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Original Article

Protective Role of Progesterone on Lung Injury Induced by Ischemia Reperfusion of the Lower Limbs

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ABSTRACT

Objective: Remote lung injury is one of the most challenging issues in patients undergoing ischemia reperfusion (IR) injury of the lower limbs. We examined the role of progesterone (PG) on the remote injury of the lungs seen after IR of the lower limbs.

Methods: Eighteen male Sprague Dawley rats were divided into three groups. (1) Control: rats had only two physiological saline injections intraperitoneally (i.p.) 2 h apart under general anesthesia. (2) IR: underwent 2 h tourniquet induced ischemia for both lower limbs followed by 2 h of reperfusion. Animals were injected with physiological saline (i.p.) before both ischemia and reperfusion. (3) IR + PG: rats underwent the same IR protocol as the IR group and were injected with PG (16 mg/kg, i.p.) before both ischemia and reperfusion. After reperfusion, rats were sacrificed, and lung tissues were taken out for histopathologic and biochemical analyses.

Results: In IR + PG group, tissue levels of malondialdehyde and nitric oxide decreased significantly compared with the IR group ($p<0.01$). Similarly, glutathione level and superoxide dismutase and glutathione S-transferase activities significantly increased in the IR + PG group than in the IR group ($p<0.05$, $p<0.01$, and $p<0.05$, respectively). In light microscopy, reduced inflammatory cell infiltration, amelioration in alveolar structure, and mild vascular congestion in the parenchyma were seen in the IR + PG group. A significant improvement in histopathologic score was seen in the IR + PG group compared with the IR group ($p<0.001$).

Conclusion: PG might be effective in attenuating remote injury of the lung in lower body IR via its antioxidant function.

INTRODUCTION

Remote lung injury (RLI) related to ischemia reperfusion (IR) of the lower limbs has been shown to be the cause of short- and long-term mortality in vascular surgical patients.[1] While the molecular mechanisms of the RLI are quite diverse, the release of inflammatory mediators and reactive oxygen species (ROS) from the skeletal muscle exposed to IR plays a pivotal role in the pathophysiology.[2] As a consequence, mitochondrial degeneration, vascular congestion, fibrin-rich microthrombus formation, and pulmonary edema cause the impairment in lung function to varying degrees.[3,4]

To tackle the issue, the protective roles of many anti-inflammatory and antioxidant agents and remote ischemic preconditioning on attenuation of the remote organ injury have been shown experimentally. Unfortunately, the beneficial outcome gathered from those studies is yet to alter our current therapeutic strategies used against the RLI in vascular surgical patients.[5]

Progesterone (PG) is shown to be a pleotropic agent, and it has a protective action in both ischemic and traumatic brain injury through the reduction of cerebral edema, oxidative stress, and apoptosis.[6] In addition to its neuroprotective action, PG has been shown to exert a protective role against the IR injury of several organs such as the ovary, retina, heart, and kidney.[7–11] Vermillion et al.[12] found that increased circulating PG during pregnancy causes a positive remodeling in the lung tissue that makes it more resistant to pulmonary inflammation related to

severe influenza infection. All these studies suggest that PG may also have a protective potential on lung tissue exposed remotely to the lower limb IR.

In this study, we aimed to study the impact of PG given before ischemia and reperfusion on acute RLI related to lower limb IR in an experimental rat model.

MATERIALS AND METHODS

Chemicals

Ketamine hydrochloride (Ketalar, 100 mg/10 mL, Pfizer, Ilacları Ltd. Sti., Turkey) and xylazine hydrochloride (Rompun % 2, Bayer, Türk Kimya San. Ltd. Şti., Turkey) were used for anesthesia. PG (Progestan, 50 mg/mL) was obtained from Koçak Farma İlaç ve Kimya Sanayi A.Ş., Turkey.

Ethical approval and animals

This study was approved by the Animal Care and Use Committee (Date: April 11, 2022, Decision no: 29.2022. mar). Eighteen male Sprague Dawley rats (3–4 months, 300–400 g) were housed in cages where they were fed standard rat pellets and water ad libitum. The cages were kept in a temperature-controlled room (22±2°C) with standardized light/dark (12/12 h) cycles.

Experimental design

Rats were divided into three groups. In the control group (n=6), rats had physiological saline (0.1 cc/100 g, intraperitoneally (i.p.)) injection two times 2 h apart under general anesthesia. In the IR group (n=6), rats were exposed to bilateral lower extremity limb ischemia for 2 h by the tourniquet method. After 2 h of ischemia, tourniquets were released, and reperfusion was allowed for 2 h. Before ischemia and reperfusion, physiological saline (0.1 cc/100 g, i.p.) was injected into rats. In IR + PG group (n=6), rats underwent the same IR protocol and were injected with PG (16 mg/kg) before ischemia and reperfusion. At the end of reperfusion, rats were sacrificed, and lung tissues were taken out for histopathologic and biochemical analyses.

Lower limb IR protocol

The rat was anesthetized with ketamine hydrochloride (100 mg/kg, i.p.) and xylazine hydrochloride (10 mg/kg, i.p.). Under general anesthesia, a rubber-band tourniquet was used to bind each hind limb proximal to the trochanter major to cause bilateral lower extremity ischemia for 2 h. Cessation of the arterial flow totally just distal to the tourniquet was confirmed using a pocket Doppler device (Doppler Ultrasonic IABP Assembly, Getinge Group) and cyanotic color changes of the sole of the foot. At the end of the ischemia period, rubber-band tourniquets were released for starting 2 h of reperfusion. Again, the reestablishment of the arterial flow was confirmed by the Doppler device.

Biochemical analysis

Lung tissue homogenates were performed using saline solution and were stored in the refrigerator at –20°C to determine the biochemical parameters. Levels of malondialdehyde (MDA), glutathione (GSH), and nitric oxide (NO), and activities of superoxide dismutase (SOD), glutathione S-transferase (GST), and catalase (CAT) were measured by the methods given in the literature.[13,14]

Histological analysis

Lung tissues were fixed with 10% neutral buffer formaldehyde and processed routinely for paraffin embedding. Five-micrometer-thick paraffin sections were stained with hematoxylin and eosin (H&E) for morphologic evaluation. For histopathologic scoring, at least five microscopic areas in each sample were investigated and scored using a semiquantitative scale (0: normal, 1: mil, 2: moderate, and 3: severe damage), including the following criteria: alveolar degeneration, inflammatory cell accumulation, congestion, and interstitial edema.[4] All stained sections were investigated under an Olympus BX51 (Tokyo, Japan) photomicroscope and photographed using a digital camera (Olympus DP72, Tokyo, Japan) linked to a microscope.

Statistical analysis

All analyses were performed using GraphPad Prism 8.42 (GraphPad Software, Inc., San Diego, CA). Results were shown as mean±standard deviation (SD). Statistical differences were assessed with analysis of variance (ANOVA) followed by Tukey's multiple comparison tests and unpaired t-test. A value of $p<0.05$ was accepted as significant.

RESULTS

Biochemical findings

The level of MDA was significantly higher in the IR group than the level in the control group ($p<0.01$, Fig. 1). Treatment with PG significantly decreased MDA levels in the IR + PG group ($p<0.01$, Fig. 1). The level of GSH decreased significantly in the IR group when compared with the control group ($p<0.05$, Fig. 1). In the IR + PG group, administration of PG significantly caused an improvement in GSH level compared with the IR group ($p<0.05$, Fig. 1). Activities of SOD and GST in the IR group significantly decreased compared with the control group ($p<0.01$, Fig. 1). Administration of PG in the IR + PG group caused a significant increase in SOD and GST activities when compared with the IR group ($p<0.01$ and $p<0.05$, respectively, Fig. 1). The level of NO significantly increased in the IR group compared with the control group ($p<0.05$, Fig. 1). Treatment with PG significantly decreased the NO level in the IR + PG group compared with the IR group ($p<0.01$, Fig. 1). There was no significant difference in CAT activities among the experimental groups.

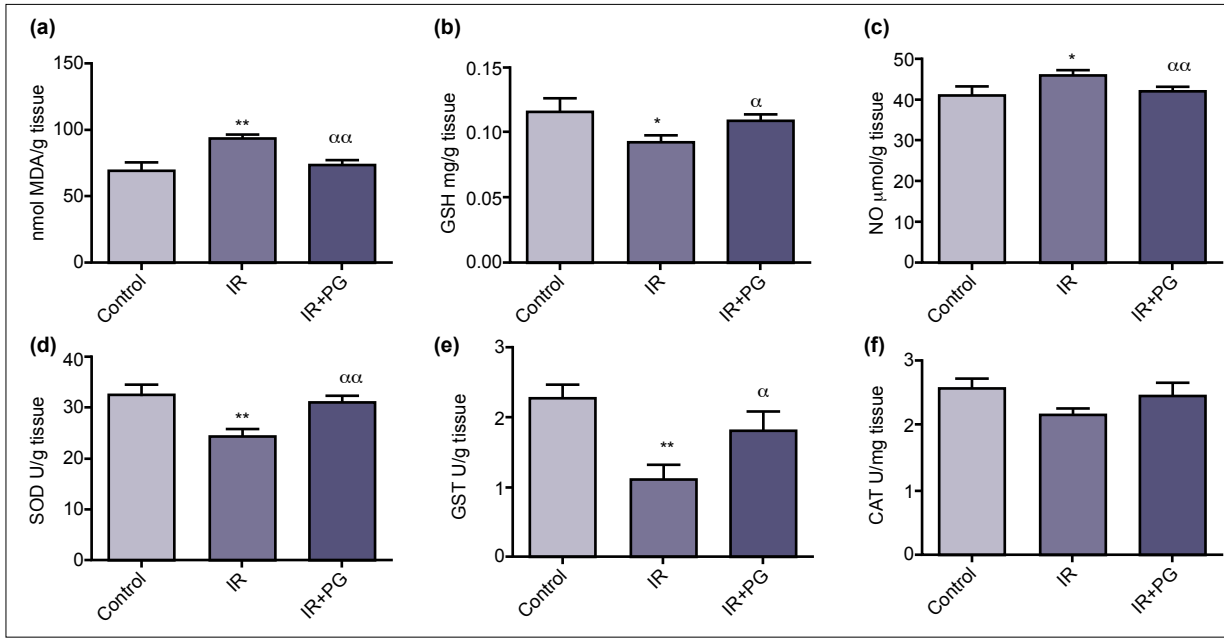

Figure 1. The lung malondialdehyde (MDA) level **(a)**, glutathione (GSH) level **(b)**, nitric oxide (NO) level **(c)**, superoxide dismutase (SOD) activity **(d)**, glutathione S-transferase (GST) activity **(e)**, and catalase (CAT) activity **(f)** in experimental groups. *P<0.05 vs control group, **p<0.01 vs control group, αp<0.05 vs the IR group, ααp<0.01 vs the IR group, IR: ischemia reperfusion, PG: progesterone.

Histopathological findings

Light microscopic investigation showed regular lung morphology in the control group (Fig. 2). Severe disturbance of alveolar structure, intense inflammatory cell infiltration, and severe hemorrhage and edema in the parenchyma were the prominent features in the IR group (Fig. 2). In the IR + PG group, amelioration in alveolar structure, reduced inflammatory cell infiltration, and mild vascular congestion in the parenchyma were observed compared with the IR group (Fig. 2). The histopathologic score was significantly increased in the IR group, and PG treatment in the IR + PG group significantly reduced the histopathologic score ($p<0.001$, Fig. 2).

DISCUSSION

Remote organ damage has remained the most critical issue dictating the morbidity and mortality after vascular surgical procedures with no currently available treatment approach. We showed that treatment with PG immediately before both ischemia and reperfusion has a protective role in preventing RLI after lower body IR. The mechanisms of its therapeutic benefit were found to be related to the attenuation of the tissue markers of oxidation.

Lower limb IR-related remote organ damage is linked to microvascular dysfunction in the muscle tissue. Briefly, activated endothelial cells release ROS at the initial periods of reperfusion with a concurrent reduction in the synthesis of N) in all segments of the microcirculation, which subsequently induce a systemic inflammatory response and cause remote organ damage.[4,15] The inflammatory response in tissues primarily exposed to IR induces the release of interleukins 1-beta, 6, and 8, and tumor necrosis factor-alpha.[16] Out of many remote organs, lungs are the most vulnerable organs to IR injury of the lower limbs, and the severity of lung dysfunction remains to be a leading determinant of early postoperative survival in vascular surgery.[17] After initiation of reperfusion, sequestration and extravasation of activated polymorphonuclear cells and macrophages in the pulmonary microvasculature is central to the development of acute RLI.[16,17] In our study, we detected a significant increase in the indicators of oxidative stress (MDA) in the lung tissues exposed to remote IR. Similarly, tissue antioxidants such as GSH level and SOD and GST activities decreased in rats exposed to IR compared with controls. Also, disturbance of alveolar structure, intense inflammatory cell infiltration, and severe hemorrhage and edema were seen in the parenchyma in accordance with the reported findings in the literature.

Previously, sex-related differences in the outcome of the cerebrovascular accident had triggered the idea that sex steroids, particularly PG, could have a therapeutic role in lessening the hypoxic–ischemic neuronal damage.[18] PG is a versatile sex steroid and has been mainly studied as a neuroprotective agent in traumatic and ischemic neuronal injury experimental models. In ischemic brain injury, Gibson et al.[19] revealed that the neuroprotective effect of PG given after cerebral ischemia (8 mg/kg) was shown to reduce the expression of interleukin 1β, transforming growth factor β2, and NO synthase 2, and thus reducing the volume of the brain tissue affected by cerebral edema. In the same study, it was reported that exogenous PG has a dose- and time-dependent neuroprotective action.

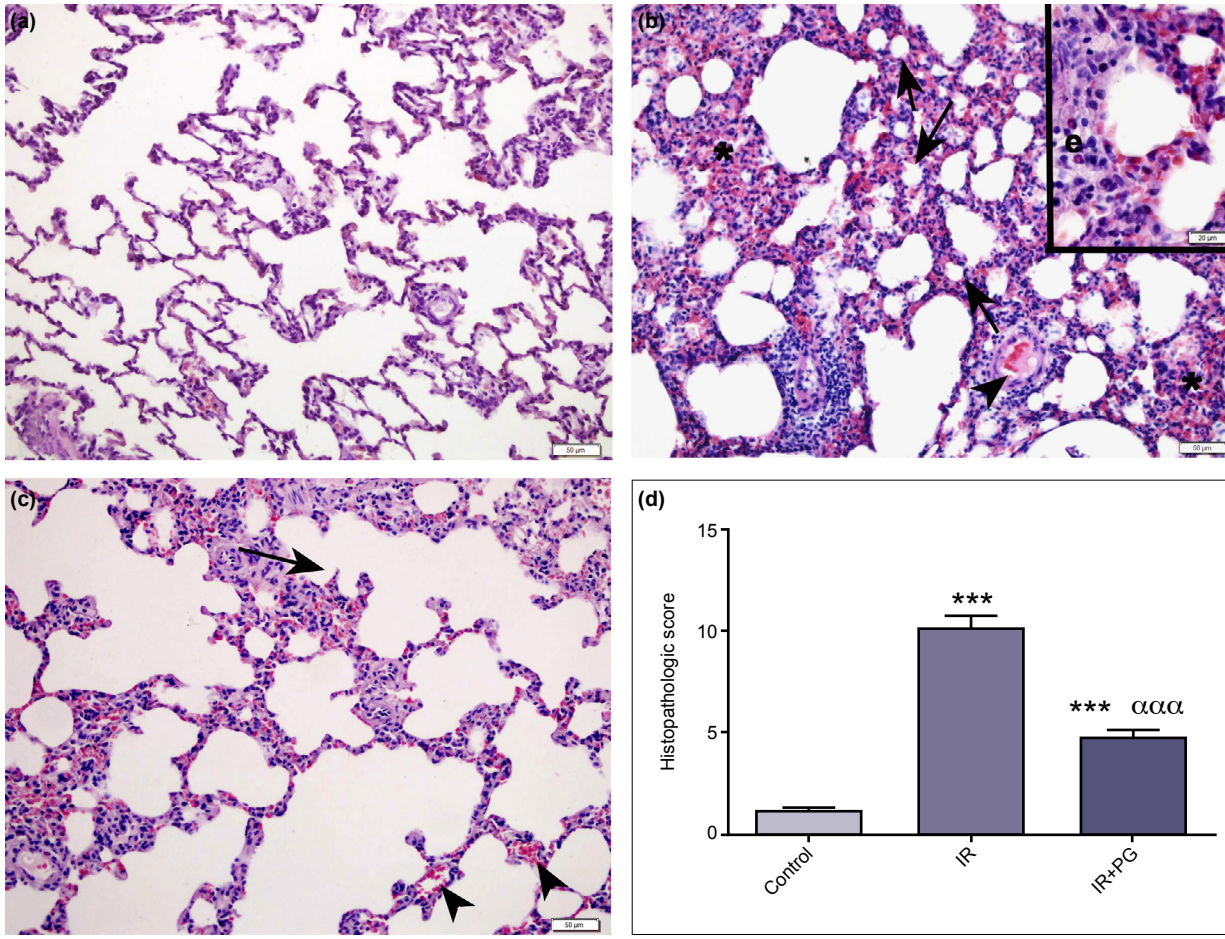

Figure 2. Representative photomicrographs of lung tissue in experimental groups **(a–c)** and the graph of histopathologic score **(d)**. Normal alveolar morphology with intact alveolar structure in the control group (a). Severe hemorrhage (*) and edema in parenchyma, inflammatory cell infiltration (e), vascular congestion (arrow head) and severe alveolar degeneration (arrows) in the IR group **(b)**. Quite regular alveolar structure (arrow), mild vascular congestion (arrow heads) in the IR + PG group **(c)**. Hematoxylin and eosin (H&E) staining, original magnification x 200 and x 400 (inset). $^{***}P<0.001$ vs control group, $^{\alpha\alpha\alpha}p<0.001$ vs the IR group, IR: ischemia reperfusion, PG: progesterone.

Higher doses of PG and abrupt termination of the therapy were claimed to result in exacerbated excitotoxicity and ischemic cell death.[6,20] In their study, Ishrat et al.[21] found that the beneficial function of the postischemic application of PG in cerebral ischemia could be attributed to its antiapoptotic action on ischemic neurons. Andrabi et al.[22] revealed the mitochondrial protective role of PG in the neurons exposed to IR.

Apart from neuroprotection, PG has been successfully used in the treatment of IR injury seen in different tissues. Sandhi et al.[11] studied the protective role of exogenous PG (given before ischemic period, 5–10 mg/kg) against renal IR injury. They concluded that PG exerts a renoprotective effect via its antioxidant action in acute kidney injury. Similarly, when it comes to myocardial cells, treatment with PG (after induction of ischemia, 2 mg/kg) was shown to cause a cardioprotective effect on myocardial I/R injury. It was mentioned that the protective effect of PG could be explained by attenuation of inflammation and its possible interaction with endogenous estrogen.[23] On the other hand, some authors claimed that pretreatment with PG inhibits the cardioprotective function of estrogens in myocardial IR injury in a rat model of the coronary artery occlusion.[24] In another study by Güleç Başer et al.,[8] 8 mg/kg PG 30 min before ovarian detorsion was shown to have a significant effect in decreasing the number of apoptotic cells and increasing the total antioxidant status of the ovary subjected to IR.

Among sex steroids, the effect of estrogen treatment on remote organ injury seen after IR has been studied in many studies. It was found that pretreatment with estradiol reduces lung inflammation after intestinal IR, and its action was shown to be through the blockage of NO synthase activity in lung tissue.[25] In a study by Nahavandi et al.,[26] preischemic application of estrogen in ovariectomized rats exposed to renal IR caused a significant improvement in lung damage via suppressing oxidative injury. The antioxidant action of estrogen has been shown to take place by both suppressing the expression of antioxidant enzymes such as SOD and the production of inflammatory cy-

tokines.[27] While the antioxidant and anti-inflammatory potential of PG in IR have been shown in several studies, its role in remote organ damage related to IR is still unknown. In this regard, our study examined the role of PG in an RLI model, and the results revealed that the application of PG in rats undergoing lower limb IR caused a significant decrease in MDA as the tissue marker of oxidation. Also, the derangement of tissue antioxidant capacity such as SOD, GST, and GSH seen in the IR group improved significantly with PG therapy. We also detected a significant decrease in the tissue level of NO in rats treated with PG, which was also shown to be protective against RLI.[25] The benefit of PG was also verified at the tissue level with reduced inflammatory cell infiltration, amelioration in alveolar structure, and mild vascular congestion in the parenchyma. The protective action of PG on RLI seems to be related to its antioxidant and anti-inflammatory action.

CONCLUSION

Our results suggest that PG ameliorates the RLI associated with IR of the lower limbs. It exerts an antioxidant effect on the lungs via suppressing the neutrophil infiltration and related acute inflammation seen after IR of the lower limb. More studies are warranted to confirm the results.

Ethics Committee Approval

This study approved by Marmara University Animal Experiments Ethics Committee (Date: 11.04.2022, Decision No: 29.2022.mar).

Informed Consent

Prospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: E.A., K.A., D.Ö.; Design: E.A., K.A., D.Ö., Ş.O. A.M.; Supervision: E.A., K.A., Ş.O.; Fundings: E.A., K.A., D.Ö., Ş.O.; Materials: E.A., D.Ö., K.A., Ş.O., A.M; Data: E.A., Ş.O., D.Ö., A.M.; Analysis: E.A., Ş.O., A.M; Literature search: E.A., K.A., D.Ö., Ş.O.; Writing: E.A.; Critical revision: E.A., K.A., D.Ö., Ş.O.

Conflict of Interest

None declared.

REFERENCES

1. Chen L, Zhao H, Alam A, Mi E, Eguchi S, Yao S, et al. Postoperative remote lung injury and its impact on surgical outcome. BMC Anesthesiol 2019;19:30. [CrossRef]
2. Yassin MM, Harkin DW, Barros DD'SaAA, Halliday MI, Rowlands BJ. Lower limb ischemia-reperfusion injury triggers a systemic inflammatory response and multiple organ dysfunction. World J Surg 2002;26:115–21. [CrossRef]
3. Kao MC, Jan WC, Tsai PS, Wang TY, Huang CJ. Magnesium sulfate mitigates lung injury induced by bilateral lower limb ischemia-reperfusion in rats. J Surg Res 2011:171: e97–106. [CrossRef]
4. Ak E, Ak K, Ustundag UV, Kervancioglu-Demirci E, Emekli-Alturfan E, Çetinel S. Milrinone attenuates heart and lung remote injury after abdominal aortic cross-clamping. Ann Vasc Surg 2020;69:391–9. [CrossRef]
5. Naito H, Nojima T, Fujisaki N, Tsukahara K, Yamamoto H, Yamada T, et al. Therapeutic strategies for ischemia reperfusion injury in emergency medicine. Acute Med Surg 2020;7:e501. [CrossRef]
6. Cai J, Cao S, Chen J, Yan F, Chen G, Dai Y. Progesterone alleviates acute brain injury via reducing apoptosis and oxidative stress in a rat experimental subarachnoid hemorrhage model. Neurosci Lett 2015;600:238–43.
7. Cavalcante LP, Ferreira SG, Pereira DR, Moraes SR, Simas R, Sannomiya P, et al. Acute administration of oestradiol or progesterone in a spinal cord ischaemia-reperfusion model in rats. Interact Cardiovasc Thorac Surg 2018; 26:196–201. [CrossRef]
8. Güleç Başer B, İslimye Taşkın M, Adalı E, Öztürk E, Hısmıoğulları AA, Yay A. Does progesterone have protective effects on ovarian ischemia-reperfusion injury? J Turk Ger Gynecol Assoc 2018;19:87–93. [CrossRef]
9. Wang J, Jiang C, Liu C, Li X, Chen N, Hao Y. Neuroprotective effects of progesterone following stroke in aged rats. Behav Brain Res 2010;209:119–22.
10. Morrissy S, Xu B, Aguilar D, Zhang J, Chen QM. Inhibition of apoptosis by progesterone in cardiomyocytes. Aging Cell 2010;9:799–809.
11. Sandhi J, Singh JP, Kaur T, Ghuman SS, Singh AP. Involvement of progesterone receptors in ascorbic acid-mediated protection against ischemia-reperfusion-induced acute kidney injury. J Surg Res 2014;187:278–88. [CrossRef]
12. Vermillion MS, Nelson A, Vom Steeg L, Loube J, Mitzner W, Klein SL. Pregnancy preserves pulmonary function following influenza virus infection in C57BL/6 mice. Am J Physiol Lung Cell Mol Physiol 2018;315:L517–25. [CrossRef]
13. Oktay S, Bayrak G, Alev B, Ipekci H, Ustundag UV, Turkyilmaz IB, et al. The effect of vitamin U on the lung tissue of pentyleneterazole-induced seizures in rats. Naunyn Schmiedebergs Arch Pharmacol 2018;391:177–84.
14. Emekli-Alturfan E, Alev B, Tunali S, Oktay S, Tunali-Akbay T, Ozturk LK, et al. Effects of edaravone on cardiac damage in valproic acid induced toxicity. Ann Clin Lab Sci 2015;45:166–72.
15. Carden DL, Granger DN. Pathophysiology of ischaemia-reperfusion injury. J Pathol 2000;190:255–66. [CrossRef]
16. Bown MJ, Nicholson ML, Bell PR, Sayers RD. Cytokines and inflammatory pathways in the pathogenesis of multiple organ failure following abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 2001;22:485–95. [CrossRef]
17. Akgun S, Tekeli A, Isbir SC, Civelek A, Ak K, Sirvanci S, et al. FK506 to prevent lung injury after hindlimb ischemia and reperfusion in a rat model: An electron microscopic study. Surg Today 2004;34:678–84.
18. Kasischke K, Huber R, Li H, Timmler M, Riepe MW. Primary hypoxic tolerance and chemical preconditioning during estrus cycle in mice. Stroke 1999;30:1256–62. [CrossRef]
19. Gibson CL, Constantin D, Prior MJ, Bath PM, Murphy SP. Progesterone suppresses the inflammatory response and nitric oxide synthase-2 expression following cerebral ischemia. Exp Neurol 2005;193:522–30.
20. Goss CW, Hoffman SW, Stein DG. Behavioral effects and anatomic correlates after brain injury: a progesterone dose-response study. Pharmacol Biochem Behav 2003;76:231–42. [CrossRef]
21. Ishrat T, Sayeed I, Atif F, Hua F, Stein DG. Progesterone is neuroprotective against ischemic brain injury through its effects on the phosphoinositide 3-kinase/protein kinase B signaling pathway. Neuroscience 2012;210:442–50.
22. Andrabi SS, Parvez S, Tabassum H. Progesterone induces neuropro-

tection following reperfusion-promoted mitochondrial dysfunction after focal cerebral ischemia in rats. Dis Model Mech 2017;10:787–96.
23. Dhote VV, Balaraman R. Gender specific effect of progesterone on myocardial ischemia/reperfusion injury in rats. Life Sci 2007;81:188–97. [CrossRef]
24. Jeanes HL, Wanikiat P, Sharif I, Gray GA. Medroxyprogesterone acetate inhibits the cardioprotective effect of estrogen in experimental ischemia-reperfusion injury. Menopause 2006;13:80–6. [CrossRef]
25. Breithaupt-Faloppa AC, Fantozzi ET, de Assis Ramos MM, Vitoretti LB, Couto GK, Lino-dos-Santos-Franco A, et al. Protective effect of estradiol on acute lung inflammation induced by an intestinal ischemic insult is dependent on nitric oxide. Shock 2013;40:203–9.
26. Nahavandi S, Ahmadi S, Sobhani SA, Abbasi T, Dehghani A. A high dose of estrogen can improve renal ischemia-reperfusion-induced pulmonary injury in ovariectomized female rats. Can J Physiol Pharmacol 2021;99:1241–52. [CrossRef]
27. Vrtačnik P, Ostanek B, Mencej-Bedrač S, Marc J. The many faces of estrogen signaling. Biochem Med (Zagreb) 2014;24:329–42.

Alt Ekstremite İskemi Reperfüzyon Sonrası Görülen Akciğer Hasarında Progesteronun Koruyucu Rolü

Amaç: Alt ekstremitede iskemi reperfüzyon (IR) hasarına maruz kalan hastalarda görülen en önemli problemlerden birisi akciğer hasarıdır. Bu çalışmamızda alt ekstremite IR sonrası ortaya çıkan akciğer hasarında progesteronun (PG) rolü araştırılmıştır.

Gereç ve Yöntem: On sekiz adet erkek Sprague-Dawley sıçan üç gruba ayrıldı: (1) kontrol: sıçanlara genel anestezi sonrası iki saat aralıkla iki kez serum fizyolojik (SF) enjeksiyonu yapıldı (intraperitoneal (i.p.)), (2) IR: sıçanlara turnike kullanılarak iki saat iskemi sonrasında iki saat reperfüzyon uygulandı. Hem iskemi hem de reperfüzyon öncesi aynı dozda SF enjeksiyonu yapıldı, (3) IR+PG: sıçanlara IR grubuyla aynı deney protokolü uygulanmış olup hem iskemi hem de reperfüzyon öncesi PG enjeksiyonu yapılmıştır (16 mg/kg, i.p.). Reperfüzyon sonrası sıçanlar sakrifiye edilerek akciğer dokusu çıkartılmış ve biyokimyasal ve histolojik analizler yapılmıştır.

Bulgular: IR+PG grubunda doku malondialdehit ve nitrik oksit seviyeleri IR grubuna kıyasla anlamlı düzeyde azalmıştır ($p<0.01$). Benzer şekilde IR+PG grubunda glutatyon seviyesi ve süperoksit dismutaz ve glutatyon S-transferaz aktiviteleri IR grubuna kıyasla anlamlı derecede artmıştır ($p<0.05$, $p<0.01$ ve $p<0.05$). Işık mikroskopik incelemede IR+PG grubunda akciğer parankiminde azalmış enflamatuvar hücre infiltrasyonu, alveol yapılarda düzelme ve hafif vasküler konjesyon görülmüştür. IR+PG grubunda IR grubuna kıyasla histopatolojik skorda anlamlı düzeyde iyileşme tespit edilmiştir ($p<0.001$).

Sonuç: Progesteron antioksidan fonksiyonundan dolayı alt ekstremite IR sonrası görülen akciğer hasarının azaltılmasında etkili olabilir.

Anahtar Sözcükler: Akciğer; alt ekstremite; iskemi; reperfüzyon; uzak organ hasarı.