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

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ABSTRACT

Introduction: Elabela and adropin (nitric oxide-mediated effects) are two new hormones that are synthesized in the heart and discovered in the last decade, which play a role in vascular system homeostasis. Therefore, the main aim of this study was to examine the changes of adropin, elabela, and nitric oxide in blood samples taken at various time intervals during a coronary artery bypass graft using cardiopulmonary bypass.

Patients and Methods: 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 the cross-clamp (T3), at the intensive care unit (T4), and at postoperative 24 (T5), 48 (T6), and 72 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 the T1 time interval were significantly lower. Elabela and lactate levels in the blood at the T1 time interval were significantly higher. In the blood samples taken at postoperative 24 (T5), 48 (T6), and 72 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

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, koroner arter baypas grefti kullanılarak 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 bakım 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 oksit; koroner baypas; greft

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Submitted: 03.08.2018
Accepted: 23.08.2018

INTRODUCTION

Despite all the advances in medicine, deaths due to cardiovascular diseases still cannot be prevented today, and they are still the primary cause of morbidity and mortality worldwide[1]. The cardiovascular system consists of the heart and blood vessels (arteries and veins). The vessels feeding the heart contract or become clogged over time. Coronary artery bypass surgery (open heart surgery) bypasses the vessels that are occluded or constricted, using vessels taken from other parts of body: left internal mammary artery (LIMA), leg vein (saphenous vein), or arm artery (radial artery), and blood flow can be restored after the 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 endocrine system of the patient and to increase or decrease the synthesis and release of peptide-structured hormones, such as B-type natriuretic peptide, antidiuretic hormone, and insulin[4-6]. In an earlier study in which we performed grafting with coronary artery bypass surgery, we reported that the amounts of salusin alpha, beta, and apelin (APLN) 36 peptides in blood samples, which were taken before anesthesia induction, before bypass, before removing the cross-clamp, and after removing the cross-clamp, were decreased, and then increased in the intensive care unit, and postoperatively at 24 and 72 hours[7].

Two new peptide-structured molecules with hormonal effects, which act on energy homeostasis and the cardiovascular system, have been discovered: adropin and elabela (ELA)[8,9]. Adropin, which is composed of 43 amino acids and has a molecular weight of 3.4 kDa, not only is involved in energy homeostasis but also plays a role in the progression of atherosclerotic lesions[10]. Decreased adropin levels in circulation lead to endothelial dysfunction[11]. Endothelial dysfunction is an important early event that occurs at the onset of atherogenesis and heart disease[12]. Adropin improves the endothelial function and protects the endothelium. Adropin increases the endothelial nitric oxide (NO) synthase level, which is responsible for the production of NO from vascular structures[13]. If adropin levels in the circulation are insufficient, the bioavailability of NO is reduced in the endothelium. The loss of NO bioavailability is a critical step leading to 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 than healthy individuals[14].

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

As noted above, since open heart surgery is performed with circulatory cardiopulmonary machinery and this non-physiological event directly affects the endocrinal system, the primary aim of this pioneering study was to determine how the amounts of adropin, ELA, and NO change in blood samples taken at various periods in patients undergoing cardiopulmonary bypass and whether they are related to certain hemodynamic parameters[2,3].

PATIENTS and METHODS

This clinical study was approved by the Firat University Local Ethics Committee with the letter dated June 17, 2014, 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. Of the 35 patients, 20 were medically healthy volunteers who applied to our hospital with no complaints due to check-up and made up the control group in our study. The remaining part of blood samples of the control group, which were taken for routine biochemical analysis, were used for the mentioned parameters with the permission of the patients. Fifteen patients who underwent coronary bypass surgery, by cardiac surgeons were included in the study; the patients gave informed consent to 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, and those treated with corticosteroids, dipyridamole, anticoagulants, or thrombolytics were excluded. A total of 105 blood samples were taken from 15 patients who underwent cardiopulmonary bypass surgery before anesthesia induction (T1), before bypass (T2), before removing the cross-clamp (T3), when taken into the intensive care unit (T4), and at postoperative 24 (T5), 48 (T6), and 72 hours (T7).

Anesthetic Approach

Anesthesia premedications were administered to all patients at least half an hour before they were taken to the operation room. After the anesthesia, the radial artery cannula was placed under local anesthesia to monitor the blood pressure. 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/min maintenance), vekuronyum (0.1 mg/kg induction), and fentanil (20-40 μg/kg induction; 0.3-1 μg/kg/min maintenance), calculated according to weight as reported earlier[17].

Surgical Technique

Following standard median sternotomy, LIMA flaps and saphenous vein-grafts according to requirement were prepared. The pericardium was opened and all the patients were heparinized in order to achieve an "activated clotting time" of 450 seconds and more (3 mg/kg heparin, Nevparin, Mustafa Nevzat). After an aortic examination with palpation, partial cardiopulmonary bypass was started with double segmented venous cannulation from the right segmental artery and right atrium in the ascending aorta. Under an aortic cross-clamp, anesthetic blood cardioplegia induced cardiac arrest with 28-30°C systemic hypothermia and local cold application. A pulsatile roller pump (Stockert Instrumente, Germany) and a membrane-type oxygenator (Dideco D 708 Simplex III, Italy) were used throughout the study. The pump prime solution contained 2.000 mL of lactated Ringer solution to maintain a 20% hematocrit level. To keep the mean pulsatile arterial pressure between 50 and 80 mmHg, the pump rate was set to 2.2-2.4 L/m/m^2. Heparin was neutralized with a 1:1.3 ratio of protamine for 10 min after cardiopulmonary bypass. After placing the epicardial pacing wires and chest tubes, the sternal incision was closed and the patients were taken into the intensive care unit, where their treatment was continued. All other details of the study, including hemodynamic parameters, are available in the work published previously by our group[18,19].

Collection of Biological Samples

A total of 105 blood samples were taken from 15 patients who underwent cardiopulmonary bypass surgery grafting before anesthesia induction (T1), before bypass (T2), before removing the cross-clamp (T3), when taken into the intensive care unit (T5), and at postoperative 24 (T6), 48 (48) and 72 hours (T7); 20 blood samples were taken from the control group. In total, 135 biological samples were taken. Collected blood samples were taken as described previously and subjected to centrifugation at 4.000 rpm for 5 min and stored at –80°C until analyses[18,19].

Biochemical Analysis

Adropin and elabela measurements

Adropin levels were studied using a human adropin ELISA kit (Phoenix, catalog no. EK 032-35, USA) and ELA levels using a human ELA ELISA kit (Catalog no. S1508, Peninsula Laboratories International, Inc., San Carlos, CA, USA) from the blood samples of study groups according to specified operating procedures. The intra-assay CV value of the adropin kit was < 10% and the inter-assay CV value was < 15%. The assay range of the adropin kit was 0-100 ng/mL. Since blood adropin levels of patients who underwent cardiopulmonary bypass operation fell below the kit detection limit, a standard amount of adropin was added to all samples. Thus, the detection kit was also provided to measure the under limit value. The standard amount of adropin 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 method described previously[20]. The assay range of the ELA kit was 0-100 ng/mL and the 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 NO levels were determined using the ELISA kit. NO levels were determined in μmol/L. There was a steady decrease in blood NO levels in patients who underwent cardiopulmonary bypass surgery. However, since NO measurements were not below the detection limit, an experiment similar to the adropin assay did not have to be designed. The hematological parameters used in this study were obtained from patient follow-up files. The blood lactate level was measured with the lactate analyzer.

Statistical Analyses

The Statistical Package for the Social Sciences (version 21, SPSS, Inc.,) was used to analyze data. The numerical values obtained were given as the mean ± standard deviation (SD). Statistical significance was accepted when the probability (p) value was less than 0.05. One-way analysis of variance was used to compare multiple groups. Correlations between the two variables were 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 years) included in the study. There was no significant difference in pre- and postoperative biochemical values of patients in the study, as 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 days), 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. A comparison of changes in some hemodynamic parameters according to the time periods of cardiopulmonary bypass operation is shown in Table 2.

When control adropin and NO blood values were compared with those taken at the T1 time interval of patients undergoing

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

Parameters	Preoperative	Postoperative
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 hemodynamic parameters according to time intervals of the 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
PCWP (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

CVP: Central venous pressure, MAP: Mean arterial pressure, MPAP: Mean pulmonary artery pressure, PCWP: Pulmonary capillary wedge pressure, HR: Hearth rate.

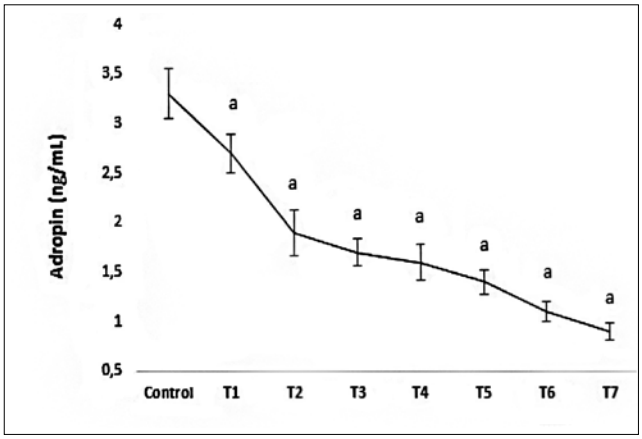

Figure 1. Comparison of blood adropin changes in patients who underwent coronary artery bypass graft operation with respect to time and blood adropin values in healthy volunteer controls. When compared with controls, there was a significant decrease before anesthesia induction (T1), before bypass (T2), before removing the cross-clamp (T3), when taken into the intensive care unit (T4), and at postoperative 24 (T5), 48 (T6), and 72 hour (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 cardiopulmonary bypass consisted of an average of 13-15 cases.

coronary artery bypass graft (CABG) operation, their levels at the T1 time interval were significantly lower. Adropin and NO levels continued to fall in blood samples taken at later time intervals (including blood samples taken at the 72nd hour). Figure 1 compares the blood adropin changes in patients who underwent CABG operation with respect to time and healthy

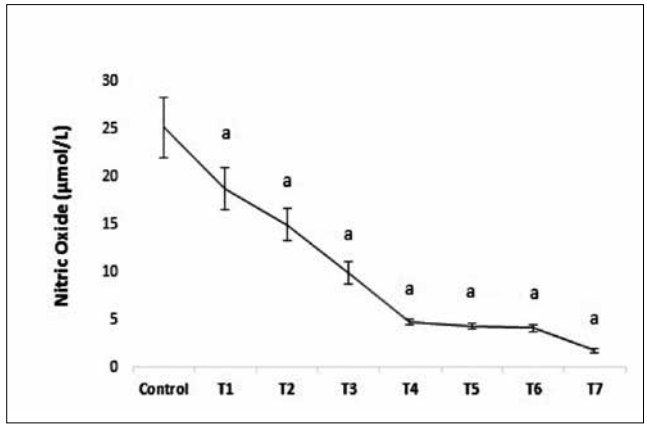

Figure 2. Comparison of blood nitric oxide (NO) changes in patients who underwent coronary artery bypass graft operation with respect to time and blood NO values in healthy volunteer controls. All other details are given in Figure 1.

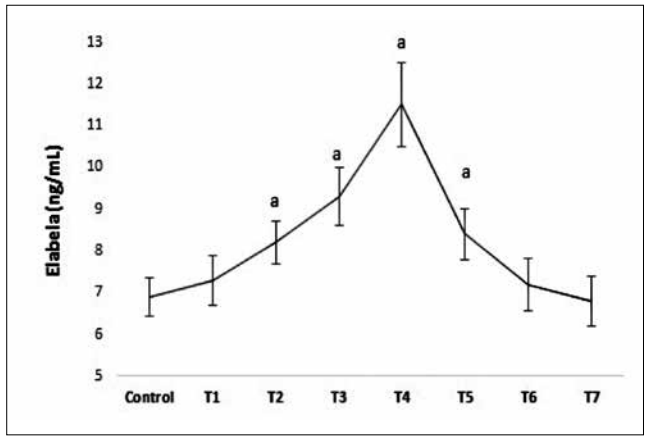

Figure 3. Comparison of blood elabela (ELA) changes in patients undergoing coronary artery bypass graft operation according to time and blood ELA values in healthy volunteer controls. All other details are given in Figure 1.

volunteer control blood adropin values. In Figure 2, changes in NO values in these patients corresponding to these time intervals are given. The maximum decrease in blood adropin and NO levels in patients undergoing CABG was observed in blood samples taken at the 72nd hour. ELA and lactate concentrations showed a gradual upward trend from the T1 to T4 time interval. The concentrations of both parameters peaked at the T4 time interval. After the T4 time interval, both parameters showed a statistically significant decrease until the T7 time interval. ELA and lactate concentrations corresponding to the T7 interval (3 days after operation) were similar to those at the T1 interval (baseline blood). Figure 3 shows the comparison of blood ELA changes in patients who underwent CABG operation according to time with healthy volunteer control blood ELA values. Figure 4 shows the change in lactate values corresponding to these time periods in these subjects.

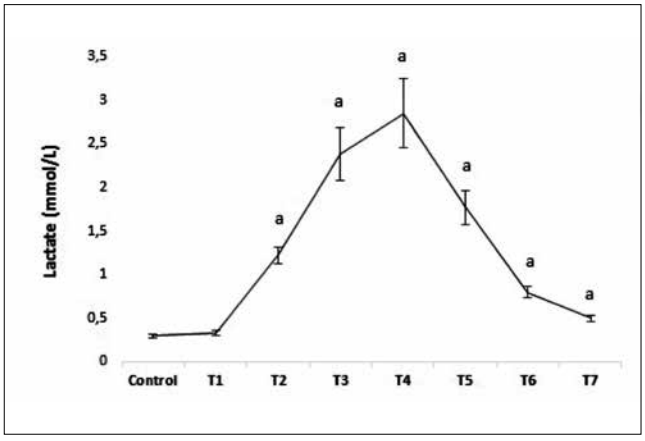

Figure 4. Comparison of blood lactate changes in patients who underwent coronary artery bypass graft operation with respect to time and blood lactate values in healthy volunteer controls. All other details are given in Figure 1.

DISCUSSION

The most important cause of death worldwide is cardiovascular disease[1]. Coronary bypass surgery, widely used since 1950, leads to permanent endothelial dysfunction in the preoperative, early postoperative (48 hours), and late postoperative (7-10 days) period[21,22]. In recent years, ELA and adropin were found to be synthesized in many tissues and organs, including the heart, and they 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 NO[8,11]. Therefore, in this study, we investigated the fate of ELA, adropin, and NO molecules before and after cardiopulmonary bypass, and their relationship with hemodynamic parameters.

In this study, when blood adropin and NO levels of patients before coronary bypass operation were compared with those of voluntary healthy individuals, both parameters were significantly lower in the former group. Low preoperative adropin levels of patients who are to undergo bypass may be associated with coronary previous atherosclerosis, coronary atherosclerosis, endothelial dysfunction, and cardiac syndrome X[14]. The low blood NO levels in patients before cardiopulmonary bypass operation may be a result of reduced adropin levels due to endothelial dysfunction in these patients, because adropin mediates endothelial cell protection and NO release[10,11]. A decrease in NO metabolites in blood samples was also reported in patients undergoing cardiopulmonary bypass at 12 and 24 hours compared with preoperative levels[23]. The trend of decreasing levels of NO and adropin after cardiopulmonary bypass operation may be due to endothelial dysfunction during cardiopulmonary bypass, because coronary artery bypass surgery was reported to cause permanent endothelial dysfunction[23,24]. Endothelial dysfunction may lead to the depletion of endothelial-derived molecules[25]. NO release was reported to decrease under hypothermia in patients undergoing cardiopulmonary bypass[26,27]. The reduction in the NO amounts observed in this study may be related to impairments in endothelial function, an increase in cardiacopulmonary bypass adaptation, an increase in NO decay, or an increase in NO inactivation[23]. It that Circulating amounts of many molecules, such as endothelin-1, p-selectin, and e-selectin, were also reported to have changed and been 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 NO 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 the migration and proliferation of vascular smooth muscle cells[30]. It also plays an important anti-inflammatory role and regulates the adhesion to and migration of inflammatory cells to the inner surface of the veins and out of the veins[31]. Low NO levels due to adropin depletion reported here might cause biochemical deterioration and therefore damage the transmission of the stimulus to surrounding tissues and cells. As NO is an important vasodilator produced in the endothelium, it inhibits the adhesion and inhibition of platelet aggregation and monocyte adhesion[32]. In the future, adropin preparations can be used to regulate NO release. The benefits of NO have already been reported in patients who have undergone NO inhalation[33]. Adropin-mediated NO release is thought to be more meaningful as it is believed to protect the endothelium.

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

Hypoxic conditions during coronary artery surgery cause hyperlactatemia. Thus, in this study, lactate changes were also studied at all times when adropin, ELA, and NO were studied. Lactate levels before anesthesia were 0.33 mmol/L, started to increase with the cross-clamping, and were close to normal physiological limits despite reaching a peak level (at T4) when the patient was taken into the intensive care unit. In our study, the probable cause of not developing hyperlactatemia was thought to be the short duration of CABG; if the CABG 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 ELA and lactate levels. ELA measurements can be an alternative parameter to lactate measurements to monitor the course of the CABG. Besides, we think that ELA 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 CABG provide insights into cardiovascular system physiology[35].

CONCLUSION

When I combine all available data, adropin and NO levels of patients who underwent CABG were low when compared with those of the controls. This decline continues before anesthesia induction (T1), before bypass (T2), before removing the cross-clamp (T3), after the patient was taken into the intensive care unit (T4), and at postoperative 24 (T5), 48 (T6) and 72 hours (T7). However, ELA and lactate levels increased before the induction (T1), before bypass (T2), before the cross-clamp removal (T3), and before the patient was taken into the intensive care unit (T4); and decreased gradually in blood samples at postoperative 24, 48, and 72 hours. This is the first study to show how adropin, NO, and ELA levels in patients undergoing coronary artery bypass grafting are altered and this is thought to provide new data on cardiovascular system physiology. I suggest that, in the future, this study be tested by an independent clinic and lab with wider subject participation, and that combined adropin, ELA, NO, and lactate measurements following bypass surgery will be beneficial in parameters in the panel of myocardium injury.

Limitations of the Study

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

ACKNOWLEDGMENT

I am honored to thank Prof. Dr. Nesimi Eren, retired instructor, surgical professor, and my thesis advisor, who supported me unreturned during the course of my studies; Assoc. Dr. İbrahim Şahin who had great contributions in the statistical analysis of my work; Prof. Dr. Süleyman Aydın who contributed to the construction of biochemical analyses; and hospital staff with whom I have worked together until today.

CONFLICT of INTEREST

The author reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

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

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