ORIGINAL RESEARCH

Med J SDU / SDÜ Tıp Fak Derg ▸ 2025:32(1):73-80 ▸ doi: 10.17343/sdutfd.1530958

Panthotenic Acid Derrivate Dexpanthenol Mitigates the Effects of Lung Ischemia-Reperfusion Induced Cardiac Damage by its Anti-Inflammatory Action

Mehtap SAVRAN[1], Melih ARLIOGLU[1], Ozlem OZMEN[2]

[1] Suleyman Demirel University, Faculty of Medicine, Department of Pharmacology, Isparta, Türkiye
[2] Burdur Mehmet Akif Ersoy University, Faculty of Veterinary, Department of Pathology, Burdur, Türkiye

Cite this article as: Savran M, Arlıoğlu M, Ozman O. Panthotenic Acid Derrivate Dexpanthenol Mitigates the Effects of Lung Ischemia-Reperfusion Induced Cardiac Damage by its Anti-Inflammatory Action. Med J SDU 2025;32(1):73-80.

Abstract

Objective
Pulmonary ischemia-reperfusion (IR) injury causes cardiac damage through inflammation related to hypoxic conditions. Dexpanthenol (DEX) has an anti-inflammatory action in various tissues such as lung, liver, and kidney. This study aimed to show the effects of DEX on myocardial damage secondary to pulmonary IR injury.

Material and Method
Thirty two rats were randomly divided into four groups as sham, IR, DEX (500 mg/kg, intraperitoneally, single dose), and IR+DEX. After left thoracotomy, non-traumatic vascular clamping was applied for 60 minutes, followed by 60 minutes of reperfusion to create a lung IR model. After sacrification, heart tissues were collected and placed in formaldehyde solution for histopathological and immunohistochemical analyses. Hyperemia, hemorrhage, and degeneration were examined, Immunostainings of cyclooxygenase-1 (COX-1), hypoxia-inducible factor 2 alpha (HIF-2α), and interferon alpha (IFα) were performed.

Results
Cardiomyocytes in the sham group appeared elongated, branching, and of normal size with well-defined intercalated discs. Delicate endomysium sheaths surrounding the cardiac cells were observed, along with a dense capillary network surrounding the cells. In contrast, the IR group exhibited alterations in cardiac tissue, including hyperemia, hemorrhage, and disruption of the cross-striated banding pattern of the cardiac cells. Also; COX-1, EPAS-1/HIF-2α, and IFα expressions were elevated in the IR group. Treatment with DEX resulted in a reduction of these pathological outcomes.

Conclusion
In the context of pulmonary IR, damage is likely to occur not only in lung tissue but also in other organs. This is attributed to the dissemination of immunomodulatory cytokines developed within the tissue to other organs through the bloodstream. DEX is a derivative of pantothenic acid, recognized for its tissue-protective effects. In this study, it was histopathologically and immunohistochemically shown that DEX could be protective against lung IR-induced cardiac damage.

Keywords: Cardiac damage, Dexpanthenol, Ischemia-reperfusion, Lung ischemia

Correspondence: M.S. / mehtapsavran@sdu.edu.tr
Received: 09.08.2024 • Accepted: 29.01.2025
ORCID IDs of the Authors: M.S: 0000-0002-7933-0453; M.A: 0009-0009-4356-5857; O.O: 0000-0002-1835-1082

Introduction

Pulmonary ischemia reperfusion (IR) injury is a serious condition that occurs especially in cases of pulmonary embolism cardiopulmonary bypass, circulatory arrest, and lung transplantation (1). Both lung IR injury and its complications may cause significant mortality and morbidity rates (2, 3). For example, severe primary graft dysfunction is observed in approximately 30% of transplant patients due to IR injury during lung transplantation, (4).

The abrupt onset of ischemia in the pulmonary artery creates resistance against right ventricular contraction. Since the heart and lungs are connected by large vessels, it is anticipated that any vascular pathology impacting one will invariably influence the other. In circumstances where there is an elevation in pulmonary artery pressure, such as in cases of pulmonary embolism, probably, there will also be an increase in pressure within the right ventricle of the heart, leading to cardiac damage (5). Another damage mechanism in cardiac tissue is the reflection of oxidative stress and inflammation that develops in other tissues (1).

When oxygenation and blood supply are impaired, hypoxia-related damage begins to develop in the tissue. Cells' energy production slows down, protein synthesis decreases, and it becomes unable to provide the resources necessary to sustain life. Disruption of ATP metabolism results in hypoxanthine accumulation and the formation of reactive oxygen species (ROS) (6). The ischemic damage ultimately results in cell death accompanied by the release of damage-associated molecules. These molecules stimulate cytokine synthesis, such as interferon alpha (IFα) and other interleukines, and the inflammatory response that can cause secondary organ injuries such as cardiac injury (1, 7) (Figure 1).

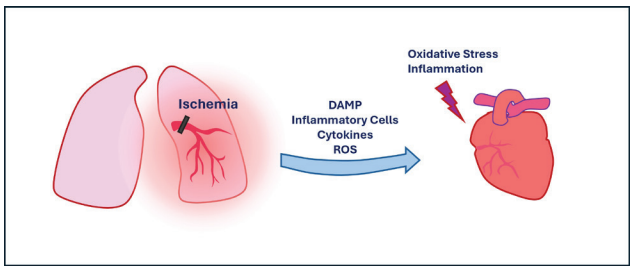

Figure 1
The mechanism of lung ischemia reperfusion induced cardiac injury. DAMP: Damage associated molecular pattern, ROS: Reactive oxygen species

Although reestablishment of blood flow and oxygenation forms the basis of recovery, it also mediates the formation of another condition called reperfusion injury. Oxygen rushing into the tissue during reperfusion becomes the substrate for the production of reactive oxygen radicals resulting from intracellular metabolic disorders. While it provides the oxygen needed by the tissue, on the other hand, it increases the formation of ROS that cause damage (6). Some studies have suggested that reperfusion injury is mediated by inflammatory cell activation in the reperfused tissue (8, 9). Exacerbation of inflammatory response in ischemic lung injury can lead to major organ dysfunction and multiple organ failure (10).

In the tissue where secondary damage develops, some pathways are activated at the cellular level, in addition the to changes mentioned above. Inflammation and ROS induced oxidative stress stimulate cyclooxygenase (COX) enzymes and hypoxia-inducible factor (HIF) derivatives involved in the production of prostaglandins, which reinforce or reduce inflammation with local hormonal effects (11, 12).

Dexpanthenol (DEX) is a derivative of vitamin B_5, used in wound healing due to its tissue-protective effect. DEX has been stated to be protective for many tissues from neurons to the liver due to its antioxidant, antiinflammatory, and antiapoptotic properties (13-16). Studies have shown that DEX reduces oxidative stress which develops through various mechanisms including IR-induced damage, by preserving levels of glutathione, myeloperoxidase, and catalase. (16). Additionally, DEX has been found to lower inflammatory cytokine levels and reduce both apoptosis and inflammation by influencing the endoplasmic reticulum stress pathway and decreasing caspase levels (15, 17, 18). There are also studies showing that DEX may be protective in cardiac damage developing with different pathological mechanisms or in IR injury of several organs by the antioxidant and anti-inflammatory pathways (19-22). However reflecting the importance of our study, there is no data on its use in lung IR injury induced cardiac damage, yet.

As lung IR injury involves several pathological mechanisms, various alternatives that provide mitochondrial protection or nitric oxide synthetase regulation, or reduce the inflammation have been included in the treatment (3). Nevertheless, there is still a need for new molecules, especially to use in combination therapies to prevent or reduce lung IR injury. Considering the therapeutic properties, we

assume that DEX may be beneficial. So, the present study was designed to deepen our understanding of the possible protective effects of DEX on lung IR induced cardiac injury.

Material and Method

Ethics and Experimental Model

Thirty-two adult male Wistar Albino rats obtained from the Suleyman Demirel University Experimental Animals Laboratory weighing range of 300-350 g were used in the experiment. Rats were kept at 21-22 degrees Celcius, 12 hours of light, and 12 hours of darkness. An ad libutium feeding regimen was applied. Rats were randomly divided into four groups, with eight rats in each group. The groups were assigned as follows:

Sham group: 1 ml/kg saline was administered intraperitoneally (i.p.) to the rats. After 30 minutes, a thoracotomy procedure was performed under anesthesia, but the IR model was not performed and hilus was visualized.

IR group: 1 ml/kg saline was administered i.p. to the rats. After 30 minutes, a thoracotomy procedure was performed under anesthesia. After the left thoracotomy, a non-traumatic vascular clamp was placed on the hilus for 60 minutes of ischemia. Then, 60 minutes of reperfusion was performed (16).

IR+DEX group: 500 mg/kg DEX (Bepanthen® 500mg/2ml flk, Bayer, Turkiye) as a single dose was administered i.p. to rats. After 30 minutes, a thoracotomy procedure was performed under anesthesia. After left thoracotomy, a non-traumatic vascular clamp was placed on the hilus for 60 minutes of ischemia. Then, 60 minutes of reperfusion was performed (16).

DEX group: 500 mg/kg DEX as a single dose was administered i.p. to rats. After 30 minutes, a thoracotomy procedure was performed under anesthesia, but the IR model was not performed.

Following a 12-hour fasting period, experimental animals were subjected to i.p. anesthesia with Ketamine (80-100 mg/kg) / Xylazine (8-10 mg/kg). Subsequently, the thoracic region was shaved, and a left thoracotomy was performed under anesthesia. After identification of the left lung hilum and trachea, non-traumatic vascular clamping was applied for 60 minutes, followed by 60 minutes of reperfusion. Once reperfusion was confirmed by visualization of blood flow, the animals were euthanized. Surgical exsanguination was carried out via abdominal incision. After sacrification, heart tissues were collected and placed in formaldehyde solution for histopathological and immunohistochemical analyses.

Histopathological Method

Heart samples were collected and preserved in a 10% neutral formalin solution. The heart samples were then embedded in paraffin wax following standard tissue processing using a fully automated tissue processing device (Leica ASP300S, Wetzlar, Germany). Subsequently, 5 µm thick sections were cut from the paraffin blocks using a fully automated rotary microtome (Leica RM2155, Leica Microsystems, Wetzlar, Germany). These sections underwent staining with hematoxylin-eosin (HE), followed by cover slipping, and examination under light microscopy.

Histological lesions in the hearts were graded semi-quantitatively using an ordinal grading system. This evaluation included assessing hyperemia, hemorrhage, inflammatory cell infiltrations, and degenerative necrotic changes in myocardial cells. Descriptions of normal (score = 0) to severe (score = 3) affections were assigned (Table 1) (23).

Table 1 Histopathological and immunohistochemical graduation of analysis

Scores	Histopathological graduation	Immunohischemical graduation
0	Normal	No expression
1	Mild: Mild hyperemia with no additional findings	Focal and weak staining
2	Moderate: Moderate hyperemia with mild hemorrhage	Diffuse and weak staining
3	Severe: Presence of degeneration in addition to marked hyperemia and hemorrhage	Diffuse and marked staining

Immunohistochemical Examination

For immunohistochemical analysis, three series of slices were cut from the paraffin blocks and mounted on slides coated with poly-L-lysine. Then sections were subjected to immunohistochemical staining following the manufacturer's instructions to assess the expression of COX-1, Endothelial PAS domain-containing protein 1 (EPAS-1)/HIF-2α, and IFα using the streptavidin-biotin method. Primary antibodies used were COX-1 [COX-1 Antibody (17): sc-19998 (Santa Cruz, Texas, USA)], HIF-2 α [EPAS-1/HIF-2α Antibody (190b): sc-13596 (Santa Cruz, Texas, USA)], and IFα [IFα Antibody (PA5-119649)] (ThermoFisher Scientific, MA, USA) at a [1/100] dilution. Immunohistochemistry was performed on the sections using streptavidin-alkaline phosphatase conjugate and a biotinylated secondary antibody after a 60-minute incubation with the primary antibodies. Mouse and Rabbit Specific HRP/DAB IHC Detection Kit - Micro-polymer (ab236466) from Abcam (Cambridge, UK) was used as the secondary antibody, and diaminobenzidine (DAB) was employed as the chromogen. For negative controls, antigen dilution solution was applied instead of primary antibodies. Each evaluation was conducted on blinded samples by a specialized pathologist.

At an objective magnification of X40, the immunohistochemical expressions were scored on a scale of 0-3. Accordingly, 0 indicates no expression, 1 indicates focal and weak staining, 2 indicates diffuse and weak staining, and 3 indicates diffuse and marked staining (Table 1) (23) The Image J 1.46r software (National Institutes of Health, Bethesda MD) was used to determine the positive immunohistochemical reaction. Olympus CX41 model microscope was used for photographing the results, and the Database Manual Cell Sens Life Science Imaging Software System (Olympus Corporation, Tokyo, Japan) was used for microphotography.

Statistical Analysis

Statistical analyzes include histopathological evaluation scores and staining levels of immunological markers. For this purpose, non-parametric Kruskall Wallis test was used for multiple group comparisons and Mann Whitney U test was used for two group comparisons - by using a a package program. The level of significance was considered at $p<0.05$.

Results

Histopathological Findings

Microscopic examination revealed no pathological findings in the myocardial tissue of the sham and DEX groups. Cardiomyocytes in these groups showed signs of elongation, branching, and normal size with well-defined intercalated discs. Delicate endomysium sheaths surrounding the cardiac cells were observed, along with a dense capillary network surrounding the cells. In contrast, the IR group exhibited alterations in cardiac tissue, including hyperemia, hemorrhage, and disruption of the cross-striated banding pattern of the cardiac cells. Treatment with DEX resulted in the amelioration of these pathological findings. The differences in the IR group compared to the sham and in the IR+DEX group compared to the IR were both statically significant ($p<0.001$ and $p<0.01$, respectively) (Figure 2).

Immunohistochemical Findings

Immunohistochemical investigations showed very low or non-existent expression of COX-1, EPAS-1/HIF-2α, and IFα in the sham group. In contrast, the myocardial cells of the IR group exhibited moderate to markedly elevated levels of COX-1, EPAS-1/HIF-2α, and IFα expressions. Treatment with DEX resulted in a reduction of these pathological outcomes (Figures 3, 4, 5).

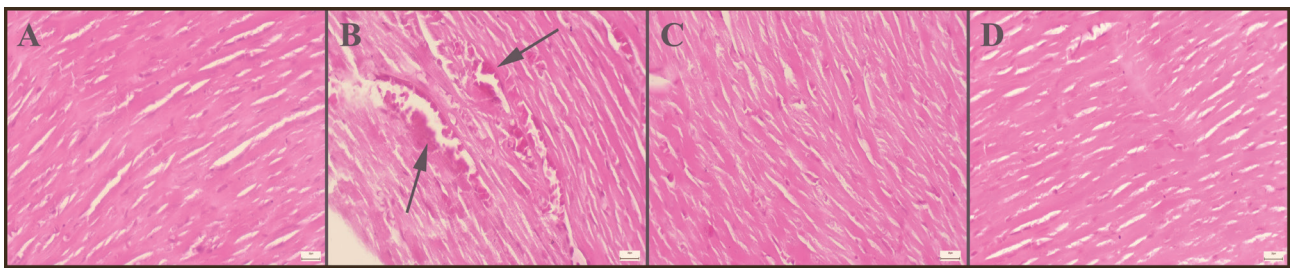

Figure 2

Representative histopathological figures A: Normal myocardial tissue histology in sham group, B: Severe hyperemia and hemorrhage (arrows) in IR group, C: Marked amelioration in IR+DEX group, D: Normal myocardium histology in DEX group, HE, scale bars=20μm

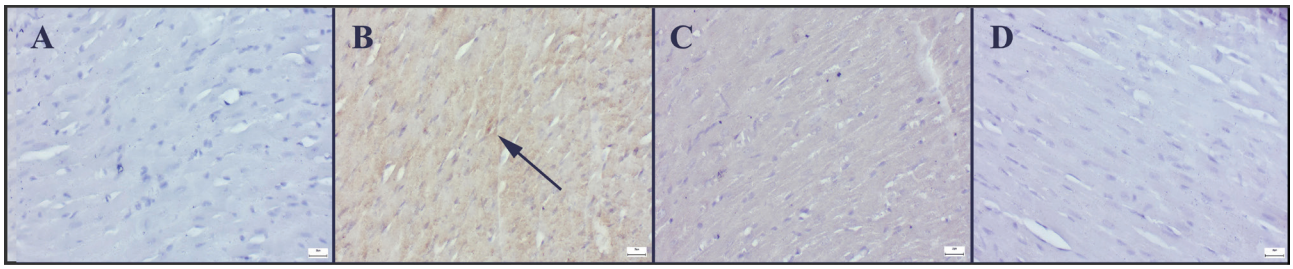

Figure 3
mmunohistochemically COX-1 expressions of heart tissues of the groups. A: Negative expression in sham group, B: Increased expressions in myocardial cells (arrows) in IR group, C: Markedly decreased expression in IR+DEX group, D: Negative expression in DEX group, Scale bars=20μm, streptavidin biotin peroxidase method.

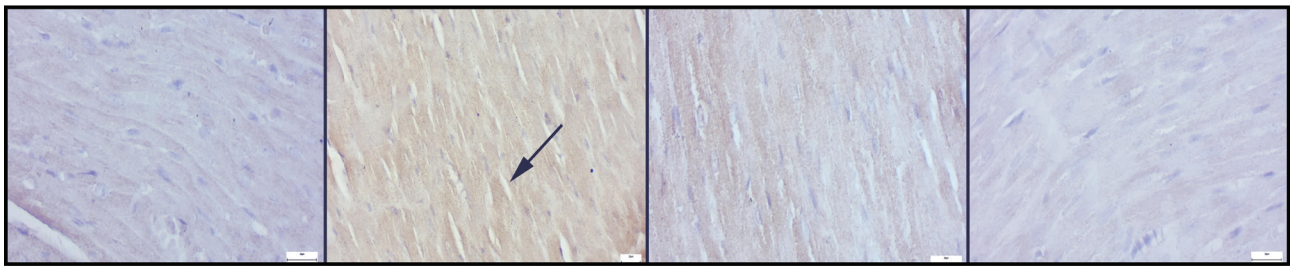

Figure 4
Immunohistochemically EPAS-1/HIF-2α expressions of heart tissues among the groups. A: Negative expression in sham group, B: Increased expressions in myocardial cells (arrows) in IR group, C: Markedly decreased expression in IR+DEX group, D: Negative expression in DEX group, Scale bars=20μm, streptavidin biotin peroxidase method.

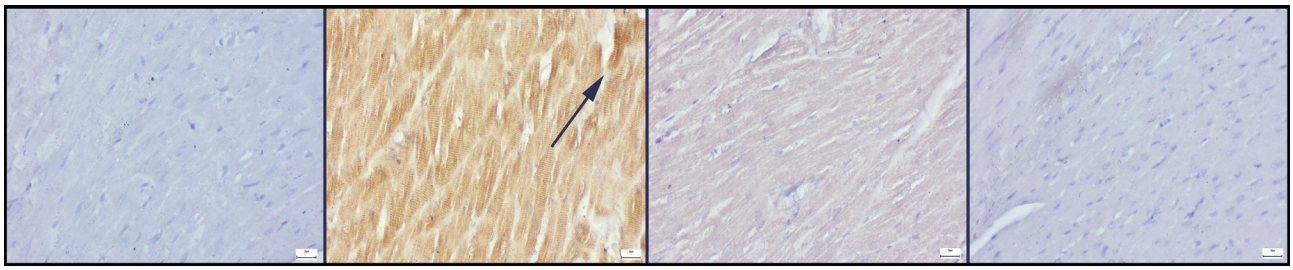

Figure 5
Immunohistochemically IFα expressions of heart tissues of the groups. A: Negative expression in sham group, B: Increased expressions in myocardial cells (arrows) in IR group, C: Markedly decreased expression in IR+-DEX group, D: Negative expression in DEX group, Scale bars=20μm, streptavidin biotin peroxidase method.

In immunohistochemical scoring, a statistically significant increase in COX-1, EPAS-1/HIF-2α, and IFα scores was observed in the IR group compared to the sham group ($p<0.001$ for all). These changes were significantly reversed in the DEX+IR group compared to the IR group ($p<0.01$ for all). One of the interesting findings of the statistical analysis was that the difference between the IR+DEX group and the sham group in terms of EPAS-1/HIF-2α was not statistically significant. Distribution of the data in groups as median and mode within parenthesis and the p values of the comparisons were shown in Table 2.

Table 2 The statical analyses of histopathological and immunohistochemical scores

Marker/Group	Sham (n=8)	IR (n=8)	IR+DEX (n=8)	DEX (n=8)
COX	0 (0)[a,b]	2.5 (3)[a,c]	1 (1)[b,c]	0 (0)
HIF-2α	0.5 (0)[a]	3 (3)[a,c]	1(1)[c]	0 (0)
IF α	0 (0)[a,b]	3 (3)[a,c]	1 (1)[b,c]	0 (0)
Histopathologic evaluation	0 (0)[a]	2 (2)[a,c]	0.5 (0)[c]	0 (0)

IR: ischaemia reperfusion, DEX: dexpanthenol, COX: cyclooxygenase, HIF-2a: hypoxia-inducible factor 2 alpha, IFa: interferon alpha, a: p<0.001, b: p=0.05, c: p< 0.01. data are expresses as mean and mode within parantheses.

Discussion

IR injury consist of ischaemia-induced tissue damage and reperfusion-induced oxidative damage. Tissue damage increases with the contribution of inflammation secondary to IR. Due to cytokines and ROS released into the circulation, damage may develops in organs other than the ones in which IR injury develops (24).

In our study, the presence of hyperemia, hemorrhage, and disruption in the cross-striated banding pattern of cardiac cells indicates the development of inflammation-related damage in the heart during lung IR injury. Disruption of the cross-striated banding pattern of the cardiac cells leads to impaired cardiac muscle contraction. Irregularity of muscle contraction may also be a symptom of arrhythmias caused by inflammation (25, 26). Regression of these findings with DEX treatment demonstrates a reduction in inflammation and is an important finding of our study.
The HIF pathway is one of the systems that protects the organism under hypoxic conditions. (27). HIF-2α predominantly controls a wide range of transcription factors and coregulators, contributing to its diverse functions in hypoxic conditions. HIF-1α stands as the most extensively studied isoform, while HIF-3α emerges as the most novel isoform. Among them, HIF-2α exhibits a more tissue-specific manner and is highly expressed in cardiac, endothelial, and hepatic tissues, etc. It was shown that an increase in HIF-2α led to enhanced vascular permeability in kidney tissue with IR, thereby prolonging inflammatory cell migration and inflammation (28). Additionally, in inflamed tissue, hypoxia is not surprising because of increased metabolic demand (29). Thus, HIF-2α expressions could be induced by hypoxia and/or inflammation directly and/or indirectly. In our study, lung IR-induced hypoxic conditions in cardiac cells were proven by increased HIF-2α levels, and decreases were shown by DEX. Importantly, it is the first report that DEX reduced HIF-2α levels in lung IR-induced cardiac damage. Considering the previous reports on the anti-inflammatory effect of DEX, it is possible that DEX decreased HIF-2α levels by its anti-inflammatory properties. One of the interesting results of our study was that the difference between sham and IR+DEX groups was not statically significant in terms of HIF-2α. It can be concluded that DEX improved the response to hypoxia in damaged tissue to the point that it approached the sham group. These results deserve more detailed studies.

It is known that COX enzymes play a role in the synthesis of prostaglandins from fatty acids such as arachidonic acid located in the cell membrane. Prostaglandins, synthesized within the cell, are predominantly locally acting products with an important role in inflammation management (12). Although COX-1 is considered as a structural enzyme and COX-2 is mostly associated with inflammatory processes, it was reported in a study that COX-1 and COX-2 were increased together in an IR injury model (30, 31). In addition, some studies have suggested the need to focus on endothelial COX-1 due to its possible contribution to vascular dysfunction (32). COX-1 activation leads to vasoactive prostaglandin and thromboxan A2 production which means further vascular constriction (33). Considering these facts, COX-1 was evaluated in this study, and the increase in COX-1 in the IR group is considered as another indicator of inflammation developing in the tissue. A decrease in COX-1 immunoexpression with DEX treatment, along with other findings, indicates the regression of inflammation. It is also known that inhibition of COX-1 reduces the impairment of endothelial dysfunction in inflamed tissue (34). HIF-2α and COX-1 are both involved in cardiac endothelial vascular changes in the case of inflammation. The decreases in the immunoexpression of HIF-2α and COX-1 with DEX could both reduce inflammation and protect the cardiac endothelium from the inflammation-related changes.

IFα is another cytokine that regulates and modulates the activation of the immune system. Its role in inflammation is somewhat intricate. As an immunoregulatory cytokine, IFα typically limits inflammation, yet elevated levels of IFα activity can, in certain instances, exacerbate inflammation and increase tissue damage (35). In our study, the observed increase in IFα levels in the IR group indicates the activation of the immune system. This immune activation signifies the occurrence of inflammation in the cardiac tissue. Conversely, in the treatment group, the lower IFα activity compared to the IR group could be interpreted as DEX reduced inflammation initiated in the cardiac tissue.

There are some limitations of the current study. Firstly, due to the acute design of the study, DEX was administrated on one day and in a single dose. The effect of repeated or different doses of DEX should be evaluated in further studies. Secondly, we used only histopathological and immunohistochemical analyses to evaluate the DEX effect on cardiac tissues. The results should be confirmed by quantitative analyses such as PCR, Elisa, or Western Blot as well as qualitative analyses. Lastly, we monitored the inflammatory changes in cardiac tissue through the immunoexpressions of the final proteins of some pathways. To conclude to how DEX affects on inflammation, the related pathways should be evaluated.

In the context of pulmonary IR, the damage is likely to occur not only in lung tissue but also in other organs, secondary. This is attributed to the dissemination of immunomodulatory cytokines developed within the tissue through the bloodstream to other organs. DEX, a derivative of pantothenic acid recognized in the literature for its tissue-protective effects and known for anti-inflammatory properties, mitigates inflammation in cardiac damage resulting from lung IR injury, as evidenced by these alterations and changes in immunological markers.

Considering the importance of the IR injury in various tissues, it is important to have a sufficent number of treatment alternatives. The fact that the treatment alternative is an easily available, inexpensive and relatively safe molecule such as DEX will provide a significant advantage for such an important clinical situation. Thus, the protective effects of DEX in IR injuries should also be studied in clinical settings.

Conflict of Interest Statement
Dr. Savran and the co-authors have no conflicts of interest to declare in association with this study.

Ethical Approval
The experimental design adhered to the guidelines for animal research set forth by the National Institutes of Health, and received approval from the Committee on Animal Research at Suleyman Demirel University prior to commencement of the study (approval no: 11.07.2024/08-309).

Funding
This study was supported by the Scientific Research Projects Coordination Unit of Suleyman Demirel University with project code TSG- 2023-9010.

Availability of Data and Materials
The data is available upon reasonable requests from the Corresponding Author.

Authors Contributions
MS: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

MA: Investigation; Formal analysis; Writing-original draft.

OO: Data curation; Formal analysis; Writing-original draft; Writing- review & editing.

References

1. Wu NC, Chen TH, Yang YC, et al. N-acetylcysteine improves cardiac contractility and ameliorates myocardial injury in a rat model of lung ischemia and reperfusion injury. Transplant Proc 2013;45(10):3550–4.
2. Ye X, Pei F, Li W, Xue J, Huang X, Huang J, Zhang L. Fibroblast growth factor 21 attenuates pulmonary ischemia/reperfusion injury via inhibiting endoplasmic reticulum stress-induced ferroptosis though FGFR1/PPARδ signaling pathway. Int Immunopharmacol 2024;25;143(Pt 1):113307. doi: 10.1016/j.intimp.2024.113307. Epub 2024 Oct 3. PMID: 39366074.
3. den Hengst WA, Gielis JF, Lin JY, Van Schil PE, De Windt LJ, Moens AL. Lung ischemia-reperfusion injury: a molecular and clinical view on a complex pathophysiological process. Am J Physiol Heart Circ Physiol 2010;299(5):H1283-99. doi: 10.1152/ajpheart.00251.2010. Epub 2010 Sep 10. PMID: 20833966.
4. Laubach VE, Sharma AK. Mechanisms of lung ischemia-reperfusion injury. Curr Opin Organ Transplant 2016;21(3):246-52. doi: 10.1097/MOT.0000000000000304. PMID: 26945320; PMCID: PMC4861054.
5. Dutta T, Frishman WH, Aronow WS. Echocardiography in the evaluation of pulmonary embolism. Cardiol Rev 2017;25(6):309–14.
6. Chen-Yoshikawa TF. Ischemia-reperfusion ınjury in lung transplantation. Cells 2021;10(6).
7. McDonough A, Lee RV, Noor S, et al. Ischemia/reperfusion ınduces ınterferon-stimulated gene expression in microglia. J Neurosci 2017;37(34):8292–308.
8. Kubes P, Jutila M, Payne D. Therapeutic potential of inhibiting leukocyte rolling in ischemia/reperfusion. J Clin Invest 1995;95(6):2510–9.
9. Pillai R, Bando K, Schueler S, et al. Leukocyte depletion results in excellent heart-lung function after 12 hours of storage. Ann Thorac Surg 1990;50(2):211–4.

10. Asimakopoulos G, Smith PL, Ratnatunga CP, et al. Lung injury and acute respiratory distress syndrome after cardiopulmonary bypass. Ann Thorac Surg 1999;68(3):1107–15.
11. Ullah K, Ai L, Humayun Z, Wu R. Targeting endothelial HIF2α/ARNT expression for ıschemic heart disease therapy. Biology 2023;12(7).
12. Yu T, Lao X, Zheng H. Influencing COX-2 Activity by COX related pathways in ınflammation and cancer. Mini Rev Med Chem 2016;16(15):1230–43.
13. Bilister Egilmez C, Azak Pazarlar B, Erdogan MA, Erbas O. Neuroprotective effect of dexpanthenol on rotenone-induced Parkinson's disease model in rats. Neurosci Lett 2024;818:137575. doi: 10.1016/j.neulet.2023.137575. Epub 2023 Nov 29. PMID: 38040406.
14. Gürler M, Selçuk EB, Özerol BG, Tanbek K, Taşlıdere E, Yıldız A, Yağın FH, Gürel E. Protective effect of dexpanthenol against methotrexate-induced liver oxidative toxicity in rats. Drug Chem Toxicol 2023;46(4):708-716. doi: 10.1080/01480545.2022.2084103. Epub 2022 Jun 2. PMID: 35655424.
15. Erdogan MA, Yigitturk G, Erbas O, et al. Neuroprotective effects of dexpanthenol on streptozotocin-induced neuronal damage in rats. Drug Chem Toxicol 2022;45(5):2160–8
16. Ucar M, Aydogan MS, Vardı N, et al. Protective effect of dexpanthenol on ischemia-reperfusion-induced liver injury. Transplant Proc. 2018;50(10):3135–43.
17. Tepebaşı MY, Büyükbayram Hİ, Özmen Ö, et al. Dexpanthenol ameliorates doxorubicin-induced lung injury by regulating endoplasmic reticulum stress and apoptosis. Naunyn Schmiedebergs Arch Pharmacol 2023;396(8):1837–45.
18. Zhao X, Zhang S, Shao H. Dexpanthenol attenuates inflammatory damage and apoptosis in kidney and liver tissues of septic mice. Bioengineered 2022;13(5):11625–35.
19. Ozcan MS, Savran M, Kumbul Doguc D, Kubra Dogan H, Altintas M, Cosan S. Dexpanthenol ameliorates lipopolysaccharide-induced cardiovascular toxicity by regulating the IL-6/HIF1α/VEGF pathway. Heliyon 2024;10(1):e24007. doi: 10.1016/j.heliyon.2024.e24007. PMID: 38268590; PMCID: PMC10806266.
20. Kalkan F, Parlakpinar H, Disli OM, Tanriverdi LH, Ozhan O, Polat A, Cetin A, Vardi N, Otlu YO, Acet A. Protective and therapeutic effects of dexpanthenol on isoproterenol-induced cardiac damage in rats. J Cell Biochem 2018;119(9):7479-7489. doi: 10.1002/jcb.27058. Epub 2018 May 18. PMID: 29775243.
21. Aydın A, Sönmez MG, Ecer G, Kılınç F, Kocabaş R, Atılgan AE, Oltulu P, Balasar M. The effect of intratesticular dexpanthenol on experimentally-induced testicular ischaemia/reperfusion injury. J Pediatr Urol 2021;17(4):440.e1-440.e7. doi: 10.1016/j.jpurol.2021.03.031. Epub 2021 Apr 8. PMID: 33883095.
22. Zakaria MM, Hajipour B, Khodadadi A, Afshari F. Ameliorating effects of dexpanthenol in cerebral ischaemia reperfusion induced injury in rat brain. J Pak Med Assoc 2011;61(9):889-92. PMID: 22360030.
23. Tepebaşi MY, Aşci H, Coşan S, Sevük MA, Karakuyu NF, Özmen Ö. Irbesartan has a curative effect on lipopolysaccharide-induced cardiotoxicity by antioxidant and antiapoptotic pathways. Rev Port Cardiol 2023;42(11):895-903. English, Portuguese. doi: 10.1016/j.repc.2023.03.018. Epub 2023 Jun 27. PMID: 37385588.
24. Katira BH, Giesinger RE, Engelberts D, et al. Adverse Heart-lung ınteractions in ventilator-induced lung injury. Am J Respir Crit Care Med 2017;196(11):1411–21.
25. Herrmann J. Adverse cardiac effects of cancer therapies: Cardiotoxicity and arrhythmia. Nat Rev Cardiol 2020;17(8):474–502.
26. Peretto G, Sala S, Rizzo S, et al. Arrhythmias in myocarditis: State of the art. Heart Rhythm 2019;16(5):793–801.
27. Taylor CT, Scholz CC. The effect of HIF on metabolism and immunity. Nat Rev Nephrol 2022 Sep;18(9):573-587. doi: 10.1038/s41581-022-00587-8. Epub 2022 Jun 20. PMID: 35726016; PMCID: PMC9208707.
28. Kapitsinou PP, Sano H, Michael M, et al. Endothelial HIF-2 mediates protection and recovery from ischemic kidney injury. J Clin Invest 2014;124(6):2396–409.
29. Majmundar AJ, Wong WJ, Simon MC. Hypoxia-inducible factors and the response to hypoxic stress. Mol Cell 2010;40(2):294-309. doi: 10.1016/j.molcel.2010.09.022. PMID: 20965423; PMCID: PMC3143508.
30. Simon LS. Role and regulation of cyclooxygenase-2 during inflammation. Am J Med 1999;31;106(5B):37S-42S. doi: 10.1016/s0002-9343(99)00115-1. PMID: 10390126.
31. Feitoza CQ, Câmara NO, Pinheiro HS, Gonçalves GM, Cenedeze MA, Pacheco-Silva A, Santos OF. Cyclooxygenase 1 and/or 2 blockade ameliorates the renal tissue damage triggered by ischemia and reperfusion injury. Int Immunopharmacol 2005;5(1):79-84. doi: 10.1016/j.intimp.2004.09.024. PMID: 15589463.
32. Félétou M, Huang Y, Vanhoutte PM. Endothelium-mediated control of vascular tone: COX-1 and COX-2 products. Br J Pharmacol 2011;164(3):894–912.
33. Vanhoutte PM. COX-1 and vascular disease. Clin Pharmacol Ther 2009;86(2):212–5.
34. Graupera M, García-Pagán JC, Parés M, et al. Cyclooxygenase-1 inhibition corrects endothelial dysfunction in cirrhotic rat livers. J Hepatol 2003;39(4):515–21.
35. Ji L, Li T, Chen H, et al. The crucial regulatory role of type I interferon in inflammatory diseases. Cell Biosci 2023;13(1):230.