Gadolinium chloride attenuates aortic occlusion-reperfusion-induced myocardial injury in rats

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ABSTRACT

Objectives: Aortic ischemia and reperfusion periods, which are often associated with infrarenal abdominal aortic cross-clamping and declamping, cause injury in distant organs including the heart. We recently reported that Kupffer cell blockage with gadolinium chloride ($GdCl_3$) attenuates lung injury induced by aortic ischemia-reperfusion (IR). Therefore, we hypothesized that $GdCl_3$ may attenuate myocardial injury induced by aortic IR.

Methods: The study was carried out in June 2005, in the Laboratory of Experimental Studies of Suleyman Demirel University Medical School, Isparta, Turkey. We studied the effect of $GdCl_3$ on myocardial injury induced by abdominal aortic occlusion-reperfusion in rats by measuring the tissue levels of superoxide dismutase, catalase, malondialdehyde and activity of myeloperoxidase in rat heart specimens. Wistar-Albino rats (8 per group) were randomized into 3 groups. The control group underwent midline laparotomy and dissection of the infrarenal abdominal aorta without occlusion; the aortic IR group underwent laparotomy and clamping of the infrarenal abdominal aorta for 30 minutes followed by 60 minutes of reperfusion; and the $GdCl_3$ + aortic IR group was pretreated with intravenous $GdCl_3$ 10 mg/kg 24 hours before the aortic IR.

Results: Aortic IR significantly increased whereas pretreatment with $GdCl_3$ significantly decreased oxygen free radical production, lipid peroxidation and neutrophil activation in the heart tissues of the rats.

Conclusion: Our results indicate that Kupffer cell blockage with $GdCl_3$ attenuates the myocardial injury induced by aortic IR. We think that the novel findings of the present study may be a basis for further studies investigating the role of $GdCl_3$ pretreatment in reducing myocardial morbidity and mortality caused by aortic IR during aortic surgery.

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Infrarenal abdominal aortic cross-clamping and declamping, which are routinely used during aortic aneurysm surgery, frequently cause 2 successive injuries. Firstly, aortic clamping leads to interruption of the blood flow, and then an ischemic state develops in the lower limbs. This ischemic state results in ischemic injury to the lower limbs and distal vasculature. Later, aortic declamping leads to sudden reestablishment of circulation to the lower limbs and rapid re-oxygenation of the ischemic tissues during reperfusion. This reperfusion period results in injury to distant organs, including the heart.[1,2] These successive injuries, which are together called aortic ischemia-reperfusion (IR) injury, may induce the development of cardiac complications during or after abdominal aortic surgery.[3] The development of IR injury-induced cardiac complications after aortic surgery not only affects recovery in the immediate postoperative period but is also associated with significant increased risk of cardiovascular death in the long term.[3] Kupffer cells (KC), the resident macrophages of the liver, are the major component of the mononuclear phagocytic system.[4] Kupffer cells may contribute to the modulation of distant organ damage after intestinal IR.[5] Gadolinium chloride ($GdCl_3$), a radiated chemical of the lanthan system, specifically inhibits KC function.[6] Towfigh et al[7] showed that KC blockage with $GdCl_3$ attenuates distant organ damage induced by intestinal IR.[7] In addition, we recently reported that KC blockage with $GdCl_3$ attenuates the lung injury induced by aortic IR.[8] However, the effect of KC blockage with $GdCl_3$ on the myocardial injury induced by aortic IR is not yet known. The purpose of this study is to determine whether KC blockage with $GdCl_3$ attenuates the myocardial injury induced by aortic IR. For this purpose, we studied the

effect of KC blockage with $GdCl_3$ in myocardial injury induced by occlusion-reperfusion of the rat infrarenal abdominal aorta by measuring the tissue levels of superoxide dismutase, catalase, malondialdehyde and activity of myeloperoxidase in rat heart specimens.

Methods. Twenty-four Wistar-Albino rats, of both sexes and weighing 200-250 g, were used for the experiment. The experimental protocols were approved by the Animal Ethics Committee of Süleyman Demirel University, Isparta, Turkey. The rats were acquired from the university vivarium sources and were housed in individual cages in a temperature and light-dark cycle-controlled environment with free access to food and water. Food, but not water, was withdrawn 12 hours prior to experiment. All rats received humane care, in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985).

The rats were randomly allocated into one of the 3 experimental groups (n=8 in each group); they are the control group, aortic IR group and $GdCl_3$ + aortic IR group. The control group underwent laparotomy and dissection of the infrarenal abdominal aorta without occlusion. The aortic IR group underwent aortic ischemia and reperfusion. The $GdCl_3$ + aortic IR group received $GdCl_3$ for KC blockage and then underwent aortic ischemia and reperfusion. Since we previously reported that $GdCl_3$ had no remarkable effect on the control group,[8] we omitted an additional control + $GdCl_3$ group in order to minimize the number of killed rats.

Kupffer cells blockage was carried out by an intravenous injection of 10 mg/kg $GdCl_3$ (Sigma Chemical Co., St. Louis, MO, USA) 24 hours before the experiment[9] in $GdCl_3$ + aortic IR group. The rats were anesthetized with ketamine hydrochloride (Ketalar®, Eczacibasi, Istanbul, Turkey, 50 mg/kg intramuscular) and anesthesia was maintained with supplementary intramuscular injections of ketamine hydrochloride. The rats were placed supine under a heating lamp. The skin was aseptically prepared and a midline laparotomy was carried out. Ten ml of warm normal saline was instilled into the peritoneal cavity to help maintain fluid balance. The abdominal aorta was exposed by gently deflecting the loops of the intestine to the left with moist gauze swabs. An atraumatic microvascular clamp (vascu-statts II, midi straight 1001-532; Scanlan Int., St. Paul, MN, USA) was placed across the infrarenal abdominal aorta. The abdomen was then closed and the wound was covered with plastic wrap to minimize heat and fluid losses. After 30 minutes, the microvascular clamp on the infrarenal abdominal aorta was removed and the lower limbs were reperfused for 60 minutes. Aortic occlusion and reperfusion were confirmed by the loss and reappearance of satisfactory pulsation on the distal aorta. Thus, no-reflow phenomenon was excluded. All rats were killed under anesthesia and each heart was carefully removed en bloc from the thorax. The specimens were harvested and stored at -78^{0}C until biochemical assays were carried out.

Frozen tissue samples of the rat hearts were weighed and homogenized (Ultra Turrax T25, Janke and Kunkel GmbH and Co., KG, Staufen, Germany) (1:10, w/v) in 100 mmol/L phosphate buffer (pH 7.4) containing 0.05% sodium azide in an ice bath. The homogenate was sonicated (Bandelin Sonoplus UW 2070, Berlin, Germany) for 30 sec and centrifuged at 5.000 g for 10 minutes. The supernatant was frozen at -78^{0}C in aliquots until used for biochemical assays. The protein content of the supernatant was determined by the Lowry method.[10]

Malondialdehyde levels, an indicator of free radical generation, were measured by the double heating method of Draper and Hadley.[11] The principle of the method is spectrophotometric measurement of the color produced by the reaction of thiobarbituric acid with malondialdehyde. For this purpose, 2.5 mL of 100 g/L trichloroacetic acid solution was added to 0.5 ml supernatant in each centrifuge tube. The tubes were placed in a boiling water bath for 15 min and then cooled in tap water. The tubes were centrifuged at 1.000 g for 10 min, and 2 mL of the supernatant was added to 1 mL of 6.7 g/L thiobarbituric acid solution in a test tube, and then the tube was placed in a boiling water bath for 15 min. The solution was then cooled in tap water and its absorbance was measured with a spectrophotometer (Shimadzu UV-1601, Kyoto, Japan) at 532 nm. The concentration of malondialdehyde was calculated by the absorbance coefficient of the malondialdehyde-thiobarbituric acid complex (absorbance coefficient e = 1.56 x 105 cm–1. M-1) and is expressed as nanomoles per milligram of protein (nmol/mg protein).

Myeloperoxidase activity, a sensitive index of tissue polimorfo nuclear leukocyte sequestration, was measured by using the peroxidase-catalyzed, H_2O_2-dependent oxidation of tetramethylbenzidine as a measure of enzymatic activity.[9] The heart specimens were weighed at one gram and placed in a 9 ml 50 mM potassium phosphate buffer of pH 6 with 0.5% hexadecyltrimethylammonium bromide (Sigma, USA). The heart specimens were homogenized (Ultra Turrax T25, Janke & Kunkel GmbH & Co., KG, Staufen, Germany) for 20 sec in an ice bath. The homogenates

were sonicated (Bandelin Sonopuls UW 2070, Berlin, Germany) for 30 sec and centrifuged at 12.000 g for 15 min at 4^{0}C. The supernatant was assayed for myeloperoxidase content spectrophotometrically by measuring the change in optical density at 460 nm over time. The assay buffer consisted of 50 mM potassium phosphate, pH 6.0 (50 ml), 0.83 ml H_2O_2 (0.3% solution; Sigma, USA) and 8.34 mg o-dianisidine hydrochloride (Sigma, USA). The supernatant was mixed 1:80 (supernatant: assay buffer). Myeloperoxidase units are expressed as ΔA/min/g tissue.

Superoxide dismutase activity was measured by the method of Spitz and Oberley[12] and Woolliams et al.[13] The determination of superoxide dismutase activity was based on the reaction of xanthine with xanthine oxidase to generate superoxide radicals, which react with 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazoliumchloride to form a red formazan dye. The superoxide dismutase activity is then determined as the degree of inhibition of this reaction. Results are expressed as units per milligram of protein (U/mg protein).

Catalase activity was measured by the method of Aebi.[14] The assay is based on the determination of the rate constant (s^-1, k) of hydrogen peroxide decomposition. The rate constant was calculated with the formula $k=(2.3/\Delta t)(a/b) \log (A_1/A_2)$, where A_1 and A_2 are the absorbance values of hydrogen peroxide at times t_1 (0^{th} second) and t_2 (15^{th} second), ('a' is a dilution factor, and 'b' is the protein content of the supernatant). Results are expressed as catalytic activity per milligram protein (k/mg protein).

Data are presented as means ± standard deviation. A computer program (SPSS 10.01, SPSS Inc. Chicago, IL, USA) was used for statistical analysis. Differences between groups were determined using one way Analysis of variance followed by a post hoc Tukey's honestly significant difference test. A probability-value of less than 0.05 was considered statistically significant.

Results. **Table 1** shows malondialdehyde (nmol/mg protein), superoxide dismutase (U/mg protein), catalase (k/mg protein) levels and myeloperoxidase (ΔA/min/g tissue) activity in the rat heart specimens in all groups. Malondialdehyde, superoxide dismutase, catalase levels and myeloperoxidase activity in the aortic IR group were significantly higher than the other groups (p<0.05). Malondialdehyde, superoxide dismutase, catalase levels and myeloperoxidase activity in the $GdCl_3$ + aortic IR group were significantly lower than the aortic IR group (p<0.05). Malondialdehyde, superoxide dismutase, catalase levels and myeloperoxidase activity in the $GdCl_3$ + aortic IR group were no significantly different than the control group.

Discussion. This study in rats shows that KC blockage with $GdCl_3$ attenuates the myocardial injury induced by aortic IR. The evidence is that malondialdehyde, superoxide dismutase, catalase levels and myeloperoxidase activity in heart specimens in the $GdCl_3$ + aortic IR group were significantly lower than the aortic IR group. Oxygen free radicals are one of the earliest and most important components of tissue injury after reperfusion of ischemic organs.[15] Aortic clamping leads to ischemia and anaerobic cellular metabolism in all tissues distal to the aortic clamp. Cellular adenosine triphosphate (ATP) levels gradually fall, and increased adenosine monophosphate (AMP) is converted to hypoxanthine and xanthine, providing substrate for the enzyme xanthine oxidase. Importantly, xanthine oxidase is upregulated by the ischemia.[16] Aortic declamping leads to rapid re-oxygenation of the ischemic tissues and results in production of reactive oxygen species, namely superoxide (O_2^-) radical, hydrogen peroxide (H_2O_2) and hydroxyl (OH^-) radical. O_2^- is produced by xanthine oxidase, the enzyme catalysing the hypoxanthine and xanthine metabolism. The enzyme superoxide dismutase rapidly reacts with O_2^- and dismutates it to less reactive H_2O_2.[17] Hydrogen peroxide is further converted to H_2O and O_2 by the

Table 1 - Results of the biochemical assays.

Groups	Malondialdehyde (nmol/mg protein)	Myeloperoxidase (ΔA/min/g tissue)	Superoxide dismutase (U/mg protein)	Catalase (k/mg protein)
Control group	2.40 ± 0.22	3.44 ± 0.39	4.11 ± 0.43	0.08 ± 0.07
Aortic ischemia-reperfusion group	3.92 ± 0.39*	6.87 ± 1.43*	5.78 ± 0.22*	0.16 ± 0.01*
Gadolinium chloride + aortic ischemia-reperfusion group	2.42 ± 0.21	3.66 ± 0.23	4.34 ± 0.29	0.11 ± 0.07

*p<0.05 compared to other groups

enzymes catalase and glutathione peroxidase, and this reaction prevents the formation of the highly reactive OH^{-}.[18] Evidence that IR elicits oxidant-mediated tissue injury suggests that the adaptation response to brief periods of ischemia could involve augmented production of antioxidant enzymes in affected tissues.[19] Furthermore, since superoxide dismutase and catalase are the important antioxidant enzyme systems protecting cells from detrimental effects of reactive oxygen species, it can be assumed that once a tissue is subject to IR injury the tissue levels of these enzymes may increase. In our study, this assumption is supported by the finding that the levels of superoxide dismutase and catalase in the aortic IR group were significantly higher than the other groups. Therefore, increased levels of catalase and superoxide dismutase in the cardiac tissue may indicate a high degree of oxidative stress resulting from increased endogenous O_2^- and H_2O_2. This finding is parallel with the findings of Portakal et al,[20] who reported increased superoxide dismutase and catalase activities in the rat liver after aortic IR. However, these results are in disagreement with the results of the study by Gurel et al,[21] who reported decreased superoxide dismutase and catalase activities in the rat kidney after aortic IR. Consequently, there is no consensus on the tissue levels of these antioxidant enzymes in the organs subjected to IR injury. It is possible that the levels of these antioxidant enzymes may be determined both by the magnitude of IR injury and by the organ subjected to IR injury. Lipid peroxidation is an autocatalytic mechanism leading to oxidative destruction of cellular membranes.[22] Cellular membranes are composed of polyunsaturated fatty acids and phospholipids which are most susceptible to peroxidatic damage. Peroxidatic damage results in structural alterations in cell membranes, increased membrane permeability, cell swelling and eventually cell death. Lipid peroxidation has been suggested to be closely related to IR injury-induced tissue damage and malondialdehyde is a good indicator of the rate of lipid peroxidation.[23] This suggestion coincides with our findings, which is that malondialdehyde levels in the aortic IR group were significantly higher than in the other groups. Similarly, in several studies, increased tissue levels of malondialdehyde were found after IR injury.[5,8,19,20] Ischemia-reperfusion elicits an acute inflammatory response characterized by activation of neutrophils.[23] This acute inflammatory response includes a number of mediators, such as interleukin-1, interleukin-6, tumor necrosis factor-alpha[24] complement 3a and 5a,[25] prostaglandins, leukotriene B4, thromboxane B2 and platelet activating factor.[16] Ample evidence supports that IR injury causes the local and systemic release of these inflammatory mediators, thereby promoting endothelial adhesion molecule expression and neutrophil activation.[19] Activated neutrophils produce potent proteases capable of degrading virtually all components of the endothelial basement membrane.[26] Thus, increased endothelial adhesion molecule expression locally as well as at distant sites may facilitate neutrophil-endothelial cell adhesion and neutrophil-mediated vascular and tissue injury. Activated neutrophils are also known to produce O_2^- and H_2O_2 and to secrete myeloperoxidase, an enzyme that catalyses the formation of hypochlorous acid from H_2O_2 and chloride ions.[19] Myeloperoxidase activity is used as a sensitive index of tissue polymorphonuclear leukocytes and increased levels of myeloperoxidase in the lung[8] and the kidney[21] were found after IR injury. These results are in agreement with one result of our study, which is that myeloperoxidase levels in the aortic IR group were significantly higher than in the other groups. Kupffer cells are a major component of the reticuloendothelial system. Activation of KC contributes to the development of liver injury after liver IR.[27] In addition, activation of KC with transhepatic passage of intestinal reperfusate contributes to the development of lung injury after intestinal IR.[5] Gadolinium chloride has been well known to have an inhibitory effect on KC functions.[5,6,8,28] These findings led to studies focused on the possible ameliorating effect of KC blockage on IR-induced distant organ damage. Supporting this possibility, KC blockage with $GdCl_3$ attenuated the lung injury induced by intestinal IR[7] and induced by aortic IR.[8] Therefore, we hypothesised that KC blockage with $GdCl_3$ may attenuate the myocardial injury induced by aortic IR. This hypothesis is based on the interactions between KC and the mediators of aortic IR-induced distant organ damage, including generation of oxygen free radicals, lipid peroxidation and activation of leukocytes. Kupffer cells play a crucial part in the mediation of hepatic IR injury by production of toxic substances like free oxygen radicals.[27] Vega et al reported that oxidative stress elicited in the liver after hind limb IR injury in rats is both KC and polymorphonuclear leukocyte dependent.[28] This oxidative stress could be partly elicited by production of free oxygen radicals by KC after activation of KC by systemic release of the inflammatory mediators. During aortic IR, oxygen free radicals can be overproduced by KC, to the degree of causing release into the systemic circulation and subsequently causing oxidative stress in distant organs. Therefore, KC blockage may reduce this oxidative stress produced by activated KC after aortic IR. In our study, we found that KC blockage with $GdCl_3$ reduced the levels of antioxidant enzymes superoxide dismutase and

catalase in the heart tissue, probably reflecting diminished tissue levels of free oxygen radicals, namely O_2^- and H_2O_2. There is interdependency between oxygen free radicals and lipid peroxidation. Oxygen free radicals start the reactions of lipid peroxidation and are also produced in these reactions.[29] Thus, diminished levels of oxygen free radicals may accompany diminished lipid peroxidation. Malondialdehyde, a terminal product of lipid peroxidation, is both an effective marker of lipid peroxidation and an indirect index of oxygen free radical activity.[30] Supporting this parallelism, we found that KC blockage with $GdCl_3$ reduced the levels of malondialdehyde levels in the heart tissue. Following aortic IR, for remote organ injury to start, reperfusion must activate circulating leukocytes and cause them adhere in remote sites.[19] Activated KC can release inflammatory mediators (such as interleukin, adhesion molecules and tumour necrosis factor-alpha),[27] which are capable of aggregating leukocytes, activating vascular endothelium and facilitating neutrophil-endothelial cell adhesion in any organ. Thus, $GdCl_3$ may inhibit the release of these mediators from activated KC following aortic IR and reduce the amount of activated leukocyte adhesion in the myocardial tissue. In our study, myeloperoxidase activity as a marker of leukocyte infiltration was significantly lower in the $GdCl_3$ + aortic IR group than in the aortic IR group. This finding indicates that $GdCl_3$ pretreatment reduced the amount of activated leukocytes in the myocardial tissue after aortic IR. Inhibition of adhesion of activated leukocytes in the myocardial tissue after $GdCl_3$ pretreatment can reduce leukocyte-endothelial cell interaction and neutrophil-mediated vascular and tissue injury.

In conclusion, the present study provides the first-ever in vivo evidence indicating that Kupffer cell blockage with $GdCl_3$ attenuates the myocardial injury induced by aortic ischemia-reperfusion. The present study may serve as a basis for studies aiming to reduce myocardial injury by $GdCl_3$ injection in the setting of aortic occlusion-reperfusion. Thus, $GdCl_3$ pretreatment may play a part in reducing cardiac mortality and morbidity during aortic surgery. However, further experimental and clinical studies are needed to clarify the exact mechanisms.

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