

## ALTERATION OF HEPARIN RESPONSE - THE ROLE OF PREOPERATIVE HEPARIN AND COUMARIN PRETREATMENT FOR ANTICOAGULATION DURING CARDIO-PULMONARY BYPASS

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Heparin resistance in patients pretreated with heparin has been reported (1). Decreased antithrombin III (AT III) activity (2) or activation of platelet factor 4 (3) was suggested to cause the lowered heparin sensitivity. There is limited information about heparin response in coumarin-pretreated patients.

We investigated the effect of preoperative anticoagulation by either heparin or coumarin on heparin consumption and release of platelet-specific proteins during cardio-pulmonary bypass (CPB).

**METHODS:** After institutional approval 45 patients undergoing open-heart surgery were studied. 25 patients received preoperative heparin therapy: 13 patients intravenously (group Hiv), 12 subcutaneously (group Hsc). Ten patients were treated by coumarin (group M) and 10 patients without anticoagulant pretreatment served as control (group C). C, Hsc and Hiv patients received 375 IU/kg and M patients only 250 IU/kg intestinal porcine heparin prior to CPB. AT III activity, factor X, plasma heparin levels, tissue plasminogen activator (tPA) (both chromogenic substrates), D-dimere (ELISA),  $\beta$ -thromboglobulin and platelet factor 4 (both utilizing RIA) were measured prior to operation, 10 min. after heparin injection (but before CPB), 30 min. after initiation of CPB, at end of CPB and at end of operation. ACT and platelet count were measured at the same instances. Heparin coefficient was calculated as units heparin/kg/anticoagulation time (IU/kg/min), heparin sensitivity as the ratio of ACT 10 min. after heparin and units heparin/kg (sec/IU/kg). Patients showing inadequate heparinisation (ACT > 400 sec) received additional heparin dosages of 125 IU/kg until ACT exceeded 400 seconds. ANOVA was used for statistics.

**RESULTS:** 10 min. after heparin the ACT was less than 400 sec. in 9 patients (1 C, 3 Hsc, 5 Hiv). There was no significant correlation between AT III activity and heparin coefficient or heparin plasma level and ACT. The platelet-specific proteins were significantly higher in Hiv and Hsc groups. In spite of increased heparin consumption the Hsc group demonstrated an enhanced fibrinolytic activity - shown by an increased tPA release and a pronounced generation of fibrin split products during CPB (end of CPB Hsc 8618+3019, M 2310+636 ng/ml,  $p < 0.05$ ).

	C	M	Hsc	Hiv
Hep. coefficient (IU/kg/min)	3.3	2.6	3.6 <sup>b</sup>	4.6 <sup>a,b,c</sup>
Hep. sensitivity (secACT/IU/kg)	1.1	4.1 <sup>a,c,d</sup>	0.96	0.78
preop AT III (%)	74	85 <sup>a,c,d</sup>	74	71
preop F X (%)	70	20 <sup>a,c,d</sup>	81	73
ACT 10'a.hep. (sec)	529	>600 <sup>a,c,d</sup>	483	406
	+109	+200	+99	+63

mean+SD,  $p < 0.05$ , <sup>a</sup>=vs C, <sup>b</sup>=vs M, <sup>c</sup>=vs Hsc, <sup>d</sup>=vs Hiv

**DISCUSSION:** The diminished heparin response was more pronounced in patients who received IV heparin preoperatively, it was not caused by either thrombocytopenia or decreased AT III activity. In contrast: cou-

marin pretreated patients demonstrated a high heparin sensitivity due to reduced preoperative F X activity. The increase of platelet-specific proteins in heparinized patients is best interpreted as perturbation of platelet integrity by heparin pretreatment. This might be due to a heparin-dependent platelet aggregation factor. Inadequate anticoagulation during CPB caused the pronounced stimulation of fibrinolysis.

**CONCLUSION:** 1. Heparin sensitivity was reduced in heparin-pretreated patients. 2. The increase in platelet-released proteins indicates an enhanced platelet fragility in heparin-pretreated patients. 3. Heparin response does not depend on heparin plasma level. 4. Coumarin-treated patients need less heparin (250 IU/kg) for adequate anticoagulation. 5. We recommend an initial heparin dosage of 500 IU/kg heparin prior to CPB for heparin-pretreated patients. Cautious ACT monitoring is mandatory for these patients.

References:

- Esposito RA: J Thorac Cardiovasc Surg 85:346-53, 1983
- Cloyd GM: J Thorac Cardiovasc Surg 95:535-38, 1987
- Anderson EF: Anesthesiology 64:504-7, 1986

Fig. 1 (mean  $\pm$  SEM)

