Effect of Dexmedetomidine on Lung Tissue Lower Extremity Ischemia Reperfusion Injury in Streptozotocin Induced Diabetic Rats

Streptozosin ile Diyabet Oluşturulan Ratlarda Alt Ekstremite İskemi Reperfüzyon Hasarında Deksmedetomidinin Akciğer Dokusu Üzerine Etkisi

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ABSTRACT

Objective: The aim of our study was to investigate the effects of dexmedetomidine on lung tissue in rat's lower extremity after undergoing an ischemia reperfusion (I/R) injury.
Material and methods: After obtaining ethical committee approval, 24 Wistar albino rats (200-270 gr) were randomly divided into four groups: (Control (Group C), diabetes-control (Group DC), diabetes I/R (Group DIR), and diabetes-I/R-dexmedetomidine (Group DIRD). In diabetes groups, single-dose (55 mg/kg) streptozotocin was administered intraperitoneally. Rats with a blood glucose level above 250 mg/dl at the 72nd hour were accepted as diabetic. At the end of four weeks, laparotomy was performed in all rats. Nothing else was done in Group C and DC. In Group DIR, ischemia reperfusion was produced via two-hour periods of clamping and subsequent declamping of infra-renal abdominal aorta. In Group DIRD, 100 µg/kg of dexmedetomidine were administered intraperitoneally.
Results: When the groups' lung tissue neutrophil infiltration/aggregation light microscopic findings were compared to each other, a significant difference was observed among the groups (p=0.003). When the groups' lung tissue injury score light microscopic findings were compared, a significant difference was observed among the groups (p=0.001). When groups were compared to each other in terms of lung tissue MDA levels and SOD activities, a significant difference was observed (p=0.002, p=0.018, respectively).
Conclusion: Our results confirm that dexmedetomidine has protective effects against the lung damage resulting from IR in diabetic rats. However, future studies should be conducted to evaluate these effects.

Key Words: Dexmedetomidine, ischemia reperfusion, lung, rat

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ÖZET

Amaç: Bu çalışmanın amacı ratlarda alt ekstremite iskemi-reperfüzyon (İ/R) modelinde iskemi öncesi uygulanan deksmedetomidinin akciğer üzerine koruyucu etkilerini araştırmaktır.
Yöntem: Etik kurul onayı alındıktan sonra, yirmi dört tane Wistar rat randomize olarak dört gruba ayrıldı (n=6). Kontrol (grup K), diyabet-kontrol (grup DK), diyabet-İR (grup DİR), diyabet-İR-deksmedetomidin (grup DİRD). Diyabet gruplarına 55 mg/kg streptozotosin tek doz intraperitoneal olarak uygulandı. 72. saat kan şekeri 250 mg/dl ve üzerinde saptananlar diyabetik olarak kabul edildi ve 4 hafta sonunda tüm gruplara anestezi altında laparotomi uygulandı. Grup K ve DK'da başka bir işlem yapılmadı. Grup DİR' da infrarenal abdominal aortaya sırayla klemp konup kaldırılması ile 2 saatlik periyodlarla İR uygulandı. Grup DİRD'de intraperitoneal olarak 100 µg/kg deksmedetomidin uygulandı.
Bulgular: Grupların akciğer dokusu nötrofil infiltrasyonu/agregasyon ışık mikroskobik bulguları birbirleriyle karşılaştırıldığında gruplar arasında anlamlı bir fark gözlendi (p=0.003). Grupların akciğer doku hasarlanma skoru ışık mikroskobik bulguları karşılaştırıldığında gruplar arasında anlamlı bir fark gözlendi (p=0.001). Akciğer dokusu MDA düzeyleri ve SOD enzim aktiviteleri açısından gruplar birbirleriyle karşılaştırıldığında anlamlı bir fark gözlendi (p=0.002, p=0.018, sırasıyla).
Sonuç: Sonuçlarımız, deksmedetomidinin diyabetik sıçanlarda İR'den kaynaklanan akciğer hasarına karşı koruyucu etkileri olduğunu doğrulamaktadır. Ancak, bu etkileri değerlendirmek için gelecekte çalışmalar yapılmalıdır.

Anahtar Sözcükler: Deksmedetomidin, iskemi reperfüzyon, akciğer, rat

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INTRODUCTION

Lower extremity ischemia reperfusion (IR) injury can be seen in various vascular traumas and diseases, as well as during reconstructive tissue transfer or after long reconstruction surgeries (1). Damage to distant organs is caused by reactive oxygen radicals occurring after lower extremity IR systemic inflammatory response (1-4). Free oxygen radicals may cause damage in many distant organs, particularly the lungs, followed by the kidneys, intestines and pancreas. Oxidative stress and lipid peroxidation are also important in distant organ damage post IR (5).

Distant organ damage after IR is most clearly seen in the lungs (6). Pulmonary oedema, followed by acute pulmonary injuries, may develop indirectly in the lungs after IR injury.

Dexmedetomidine is an α_2 agonist drug that has been used for sedation in anesthetic intensive care units (ICUs) in the past (7). Recently, dexmedetomidine has been used as a sedative because of its low respiratory depression (8). Besides its sedative effects, the analgesic and anxiolytic effects of dexmedetomidine have also been shown. Recent studies have shown that dexmedetomidine reduces systemic inflammatory response, inhibits release of inflammatory cytokines and suppresses pulmonary and hepatic inflammation. The suppressive effect of inflammatory cytokines on the tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6 and the macrophage inflammatory protein-2 (MIP-2) has been demonstrated. Thus, it is understood that dexmedetomidine alleviates acute organ damage and reduces inflammation in sepsis. Animal studies have shown that dexmedetomidine reduces IR injury in various organs (myocardial, lung, liver, cerebral and kidney) (9). Dexmedetomidine is not only effective in preventing IR injury, but also has a lung injury-reducing effect in haemorrhagic shock, in ventilator-related lung injury and in rats with pneumoperitoneum created by and pulmonary contusions occurring after blunt trauma.

Although the mechanism of action of dexmedetomidine and its relation to inflammation have been described, its effects on indirect lung injury following lower extremity reperfusion are unclear. In this study, we investigated how malondialdehyde (MDA) levels and superoxide dismutase (SOD) activities change in the lungs in indirectly occurring distant organ damage and what type of histopathological changes are seen.

MATERIALS and METHOD

After obtaining ethical committee approval, 24 Wistar albino rats (200-270 gr) were randomly divided into four groups: Group C, Group DC, Group DIR and Group DIRD. Diabetes was induced using streptozotocin (Sigma Chemical Corp., St. Louis, MO, USA) with a single 55 mg/kg dose in a citrate buffer (100 mmol/L, pH 4.5). Rats with a blood glucose level determined by means of a sensor (Gluco Dr Super Sensor; All Medicus Co., Ltd., Gyeonggi-Do, Korea) from blood samples drawn via the tail vein with a reading above 250 mg/dl were accepted as diabetic. No additional intervention was done in Group C and Group DC. After a four week follow-up period, laparotomy was performed in all groups using the following procedure. General anaesthesia induction was done using an intramuscular injection of 100 mg/kg ketamine hydrochloride (Ketalar® flakon; Parke-Davis, Detroit, MI, USA). Rats were kept under a heating lamp, and all procedures were performed with the rats in a supine position. Then, a skin asepsis midline laparotomy was performed. After removing the intestines from the surgical field, the infrarenal abdominal aorta was explored. The aorta was clamped using an atraumatic microvascular clamp, which was removed at the end of 120 min of an ischemia period, and then reperfusion was done for another 120 min.

Ischemia was determined by the disappearance of distal aorta pulsation, while reperfusion was determined by the reappearance of distal aorta pulsation. In the control group, laparotomy and abdominal aorta dissection were applied during the same time period (240 min); however, IR was not applied in these groups. In the other groups, in order to minimize heat and fluid loss, intraperitoneal serum physiological was administered at the clamping and declamping. Also, the abdominal incision was covered with wet gauze. In Group DIRD, 100 µg/kg dexmedetomidine was administered intraperitoneally 30 min before the ischemia period. At the end of the reperfusion period, biochemical and histopathological evaluations of lung tissue specimens were performed. Rats were decapitated at the end of the experiment.

Histopathological evaluation was performed in the Kirikkale University School of Medicine Histology and Embryology Department. After a routine fixation process, specimens were embedded in paraffin blocks, and 5 µ tissue sections were mounted on slides for staining with hematoxylin and eosin (H&E).

Histopathological Evaluation of the Lungs

All lung samples were examined histopathologically using light microscopy by the same embryologist who was blinded to the study. Ten random areas were evaluated microscopically in the H&E stained sections. Lung injury in each area was evaluated by determining the alveolar thickness and neutrophil infiltration or aggregation. Each parameter was evaluated as none (0 points), slight (1 point), moderate (2 points) or severe (3 points); the two scores were added, and the total score was interpreted as the lung injury score (10).

Biochemical evaluation was performed in the Gazi University School of Medicine Medical Biochemistry Department Research Laboratory. Oxidative stress and lipid peroxidation were evaluated based on MDA levels and measured according to the procedure described by Van Ye et al. using MDA levels in lung tissue (11). Also, SOD activities were measured according to the method described by Durak et al (12).

Statistical Analyses

IBM SPSS Statistics ver. 20.0 (IBM, Armonk, NY, USA) was used for statistical analysis. The Kolmogorov–Smirnov test was used for the comparisons to determine the distribution of all variable groups. Variations in SOD activities and MDA levels and histopathological parameters were assessed using the Kruskal-Wallis test. A Bonferroni adjusted Mann-Whitney *U* test was used after a significant Kruskal-Wallis to determine which groups differed from the others. Results were expressed as mean ± standard error (*SE*). Statistical significance was set at a p value < 0.05.

RESULTS

When the groups' lung tissue neutrophil infiltration/aggregation light microscopic findings were compared to each other, a significant difference was observed among the groups *(p*=0.003). Neutrophil infiltration/aggregation was found to be significantly higher in the DIR group compared to the C, DC and DIRD groups (*p*<0.0001, *p*=0.010 and *p*=0.010, respectively) (Table 1) (Figures 1-4). Alveolar wall thickening in lung tissue was found to be significantly higher in the DIR group compared to the C and DC groups (*p*<0.0001, *p*=0.004, respectively) (Table 1) (Figures 1-4).

Additionally, alveolar wall thickening was found to be significantly higher in the DIR and DIRD groups compared to the C group (*p*<0.0001, *p*=0.012, respectively). When the groups' lung tissue injury score light microscopic findings were compared, a significant difference was observed among the groups (*p*=0.001). The lung tissue injury score was found to be significantly higher in the DIR group compared to the C, DC and DIRD groups (*p*<0.0001, *p*=0.003 and *p*=0.017, respectively) (Table 1) (Figures 1-4). Additionally, the lung tissue injury score was found to be significantly higher in the DIR and DIRD groups compared to the C group (*p*<0.0001, *p*=0.029, respectively).

Table 1. Histopathological lung tissue findings (Mean ± *SE*)

	Group C (*n* = 6)	Group DC (*n* = 6)	Group DIR (*n* = 6)	Group DIRD (*n* = 6)	*P***
Neutrophil infiltration/aggregation	0.50 ± 0.22*	1.00 ± 0.26*	2.00 ± 0.26	1.00 ± 0.26	0.003
Alveolar wall thickening	0.50 ± 0.22*	1.00 ± 0.26*	2.17 ± 0.37[&]	1.50 ± 0.22[&]	0.001
Score	1.00 ± 0.37*	2.00 ± 0.45*	4.17 ± 0.54[&]	2.50 ± 0.43*,[&]	0.001

p:** Statistical significance was set at a *p* value < 0.05 for the Kruskal-Wallis test **, ****p* **< 0.05:** When compared with Group DIR, [&]***p* < 0.05:** When compared with Group C

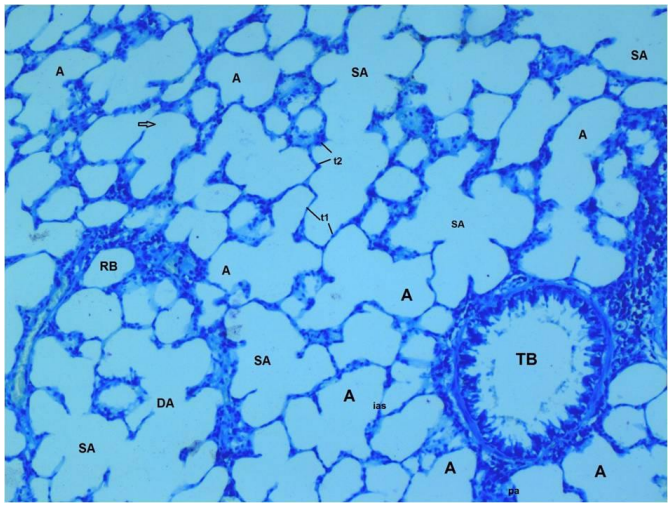

Figure 1: Normal structural lung tissue parenchyma in the control group, H&E x 100 (A: alveolus, TB: terminal bronchiole, RB: respiratory bronchiole, SA: saccus alveolaris, DA: ductus alveolaris, PA: pulmonary artery, ias: interalveolar septum, t1: type 1 alveolar cell nucleus, t2: type 2 alveolar cell nucleus and ⇨: interalveolar Kohn pores)

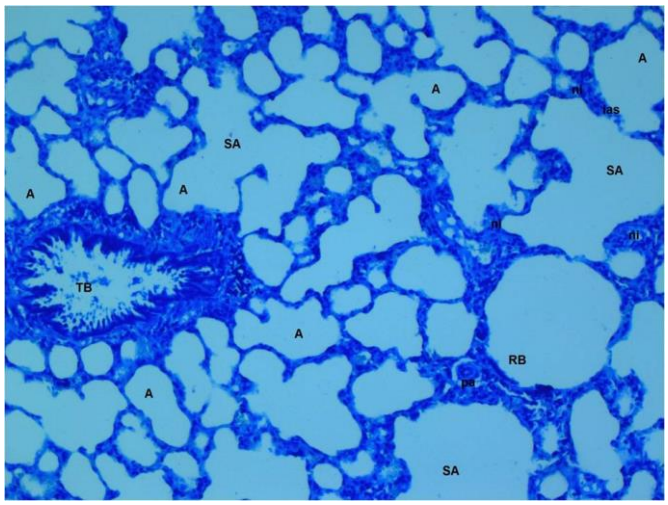

Figure 2: Mild neutrophilic infiltration and increased alveolar wall thickness in DC group, H&E x 100 (A: alveol, TB: terminal bronchiole, RB: respiratuar bronchiole, SA: saccus alveolaris, PA: pulmonary artery, ias: interalveolar septum and ni: neutrophil infiltration)

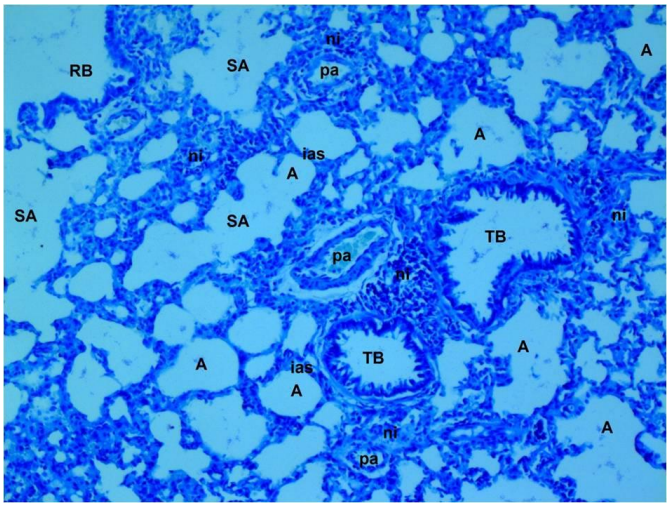

Figure 3: Severe neutrophilic infiltration and increased alveolar wall thickness in DIR group, H&E x 100 (A: alveol, TB: terminal bronchiole, RB: respiratuar bronchiole, SA: saccus alveolaris, PA: pulmonary artery, ias: interalveolar septum and ni: neutrophil infiltration)

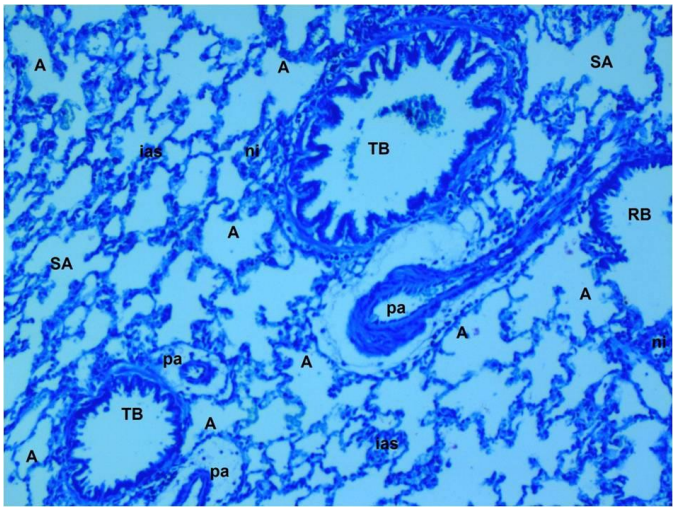

Figure 4: Mild neutrophilic infiltration and increased alveolar wall thickness in DIRD group, H&E x 100 (A: alveol, TB: terminal bronchiole, RB: respiratuar bronchiole, SA: saccus alveolaris, PA: pulmonary artery, ias: interalveolar septum and ni: neutrophil infiltration)

When the groups were compared to each other in terms of lung tissue MDA levels, a significant difference was observed (p=0.002). The MDA level was found to be significantly higher in the DIR group compared to the C, DC and DIRD groups (p<0.0001, p=0.004 and p=0.015, respectively) (Table 2). When the groups were compared to each other in terms of SOD enzyme activity, a significant difference was observed (p=0.018). SOD enzyme activity was found to be significantly higher in the DIR group compared to the C, DC and DIRD groups (p=0.002, p=0.041 and p=0.042, respectively) (Table 2).

Table 2. Oxidant status parameters of rat lung tissue (Mean ± *SE*)

	Group C (n = 6)	Group DC (n = 6)	Group DIR (n = 6)	Group DIRD (n = 6)	*P***
MDA (nmol/mg prot)	0.81 ± 0.32*	1.25 ± 0.39*	1.61 ± 0.27	0.73 ± 0.23*	0.002
SOD (IU/mg prot)	68.92 ± 14.99*	219.35 ± 26.15*	431.36 ± 138.52	210.74 ± 30.62*	0.018

p**: Statistical significance was set at a p value < 0.05 for the Kruskal-Wallis test
*****p* < 0.05:** When compared with Group DIR

DISCUSSION

Damage associated with IR in the lungs may occur in different situations. Damage may occur directly with ischemia developing in the lung tissue followed by reperfusion, and the damage that occurred may be associated with the mediators released into systemic circulation due to reperfusion after ischemia occurring in the other distant organs, such as extremities (1,2,6). Many human and animal studies exist on this subject. Furthermore, damage to the lungs has been studied in ischemic pre- and postconditions and through some externally administered medications; thus, its damage reducing role has been explored.

Changes in microcirculation are among the leading causes of lung tissue damage. Diabetes affects and disturbs microcirculation independently of these factors (13). Changes in microcirculation may negatively affect the ischemic period, causing enlargement of the ischemic area (13,14). For this reason, our study was conducted on diabetic rats. These changes also trigger the systemic inflammatory response. Damage to microcirculation shows the degree of organ damage and provides the opportunity to monitor the effectiveness of the interventions being made.

As in many other studies, our study histopathologically evaluated how the damage occurring in lung tissue changes with the interventions attempted. In our study, histopathogically alveolar wall thickness and neutrophil infiltration/aggregation were notably less prominent and statistically significant in the dexmedetomidine administered group. Similarly, Jiang et al. investigated the effect of dexmedetomidine in preventing pulmonary IR injury (15). They found that, whereas significant lung injury was histopathologically observed in the IR group, IR damage was less in the rats which were treated with 2.5 µg/kg/h of dexmedetomidine one h before IR. Another study on this subject was performed by Gu et al. (16) which reported that lung injury developed as a distant organ when compared to normal lung tissue after kidney IR, whereas dexmedetomidine reduced this damage. In this study, the histopathological findings indicated loss of integrity with haemorrhage in the lamina propria, increased interstitial cellularity, and deterioration of alveolar and pulmonary structures in the groups which were not given dexmedetomidine. Histopathological evaluation was carried out and scored in some studies. Shen et al. evaluated lung histopathology with semi-quantitative scoring (17). Pulmonary oedema, presence of inflammatory cells, presence of alveolar haemorrhage, hyaline membranes and alveolar atelectasis were evaluated as criteria. No observed lesion was classified as Score 0; damaged lung area ≤ 25% as Score 1; damaged lung area 26-50% as Score 2; damaged lung area 51-70% as Score 3; damaged lung area 70-90% as Score 4 and damaged lung area > 90% as Score 5. According to that study, pulmonary injury after intestinal IR was less frequent in the dexmedetomidine group. In a study by Yang et al. investigating the effects of dexmedetomidine in ventilatory-induced lung injury, morphological lung tissue injury, swelling in the alveolar epithelium, alveolar wall changes and the presence of the infiltration of polymorphonuclear leukocytes were classified as normal, mild, moderate or severe (18).

Some enzymes act as antioxidants in cells against damage caused by oxidative stress resulting from IR. A high level of these enzyme activities can be considered an indicator of cell protection against inflammation and subsequent lung damage. In our study, we measured SOD and MDA enzyme activities and investigated how the amount of cell protective enzymes was affected by dexmedetomidine. MDA is one of the final products of lipid peroxidation and is also evaluated to determine peroxidation of the cell wall. For this reason, MDA plasma and tissue levels are considered indicators of oxidative stress and systemic responses that occur after IR (19). All SOD aerobic cells contain SOD. Found in both the cytosol and mitochondria, this enzyme inactivates superoxide radicals, protecting the cells from the harmful effects of superoxide radicals (20). In our study, MDA and SOD levels were significantly higher in Group DIR than the DIRD levels in Group C. These findings may be a result of dexmedetomidine reducing oxidative stress. Shen and colleagues studied damage occurring in the lung after IR and the effect of dexmedetomidine on this damage in bronchi alveolar lavage fluid (17). They measured TNF-α and IL-6 concentration values by the enzyme-linked immunosorbent assay (ELISA) (Bio-Swamp Life Science, Wuhan, China) method. Accordingly, dexmedetomidine suppresses the production of cytokines, such as TNF-a and IL-6, which is more prominent at higher doses. In the study by Yang et al., ventilator-induced lung injury was assessed (18). They found that levels of chemokines and cytokines, such as TNF-α, IL-1β, IL-6 and MIP-2, were significantly lower in the groups treated with 5.0 µg/kg dexmedetomidine compared with the other groups. In our study, the levels of the above-mentioned inflammatory cytokines were not studied, and this may be considered a limitation of our study.

In a study by Yang et al., no positive effects of blood gas values (PO_2, OH and PCO_2) were observed with the administration of dexmedetomidine at low doses, but a significant elevation of PO_2 values was detected at higher doses (18). On the other hand, in the study of Jiang et al., no change was found between the groups in blood gas analysis (15). Similarly, blood gas changes were not significant in the study of Shen and colleagues (17). Since we could not perform blood gas analysis in our study, this may be considered another limitation of the study.

In conclusion, the results of this study support that dexmedetomidine is effective in preventing pulmonary damage after lower extremity IR. Although our study has some limitations, further studies should be performed to investigate this issue in greater depth.

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

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