aware of reasons for heparin resistance, to anticipate this occurrence in any patient requiring heparinization in cardiovascular surgery, and to verify the anticoagulant effect of heparin before CPB.

In conclusion, a case has been presented in which a substantial amount of heparin was needed for adequate anticoagulation before the initiation of CPB. In this patient, possible reasons for the apparent heparin resistance included prolonged preoperative heparin infusion, the presence of a thrombus within the left ventricle, a decrease in AT-III activity, and active clotting with ongoing heparin use. The important point is that adequate anticoagulation with a standard heparin dose before CPB cannot be assumed. As can be seen from this report, there is an occasional patient in which a large amount of heparin is required for adequate anticoagulation. Failure to verify the degree of anticoagulation before CPB, even in an emergency situation, could lead to disastrous results.

References


Vecuronium for Muscle Relaxation in Patients with Myasthenia Gravis

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The shorter duration of action of atracurium and vecuronium might facilitate inducing controlled muscle relaxation in patients with neuromuscular disease as compared with longer-acting drugs such as pancuronium.1 After encouraging results with atracurium,2-5 we examined vecuronium for its neuromuscular blocking potency and duration of action in patients with myasthenia gravis.

METHODS

Five patients undergoing thymectomy for myasthenia gravis (table 1) and five patients without neuromuscular disease scheduled for general surgical procedures gave their informed consent to participate in the study. The patients were not subjected to plasmapheresis before surgery. Anticholinesterase therapy was discontinued the night before the operation. Atropine 0.5 mg, meperidine 50 mg, and trifluromazine 10 mg were injected im 45 min before induction of anesthesia, which was with thiopental 250 mg to 350 mg and fentanyl 0.5 mg iv. The trachea was intubated following topical anesthesia without the administration of a muscle relaxant. Anesthesia was maintained with 70% nitrous oxide in oxygen with controlled ventilation. Increments of fentanyl 0.1 mg were injected iv as needed. Neuromuscular transmission was monitored by measuring the evoked twitch tension of the left adductor pollicis muscle in response to supramaximal train-of-four stimulation of the ulnar nerve at the wrist every 15 s as previously described.7 In two myasthenic patients, the evoked compound electromyogram (EMG) of the ipsilateral thenar eminence was recorded simultaneously. At least 30 min after the induction of anesthesia, vecuronium was injected iv in divided doses for 90% twitch depression: 2-5 μg·kg⁻¹ increments in myasthenic patients and 7.5 μg·kg⁻¹ increments in control patients. Neuromuscular transmission was then allowed to recover spontaneously. Any further muscle relaxant or anticholinesterase medication was withheld as long as twitch tension had not returned to at least 75% of control. Postoperatively, the trachea remained intubated to facilitate ventilatory support. Twitch tension and EMG recordings were evaluated for cumulative 50% and 90% blocking doses (ED₅₀ and ED₉₀)8 and for duration of neuromuscular blockade. All variables were calculated as means and standard deviations. Statistical significance of differences between means and variances were assessed by unpaired Student's t-test and F test, respectively.

RESULTS

Compared with healthy individuals, those with myasthenia gravis required an average 61% and 57% dose reduction for 50% and 90% twitch depression, respectively (table 2). The time from maximum twitch depression to 25% recovery had a significantly greater variance in myasthenic than in control patients (P < 0.01), while the difference of the means, although amounting almost to a factor of 2, was not significant. The recovery time (i.e., the time for recovery from 25% to 75% of control twitch tension), showed a marked individual variation and was three times as long in myasthenic than in normal patients, not including two patients who had failed to recover 75% of control twitch tension (table 2). In two patients with simultaneous twitch and EMG recording (table 3), the 90% blocking doses determined by mechanical twitch tension amounted to 65% and 69% of those determined by EMG. In addition to such increased sensitivity to vecuronium, twitch tension took 25 to 38 min longer than

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