ORIGINAL RESEARCH

The utilization of c-type natriuretic peptide levels on experimental muscle and kidney ischemia/ reperfusion model

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Abstract

Introduction

C-type Natriuretic Peptide (CNP) is the third natriuretic peptide (NP) identified from the nervous system and endothelial cells. CNP is believed to be produced locally in tubular cells and glomeruli of kidneys. We aim to determine the clinical value of CNP levels at lower extremity muscle ischemia/reperfusion (I/R), kidney I/R, and both I/R models and evaluate them in laboratory practices.

Method

This study is an original experimental study and was carried out on a total of 40 rats. (8-12 weeks and 321±69 gr). The rats were assigned into 5 groups, each containing 8 rats. CNP levels in the plasma were evaluated in the control group. CNP and muscle biopsies were held after ischemia/reperfusion from the left lower extremity in Group E and bilateral muscle ischemia/reperfusion in Group BE. CNP and renal biopsies were held after right nephrectomy+left renal I/R at Group R. CNP, muscle, and renal biopsies were held after right nefrectomy+left renal ischemia+bilateral renal ischemia in Group BER.

Results

The plasma level of CNP in the control group was determined as 144.99±33.04 pg/ml. There was no significant difference between groups at plasma CNP levels in predicting ischemia. Although in terms of reperfusion between Control-Group E, Control-Group BER, Group E-Group BE, Group E-Group R, Group BE-Group BER, Group R-Group BER; statistical significance was determined ($p<0.05$).

Conclusion

This study suggests that as a laboratory test, the endothelial-derived vasodilator CNP level cannot predict the location and degree of muscle and renal ischemia at the specified time. Similarly, the CNP level is valuable in evaluating adjunct muscle reperfusion to renal reperfusion. As a result, CNP levels may not be useful in predicting ischemia at a particular period, but they can be used to predict reperfusion.

Keywords: Plasma, natriuretic peptide, C-type, ischemia, reperfusion injury, muscles, kidney

Introduction

Acute lower extremity ischemia is a serious problem that causes morbidity and mortality. However, the risk of morbidity and mortality continues after reperfusion formation and disappearance of ischemia. Lower extremity ischemia/reperfusion (I/R) injury leads not only local effects in musculoskeletal tissue and vessel endotel but also systemic effects in varied tissues primarly lung, heart, brain and kidney[1].

I/R injury is characterized by microvascular dysfunction, in particular, the loss of endothelium-derived dilators, such as nitric oxide (NO) and prostacyclin, that results in capillary constriction and decreased perfusion, increased fluid and cellular extravasation, and leukocyte plugging. Hence, considerable attention has focused on identifying endogenous pathways and therapeutic interventions that prevent or reverse microvascular dysfunction and thereby minimize I/R injury[2,3].

The Natriuretic Peptide (NP) system is a family of hormones with similar molecular structure and physiological function involved in regulation of blood pressure, electrolyte, and volume homeostasis[4]. Natriuretic peptides are secreted by

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the heart and vascular structures; their diuretic, natriuretic and vasodilator specialities relieve the load of insufficient heart. A type Natriuretic Peptide (ANP) is especially secreted from atrial wall as a response of atrial expansion. Brain Natriuretic Peptide (BNP) is synthesized from ventriculer muscle according to increased end diastolic pressure and volume[5]. Moreover, NP system also plays a significant role in inhibiting vascular remodeling after injury. The major sites of CNP expression are the nervous system and endothelial cells. In addition, CNP is believed to be produced locally in tubular cells and glomeruli of normal human kidneys. Therefore, it is thought that CNP production in the kidney may be affected by the effect of ischemia due to vascular occlusion in the renal artery. CNP provides vasodilatation of afferent arterioles via the release of cGMP and nitric oxide [endothelial-derived relaxing factor (EDRF)], and vasoconstriction of efferent arterioles selectively, which may attribute to the varied distribution of NP receptors in kidney[4].

CNP is a hormone secreted from endothelial cells after shear stress (5). CNP has anti-proliferative and anti-migratory functions and also identified as an EDRF. Furthermore, CNP inhibits neointimal restenosis, reduces vascular constrictive remodeling and cardiac I/R injury. In addition, CNP is also responsible in the development of atherosclerotic plaque formation[6,7]. The main function of CNP is vasodilatation in response to injury and suppressing reactive smooth muscle cell proliferation and intimal growth at blood vessels[8-10].

The primary hypothesis of this study is that CNP can serve as a diagnostic measure for extremity ischemia. The primary outcome is to detect changes in CNP during lower extremity I/R damage. Its secondary outcome is to identify the CNP alteration in renal and renal+bilateral lower extremity I/R injury. In this study, we investigate the CNP levels during the critical times of peripheral and renal I/R and combination of both at inducible experimental rat models.

Materials And Methods

In this interventional animal study, 40 male Wistar Albino rats (aged 8-12 weeks and weighting 321±69 g) were included to study. The ethical approval confirmed from institutional ethics committee of Giresun University. The animals were obtained from the same unit, and kept in standard temperature (22±2 0C) and humudity (50±5 %) at conventional animal house with a 12–12 h light–dark cycle and free access to food and water during the study. After the research, all rats were anesthetized and then killed by cervical decapitation. 2 of 5 rats died during anesthesia, and 3 rats died during renal and renal+bilateral muscle ischemia. The other rats were divided into five groups, each containing 7 rats.

During the interventions, the rats were anesthetized with 50 mg/μl (8.5 cc) of ketamine hydrochloride (HCL) (Ketalar®, Pfizer, Inc., İstanbul, Turkey) and 23.32 mg/ml (1.5 cc) of Xylasine (Rompun®, Bayer Healthcare AG, Leverkusen, Germany) at the amount of 0.3-0.5 cc via intraperitoneal line. Vital parameters were followed observational during anesthesia. Extremity was ligated with number 0 silk suture at the level of the femoral artery to form the lower extremity ischemia (Figure1). Cyanosis and coldness of the extremity were followed during ischemia. The abdomen was opened with a median incision to achieve renal ischemia. The right kidney was ligated at the level of artery-vein entrance to perform, and a nephrectomy was achieved. Left renal artery-vein explored and ischemia performed with 3/0 prolen suture (Figure2).

We used the jamming suture technique to reduce the endothelial damage during the I/R procedure. The discoloration of the kidney was seen directly. 1 ml of a blood sample after ischemia obtained from inferior vena cava. We used the inferior vena cava approach because the abdomen was already opened, and the blood sampling was performed before sacrification in the others. In the control group, abdomen was opened with median incision after anesthesia to obtain 3 ml of blood sample from heart and than rats were sacrificed.

The following procedures were applied below to the groups consecutively:

Group C (Control)

(n=7): The baseline characteristics of the CNP levels were determined without any application in this group. Intracardiac blood samples were obtained from each rat, and then all were sacrificed.

Group E

(Extremity) (n=7): Ischemia performed during 4 hours by ligating left lower extremity rat femoral level. 1 ml of blood was collected after waiting the tail in hot water. 1 cm vertical incision was performed at surgical site and soleus muscle biopsy was performed. Reperfusion was achieved during 30 minutes after ischemia by eliminating extremity tourniquet. Soleus muscle biopsy was performed after reperfusion. Rats were sacrified after 3 ml intracardiac blood extraction. CNP was studied from this collected blood.

Group BE

(Bilateral Extremity) (n=7): We used the same procedures of Group 1 to both lower extremities.

Group R

(Renal) (n=7): Abdomen was explored after median incision. Right kidney was removed. Ischemia was performed during 1 hour by ligating the left renal artery. 1 ml blood was obtained from the inferior vena cava after the ischemia to research CNP. Reperfusion was achieved during 90 minutes. Kidney biopsy was performed. Rats were sacrified after 3 ml intracardiac blood extraction.

Group BER

(Bilateral Extremity+Renal) (n=7): We used the same procedures of Group 3 in addition of both lower extremities.

All blood samples were emplaced to citrated tubes and centrifuged at 4000 rpm and 4 ºC during 15 minutes. The plasma was subsequently transferred into small microcentrifuge tubes (Eppendorf AG, Hamburg, Germany) and stored at -80 ºC until further processing.

Plasma CNP levels were determined by enzyme linked immunosorbent assay [Rat CNP (C-type natriuretic peptide) ELISA Kit, Catalog No: E-EL-R0284, WuHan, Hubei Province]. Rat CNP levels were expressed as pg/ml.

Histopathological Assessment

Necrosis was unable to observe between groups at the sampled muscle tissues. Mild hyalinization was determined at the tissue surface (Figure 3). Renal tissue was fixed at %10 tamponed neutralized formaldehyde solution. Paraffin blocks were prepared for samples. Sections were obtained from paraffin blocks by aid of microtoms and stained with

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hematoxilyn and eosin (H&E). Histopathological assessment was performed with light microscope. Renal tissues was explored for tubular necrosis-atrophy, glomerular injury, vascular congestion-thrombosis and interstisial inflammation (Figure 4). Histopathological score was evaluated (Table 1).

Methods of Measuring CNP Levels

There are two kinds of immunoassays to evaluate cardiac natriuretic peptides: Competitive (RIA, enzyme immunoassay, luminescence immunoassay, etc) and noncompetitive (two-site IRMA, ELISA, immunoluminometric assay, etc). Their analytical characteristics and clinical relevance are different. Developing sensitive, precise, and accurate immunoassays for cardiac natriuretic peptides is difficult because of their low concentrations (on average, approximately 3-6 pmol/L) in healthy subjects and their structural, metabolic, and physiological characteristics. Competitive assays have historically suffered from lack of sensitivity and specificity for the biologically active peptides. These usually require tedious extraction procedures prior to analysis. Recently, immunometric assays have been developed with high sensitivity and specificity and appear to be the methods of choice at future[11].

Statistical analysis

Values were presented as mean±standard deviation (SD). Statistical analysis was performed with the SPSS version 21.0 for Windows software program (SPSS Inc., Chicago, IL, USA) and a p value of <0.05 was established as the threshold for significance. One way ANOVA test was performed to establish normalization of all groups and because of homogeneous variance of groups for determining diffrences between groups CNP levels at ischemia. Kruskal-Wallis test was used to evaluate any difference between groups in terms of CNP value for reperfusion process. Mann-Whitney test was used to determine which groups causes the diversity.

Results

Ischemia and reperfusion supporting evidences was determimed in the muscle tissue histopathologically. Periodic acid-Schiff (PAS) stain was applied to investigate hyalinisation in ischemia. Trichrome stain was performed to differantiate tissue characteristics and the presence of fibrosis. Tissue fibrosis was not observed. Acute inflamation evidences was not observed due to consistent of ischemia duration.

Mild dilatation was observed at glomerular capillary and Bowman's Capsule. Hemorrhage and congested vessels was observed at all renal sections. Hyalinised material was seen at tubule lumens at some sections (cast formation). Mean histopathologic scores of group 3 and 4 were 7.42 and 7.71.

There was no difference between groups in terms of CNP at ischemia with %95 confidence ($p=0.465$, $>\alpha=0.05$). There was a significant difference between groups at reperfusion with %95 confidence ($p=0.009$, $<\alpha=0.05$).

It was determined that to predict ischemia for muscle and kidney the use of CNP levels was not appropriate for clinic and laboratory practice. Whereas to predict reperfusion difference between the groups was seen as shown in Table 4. CNP was statistically significant to determine unilateral lower extremity reperfusion, although unable to determine bilateral lower extremity+kidney group. CNP was statistically significant in bilateral lower extremity reperfusion in comparison with unilateral lower extremity and bilateral lower extremity+kidney groups. CNP was also statistically significant in kidney reperfusion in comparison with unilateral lower extremity and bilateral lower extremity+kidney groups.

Table1. Histopathologic assessment score of Group R and BER at reperfusion

H&E	R/1	R/2	R/3	R/4	R/5	R/6	R/7	BER/1	BER /2	BER /3	BER /4	BER /5	BER /6	BER /7
tub.dil	1	1	1	1	2	2	1	1	3	1	1	1	0	1
cel.deg	1	1	1	1	1	1	1	1	1	1	1	1	1	1
con.tro	3	2	2	3	3	3	2	2	2	2	2	3	3	3
cast fr	2	1	1	1	2	2	2	2	2	2	1	2	1	2
atr.tub	0	0	1	1	0	0	0	1	0	1	0	0	0	1
intes.inf	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Glo.chan	1	1	1	1	1	1	1	1	1	1	1	1	1	1

H&E: hematoksilen eozin, tub.dil: tubuler dilatation, cel.deg: celluler dilatation, cast fr: cast formation, atr.tub: atrophic tubules, intes.inf: interstisiel inflammation, glo.chan: glomeruler changes, R/: Rat of Group R, BER/: Rat of Group BER, (0) normal, (1) mild, (2) moderate, (3) severe, (4) extremely severe

Table 2. Variations in serum C-type natriuretic peptide levels in prolonged ischemia and reperfusion

Groups	Control	Group E	Group BE	Group R	Group BER
Ischemia Mean±Sd CNP (pg/ml)	144.99±33.04	115.79±28.84	189.25±34.63	136.06±24.08	112.06±38.69
Reperfusion Mean±Sd CNP (pg/ml)	144.99±33.04	41.99±18.07	187.10±58.07	140.97±37.19	49.47±13.46

Sd: Standard deviation

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Table 3. Comparison between groups for ischemia-reperfusion in terms of CNP levels

Groups	Group E	Group BE	Group R	Group BER
p	0.128	**0.027***	0.867	0.211
Test	Wilcoxon test	Dependent t-test	Dependent t-test	Dependent t-test

Table 4. Comparision between groups for reperfusion in terms of CNP levels

Groups	p
Control-Group E	**0.038***
Control-Group BE	0.710
Control-Group R	0.902
Control-Group BER	**0.026***
Group E-Group BE	**0.004***
Group E-Group R	**0.038***
Group E-Group BER	0.259
Group BE-Group R	0.710
Group BE-Group BER	**0.017***
Group R-Group BER	**0.038***

*statistically significant

Figure - 1

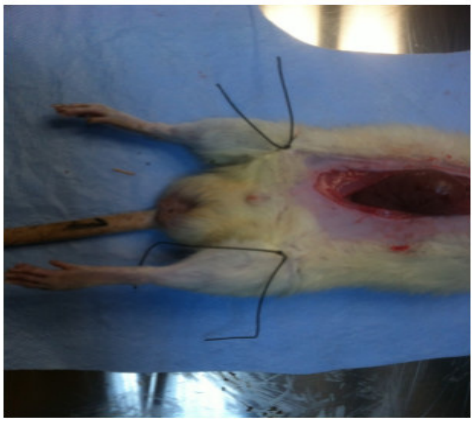

Figure 1. Lower extremity ischemia with silk suture 0

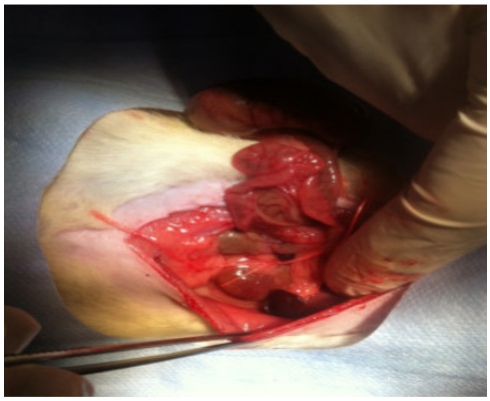

Figure 2. Renal ischemia with prolene suture 3/0

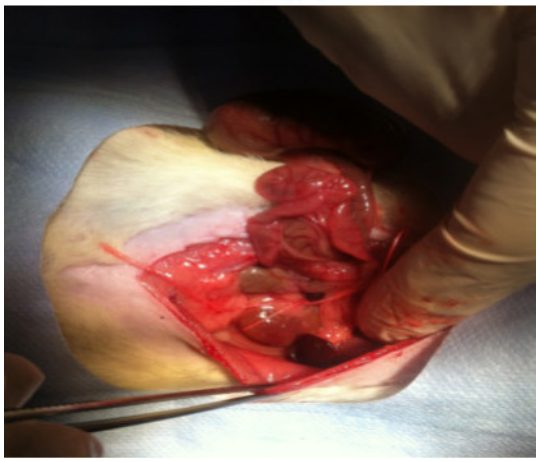

Figure 3. Mild hyalinization was determined at the tissue surface

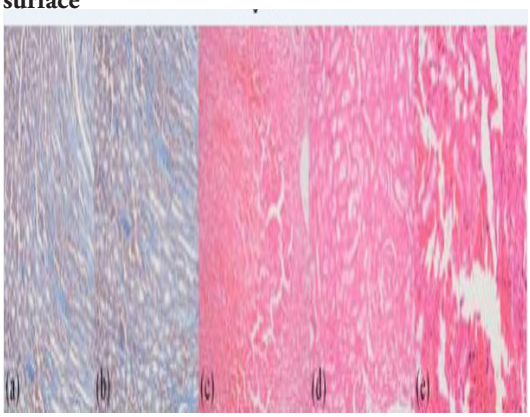

Figure 4. Renal tissues was explored for tubular necrosis-atrophy, glomerular injury, vascular congestion-thrombosis and interstisial inflammation

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In the muscle groups; CNP was important to determine unilateral lower extremity reperfusion, although unable to determine bilateral lower extremity reperfusion due to compensation mechanisms. The statistically difference between Group 1 and Group 2 indicated the importance of CNP in unilateral-bilateral lower extremity reperfusion.

In the kidney groups; CNP value was insignificant in solely kidney reperfusion group. In the bilateral lower extremity group, CNP was unable to determine bilateral lower extremity reperfusion due to compensation mechanisms.

Discussion

The study revealed that there was no significant increase in CNP levels in cases of bilateral lower extremity and isolated renal ischemia and reperfusion. It was found that there was no significant alteration in CNP levels in cases of unilateral lower extremity and bilateral lower extremity renal ischemia. However, there was a significant decrease in CNP levels during reperfusion.

Clinically, ischemia/reperfusion (I/R) injury is a life-threatening vascular crisis and frequently occurs after acute mesenteric ischemia, shock, and major operations. It is known that tissue damage caused by I/R is not limited to the area where ischemia occurs, but also causes varying degrees of damage to other organ systems. I/R injury is a major problem frequently encountered in vascular surgery. Acute I/R injury of lower extremity usually occures while temporarily cross-clamping of the abdominal aorta. Ischemic area may lead local tissue injury at lower extremity and also remote organ injury. Kidneys are the target organs especially after I/R periods at lower extremity and this situation is clinically considerable[12,13].

CNP is a recently discovered member of the natriuretic peptide family that shares similar properties in terms of its structure and function. Nevertheless, CNP exhibits a reduced blood concentration and a shorter circulatory half-life as a result of its release from the vascular endothelium[14,15]. There are studies in the literature that examine the impacts of natriuretic peptides, other than CNP, in different models of ischemia. Nevertheless, there are limited studies demonstrating the impact of CNP on I/R injury[15-17].

In vascular surgery, ischemic period at lower extremity vessels and renal artery level of abdominal aorta leads rising of certain biochemical parameters in blood. Caliskan et al.[15] revealed CNP levels at plasma to be increased significantly depending on time with femoral artery ischemia at rats. In our study, it was found that CNP levels in blood samples taken at the 4th hour of lower extremity ischemia increased only in the group with bilateral lower extremity ischemia, and decreased in unilateral ischemia. However, since these differences were not statistically significant, it was concluded that CNP at the 4th hour of lower extremity ischemia would not be diagnostically significant. The study conducted by Caliskan et al.[15] evaluated the levels of CNP at 2, 5, and 8 hours of ischemia in the unilateral femoral artery ischemia model. The results showed a substantial increase in CNP levels as the duration of ischemia increased. In contrast to the findings of the present study, our research revealed a decrease in the phenomenon during the fourth hour of bilateral lower extremity ischemia and an increase in the same at the same time. Nevertheless, considering the lack of statistical significance in these changes, it was determined that CNP does not possess diagnostic value for lower extremity ischemia. The findings derived from our investigation align with those of Çalışkan et al. The discrepancy between the findings of the study conducted by[15] and the diagnostic efficiency of CNP in ischemia reveals a dispute nature. Given the paucity of research on this topic, it is evident that a large number of clinical and experimental studies are required to ascertain the diagnostic significance of CNP.

Tokudome et al. [18] reported in the literature that endogenous ANP and BNP had a reconstructive impact on vascular remodeling in limb ischemia. In the same way, Park et al.[19] documented that ANP effectively restored angiogenesis, which had been impaired by ischemia, in a model of extremity ischemia performed on diabetic mice. Based on the existing research, it is evident that ANP and BNP have a beneficial impact on vascular remodeling in cases of limb ischemia. Due to limited research on the impact of CNP on extremity ischemia and inconsistent findings, the conclusive demonstration of CNP's influence on ischemia remains uncertain. The findings derived from our investigation did not yield adequate evidence for the utilization of CNP in clinical settings for assessing the state of ischemia. Given that CNP has a lower concentration and shorter blood circulation half-life compared to other natriuretic peptides, our study did not find any evidence to support its use as a diagnostic parameter in the early stages of ischemia. This is because we only measured CNP levels at the 4th hour of limb ischemia in our study. Given the characteristics of CNP, its levels can be utilized as an early diagnostic measure for ischemia and can provide information on its physiological effects. Insufficient data exists on the role of CNP in peripheral ischemia situations, and there is a lack of information regarding its impact on cardiac illnesses[19]. Passino et al.[20] observed that the reduction in CNP levels following exercise in individuals with heart failure could indicate an improvement in endothelial function. Our work indicates that there is a significant decrease in CNP levels, which may serve as a protective mechanism to compensate for renal ischemia reperfusion injury in the presence of bilateral lower limb ischemia reperfusion. Nevertheless, definitive evidence could not be acquired to reveal the underlying mechanism.

The existing literature does not have sufficient data to clarify the mechanism by which CNP acts in renal I/R injury. A study conducted by Jin et al.[21] found that intravenous injection of CNP suppressed apoptosis and oxidative stress pathways. Our investigation revealed that there was no notable alteration in CNP levels during renal I/R injury alone. However, a significant reduction in CNP levels was detected when renal I/R injury was paired with lower extremity I/R injury. We included renal ischemia in our analysis along with bilateral lower extremities ischemia since the kidney can also be affected when there is a blockage in the blood vessels at a higher level. Given the knowledge that CNP is also secreted in renal tubule cells, it was hypothesized that this could result in elevated CNP concentrations. However, the findings of our investigation did not support this idea. This situation is believed to be a defensive mechanism whose underlying mechanism remains unknown. Due to insufficient literature data on the effects of CNP in renal I/R, we were unable to compare our study results. The findings from our investigation indicate that CNP does not possess any diagnostic value in assessing the status of renal ischemia/reperfusion. Nevertheless, there is a belief that the reduction in CNP levels could be useful for diagnosing bilateral lower-

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extremity reperfusion injury caused by proximal aortic stenosis, which might affect the renal artery.

This investigation utilized a 4-hour limb ischemia model to investigate the onset of structural abnormalities in the muscle, which typically occur after the 4th hour. Additionally, changes in the CNP level within this time frame were expected[22,23]. Elective abdominal aortic surgery frequently leads to acute renal failure. The primary mechanism underlying acute renal failure is dependent on reperfusion, with ischemia also playing a significant role. In this investigation, we used a 1-hour ischemia and 90-minute reperfusion model, which is consistent with other findings in the literature[24-31]. This model allowed us to examine the release of CNP from renal tubule cells. This study also assessed the impact of renal-derived CNP on bilateral lower limb ischemia caused by aortic stenosis coming from the supraaortic level.

Blood supply, vascular resistance and hemodynamic variations are regulated by sensitive interactions between the heart and kidneys. Ischemic muscles may trigger the release of substances via humoral or neutrogenic pathways[32]. Catecholamines and other mediators may released by the intramyocardial sympathetic system. During the chronic or prolonged ischemia, these pathways are activated by integrating ischemic preconditions or adaptive mechanisms during low perfusion[33]. Lack of variations in terms of reperfusion between control group and kidney+ bilateral muscle ischemia groups, suggests these mechanisms come into play a role. The difference between muscle and kidney in terms of reperfusion for CNP levels, exposes a valuable evidence in clinical and laboratory practise. CNP level may also valuable even if the severity of reperfusion increases at muscle (bilateral muscle I/R). Similarly, CNP levels are significant to evaluate in addition of kidney reperfusion to muscle reperfusion.

Conclusion

There is substantial evidence in the literature indicating that ANP and BNP, which are two types of natriuretic peptides, can be utilized for the assessment of I/R injury. Nevertheless, there is a scarcity of studies elucidating the impact of CNP, a novel member of the natriuretic peptide family, on I/R injury, and its underlying mechanism remains unknown. Based on the findings of this investigation, it was determined that CNP is not an useful diagnostic measure for unilateral and bilateral extremities and renal ischemia. However, it is believed that the reduction in CNP levels in instances of unilateral lower limb and renal ischemia, as well as bilateral lower extremity reperfusion, can serve as a diagnostic criterion in assessing I/R injury. Nevertheless, we assert that additional extensive clinical and experimental investigations are necessary to discover the precise mechanism by which CNP acts. Based on the findings of this experiment, we believe that CNP can serve as a diagnostic parameter in clinical settings for cases of bilateral lower extremities I/R injury caused by occlusions at the unilateral lower extremity and suprarenal aortic level.

Limitations of this study;

1. It is an experimental study

2.Absence of CNP levels in the early stages of ischemia

3.Renal compensatory mechanisms cannot be revealed

Ethics

I and all authors have no conflict of interest

I and all authors have no financial support

Declaration of conflicting interests:

In this study, datas of 'SAĞ-BAP-A-250414-78' numbered Project of Giresun University used which was carried out by me. Additionally this article was presented as an oral presentation in 12th International Congress of Cardiology and Cardiovascular Surgery (2016, 10-13 March) and awarded with the 2nd best oral presentation prize.

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