RENAL FAILURE

Taylor & Francis
Taylor & Francis Group

Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: https://www.tandfonline.com/loi/irnf20

The effect of hyperbaric oxygen therapy on rhabdomyolysis-induced myoglobinuric acute renal failure in rats

Gamze Cebi, Şenol Yildiz, Gunalp Uzun, Yeşim Oztas, Suna Sabuncuoglu, Ayhan Kutlu, Yasin Ilgaz, Iclal Karatop-Cesur, Eyup Dogan & Emin Oztas

To cite this article: Gamze Cebi, Şenol Yildiz, Gunalp Uzun, Yeşim Oztas, Suna Sabuncuoglu, Ayhan Kutlu, Yasin Ilgaz, Iclal Karatop-Cesur, Eyup Dogan & Emin Oztas (2016) The effect of hyperbaric oxygen therapy on rhabdomyolysis-induced myoglobinuric acute renal failure in rats, Renal Failure, 38:9, 1554-1559, DOI: 10.1080/0886022X.2016.1227925

To link to this article: https://doi.org/10.1080/0886022X.2016.1227925

Published online: 20 Oct 2016.

Submit your article to this journal

Article views: 695

View related articles

View Crossmark data

Citing articles: 1 View citing articles

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=irnf20

RENAL FAILURE, 2016
VOL. 38, NO. 9, 1554–1559
http://dx.doi.org/10.1080/0886022X.2016.1227925

Taylor & Francis
Taylor & Francis Group

LABORATORY STUDY

The effect of hyperbaric oxygen therapy on rhabdomyolysis-induced myoglobinuric acute renal failure in rats

Gamze Cebi[a], Şenol Yildiz[a], Gunalp Uzun[a], Yeşim Oztas[b], Suna Sabuncuoglu[c], Ayhan Kutlu[d], Yasin Ilgaz[d], Iclal Karatop-Cesur[a], Eyup Dogan[e] and Emin Oztas[d]

[a]Department of Undersea and Hyperbaric Medicine, Gülhane Military Medical Academy, Ankara, Turkey; [b]Department of Biochemistry, Faculty of Medicine, Hacettepe University, Ankara, Turkey; [c]Department of Toxicology, Faculty of Pharmacy, Hacettepe University, Ankara, Turkey; [d]Department of Medical Histology and Embryology, Gülhane Military Medical Academy, Ankara, Turkey; [e]Department of Medical Microbiology, Gülhane Military Medical Academy, Ankara, Turkey

ABSTRACT
Myoglobinuric acute renal failure (MARF) may develop after severe muscle injury. Heme oxygenase-1 (HO-1), a stress-response protein, has been implicated as a protective agent against MARF. We hypothesized that hyperbaric oxygen therapy (HBOT) may alleviate MARF by inducing renal HO-1 expression. Wistar-Albino rats were randomly assigned into three groups: Control ($n = 4$), MARF ($n = 8$), MARF + HBO ($n = 8$). MARF was induced by intramuscular glycerol (50%, 8 mL/kg) injection. Saline (8 mL/kg) was injected into the hind limb of the animals in the control group. Animals in the MARF + HBO group received two sessions of HBO therapy (90 min at 2.5 atm) 2 and 18 h after glycerol injection. Serum and tissue samples were taken at 24 h. Serum urea and creatinine levels increased in the MARF and MARF + HBO groups confirming the development of MARF. But, serum urea and creatinine levels were similar in MARF and MARF + HBO groups. Oxidative stress parameters were similar among all groups. Histological renal injury score was similar in MARF and MARF + HBO groups. HO-1 level, determined by immunohistochemistry, was significantly higher in MARF and MARF + HBO groups, compared to the control group. Although HO-1 level in MARF + HBO group was higher than MARF group, it was not statistically significant. We found that HBOT did not reduce renal injury in experimental MARF model. HBOT is used to reduce the muscle damage after crush injury, which may be accompanied by MARF. Therefore, more studies are needed to understand the effects of HBO treatment on renal functions after MARF.

ARTICLE HISTORY
Received 30 May 2016
Revised 20 July 2016
Accepted 18 August 2016
Published online 21 October 2016

KEYWORDS
Kidney; crush injury; rhabdomyolysis; hyperbaric oxygen

Introduction

Rhabdomyolysis, the breakdown of skeletal muscle cells, occurs due to traumatic and non-traumatic etiologies. The intracellular constituent of damaged muscle cells, which are released into systemic circulation, leads to several clinical manifestations. Myoglobinuric acute renal failure (MARF) is a frequent and severe complication of rhabdomyolysis. MARF develops in 7–33% of patients with rhabdomyolysis.[1]

The mechanisms involved in the pathogenesis of MARF are intrarenal vasoconstriction, tubular injury, and tubular obstruction.[2,3] Myoglobin is a heme protein and contains iron in ferrous form (Fe^{+2}), which is required for the binding of molecular oxygen. Myoglobin is freely filtered through the renal glomerulus and taken into tubular epithelial cells by endocytosis, where it is metabolized into three final products; bilirubin, carbon monoxide (CO), and Fe^{+2}. Fe^{+2} lead to the free radical formation by Fenton and Haber–Weiss reaction. The role of oxidative stress and hydroxyl radicals are well-known in the pathogenesis of this disease. Reactive oxygen species result in oxidative stress that causes protein denaturation, DNA damage, and lipid peroxidation.[4] Increased oxidative stress in MARF was shown by several studies.[5–7] Hydroxyl radicals cause endothelial dysfunction and augment responses to renal sympathetic nerve stimulation in isolated perfused kidneys. These impaired vascular responses are normalized by hydroxyl radical scavengers.[8] The levels of malondialdehyde (MDA) increases, and superoxide dismutase (SOD) and catalase (CAT) decrease in kidney tissue after MARF in rats.[9] As a result, oxidative stress causes tubular injury.[7,10] Damaged tubular epithelial cells pour into the lumen and cause distal tubular obstruction. Furthermore, excess myoglobin may form intraluminal plugs in the tubular lumen and contribute to tubular obstruction.[10] Hypovolemia-induced activation of the renin–angiotensin system and sympathetic nervous

CONTACT Şenol Yildiz drsenolyildiz@gmail.com Department of Undersea and Hyperbaric Medicine, Gülhane Military Medical Academy, Ankara, Turkey

© 2016 Informa UK Limited, trading as Taylor & Francis Group

system facilitates intrarenal vasoconstriction.[2] Hypovolemia, together with renal vasoconstriction concentrate myoglobin along the tubular lumen and increase the tubular obstruction.[11,12]

Hyperbaric oxygen (HBO) therapy involves inhalation of 100% oxygen at higher atmospheric pressures. HBO therapy is used to reduce muscle damage after crush injury in earthquake victims.[13] However, our knowledge regarding the effect of HBO therapy on renal functions in such patients is limited. A study by Sever et al reporting a 15.2% mortality rate among 639 earthquake victims with acute renal failure revealed that all 28 patients who received HBO therapy had survived.[14] On the other hand, experimental studies conducted by our group and others have shown that HBO therapy alleviates renal injury induced by chemotherapy, ischemia/reperfusion (I/R) injury, and sepsis.[10,15–17] Furthermore, Ayvaz et al. reported that HBO therapy (2.5 ATA 90 min, for 2 days) had a protective effect in an experimental MARF model in rats.[9] Therefore, further studies to elucidate the potential protective role of HBO therapy in MARF are warranted.

Heme oxygenase-1 (HO-1), known to be protective against cellular stress,[18,19] may have a key role in the pathogenesis of MARF. It was shown that increased HO-1 expression reduces kidney damage, whereas HO-1 inhibitors increase kidney damage at MARF models, while increased kidney damage was observed in HO-1 knockout mouse.[20–22] HBO therapy was also shown to increase renal HO-1 levels in experimental models of renal I/R injury and sepsis.[21,23] We hypothesized that HBO therapy may alleviate renal injury in MARF by inducing renal HO-1 expression. In this study, we investigated the effects of HBO therapy on renal functions, oxidant/antioxidant system and renal HO-1 expression in an experimental MARF model in rats.

Materials and methods

Animals

A total of 20 male Wistar-Albino rats weighing 250–300 g were used in the study. Animal Ethical Committee of Gulhane Military Medical Academy (GMMA) approved the study protocol. Rats were housed under standard laboratory conditions (22 ± 1C, 12 h light/dark cycle) and fed with standard rat chow and tap water *ad libitum*.

Experimental groups

Animal were randomly assigned into three groups: Control ($n = 4$), MARF ($n = 8$), and MARF + HBO ($n = 8$). In the control group 8 mL/kg saline was injected into the hind limb of rats and in the MARF and MARF + HBO groups 50% glycerol (8 mL/kg) was injected into hind limb of rats. Animals in the MARF + HBO group received two sessions of HBO therapy (two and 18 h after glycerol injection) in an experimental hyperbaric chamber. The chamber was compressed with 100% O_2 at 2.4 ATA in 10 min. After 70 min at 2.4 ATA, the chamber was decompressed to normal atmospheric pressure in 10 min. Twenty-four hours after glycerol injection, animals were anesthetized with intramuscular ketamine and chlorpromazine. Anterior abdominal laparotomy was performed and both kidneys were removed. Then, median sternotomy was applied and blood samples were collected using intracardiac puncture. Euthanasia was administered by aortic dissection.

Blood samples were centrifuged at 3000 rpm for 5 min to obtain plasma. Plasma samples were kept at −80 °C until being analyzed. Levels of aspartate amino transferase (AST), alanine amino transferase (ALT), urea, creatinine, Na^+, K^+, and creatine kinase (CK) in plasma were measured with a Cobas 6000 biochemistry analyzer (Roche, Germany) using commercial kits.

Half of the right kidney was put into formalin solution for histological and immunohistochemical examination. Rest of the kidney tissues were frozen in liquid nitrogen and preserved at −80 until analysis of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and malonyl dialdehyde (MDA).

Biochemical analysis

Preparation of tissue samples and determination of oxidative stress

Kidney tissue samples were weighed and homogenized in 2 mL buffer (Tris (10 mM), diethylenetriaminepentaacetic acid (1 mM), phenylmethanesulfonyl fluoride (1 Mm; pH 7.4)] at +4 C^0 by a homogenizator (Thermo Scientific, Waltham, MA). The tissue samples were diluted to a final concentration of 100 mg/mL. The diluted samples were centrifuged at 3000 rpm for 20 min (Heraeus Biofuge A, Germany).

SOD, CAT, GPx, and MDA levels in tissue homogenates were measured by rat ELISA Kits (YH-Biosearch, Public Republic of China). The absorbances were read at 450 nm by an ELISA plate reader (Spectramax M2, Molecular Devices, Sunnyvale, CA).

The protein content of kidney homogenates was measured by using Biuret's method.[13]

Histology and immunohistochemistry

Kidney tissues were fixed with formalin, embedded in paraffin, sectioned at 4 μm thickness and then stained with hematoxylin-eosin (H&E) and examined using a light microscope. Kidney tissue damage was assessed using a modified semi-quantitative scale as previously reported.[24] Kidney damage parameters as designated by examining proximal tubular structural changes, proximal tubular atrophy, loss of edge of tubular, tubular dilation, caste formation, vacuolization, mononuclear cell infiltration, erythrocyte extravasation, changing in renal corpuscle morphology, and interstitial area. For each parameters tissue damage score was obtained by calculating percentage of damaged structure in image area (0 = normal; 1 = 0–25%; 2 = 25–50%; 3 = 50–75%; 4 > 75%).

Immunohistochemistry was carried out in formaldehyde fixed and, paraffin-embedded kidney tissue sections mounted on poly-L-lysine coated slides. The slides were deparaffinized and boiled in citrate buffer (pH = 6) in a microwave oven for 20 min for antigen retrieval. The tissue sections were then incubated for 30 min in 3% H_2O_2 to block the endogenous peroxidase activity. After subsequent treatment with normal goat serum, sections were incubated at 37 °C for 1 h with the primary anti-HO-1 antibody (1:200; AB1284; Millipore, Boston, MA). Biotin-labeled goat antirabbit IgG secondary antibody (GGHL-15P; ICLLab, Newberg, OR) was used, and diaminobenzidine was used for the color development. Sections were counterstained with Mayer's hematoxylin. The observer performed light microscopy and scored semiquantitatively the quantity of HO-1 staining in the whole section as 0 for negative, 1 for weak (+), 2 for moderate (++), and 3 for strong (+++) staining as described before.[25]

Statistical analysis

SPSS version 20.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. All data are presented as mean ± standard deviations (SD). The Kruskal–Wallis test was used for non-normally distributed data, and dual comparisons between groups were evaluated with Mann–Whitney *U* test with Bonferroni's correction. *p* Values less than .05 were considered as statistically significant.

Results

One animal in the MARF + HBO group died during the study and the results of seven animals were included in the final analysis.

Biochemistry

Urea, creatinine, AST, and ALT levels were significantly higher ($p < .05$) in MARF and MARF + HBO group compared to the control group. Mean CK level in MARF group was found to be significantly higher than the control group ($p < .05$). These results are shown in Table 1.

MARF + HBO and MARF groups had statistically higher MDA levels compared to control group. There was no statistical difference in tissue levels of SOD, CAT, and GPx among the groups. These results are shown in Table 2.

Histology and immunohistochemistry

Control group sections showed a normal structure of kidney tissue. Tubular necrosis, glomerular damage, tubular dilation, myoglobin accumulation were observed in MARF and MARF + HBO groups (Figure 1). Histological scores were statistically higher ($p < .05$) in MARF (3.0 ± 0.81) and MARF + HBO group (3.57 ± 0.53) compared with the control group. Histological scores were similar in MARF and MARF + HBO groups ($p > .05$). Cytoplasmic HO-1 immunostaining was seen in all groups (Figure 1). Distal tubules showed more intense HO-1 staining. HO-1 immunostaining score in the control group was 0.75 ± 0.5. Immunostaining scores were statistically higher ($p < .05$) in MARF (2.25 ± 0.46) and MARF + HBO (2.71 ± 0.48) groups compared to the control group. Figure 1 summarizes H&E staining and immunohistochemistry findings.

Discussion

We used a well-established experimental model, intramuscular glycerol injection-induced rhabdomyolysis, to induce MARF in rats.[3,12,26] Renal failure was demonstrated by increased serum levels of urea and creatinine and histological findings; glomerular damage, tubular dilatation, tubular necrosis, and intraluminal plugs. However, HBO therapy did not prevent kidney injury in experimental MARF model in this study.

The effect of HBO therapy on renal injury may be related to duration and frequency of the treatment. It was shown that seven sessions of HBO therapy (at 2.5 ATA, for 60 min) reduced plasma urea and creatinine levels in addition to proximal tubular necrosis and apoptotic cell count in cisplatin-induced acute renal failure.[27] HBO therapy also prevented histological damage after experimental renal I/R injury.[21] It was reported that HBO therapy could reduce the urea and creatinine levels and improve histological findings after I/R injury

Table 1. Serum urea, creatinine, CK, Na^+, K^+, AST, and ALT levels in each group (mean ± SD).

	Control	MARF	MARF + HBO
Urea (mg/dL)	59.0 ± 3.3	122 ± 62[a]	185 ± 61[a]
Creatinine (mg/dL)	0.46 ± 0.02	1.18 ± 0.68[a]	1.70 ± 0.42[a]
CK (U/L)	599 ± 179	3600 ± 3347[a]	1274 ± 652
Na^+ (mmol/L)	139 ± 1.08	141 ± 3.44	141 ± 2.44
K^+ (mmol/L)	5.61 ± 0.11	5.41 ± 0.21	5.10 ± 0.35
AST (U/L)	126 ± 16	1144 ± 626[a]	992 ± 245[a]
ALT (U/L)	65.2 ± 10.3	305 ± 153[a]	450 ± 667[a]

[a]$p < .05$ compared with Control.

Table 2. Renal MDA, SOD, CAT, and GPx levels in each group (mean ± SD).

	Control	MARF	MARF + HBO
MDA (nmol/mg protein)	0.019 ± 0.002	0.284 ± 0.121[a]	0.321 ± 0.128[a]
SOD (U/g protein)	19.4 ± 5.5	21.2 ± 7.7	24.2 ± 13.4
CAT (ng/mg protein)	7.1 ± 4.2	5.8 ± 2.6	8.6 ± 5.1
GPx (U/g protein)	23.8 ± 4.2	28.9 ± 12.6	34.0 ± 21.7

[a]$p < .05$ compared with Control.

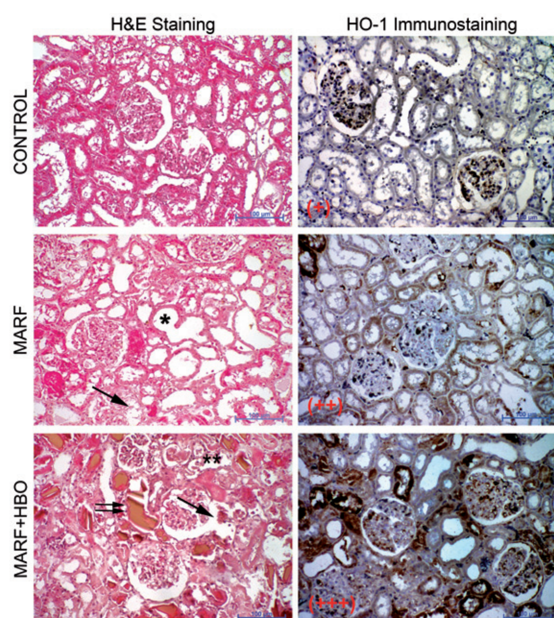

Figure 1. Rhabdomyolysis promotes kidney damage and HO-1 expression in rat kidney tissues. Representative images showing hematoxylin and eosin (H&E) staining images shows tubular damage (double stars), tubular dilatation (star), glomerular damage (arrow), myoglobin accumulation (double arrows) are seen in MARF and MARF + HBO groups. Representative immunohistochemical expression of HO-1 images indicates weak (+), moderate (++), strong (+++) intensity of staining. MARF + HBO group shows more intense immunopositivity. Scale bar 200 μM.

in different studies.[10,28] In these studies, HBO therapy was administered more frequently and longer compared to our study. Studies indicating negative effects of the HBO therapy are also available. In a study of nephrotoxicity model due to cyclosporine A, they found that there were more apoptotic cells on histopathologic examination in cyclosporine A + HBO group compared to only cyclosporine A group.[29] They suggested that HBO therapy might potentiate the nephrotoxic effect of cyclosporine.

When studies demonstrating beneficial effects of HBO therapy in different ARF models were compared, it was seen that HBO administration frequency was different from each other. The therapy pressure changes 2 to 2.5 ATA, frequency 1–4 per days, duration 60 to 90 min and number of session 4 to 5.[15–17,27] In our study, we performed two sessions of HBO therapy and our study has the least session compared with other studies. Future studies should have more HBO therapy sessions and longer follow-up after MARF.

Aydinöz et al.[30] compared once a day and twice a day HBO therapy in cisplatin-induced nephrotoxicity model. They performed HBO therapy in the first group at 2.5 ATA, for 60 min, once a day, for 6 days and HBO therapy at 2.5 ATA, for 60 min, twice a day, for 6 days in the second group. Beneficial effects of HBO therapy was observed in once a day HBO session, whereas renal derangement was reported histologically in twice a day HBO session. Twice a day HBO session could potentiate nephrotoxicity induced by cisplatin. In our study, HBO therapy (at 2.4 ATA, for 90 min) was performed 2 h and 18 h after intramuscular injection. The absence of optimal HBO therapy frequency may be a reason that we could not reach expected results about HBO therapy.

Ayvaz et al.[9] reported the effectiveness of HBO therapy in MARF model with intramuscular glycerol injection (both hind legs, totally 8 mL/kg). They showed that urea, creatinine, and CK levels were significantly decreased in MARF + HBO group compared to MARF group. They stated that HBO therapy could significantly improve MARF induced renal failure in histological examination. They found that SOD and CAT activities were significantly higher in MARF + HBO group compared to MARF group ($p < .001$) and significantly lower in MARF group compared to control group ($p < .05$). In contrast to our study, the rats received HBO therapy (2.5 ATA %100 oxygen for 90 min) once a day for two consecutive days. This may explain the differences between their results and ours. Twice daily HBO therapy did not prevent renal injury after MARF.

The most appropriate method for diagnosing rhabdomyolysis is the long-term increase in plasma levels of CK compared to myoglobin.[31,32] Therefore, in our study, we evaluated CK level instead of plasma myoglobin. Ayvaz et al showed that increase of CK was significantly lower in MARF + HBO group compared to MARF group.[9] In our study, there was no significant difference between MARF + HBO group and MARF group in terms of CK levels. The absence of significant difference might be again related to duration and frequency of HBO

therapy. We found that serum Na + and K + levels unchanged in our study. Although this finding is contradictory to the study by Ayvaz et al, these may be due to shorter duration of our study.

Rhabdomyolysis-induced hypovolemia and vasoconstriction aggravate renal perfusion defect.[33] In our study, rats did not receive water during HBO therapy for 90 min, which started 2 h after glycerol injection. This may have contributed to hypovolemia in HBO treated rats. Furthermore, HBO is known to induce vasoconstriction and reduce renal blood flow. Taken together, water abstinence during HBO therapy and HBO-induced renal vasoconstriction may be responsible for histological changes observed in HBO-treated rats. Experimental hyperbaric chambers should be modified to allow water during HBO therapy. It is also reasonable to monitor the weight of animals to evaluate dehydration due to MARF. Future studies should consider these points.

The HO-1 system is a cytoprotective mechanism activated during cellular stress[34] and it is reported that high levels of HO-1 protein secretion could protect the renal tissue against injury mediated by free radicals.[35] HBO therapy applied before lung damage increases the expression of HO-1in rats.[36] But there is no previous study whether HBO therapy had an effect on the HO-1 enzyme in MARF model. In this study, HO-1 expression was higher in MARF and MARF + HBO groups compared to the control group ($p < .05$), however, there was no significant difference between MARF (2.25 ± 0.46) and MARF + HBO (2.71 ± 0.48) groups. Our findings do not support the idea that HBO therapy is protective against MARF through the activation of renal HO-1 levels in rats.

Conclusion

We found that HBO therapy did not reduce renal injury in experimental MARF model. HBO therapy is used to reduce the muscle damage after crush injury, which may be accompanied by MARF. Therefore, more studies are needed to understand the effects of HBO treatment on renal functions after MARF.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding

This work was supported by Scientific and Technological Research Council of Turkey (TÜBİTAK) [214S319].

References

1. Beetham R. Biochemical investigation of suspected rhabdomyolysis. *Ann Clin Biochem*. 2000;37:581–587.
2. Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. *N Engl J Med*. 2009;361:62–72.
3. Zager RA. Rhabdomyolysis and myohemoglobinuric acute renal failure. *Kidney Int*. 1996;49:314–326.
4. Miwa S, Muller FL, Beckman KB. Oxidative stress in aging: from model systems to human diseases. In: Miwa S, Beckman KB, Muller FL, eds. *Aging Medicine*. 1st ed. New York: Springer; 2008: xiii, 320.
5. Paller MS. Hemoglobin- and myoglobin-induced acute renal failure in rats: Role of iron in nephrotoxicity. *Am J Physiol*. 1988;255:F539–F544.
6. Paller MS, Hedlund BE. Role of iron in postischemic renal injury in the rat. *Kidney Int*. 1988;34:474–480.
7. Emerit J, Beaumont C, Trivin F. Iron metabolism, free radicals, and oxidative injury. *Biomed Pharmacother. = Biomedecine Pharmacotherapie*. 2001;55:333–339.
8. Cil O, Ertunc M, Gucer KS, Ozaltin F, Iskit AB, Onur R. Endothelial dysfunction and increased responses to renal nerve stimulation in rat kidneys during rhabdomyolysis-induced acute renal failure: Role of hydroxyl radical. *Ren Fail*. 2012;34:211–220.
9. Ayvaz S, Aksu B, Kanter M, et al. Preventive effects of hyperbaric oxygen treatment on glycerol-induced myoglobinuric acute renal failure in rats. *J Mol Histol*. 2012;43:161–170.
10. Solmazgul E, Uzun G, Cermik H, Atasoyu EM, Aydinoz S, Yildiz S. Hyperbaric oxygen therapy attenuates renal ischemia/reperfusion injury in rats. *Urol Int*. 2007;78:82–85.
11. Zager RA. Studies of mechanisms and protective maneuvers in myoglobinuric acute renal injury. *Lab Invest*. 1989;60:619–629.
12. Ustundag S, Yalcin O, Sen S, Cukur Z, Ciftci S, Demirkan B. Experimental myoglobinuric acute renal failure: The effect of vitamin C. *Ren Fail*. 2008;30:727–735.
13. Gornall AG, Bardawill CJ, David MM. Determination of serum proteins by means of the biuret reaction. *J Biol Chem*. 1949;177:751–766.
14. Sever MS, Erek E, Vanholder R, et al. Treatment modalities and outcome of the renal victims of the Marmara earthquake. *Nephron*. 2002;92:64–71.
15. Ay H, Uzun G, Onem Y, et al. Effect of hyperbaric oxygen on cyclosporine-induced nephrotoxicity and oxidative stress in rats. *Ren Fail*. 2007;29:495–501.
16. Ilhan H, Eroglu M, Inal V, et al. Hyperbaric oxygen therapy alleviates oxidative stress and tissue injury in renal ischemia/reperfusion injury in rats. *Ren Fail*. 2012;34:1305–1308.
17. Edremitlioglu M, Kilic D, Oter S, et al. The effect of hyperbaric oxygen treatment on the renal functions in septic rats: Relation to oxidative damage. *Surg Today*. 2005;35:653–661.
18. Nath KA. Heme oxygenase-1: A redoubtable response that limits reperfusion injury in the transplanted adipose liver. *J Clin Invest*. 1999;104:1485–1486.
19. Dong Z, Lavrovsky Y, Venkatachalam MA, Roy AK. Heme oxygenase-1 in tissue pathology: The Yin and Yang. *Am J Pathol*. 2000;156:1485–1488.

20. Nath KA, Balla G, Vercellotti GM, et al. Induction of heme oxygenase is a rapid, protective response in rhabdomyolysis in the rat. *J Clin Invest*. 1992;90:267–270.
21. He X, Xu X, Fan M, et al. Preconditioning with hyperbaric oxygen induces tolerance against renal ischemia-reperfusion injury via increased expression of heme oxygenase-1. *J Surg Res*. 2011;170:e271–e277.
22. Nath KA, Haggard JJ, Croatt AJ, Grande JP, Poss KD, Alam J. The indispensability of heme oxygenase-1 in protecting against acute heme protein-induced toxicity *in vivo*. *Am J Pathol*. 2000;156:1527–1535.
23. Chang KY, Tsai PS, Huang TY, Wang TY, Yang S, Huang CJ. HO-1 mediates the effects of HBO pretreatment against sepsis. *J Surg Res*. 2006;136:143–153.
24. Wang J, Wang D, Li Y, et al. Rhabdomyolysis-induced acute kidney injury under hypoxia and deprivation of food and water. *Kidney Blood Press Res*. 2013;37:414–421.
25. Rosenberger C, Mandriota S, Jurgensen JS, et al. Expression of hypoxia-inducible factor-1alpha and -2alpha in hypoxic and ischemic rat kidneys. *J Am Soc Nephrol*. 2002;13:1721–1732.
26. Lieberthal W, Nigam SK. Acute renal failure. II. Experimental models of acute renal failure: imperfect but indispensable. *Am J Physiol Renal Physiol*. 2000;278:F1–F12.
27. Atasoyu EM, Yildiz S, Bilgi O, et al. Investigation of the role of hyperbaric oxygen therapy in cisplatin-induced nephrotoxicity in rats. *Arch Toxicol*. 2005;79:289–293.
28. Rubinstein I, Abassi Z, Milman F, et al. Hyperbaric oxygen treatment improves GFR in rats with ischemia/reperfusion renal injury: A possible role for the antioxidant/oxidant balance in the ischemic kidney. *Nephrol Dialysis Transpl*. 2009;24:428–436.
29. Atasoyu EM, Yildiz S, Cimsit M, et al. Investigation of the effect of hyperbaric oxygen on experimental cyclosporine nephrotoxicity. *Basic Clin Pharmacol Toxicol*. 2006;98:150–154.
30. Aydinoz S, Uzun G, Cermik H, *et al*. Effects of different doses of hyperbaric oxygen on cisplatin-induced nephrotoxicity. *Ren Fail*. 2007;29:257–263.
31. Vanholder R, Sever MS, Erek E, Lameire N. Acute renal failure related to the crush syndrome: Towards an era of seismo-nephrology? *Nephrol Dialysis Transpl*. 2000;15:1517–1521.
32. MacLean JG, Barrett DS. Rhabdomyolysis: A neglected priority in the early management of severe limb trauma. *Injury*. 1993;24:205–207.
33. Warren JD, Blumbergs PC, Thompson PD. Rhabdomyolysis: A review. *Muscle Nerve*. 2002;25:332–347.
34. Fernandez L, Carrasco-Chaumel E, Serafin A, et al. Is ischemic preconditioning a useful strategy in steatotic liver transplantation? *Am J Transpl*. 2004;4:888–899.
35. Shimizu H, Takahashi T, Suzuki T, et al. Protective effect of heme oxygenase induction in ischemic acute renal failure. *Critic Care Med*. 2000;28:809–817.
36. Huang TY, Tsai PS, Wang TY, Huang CL, Huang CJ. Hyperbaric oxygen attenuation of lipopolysaccharide-induced acute lung injury involves heme oxygenase-1. *Acta Anaesthesiol Scand*. 2005;49:1293–1301.