Original Article

Derangement of Basic Amino Acids and Nitric Oxide Levels in Patients Undergoing Cardiothoracic Surgery

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Abstract

Background: A cyclic relationship exists, between; arginine, citrulline, and ornithine. Arginase is a specific enzyme that plays a role in this relationship. These basic amino acids have a role in the induction of nitric oxide (NO) and as anti-inflammatory and antioxidant. This study aimed to elucidate the role of surgical injuries and anesthesia on plasma levels of the above-mentioned amino acids and NO and to determine whether the changes in these levels can be correlated to the duration of surgery and anesthesia exposure.

Materials and Methods: The study included: group A (41 patients) who underwent coronary bypasses and group B (17 patients) who underwent lung cancer surgery. An amino acid analyzer was used for the detection of amino acids, while NO was estimated by a Spectrophotometric method.

Results: The study revealed a significant decrease in the intra-operative levels of arginine, citrulline, ornithine, and NO compared to their pre-operative levels in both groups.

Conclusion: Depletion of these basic amino acids is possibly multifunctional and can be associated with an increase in arginase, surgical trauma, anesthesia, and stress.

Keywords: Basic amino acids, Nitric oxide, Cardiothoracic surgery, Anesthesia, Coronary Artery Bypass, Injuries, Lung

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Introduction

Basic amino acids are acids that contain amino groups more than carboxylic groups. At least five basic amino acids namely, arginine, citrulline, ornithine, lysine, and hydroxylysine are metabolized in our body. Arginine amino acid is known as a semi-essential or conditionally essential amino acid. In adults, it is classified as non-essential as its endogenous synthesis from citrulline is enough. While, in acute events; just like trauma, endogenous synthesis is not sufficient making it essential during these circumstances (1).

Arginine plays an integral role in the maintenance of immune function, host defense, inflammatory processes, wound healing, and other series of postoperative and post-traumatic states of pathophysiologic adaptations (2). In addition, arginine plays a central role in cell proliferation, protein synthesis, energy metabolism, and ammonia detoxification. Moreover, citrulline is synthesized from arginine by nitric oxide synthase (NOS) (3).

Ornithine is converted to citrulline in the urea cycle; in turn, citrulline is converted to arginine (4). NO, a signal molecule resulting from the oxidation of the amino group of arginine by NOS, is required for the maintenance of endothelial function, vascular tone, and organ perfusion (5, 6).

NO is a biological molecule involved in vascular vasodilation and bacterial cell killing (5). Its deficiency leads to the development of vascular disease. Arginase could inhibit NO production via several mechanisms: competition with NOS, uncoupling of NOS, resulting in the generation of NO scavenger, superoxide, and peroxynitrite, repression of the inducible NOS protein stability, inhibition of inducible NOS activity and sensitization of NOS to its endogenous inhibitor, asymmetric dimethyl-L-arginine (6).

The L-arginine–NO pathway is a crucial signaling pathway for cardiovascular functional integrity. Early stages of cardiovascular diseases could be due to NO which is formed from L-arginine. A lack of biologically active NO is widely believed to contribute to the pathogenesis of various cardiovascular diseases (7).

In humans normal daily diet contains 5.4 g L-Arginine from which approximately 30–50% enters the circulation (8). Although, a huge amount of information has been revealed on metabolic alterations occurring after surgery (9). So far the immediate effects of surgical trauma and anesthesia on basic amino acids catabolic response are still unclear in humans. Moreover, the metabolic stress response to cardiothoracic surgery with cardiopulmonary bypass (CPB) induces catabolism and protein turnover. Thus, we hypothesize that some changes in the intra-operative and post-operative levels of basic amino acids and NO will occur with coronary artery bypass grafting and thoracic surgery both.

The goal of the study was to assess changes in concentrations of plasma arginine, citrulline, ornithine, and NO in patients undergoing coronary artery bypass grafting or surgical lobectomy and to determine whether these changes can be correlated to the duration of surgery and hence anesthesia exposure.

Methods

A Cohort longitudinal study was carried out in the Cardiothoracic Surgery Department, Faculty of medicine from 2018 to 2019, on 58 male patients divided into two groups; group A; included 41 patients undergoing coronary artery bypass grafting surgery, their ages ranged from 55-75 years old. Group B: included 17 patients; 10 of whom had adenocarcinoma (Ac); in the upper loop of the left lung peripherally for left upper lobectomy and 7 patients had squamous cell carcinoma for right upper lobectomy, their ages ranged from 55-70 years old. An institutional board review registration No13700418 and a clinical trial registration (NCT04431492) were obtained. Patient consent to participate was obtained before the operation.

Inclusion criteria were Elective surgery, American Society of Anesthesia (ASA) II and III; and Age range 55-75 years. Exclusion criteria were associated with renal, liver, or blood diseases; Mechanical prosthetic valve, and for lung cancer, the exclusion criteria include radiation therapy or chemotherapy before surgery.

Patient preparation (two days before the operations, the following items had been done)

1. Full history and clinical exanimation.
2. X-ray chest, CT chest, ECG, Echocardiography, and coronary angiography evaluation.
3. Routine investigations include cardiac enzymes; complete blood count (CBC), prothrombin time and concentration, serum electrolytes, renal and liver function tests, fasting blood sugar and lipid profile, and arterial blood gases (Table 1).

Anesthesia Technique

All patients received the same protocol of general anesthesia, induction was done by propofol (1-2 mg/kg), titrated slowly intravenous till loss of verbal contact, cisatracurium (0.15mg/kg), fentanyl (2mic/kg), and lidocaine (1.5 mg/kg). Following induction; an invasive blood pressure (IBP), a central venous catheter (CVP), and a urinary catheter were inserted. Maintenance of anesthesia was done by mechanical ventilation, Isoflurane anesthesia, fentanyl infusion, and muscle relaxant. Monitoring was done by IBP, ECG, pulse oximetry, urinary output (UOP), and temperature. For patients on cardiopulmonary bypass, maintenance of anesthesia continues with propofol infusion and muscle relaxant.

Surgical approach

For coronary bypass: Group A patients were approached via a median sternotomy approach. Standard aortic and bicaval cannulation was done. An initial dose of 400 µg/kg heparin was used to obtain an activated clotting time. The blood pressure range was kept at 50-70 mmHg and blood flow was 2-2.4 L/min. priming solution contained mannitol and heparin was given. Hypothermia occurred for 25-30 minutes. Cold crystalloid cardioplegic (-4°C) arrest was used after aortic cross-clamping. Coronary bypass grafting was done using venous and arterial conduits. Aortic clamping time is as long as the operation time takes bypass duration is as the operation takes. Intensive care unit (ICU) follow-up was done for hemodynamic changes in the heart rate, arterial blood pressure, and central venous pressure. Antipyretics and potent antibiotic therapy were given. Before discharge from the operative theater, a patient must have met the following: awareness, impulsive breathing, and detached endotracheal tube. Usually, the extubation can be done at the ICU after being sure that the following criteria are normal conscious level, ABG, electrolytes, motor power, cardiac function, and temperature.

For lung cancer surgery: The diagnosis was done by bronchial biopsy. All patients were operable (stage I and II with no metastasis).

Laboratory investigations: A blood sample (4ml) venous was drawn from every participant into two tubes, 2 ml of heparin for amino acids and 2 ml on edit for NO, at four-time points; pre-operatively, intra-operatively; 10 minutes before the end of the operation and 72 hours postoperatively). Samples were centrifuged at 3500rpm for 15 minutes at 4 °C, and then plasma was stored at -20°C. Preparation of free amino acids samples from plasma depends on the precipitation of acidic protein using sulfosalicylic acid after centrifugation. The free amino acids remaining in the supernatant were stored at -20°C till the time of analysis.

The amino acids profile was determined by HPLC using Sykam automatic amino acid analyzer S 433 supplied by Sykam Gmbh, Germany CAT. NO.112001. Plasma NO was determined by using a spectrophotometric kit (supplied by bio diagnostics, Cairo, Egypt). The basis of the assay is that in an acid medium and the presence of nitrite (endogenous nitrite concentration as an indicator of nitric oxide production), the formed nitrous acid diazotize sulphanilamide and the product is coupled with N-(1-naphthyl) ethylene diamine. The resulting azo dye has a bright reddish-purple color which can be measured. NO was measured using T60 UV visible spectrophotometer. PG Instruments Limited, Alma park wibtoft, Leicester Cheshire, England. LE17SBE. Serial No.20-1650-01-0010.

Statistical analysis: Statistical analysis was performed using Graph Pad Prism (Graph Pad, Inc., San Diego, USA). Results were expressed as mean ± SE. Comparison between the two groups was done by the Mann-Whitney test. Analysis of variance was done by one-way ANOVA. P-value <0.05 was considered significant. An institutional board review registration No13700418 and a clinical trial registration (NCT04431492) were obtained. Patient consent to participate was obtained before the operation.

Results

Routine investigations revealed that there was significant leukocytosis in both groups during operations which started to decline post-operatively. Moreover, neutrophilia was significantly marked during operation in the two groups and accompanied by lymphopenia. In addition, the creatinine clearance test decreased significantly in two groups during operation and started to be normalized postoperatively. Surgery duration was significantly higher in group A than in group B (353.17±19.8 versus 182.35±23.79, P-value <0.001) (Table 1).

Table 1: Demographic data and surgical characteristics of the two groups:

Parameter		**Coronary Artery Bypass Graft**		**Lobectomy**	
Age (Years)		55-75 (61.8±4.41)		55-70 (61.53±4.27)	P=<0.828
Sex		Male 100%		Male 100%	
Smoking		39%		82%	
Weight (kg)		67.56±2.92		68.29±3.57	P= <0.418
Surgery duration (min)		353.17±19.8		182.35±23.79	P= <0.001**
Blood transfused (ml)		1319.51±165.79		1385.29±165.61	P= <0.174
Fluids (ml)		684.15±177.28		723.53±200.87	P= <0.462
HTN		78%		42%	
Diabetes		4.10%		2.90%	
Obesity (BMI)		27 - 31		29-33	
WBC	Pre	6.2 (0.78)	P1 = -0.01696705	5.8 (0.83)	P1 = -0.019608702
	During	18.9 (1.4)	P2 = 0.046066109	10.4 (1.54)	P2 = 0.806930802
	Post	8.9 (0.95)	P3 = -0.071213528	7.66 (0.96)	P3 = 0.195873084
Lymphocytes	Pre	31%		35%	
	During	7%		12%	
	Post	18%		28.50%	
Neutrophils	Pre	69%		65%	
	During	93%		88%	
	Post	82%		71.50%	
Creatinine Clearance	Pre	113.3 (3.41)	P1 = 0.059485408	118.4 (1.62)	P1 = 0.096469819
	During	97.7 (2.20)	P2 = 0.034539536	100.4 (3.24)	P2 = 0.093784184
	Post	111.4 (1.12)	P3 = 0.0067252	115.1 (1.56)	P3 = 0.38491104
I.C.U length of stay		12 - 24 hr		0 - 12 hr	
Hosptial length of stay		5 - 7 Days		4 - 6 Days	
Initiation of Nutrition (parenteral , Enteral)		24 - 36 hr		24 - 36 hr	

P1 =difference between Pre & During, P2 = difference between During & Post, P3 = difference between Post & Pre.

No statistically significant differences were found in the pre-operative, intra-operative, and post-operative NO levels between the two studied groups (Table 2). However, a high statistically significant difference was noticed by comparing the pre-operative, intra-operative, and post-operative levels of NO in the same study groups (Table 3). The levels of plasma arginine 24 hours' pre-operative, 10 minutes before the end of the operation, and 72 hours' post-operative did not significantly differ between the two groups (Table 4). A comparison of the levels of Arginine amino acid in the same surgical group showed in Table 5.

Table 2: Comparison of NO level between the two surgical groups: (Mean ±SD)

NO (umol/ml)	**Group A (n=41)**	**Group B (n=17)**	**P. value**
Preoperative	61.24 ± 1.162	61.71 ± 1.861	0.8319
Intraoperative	32.95 ± 0.6285	31.18 ± 0.8713	0.1209
Postoperative	45.56 ± 0.6139	46.41 ± 0.9118	0.4507

Table 3: Comparison of NO level in the same surgical group: (Mean SD)

Group A (n=41)			P value		
Preoperative	**Intraoperative**	**Postoperative**	**P 1**	**P2**	**P3**
61.24 ± 1.162	32.95 ± 0.6285	45.56 ± 0.6139	< 0.007**	< 0.001**	<0.008**
Group B (n=17)			**P value**		
Preoperative	**Intraoperative**	**Postoperative**	**P 1**	**P2**	**P3**
61.71 ± 1.861	31.18 ± 0.8713	46.41 ± 0.9118	<0.008**	< 0.005**	< 0.003*

P1: comparison between preoperative and intraoperative, P2: comparison between preoperative and postoperative, P3: comparison between postoperative and intraoperative. *P ≤ 0.05, **P ≤ 0.01,***P ≤ 0.001.

Table 4: Comparison of the levels of Arginine between the two surgical groups: (Mean ±SD)

Arginine (umol/ml)	Group A (n=41)	Group B (n=17)	P. value
Preoperative	75.95 ± 1.312	74.47 ± 1.910	< 0.54
Intraoperative	58.88 ± 1.774	59.24 ± 1.115	< 0.86
Postoperative	67.00 ± 1.147	65.00 ± 0.6198	< 0.1

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Table 5: Comparison of the levels of Arginine amino acid in the same surgical group (Mean ±SD)

Group A (n=41)			P value		
preoperative	**intraoperative**	**postoperative**	**P 1**	**P2**	**P3**
75.95 ± 1.312	58.88 ± 1.774	67.00 ± 1.147	< 0.003**	< 0.001**	< 0.003**
Group B (n=17)			**P value**		
Preoperative	**Intraoperative**	**postoperative**	**P 1**	**P2**	**P3**
74.47 ± 1.910	59.24 ± 1.115	65.00 ± 0.6198	< 0.004**	< 0.006**	< 0.005**

P1: comparison between preoperative and intraoperative, P2: comparison between preoperative and postoperative, P3: comparison between postoperative and intraoperative.

No statistically significant difference was found by comparing pre-and post-operative plasma citrulline levels between the two groups (Table 6). However, a significant difference was detected in the intra-operative levels of plasma citrulline between the two groups (P<0.01).

A comparison of the levels of Citrulline amino acid in the same surgical group showed in Table 7. No difference was detected by comparing pre-, intra-and post-operative ornithine levels between the two groups (Table 8).

A comparison of the levels of ornithine in the same surgical group showed in Table 9. Both negative and positive correlations were observed between

Table 6: Comparison of the levels of Citrulline between the two surgical groups: (Mean ±SD)

Citrulline (umol/mL)	Group A (n=41)	Group B (n=17)	P. value
preoperative	42.95 ± 0.6217	44.47 ± 1.399	< 0.25
Intraoperative	28.78 ± 0.5233	32.18 ± 1.600 N=17	< 0.01*
Postoperative	21.40 ± 0.2738	21.18 ± 0.5371	< 0.7

Table 7: Comparison of the levels of Citrulline amino acid in the same surgical group (Mean ±SD)

Group A (n=41)			P value		
Preoperative	**Intraoperative**	**Postoperative**	**P 1**	**P2**	**P3**
42.95 ± 0.6217	28.78 ± 0.5233	21.40 ± 0.2738	< 0.01**	< 0.003**	< 0.01**
Group B (n=17)			**P value**		
Preoperative	**Intraoperative**	**Postoperative**	**P 1**	**P2**	**P3**
44.47 ± 1.399	32.18 ± 1.600	21.18 ± 0.5371	< 0.004**	<0.006**	< 0.005**

P1: comparison between preoperative and intraoperative, P2: comparison between preoperative and postoperative, P3: comparison between postoperative and intraoperative

Table 8: Comparison of the levels of ornithine between the two surgical groups: (Mean ±SD)

Ornithine (umol/mL)	Group A (n=41)	Group B (n=17)	P. value
preoperative	113.1 ± 1.471	112.8 ± 1.946	< 0.9
Intraoperative	90.71 ± 0.8288	88.35 ± 1.685	< 0.2
Postoperative	101.0 ± 0.7010	102.35 ± 1.685	< 0.3

Table 9: Comparison of the levels of ornithine in the same surgical group: (Mean ±SD)

Group A (n=41)			P value		
Preoperative	**Intraoperative**	**Postoperative**	**P 1**	**P2**	**P3**
113.1 ± 1.471	90.71 ± 0.8288	101.0 ± 0.7010	< 0.01**	< 0.005**	< 0.003**
Group B (n=17)			**P value**		
Preoperative	**Intraoperative**	**Postoperative**	**P 1**	**P2**	**P3**
112.8 ± 1.946	88.35 ± 1.685	10235 ± 1.685	< 0.0031**	0.0049**	< 0.001**

P1: Comparison between preoperative and intraoperative, P2: comparison between preoperative and postoperative, P3: comparison between postoperative and intraoperative

surgery duration and plasma levels of amino acids concentration in the two studied two groups A&B (Fig.

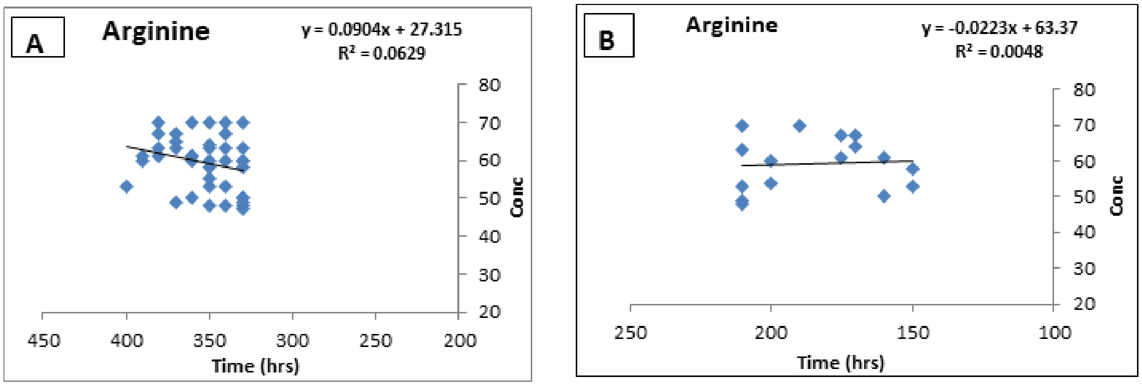

Figure 1. Correlations between arginine amino acid and time of the operation in the two groups (A) *coronary bypass* and (B) *lung cancer surgery*.

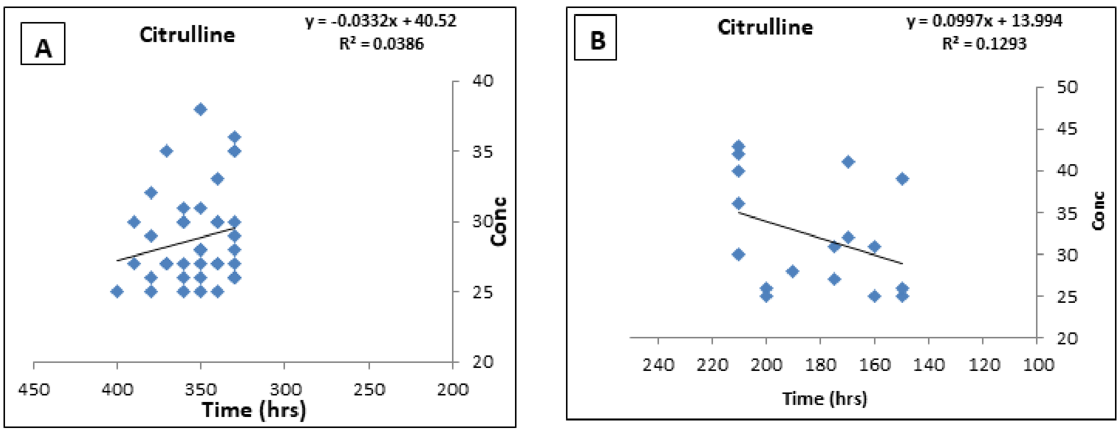

Figure 2. Correlations between citrulline amino acid and the time of operation in the two groups (A) *coronary bypass* and (B) *lung cancer surgery*.

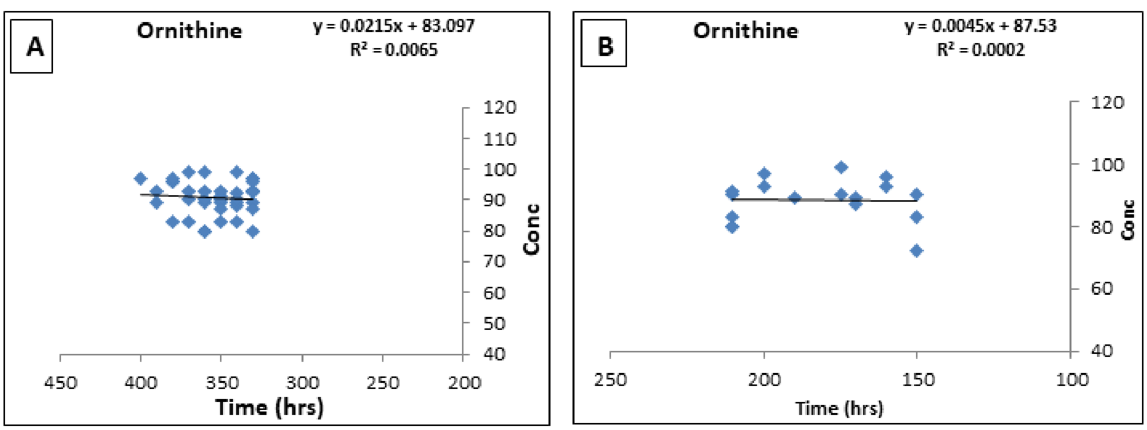

Figure 3. Correlations between ornithine amino acid and the time of operation in the two groups (A) *coronary bypass* and (B) *lung cancer surgery*.

1-4). There was a positive correlation in arginine, ornithine, and NO level in group A and group B in citrulline and ornithine, while a negative correlation in citrulline in group A and arginine and NO level in group B.

Discussion

The present study revealed that the two major surgeries (coronary artery bypass grafting and lung cancer resection) have a profound effect on plasma levels of

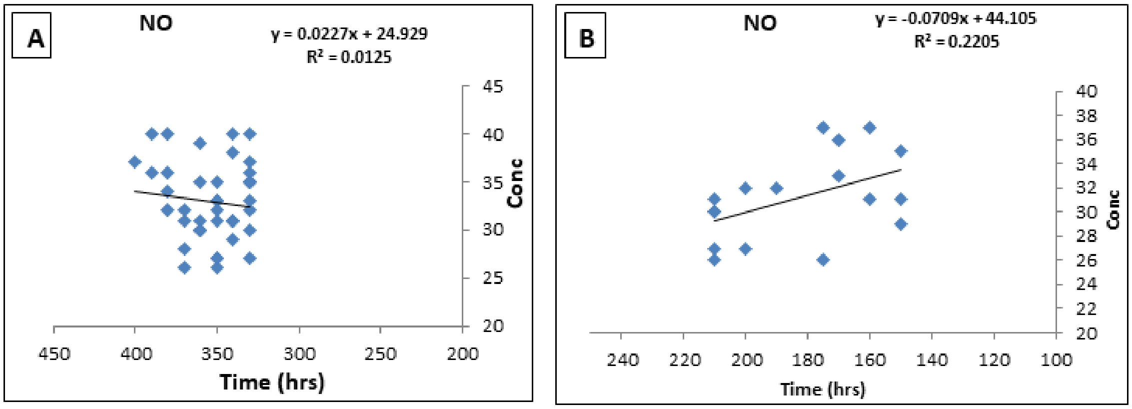

Figure 4. Correlations between NO and the time of operation in the two groups (A) *coronary bypass* and (B) *lung cancer surgery*.

basic amino acids and NO. Reduction in basic amino acids and NO started intra-operatively and continued post-operatively. NO is one of the most potent vasodilators known and is essential to vascular homeostasis, while the amino acid arginine is the sole precursor of NO. Citrulline is an important precursor for arginine (10, 11).

Arginine and its product NO are essential for early post-operative recovery as they play important roles in wound healing. Surgery reduces systemic arginine availability due to enhanced catabolism, which negatively affects NO synthesis (12). L-Arginine has a beneficial effect on endothelial function in patients with ischemic heart disease and dilates the atherosclerotic, stenotic coronary arteries (12, 13). Clinical consequences of arginine depletion in these conditions are mainly associated with endothelial dysfunction and NO imbalance; however, pathophysiological consequences of arginine deficiency are yet to be elucidated (14).

Since surgical trauma may have a biochemical effect on NO metabolism; so increase in arginase activity is observed after moderate trauma in humans. This increase could occur due to neutrophil activation or a release from the injured vascular endothelium (6). Loss of body proteins represents a typical feature of the catabolic response to surgery.

The present study showed that despite of longer duration of a coronary artery bypass operation, no significant difference was recorded between it and lung cancer surgery except in intra-operative citrulline level which was lower in group A than group B. A reduction in citrulline production will result in a decrease in endogenous arginine synthesis which may also contribute to the depletion of arginine (15). Ischemia-reperfusion injury of the gut may lead to a lack of recovery of citrulline. Inflammatory response due to exposure of inflammatory cells to foreign surfaces of the bypass circuit, mechanical shear stress, tissue ischemia with reperfusion, hemodynamic changes, and exposure to blood products (16). Our study reported reduced NO levels compared to the pre-operative levels and this is in harmony with the results of Kan et al. (8). Moreover, in agreement with our finding; Engelen et al. (2018) found that surgery in early-stage breast cancer reduces plasma arginine, citrulline, and NO concentrations and concluded that the reduced systemic arginine availability in the early postoperative phase is due to a combined process of increased catabolism and impaired endogenous synthesis of arginine (17). Chiarla *et al*. (2006) found a reduced plasma concentration of arginine (approximately 50%) and ornithine amino acids following trauma and sepsis (2).

Moreover, Barr et al. (2003) studied the effect of cardiopulmonary bypass on NO and urea cycle intermediates in congenital heart surgeries. They revealed that cardio-pulmonary bypass significantly reduces plasma levels of arginine, citrulline, and nitric oxide metabolites in the postoperative period. Reduction of NO and related amino acid precursors (citrulline, arginine, and ornithine) increases the risk of postoperative pulmonary hypertension (18). In addition, Chaloupecký et al. (1997) and Gielen et al. (2014) also confirmed a post-operative reduction of NO and its related amino acids precursors in pediatric cardiac surgery (19).

Furthermore, Hol *et al.* (2013) concluded that major surgery (laparotomy) is associated with lower postoperative plasma levels of citrulline and NO metabolites than minor surgery (vulvectomy). They suggested that surgical trauma stimulates the laparotomy group to consume significantly more ornithine, possibly for use in wound healing (20). The authors explained that the increase in amino acid concentration during bypass appears to be a physiologic response unrelated to protein denaturation and possibly secondary to hepatic hypoxia, which may produce an enzymatic block in protein synthesis.

Bernard *et al.* (2000) reported that the significant decrease in arginine levels reported during operations can be explained by the stress induced by catecholamine endogenous synthesis. Catecholamine stimulates arginase activity annulled with catecholamine inhibitors. Catecholamine alone could increase macrophage arginase activity through the activation of beta-adrenoceptors. Moderate trauma-induced increase in splenic arginase activity that is suppressed by the beta-adrenoceptor blockade, suggesting that trauma-induced arginase activity is partly mediated by endogenous catecholamines (21). Arginase, the specific enzyme for arginine catabolism has two isoforms. Arginase I mainly found in the lung, kidneys, and macrophages. Arginase II is limited to the liver and leukocytes (22). The equivalent arginine level drop in the studied groups may be explained that the arginase has equally been activated and that equal levels of ornithine are obtained. Satriano *et al.* (2004) added that more, ornithine could be consumed in such major operations in the production of proline and polyamines required for wound healing (23).

The present study revealed that leukocytosis with mainly neutrophilia with the reduction in the number of lymphocytes during operation in both groups. Foreign surfaces may activate neutrophils and start an inflammatory cascade that leads to macrophage activation and lymphocyte depletion. McGuiness *et al.* (2008) also demonstrated a similar pattern of inflammation with a peak of leukocytosis at 24 hours compared to neutrophilia followed by monocytosis and a reduction in the number of lymphocytes (24). Apoptosis has a role in lymphocyte depletion in the postoperative period after CPB. Kim *et al.* (2015) reported that in adults undergoing bypass. It has been reported that increased neutrophil/leukocyte (N/L) ratio is associated with adverse outcomes such as renal impairment (25). Our findings also reported a decrease in creatinine clearance during operation which may reveal that the inflammatory process may be associated with renal impairment. Increased N/L ratio and monocytosis were associated with decreased creatinine clearance during operation and postoperative. The association between the severity of inflammation and depletion of arginine and citrulline in critically ill children has been described by Van Waardenburg (26). In addition, it is known that T-cells are exquisitely sensitive to nutritional status, and the proliferation of T-cells is blunted in the arginine-depleted state (27).

The mechanisms involved in the association of arginine and inflammation remain under investigation. In postoperative patients, due to concerns for fluid overload, feeding or parenteral nutrition has advanced slowly. Most parenteral nutrition formulations don't contain citrulline or glutamine (14).

Popovic *et al.* (2007) reported that multiple risk factors could contribute to arginine depletion. First, patients remained undernourished during the early postoperative period. Second, there was a depletion of citrulline, which is the precursor for arginine synthesis, and an increase in plasma arginase levels. And finally, arginine requirements were likely increased due to inflammation, surgical tissue damage, and ischemia-reperfusion injury (28). Our explanation of arginine depletion in the present study goes hand in hand with the explanation of Popovic *et al.* (2007).

According to our best knowledge, we could trace very few studies in Egypt that reflect the effect of cardiothoracic surgery in adults on the levels and metabolic pathways of these basic amino acids. Indeed, the decrease in the intra-operative synthesis of NO is important for vasoconstriction to decrease bleeding during the operation. But the normalization of NO postoperatively is important to help vasodilation to maintain adequate blood flow to the heart and the same for ornithine to help in healing. So, the present study elucidates the effect of two major cardiothoracic surgeries on the cyclic metabolic pathway of arginine, ornithine, citrulline, and NO. Considering the role of stress in this scenario it is important to regulate the plasma levels of NO in those patients to ensure good endothelial function.

We recommend pre-operative short-term oral amino acid supplementation with β-hydroxy β-methyl butyric acid (HMB), I-glutamine, and I-arginine to elderly patients undergoing cardiothoracic surgery. The small sample size, undernourishment of our patients, and lack of arginase estimation.

Conclusion

We concluded that depletion of conditionally basic amino acids (arginine, citrulline, and ornithine) is possibly multifactorial and can be associated with an increase in arginase which is activated by surgical trauma, anesthesia and stress, and low nutritional status. The previous findings could help in understanding the pathophysiology of systemic inflammatory response syndrome; also, elucidate hemolysis and ischemia-reperfusion injury which results in low systemic oxygen delivery and multiple organ dysfunctions in this population.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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