Heparin pretreatment does not alter heparin requirements during cardiopulmonary bypass

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Heparin infusion may cause heparin resistance and may affect monitoring by measurement of the activated coagulation time (ACT), making the assessment of anticoagulation difficult, with the risk of over- or undertreatment, especially during cardiac surgery. We studied two groups of patients undergoing cardiopulmonary bypass (CPB): patients on heparin infusions (group H) and heparin-naive controls (group C). All patients received heparin 300 IU kg⁻¹ before CPB and a further dose of 5000 IU if the ACT 5 min after commencing bypass was less than 400 s. Measurements of ACT, heparin concentration, antithrombin-3, thrombin–antithrombin complex, prothrombin fragment F₁₋₂ and D-dimers were made before and 5 and 20 min after start of CPB. A second dose of heparin was given to eight out of 18 patients in group C and 10 out of 24 in group H. Antithrombin-3 in group H was significantly less than in group C at 5 min [59 (14) vs 52 (9)%, P<0.05]. ACT was significantly lower in group H than group C at 20 min [387 (64) vs 431 (67) s, P<0.05]. Despite ACTs of less than 400 s in both groups, no coagulation was seen, suggesting that 300 IU kg⁻¹ heparin is a safe dose for anticoagulation in CPB even after heparin therapy.

Br J Anaesth 2001; 87: 844–7

Keywords: blood, anticoagulants, heparin; blood, antithrombin; surgery, cardiovascular

Accepted for publication: July 13, 2001

In addition to the large variation in patient response to heparin,¹ some patients who receive an i.v. infusion of heparin need large doses of heparin to achieve anticoagulation.²³ This is often termed ‘heparin resistance’. The precise mechanism of this heparin resistance is still unknown; it could be caused by a decrease in antithrombin (AT-3) concentration during heparin infusion.³⁻⁵ Release of platelet factor 4 can also cause heparin resistance.⁶⁻⁸

Patients with unstable angina are commonly managed with i.v. heparin therapy and often present for urgent coronary revascularization. In such patients, the management of their anticoagulation for cardiopulmonary bypass (CPB) can be difficult. The AT-3 concentration can be increased either by giving fresh frozen plasma or AT-3 concentrate⁵ ⁹ or more heparin can be given until an acceptable degree of anticoagulation is achieved.⁵ ⁷ ¹⁰ The former is expensive and time-consuming. The latter method, which is the more usual clinical approach, is difficult to monitor, and patients given greater doses of heparin have a greater risk of postoperative bleeding and blood transfusion.⁹ ¹¹ It is uncertain what constitutes adequate anticoagulation in these patients.

In our department we monitor heparinization peroperatively with activated coagulation time (ACT) and we obtain an ACT of 400 s or greater for CPB. However, we accept a lower ACT in patients who show marked heparin resistance (i.e. failure to obtain clinically adequate ACT despite apparently sufficient heparin).

We assessed heparin resistance in our patients, the relationship between this and indices of coagulation and anticoagulation, and verified that accepting a lower ACT did not increase subclinical coagulation or harm the patient. We feel this will clarify the management of this patient group and prevent the potential complications and disadvantages associated with further doses of heparin or the use of fresh frozen plasma or AT-3 concentrate.

Methods

We studied patients undergoing coronary artery graft surgery over a 9-month period. Group H had received an i.v. heparin infusion for unstable angina for more than 72 h before surgery. Group C were selected as a control group, as the next suitable patient on the operating list after a patient
admitted to group H. The study conformed to local hospital ethics committee guidelines. Exclusion criteria were age over 75 yr, surgery other than first-time coronary artery grafts, patients not requiring CPB and the administration of any anticoagulants other than i.v. heparin.

All blood samples were taken either from the arterial cannula after the removal of 15 ml of blood and fluid from the connecting catheter or directly from the bypass circuit. Anaesthesia was induced with fentanyl (15 \( \mu g \) kg\(^{-1} \)) and a sleep dose of either thiopentone or etomidate, and pancuronium (0.1 mg kg\(^{-1} \)); anaesthesia was maintained with halothane. Arterial and internal jugular cannulae were inserted and connected to an infusion of saline (0.9% w/v) with sodium heparin 1 U ml\(^{-1} \) (Leo Laboratories, Princes Risborough, UK) running at 3 ml h\(^{-1} \) to maintain cannula patency. Before cannulation of the aorta, sodium heparin was given i.v. at a dose of 300 IU kg\(^{-1} \). Cannulation was performed and the patient commenced on CPB. Blood was analysed for ACT (Hemochron 401; Technidyne Corporation, Edison, NJ, USA), haematocrit, heparin concentration, AT-3, thrombin–antithrombin complex (TAT-c), prothrombin fragment F\(_{1+2} \) (PF\(_{1+2} \)) and D-dimers after induction of anaesthesia but before sternotomy, and 5 and 20 min after establishing CPB. If the first dose of heparin did not achieve an ACT of greater than 400 s at 5 min of CPB, a further 5000 IU of heparin was given; if this still did not achieve an ACT of greater than 400 s, this was accepted and no further heparin was administered.

Assays
Prothrombin fragment F\(_{1+2} \), TAT-c and D-dimers were all measured using commercial ELISA kits from Dade Behring (Walton Manor, Milton Keynes, UK); the kits were Enzygnost F\(_{1+2} \) micro, Enzygnost TAT micro and Enzygnost D-dimer micro respectively. Antithrombin was measured with a chromogenic kit (Coamatic Antithrombin; Chromogenics, Quadrateck, Epsom, UK). Heparin concentration was measured using a heparin anti-Xa assay (Organon-Teknika, Boxtel, Netherlands) with appropriate dilutions of patients’ samples. All the tests were performed according to the manufacturer’s instructions.

Statistics
Results are mean (SD). Paired and unpaired Student’s \( t \) tests were used throughout except for the numbers of patients in each group requiring second doses of heparin, which were analysed with the \( \chi^2 \) test. Linear regression analysis by the least-squares method was performed for each measurement with ACT as a continuous independent variable. Significance was set at \( P<0.05 \).

Results
Complete data were obtained for 24 patients in group H and 18 in group C. The patients in group H received a mean (SD) dose of heparin of 1106 (220) IU h\(^{-1} \) for 7.5 (0.8) days. Heparin was stopped 3.5 (0.4) h before surgery. There was no significant difference in age, height, weight, number of grafts performed or time of CPB between the two groups (Table 1). There was no significant difference in the haematocrit between the two groups at any time point (data not shown).

Eight out of 18 patients in group C and 10 out of 24 in group H required a second dose of heparin because the ACT 5 min after the start of CPB was less than 400 s (not statistically significant). The ACT was significantly lower at 20 min in group H than in group C [387 (64) vs 432 (55) s, \( P<0.05 \)] but at all other times there was no significant difference between the two groups (Fig. 1). If patients receiving a second dose of heparin are excluded, the mean ACT at 20 min was 397 (58) (group H) and 448 (69) s (group C) (\( P=0.067 \)). Despite this, plasma heparin concentrations were similar (Fig. 2A). AT-3 was significantly less in group H 5 min after starting CPB (\( P<0.05 \)) and approached significance (\( P=0.052 \)) at 20 min (Fig. 2B). A weak correlation between AT-3 and ACT was observed in control patients 5 min after commencement of CPB (\( r^2=0.343, p=0.01 \)) but no correlation was observed between any measured variable and ACT at any other time point in either group (data not shown).

Table 1 Patient characteristics. Mean (range) or mean (SD). No significant differences between groups

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=18)</th>
<th>Heparin infusion group (n=24)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>59 (44–73)</td>
<td>60 (39–75)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 (11)</td>
<td>171 (9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81 (14.1)</td>
<td>76.4 (11.6)</td>
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Fig 1 Activated clotting time (ACT, in s) in heparin-naive (controls, group C) patients and patients receiving i.v. heparin for more than 72 h (group H) before coronary artery surgery. Measurements at baseline (pre-heparin), 5 and 20 min after 300 IU kg\(^{-1} \) heparin in patients for coronary artery graft surgery. For further details see text. Results are mean (SD) for n=18/24. *Significant difference between control and heparin infusion groups (\( P<0.05 \)).
There was no significant difference between the two groups in activation of coagulation as measured by TAT-c, PF1+2 and D-dimers at any time point (Fig. 3).

Ten of the 18 controls and 19 of the 24 patients in the heparin infusion group had an ACT less than 400 s 5 or 20 min after commencing CPB (this was not statistically significant). When those with ACT<400 s were compared with those with ACT>400 s in the same group, the only marker of coagulation showing a significant difference was TAT-c at 20 min in group H [18.3 (10.2) µg litre⁻¹ in ACT>400 s and 44.9 (22.5) µg litre⁻¹ in ACT<400 s]. Unexpectedly, AT-3 in those patients in group H with all ACT>400 s was significantly lower [45.3 (8.3)%] than in those with an ACT<400 s [53.8 (7.8%), P<0.05]. There was a similar difference between the corresponding values in group C [50.4 (8.5)% in ACT>400 s vs 65.8 (11.4)% in ACT<400 s; P<0.05].

Three patients in group C and 10 in group H had an ACT<350 s at either 5 or 20 min. When these two subgroups were compared within their parent group, the pre-CPB AT-3 in those patients of group C who subsequently had ACT<350 s was significantly lower than those with all ACT>350 s [83.4 (15.7)% in ACT>350 s and 48.8 (15.3)% in ACT<350 s; P<0.01]. There was no significant difference between the measurements of activation of coagulation between the subgroups. No patients had an ACT<300 s.

**Discussion**

An ACT of more than 400 s is widely considered to indicate adequate heparinization/anticoagulation for patients undergoing CPB, but the basis for this arbitrary level is uncertain and the safe lower limit of ACT is undefined. In particular, the relationship of this measurement to the phenomenon of heparin resistance is obscure. We examined some indices of coagulation and anticoagulation in patients having prior heparin infusion to determine whether possible heparin resistance is clinically important, if ACT is the sole measure of anticoagulation. Therefore, although ACT was analysed as a continuous variable, the effects of ACT values less than 400 and 350 s were examined as clinically relevant divisions.

In contrast to other groups,² ³ ⁸ ¹² we did not show a decreased response to initial heparin dose in patients receiving i.v. heparin therapy before cardiac surgery, although at 20 min of CPB the ACT was significantly less in the heparin group, which may indicate an overall increased requirement for heparin.

The AT-3 concentration was lower at all times in the heparin infusion group, but this only reached statistical significance 5 min after CPB. The AT-3 concentration was lower in the few control patients who had an ACT of less
than 350 s after heparinization at either 5 or 20 min of CPB, but this difference was not seen between the two heparin groups with ACT greater than or less than 350 s. Therefore, our findings, based on relatively small numbers, cannot statistically support the theory that long-term heparin infusion decreases AT-3 or that this is responsible for the heparin resistance, as those patients with ACT <400 s in both the control and heparin groups had AT-3 concentrations greater than those who showed no heparin resistance. There was no correlation between AT-3 and heparin concentrations in either group.

In no case was the degree of activation of coagulation pathways greater in patients given heparin infusions than in patients in the control group. Both TAT-c and D-dimers increased over the operative period in both groups, which is the response seen to all surgery, not just that involving CPB. TAT-c was greater in the subgroup of heparin-infused patients who had ACT <400 s compared with those with ACT >400 s; however, this was not supported when the arbitrary division was taken as 350 s, or in the control group using either subdivision. This cannot be seen to be evidence of activation of coagulation.

The choice of ACT above which anticoagulation for CPB is considered to be adequate to prevent coagulation has always been controversial. Bull and colleagues suggested that below 300 s coagulation was activated and suggested a choice of 480 s as a safeguard, so that the value of 300 s was never reached. By measuring markers of activation of coagulation, Young and colleagues demonstrated that below 348 s activation was seen in rhesus monkeys, and rounded this figure up to 400 s. Gravlee and colleagues measured the activation of coagulation in humans and stated that ACTs greater than 350 s were not associated with any greater activation of coagulation. This is often interpreted to mean that the ACT should never fall below 400–480 s and a lower value is unacceptable. This encourages the practice of giving greater doses of heparin with all the attendant disadvantages of increased postoperative blood loss. We confirmed that, even when the ACT fell to less than 350 s no activation of coagulation was seen. Perfusionists, blinded to the ACT and patient group, reported no clotting in their pumps or problems with the oxygenators and there were no differences in the postoperative outcomes of the two groups at 24 h (data not shown). Perhaps the way to avoid the peaks in AT-3 and heparin concentration showed no significant difference between the groups at any time and did not correlate with the ACT. Possibly the time has come to move away from these older tests in favour of more sophisticated monitoring of heparinization and anticoagulation status.

Acknowledgement
This work was supported by Oxford Cardiac Surgical Sciences Trust Fund.

References
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