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REDUCTION IN BLEEDING AFTER HEART OPERATIONS WITH THE USE OF PROPHYLACTIC EPSILON-AMINOCAPROIC ACID

BY

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ABSTRACT

Excessive postoperative bleeding after heart operations continues to be a source of morbidity. This double blind prospective study evaluates epsilon-aminocaproic acid (EACA) as an agent to reduce postoperative bleeding; and investigates its mode of action. One hundred three patients were randomly assigned to receive either 30 g. of EACA (51 patients) or an equivalent volume of placebo (52 patients). In a subset of these patients (14 EACA, 12 placebo), tests of platelet function and fibrinolysis were performed.

Results: By multivariate analysis, three factors were associated with decreased blood loss in the first 24 hours postoperatively: EACA vs. placebo (647 ml vs 839 ml, $p = 0.004$); surgeon 1 vs all other surgeons (582 ml vs 978 ml, $p = 0.002$); and no intraaortic balloon (IABP) vs IABP use (664 ml vs 1410 ml, $p = 0.02$). No significant difference in platelet function between the two groups could be demonstrated. Fibrinolysis, as reflected in the EACA group by less depression of the euglobulin clot lysis and no rise in D-dimer levels was significantly inhibited when compared to the placebo group.

Conclusion: The intraoperative use of EACA reduces postoperative cardiac surgical bleeding.

MINI-ABSTRACT

A randomized study of the use of intraoperative epsilon-aminocaproic acid (EACA) was conducted in 103 patients having a heart operation. EACA significantly reduced postoperative bleeding.

Bleeding after heart operations continues to be a concern to cardiac surgeons. Treatment during the operation with aprotinin reduces bleeding, but the drug is expensive and may lead to complications such as renal failure, coronary graft occlusion and myocardial infarction, and allergic reactions.[1-4] Treatment of bleeding after heart operations with epsilon aminocaproic acid (EACA) was reported in 1967 by Lillehei.[5] Several other authors have since reconfirmed its effectiveness but the drug seems to occupy a position of secondary importance compared to aprotinin.[6-10] We previously investigated the use of EACA in a low dose and found that post cardiac surgical bleeding was diminished.[11] However, we and others have begun prophylactic use of the drug in larger doses.[10] This randomized double blind prospective study compares patients administered high dose EACA (Group EACA) with control patients administered a placebo (Group C), and investigates the mechanism of action of EACA during cardiopulmonary bypass (CPB).

Material and Methods

After protocol approval by the Human Subjects Research Committee of the University of Massachusetts Medical Center, informed consent was obtained from 103 patients who were then prospectively randomized to receive EACA (Amicar, Lederle Laboratories, Pearl River, New York) (51 patients) or a similar volume of 0.9% saline (52 patients) in a double blind study. Surgeons, anesthesiologists and all lab personnel were blinded as to whether the patient received placebo or EACA. Patients in the treatment arm received a total of 30 g. EACA: 10 g. IV prior to the skin incision, 10 g. IV after heparinization, and 10 g. IV at the discontinuation of cardiopulmonary bypass but before protamine administration. Patients in the control arm were administered saline in the same volumes, and with the same timing. Heparin was administered per protocol at 400 U per kg., and incremental doses were given during the operation to maintain the activated clotting time above 400 seconds. Neutralizing protamine was administered per protocol at 1 mg per 100 U total heparin dose. Patients requiring emergency operations, or with abnormal preoperative bleeding studies, or who were pregnant were excluded from the study; no other exclusion criteria were used. Eligible patients included those needing coronary bypass or valve operations. Closure

time was defined as the time from termination of cardiopulmonary bypass to the application of the dressing.

In all patients, routine preoperative and postoperative hematologic and coagulation studies performed consisted of complete blood count (CBC), prothrombin time (PT), partial thromboplastin time (PTT), bleeding time, and thrombin time (TT). Postoperative blood loss as measured from the chest tube drainage, and blood component therapy was recorded. In a subset of 26 patients (14 EACA, 12 control), various hemostatic tests were obtained. These tests were of two types: those evaluating platelet function and those measuring fibrinolysis. These included fibrinogen, plasminogen, plasmin, antiplasmin, D-dimer, euglobulin lysis time, antithrombin III, and platelet count measured before surgery, after heparin administration, 45 minutes after initiation of cardiopulmonary bypass, 5 minutes after protamine administration, 2 hours postoperatively and 24 hours postoperatively. Bleeding time was measured preoperatively and two hours postoperatively. In addition, and at the same time intervals, whole blood flow cytometry (performed as previously described)[12] was used to measure the expression of platelet surface glycoprotein (GP) Ib, GPIIb-IIIa complex, fibrinogen binding to the GPIIb-IIIa complex, and P-selectin. The following monoclonal antibodies were used in these studies. S12 (Centocor, Malvern, Pa.) is directed against P-selectin.[13,14] P-selectin is a component of the α granule membrane of resting platelets that is only expressed on the platelet surface membrane after platelet degranulation and secretion.[13,15] 6D1 (provided by Dr. Barry S. Coller, Mount Sinai Medical Center, New York) is directed against the von Willebrand factor binding site on the amino terminal domain of platelet membrane GP Ibα.[16,17] Y2/51 (DAKO, Carpinteria, CA.) is directed against platelet membrane GPIIIa.[18] 7E3 (provided by Dr. Coller) is directed at the fibrinogen binding site on the GPIIb-IIIa complex.[19] F26 (provided by Dr. Harvey Gralnick, NIH Clinical Center, Bethesda, MD.) is directed against a conformational change in fibrinogen bound to the GPIIb-IIIa complex.[20,21] S12, 6D1, 7E3, and F26 were biotinylated as previously described.[12,22] Fluorescein isothiocyanate (FITC)-conjugated Y2/51 was purchased from DAKO.

In a pilot study, we compared preoperative blood obtained by peripheral venipuncture to preoperative blood obtained by Swan-Ganz catheter and found no statistical difference in the binding of moabs S12, 6D1, 7E3, and F26 (n = 9), demonstrating that drawing of the blood through the Swan-Ganz catheter did not result in platelet activation or other platelet surface changes. Blood was therefore obtained from the Swan-Ganz catheter in all subsequent studies.

Statistical methods

The primary outcome variable was blood loss from the chest tubes at 24 hours. Baseline characteristics and operative data for the control and EACA groups were compared by an unpaired t-test for continuous variables and by Chi-square tests of association of categorical variables. A multivariate analysis was used to adjust for confounding factors in the blood loss correlation and to define those factors independently predictive of blood loss. Because of skewed (non-normal) distribution of the blood loss and large, unequal variances, the natural log of the blood loss rather than the actual blood loss was used for the calculation of statistical significance.

Results

Preoperative patient variables did not differ significantly between the EACA and control groups with respect to age, sex, redo operations, or preoperative clotting factors, all of which were normal (Table I). Operative variables of surgeon, cardioplegia temperature, operation performed, and use of internal mammary grafts also did not differ significantly between the two groups (Table II). However the cardiopulmonary bypass time was longer in the EACA group (148 min, EACA vs 129 min, control, $p = 0.02$) as was the cross clamp time (85 min, EACA vs 73 min, control, $p = 0.04$).

Mean closure time was 58 min. in the EACA group and 54 min. in the control group ($p = 0.2$) Closure time for surgeon 1 was 55 min. and for the other surgeons was 58 min. ($p = 0.3$).

In the subset of 26 patients who had more extensive hematologic testing, platelet surface glycoprotein expression and the fibrinolytic system were evaluated. By whole blood flow cytometry before, during and after CPB, platelet surface expression of GPIb (von Willebrand factor receptor) did not change significantly, irrespective of whether or not the patients received EACA (Fig. 1). Platelet surface expression of the GPIIb-IIIa complex (fibrinogen receptor) was also unchanged during or after CPB, irrespective of the use of EACA (Fig. 2). In addition, we used monoclonal antibody F26 to measure directly the amount of fibrinogen bound to the platelet surface GPIIb-IIIa complex, which reflects "activation" of the complex because F26 binds only to surface-bound fibrinogen.[20,21] As shown in Fig. 3, platelets circulated during CPB with little bound fibrinogen, irrespective of whether or not the patients received EACA. Furthermore, and irrespective of whether or not the patients received EACA, the platelets were normally reactive to a combination of ADP and epinephrine as determined by their ability to bind fibrinogen to the GPIIb-IIIa complex (Fig. 3). Finally, the platelet surface expression of P-selectin was minimal, irrespective of whether EACA was used (Fig. 4).

In evaluation of the fibrinolytic system, euglobulin clot lysis time was significantly less depressed in the patients receiving EACA than in the control patients (Fig. 5). Further evidence of fibrinolytic inhibition by EACA was obtained from the obliteration of the CPB-associated increased in circulating plasma D-dimer in patients receiving EACA (Fig. 6).

Circulating plasma levels of plasmin increased to a similar degree in both groups after heparin administration and remained elevated during bypass (Fig. 7). . Plasma fibrinogen fell in both groups but with no difference between the two groups (data not shown). Plasma antiplasmin and antithrombin III fell to a similar degree in both groups (data not shown).

In these same 26 patients, the platelet count fell during the operation and then rose postoperatively, but with no difference between the EACA and placebo groups (data not shown). The preoperative bleeding times were 4.3 ± 0.74 min. in the EACA group and 4.5 ± 0.26 min. in the control group ($p = NS$), and postoperatively were 5.3 ± 0.4 min. in the EACA group and 7.2 ± 1.3 min. in the control group ($p = NS$). Within each group, the

rise in bleeding time from preoperatively to postoperatively was statistically significant: $p = 0.02$ in both the EACA and control groups.

Postoperative bleeding was decreased in the EACA group (Table III). At 12 hours, blood retrieved from the chest tubes was 425 ml in the EACA group and 565 ml in the control group ($p < 0.004$). At 24 hours, blood retrieved from the chest tubes was 647 ml in the EACA group and 839 ml in the control group ($p = 0.002$). No significant difference, however, was observed in the number of packed red blood cells administered to the two groups during the first 24 hours (0.94 units in the EACA group and 1.12 units in the control group). Neither did a significant difference exist in other blood products (cryoprecipate and fresh frozen plasma) administered to the two groups. Postoperative hematocrit at discharge, and immediate postoperative clotting studies were also similar in the two groups (Table III).

By multivariate analysis, three factors correlated with postoperative blood loss at 24 hours (Table IV). Besides the use of EACA, surgeon 1 had less bleeding than the other surgeons in aggregate (582 ml vs 978 ml, $p = 0.002$). Intraaortic balloon pump (IABP) use increased blood loss compared to patients not requiring an IABP (1410 ml vs 664 ml, $p = 0.02$). Despite the fact that a disproportionate number of the control cases were performed by the surgeon with the lowest bleeding rate, the EACA group had less bleeding. Although by univariate analysis, bypass time and cross clamp time were longer in the EACA group, by multivariate analysis, these factors were not associated with postoperative bleeding.

Although the blood transfusion requirement was not significantly different between the EACA and control groups, two other variables did affect blood use during the first 24 hours (Table V). Males received a mean of 0.78 units of packed red cells compared to females who received 1.68 units ($p = 0.0001$). When normalized for body surface area, the transfusions per patient/m^2 were 0.41 for males and 0.98 for females. Patients with primary operations received 0.84 units compared with 2.42 units for patients with redo operations ($p = 0.005$). Similarly, patients requiring an intra-aortic balloon received 2.64 units compared to 0.83 units for those not requiring an intra-aortic balloon ($p = 0.008$). One patient died in the EACA group and none in the placebo group. The single death occurred in a 71 yr. woman three days

after a redo coronary artery bypass when free rupture of the posterior left ventricle occurred from a perioperative myocardial infarction (with all coronary grafts patent at autopsy).

Other than the decreased bleeding in the EACA group, no differences in complications were observed between the control and EACA groups. Although a trend for an increased incidence of electrocardiographically diagnosed myocardial infarction (new Q waves or loss of R waves) was observed in the EACA group compared with the control group (5 of 51 vs 2 of 52; $p = 0.08$). this difference was not statistically significant. Furthermore, no difference in postoperative CPK or CPK- index was seen between the two groups. No cerebrovascular accidents occurred in the EACA group; two occurred in the control group ($p = 0.33$). One patient in the EACA group and three in the control group required reexploration for postoperative bleeding ($p = 0.6$).

Discussion

Multiple factors contribute to the bleeding diathesis seen following cardiac operations performed using cardiopulmonary bypass. Not all are understood, and disagreement exists as to their relative importance. The two major hematologic abnormalities leading to increased postoperative hemorrhage are decreased platelet function and increased fibrinolysis.[23-25] Bleeding time increases during and after cardiopulmonary bypass. While this has long been considered to reflect an intrinsic platelet defect caused by the non-physiologic nature of cardiopulmonary bypass, Kestin et.al. have proposed that the platelet defect occurs because of an antagonistic external force- such as cold, or lack of availability of platelet agonists.[24]

The mechanism of the fibrinolysis is more clearly understood.[23,25,26] Blood, coming into contact with foreign surfaces in the cardiopulmonary bypass circuit, initiates the contact phase of coagulation, and generates kallikrein. This, in turn stimulates bradykinin release and both molecules activate tissue plasminogen activator that converts plasminogen to plasmin, a potent fibrinolytic and fibrinogenolytic agent. Heparin also increases plasmin activity, and kallikrein catalyzes the conversion of prourokinase to urokinase, another fibrinolytic agent.[27,28] A further consequence of cardiopulmonary bypass is the reduction of α_2-antiplasmin, and the

production of fibrin degradation products during fibrinolysis. These fibrin degradation products inhibit platelet aggregation.[29]

Aprotinin has been shown by numerous studies to reduce bleeding after cardiac operations.[1,2,30,31] It interrupts several steps in the cascade of hematologic changes during cardiopulmonary bypass that lead to the bleeding diathesis.[25,32-37] These salutary effects occur, at least in part, by its direct antiplasmin activity, its inhibition of kallikrein, its urokinase inhibition, and its preservation of normal levels of α_2-antiplasmin. It has also been reported to preserve platelet function,[1,38] although other reports suggest that its role in platelet preservation is absent or minimal compared to its interruption of fibrinolysis.[39,40]

Although of unquestioned value in reducing blood loss, aprotinin is expensive, and questions have been raised about its safety. Suggestions of it causing abnormal intravascular clotting leading to organ dysfunction have been made by several investigators.[2-4]

For these two reasons, we investigated the ability of epsilon aminocaproic acid (EACA) to reduce postoperative bleeding, and the mechanism of its action. EACA exerts its antifibrinolytic effect by binding with plasminogen and plasmin, thus displacing them from fibrin.[23] It also inhibits tissue plasminogen activator activity.[6] Because plasmin reduces the platelet GPIb receptors[41] and thereby reduces platelet adhesion, and because the fibrin degradation products of fibrinolysis also inhibit platelet function, we measured the effect of EACA upon platelet function in 26 patients in whom detailed hematologic testing was performed.

In this study, the platelet surface expression of P-selectin, GPIb, the GPIIb-IIIa complex, and fibrinogen binding to platelet surface GPIIb-IIIa were all unaffected by the administration of EACA to patients during CPB. Each of these antigens is of functional importance. P-selectin, an α granule membrane protein that is only expressed on the platelet surface after degranulation,[13,15] mediates adhesion of activated platelets to neutrophils and monocytes.[42,43] GPIb is a receptor for von Willebrand factor that is critical for platelet adhesion to damaged blood vessel walls.[44] The GPIIb-IIIa complex is a receptor for fibrinogen, von Willebrand factor, and fibronectin

that is critical for platelet aggregation.[45] The lack of any effect of EACA on P-selectin, GPIb, the GPIIb-IIIa complex, and fibrinogen binding to the GPIIb-IIIa complex strongly suggests that the EACA-dependent decrease in CPB-associated blood loss is not mediated via a platelet-dependent mechanism.

In the same subset of the study population, we examined the fibrinolytic system. In the control group, evidence of increased fibrinolysis was seen as has been previously reported during cardiopulmonary bypass.[25] We found a marked increase in plasma D-dimer concentrations and a corresponding drop in euglobulin lysis time in the control group, whereas in the EACA group, no change occurred in D-dimer concentrations and while the euglobulin clot lysis fell slightly, it did so less than in the control group. The lack of difference in plasma plasmin levels between patients receiving EACA and control patients (Fig. 7) is consistent with the fact that EACA, a lysine analogue, in known not to block plasmin generation, but to block the binding of plasmin to fibrin.[46]

The major endpoint of the study was postoperative bleeding. At both 12 hours and 24 hours postoperatively, univariate and multivariate analysis demonstrated a significant reduction in blood loss in the EACA group. This is consistent with our previous study and with several others showing reduced bleeding as a result of EACA use.[6,7,9-11] We assessed bleeding by measuring chest tube effluent directly. When the same measurements were normalized by body surface area, the conclusions did not change.

In our previous study of EACA, we limited the patient population to those patients undergoing elective coronary artery bypass operations, as did Daily and colleagues in their recent publication.[10,11] Because the difference in bleeding at 12 hours between the control (332 ml) and EACA (272 ml) groups in our earlier study was statistically significant but clinically insubstantial, we broadened the inclusion group in the current study. All patients undergoing coronary bypass operations or valve operations or a combination of the two were included. Excluded were pregnant women and those patients with known bleeding disorders or requiring an emergency operation.

Bleeding after heart operations has been a problem of such magnitude that it is curious that little recognition or importance seems to have been given to reports published during the infancy of cardiac surgery demonstrating the efficacy of EACA. In 1967, Sterns and Lillehei nearly halved postoperative bleeding by giving EACA at the conclusion of cardiopulmonary bypass.[5] In 1976, Lambert and colleagues showed prompt resolution of established postoperative bleeding by EACA treatment.[8] It would seem that the interest in aprotinin therapy has rekindled interest in EACA.

This rekindled interest assumes greater significance with the current focus on medical costs. Purchased through our hospital pharmacy, the commonly used high dose aprotinin regimen (200 mg prebypass, 200 mg in heart-lung pump, and after one hour, 50 mg/hr for the duration of the operation) costs our hospital $149 per 100 mg or about $780 per patient. Thirty grams of EACA (the total dose used in this study) costs our hospital $6.96, or a difference between the two drugs of about $773 per patient. This places aprotinin at a considerable disadvantage when choosing between the two drugs on the basis of a cost-benefit analysis.

As in our previous investigation of EACA, we found no morbidity associated with the drug.[11] Other studies have also shown no increase in complications from EACA use.[7,9,10] However, because of the statistically insignificant increase in perioperative myocardial infarctions in the treatment group this question must still be considered unanswered.

Increased attention to controlling bleeding in the terminal stages of the operation may be one cause of decreased postoperative bleeding. While that increased attention cannot directly be measured, the operative time spent after the patient has been weaned from cardiopulmonary bypass and all the cardiac portions of the operation have been completed might be used as a surrogate measure. In fact, no difference existed in closure time (termination of bypass to dressing application) between the EACA and control groups. An unexpected and unexplained finding in this study was that one surgeon had significantly less bleeding than the other surgeons. In retrospect, we have since discovered that this result parallels that in our total patient data base extending back several years. In this study, the closure time for surgeon 1 was slightly but not significantly less than for the

aggregate of the other surgeons. Thus, we could not conclude that extra time (or care) in closing contributed to the difference in bleeding between surgeons.

We conclude that EACA reduces postoperative bleeding after heart operations at far less expense than aprotinin, and with no detectable morbidity. The EACA-dependent decrease in the CPB-associated blood loss is mediated via inhibition of the fibrinolytic system, not via a platelet-dependent mechanism.

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TABLE I

	EACA (51)	CONTROL (52)	p =
Male/Female	35/16	40/12	NS
Age	64.7 ± 12.1	64.2 ± 12.4	NS
Redo Operation	5 (9.8%)	7 (13.5%)	NS
Hct (preop)	40.4 ± 4.9	40.5 ± 4.0	NS
PT (preop)	13.0 ± 0.98	13.1 ± 0.93	NS
PTT (preop)	43.3 ± 18	43.9 ± 22	NS
BSA	1.98 ± 0.27	1.94 ± 0.24	NS

(Values are means ± standard deviation)

TABLE II

	EACA (51)	CONTROL (52)	p =
Surg 1/Other surgeons	27/24 (44% / 57%)	34/18 (56% / 43%)	0.2
CABG only	39	38	NS
# grafts (CABG only)	3.80 ± 0.76	3.63 ± 0.88	NS
# grafts (All CABG)	3.63 ± 0.97	3.54 ± 0.92	NS
IMA graft	30	29	NS
Valve	10	12	NS
Valve/CABG	4	4	NS
Bypass time	148 ± 41	129 ± 42	0.02
Cross clamp time	85 ± 28	73 ± 29	0.04

(Values are means ± standard deviation)

TABLE III

	EACA	CONTROL	p =
Blood loss, 12 hours	425 ± 412 ml	565 ± 488 ml	0.004
Blood loss, 24 hours	647 ± 488 ml	839 ± 634 ml	0.002
Units RBC, 24 hours	1.13 ± 1.37	1.35 ± 2.02	NS
Units FFP, 24 hours	0.2 ± 0.8	0.38 ± 1.24	NS
Hct, at discharge	29.9 ± 3.6	29.8 ± 3.2	NS
PT (postop)	14.1 ± 1.0	14.0 ± 1.3	NS
PTT (postop)	34.5 ± 6.2	35.0 ± 9.2	NS
TT (postop)	19.0 ± 5.4	17.4 ± 8.5	NS
Reexplore (bleeding)	1 patient	3 patients	NS

(Values are means ± standard deviation)

TABLE IV

VARIABLE	BLOOD LOSS @ 24 hrs.	p =
Surgeon 1	582 ± 262 ml	0.003
Other surgeons	978 ± 786 ml	
EACA	647 ± 488 ml	0.002
Control	839 ± 634 ml	
IABP	1410 ± 1089 ml	0.02
No IABP	664 ± 419 ml	
Pericardium closed	562 ± 280 ml	0.2
Pericardium left open	796 ± 622 ml	
Male	792 ± 575 ml	0.2
Female	615 ± 551 ml	
Male/BSA	400 ± 310 ml	0.5
Female/BSA	354 ± 329 ml	
Redo operation	972 ± 738 ml	0.1
Primary operation	714 ± 544 ml	

(Multivariate analysis)

(Values are means ± standard deviation)

TABLE V

VARIABLE	BLOOD GIVEN (units in 24 hrs)	p =
Male	0.78 ± 1.40	0.0001
Female	1.68 ± 1.25	
Primary operation	0.84 ± 1.17	0.005
Redo operation	2.42 ± 2.19	
No IABP	0.83 ± 1.10	0.008
IABP	2.64 ± 2.42	
EACA	0.94 ± 1.21	0.3
Control	1.12 ± 1.58	
Surgeon 1	0.87 ± 1.16	0.5
Other surgeons	1.28 ± 1.71	

(Multivariate analysis)

(Values are means ± standard deviation)

FIGURE LEGENDS

Fig 1. The platelet surface expression of GPIb (the von Willebrand factor receptor) did not change significantly during or after CPB, irrespective of whether the patients received EACA (closed circles) or not (open circles). Platelet surface GPIb was determined at the indicated time points by whole blood flow cytometry with monoclonal antibody 6D1. PRE-OP = pre-operative. HEPARIN = 5 minutes after initial heparin administration. 45 MIN CPB = 45 minutes into CPB. PROTAMINE = 5 minutes after protamine administration. 2 H POST = 2 hours after skin closure. Data are mean ± S.E.M., n = 13 patients for EACA and n = 10 patients for placebo.

Fig 2. The platelet surface expression of the GPIIb-IIIa complex (the fibrinogen receptor) did not change significantly during or after CPB, irrespective of whether the patients received EACA (closed circles) or not (open circles). The platelet surface GPIIb-IIIa complex was determined at the indicated time points by whole blood flow cytometry with monoclonal antibody 7E3. Data are mean ± S.E.M., n = 13 patients for EACA and n = 9 patients for placebo.

Fig 3. Irrespective of whether patients received EACA (solid symbols) or not (open symbols): a) platelets circulated during and after CPB with little bound fibrinogen (circles); b) platelets were normally reactive to a combination of ADP and epinephrine, as determined by their ability to bind fibrinogen to the GPIIb-IIIa complex (squares). Fibrinogen binding to the platelet surface GPIIb-IIIa complex was determined at the indicated time points by whole blood flow cytometry with monoclonal antibody F26. Data are mean ± S.E.M., n = 12 patients for EACA and n = 7 patients for placebo.

Fig 4. The platelet surface expression of P-selectin (reflecting a granule secretion) was minimal, whether the patients received EACA (closed circles) or not (open circles). Platelet surface P-selectin was determined at the indicated time points by whole blood flow cytometry with monoclonal antibody S12. S12 binding to pre-operative samples incubated with thrombin 2 U/mL was defined as 100%. Data are mean ± S.E.M., n = 12 patients for EACA and n = 9 patients for placebo.

Fig 5. The euglobulin clot lysis time, an assay of fibrinolytic activity, was significantly longer, indicating less fibrinolysis, in the patients receiving EACA (closed circles) than in the control patients (open circles). Data are mean ± S.E.M., n = 14 patients for EACA and n = 11 patients for placebo.

Fig 6. Administration of EACA inhibited fibrinolysis, as evidenced by obliteration of the CPB-associated increase in circulating plasma D-dimer. Data are mean ± S.E.M., n = 14 patients for EACA and n = 10 patients for placebo.

Fig 7. Circulating plasma concentrations of plasmin increased after heparin administration and remained elevated during CPB, whether the patients received EACA (closed circles) or not (open circles). Data are mean ± S.E.M., n = 14 patients for EACA and n = 11 patients for placebo.

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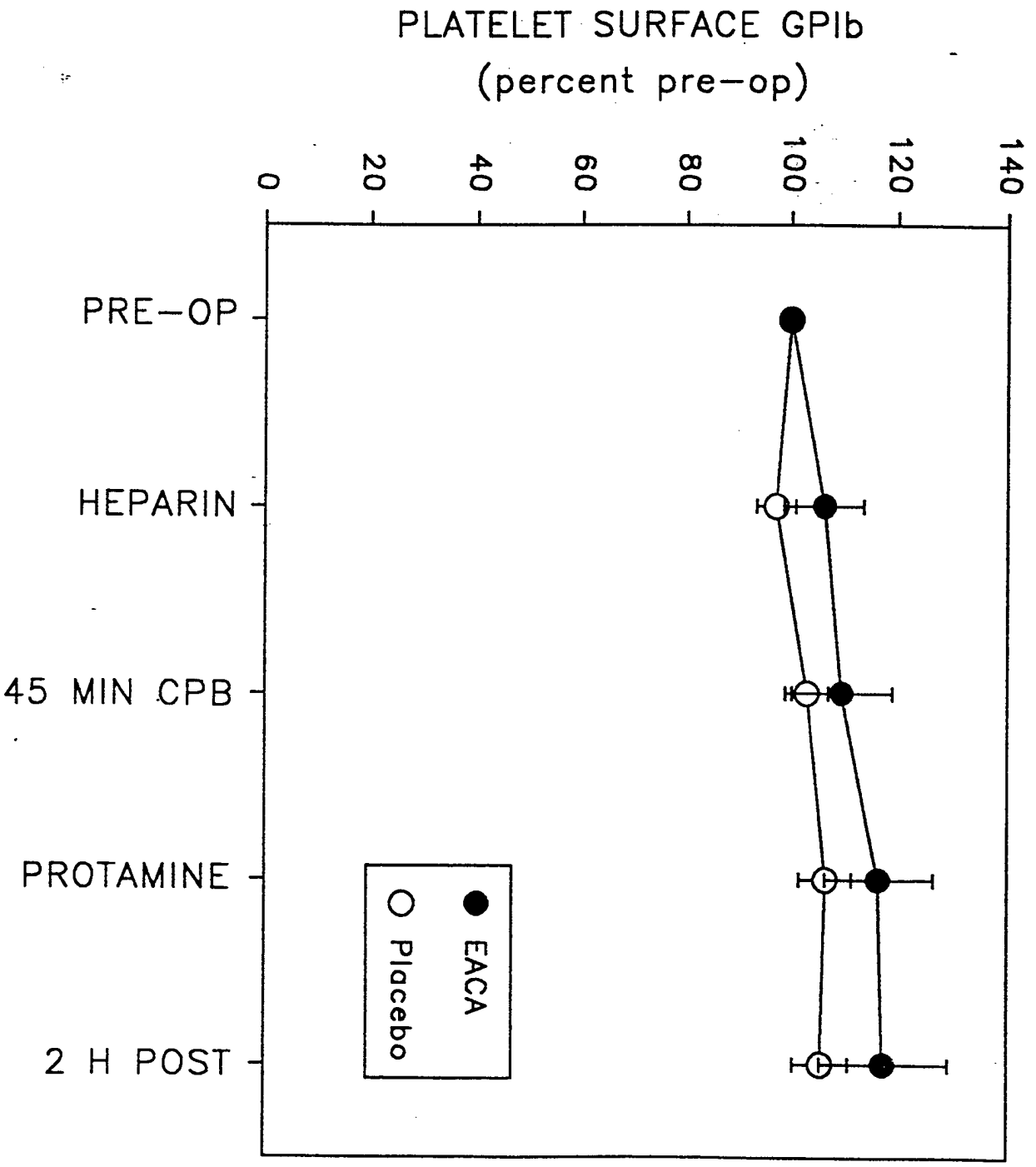

PLATELET SURFACE GPIb
(percent pre-op)
0
20
40
60
80
100
120
140
PRE-OP
HEPARIN
45 MIN CPB
PROTAMINE
2 H POST
EACA
Placebo

Fig 1

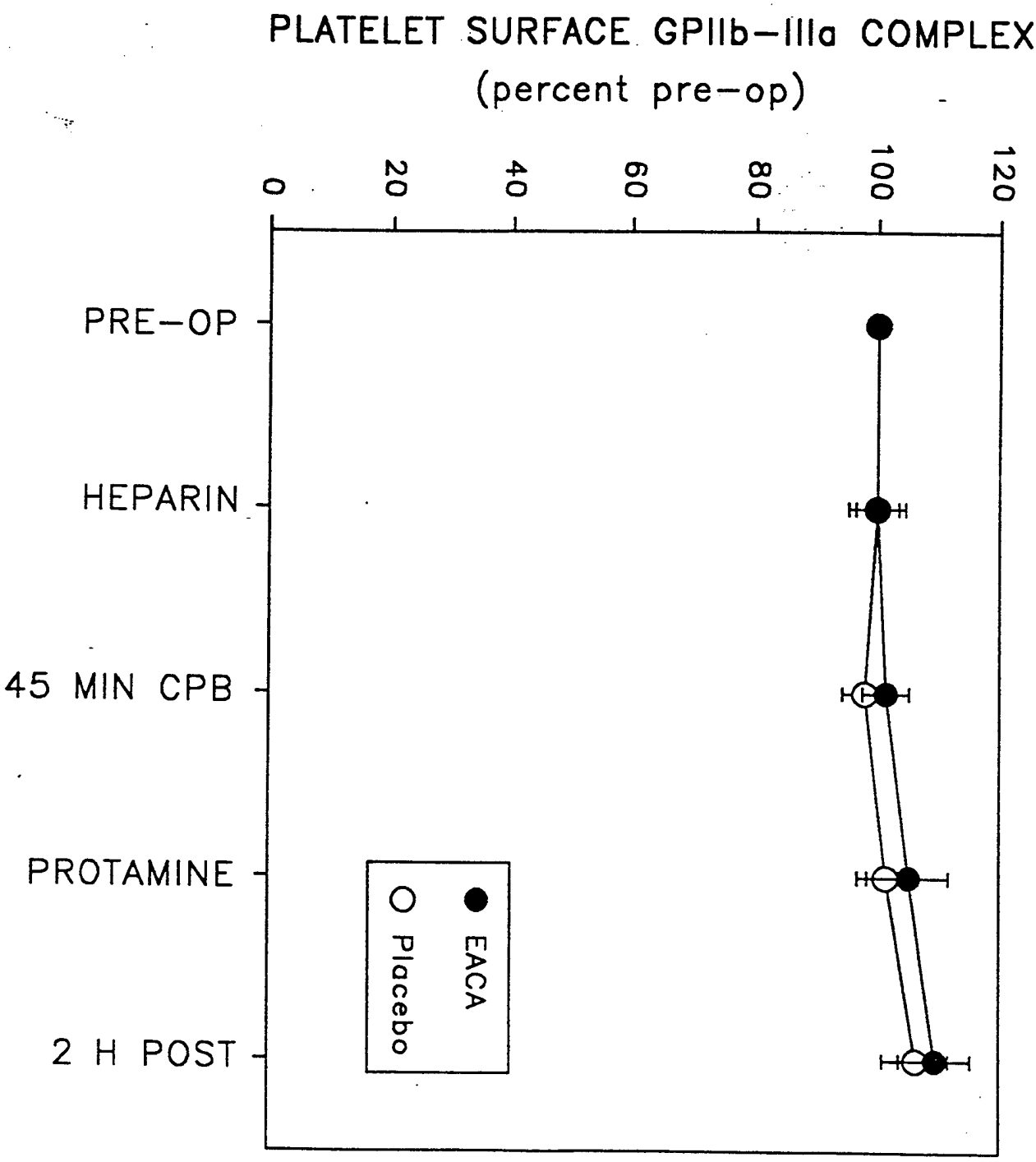
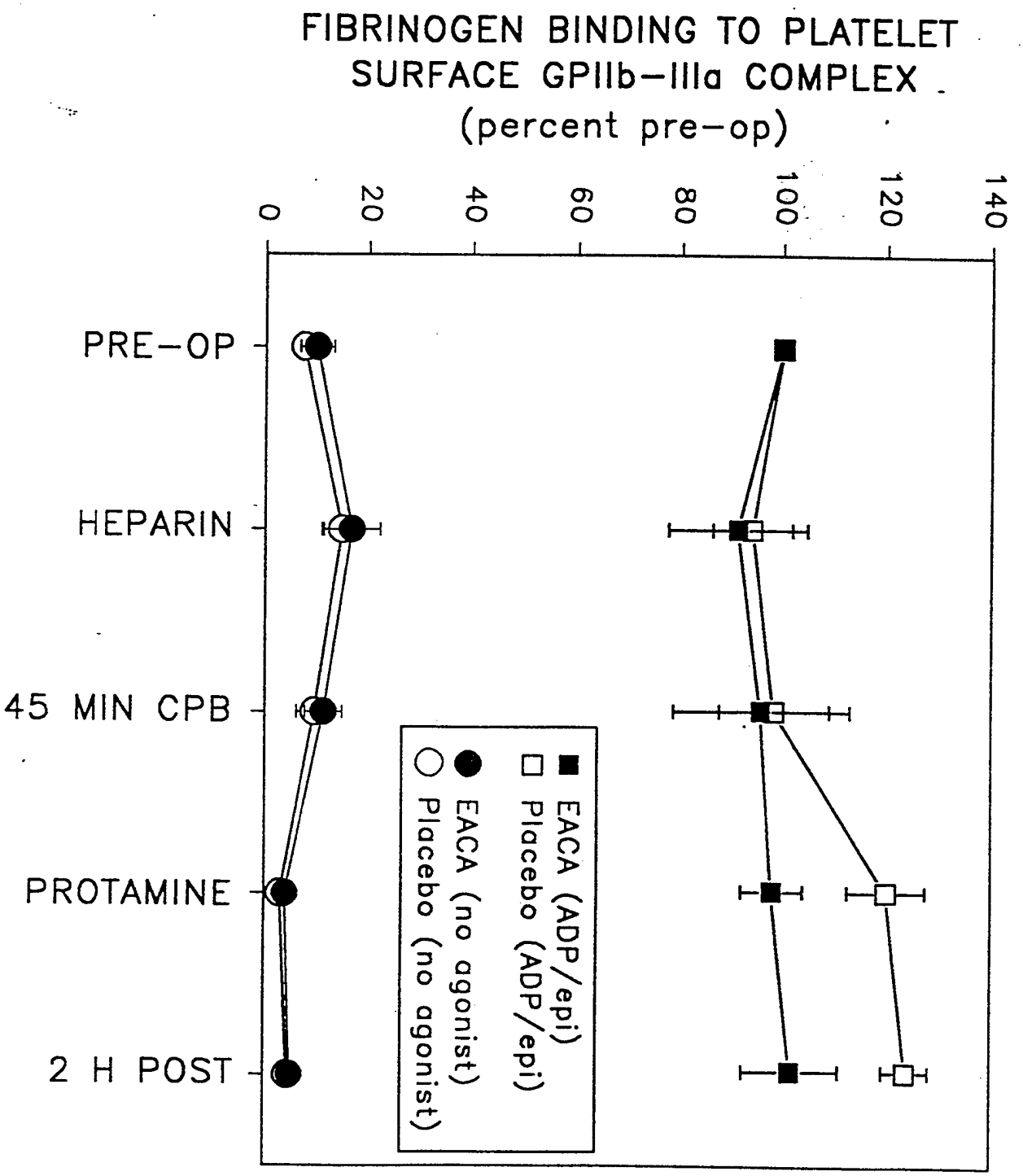
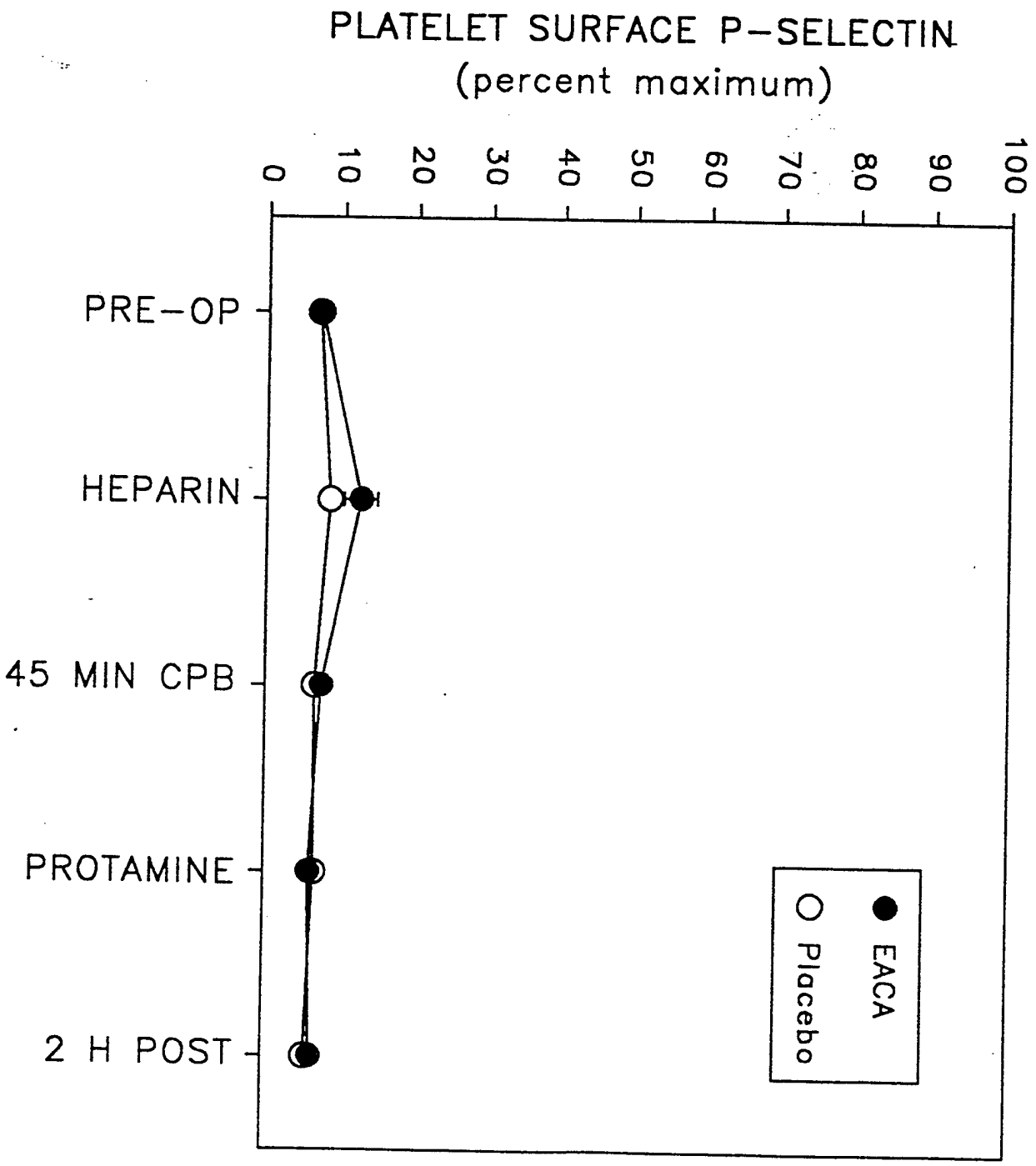

PLATELET SURFACE GPIIb–IIIa COMPLEX
(percent pre–op)
0
20
40
60
80
100
120
PRE–OP
HEPARIN
45 MIN CPB
PROTAMINE
2 H POST
EACA
Placebo

Fig 2


FIBRINOGEN BINDING TO PLATELET
SURFACE GPIIb–IIIa COMPLEX
(percent pre–op)
0
20
40
60
80
100
120
140
PRE–OP
HEPARIN
45 MIN CPB
PROTAMINE
2 H POST
EACA (ADP/epi)
Placebo (ADP/epi)
EACA (no agonist)
Placebo (no agonist)


PLATELET SURFACE P-SELECTIN
(percent maximum)
0
10
20
30
40
50
60
70
80
90
100
PRE-OP
HEPARIN
45 MIN CPB
PROTAMINE
2 H POST
EACA
Placebo

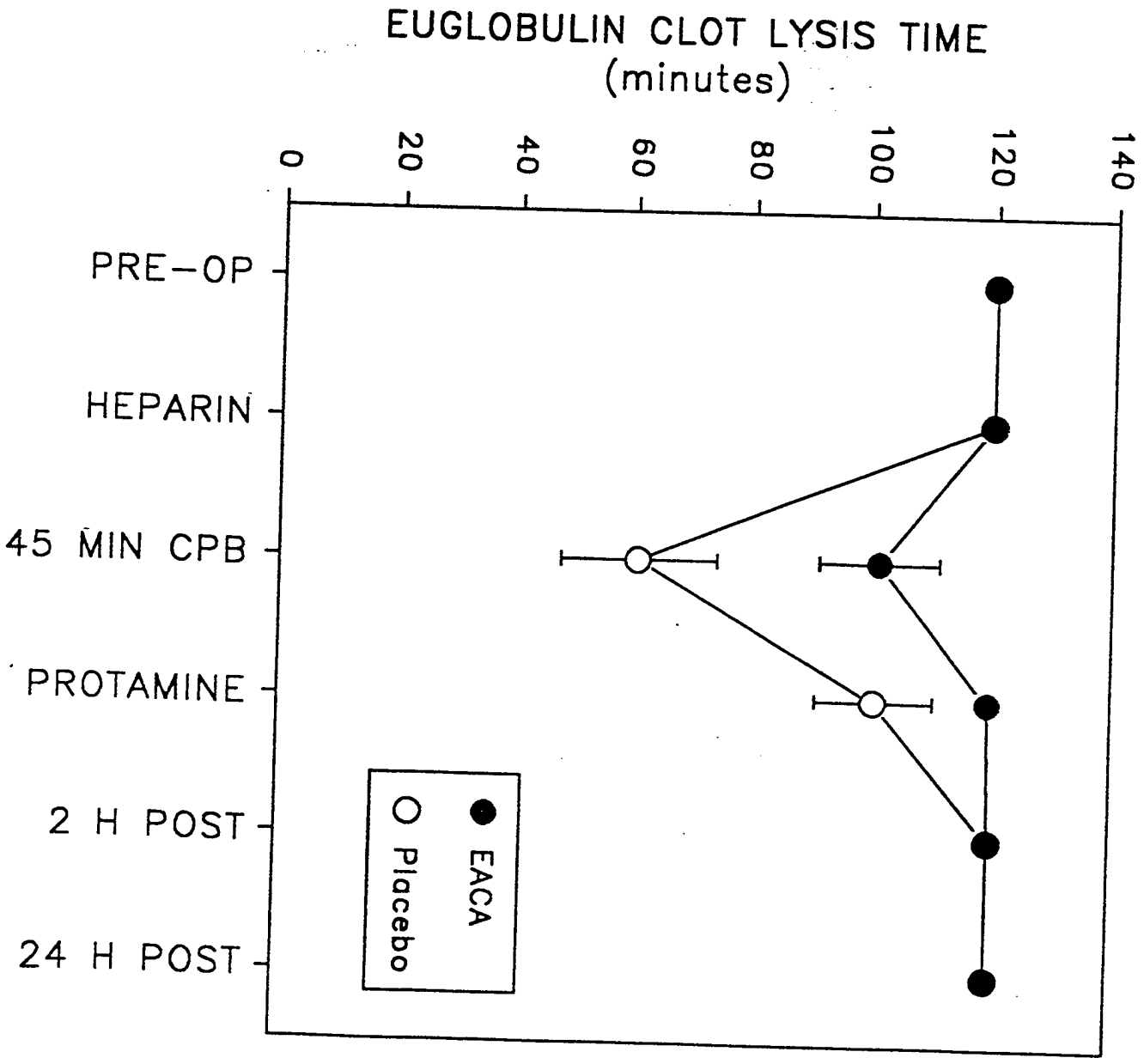
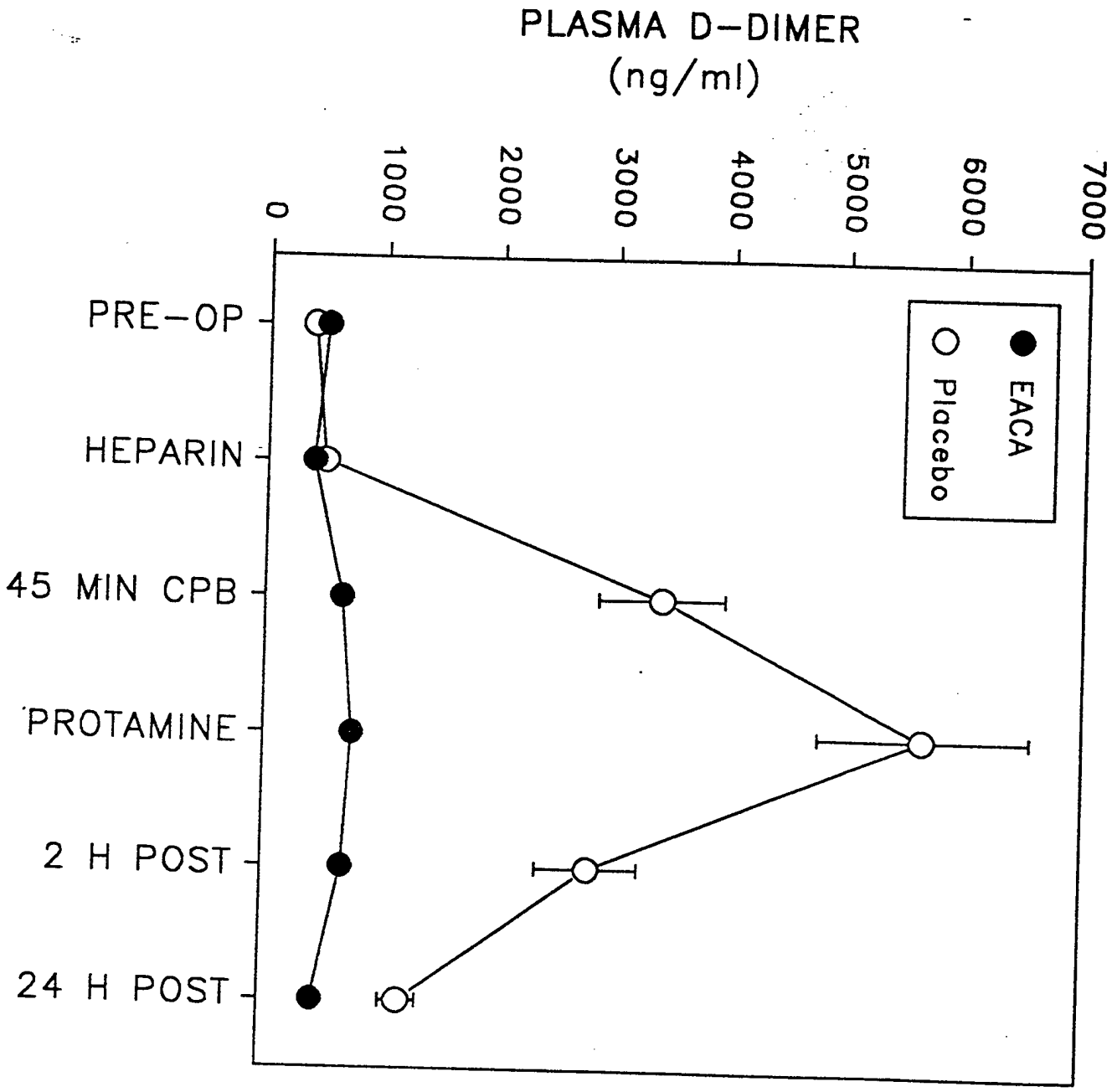
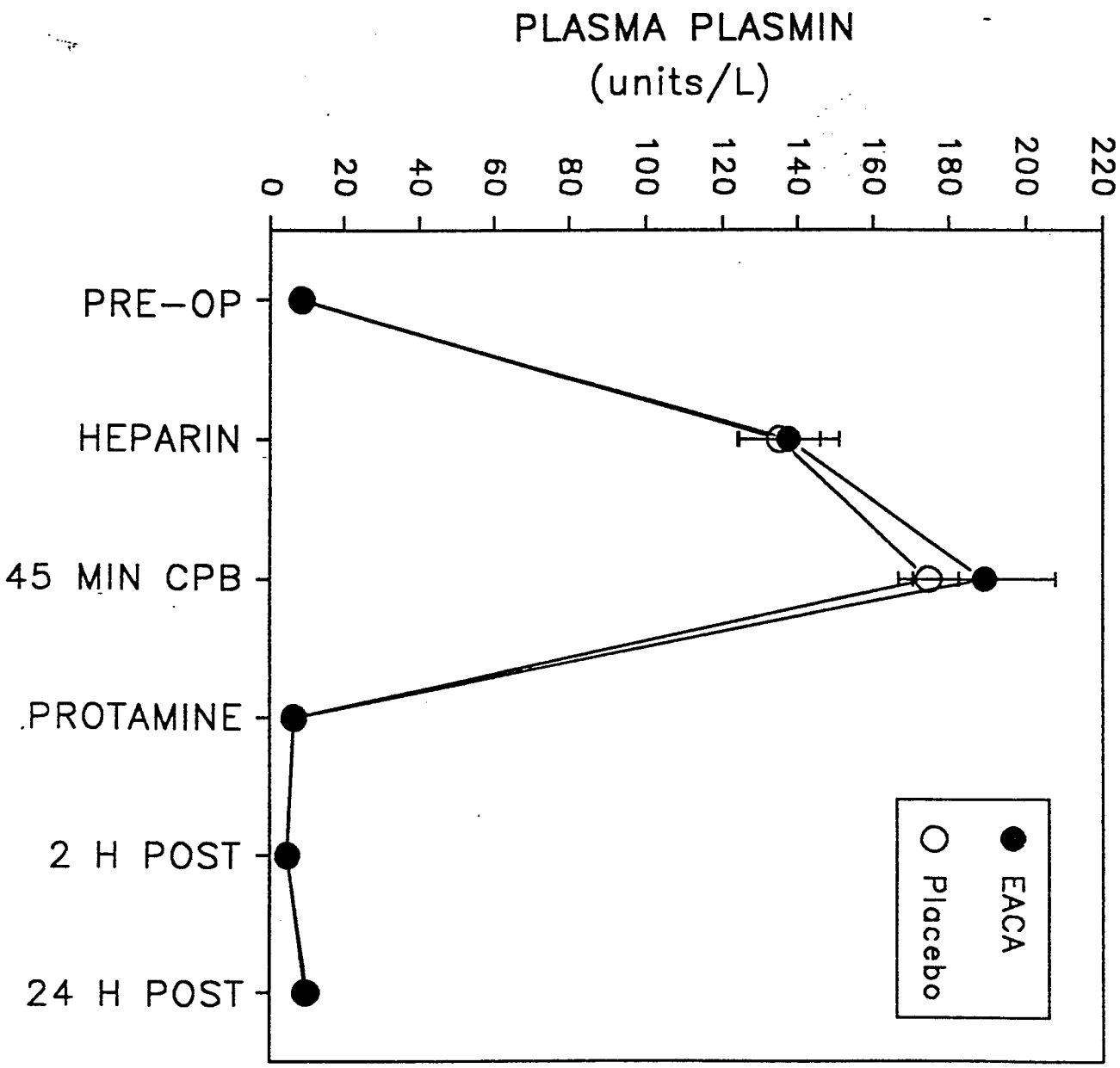

EUGLOBULIN CLOT LYSIS TIME
(minutes)
0
20
40
60
80
100
120
140
PRE-OP
HEPARIN
45 MIN CPB
PROTAMINE
2 H POST
24 H POST
EACA
Placebo

Fig 5


PLASMA D-DIMER
(ng/ml)
0
1000
2000
3000
4000
5000
6000
7000
PRE-OP
HEPARIN
45 MIN CPB
PROTAMINE
2 H POST
24 H POST
EACA
Placebo


PLASMA PLASMIN
(units/L)
0
20
40
60
80
100
120
140
160
180
200
220
PRE-OP
HEPARIN
45 MIN CPB
PROTAMINE
2 H POST
24 H POST
EACA
Placebo