Physiology and Pharmacology 26 (2022) 168-177
Original Article

Time course of renal ischemia/reperfusion and distance organ: lung dysfunction in male and female rats

Fariba Azarkish[1], Ali Atash Ab Parvar[2], Mehdi Nematbakhsh[3], Aghdas Dehghani[4*]

1. Molecular Medicine Research Center, Hormozgan Health Institute, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
2. Department of Pathology, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
3. Water and Electrolytes Research Center/Department of Physiology, Isfahan University of Medical Sciences, Isfahan, Iran
4. Endocrinology and Metabolism Research Center/Department of Physiology, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran

ABSTRACT

Introduction: Renal ischemia/reperfusion injury (IRI) may influence distance organ such as lung. The severity of IRI induced- lung insult can be affected by gender and reperfusion time alteration. The aim of this study was to determine gender differences in renal IR induced-lung injury in different reperfusion time.

Methods: Eighty male and female rats were assigned into 8 groups, 4 groups in each gender including: sham, renal ischemia for 45min by clamping renal vessels followed by 3, 24 or 48h reperfusion. Blood samples were obtained for measuring the serum level of blood urea nitrogen (BUN), creatinine (Cr), nitrite and malondialdehyde (MDA). The kidneys and lung tissues were removed and used for MDA and nitrite measurements and the histological changes evaluation. The lung water content was calculated.

Results: In both genders, the rise in Cr and BUN reached the peak at 24h reperfusion. A significant increment was seen in female serum level of nitrite compared with males after 3h reperfusion. The renal MDA level of male increased during 3h reperfusion but not seen in females. The enhanced lung and renal tissues damages were depended to reperfusion time in both genders. The water content of lung was reduced in 3h of reperfusion groups.

Conclusion: Sex effects and the time of reperfusion may be the important factors to consider clinical therapeutic of renal IRI as well as its impact on remote organs.

Keywords:
Renal ischemia-reperfusion
Lung
Gender
Distant organ

Introduction

Renal ischemia/reperfusion injury (IRI), the most frequent devastating complication of hospital care, may lead to acute kidney injury (AKI) (Granger and Kvietys, 2015). In the post-ischemic kidney, the release of vasoconstrictive agents increases and vasodilatory responses decrease. For example, endothelial nitric oxide synthase (eNOS) function is mostly lost following a renal ischemic injury (Tripatara et al., 2007). In addition, the reoxygenation process during the reperfusion period contributes into more pathological conditions by releasing reactive oxygen species and inflammatory factors in cir-

* Corresponding author: Aghdas Dehghani, aghdas.dehghani@hums.ac.ir
Received 19 November 2020; Revised from 18 April 2021; Accepted 14 June 2021

Citation: Azarkish F, Atash Ab Parvar A, Nematbakhsh M, Dehghani A. Time course of renal ischemia/reperfusion and distance organ: lung dysfunction in male and female rats. Physiology and Pharmacology 2022; 26: 168-177. http://dx.doi.org/10.52547/phypha.26.2.3

culation leads to kidney tissue damage and distant organ failure (Abogresha et al., 2016; Granger and Kvietys, 2015). So, the impact of renal IRI on remote organs such as lung, brain, liver, heart and gut is well recognized in patients with AKI, resulting in high rate of morbidity and mortality (Abogresha et al., 2016; Kao et al., 2019). The lung capillary network is known as a complex system. The increasing of pulmonary vascular permeability, interstitial edema, alveolar hemorrhage and existence of leukocytes in lung occure after renal IRI. Additionally, the *mortality rates* for *AKI combined* with acute *lung injury* reported to be about 80% (Doi et al., 2011; Paladino, 2009). It was indicated that the incidence, prevalence and progression of renal IRI induced-AKI are altered by gender (Kher et al., 2005; Neugarten et al., 2018). Some previous studies have reported that female is more resistant to renal IRI compared with male (Ibrahim et al., 2013; Tanaka et al., 2017). In this regard, estrogen, the most effective factor in progressing ischemic insult that may cause these differences. Moreover, the antioxidant function and chiefly activation of antioxidant enzymes like superoxide dismutase, have been documented in some studies (Barp et al., 2002; Lean et al., 2003). This sex hormone could also enhance synthesis of NO and consequently the renal blood flow would increase (Ibrahim et al., 2013). Muller et al. in their study have reported that renal blood flow recovers slowly after IRI in male due to more increase of renal vascular resistance compared to female (Müller et al., 2002).

There is a growing number of evidences on the severity of kidney and lung injury after renal IRI that can be affected by reperfusion time alteration. Initially, the deterioration of renal function was less apparent for several hours, while a rapid change occurred after 24h (Campanholle et al., 2010; Ko et al., 2017). However, another study indicated that the most severely injured period was associated with 48h reperfusion time (Wei and Dong, 2012). Moreover, others studies have examined the side effects of renal IRI on lung tissue during different time periods of reperfusion process in male rat. As a result, they found the majority of damages by passing 24 and 48h from the reperfusion process (Campanholle et al., 2010; Kramer et al., 1999).

Regarding gender differences in renal IRI and lung disturbances, the mechanism of renal IR induced- lung injury in male and female cases needs to be more investigated. In addition, it was shown that the severity of IRI induced- lung injury can be affected by reperfusion time alteration. Therefore, this study aimed to investigate gender differences in IRI induced- lung injury in different reperfusion time durations.

Materials and methods

Experimental animals and ethical approval

Eighty male and female Wistar rats (weighting 230±20g) were maintained at a constant temperature of 23-25ºC and 12h light/dark cycle. The rats were fed with rat chow and water *ad libitum*. The rats were purchased from Animal House of Hormozgan University of Medical Sciences, Bandar Abbas, Iran. The protocol of experiment was approved in advance by the Hormozgan University of Medical Sciences Ethics Committee (HUMS.REC.1396.138). The research was conducted in accordance with the internationally accepted principles for laboratory animal use and care as found in the US guidelines (NIH publication #85-23, revised in 1985).

Research design

The animals were randomly assigned into 8 experimental groups, n=10 in each groups, (4 groups of male and 4 groups of female. Group1 (sham): male rats were exposed to surgery without ischemia process. Groups 3, 5 and 7 (named ISC3hr, ISC24hr, and ISC48hr): male rats were subjected to renal ischemia with 3, 24 or 48h reperfusions respectively. Groups 2, 4, 6 and 8 were subjected to same procedure of the groups 1, 3, 5 and 7 respectively except female rats used instead of male. For renal ischemia induction, the animal's body weights were measured and they were anesthetized, the kidneys were carefully excised. Special care was done to avoid damage to the organs. The both kidney arteries and veins were occluded for 45min by clamping.

The occurrence of ischemia was visually confirmed by the observation of renal blanching. After 45min, the clamps were removed with care to initiate kidney reperfusion. The kidneys were observed for about 10min to ensure reperfusion. The animals that didn't have adequate restoration of blood flow into kidneys were excluded from the study. Then, the skin and tissue were sutured and the animals were kept in the animal room under direct observation for 3, 24 and 48h as assigned. At the end of reperfusion times, the animals were anesthetized again and the blood samples were obtained via heart puncture. Blood samples were centrifuged at

2500g for 10min to obtain serum samples for measuring the serum level of blood urea nitrogen (BUN), creatinine (Cr), nitrite and malondialdehyde (MDA). Serum samples were sorted at -80ºC until measurement.

Preparation of kidney and lung tissue

The kidneys and lung tissues were also removed and weighted immediately. The kidney weight was normalized to the body weight and reported as kidney weight/100g of body weight. The right kidney and lung tissues were fixed in 10%formalin for histopathological investigation. The removed left kidney was transferred into liquid nitrogen very quickly and then was stored at -80ºC refrigerator until measurement. In addition, a small part of kidney and lung tissues were weighted, homogenized and centrifuged at 15,000g for 2min and the supernatant was used for MDA and nitrite measurements.

To evaluate the effects of IRI on lung histology, the right bronchi was tied with 3-0 silk and one needle was placed in the right bronchi. Then, 1ml of 10% formalin was instilled into the right lung to achieve inflation *ex-vivo*. Finally, it was removed and again fixed in 10% formalin for pathological examinations. To determine lung water content (index of edema), a sample of left lung tissue was taken and immediately weighed as lung wet weight.

Measurement of pulmonary water content

Pulmonary edema was measured by determination of lung water content. The left lung was dried in the oven under 100°C for at least 48h until constant weight was obtained. The percentage of lung water content was calculated by the following formula:

Water content% = [(lung wet weight– lung dry weight)/ lung wet weight]× 100

Biochemical assay

The serum levels Cr and BUN were determined using quantitative diagnostic kits (Pars Azmoon, Iran). Serum and kidney nitrite levels (stable metabolite of NO) were measured using an assay kit (Promega Corporation, USA). The nitrite concentration of samples was determined by comparison with the nitrite standard reference curve. The serum and kidney levels of MDA were quantified according to the thiobarbituric acid method (Kei, 1978).

Histopathological procedures

The kidney and lung tissues were fixed in 10% formalin solution and embedded in paraffin for histopathological staining. The hematoxylin and eosin stain was applied, and to determine the kidney damage, presence of tubular atrophy, ischemic necrosis, inflammation, vessels congestion, hyaline casts, vacuolization and debris were evaluated. Based on the damage intensity and damage percentage, the samples were scored as 1-4 while score zero was assigned to normal tissue. To determine the lung tissue damage, presence of congestion, inflammation and fibrosis were evaluated and graded.

Statistical analysis

The data are presented as mean±SEM. Differences among groups in serum levels of BUN, Cr, NO and MDA, kidney levels of MDA and NO, kidney weight and lung water content were compared with each other by two-way ANOVA followed by the Tukey post hoc test. In addition, the independent t-test was used for comparisons between male and female within ischemia-reperfusion groups. Due to the qualitative nature of scoring, Kruskal-Wallis test was used to compare the pathological damage score of the groups. Values of $P<0.05$ were considered statistically significant.

Results

Effect of reperfusion time on renal function

By compare with sham groups, the renal ischemia animals showed significant enhancement in the serum level of BUN and Cr at 24h reperfusion (Pgroup<0.0001) in both male and female rats (Figure 1). Kidney weights also have an enhancement trend in 3 and 24h after IR; however, after 48h of reperfusion return near basal level in male and female rats.

Effect of reperfusion time on nitrite and MDA level

The significant increase was seen in plasma nitrite level of female rats at 3h reperfusion point (Pgroup$= 0.025$) and a reduction trend was observed following 24 and 48h of reperfusion period compare with sham groups; while, this observation was not occurred in male animals (Pgender$= 0.007$). The nitrite concentration in kidney of both genders was not changed in different time of reperfusion.

To consider of plasma MDA concentration, there isn't any significant difference in 3, 24 and 48h reperfusion

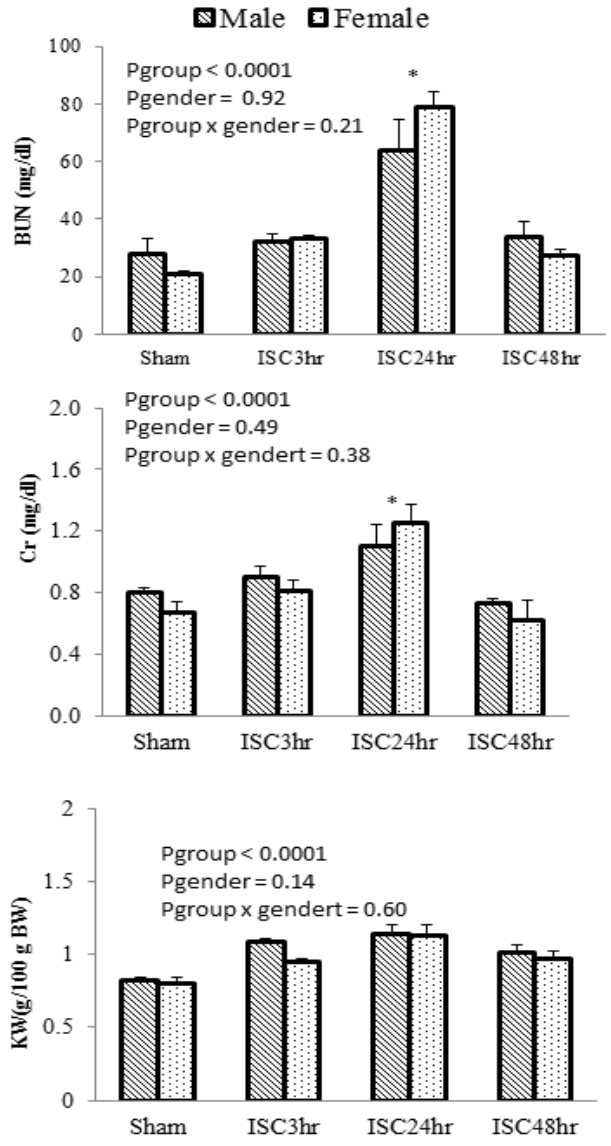

FIGURE 1. The serum levels of BUN and Cr and normalized KW. The P-values were derived from two-way ANOVA. Data are presented as mean±SEM. BUN: blood urea nitrogen; Cr: creatinine; KW: kidney weight. *P<0.05 ISC24hr group vs other groups in both gender. #P<0.05 ISC48hr group vs sham and ISC3hr groups in both gender

groups compare with sham groups in female and male rats. In male rats underwent IRI, we observed a significant difference in renal MDA trend compared with female (*P*gender= 0.033). So that in male rats, the factor increased in 3h reperfusion group then decreased in 24 and 48h reperfusion group (Figure 2).

Effect of reperfusion time on renal and lung histological changes and water content of lung in male and female rats during renal IR

Histology score of kidney obtained from summation of tubular atrophy, ischemic necrosis, inflammation, vessels congestion, hyaline casts, vacuolization and debris. Histological score of kidney was significantly increased during 24 and 48h reperfusion compared with 3h reperfusion and sham-operated groups. This trend was similar in male and female groups (Figures 3 and 4). Histological score of lung was measured (base on intensity of damage) by summation of congestion, inflammation and fibrosis. It was enhanced reperfusion time dependently in both gender especially 24 and 48h reperfusion (Figures 3 and 5). The water content of lung was reduced in 3h of reperfusion then significant increase were observed during 24 and 48h reperfusion in both gender (*P*group = 0.06; Figure 2)

Discussion

The purpose of the present study was to determine the severity of different times of reperfusion process following renal ischemia as well as investigating its impact on kidney and lung histological changes in male and female rats. The peak of the elevation in serum BUN and Cr occurred at 24h reperfusion which, then returned to the normal state by passing 48h from reperfusion in both male and female groups. The renal MDA level increased in 3h reperfusion and then reduced at 24 and 48h time points in male, but not in female rats. The peak of the elevation in serum nitrite level took place in 3h reperfusion in female rats. However, this trend was not observed in male rats. The severity of renal and lung histological damage time-dependently increased in reperfusion phase time dependently in both genders.

As it is well-known, the rise in plasma Cr is typically used as an indicator for the diagnosis of clinical renal IR. In the current research, the peak of the elevation of creatinine occurred by passing 24h from the ischemic injury due to existence of lag period between the onset of renal damage and the following elevation in Cr (Ko et al., 2017). In accordance to our results, the rises in both Cr and BUN reached the peak at 24h reperfusion in both genders. So, it can be said that a change in renal function markers may depend on kidney reperfusion time as well as the mechanism of AKI.

Notably, NO plays an important role in both renal vascular tone and hemodynamics (Reckelhoff et al., 1998). Nitrite is a stable metabolite of NO that involves nearly 70% of oxidative product of NO (Tripatara et al., 2007). It is well documented that there are sex differences in re-

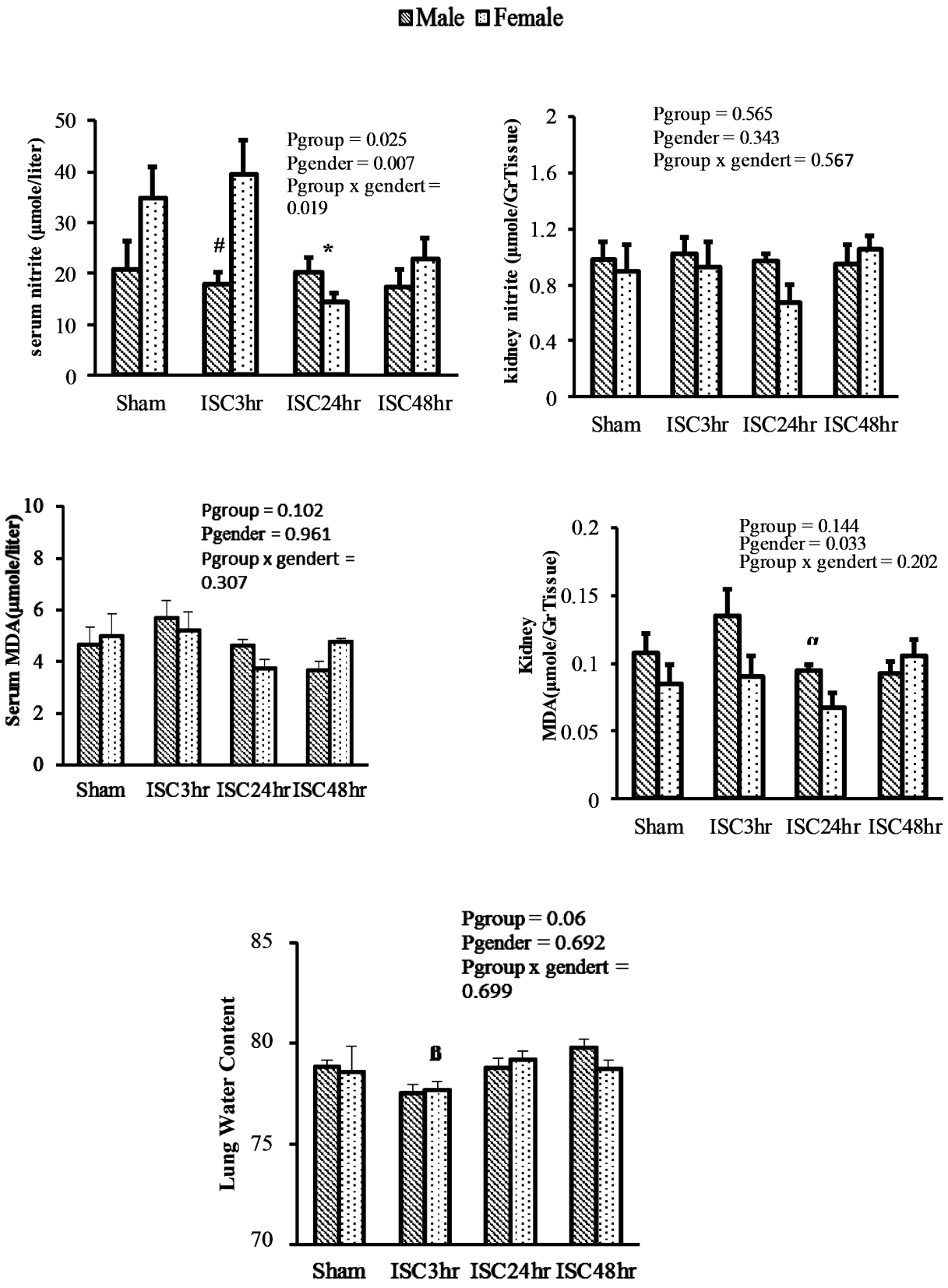

FIGURE 2. The serum and renal levels of nitrite and malondialdehyde (MDA), and lung water content. The *P* values were derived from two-way ANOVA and t-test. Data are presented as mean±SEM. $^{*}P<0.05$ ISC24hr group vs sham and ISC3hr groups in both gender analized by two-way ANOVA and tukey posthoc. $^{\#}P<0.05$ male-group vs female group after 3h reperfusion (ISCH3hr) analized by t-test. $^{\alpha}P<0.05$ male group vs female group after 24h reperfusion (ISCH3hr) analized by t-test. $^{\beta}P<0.05$ ISC24hr group vs other groups in both gender analized by two-way ANOVA and tukey posthoc.

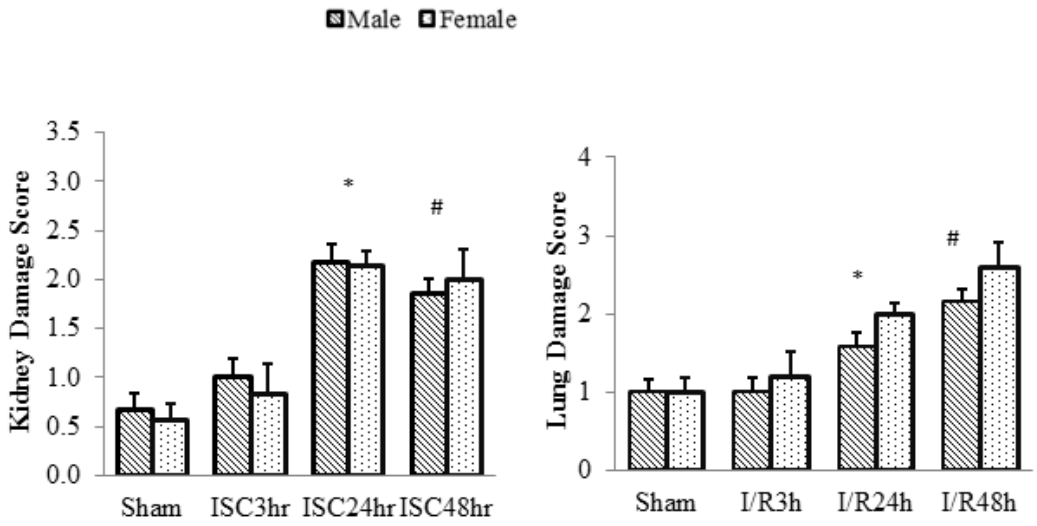

FIGURE 3. Lung and kidney score damage. Data are presented as mean±SEM. The *P* values were derived from Kruskal-Wallis tests. $^{*}P<0.05$ ISC24hr group vs sham and ISC3hr groups in both gender. $^{\#}P<0.05$ ISC48hr group vs sham and ISC3hr groups in both gender.

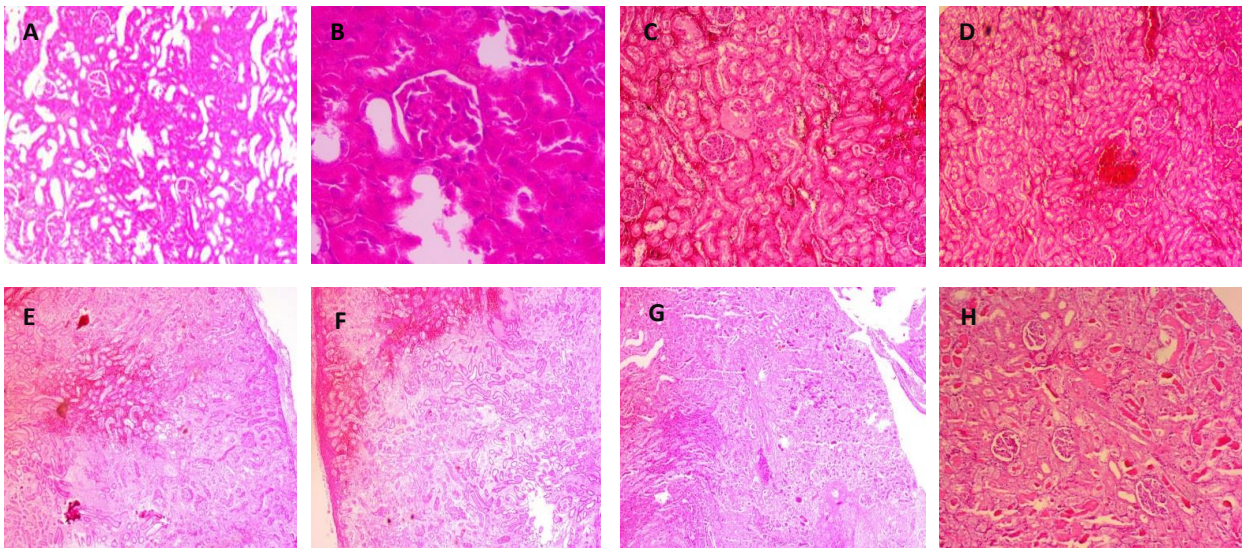

FIGURE 4. Renal histology showed that tubular atrophy, ischemic necrosis, inflammation, vessels congestion, hyaline casts, vacuolization and debris was significantly increased during 24 and 48h reperfusion time compared with 3h reperfusion and sham-operated groups. A & B: male and female sham; C & D: male and female ISC3hr; E & F: male and female ISC24hr; G & H: male and female ISC48hr.

nal NO expression and females cases have higher levels of eNOS compared to male ones (Dehghani et al., 2015; Saberi et al., 2016; Reckelhoff et al., 1998). In this study, female rats showed the peak elevation of serum nitrite level in 3h reperfusion, which then reduced at 24 and 48h time points. Therefore, nitrite production was found to be related to reperfusion time in female rats, but not in male ones. Park et al. (2004) in their study reported that fundamental NOS activity is higher in female compared to male in rat model of renal IR injury and estrogen administration also increased NOS activity, while testosterone decreased it. The research done by Lu et al. (2005) on liver revealed that serum NO levels of basal and post-ischemic were higher in female rats than male rats. As well also in accordance with our study in the first hours of reperfusion time, nitrite level increased. In addition, other researches in line with our study reported that the maximum inducible NOS (iNOS) and eNOS activities occurred 2 and 4h after reperfusion, respectively and then the level of these enzymes reduce (Choi et al., 2017; Tripatara et al., 2007). Therefore, the imbalance between the activity of iNOS and eNOS can be considered as an important contributor to the pathology of AKI and female gender exhibits a sensitivity to nitric oxide

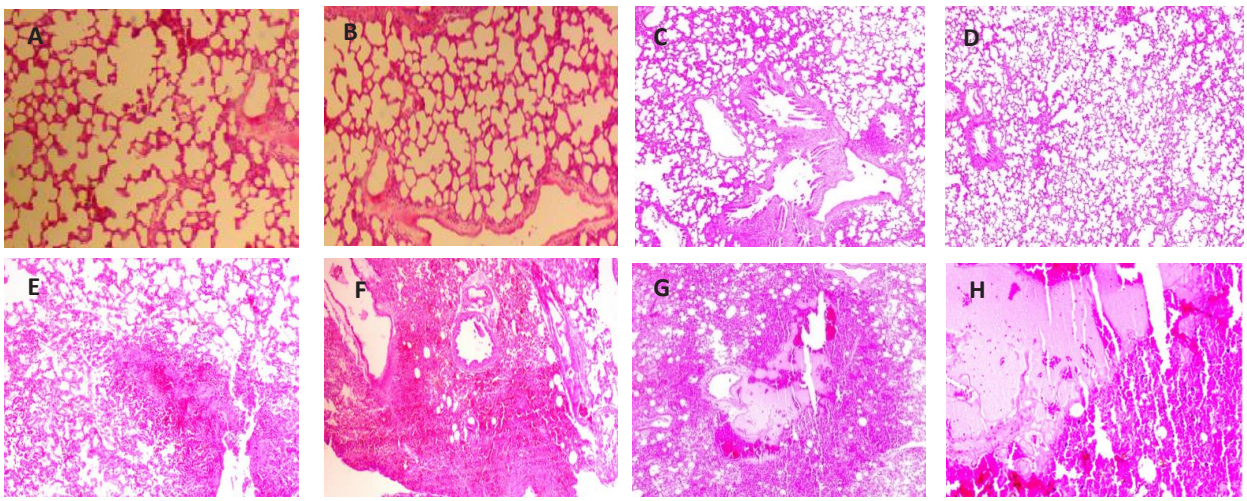

FIGURE 5. RLung histology showed congestion, inflammation and fibrosis. These were enhanced during 24 and 48h reperfusion time compared with 3h reperfusion and sham-operated groups. A & B: male and female sham; C & D: male and female ISC3hr; E & F: male and female ISC24hr; G & H: male and female ISC48hr.

system during renal IR.

The important mechanism of renal insult after IR is an imbalance between oxidant and anti-oxidant pathways, which is called, oxidative stress. In this situation, over-production of some oxidant agents like reactive oxygen species can lead to MDA release, which is a marker of lipid production (Yang et al., 2013). It is important to consider the gender mechanism of AKI by contributing which male is particularly susceptible to glomerular and tubular dysfunction compared to female (Tanaka et al., 2013). In line with this point, we identified that IRI increased the production of kidney MDA of male by passing 3h from the reperfusion, but not in females. Kiris et al. (2008) in their study observed enhancement in MDA level by passing 30 and 60min from reperfusion. In addition, another study showed that the peak of MDA usually takes place after 6h reperfusion time (Sener et al., 2002). These data are similar to those of our study, suggesting that MDA increased in the first hours of reperfusion and then reduced. Accordingly, this reduction may be due to improvement of antioxidant capacity.

The lungs with large and complex capillary net can be affected by unknown uremic toxins, which are renal reperfusion products. Some previous studies demonstrated increasing pulmonary vascular permeability, interstitial edema, alveolar hemorrhage and existence of leukocytes in lung as a remote organ after renal ischemia reperfusion. Mechanisms of AKI-induced lung injury can act in the dysregulation of water clearance, inflammatory reaction, immune response, oxidative stress and apoptosis. Moreover the epithelial transporters of salt and water of rat lungs down-regulated resulting in the reduced alveolar fluid clearance during renal ischemia (Basu and Wheeler, 2013; Doi et al., 2011; Kao et al., 2019; Paladino et al., 2009). The result of the present study showed that damage scores of lung and kidney tissues significantly increased during 24 and 48h reperfusion times. Our research is in agreement with the study reported by Kramer et al. (1999) in male rat. Previous studies have examined side effects of ischemia-reperfusion injury on lung tissue in male rat during different time periods of reperfusion. They found the majority of damages in male rat's lungs by passing 24 and 48h from the ischemia reperfusion injury (Kramer et al., 1999). Of note, during the ischemia, vascular endothelium, interstitial compartments and epithelium cells are involved. So, the disturbed structural integrity of tissue is observed. The disturbed alveolar epithelium barrier and capillary endothelium occur with the accumulation of inflammatory cells in the air spaces and parenchyma, suggesting pulmonary cellular apoptosis as a consequence of IRI (Hassoun et al., 2009).

Overacting and migration of neutrophils to other organs are the important immune processes in response to multiple organs failure of IRI. It was observed that

capillaries reperfusion of tissue occludes with the neutrophils results in tissue necrosis. In this regard, recently performed studies indicated that migration of these cells into the interstitial matrix drives not only vascular permeability and renal damage, but also broadening distance organ insult like lung histological change. As well, systemic secretion of proinflammatory cytokines, chemokines, and renin-angiotensin system (RAS) produce highly toxic peroxynitrite that can worsen the pathological situation (Doi et al., 2011; Hassoun et al., 2009; Schofield et al., 2013).

Altogether, some evidences indicated that complexity of kidney–lung crosstalk exists by regulating acid-base balance, oxygen carrying capacity and control of blood pressure through the renin-angiotensin system, so that these mechanisms can provide the pathophysiology of lung injury associated with IRI. In this regard, abnormal protein homeostasis, the reducted of lung capillary oncotic pressure, disrupted capillary integrity, decreased expressions of the epithelial sodium channel, the sodium-potassium-ATPase pump and volume overload in respiratory system are resulted from renal dysfunction (Basu and Wheeler, 2011; Hassoun et al., 2009).

In the current research, we showed that water content of lung decreased in both genders by passing 3h from IR. Moreover, we observed pathological damages such as the presence of necrosis, congestion, inflammation and hemorrhage in lung according to other studies (Azarkish et al., 2013; Hassoun et al., 2009; Klein et al., 2008; Kramer et al., 1999; Moeini et al., 2013). Correspondingly, this means that the changes of water content in the first time of reperfusion may be related to the alternation of hydrostatic pressure at the time of reperfusion.

Conclusion

Our results demonstrated that renal complete ischemia induced kidney and lung dysfunction while the intensity of the injury was depended on reperfusion time. The alteration of biochemical markers was also depended on duration of reperfusion. However, changes in biochemical findings are not exactly consistent with histological changes which reveals that normalization of some biochemical biomarkers in 48h after ischemia does not indicate normalization of renal tissue. Although some parameters, serum nitrite and kidney MDA levels, were gender dependent, a significant role for gender could not be imagined. Therefore, sex effects and the time of reperfusion may be the important factors to consider clinical therapeutic of renal IRI as well as its impact on remote organs.

Acknowledgment

We greatly appreciate all participants in the project. This project has been approved and supported by Deputy of Research of Hormozgan University of Medical sciences.

Conflicts of interest

The authors declare that they have no competing interests.

References

Abogresha NM, Greish SM, Abdelaziz EZ, Khalil WF. Remote effect of kidney ischemia-reperfusion injury on pancreas: role of oxidative stress and mitochondrial apoptosis. Arch Med Sci 2016; 12: 252. https://doi.org/10.5114/aoms.2015.48130

Azarkish F, Nematbakhsh M, Fazilati M, Talebi A, Pilehvarian AA, Pezeshki Z, et al. N-acetylcysteine prevents kidney and lung disturbances in renal ischemia/reperfusion injury in rat. Int J Prev Med 2013; 4: 1139-46.

Barp J, Araújo ASdR, Fernandes TRG, Rigatto KV, Llesuy S, Belló-Klein A, et al. Myocardial antioxidant and oxidative stress changes due to sex hormones. Braz J Med Biol Res 2002; 35: 1075-81. https://doi.org/10.1590/S0100-879X2002000900008

Basu RK, Wheeler, DS. Effects of ischemic acute kidney injury on lung water balance: nephrogenic pulmonary edema? Pulm Med 2011; 2011. https://doi.org/10.1155/2011/414253

Basu RK, Wheeler DS. Kidney-lung cross-talk and acute kidney injury. Pediatr Nephrol 2013; 28: 2239-48. https://doi.org/10.1007/s00467-012-2386-3

Campanholle G, Landgraf RG, Gonçalves GM, Paiva VN, Martins JDO, Wang PHM, Teixeira VPA. Lung inflammation is induced by renal ischemia and reperfusion injury as part of the systemic inflammatory syndrome. Inflamm Res 2010; 59: 861-9. https://doi.org/10.1007/s00011-010-0198-0

Choi EK, Jung H, Kwak KH, Yi SJ, Lim JA, Park SH, et al. Inhibition of oxidative stress in renal ischemia-reperfusion injury. Anesth Analg 2017; 124: 204-13. https://doi.org/10.1213/ANE.0000000000001565

Dehghani A, Saberi S, Nematbakhsh M. Role of Mas recep-

tor antagonist A799 in renal blood flow response to Ang 1-7 after bradykinin administration in ovariectomized estradiol-treated rats. Adv Pharmacol Pharm Sci 2015; 2015. https://doi.org/10.1155/2015/801053

Doi K, Ishizu T, Fujita T, Noiri E. Lung injury following acute kidney injury: kidney-lung crosstalk. Clin Exp Nephrol 2011; 15: 464-70. https://doi.org/10.1007/s10157-011-0459-4

Granger DN, Kvietys PR. Reperfusion injury and reactive oxygen species: the evolution of a concept. Redox biology 2015; 6: 524-51. https://doi.org/10.1016/j.redox.2015.08.020

Hassoun HT, Lie ML, Grigoryev DN, Liu M, Tuder RM, Rabb H. Kidney ischemia-reperfusion injury induces caspase-dependent pulmonary apoptosis. Am J Physiol Renal Physiol 2009; 297: 125-37. https://doi.org/10.1152/ajprenal.90666.2008

Ibrahim IY, Elbassuoni EA, Ragy MM, Habeeb WN. Gender difference in the development of cardiac lesions following acute ischemic-reperfusion renal injury in albino rats. Gen Physiol Biophys 2013; 32: 421-8. https://doi.org/10.4149/gpb_2013036

Kao CC, Yang WS, Fang JT, Liu KD, Wu VC. Remote organ failure in acute kidney injury. J Formos Med Assoc 2019; 118: 859-66. https://doi.org/10.1016/j.jfma.2018.04.005

Kei S. Serum lipid peroxide in cerebrovascular disorders determined by a new colorimetric method. Clin Chim Acta 1978; 90: 37-43. https://doi.org/10.1016/0009-8981(78)90081-5

Kher A, Meldrum KK, Wang M, Tsai BM, Pitcher JM, Meldrum DR. Cellular and molecular mechanisms of sex differences in renal ischemia-reperfusion injury. Cardiovasc Res 2005; 67: 594-603. https://doi.org/10.1016/j.cardiores.2005.05.005

Kiris I, Kapan S, Kılbas A, Yılmaz N, Altuntaş I, Karahan N, et al. The protective effect of erythropoietin on renal injury induced by abdominal aortic-ischemia-reperfusion in rats. J Surg Res 2008; 149: 206-13. https://doi.org/10.1016/j.jss.2007.12.752

Klein CL, Hoke TS, Fang WF, Altmann CJ, Douglas IS, Faubel, S. Interleukin-6 mediates lung injury following ischemic acute kidney injury or bilateral nephrectomy. Kidney Int 2008; 74: 901-9. https://doi.org/10.1038/ki.2008.314

Ko SF, Yip HK, Zhen YY, Lee CC, Lee CC, Huang SJ, et al. Severe bilateral ischemic-reperfusion renal injury: hyperacute and acute changes in apparent diffusion coefficient, T1, and T2 mapping with immunohistochemical correlations. Sci Rep 2017; 7: 1-10. https://doi.org/10.1038/s41598-017-01895-x

Kramer AA, Postler G, Salhab KF, Mendez C, Carey LC, Rabb H. Renal ischemia/reperfusion leads to macrophage-mediated increase in pulmonary vascular permeability. Kidney Int 1999; 55: 2362-7. https://doi.org/10.1046/j.1523-1755.1999.00460.x

Lean JM, Davies JT, Fuller K, Jagger CJ, Kirstein B, Partington GA, et al. A crucial role for thiol antioxidants in estrogen-deficiency bone loss. J Clin Invest 2003; 112: 915-923. https://doi.org/10.1172/JCI200318859

Lü P, Liu F, Wang CY, Chen DD, Yao Z, Tian Y,. Gender differences in hepatic ischemic reperfusion injury in rats are associated with endothelial cell nitric oxide synthase-derived nitric oxide. World J Gastroenterol 2005; 11: 3441. https://doi.org/10.3748/wjg.v11.i22.3441

Moeini M, Nematbakhsh M, Fazilati M, Talebi A, Pilehvarian AA, Azarkish F, et al. Protective role of recombinant human erythropoietin in kidney and lung injury following renal bilateral ischemia-reperfusion in rat model. Int J Prev Med 2013; 4: 648-55.

Müller V, Losonczy G, Heemann U, Vannay Á, Fekete A, Reusz G, et al. Sexual dimorphism in renal ischemia-reperfusion injury in rats: possible role of endothelin. Kidney Int 2002; 62: 1364-71. https://doi.org/10.1111/j.1523-1755.2002.kid590.x

Neugarten J, Golestaneh L, Kolhe NV. Sex differences in acute kidney injury requiring dialysis. BMC Nephrol 2018; 19: 131. https://doi.org/10.1186/s12882-018-0937-y

Paladino JD, Hotchkiss JR, Rabb H. Acute kidney injury and lung dysfunction: a paradigm for remote organ effects of kidney disease? Microvasc Res 2009; 77: 8-12. https://doi.org/10.1016/j.mvr.2008.09.001

Park KM, Kim JI, Ahn Y, Bonventre AJ, Bonventre JV. Testosterone is responsible for enhanced susceptibility of males to ischemic renal injury. J Biol Chem 2004; 279: 52282-92. https://doi.org/10.1074/jbc.M407629200

Reckelhoff JF, Hennington BS, Moore AG, Blanchard EJ, Cameron J. Gender differences in the renal nitric oxide (NO) system. Am J Hypertens 1998; 11: 97-104. https://doi.org/10.1016/S0895-7061(97)00360-9

Saberi S, Dehghani A, Nematbakhsh M. Role of Mas receptor in renal blood flow response to angiotensin-(1-7) in ovariectomized estradiol treated rats. Res Pharm Sci 2016; 11: 65-72. https://doi.org/10.1155/2015/801053

Schofield ZV, Woodruff TM, Halai R, Wu M CL, Cooper

MA. Neutrophils-a key component of ischemia-reperfusion injury. Shock 2013; 40: 463-70. https://doi.org/10.1097/SHK.0000000000000044

Sener G, Sehirli AÖ, Keyer-Uysal M, Arbak S, Ersoy Y, Yeğen BÇ. The protective effect of melatonin on renal ischemia-reperfusion injury in the rat. J Pineal Res 2002; 32: 120-6. https://doi.org/10.1034/j.1600-079x.2002.1848.x

Tanaka R, Yazawa M, Morikawa Y, Tsutsui H, Ohkita M, Yukimura T, et al. Sex differences in ischaemia/reperfusion-induced acute kidney injury depends on the degradation of noradrenaline by monoamine oxidase. Clin Exp Pharmacol Physiol 2017; 44: 371-7. https://doi.org/10.1111/1440-1681.12713

Tanaka R, Tsutsui H, Ohkita M, Takaoka M, Yukimura T, Matsumura, Y. Sex differences in ischemia/reperfusion-induced acute kidney injury are dependent on the renal sympathetic nervous system. Eur J Pharmacol 2013; 714: 397-404. https://doi.org/10.1016/j.ejphar.2013.07.008

Tripatara P, Patel NSA, Webb A, Rathod K, Lecomte F MJ, Mazzon E, et al. Nitrite-derived nitric oxide protects the rat kidney against ischemia/reperfusion injury in vivo: role for xanthine oxidoreductase. J Am Soc Nephrol 2007; 18: 570-80. https://doi.org/10.1681/ASN.2006050450

Wei Q, Dong Z. Mouse model of ischemic acute kidney injury: technical notes and tricks. Am J Physiol Renal Physiol 2012; 303: 1487-94. https://doi.org/10.1152/ajprenal.00352.2012

Yang Shun, Chou Wei-Ping, Pei Ling. Effects of propofol on renal ischemia/reperfusion injury in rats. Exp Ther Med 2013; 6: 1177-83. https://doi.org/10.3892/etm.2013.1305