Control of Blood Coagulation During Cardiopulmonary Bypass.

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SUMMARY :

Activation of the coagulation cascade occurs during Cardio-pulmonary bypass surgery and must be successfully inhibited to make extracorporal circulation possible. This paper reviews the recent data on the rationale and methodology for successful control of blood coagulation during cardiopulmonary bypass surgery. Guidelines are also suggested in areas where the pathology (hematology) laboratory can be of assistance to the cardiothoracic surgical team.

INTRODUCTION :

Despite many technological modifications to the cardio-pulmonary bypass (CPB) equipment, pathological conditions arising as a consequence of changes to blood constituents remains a significant cause of morbidity and mortality. Clinically, coagulation problems associated with CPB fall into three general categories. 1) Activation of coagulation mechanisms by the non-biological surface of the CPB equipment, expressed as embolic phenomena and obstruction of the CPB equipment. 2) Often as a direct result of intra-operative activation of the coagulation mechanisms, abnormal haemostasis in the immediate post-operative period, expressed as excessive blood loss. 3) Clinical complications arising in the later post-operative period, including the post-pump syndrome and coronary graft re-thrombosis, which may be attributed to a relative over-activity of the coagulation process (1, 2, 3).

ANTICOAGULATION DURING CPB

Activation of the coagulation cascade during CPB surgery is well recognised (4, 5, 6). This type of surgery has always necessitated the use of potent doses of anticoagulant, and the precise mechanisms involved in this activation remain poorly defined. Furthermore, optimum dosage and monitoring of anticoagulation during CPB is unknown.

Heparin Monitoring

Heparin is the anticoagulant of choice during CPB surgery, due to its immediate anticoagulant action, potential for rapid reversal and ease of administration. Analytical techniques for the assessment of the heparin effect on coagulation fall into two broad groups. 1) Global coagulation tests which measure the overall influence of heparin on the coagulation cascade and include the kaolin cephalin clotting time (KCCT) and the whole blood activated clotting time (WBACT). These tests are relatively non-specific to the anticoagulant effect of heparin, and consequently cannot give a precise measure of heparin levels. 2) Assays which measure the effect of heparin at a specific point of the coagulation cascade. Although these tests are highly specific and sensitive, and include clotting, chromogenic and fluorometric techniques, they fail to provide information regarding the anticoagulant effect on the entire coagulation process. The thrombin time (TT) can measure the inhibitory effect of heparin

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on the conversion of fibrinogen to fibrin, but as it may respond to influences other than heparin levels, it cannot be considered as a specific heparin assay.

All of these test systems will produce predictable in-vitro functions of assay results to heparin levels — or linear dose/response curves. All are reproducible up to a heparin concentration of approximately 1.0 iu/ml (7). The sensitivity of the non-specific global assays of heparin in this analytical range is approximately 0.1 iu/ml, while specific chromogenic and fluorometric assays may be twice as sensitive (8).

As high levels of heparin are required during CPB, many of these techniques are inadequate for intra-operative monitoring, due to either analytical complexity or difficulty in determining an end-point of the assay (9). Only the Hemochron, a semi-automated modification of the Lee White Clltting Time (or variants of this technique), have found general acceptance for this purpose (10).

A 12-fold variation of individual heparin requirements, as assessed by Hemochron values, has been observed during CPB (11). Extrapolating these results to a computer model programmed with 42 heparinisation protocols, Bull et al found that none was satisfactory in all cases, based on an arbitary therapeutic range of Hemochron responses. These investigators concluded that the appropriate heparin dosage could be predicted from an ex-vivo dose/response curve (Hemochron value following a standard dose of heparin) (12). Subsequent studies have shown that this technique resulted in less post-operative blood loss and lower heparin requirements during CPB (13, 14).

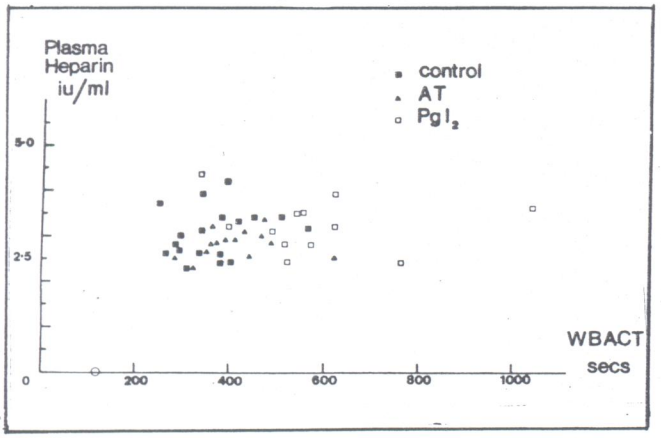

Fig. I.

The relationship between WBACT reading and administered and measured heparin.

control = routine anticoagulation protocol.
AT = + antithrombin III concentrates.
PGI_2 = + prostacyclin infusion.

Recent reports, however, have suggested that a poor correlation is obtained when specific heparin assays are compared with the Hemochron using samples collected during open-heart surgery (15, 16). When such a comparison was made in this laboratory in 30 routine CPB cases (Fig. 1), the Hemochron times ranged from 254-1045 seconds, and corresponded to plasma heparin levels of only 2.3 — 4.2 iu/ml. The longest Hemochron times were found in those patients who had received prostacyclin, a potent inhibitor of platelet aggregation, suggesting that platelet function may have played a part in the Hemochron reaction. To examine this possibility, Hemochron values were compared to platelet conts obtained on the same samples and a good correlation was observed ($p < 0.02$, $r = 0.65$), Fig. 11). This corrleation was further improved when the packed cell volume (PCV) was incorporated into the calculations ($p < 0.01$, $r = 748$) (Fig. 111). Multivariant analysis of these data suggested that the Hemochron was responsive not only to the heparin level, but also to the platelet number, the platelet function and the PCV,

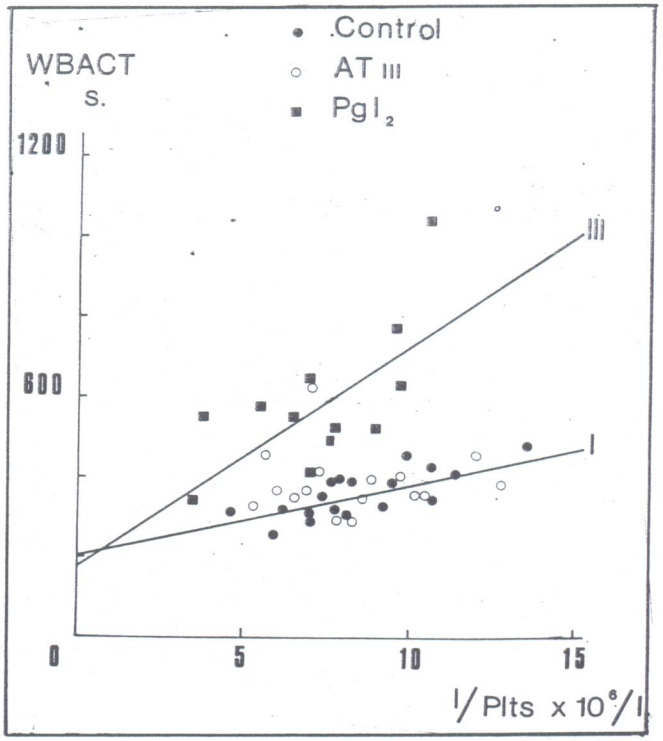

Fig. II.

The relationship between the WBACT reading and the platelet count.

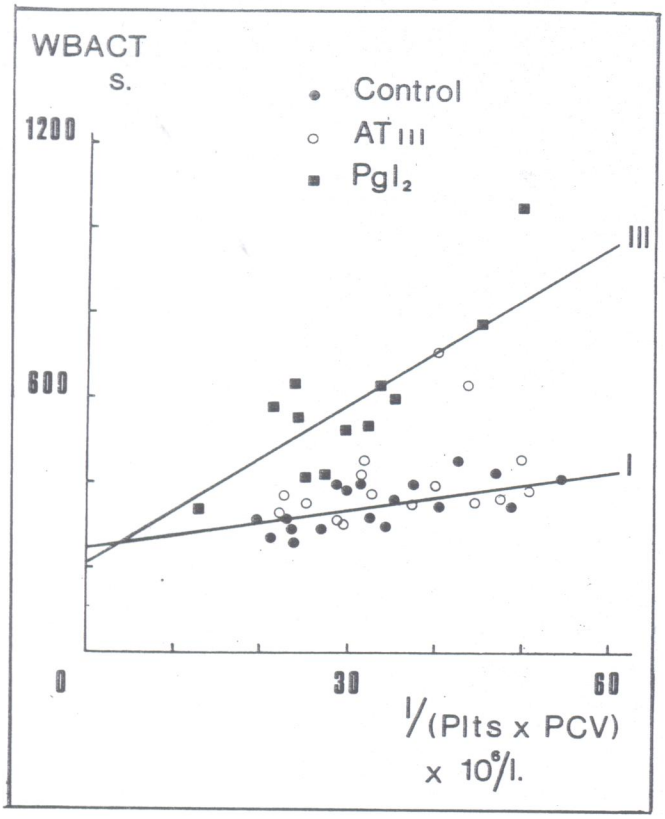

Fig. III.
The relationship between the WBACT reading and both the platelet count and the PCV.

below a value of approximately 25% (17).

Thus, allowances may need to be taken for variations in these parameters when determining the therapeutic range of the Hemochron during CPB. Similarly, these variables may need to be considered before action is taken to correct a Hemochron value which lies outside such a therapeutic range.

HEPARIN REBOUND AND HEPARIN REVERSAL :

Due to the high levels of heparin used during CPB, prompt reversal of the anticoagulant effect is essential at the time of decannulation, in order that the surgeon may close the chest with a dry operating field. The agents generally used for this purpose are protamine sulphate (PS) or protamine chloride. These are large negatively charged molecules which rapidly neutralise heparin activity rapidly (in-vitro) in a 1:1 (W/W) stoichiometric ratio. It is of some clinical importance that the optimum dose of PS is administered, as insufficient reversal may lead to excessive blood loss (18), and excess PS is associated with many side-effects including platelet inhibition and prolongation of the KCCT. Although many protocols have been recommended for the prediction of the correct PS dose, based on the Hemochron value (19), none has been found to be satisfactory in all cases. Indeed, most centres rely on an arbitary PS dosage, titrated against routine global coagulation tests (either TT or WBACT). These non-specific assays may be influenced by factors other than the heparin level, and consequently may lead to an incorrect prediction of the required PS dosage.

Following 30 routine CPB operations for CABG, and using a standard heparin anticoagulation protocol, the heparin effect was reversed with a bolus injection of PS. The dose of PS was calculated at a weight equivalent to the administered loading dose of heparin (i.e. loading dose of heparin in mgs = reversing dose of PS in mgs). Plasma heparin levels were determined (by fluorometric assay) prior to reversal, and 1/2 and 2 hours after decannulation.

No heparin was detectable immediately after PS administration, but in 10/35 cases heparin levels were again demonstrable 2 hours post-CPB. Comparing the clinical and laboratory data of the two groups formed using this criteria, no significant difference could be demonstrated with respect to age, sex, weight, height, preoperative PCV and platelet count, duration of bypass or number of grafts performed (Table-I). However, the groups were significantly different with respect to the total circulating load of heparin immediately prior to decannulation (plasma heparin level x plasma volume); the total PS : heparin ratio (total administered PS : total circulating heparin load); and the post-operative blood loss.

It is of interest that in all patients the PS dosage administered was equivalent to a PS : heparin ratio of greater than 1.0, but those patints without demonstrable postoperative heparin levels the ratio was greater than 1.5 (20). This data suggests that the dose of PS required to reverse a given heparin concentration in-vivo may be significantly greater than the dose predicted by in-vitro experiments.

These observations are consistent with recent reports indicating that PS is metabolised more rapidly than heparin, resulting in the liberation of free heparin into the circulation (21). Further-

more, heparin has been reported to bind to vascular endothelium, and to escape into the extracellular space (22, 23), from which sites it may subsequently return to the circulation. Thus it may prove impossible to predict the exact amount of PS required to reverse a given plasma heparin level. Some investigators have suggested that the administration of large boluses of PS may overcome this problem (24), however as PS in excess will itself act as an anticoagulant, this course of action may not be beneficial to the patient.

A possible solution to this dilemma is to administer the PS in two separate doses. First as a bolus, at the time of decannulation, in a dose sufficient to reverse the bulk of the circulating heparin and sufficient to enable the surgeon to close the chest with a dry operating field. The practice in this surgical unit has been to administer PS at a 1:1 weight ratio of the initial heparin loading dose. The second dose, of the same magnitude as the first, is given as an infusion over 1—2 hours. The continuous, low, circulating levels of PS which result do not in themselves cause coagulation problems, and yet are sufficient to neutralise any heparin re-entering the circulation.

PLATELETS .

The profile of platelet counts obtained during 30 routine coronary artery bypass procedures (with bubble oxygenator) is shown in Fig. IV. As expected, platelet counts were in the normal range pre-operatively, and fell dramatically on institution of bypass, due predominantly to a haemodilution effect. However, when corrections were made for the effect of haemodilution, approximately one third of the circulating mass of platelets appeared to have been lost in the first 20 minutes of bypass. Subsequent loss of platelets was more gradual, and proportional to the duration of bypass, until a further sharp fall was observed in association with decannulation, heparin reversal and post-operative coagulation. It is of interest that platelet counts remained depressed for 2—3 post-operative days, followed by a rebound thrombocytosis peaking at about the 7th post-operative day.

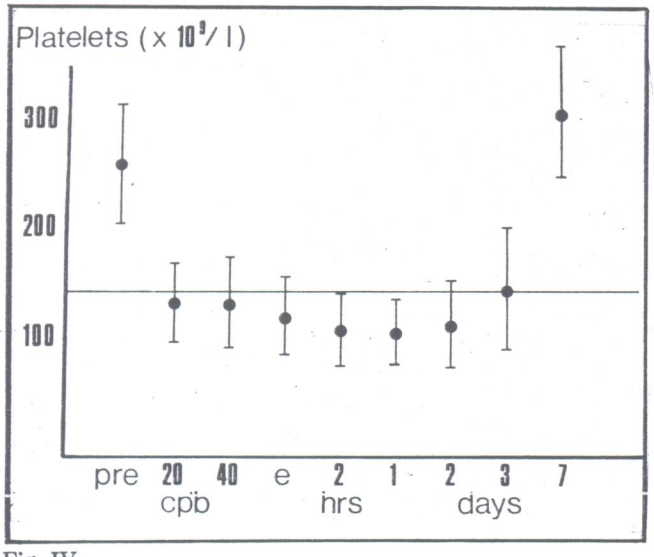

Fig. IV.
Platelet counts throughout CPB. (mean ± SEM).

In contrast, the pattern of platelet function observed throughout CPB revealed some important differences. The profile of platelet aggregation responses to 2 umol ADP, throughout the period of surgery, is shown in Fig. V. Platelet function was slighlty increased (compared to normal controls) pre-operatively, but fell gradually and progressively throughout CPB. Although platelet function was depressed immediately post-operation, function had returned to normal by the following day in 38% of cases (improving in 63%).

Other studies using ^{111}In-labell platelets (25) and PF4/BTG release (26), and this data, all indicate that major platelet damage occurs at three stages of CPB (excluding the rare case with overt intra-operative DIC).

1) at the time of cannulation, and as a result of platelet adhesion to the non-biological surfaces of the CPB apparatus.

2) Associated with prolonged CPB, and related to the cumulative effects of the above

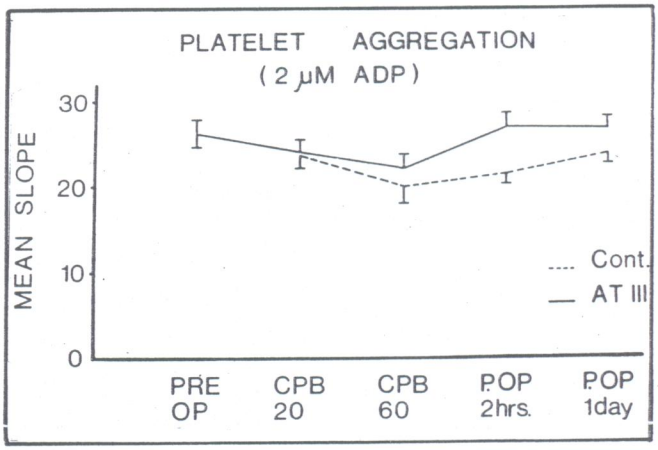

Fig. V.
Mean slope of aggregation (2uM ADP) throughout CPB (mean ± SEM).

mechanism, exposure to gas bubbles and mechanical trauma.

3) Associated with the early post-operative period. It should be noted that during this phase of surgery platelet numbers are reduced for up to 3 days, at a time when plasma AT 111 levels are also reduced, platelet function is returning to normal and platelet turnover is increased (26). Laboratory parameters at this stage of surgery are consistent with a diagnosis of DIC. Similar, but less marked changes may occur after any major surgery, but such changes are usually only short-lived (27). It is as yet unknown how much of this hypercoagulable state is essential to normal post-operative haemostasis, and how much is pathological, predisposing the patient to complications such as graft rethrombosis and post-perfusion syndromes (28).

The ideal control of platelet numbers and function during CPB suggests the total inhibition of platelet activation immediately prior to, and during CPB, with rapid normalisation of platelet function at decannulation. Paradoxically, platelet function may need re-suppression during the period of post-operative hypercoagulability, when 10% of graft rethromboses are reported to occur.

CONCLUSION .

In which areas may the haematology laboratory be of assistance to the cardiothoracic surgeon.

1. Pre-operative assessment. It is clear that even under optimal conditions CPB represents a severe insult to the patient's coagulation system. In routine cases, the patient's reserve is sufficient to withstand this damage and the outcome is usually satisfactory. However, the presence of even minor defects, either in the coagulation cascade or platelet axis, may precipitate catastrophic results if undetected prior to surgery. Thus, the pre-operative screen should include an examination of platelet number and the function of the coagulation cascade. If these are abnormal, or a history is obtained of abnormal bleeding or thrombosis, more extensive and specific tests may be recommended.

2. Intra-operative Monitoring. Some of the difficulties encountered in this area have been discussed. Although no ideal heparin assay is yet available for use during CPB, more experience with chromogenic and fluorometric assays should provide the clinician with better control of intra-operative anticoagulation.

3. Heparin Reversal. It is important to achieve adequate reversal of all circulating heparin, while avoiding high levels of protamine sulphate. A possible technique for the administration of slightly larger than standard dses of PS has been described.

4. Early post-operative phase. All patients show laboratory evidence of DIC immediately after surgery, and the majority of patients have a platelet function defect. With this background, the interpretation of laboratory data in the bleeding patient is often difficult. However, if a coagulopathy is suspected, an examination of the function of the coagulation cascade (e.g. prothrombin time and kaolin clotting time), platelet number, and platelet function (e.g. Template bleeding time) should be performed. Appropriate action will depend on the type and severity of the disorder.

5. Late post-operative phase. There are two specific problems at this stage of surgery in which the haematologist may be of assistance: 1) the post-perfusion syndrome — an association of normal blood pressures with hypoxia, pulmonary exudates and proteinaceous fluid in the bronchi. Evidence has been presented indicating that this syndrome may be related to complement activation and neutrophil adhesion within the pulmonary vasculature, and may represent a form of DIC-like pathology. The reported incidence of graft re-thrombosis in the first post-operative week is approximately 10%, and occurs during a phase of definite hypercoagulability. It is clear that a disturbed coagulation system may give rise to serious pathology during the post-operative phase, and that better understanding of these changes may reduce the morbidity and mortality of this procedure.

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