

# Changes in activated partial thromboplastin time and international normalised ratio after on-pump and off-pump surgical revascularization of the heart

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## ABSTRACT

Surgical revascularization of the heart (CABG - coronary artery bypass grafting) is one way of treating coronary heart disease. Bleeding is one of the serious and frequent complications of heart surgery and can result in increased mortality and morbidity. Hemostasis disorder may be secondary consequences of surgical bleeding, preoperative anticoagulant therapy, and the use of cardiopulmonary bypass. Tests used for routine evaluation of the coagulation system are activated partial thromboplastin time (APTT) and international normalized ratio (INR). The study encountered 60 patients who were hospitalized at the Clinic for Cardiovascular Diseases, University Clinical Center Tuzla. Patients underwent elective coronary artery bypass heart surgery either with cardiopulmonary bypass (on-pump CABG) or without it (off-pump CABG). The aim of this study was to compare the changes in coagulation tests (APTT, INR) in patients who were operated on-pump and patients operated off-pump. Our study showed that the values of APTT and INR tend to increase immediately after surgery. Twenty-four hours after surgery these values are declining and they are approaching the preoperative values in all observed patients ( $p < 0.05$ ). Comparing APTT between the groups we found that postoperative APTT levels are significantly higher in the group of patients who underwent surgery with cardiopulmonary bypass ( $p < 0.05$ ). Changes in coagulation tests after surgical revascularization of the heart are more pronounced in patients who were operated with on-pump technique compared to patients operated off-pump technique.

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KEY WORDS: CABG, on-pump, off-pump, APTT, INR

## INTRODUCTION

Surgical revascularization of the heart (CABG coronary artery bypass grafting) is one way of treating coronary heart disease. CABG improves blood flow to the heart. Healthy artery or vein is used to bypass the occluded coronary artery. It creates a new path for blood flow to the heart muscle. The operation is performed with the use of cardiopulmonary bypass (CPB) called on-pump technique or without the use of CPB called off-pump technique. Opinions are still divided on which is

the better way. On-pump CABG procedure is performed while the heart is stopped. The blood supply must be provided to the rest of the body when the heart is stopped. Therefore, surgeons use the CPB as an artificial circulation system that does the work of the heart and the lungs. On-pump CABG today is a safe procedure that has a small risk of death and/or complications. The average risk of this procedure for a low-risk patient is 1% to 2%. The patient's other health-threatening conditions increase these risks. Some of the important complications that can occur with this technique are stroke, kidney or liver failure, decrease in higher mental function, and bleeding. These complications have been ascribed to the use of the pump and the need to manipulate both the heart and the large arteries to place the patient on CPB. Off-pump CABG is considered as the new method of performing CABG. The complications of on-pump CABG, spurred the development of this technique. This procedure is performed with the heart beating and without the use of the CPB. Grafts are

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attached to the heart while it is constantly moving and filled with blood. Special devices can mechanically stabilize the relevant part of the heart so that the suturing can be performed on a relatively immobile platform. The risk of death and/or complications from off-pump CABG is also about 1% to 2% in a low-risk patient. The choice of procedure should depend on the comfort level of the surgeon performing the procedure on a particular patient because these two procedures seem equally effective [1]. Postoperative bleeding is common after heart surgery. Nearly 20% of patients had increased postoperative bleeding, and 4% required reoperation because of excessive bleeding [2]. Bleeding is one of the serious and frequent complications of heart surgery and can result in increased mortality and morbidity [3]. It can be caused by surgical error, disorder of hemostasis, or a combination of both. Hemostasis disorder may be secondary consequences of surgical bleeding, preoperative anticoagulant therapy and use of cardiopulmonary bypass. Hemostatic system consists of a coagulation system, endothelial cells, regulatory proteins, platelets and fibrinolysis [4]. These elements work together to prevent the loss of blood from damaged blood vessels without occluding the entire vessel. In some situations, this activation can spread to the entire body causing coagulation and thrombotic complication. Cardiac surgery, especially with the use of CPB leads to such a scenario [5]. CPB is, however, associated with massive activation of the inflammatory and coagulation systems because of conversion to laminar flow, blood contact with the artificial bypass surface, cold cardiac ischemia and hypothermia. The causes of coagulopathy after CPB are reduced platelet function or count, excessive fibrinolysis, reduced circulating levels of coagulation factors, hypothermia [2]. Development of cardiac immobilization techniques allows complete revascularization on the beating heart (off-pump). This strategy avoids inflammation and hemostatic problems caused by CPB and reduce the pro-inflammatory stimulus to sternotomy and the revascularization procedure itself. Tests used for routine evaluation of the coagulation system are activated partial thromboplastin time (APTT) and international normalized ratio (INR). APTT is used to screen for abnormalities of the internal factor coagulation pathway (reduction or defect factors VIII, IX, XI and XII), as well as the common path (fibrinogen, factors II, V, X). It is also used for monitoring heparin therapy. Normal values are 26 - 33 s. INR allows standardization of the results of the prothrombin test (PT) in different laboratories. Normal values are from 1 - 2. PT test is used to evaluate the activity of coagulation factors involved in an external way of coagulation (factor II, V, VII, X), assessment of synthetic liver function, control dose of oral anticoagulant therapy with coumarins. It measures the time in seconds it takes to form fibrin. The activated clotting time (ACT) is the most commonly used functional

test to measure heparin anticoagulation during cardiac surgery. This test is based on the ability of whole blood to form a visible fibrin monomer within a glass tube. Studies that compared coagulation in on-pump versus off-pump CABG were done before [6, 7]. These studies proved that coagulation is more disrupted after on-pump operation. Tests used in these studies are not routinely used. That's why our study is based on routinely used coagulation tests (APTT, INR). The aim of this study was to compare changes in APTT and INR in patients operated by on-pump and off-pump technique. In accordance with previous studies we hypothesis that postoperative levels of APTT and INR will be above referent limit in both groups of patients. We expect that APTT and INR will be significantly higher in the on-pump group.

## MATERIALS AND METHODS

### *Patients*

The study was prospective in character and referred to the monitoring of changes in coagulation tests after surgical revascularization of the heart. The sample included 60 consecutive patients who were hospitalized at the Clinic for Cardiovascular Diseases University Clinical Center Tuzla diagnosed with coronary artery disease. Patients underwent elective coronary artery bypass heart surgery. Written consent was obtained from all the patients included in the study. The study has been approved by the Local Ethic Committee. Investigations were carried out in accordance with the Declaration of Helsinki as revised in 2008.

### *Procedures*

Patients included in the study had normal preoperative coagulation, ejection fraction >35%, no liver and renal disease. Clopidogrel and warfarin were excluded from therapy five days before the operation and acetylsalicylic acid one day before. Patients were randomly allocated to one of two groups with 30 patients per group. Group 1 was operated with the use of CPB, called on-pump technique, and group 2 was operated without the use of CPB, called off-pump technique. Balanced anaesthesia was used in both groups. Patients were pre-medicated using midazolam 2 - 2.5 and fentanyl 200-300 µg. Induction of anaesthesia was by midazolam 0.2 mg/kg and pankuronium 0.1 mg/kg. Anaesthesia was maintained with continuous infusion of midazolam, fentanyl, pankuronium and sevoflurane in both groups. During CPB in on-pump group, anaesthesia was maintained only by continuous infusion of midazolam, fentanyl and pankuronium. In the on-pump group, before connection to CPB, unfractionated heparin (300-400 IU/kg) was administered to achieve ACT more than 450 s. CPB was managed with a minimal nasopharyngeal temperature of 32°C. Myocardial protec-

tion was achieved with cold (4°C) potassium cardioplegia. In the off-pump group, CABG was performed on the beating normothermic heart with local cardiac wall immobilization. Before the anastomosis was started, unfractionated heparin was administered (100 IU/kg.b.w), followed by additional 2000-3000IU of heparin to maintain ACT >250 s. The heparin was reversed by the administration of protamine. We used a different target ACT for both procedures, because there were different indications for the use of anticoagulation. Whereas in the on-pump group heparin was mainly used to prevent clotting in the CPB system, in the off-pump group it was needed to prevent clotting in the harvested internal mammary arteries and in the native coronary system during grafting. The postoperative ACT after protamine infusion was the same in both groups (<130). Hypothesizing that off-pump would not influence hemostasis, we decided to study the effects after the operation. Protamine sulfate binds to negatively charged unfractionated heparin. The resultant protamine-heparin complex is rapidly cleared by the reticuloendothelial system. Protamine is routinely administered postoperatively to reverse the high concentrations of heparin required for patients undergoing cardiac surgery. In group 1 after completion of CPB, the heparin was reversed by administration of 1mg protamine/ 100 IU of heparin. In group 2, patients received 0.3-0.5 mg protamine/100 IU heparin. If the ACT remained elevated following the initial dose of protamine, an additional dose of 20-50mg protamine was given to decrease ACT <130s. For ACT measurement we used Medtronic ACT II coagulation analyzer. Assessment of coagulation status of patients was done using coagulation tests: activated partial thromboplastin time (APTT) and international normalized ratio (INR). INR is the international normalized value for prothrombin time (PT). For both tests we used automatical coagulation analyzer Siemens Sysmex CA-1500th System. The blood sample for analysis was obtained from the peripheral vein in a tube with anticoagulant sodium citrate and in the ratio of 1:9, one part anticoagulant and nine parts of blood. As a reagent for the PT test is used Thromborel S, and for APTT Pathtromtin SL. Blood samples were collected preoperatively, at admission in intensive care unit (ICU) and the day after surgery. Time elapsed from sampling to analysis was not greater than one hour.

#### Statistical analysis

Statistical analysis was performed by using the MedCalc for Windows version 8.1.0.0 (MedCalc Software, Mariakerke, Belgium) statistical package. The values were expressed as mean  $\pm$  SEM. Two groups of continuous variables with normal distribution of data were compared using ANOVA for repeated measures after their categorization. The level of significance was  $p < 0.05$ .

**TABLE 1.** Demographic characteristics of patients

	On-pump		Off-pump		<i>p</i>
N	30		30		
Age	59.47 $\pm$ 7.31		57.03 $\pm$ 7.56		1.0
Gender	n	%	n	%	
Male	21	70.0	20	66.7	0.78
Female	9	30.0	10	33.3	0.78

**TABLE 2.** Changes in APTT and INR in the on-pump group

Variable	Time I	Time II	Time III
APTT (N=30)	33.70 $\pm$ 0.96*	39.16 $\pm$ 1.63**	34.36 $\pm$ 1.37
INR (N=30)	1.07 $\pm$ 0.019***	1.43 $\pm$ 0.04****	1.19 $\pm$ 0.022

Values are expressed as mean  $\pm$  SEM. APTT activated partial thromboplastin time; INR International Normalization Ratio; Time I – preoperative; Time II –after admission in intensive care unit; Time III –24 hours after the operation; \*  $p < 0.05$  Compared to Time II; \*\*  $p < 0.05$  Compared to Time III; \*\*\*  $p < 0.05$  Compared to Time II and Time III; \*\*\*\*  $p < 0.05$  Compared to Time III.

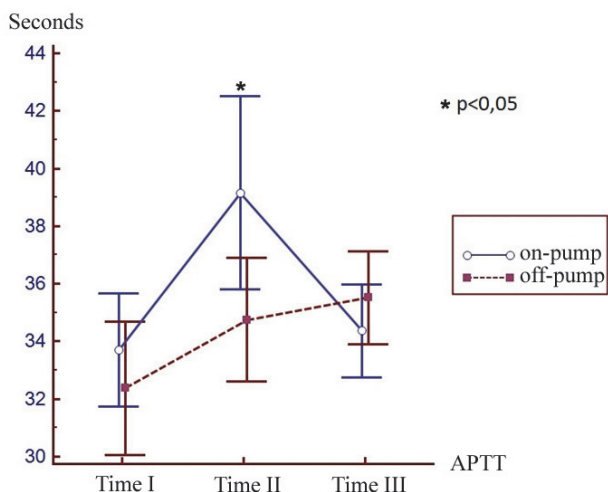
**TABLE 3.** Changes in APTT and INR in the off-pump group

Variable	Time I	Time II	Time III
APTT (N=30)	32.38 $\pm$ 1.13*	34.75 $\pm$ 1.05	35.51 $\pm$ 0.79
INR (N=30)	1.13 $\pm$ 0.02**	1.31 $\pm$ 0.064***	1.18 $\pm$ 0.016

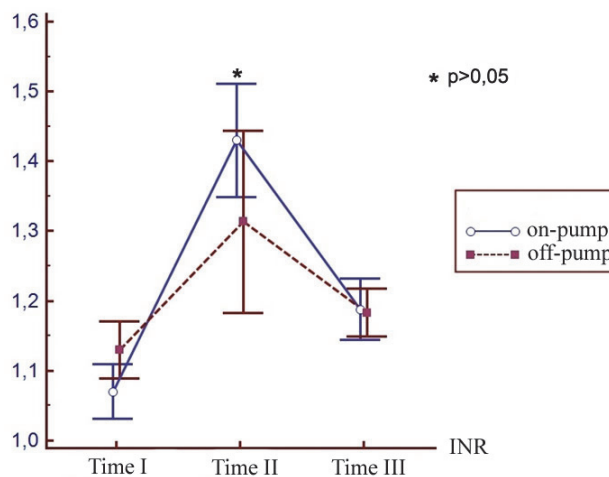
Values are expressed as mean  $\pm$  SEM. APTT activated partial thromboplastin time; INR International Normalization Ratio; Time I – preoperative; Time II –after admission in intensive care unit; Time III –24 hours after the operation; \*  $p < 0.05$  Compared to Time III; \*\*  $p < 0.05$  Compared to Time II and Time III; \*\*\*  $p = 0.05$  Compared to Time II.

## RESULTS

We randomly assigned 60 patients who were scheduled for elective first-time CABG to undergo the procedure either with cardiopulmonary bypass (on-pump CABG) or without it (off-pump CABG). In the on-pump group, 9 (30%) were female and 21 (70%) male, and the mean age was 59.47  $\pm$  7.31 years. In the off-pump group, 10 (33.3%) individuals were female and 20 (66.7%) were male, with a mean age of 57.03  $\pm$  7.56 years. There were no significant differences in the age or sex ratio between groups (Table 1). In our study we compared the values of APTT and INR in patients operated with the use of CPB (on-pump) and patients operated off-pump. Tests were performed before surgery (Time I), after admission in the ICU (Time II) and the day after surgery (Time III). Mean APTT levels were found to be significantly higher in Time II compared to Time I and Time III in on-pump group. A significant difference was not found between Time I and Time III in the on-pump group (Table 2). In the off-pump group mean APTT levels were found to be significantly higher in Time I compared to Time III. A significant difference was not found between Time I and Time II in the off-pump group (Table 3). Comparing APTT



**FIGURE 1.** Comparison of APTT changes between on-pump and off-pump group  
Time I – preoperative APTT; Time II – APTT after admission in intensive care unit; Time III – APTT 24 hours after the operation; \*  $p < 0.05$  – Time II on-pump compared to Time II off-pump.



**FIGURE 2.** Comparison of INR changes between on-pump and off-pump group  
Time I – preoperative INR; Time II – INR after admission in intensive care unit; Time III – INR 24 hours after the operation; \*  $p > 0.05$  – Time II on-pump compared to Time II off-pump.

between the groups we found mean APTT levels in Time II to be significantly higher in the on-pump group (Figure 1). Mean INR levels were found to be significantly higher in Time II compared to Time I and Time III in the on-pump group (Table 2). Mean INR levels were found to be significantly higher in Time II compared to Time I in the off-pump group. In the off-pump group mean INR levels were found to be significantly higher in Time III compared to Time I (Table 3). Comparing INR between the on-pump and off-pump group, significant difference was not found (Figure 2).

## DISCUSSION

APTT and INR are used as a routine tests to check patient’s coagulation system. APTT is most commonly used for monitoring anticoagulation therapy with heparin. Various studies have measured APTT following cardiac surgery and have found it to be commonly elevated [6-9]. Some studies have shown a positive correlation between APTT and postoperative hemorrhage following cardiac surgery [8-13]. Our study showed prolonged APTT and INR after the surgery despite neutralization of heparin with protamine. Our findings are in accordance with other studies that have shown massive activation of hemostasis during and early after cardiac surgery performed with the use of CPB [6,7]. APTT was more elevated in patients who underwent surgery with the use of CPB. After the operation, when patients were received in the ICU, APTT values were higher than normal in the majority of patients operated with the on-pump technique. APTT was slightly higher in patients operated with the off-pump technique, but significant difference was not found. Twenty-four hours after surgery APTT values in

both groups of patients decreased to preoperative values. In the on-pump group, statistically significant difference was not found between preoperative values and values 24 hours after the operation. In the off-pump group we found significant difference between those two measurements. This can be explained by “heparin rebound” phenomenon. “Heparin rebound” phenomenon usually occurs 1-8 hours after neutralization of heparin with protamine [14]. This phenomenon is often attributed to reappearance of circulating heparin. Theories accounting for “heparin rebound” include late release of heparin sequestered in tissues, delayed return of heparin to the circulation from the extracellular space via lymphatics, clearance of an unrecognized endogenous heparin antagonist, and more rapid clearance of protamine in relation to heparin [15,16]. Ravi Taneja and colleagues showed that in the majority of patients APTT was increased postoperatively but according to their research it is not due to “heparin rebound” phenomenon [17]. They speculate that elevated APTT may have been related, at least in part, to an excessive protamine dose in an attempt to reverse heparin. Higher APTT values after heart surgery can be explained by hemodilution and reduction of coagulation factors by 50% in patients operated with CPB, whereas in patients operated with the off-pump technique due to increased consumption intraoperatively and postoperatively [18]. According to some studies large doses of protamine can increase APTT values [19]. Agnese Ozolina in her study also found that after heart surgery APTT was increased, but increased APTT was not correlated with increased postoperative bleeding [20]. INR values showed the least change in both groups of patients. After surgery in patients operated with cardiopulmonary bypass INR was slightly elevated. This is consistent with



previous studies [21]. In patients operated by the off - pump technique the average value of INR after operation was normal. Pawan K et al showed that preoperative INR greater than 2 affects postoperative bleeding [22]. In our study, all patients had preoperative INR less than 2. Comparing INR between the groups, statistically significant difference was not found.

## CONCLUSION

This study has shown that surgical revascularization of the heart leads to prolonged coagulation tests (APTT and INR) above the reference value. These tests are used to routinely check internal, external and common coagulation pathway. APTT and INR after the operation are above referent limit in both groups of patients. This indicates that there is a disorder of coagulation in terms of hypocoagulability. APTT values are significantly more elevated in patients operated with the use of CPB, indicating that hypocoagulability is more pronounced in these patients. Hypocoagulability increases the risk for massive postoperative bleeding and the need for blood transfusion.

## DECLARATION OF INTEREST

The authors declared no conflicts of interest.

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