HEMOSTATIC MARKERS AND RENAL FUNCTION AFTER CARDIOPULMONARY BYPASS

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ABSTRACT

To evaluate coagulation status after cardiopulmonary bypass and its relation to renal function, thrombin-antithrombin III complex and prothrombin fragment 1+2 were measured as thrombotic markers in 46 patients undergoing coronary artery bypass grafting. Postoperative serum creatinine values exceeded 20 mg·L^{-1} in 12 patients, indicating compromised renal function; there was a statistically significant increase in the postoperative levels of thrombotic markers in these patients. These data indicate that patients with renal dysfunction after cardiopulmonary bypass have a thrombotic tendency. Anticoagulant treatment is recommended in such patients.

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INTRODUCTION

Cardiopulmonary bypass (CPB) is important in cardiovascular surgery. The extracorporeal circulation system that replaces the functions of the heart and lungs, consists of a pump, disposable oxygenator, reservoirs, and tubing. Blood flow, gas exchange, blood-surface interface effects, and reticuloendothelial function are altered by CPB, with consequent changes in renal, neurological, hepatic, and other functions.[1–3] The organism is temporarily faced with unphysiological conditions such as non-pulsatile flow, anticoagulation, hemodilution, hypothermia, and relative hypoperfusion. All of these factors affect platelet function, coagulation, and the fibrinolytic system.[1,4–6] Normally, there is continuous fibrin formation on the endothelial surface, which is balanced by concomitant fibrinolysis. If this balance is upset, the clotting mechanism is activated.[4] Heparinization is used to prevent blood coagulation during CPB. Initially, the levels of factors V and VIII, antithrombin III, plasminogen, and alpha-2 antiplasmin decrease during CPB, mainly due to hemodilution, and they subsequently increase due to synthesis by the liver. Plasminogen is activated. Fibrinogen is known to be absorbed onto the circuit surface, which binds to platelets. The concentration of platelets drops, their functions alter (they become insensitive to adenosine diphosphate and epinephrine), and they are activated. Complement activation through an alternative pathway has also been demonstrated during CPB.[5,6]

It is now possible to evaluate the hemostatic system more accurately with molecular markers of in-vivo coagulation. Among these markers are the thrombin-antithrombin III complex (TAT), a marker of intravascular thrombin formation, and prothrombin fragment 1+2 (PF 1.2), a peptide fragment generated when prothrombin is activated to thrombin.[4] Studies on hemostatic system changes have been carried out in patients undergoing hemodialysis, and

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it has been well documented that patients with end-stage renal failure exhibit thrombotic complications. The aim of this study was to evaluate hemostatic status in relation to renal function in patients undergoing coronary artery bypass grafting with CPB.

PATIENTS AND METHODS

The study was carried out on 36 men and 10 women, aged 38 to 67 years, who underwent coronary artery bypass grafting in the Department of Thoracic and Cardiovascular Surgery, Hacettepe University. Patients with bleeding diathesis who received salicylic acid, heparin, warfarin, nonsteroidal antiinflammatory drugs, or fibrinolytic medication, were excluded from the study. A Univox membrane oxygenator, DeBakey roller pump, and Bentley Duraflo II pump system (Bentley, Irvine, CA, USA) were used in all patients for CPB. Patients were cooled to 28°C and cold potassium cardioplegia was applied. The

Table 1. **Renal and Hemostatic Parameters in Group 1 and Group 2 (Postoperative Creatinine ≥ 20 mg·L^{-1})**

	Preoperative		Postoperative	
Parameter	Group 1 (n = 34)	Group 2 (n = 12)	Group 1 (n = 34)	Group 2 (n = 12)
Blood urea nitrogen (mg·L^{-1})	185.6 ± 22	186.2 ± 19	248.1 ± 29	333.8 ± 4*
Serum creatinine (mg·L^{-1})	9.9 ± 1	10.1 ± 1	14.2 ± 2	23.9 ± 2*
Thrombin-antithrombin III (ng·mL^{-1})	4.37 ± 2.4	3.42 ± 0.9	4.46 ± 3.5	13.1 ± 5.4*
Prothrombin fragment 1+2 (nmol·L^{-1})	2.87 ± 1	2.89 ± 1.6	3.82 ± 2.5†	5.47 ± 2*†

*Significantly higher than group 1. †Significantly higher than preoperative values.

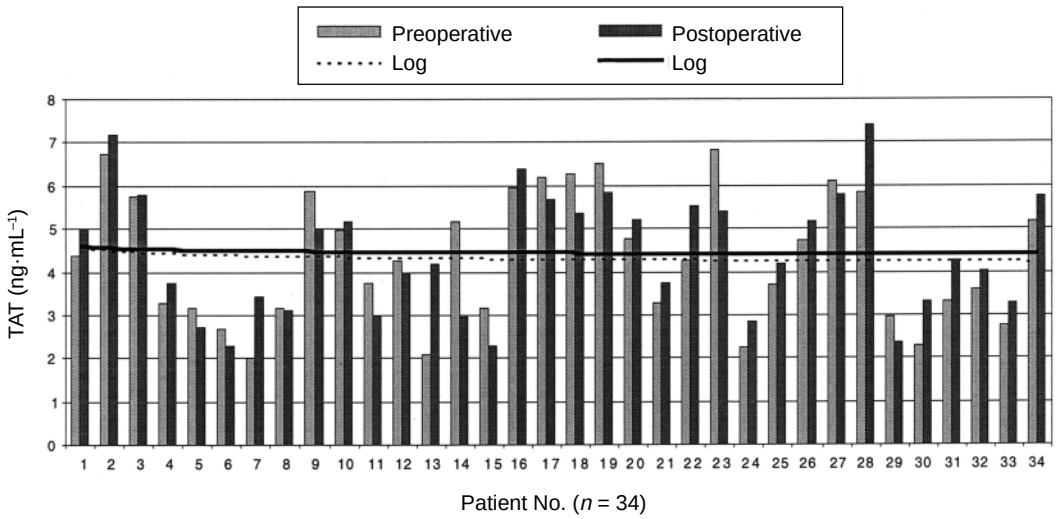

Figure 1. Preoperative and postoperative thrombin-antithrombin III complex (TAT) in group 1 (serum creatinine < 20 mg·L^{-1}).

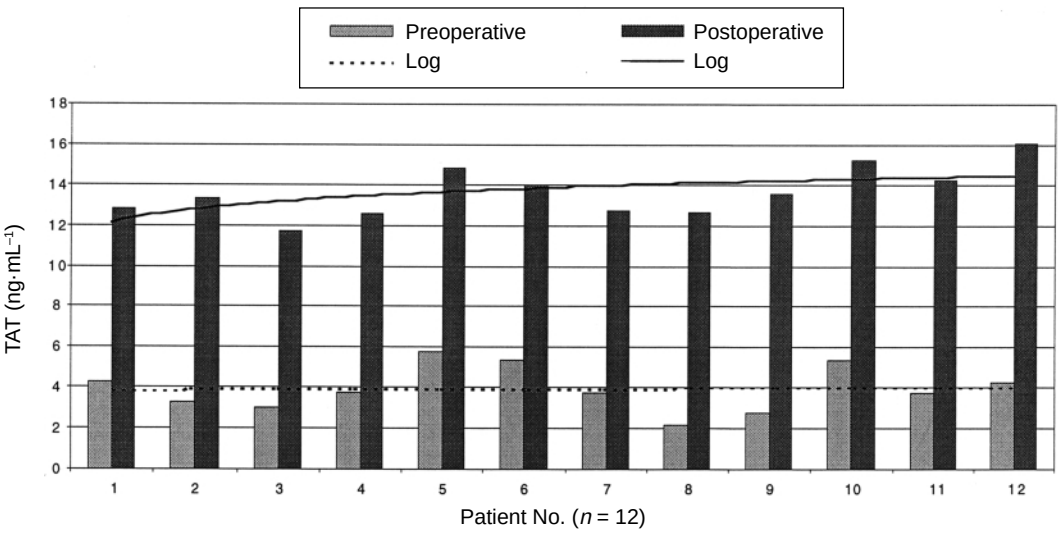

Figure 2. Preoperative and postoperative thrombin-antithrombin III complex (TAT) in group 2 (serum creatinine ≥ 20 mg·L^{-1}).

perfusion pressure was kept above 40 mm Hg. Bypass flow rates were maintained at 2.4 $L \cdot m^{-2} \cdot min^{-1}$. Heparin 3 $mg \cdot kg^{-1}$ (Liquemine; La Roche Ltd, Basel, Switzerland) was given before cannulation. The activated clotting time was monitored (Hemachron; Technidyne, Edison, NJ, USA) and kept at approximately 400 seconds. Neutralization of heparin after CPB was achieved with protamine (Protamin; La Roche Ltd, Basel, Switzerland) administration. Blood samples were obtained before CPB and 24 hours postoperatively to determine PF 1.2 and TAT levels. PF 1.2 and TAT concentrations in plasma were measured using solid-phase sandwich enzyme-linked immunosorbent assays (Enzygnost F 1+2 and Enzygnost TAT; Behring, Frankfurt, Germany). Preoperative and postoperative blood urea nitrogen and serum creatinine values were also determined.

Results were expressed as mean ± standard error of the mean. Values of $p < 0.05$ were accepted as significant. Student's *t* test for paired samples was used for comparison of preoperative and postoperative plasma PF 1.2 and TAT values. SPSS version 5.01 for Windows (Statistical Package for Social Sciences, Inc., Chicago, IL, USA) was used to analyze the data.

RESULTS

Patients were grouped according to their postoperative serum creatinine values: group 1, $n = 34$, creatinine < 20 $mg \cdot L^{-1}$; and group 2, $n = 12$, creatinine ≥ 20 $mg \cdot L^{-1}$. Plasma concentrations of TAT and PF 1.2, blood urea nitrogen, and serum creatinine are shown in Table 1 and Figures 1 to 4. In group 1, preoperative and postoperative TAT values were not significantly different ($p = 0.416$), but PF 1.2 levels were significantly higher postoperatively ($p < 0.05$). In addition to blood urea nitrogen and creatinine, postoperative TAT and PF 1.2 values were significantly higher in group 2 than in group 1. The PF 1.2 level in group 2 was higher postoperatively than preoperatively ($p < 0.05$).

DISCUSSION

The coagulation cascade is a series of linked proteolytic reactions leading to thrombin generation and fibrin formation. CPB causes hemostatic abnormalities by

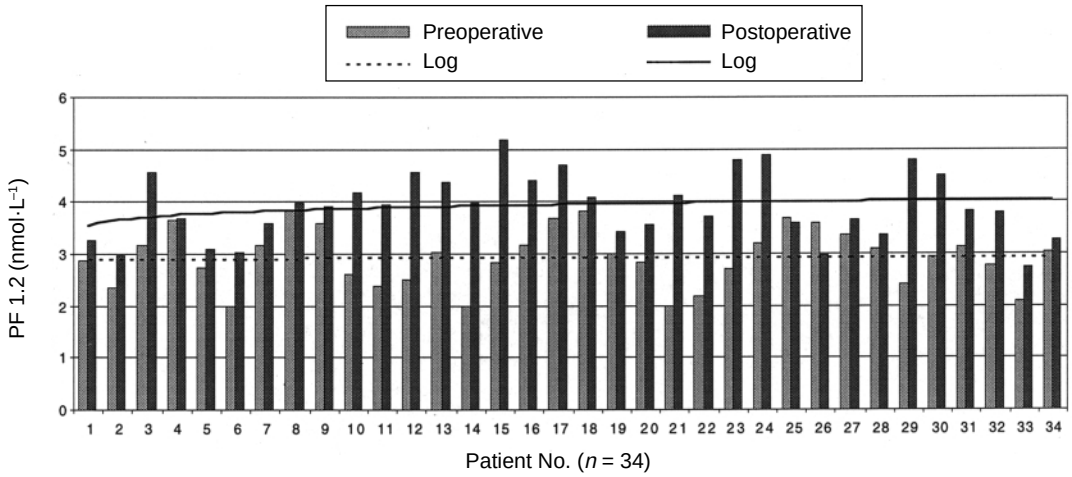

Figure 3. Preoperative and postoperative prothrombin fragment 1+2 (PF 1.2) in group 1 (serum creatinine < 20 $mg \cdot L^{-1}$).

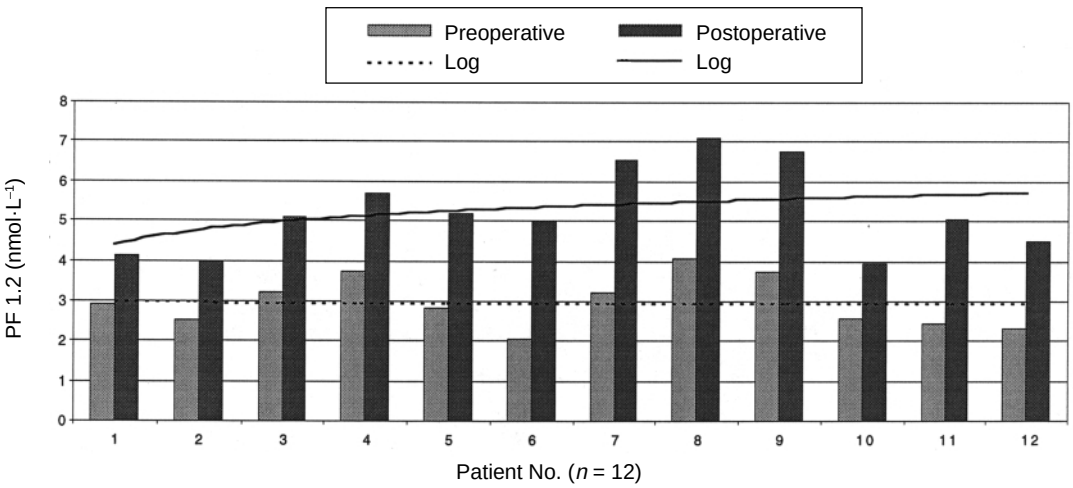

Figure 4. Preoperative and postoperative prothrombin fragment 1+2 (PF 1.2) in group 2 (serum creatinine ≥ 20 $mg \cdot L^{-1}$).

influencing the coagulation factors, fibrinogen and the fibrinolytic system, as well as the number and function of platelets. The coagulation activation markers are useful for studying coagulation status in vivo.[7] PF 1.2, the peptide fragment generated when prothrombin is activated to thrombin, is found during the activation of coagulation. When thrombin is formed, it combines in a complex with the serine protease inhibitor antithrombin III. These in-vivo molecular markers of coagulation circulate in the blood of patients with thrombotic disorders, indicating hemostatic system activation.[4,8]

The results of this study show that CPB induces thrombin generation. Although PF 1.2 levels increased slightly when renal function was not affected (group 1), levels of both markers showed marked increases when renal function was compromised (group 2). Further study is required to determine whether only TAT or both TAT and PF 1.2 are important in the thrombotic tendency. However, it is well known that acute renal failure after open heart surgery correlates with longer durations of CPB and aortic crossclamping. The correlation between renal failure and thrombotic tendency has been established.[9–14] It seems that postoperative impairment of renal function gives rise to a thrombotic tendency.[14]

The findings in this study suggest that the thrombotic tendency imposed by CPB is augmented by impairment of renal function. CPB times in all patients were more than 60 minutes. Serum creatinine levels were above 20 $mg \cdot L^{-1}$ in the early postoperative period (24 hours) in the 12 patients in group 2, but they had decreased to less than 20 $mg \cdot L^{-1}$ by the 5th postoperative day in all except one of them. This suggests that coronary artery bypass graft patients should be anticoagulated during periods when creatinine levels are above 20 $mg \cdot L^{-1}$, to prevent graft thrombosis. This increased thrombotic tendency is important in early and long-term graft patency. Therefore, prophylactic anticoagulation treatment is recommended when TAT and PF 1.2 values are increased in patients with renal impairment.

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