Effect of L-arginine on Hemodynamic, Biochemical, and Histopathological Outcomes in a New Zealand Rabbit Model of Renal Ischemia–Reperfusion Injury

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ABSTRACT

Objective: In this study, we investigated the effect of L-arginine on hemodynamic, biochemical, and histopathological changes in a rabbit model with renal ischemia.

Methods: Forty white New Zealand rabbits were used. The rabbits were divided into two groups as the control group (n=20) and L-arginine group (n=20). They were monitored by cannulating the auricular and femoral arteries. An aortic occlusion catheter was inserted through the contralateral femoral artery and was extended to the distal aspect of the left subclavian artery; it was then inflated, and occlusion was performed for 30 min. All rabbits received 4 mL/kg/h of NaCl infusion during the course of occlusion and within the first 60 min of reperfusion. In the L-arginine group, L-arginine was infused at a dosage of 3 mg/kg/h through the auricular vein during the first 60 min of occlusion and perfusion. Blood samples for biochemical parameters [glucose, lactate, hematocrit, blood urea nitrogen (BUN), and serum creatinine] were obtained in the peri-ischemic period, in the 20th minute of reperfusion, and just before sacrificing (48th hour). A histopathological examination was performed in both renal tissues. Histopathological scoring was performed by taking tubular epithelial cell flattening, brush border loss, cytoplasmic vacuolization, cell necrosis, and tubular lumen obstruction into consideration. All animals were sacrificed 48 h after the procedure.

Results: A significant difference was found between the L-arginine and control groups in terms of the hemodynamic outcomes and 48th hour BUN and serum creatinine levels ($p<0.05$). The histopathological examination revealed a mean score of 3.2±0.89 in the control group and 2.60±0.68 in the L-arginine group ($p<0.05$) ($p=0.022$).

Conclusion: It can be suggested that L-arginine reduces renal ischemia–reperfusion injury and in particular, the histopathological effects. *(JAREM 2016; 6: 24-30)*

Keywords: L-arginine, ischemia–reperfusion injury, kidney

INTRODUCTION

The kidneys perform an important task by regulating intravascular volume and electrolyte balance in the body. Under normal circumstances, the kidneys receive approximately one-fourth of the cardiac output (1).

Ischemic renal injury is frequently encountered after trauma, serious hypovolemia, severe sepsis, burns, and major surgical interventions. Injury in the ischemic kidney occurs not only during the ischemic period but also during the subsequent reperfusion period. After major surgical intervention, renal functions are widely influenced from minimal natriuresis to fulminant acute renal insufficiency that could progress to dialysis (1, 2). Preserving renal function in patients who undergo cross-clamping over the renal arteries during aortic surgery is closely associated with patient age, ischemia duration, and preoperative renal functions.

In the present study, hemodynamic parameters, biochemical changes, and primarily the cytopathological effects of L-arginine in renal ischemia were investigated in a renal ischemia model.

METHODS

In the present study, 40 New Zealand rabbits weighing between 2150 grams (g) and 3450 g were used. The study was conducted in line with Experimental Medicine Training and Research Center, Directives of Ethics Committee for Experimental Animals, which have been prepared based on the Universal Declaration on Animal Welfare, European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, and the Guide for the Care and Use of Laboratory Animals. Moreover, the study was conducted at the Experimental Medicine Training and Research Center after the approval of ethics committee of Selçuk University Meram School of Medicine. In the present study, 30 min, which is the minimum time for cross-clamping to be tolerated without complication under normothermic conditions, was taken as the basis.

Groups

The rabbits included in the study were divided into two groups as the control group (Group 1) and L-arginine group (Group 2), with each group including an equal number of rabbits. While the weight of the rabbits was between 2150 g and 3200 g in Group 1, it was between 2250 g and 3450 g in Group 2.

Thirty-minute suprarenal occlusion was performed in all animals. The rabbits in both groups received an isotonic fluid (Mediflex® 0.9% NaCl, Eczacıbaşı-Baxter, İstanbul, Turkey) infusion at a dosage of 4 milliliters (mL)/kilograms (kg)/hours (h) over the course

This study was presented at the Turkish Society of Cardiovasculary Surgery 13th International Congress, 30 October - 2 November, Antalya, Turkey.

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Received Date: 25.06.2015 **Accepted Date:** 29.07.2015

Available on-line at www.jarem.org
DOI: 10.5152/jarem.2015.819

of the procedure and for 60 minutes (min) after the clamp was removed. In the L-arginine group (n=20), L-arginine, which had been diluted using 10-mL distilled water, was administered at a dosage of 3 mg/kg/h as an intravenous continuous infusion from the onset of aortic occlusion to the end of 60 min following the removal of the aortic clamp.

Anesthesia and Monitoring

Intramuscular ketamine hydrochloride (50 mg/kg) (Ketalar® Pfizer, Paris, France) and xylazine (10 mg/kg) (Xylazinbio® 2% Bioveta, Ankara, Turkey) were administered to the animals. The dose was repeated as a cocktail containing ketamine (25 mg/kg) and xylazine (5 mg/kg) when necessary. After the anesthesia, the animals were left for spontaneous breathing and were provided with nasal oxygen (O_2) support at a dose of 2 liters (l)/min. An intravenous catheter (24 gauge) was placed in each rabbit through the marginal ear vein. Over the course of the procedure, a 0.9% sodium chloride (NaCl) solution was infused at a rate of 4 mL/kg/h. A catheter (22 gauge) was placed into the ear artery, and another catheter (20 gauge) was placed into the right femoral artery via surgical exploration to monitor blood pressure. The anterior thoracic area was shaved. Electrocardiography (ECG) was performed with electrodes placed on the anterior thoracic wall; blood pressures, including proximal (via the ear artery catheter) and distal (via the femoral artery catheter), were monitored by connecting the catheter placed into the ear artery to the pressure transducer (Mennen medical incorporated, Model: Mercury, Revohot, Israel). In this way, all rabbits were continuously monitored during the surgical procedure, before aortic clamping, and after declamping.

Surgical Procedure

The rabbits were placed on the operating table in the supine position. Sacrificing was planned to be performed after a 48-h monitoring period. The left femoral arteries of the rabbits were explored and suspended by tapes. Arteriotomy was performed in the left femoral artery 5 min after causing anticoagulation in the the animals with standard heparin (Nevparin® Mustafa Nevzat, Ankara, Turkey) at a dose of 100 units (U)/kg. An aortic occlusion catheter (3 French, Promited Laboratories, Ref No: 2211100, Meuilly-En-Thelle, France) was pushed through the femoral artery to the approximately 22 centimeter (cm) proximal aspect (up to the distal aspect of the left subclavian artery). The occlusion catheter cuff was inflated and a decrease in the distal aortic pressure was observed. Aortic occlusion was performed for 30 min in this way in all animals. At the end of this period, the catheter cuff was deflated, and an increase in the distal blood pressure was observed from the right femoral artery cannula. Thereafter, the occlusion catheter was pulled back, and pulsatile flow in the left femoral artery was observed. The layers were duly closed with appropriate suture materials.

Postoperative Care

The rabbits were put in cages after they woke up. They were allowed to be fed in the postoperative 6th hour. The bladders of the paraplegic animals were emptied by the Crede maneuver, which was performed at least two times daily.

Sacrificing

At the end of 48 h, all rabbits were sacrificed after the renal histopathological samples were obtained. Sacrificing was done with intracardiac 10% formaldehyde after administering intramuscular ketamine (50 mg/kg) and xylazine (10 mg/kg).

Histopathological Evaluation

The excised tissues were put into a 10% neutral formaldehyde solution and were stored in this way until the time of study. The sections were obtained and stained with hematoxylin–eosin and were then examined under a light microscope by the pathologist from the SUM Faculty of Medicine, who was blinded. In the present study, pathological examination under the light microscope was performed to investigate ischemia-related alterations in the kidney tissue. The scoring performed by Rhoden et al. (3) who took ischemia-related changes in tubular epithelial cells as the basis was used.

According to this scoring, alterations in tubular epithelial cells and tubule structure are taken into account. Scoring was as follows: 1 point for tubular epithelial cell flattening (Figure 1), 1 point for brush border loss (Figure 2), 1 point for cytoplasmic vacuolization (Figure 3), 1 or 2 points for cell necrosis (2 if it is widespread in the section area and 1 if it is less) (Figure 4), and 1 or 2 points for tubular lumen obstruction (2 if it is widespread in the section area and 1 if it is less) (Figure 4).

Statistical Analysis

Data were transferred to electronic media. Statistical analyses were done by the SPSS program (SPSS Inc.; Chicago, IL, USA). Among the data collected from the rabbit groups, those not distributed normally were evaluated by Kolmogorov–Smirnov test. The data were compared by Mann–Whitney U test. The level of statistical significance was considered to be $p<0.05$.

RESULTS

A total of 40 New Zealand rabbits were used in the study. The weights of the rabbits ranged from approximately 2200 g (minimum) to 3500 g (maximum). The difference between the proximal mean arterial blood pressure (pMAP) in the 10th and 30th minutes of ischemia in both groups was statistically significant ($p<0.05$), whereas the difference between the distal mean arterial blood pressure (dMAP) was not statistically significant ($p>0.05$). In the peri-ischemic period, it was observed that the heart rate was higher in the L-arginine group than in the control group ($p<0.05$).

A sudden increase in pMAP and sudden decrease in dMAP were simultaneously determined with aortic occlusion in both groups. The heart rate showed a sudden decrease simultaneously with aortic occlusion in all rabbits. Over the course of the ischemic period, it was observed that the difference in terms of dMAP was not statistically significant in both groups ($p>0.05$), whereas the heart rate was found to be higher in the 10th minute of ischemia in the L-arginine group ($p<0.05$). After the end of aortic occlusion, while a decrease was observed in pMAP, an increase was observed in dMAP in both groups during the reperfusion period compared with that during the ischemic period. The heart rate increased in the reperfusion period compared with that in the ischemic period in all rabbits. In the reperfusion period, the difference between the groups in terms of pMAP and dMAP was found to be sta-

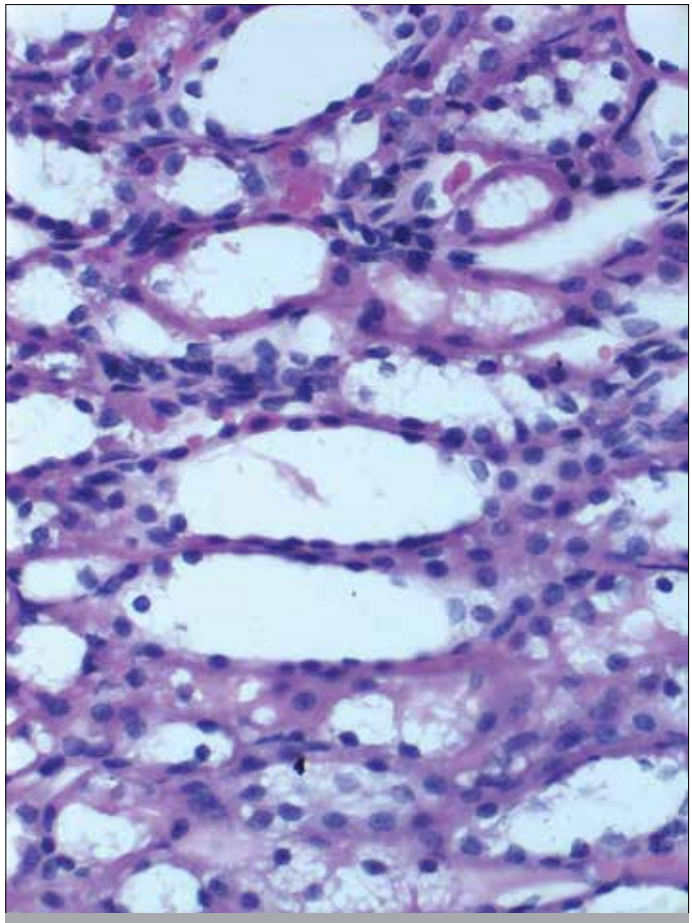

Figure 1. Tubular epithelial cell flattening (HE ×40)

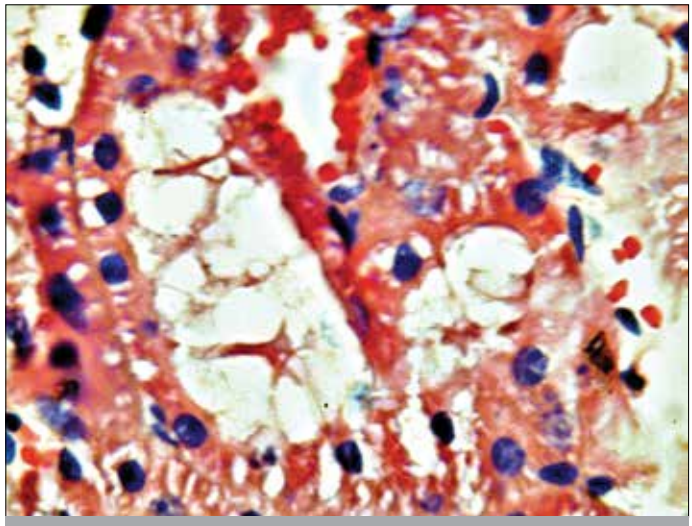

Figure 2. Loss of brush border (HE ×40)

tistically insignificant. It was determined that the heart rate was statistically significantly higher in the L-arginine group than in the control group in the reperfusion period ($p<0.05$).

The pH in the 20th minute of ischemia was higher in the L-arginine group than in the control group, and it was found to be statistically significant ($p<0.05$). A lower pH in the L-arginine group than

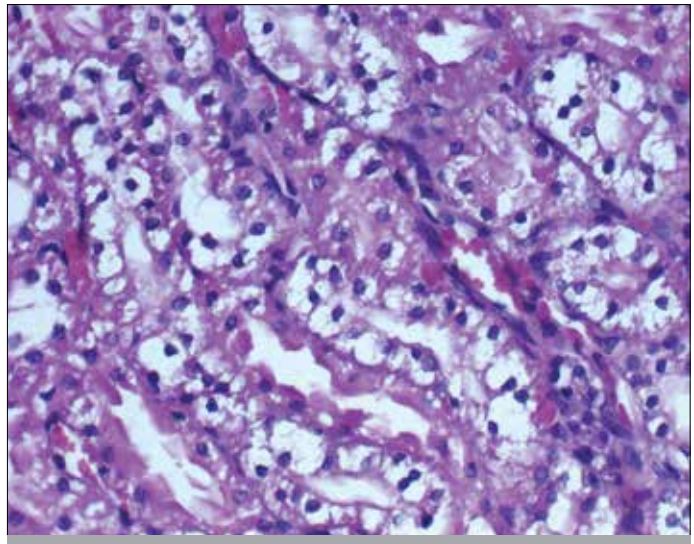

Figure 3. Cytoplasmic vacuolization (HE ×40)

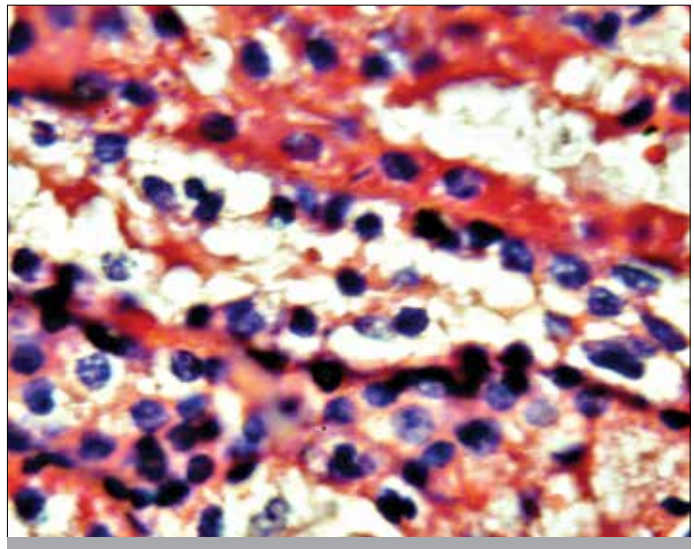

Figure 4. Tubular lumen obstruction (HE ×40)

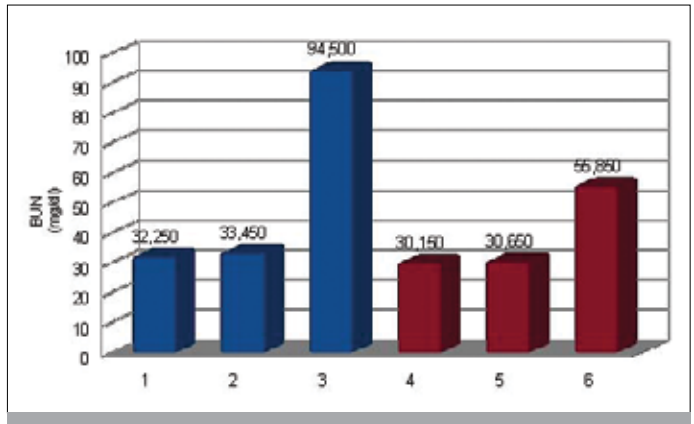

Figure 5. BUN levels according to groups in some periods. Group 1-blue (1: pre-ischemic period, 2: 20th minute in the reperfusion period, 3: 48th hour in the postoperative period). Group 2-red (4: pre-ischemic period, 5: 20th minute in the reperfusion period, 6: 48th hour in the postoperative period)

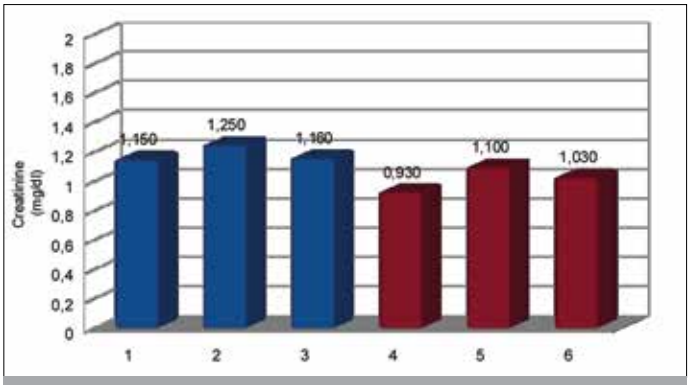

Figure 6. Creatinine levels according to groups in some periods. Group 1-blue (1: pre-ischemic period, 2: 20th minute in the reperfusion period, 3: 48th hour in the postoperative period). Group 2-red (4: pre-ischemic period, 5: 20th minute in the reperfusion period, 6: 48th hour in the postoperative period)

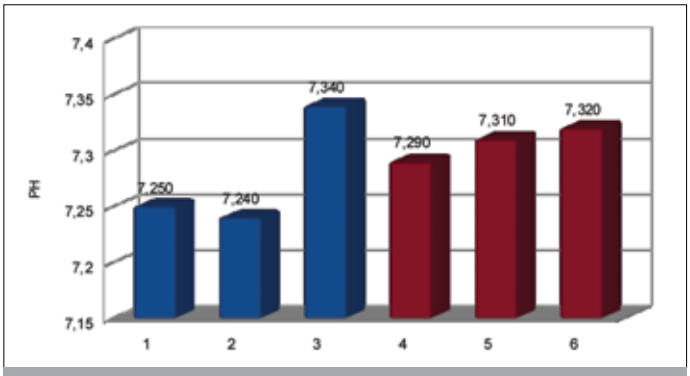

Figure 7. pH according to groups in some periods. Group 1-blue (1: pre-ischemic period, 2: 20th minute in the ischemic period, 3: 20th minute in the reperfusion period). Group 2-red (4: pre-ischemic period, 5: 20th minute in the ischemic period, 6: 20th minute in the reperfusion period)

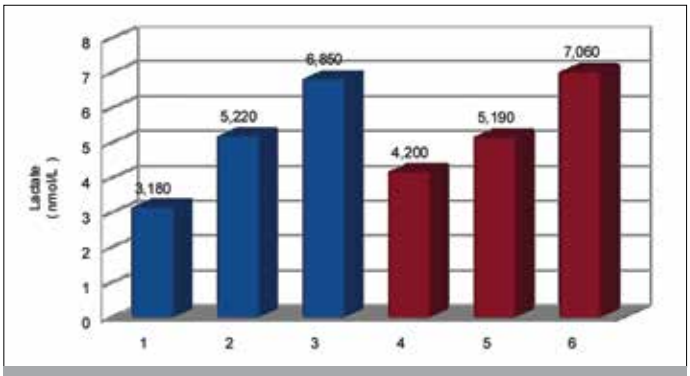

Figure 8. Lactate levels according to groups in some periods. Group 1-blue (1: pre-ischemic period, 2: 20th minute in the ischemic period, 3: 20th minute in the reperfusion period). Group 2-red (4: pre-ischemic period, 5: 20th minute in the ischemic period, 6: 20th minute in the reperfusion period)

in the control group during the reperfusion period was found to be statistically significant (p>0.05). Blood acidity (pH), blood urea nitrogen (BUN), serum creatinine (Scr), arterial partial carbon dioxide pressure (pCO_2), arterial partial oxygen pressure (pO_2), blood glucose, and blood lactate levels and hematocrit (hct) of all rabbits in the L-arginine and control groups are demonstrated in Table 1 and Table 2. BUN, Scr, pH, and lactate levels according to the groups are shown in Figures 5, 6, 7 and 8.

DISCUSSION

In the present study, a significant difference was found between the L-arginine and control groups in terms of some hemodynamic parameters (pMAP in the 10th and 30th minutes of ischemia and heart rate in the pre-ischemic period) and 48th-hour BUN and creatinine levels (p<0.05). The histopathological examination revealed a mean score of 3.2±0.89 in the control group and 2.60±0.68 in the L-arginine group (p<0.05) (p=0.022).

Acute renal injury due to ischemia and reperfusion (I/R) is a clinical and experimental consequence characterized by a decrease in the glomerular filtration rate, extensive tubular injury, tubular cell necrosis, and obstruction due to hyaline debris. Acute tubular necrosis can be created by hypoperfusion or by completely interrupting the renal blood flow. In clinical practice, suprarenal aortic aneurism surgery is a good example for an injury caused by ischemia due to renal blood flow interruption and subsequent reperfusion.

Lahera et al. (4) performed hemodynamic examinations to keep renal injury at a minimum level and demonstrated a mean decrease of 10%–15% in blood pressure following L-arginine infusion in rats. In another study conducted in rats, Waz et al. (5) determined a decrease in urine volume and urinary sodium excretion 60 min after low-dose L-NAME (0.1–1.0 μg/kg/min) infusion, which is a nitric oxide synthase (NOS) inhibitor. It was reported that high-dose L-NAME (10–50 μg/kg/min) infusion increases systemic blood pressure by decreasing the renal blood flow and glomerular filtration rate. Bhardway and Moore (6) demonstrated that L-arginine decreases renal vascular resistance but notably increases post-ischemic renal functions. The protective effect of L-arginine results from the ability of nitric oxide (NO) to prevent leukocyte accumulation and its vasodilator effect during ischemia (7).

The kidneys are more sensitive than other organs against the inhibition of NO production by L-NAME. A decrease in NO production leads to a decrease in glomerular flow, diuresis, and natriuresis (8). Kobayashi et al. (9) reported a remarkable decrease in renal blood flow in rats by administering L-NAME and prevented this by administering L-arginine. Another study demonstrated that L-NAME administration in rats remarkably decreases creatinine clearance (8).

Basal NO production is necessary for the maintenance of normal glomerular filtration and during the renal I/R period. The inhibition of NO enhances renal dysfunction (8). During renal I/R, NO production is decreased due to endothelial cell injury. After the inhibition of NO synthase, a notable increase is observed in creatinine levels in the 24th, 96th, and 192nd hours of renal I/R (8).

Many studies have stated that NO has favorable effects on renal tissue in I/R. Paller et al. (10) demonstrated that NO protects ischemic tissue via its vasodilator effect and decreases leukocyte adhesion, neutrophil infiltration, and inflammatory mediator formation during ischemia–reperfusion. During reoxygenation, NO reacts with superoxide and prevents the formation of additional

Table 1. Statistically data with matched normal dissociation

	Group 1	Group 2 (L-arginine)	p
pMAP (mmHg) (Pre-ischemic period)	60.20±3.33	60.85±3.48	0.55
dMAP (mmHg) (Pre-ischemic period)	60.30±3.45	61.35±3.22	0.326
pMAP (mmHg) (10th minute in the ischemic period)	97.75±3.75	94.90±3.09	0.013*
dMAP (mmHg) (10th minute in the ischemic period)	10.25±2.22	9.20±1.54	0.09
dMAP (mmHg) (30th minute in the ischemic period)	10.70±1.89	10.95±1.93	0.682
pMAP (mmHg) (10th minute in the reperfusion period)	51.80±4.07	56.55±5.26	0.3
dMAP (mmHg) (10th minute in the reperfusion period)	55.00±5.76	56.60±5.69	0.382
pMAP (mmHg) (30th minute in the reperfusion period)	44.95±5.45	45.95±10.49	0.71
dMAP (mmHg) (30th minute in the reperfusion period)	48.40±5.48	50.50±4.41	0.190
Heart rate (beat/min) (10th minute in the ischemic period)	104.85±14.45	110.70±11.96	0.172
Heart rate (beat/min) (30th minute in the reperfusion period)	146.60±8.44	159.70±5.52	<0.001*
pCO_2 (mmHg) (Pre-ischemic period)	56.75±5.34	51.50±4.67	0.002*
pCO_2 (mmHg) (20th minute in the ischemic period)	54.55±5.10	49.90±4.64	0.005*
pCO_2 (mmHg) (20th minute in the reperfusion period)	41.00±4.57	45.55±7.35	0.025*
Lactate (mmHg) (Pre-ischemic period)	3.18±0.90	4.20±1.01	0.002*
Lactate (mmHg) (20th minute in the ischemic period)	5.22±0.60	5.19±0.79	0.890
Lactate (mmHg) (20th minute in reperfusion period)	6.85±0.83	7.06±0.70	0.383
Glucose (mg/dL) (Pre-ischemic period)	200.25±49.38	197.65±31.21	0.843
Glucose (mg/dL) (20th minute in the ischemic period)	247.65±44.31	272.55±44.31	0.084
BUN (mg/dL) (Pre-ischemic period)	32.25±5.83	30.15±4.46	0.209
BUN (mg/dL) (20th minute in the reperfusion period)	33.45±6.34	30.65±4.93	0.128
PH (20th minute in the reperfusion period)	7.34±0.05	7.32±0.12	0.513
Hct (20th minute in the reperfusion period)	26.20±2.46	25.35±2.80	0.314
Histopathological scoring	3.20±0.89	2.60±0.68	0.02*

* Statistically significant values
pH: blood acidity; BUN: blood urea nitrogen; pCO_2: arterial partial carbon dioxide pressure; pO_2: arterial partial oxygen pressure; Glucose: blood glucose; Hct: blood lactate and hematocrit

oxygen radicals such as hydroxyl and hydrogen peroxide (10). The increased superoxide due to a higher production of superoxide or impaired NO synthesis gets converted to hydrogen peroxide (8). The production of proinflammatory lipid mediators, such as platelet-activating factor and leukotriene B4, results in enhanced leukocyte adhesion and enhanced tissue injury in I/R (8).

Ischemia-related acute renal insufficiency is a complex syndrome comprising renal vasoconstriction, extensive tubular injury, tubular cell necrosis, impaired glomerular filtration, and glomerular injury (3-11). Decrease in the oxidative phosphorylation of the mitochondria, secretion of lysosomal enzymes, loss of membrane functions, and increase in tubular permeability occur due to ischemia–reperfusion in the renal tissue. Renal oxidative stress due to reoxygenation may theoretically result in injury in renal endothelial cells, glomerular mesenchymal cells, and tubular epithelial cells. Consequently, both renal structure and function are influenced (12). Renal cells contain different antioxidant enzyme systems such as superoxide dismutase and catalase, which reduce oxidative stress injury. Endothelial cell injury that results from renal I/R decreases NO production. NO inhibition further increases renal dysfunction (8).

It has been reported that NO decreases renal vascular resistance and facilitates renal function return after ischemic injury (13). Caramelo et al. (14) administered superoxide dismutase together with L-arginine and demonstrated that there is a remarkable increase in renal functions and urine volume and that this arises from the synergistic effects of these two substances. Burra et al. (15) expressed that L-arginine therapy reduces histopathological injury in pigs that have been exposed to renal I/R. In another study, Weight et al. (16) emphasized that L-NAME causes no significant alteration in the histology in rats that underwent renal I/R. Schneider et al. (17) suggested that in vivo acute L-arginine administration has

Table 2. Statistically data with no-matched normal dissociation

	Group 1	Group 2	p
pMAP (mmHg) (30th minute in the ischemic period)	103.30±3.40	140.80±202.52	<0.001
HR (beat/min) (Pre-ischemic period)	157.10±4.69	178.70±5.06	<0.001
HR (beat/min) (10th minute in the ischemic period)	97.75±3.35	107.80±4.29	<0.001
HR (beat/min) (10th minute in the reperfusion period)	146.35±7.73	170.30±7.73	<0.001
pO_2 (mmHg) (Pre-ischemic period)	168.95±23.68	123.45±13.92	<0.001
pO_2(mmHg) (20th minute in the ischemic period)	215.85±30.38	173±27.28	<0.001
pO_2 (mmHg) (20th minute in the reperfusion period)	245.10±44.12	165.50±44.48	<0.001
BUN (mg/dL) (48th hour in the postoperative period)	94.50±28.66	55.85±14.92	<0.001
Glucose (mg/dL) (20th minute in the reperfusion period)	265.95±62.46	401.20±59.60	<0.001
Creatinine (mg/dL) (Pre-ischemic period)	1.15±0.08	0.93±0.04	<0.001
Creatinine (mg/dL) (20th minute in the reperfusion period)	1.25±0.12	1.10±0.07	<0.001
Creatinine (mg/dL) (48th hour in the postoperative period)	1.16±0.14	1.03±0.11	0.003
pH (Pre-ischemic period)	7.25±0.41	7.29±0.05	0.565
pH (20th minute in the ischemic period)	7.24±0.03	7.31±0.03	<0.001
Hct (Pre-ischemic period)	31.95±2.52	26.95±2.37	<0.001
Hct (20th minute in the ischemic period)	30.45±1.67	25.60±6.09	<0.001

* Statistically significant values, pH: blood acidity
BUN: blood urea nitrogen; Creatinine: serum creatinine; pCO_2: arterial partial carbon dioxide pressure; pO_2: arterial partial oxygen pressure; Glucose: blood glucose; Hct: blood lactate and hematocrit

favorable effects on renal ischemia. However, it has been reported that oral administration might presystemically and systemically be largely eliminated by bacteria and arginases (18).

While adenosine triphosphate (ATP) decreases due to renal ischemia, ATP products such as adenosine, inosine, and hypoxanthine increase (11, 12). Endothelium injury in renal ischemia leads to an increase in vasoconstrictor substances such as endothelin but a decrease in vasodilator substances such as NO (19). Lopez-Neblina et al. (20) conducted a study in rats and demonstrated that nitroprusside has a protective effect on serum creatinine level but that this protective effect is not observed with L-arginine. There are studies reporting that NO-dependent improvement in I/R depends on intact endothelium as well as L-arginine consumption.

Procedures that focus on reducing renal ischemia or metabolic needs during ischemia are implemented to preserve renal functions during aortic surgery in humans. It is stated that enhancing cardiac performance, low-dose dopamine support, hypothermia, and using vasodilator and antioxidant drugs play a protective role against the development of renal complications (21).

CONCLUSION

The present study determined fewer histopathological changes and lower mean scores in the L-arginine group compared with those in the control group in the rabbits in which a renal ischemia–reperfusion model was created by aortic clamping (2.60±0.68 vs. 3.2±0.89, respectively; p=0.022). Moreover, a statistically significant decrease was observed in terms of 48th hour BUN and serum creatinine levels in the L-arginine group compared with those in the control group (55.85±14.92 vs. 94.50±28.66, respectively; p<0.001) (1.03±0.11 vs. 1.16±0.14, respectively; p=0.003). Based on the data and results of the present study, it can be suggested that L-arginine, which is administered as an intravenous infusion over the course of the renal ischemic period, protects the kidneys from I/R injury.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Selçuk Üniversitesi Meram School of Medicine.

Informed Consent: Due to the experimental animal study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.Ö.; Design - M.Ö.; Supervision - M.Ö.; Resource - M.Ö.; Materials - M.Ö.; Data Collection and/or Processing - M.Ö.; Analysis and/or Interpretation - F.A.; Literature Review - M.Ö.; Writer - F.A.; Critical Review - F.A.; Other - F.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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