Effects of Cardiopulmonary Bypass Operation on Circulating Level of Adropin, Elabela and Nitric Oxide Depending on the Time Intervals

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ABSTRACT

Introduction: Elabela and adropin (nitric oxide mediated effect) are two new hormones that are synthesized in the heart and discovered in the last years with the role in vascular system homoeostasis. Therefore, the main aim of this study is to examine the changes of adropin, elabela and nitric oxide in blood samples taken at various time intervals of the coronary artery bypass graft using cardiopulmonary bypass.

Patient and method: This study included 20 healthy individuals and 15 patients undergoing cardiopulmonary bypass surgery. Blood samples were taken from patients who had cardiopulmonary bypass surgery before anesthesia induction (T1), before bypass (T2), before removing cross clamp (T3); at intensive care unit (T4), postoperative 24th (T5), 48th (T6) and 72nd hours (T7). A blood sample was taken once from the healthy volunteer control group. Blood adropin, elabela and nitric oxide quantities were measured by ELISA

Results: When the control adropin and nitric oxide blood values were compared with the adropin and nitric oxide blood values obtained at T1; adropin and nitric oxide levels in the blood collected during T1 time interval were significantly lower. Elabela and lactate levels in the blood at T1 time interval were significantly higher. In the blood samples taken at postoperative 24th (T5), 48th (T6) and 72nd hours (T7), both blood elabela and blood lactate began to decrease significantly.

Conclusion: Significant changes in the amount of these molecules in blood samples taken at various time intervals during cardiopulmonary bypass operation are promising in the monitoring of coronary artery bypass surgery.

Key words: Adropin; elabela; nitric oxide; coronary artery bypass; graft

Kardiyopulmoner Baypas Ameliyatının Zaman Aralıklarına Bağlı Olarak Sirküle Adropin, Elabela ve Nitrik Oksitin Düzeyine Etkisi

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ÖZET

Giriş: Elabela ve adropin (nitrik oksit aracılı etki), kalpte sentezlenen ve vasküler sistem homoeostazındaki rolü olan, son yıllarda keşfedilen iki yeni hormondur. Bu nedenle, bu çalışmanın temel amacı, coroner arter baypas grefti kulaanılarak yapılan kardiyopulmoner baypasın farklı zaman aralıklarında alınan kan örneklerinde adropin, elabela ve nitrik oksit değişikliklerini incelemektir.

Hastalar ve Yöntem: Bu çalışmada 20 sağlıklı birey ve kardiyopulmoner baypas ameliyatı olan 15 hasta bulunmaktadır. Kan örnekleri kardiyopulmoner baypas ameliyatı olan hastalardan; anestezi indüksiyonundan önce (T1), baypastan önce (T2), çapraz kelepçe çıkarılmadan önce (T3), yoğun baklım ünitesinde (T4), operasyon sonrası 24. saatte (T5), 48. saatte (T6) ve 72. saatte (T7) alındı. Sağlıklı gönüllü kontrol grubundan bir kez kan örneği alındı. Kan adropin, elabela ve nitrik oksit miktarları ELISA ile ölçüldü.

Bulgular: Kontrol adropin, ve nitrik oksit kan değerleri T1'den elde edilen adropin, ve nitrik oksit kan değerleri ile karşılaştırıldığında; T1 süresince toplanan kan adropin, ve nitrik oksit kan değerleri istatistiksel olarak anlamlı şekilde düşüktü. T1 deki kan elabela ve laktat düzeyi istatistiksel olarak anlamlı şekilde yüksekti. Bu artış hastalar yoğun bakım ünitesine alınıncaya (T4) kadar devam etti. Operasyon sonrası 24. (T5), 48. (T6) ve 72. (T7) saatlerinde alınan kan örneklerinde hem elabela hem de laktat istatistiksel olarak anlamlı şekilde düştü.

Sonuç: Kardiyopulmoner baypas ameliyatının farklı zaman aralıklarında alınan kan örneklerinde bu moleküllerin miktarlarındaki değişiklikler koroner arter baypas ameliyatının izlenmesinde umut vericidir.

Anahtar kelimeler: Adropin; elabela; nitrik oksid; Koroner baypas; greft

INTRODUCTION

Despite all the advances in medicine, deaths due to cardiovascular diseases still can not be prevented today, and they are still the first in terms of morbidity and mortality worldwide[1]. The cardiovascular system consists of the heart and blood vessels (arteries and veins). The vessels feeding the heart are contracting or clogging over time. Coronary artery by-pass surgery (open heart surgery) bypasses these vessels, which occlude or constrict, by using vessels taken from other parts of body (left breast artery (LIMA), leg vein (saphenous vein), or arm artery (radial artery) and blood flow can be restored after bypass (bridging)[2,3].

The heart-lung machine provides circulation when this open heart surgery is performed[3]. This non-physiological event has been reported to directly affect the endocrinal system of the patient and to increase or decrease the synthesis and release of peptide-structured hormones such as B-type natriuretic peptide (BNP)[4] antidiuretic hormone (ADH)[5] and insülin[6]. In an earlier study in which we performed grafting with coronary artery bypass surgery; we reported that the amount of salusin alpha, beta and apelin 36 peptides in blood samples, that were taken before anesthesia induction, before bypass, before removing cross clamp and after removing cross clamp, were decreased and then increased at intensive care unit, postoperative 24th and 72nd hours[7].

In recent years, peptide-structured two new molecules with hormonal effects that act on energy homeostasis and cardiovascular system have been discovered: adropin[8] and elabela[9]. Adropin, which is composed of 43 amino acids and has a molecular weight of 3.4 kDa, is not only involved in providing energy homeostasis but also plays a role in the progression of atherosclerotic lesions[10]. Decreased adropin levels in circulation leads to endothelial dysfunction[11]. Endothelial dysfunction is an important early event that occurs at the onset of atherogenesis and heart disease[12]. Adropin improves endothelial function and protects the endothelium. Adropin increases endothelial nitric oxide synthase (eNOS) levels which is responsible for the production of nitric oxide from vascular structures[13]. If adropin levels in the circulation are insufficient, bioavailability of nitric oxide is reduced in the endothelium. The loss of nitric oxide bioavailability is a critical step in the formation of endothelial dysfunction, which is an independent determinant of the onset of coronary artery disease. Patients with Cardiac Syndrome X characterized by endothelial dysfunction were reported to have lower levels of adropin when compared with healthy individuals[14].

Another newly discovered Elabela (ELA) is composed of 32 amino acids and, together with apelin (APLN), is an important signaling axis for early cardiovascular development[9]. ELA hormone has been reported to stimulate angiogenesis in human umbilical vascular endothelial cells[15]. Vascularization (angiogenesis) is very important in the supply of the heart. Studies have also shown that both ELA and apelin are synthesized in abundant amounts in cardiac and vascular endothelial tissues. ELA increased cardiac contractility, ejection fraction, and cardiac output, and it elicited vasodilatation in anesthetized rats *in vivo*. ELA administration to rats reduces pulmonary arterial hypertension (PAH)[16].

As noted above, since open heart surgery is performed with circulatory cardiopulmonary machinery and this non-physiological event directly affects the endocrinal system[2,3], the primary aim of this pioneering study is to determine how the amounts of adropin, elabela, and nitric oxide change in blood samples taken at

various periods in patients undergoing cardiopulmonary bypass and whether they are related to certain haemodynamic parameters.

MATERİAL and METHOD

This clinical study was approved by XXXX University Local Ethics Committee with the letter dated 17.6. 2014 and no. 02. The work was carried out in accordance with the Declaration of Helsinki-Ethical principles for medical research. This retrospective randomized study included 35 individuals with similar body mass indexes and ages. 20 out of 35 patients were medically healthy volunteers who applied to our hospital with no complaints due to check-up and the control group in our study was made up of these healthy volunteers. No biological samples were taken from control group. So that the remaning part of blood samples of control group, which were taken for routine biochemical analysis, were used for the mentioned parameters with permission of the patients. Fifteen patients who underwent coronary bypass surgery by the cardiac surgeon team (cardiologist and cardiovascular surgeons) were included in the study and the patients were informed about the study. Among these, patients with chronic renal failure, thyroid disease, congestive heart failure, uncontrolled hypertension, liver failure, coagulation disorder, diabetes mellitus, chronic pulmonary disease, active infections or malignancy, ejection fraction lower than 30% or a heart rate of 60 / min, who underwent cardiac surgery or reoperations due to myocardial infarction in the previous month, patients treated with corticosteroids, dipyridamole, anticoagulants or thrombolytics were excluded. A total number of 105 blood samples were taken from 15 patients who underwent cardiopulmonary bypass surgery before anesthesia induction (T1), before bypass (T2), before removing cross-clamp (T3) and when taken into intensive care unit (T4), postoperative 24th (T5), 48th (T6) and 72nd hours (T7).

Anesthetic approach

Anesthesia premedications of all patients were performed at least half an hour before they were taken to the operation room. Before the anesthesia, the radial artery cannula was placed under local anesthesia for blood pressure monitoring. Following anesthesia, a central venous cannula and urine catheter were placed. Anesthesia induction and maintenance were similar for all patients and median stenosis was achieved by applying standard median sternotomy under general anesthesia with midazolam (0.1 mg / kg induction; 0.8 µg / kg / minute maintenance), vekuronyum (0.1 mg / kg induction) ve fentanil (20-40 µg / kg induction; 0.3-1 µg / kg / minute maintenance) calculated according to weight as reported earlier[17].

Surgical technique

Following standard Median sternotomy, LIMA flaps and saphenous vein-grafts (SVG) according to requirement were prepared. The pericardium was opened and all the patients were heparinized in order to achieve "activated clotting time" (ACT) of 450 seconds and more (3 mg / kg heparin, Nevparin, Mustafa Nevzat). After aortic examination with palpation; partial cardiopulmonary bypass was started with double segmented venous cannulation from the right segmental arterial and right atrium in ascending aorta. Under an aortic cross clamp, anesthetic blood cardioplegia provided cardiac arrest with 28-30° C systemic hypothermia and local cold application. Pulsatil roller pump (Stockert Instrumente, Germany) and Membrane type oxygenator (Dideco D 708 simplex III, Italy) were used throughout the study. Pump prime solution contained 2000 mL of lactated Ringer solution in order to maintain hematocrit at 20% level. To keep the mean pulsatile arterial pressure between 50-80 mmHg, the pump rate was set to 2.2-2.4 L / m / m^2. Heparin was neutralized with 1: 1.3 ratio of protamine for 10 minutes after CPB. After placement of the epicardial pacing wires and chest tubes, the sternal incision was closed and the patients were taken into the intensive care unit and their treatment was continued in the intensive care unit. All other details of the study, including hemodynamic parameters, are available in the work previously published by our group[18,19].

Collection of biological samples

A total number of 105 blood samples were taken from 15 patients who underwent cardiopulmonary bypass surgery grafting before anesthesia induction (T1), before bypass (T2), before removing cross-clamp (T3) and when taken into intensive care unit (T5), postoperative 24th (T6), 48 th (48) and 72nd hours (T7) and 20 blood samples were taken from control group. In total 135 biological samples were taken. Collected blood samples were taken as described previously and subjected to centrifugation at 4000 rpm for 5 minutes and stored at -80°C until analyzed[18,19].

Biochemical Analysis

Adropin and Elabela measurements

Adropin levels were studied with human adropin ELISA kit (phoenix, catalog no. EK 032-35, USA) and Elabela levels with human elabela ELISA kit (Catalog no: S1508 Peninsula Laboratories International, Inc. San Carlos, USA) from the blood samples of study groups according to specified operating procedures. Intra-assay: CV value of adropin kit was <10% and Inter-Assay: CV value was <15%. Assay range of the adropin kit was 0.0 -100 ng/mL. Since cardiopulmonary bypass operation patients' blood adropin levels fell below the kit detection limit; adropin was added to all samples in standard amount. Thus, detection kit was also provided to measure the under limit value. The amount of adropin in the standard amount added was subtracted at the end of the experiment so that the true adropin values of the samples were found. All these validation procedures were performed according to the previously described method[20]. Assay range of the elabela kit was 0-100 ng/mL ng/ml and sensitivity was 0.3 ng/mL. Test results for both parameters were reported in ng/mL. Plate washes were performed with an automatic washer Bio-Tek ELX50 (BioTek Instruments, USA) and absorbance readings with ChroMate, Microplate Reader P4300 (Awareness Technology Instruments, USA).

Nitric oxide measurement

Serum total nitric oxide (NO) were determined using the kit. NO levels were determined as micromol/liter. There was a steady decrease in blood nitric oxide levels in patients with cardiopulmonary bypass surgery. However, since nitric oxide measurements were not below the detection limit, an experiment similar to the adropin assay did not have to be designed. The haematological parameters used in this study were obtained from patient follow-up files. Blood lactate (LA) was measured with the instrument.

Statistical analyzes

Statistical package program was used for statistical package for the social sciences (SPSS-21). The numerical values obtained were given as mean ± standard deviation (SD). Statistical significance was accepted when the Probability (*p*) value was less than 0.05. One-way ANOVA was performed to compare multiple groups. Correlation between the two variables was determined with Pearson's correlation test.

RESULTS

There was no statistically significant difference between the body mass indexes (28.2±3.7) and average ages of the subjects (67.9±9.4) included in the study. There was no significant difference in pre-operative and post-operative biochemical values of patients in the study. This situation is summarized in table 1. Some hemodynamic parameters were statistically different between different cardiopulmonary time intervals. The graft number of our patients (3.6 ± 0.5); ejection fraction percentage (45.7 ± 4.6), cardiopulmonary bypass time (158 ± 11.9 min); cross-clamp duration (97 ± 6), intensive care stay (2.6 ± 1 day) and total hospital stay (8.5 ± 1.9 days) were reported. This means that every numerical value given is the average of the values of 13-15 patients. In addition, the comparison of the changes of some hemodynamic parmeters according to the time periods of cardiopulmonary bypass operation is shown in table 2.

When control adropin and nitric oxide blood values were compared with the values of adropin and nitric oxide blood taken at T1 time interval of patients undergoing coronary artery bypass graft operation; adropin and nitric oxide levels at T1 time interval were significantly lower. It was observed that adropin and nitric oxide levels continued to fall in blood samples taken at later time intervals (including blood samples taken at 72nd hour). Figure 1 compares the blood adropin changes in patients who underwent coronary artery bypass graft operation with respect to time and healthy volunteer control blood adropin values. In Figure 2, changes of nitric oxide values corresponding to these time intervals were given in these patients. The maximum decrease in blood adropin and nitric oxide levels in patients undergoing coronary artery bypass grafting was observed in blood samples which were taken at 72nd hour.

Elabela and lactate concentrations showed a gradual upward trend from T1 to T4 time intervals. The concentrations of both parametres peaked at T4 time interval. After T4 time interval, both parameters showed a statistically significant decrease until T7 time interval. Elabela and lactate concentrations corresponding to T7 time interval (three days after operation) were similar to T1 time interval (baseline blood). Figure 3 shows the comparison of blood Elabela changes of patients who underwent coronary artery bypass graft operation according to time and according to healthy volunteer control blood Elabela values. Figure 4 shows the change in lactate values corresponding to these time periods in these subjects.

DISCUSSION

The most important cause of death worldwide is cardiovascular diseases[1]. Coronary bypass surgery, widely used worldwide since 1950, leads to permanent endothelial dysfunction in the preoperative, early postoperative (48 hours) and late (7-10 days) postoperative period[21,22]. In recent years, it was found that Elabela and adropin are synthesized in many tissues and organs, including heart tissue, and are involved in the homeostasis of the cardiovascular system[9]. Furthermore, adropin has been reported to contribute to the preservation of endothelial cells and the formation of nitric oxide[8,11]. Therefore, in this study, we investigated the fate of elabela, adropin and nitric oxide molecules before and after cardiopulmonary bypass, and their relationship with hemodynamic parameters.

In this study, when blood adropin and nitric oxide levels of patients before coronary bypass operation were compared with blood adropin and nitric oxide levels of voluntary healthy individuals, patients with coronary bypass had significantly lower blood adropin and nitric oxide levels before surgery. Pre-operative low adropin levels of patients who will undergo bypass may be associated with coronary atherosclerosis. Because adropin levels have been reported to be lower in patients with previous coronary atherosclerosis, endothelial dysfunction and Cardiac Syndrome X[14]. In this study, when volunteer control blood nitric oxide level was compared with blood nitric oxide levels of patients before cardiopulmonary bypass operation; the low course of blood nitric oxide levels in patients before cardiopulmonary bypass operation may result from reduced adropin levels due to endothelial dysfunction in these patients. Because adropin mediates endothelial cell protection and nitric oxide release[10,11].

It has been also reported that there was a decrease in nitric oxide metabolites in blood samples taken from patients undergoing cardiopulmonary bypass at 12 and 24 hours compared with preoperative levels[23]. The trend of decreasing levels of nitric oxide and adropin after cardiopulmonary bypass operation may be due to endothelial dysfunction due to cardiopulmonary bypass[23]. Because coronary artery bypass surgery was reported to cause permanent endothelial dysfunction[24]. It has been reported that the formation of endothelial dysfunction may lead to the depletion of endothelial-derived molecules[25]. It has been reported that nitric oxide release decreases under hypothermic in patients undergoing cardiopulmonary bypass[26,27]. The reduction in the amounts of nitric oxide observed in this study may be related to impairment in endothelial function or to an increase in cardiacopulmonary bypass adaptation or increase in nitric oxide decay or increase in nitric oxide inactivation[23]. It has also been reported that circulating amounts of many molecules such as endothelin-1, p-selectin and e-selectin are changed and activated in order to maintain the normal physiological function of endothelial tissue during cardiopulmonary bypass[28,29].

If, as in this study, endothelial dysfunction occurs due to adropin insufficiency, this may not only affect nitric oxide release but also impair the normal physiological function of the vessel wall. As is known, the endothelial cell layer inhibits contractility and, on the other hand, inhibits migration and proliferation of vascular smooth muscle cells[30]. It also has an important anti-inflammatory role and regulates the adhesion and migration of inflammatory cells to the inner surface of the veins and out of the veins[31]. Low levels of nitric oxide due to adropin depletion reported here might cause biochemical deterioration and therefore causes damage to stimulus transmission to surrounding tissues and cells. Because nitric oxide is an important vasodilator produced in the endothelium, it inhibits adhesion and inhibition of platelet aggregation

and monocyte adhesion[32]. Adropin preparations can be used to regulate nitric oxide release in the future. Nitric Oxide benefits have already been reported in patients who have already undergone nitric oxide inhalation[33]. Adropin-mediated nitric oxide release is thought to be more meaningful when it is thought that adropin has a protective role for endothelium.

In this study, the levels of Elabela in CABG patients before induction of anesthesia (T1) were statistically significantly higher when compared with healthy controls. High levels of elabela were detected in blood samples taken after surgery was started, before bypass (T2), before cross-clamp removal (T3) and taken after the intensive care unit admission (T4). In the blood samples at postoperative 24th (T5), 48 th (T6) and 72nd (T7) hours, the concentrations of elabela decreased significantly and were similar to healthy control levels at 72nd hour (T7). In this study, when the levels of elabela in the initial (T1) blood of CABG patients and in circulation during cardiopulmonary bypass operation were compared with healthy controls; significant increase might be due to increase of G-protein-coupled apelin receptor as compensator in order to maintain homeostasis of the cardiovascular system[34]. Beacuse Elabela is an endogenous agonist of the Apelin APJ receptor in the cardiovascular system. Elabela levels were not also correlated with ventricular diameter while were correlated with preoperative left ventricular volumes (both end-systolic and end-diastolic volume). This means that the level of the Elabela is a sign of volumetric changes directly but not related with ventricular diameters. In this study, a positive correlation was found between the aortic cross-clamp duration and the Elabela levels. As myocardial interstitial fluid (edema) increases, we see that the elabela levels increase in response.

Hypoxic condition during coronary artery surgery causes hyperlactatemia. Thus, in this study, lactate changes were also studied at all times when adropin, elabela and nitric oxide were studied. Lactate levels before anesthesia were 0.33 mmol/L and was started to increase with the cross clamping and were close to normal physiological limits despite reaching a peak level at (T4) when patient was taken into intensive care unit. In our study, it is thought that the probable cause of not developing hyperlactatemia is due to the short duration of Coronary Artery Bypass grafting. Because if the Coronary Artery Bypass grafting time is long, the oxygen level may fall below the critical threshold and lead to lactic acidosis[18]. The most important end result of this study is to observe the parallel increase and decrease in Elabela and lactate levels. Elabela measurement can be an alternative parameter to lactate measurement to monitor the course of the Coronary Artery Bypass graft. Besides we think that elabela is a new regulator of the cardiovascular system such as other cardiac performance indicators including norepinephrine, adrenomedulline, renin activity, vasopressin, endothelin-1, tumor necrosis factor-α, atrial natriuretic factor, brain natriuretic factor and Cardiac performance indicators during and after Coronary Artery Bypass grafting provide insight into cardiovascular system physiology[35].

CONCLUSION

When I combine all available data, adropin and nitric oxide levels of patients who underwent Coronary Artery Bypass grafting were low when compared with control adropin and nitric oxide. This decline continues before anesthesia induction (T1), before bypass (T2), before removing cross-clamp (T3) and after patient was taken into intensive care unit (T4), at postoperative 24th (T5), 48th (T6) and 72nd hours (T7). However, levels of elabela and lactate increase before the induction (T1), before bypass (T2), before the cross clamp

removal (T3), taken in intensive care unit (T4) and it was found in blood samples at post operative 24th hour, 48th hour and 72nd hour that the amount of elabela and lactate gradually decreased. This is the first study to show how adropin, nitric oxide and elabela levels in patients undergoing Coronary Artery Bypass grafting are altered and it is thought to provide new data about Cardiovascular system physiology. It is suggested in the future that this study will be tested by an independent clinic and lab with wider subject participation and that the co-operation of adropin, elabela, nitric oxide and lactate measurements following the bypass surgeon will be of beneficial.

Limitations of the Study

The low number of subjects in this study is the main limitation.

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CONFLICT of INTEREST

None.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: SA
Analysis/Interpretation: SA
Data Acquisition: SA
Writting: SA
Critical Revision: SA
Final Approval: SA

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Table 1. Pre-operative and post-operative biochemical values of patients in the study

Parameters	Pre-operative	Post-operative
Glucose (mg/dL)	93.6± 10.2	88.3±8.5
Calcium (mg/dL)	9.8±0.9	9.6±0.2
Potassium (mEq/mL)	4.4±0.3	4.4±0.2
Sodium (mEq/mL)	141.2±3.1	140.2±2.7

Table 2. Comparison of changes of some haemodynamic parmeters according to time intervals of cardiopulmonary bypass operation

Parameters	T1	T2	T3	T4	T5	T6	T7
CVP (mmHg)	8.2	7.9	7.6	7.3	7.9	8.1	8.3
MAP (mmHg)	99.2	84.3	62.2	74.4	88.6	87.2	98.7
MPAP (mmHg)	23.2	23.1	22.9	22.8	23.2	23.1	22.7
PCVWP (mmHg)	15.1	14.7	14.9	14.7	14.8	14.9	14.9
HR(beat/min)	88.2	76.4	87.3	88.9	84.2	87.2	85.6

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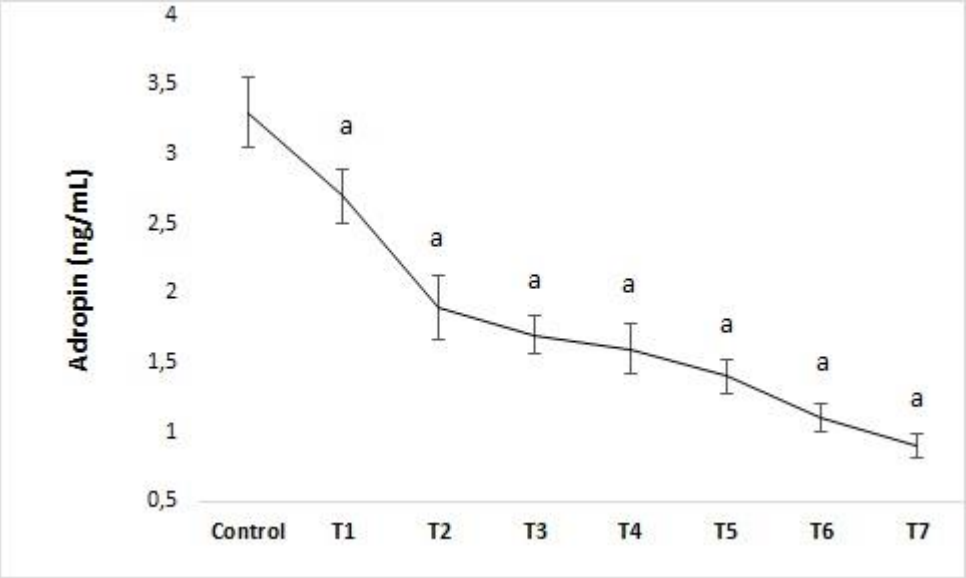

Figure 1. Comparison of blood adropin changes in patients who underwent coronary artery bypass graft operation with respect to time and healthy volunteer control blood adropin values. When compared with control, there was a significant decrease at before anesthesia induction (T1), before bypass (T2), before removing cross-clamp (T3), when taken into intensive care unit (T4), postoperative 24th (T5), 48th (T6) and 72nd hours (T7) time intervals (p< 0.05). Each data point of the control group consisted of a mean of 20 subjects and the data point corresponding to each time period of the patients who had CPB consisted of the average of 13-15 cases.

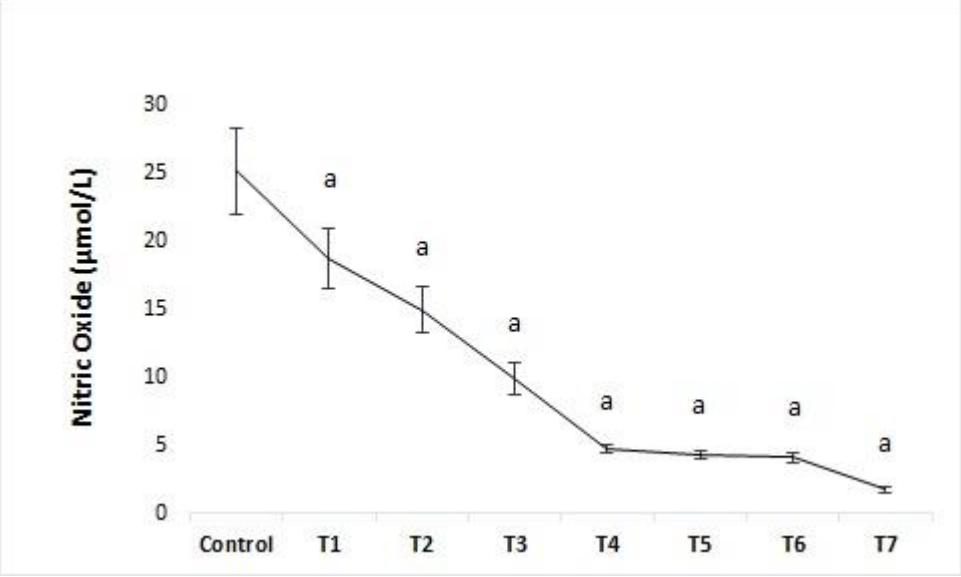

Figure 2. Comparison of blood NO (nitric oxide) changes in patients who underwent coronary artery bypass graft operation with respect to time and healthy volunteer control blood NO values. All other details are given in figure 1.

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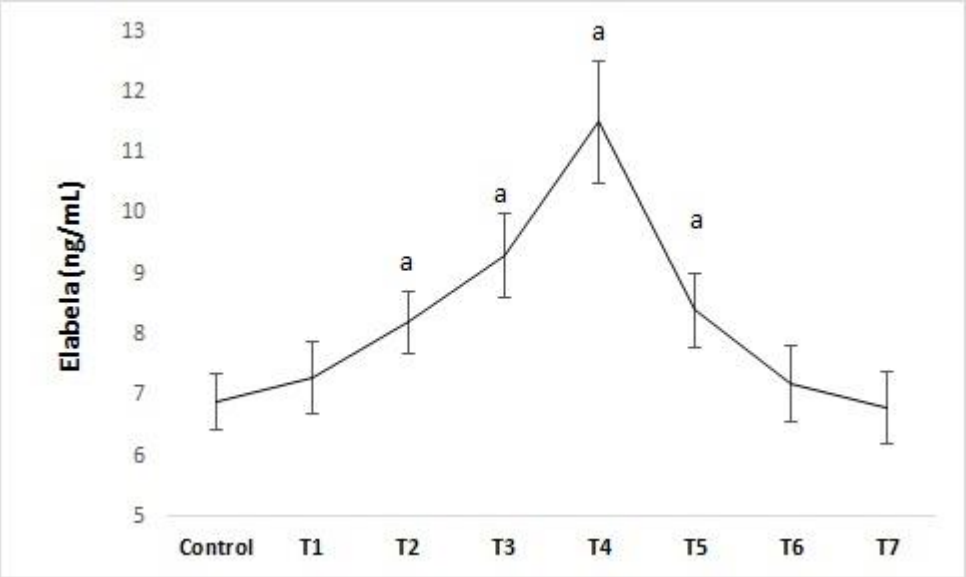

Figure 3. Comparison of blood elebela changes in patients undergoing coronary artery bypass graft operation according to time and healthy volunteer control blood elabela values. All other details are given in figure 1.

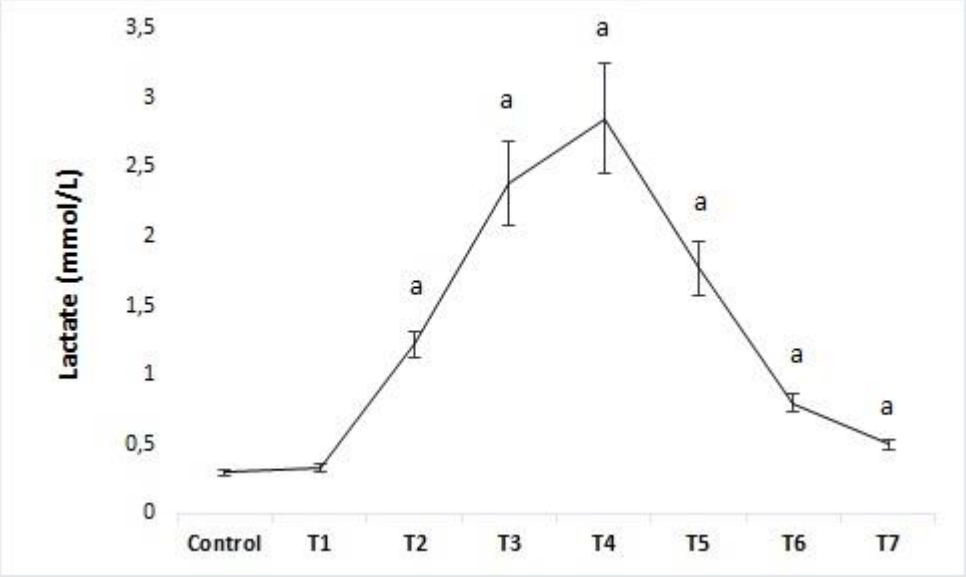

Figure 4. Comparison of blood lactate changes in patients who underwent coronary artery bypass graft operation with respect to time and healthy volunteer control blood lactate values. All other details are given in figure 1.