Resveratrol, a red wine polyphenol, protects spinal cord from ischemia-reperfusion injury

Ugursay Kiziltepe, MD,a N. Nilufer D. Turan, PhD,b Unsal Han, MD,c A. Tulga Ulus, MD,d and Fatma Akar, PhD,b Ankara, Turkey

Objective: The cardioprotective effect of red wine has been attributed to resveratrol. The resveratrol-induced protection against ischemia-reperfusion (I/R) injury has been documented in heart, kidney, and brain. Resveratrol scavenges free O2 radicals and upregulates nitric oxide (NO). However, the presence of resveratrol-induced spinal cord protection against I/R injury has not been reported in the literature. The objective of this study was to evaluate the effects of resveratrol on neurologic functions, histopathologic changes, and NO metabolism following temporary spinal cord ischemia (SCI) in rabbits.

Material and methods: SCI was induced with occlusion of the infrarenal aorta in rabbits. In addition to the sham group (group S, n = 7), group C (n = 7) received vehicle 30 minutes before ischemia. Group R1 (n = 7) and R10 (n = 7) received 1 mg/kg and 10 mg/kg resveratrol instead of vehicle, respectively. Blood samples were taken to obtain nitrite/nitrate levels during the surgical procedure. After neurologic evaluation at the 48th hour of reperfusion, lumbar spinal cords were removed for histopathologic examination and malondialdehyde measurement as a marker of oxidative stress.

Results: Five animals in group C had paraplegia while 5 in group R10 had normal neurologic functions. The average Tarlov score of group R10 was significantly higher than that of group C (4.1 ± 1.2, vs 1.2 ± 2.2; P = .014). Histopathologic examination revealed higher neuronal viability index in group R10 compared with that of group C (0.82 ± 0.24 vs. 0.46 ± 0.24; P = .018). Nitrite/nitrate levels decreased in group C (from 357 ± 20.15 μmol/L to 281 ± 47.9 μmol/L; P < .01) whereas they increased both in group R1 and group R10 (from 287±28 μmol/L to 310 ± 33.9 μmol/L and from 296 ± 106 μmol/L to 339 ± 87 μmol/L, respectively) during SCI. Malondialdehyde levels of group R10 was lower than those of group C (55 ± 12.9 nmol/mg protein vs 83.9 ± 15.1 nmol/mg protein; P = .001, respectively).

Conclusions: In this model of SCI, resveratrol decreased oxidative stress, increased NO release, and protected spinal cord from I/R injury. Resveratrol-induced neuroprotection is probably mediated by its antioxidant and NO promoting properties. Before considering the clinical use of this natural antioxidant, further research is warranted about its mechanism of effects, timing, and optimum dose. (J Vasc Surg 2004;40:138-45.)

Clinical Relevance: Paraplegia that results from spinal cord ischemia is a catastrophic complication of thoracic and thoracoabdominal aorta surgical procedures. Despite several surgical modifications and pharmacologic approaches, paraplegia has not been totally eliminated. On clinical grounds, the efficiency of currently used pharmacologic agents to prevent spinal cord injury during thoracic and thoracoabdominal aorta surgery is very limited and their benefit is controversial. Preischemic infusion of resveratrol protects the spinal cord from ischemia reperfusion injury in rabbits. Following clarification of the underlying protective mechanism, optimal dose, and timing, resveratrol may be used in humans as an adjunct to eliminate this catastrophic complication.

Paraplegia that results from spinal cord ischemia (SCI) is a catastrophic complication of surgical procedures performed on the thoracic and thoracoabdominal aorta. Neurologic injury due to ischemia-reperfusion (I/R) injury of the spinal cord has an incidence of between 2.9% and 23%.1 Despite several surgical modifications and pharmacologic approaches, postoperative spinal cord dysfunction has not been totally eliminated.2 Energy failure, excitotoxicity, and oxidative stress have been implicated in the pathogenesis of neurologic injury after SCI.3,4 Among these factors, the role of oxidative stress becomes much greater with massive production of free O2 radicals (FOR) in previously ischemic tissue.5 In addition to these factors, there is an ongoing controversy regarding the role of the nitric oxide (NO) in neurotoxicity or neuroprotection following I/R of neural tissues.6-9

Decreased cardiac mortality has been demonstrated in regular consumers of red wine. This phenomenon was referred as French paradox.10 This cardioprotection is attributed to resveratrol, which is the active constituent of red wine. Resveratrol has shown to upregulate NO and also to inhibit peroxidation of membrane lipids, scavenge FOR, inhibit platelet aggregation, and protect several organs from I/R injury.11,12

The aim of this study is to evaluate if resveratrol administration can protect rabbit spinal cord from I/R injury.
assess the ability of resveratrol to prevent neurologic injury, we evaluated hind-limb motor functions and histopathologic examination of the spinal cords. Furthermore, the effects of resveratrol administration against oxidative stress were evaluated via measurement of malondialdehyde (MDA) level in spinal cord homogenates for estimation of lipid peroxidation.

**MATERIAL AND METHODS**

**Animal care**

Fifty-two male New Zealand white rabbits weighing 2.0 to 3.5 kg were used in these experiments. The rabbits were allowed access to standard rabbit food and water ad libitum. All rabbits were neurologically intact before anesthesia. This work was approved by the local institutional review board, and the animal care complied with the National Research Council’s Guide for the Care and Use of Laboratory Animals.

**Anesthesia and monitoring.** Animals were anesthetized with intramuscular ketamine (50 mg/kg) and xylazine (10 mg/kg), placed in the supine position, and allowed to breathe spontaneously without mechanical ventilation. Supplemental intravenous doses of ketamine were administered as needed throughout the experiments. The core temperature was continuously monitored with a rectal probe inserted 5 cm into the rectum. Rectal temperature was maintained between 37°C to 38.5°C by a heating lamp throughout the procedure. A catheter (24 gauge) was steriley placed in a marginal ear vein for intravenous drug administration. Another catheter (24 gauge) was placed in the central ear artery to monitor arterial blood pressure and to obtain blood samples. Preoperative Cefazolin (10 mg/kg) was given as a single dose. The heartbeat and arterial blood pressure were continuously monitored throughout the procedure.

**Surgical procedure.** All animals were prepared and draped in a sterile fashion. After the rabbits had been stabilized, a 10-cm-long median laparotomy was performed. After reflection of intestine to the right, the abdominal aorta was dissected just caudal to the left renal artery and above the bifurcation of the aorta. The aorta was then encircled with a silk ligature both distal to the renal artery and proximal to the bifurcation to facilitate secure occlusion. Animals were anticoagulated with 200 units/kg of heparin before aortic cross-clamping. The aorta was occluded distal to the left renal artery and proximal to the bifurcation with atrumatic vascular clamps to induce spinal cord ischemia. After completion of the ischemia period, ligatures and cross-clamps were removed, the abdomen was closed in 2 layers, and the animals were allowed to recover. After the operations, the animals were returned to their cages and allowed free access to water and food. Sham-operated animals underwent same procedures without administration of tested drugs and induction of SCI by aortic occlusion.

**Experimental groups**

After anesthesia and baseline hemodynamic measurements, rabbits were placed in 1 of the 5 groups. Animals in group S underwent a sham operation. The control group (group C) received vehicle (50% alcohol, 2 mL) 30 minutes before the 30-minute SCI period whereas animals of groups R1 and R10 received resveratrol (Sigma, St. Louis, Mo)—1 and 10 mg/kg dissolved in 2 mL 50% alcohol, again 30 minutes before SCI. All groups underwent 30 minutes of aortic occlusion. The vehicle and resveratrol solution were infused in 5 minutes in all animals. The resveratrol infusion doses were selected according to the doses used in brain ischemia models in the literature.14,15

**Data collection**

Temperature and hemodynamic measurements were recorded at following timepoints: after anesthesia, after laparotomy, during cross-clamping, after removal of the cross-clamp, and after closure. Arterial blood samples for nitrite/nitrate measurements were drawn immediately after insertion of the arterial catheter (before the administration of test drug) (preischemia), 2 minutes before the removal of the cross-clamp (ischemia), and after skin closure (postischemia).

**Neurologic evaluation**

Neurologic status was scored by assessment of hind-limb neurologic function 48 hours after the procedure, using the modified Tarlov Scoring System.16 Neurologic status of animals was assessed blindly by 2 researchers. Crede’s maneuver was used for evacuation of the urinary bladder when necessary.17 A score of 0 to 5 was assigned to each animal as follows: 0, no voluntary hind-limb movement; 1, movement of joints perceptible; 2, active movement but unable to sit without assistance; 3, able to sit but unable to hop; 4, weak hop; 5, complete recovery of hind-limb function.

**Histopathologic evaluation**

All rabbits were sacrificed by using sodium pentobarbital (100 mg/kg) and KCl administered intravenously through an ear vein at the 48th hour of reperfusion. The lumbar spinal cord segment was immediately procured and flash-fixed in 10% buffered formalin for 15 days. Segments were embedded in paraffin, and serial transverse sections were cut (4μ) for hematoxylin and eosin staining. Histopathologic evaluations were performed by a pathologist blinded to the study groups. Histopathologic sections were evaluated both by qualitative and quantitative methods in order to maximize scientific accuracy. Histologic damage was scored qualitatively, using a previously defined system.18 A score of 1 to 5 was assigned to each section as follows: 1, frank necrosis; 2, severe cellular damage; 3, moderate cellular damage; 4, mild cellular damage; and 5, normal histologic appearance. As a quantitative method, the neuronal viability index was also calculated.19 Features consistent with neuronal injury included eosinophilic cyto-
Fig 1. Histopathologic findings of anterior horn of lumbar spinal cord segments procured 48 hours after reperfusion and stained with hematoxylin-eosin. A, Normal appearance of neurons in sham operated animals (arrows, Nissl substance, ×40). B, Eosinophilic neuronal degeneration in group C, exhibiting inflammatory cell accumulation, destruction and vacuolization of the gray matter, pyknosis of neurons and capillary proliferation (single arrow, necrotic neuron bodies without Nissl substance; double arrow, new capillary vessels [neovascularization], ×40).
plasm, vacuolization, and pyknotic appearance (loss of nuclear structure). Cells that contained Nissl substance in the cytoplasm, loose chromatin, and prominent nucleoli were considered viable. The viability index was calculated as the number of clearly viable neurons divided by the total neuronal count within the anterior horn of each section for each animal.

**MDA measurements**

As a marker of oxidative stress and FOR-mediated damage, MDA levels were measured at the lumbar segments of spinal cords that were removed from sacrificed animals at the 48th hour of reperfusion. Samples were stored at −70°C until the analysis. Each sample was homogenized in 100 mmol/L phosphate buffer (pH 7.4) in an ice bath. The homogenate was sonicated 2 times for 20 seconds and centrifuged. Fifty μL of sample was added to a mixture containing 200 μL phosphate buffer solution, 0.88% butylated hydroxytoluene, and trichloroacetic acid (30%). After mixing, samples were kept at +4°C for 2 hours and then centrifuged at 4000 rpm for 15 minutes. Two hundred and fifty μL of supernatant was added to a mixture 0.1 mol/L EDTA-NaH₂O and thiobarbituric acid (1%) and then boiled for 15 minutes. The absorbance of the mixture was measured at 490 nm with microplate reader (ELX-800, BioTek). MDA concentrations in the samples were calculated by a standard calibration curve of 1,1,3,3-tetraethoxypropone prepared in the same manner. Each measurement was performed in duplicate. MDA concentrations were expressed as μmol/L.

**Nitrite/nitrate measurements**

Plasma concentrations of nitrite/nitrate were assayed with a commercially available nitric oxide assay kit (Assay Designs, Inc, Ann Arbor, Mich). The kit allows the enzymatic conversion of nitrate to nitrite, by the enzyme nitrate reductase, followed by colorimetric detection of nitrite as a colored azo dye product of the Griess reaction. We investigated to determine total NOx production; nitrate was reduced to nitrite by reduced nicotinamide-adenine dinucleotide in the presence of nitrate reductase and reading the optical density at 540 nm.

**Statistical analysis**

All data are expressed as mean ± standard deviation. Statistical analysis of the neurologic scores, neuronal viability index, histologic score, and MDA values were analyzed by using Kruskal-Wallis one-way analysis of variance. Where differences were identified, a multiple comparison test was performed. Statistical analyses of hemodynamic and temperature measurements were done with the unpaired Student t test. Nitrite/nitrate measurements were analyzed with the Friedman 2-way analysis of variance followed by a multiple comparison test when significant. All analyses were performed by using the SPSS software package (SPSS, Inc, Chicago, Ill).

**RESULTS**

**Perioperative data.** Two animals both in groups C and R1 and 3 animals in group R10 were dead before the
Table I. Heart rate and systolic blood pressure values (mm Hg)

<table>
<thead>
<tr>
<th></th>
<th>After anesthesia</th>
<th>After laparotomy</th>
<th>During cross-clamping</th>
<th>After removal of cross clamp</th>
<th>After closure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group S</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>297 ± 11</td>
<td>300 ± 10</td>
<td>–</td>
<td>297 ± 8</td>
<td>298 ± 8</td>
</tr>
<tr>
<td>SBP</td>
<td>87.5 ± 4.3</td>
<td>87.1 ± 2.3</td>
<td>–</td>
<td>87.7 ± 3.9</td>
<td>87.3 ± 5.6</td>
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<tr>
<td>Group K</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>303 ± 13</td>
<td>304 ± 15</td>
<td>300 ± 14</td>
<td>309 ± 13</td>
<td>313 ± 13</td>
</tr>
<tr>
<td>SBP</td>
<td>87.4 ± 4.5</td>
<td>85.8 ± 3.7</td>
<td>86.5 ± 5.3</td>
<td>84.3 ± 4.4</td>
<td>86.7 ± 4.5</td>
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<tr>
<td>Group R1</td>
<td></td>
<td></td>
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<tr>
<td>HR</td>
<td>298 ± 17</td>
<td>303 ± 18</td>
<td>268 ± 25</td>
<td>296 ± 19</td>
<td>280 ± 24</td>
</tr>
<tr>
<td>SBP</td>
<td>89.3 ± 3.1</td>
<td>84.4 ± 2.9</td>
<td>87.3 ± 2.8</td>
<td>85.6 ± 5.1</td>
<td>84.5 ± 7.2</td>
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<td>Group R10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>308 ± 16</td>
<td>286 ± 21</td>
<td>259 ± 17</td>
<td>293 ± 17</td>
<td>285 ± 15</td>
</tr>
<tr>
<td>SBP</td>
<td>86.8 ± 5.7</td>
<td>87.3 ± 5.7</td>
<td>88 ± 3.9</td>
<td>85.1 ± 3.2</td>
<td>84.2 ± 4.8</td>
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<tr>
<td>Group L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>298 ± 11</td>
<td>301 ± 22</td>
<td>318 ± 25</td>
<td>306 ± 19</td>
<td>311 ± 19</td>
</tr>
<tr>
<td>SBP</td>
<td>92 ± 6.4</td>
<td>84.5 ± 9.2</td>
<td>82.2 ± 11.9</td>
<td>74.3 ± 10.7*</td>
<td>76.3 ± 13.1†</td>
</tr>
</tbody>
</table>

HR, Heart rate; SBP, systolic blood pressure.

*P < .05, vs groups S, K, R1, and R10.
†P < .05, vs groups S and K.

48th hour of reperfusion. Three of those animals died of surgical complications intraoperatively.

Examination of the systolic blood pressure data revealed that there was a transient and non-significant decrease in MAP in the groups R1 and R10 following resveratrol infusion (Table I).

All animals had a slight decrease in rectal temperature after laparotomy followed by slow elevation back to prelaparotomy levels until the completion of experiment. None of the animals had temperatures less than 37.5°C, and rectal temperatures were similar in all groups.

Neurologic evaluation. Five animals in Group C had paraplegia while 5 animals in Group R10 had normal or near normal neurologic functions (Table II). The average Tarlov score for group R10 was significantly higher than that for group C. The difference between groups R1 and C was not significant.

Histopathologic evaluation. No sign of spinal cord damage was observed in hematoxylin-eosin–stained sections in the sham-operated rabbits (Fig 1, A). However, in most of the control rabbits, histologic sections showed severe neuronal damage, as evidenced by eosinophilic neuronal degeneration, inflammatory cell accumulation, swollen motor neuron cells in which the Nissl bodies and nuclei had disappeared, and vacuolization of gray matter (Fig 1, B). Sections of rabbits that received 1 mg/kg resveratrol showed only slightly improved histopathologic appearance. In contrast, examinations of the most of the rabbits that received 10 mg/kg resveratrol showed almost intact-looking light microscopic findings with minimal inflammatory cell accumulation (Fig 1, C). The histopathologic score of animals in group R10 was significantly higher than that for both groups R and C (Table III). Similarly viable neuron count at the anterior lumbar spinal cord sections revealed a higher neuronal viability index in group R10 compared with both R1 and C (Table III).

MDA levels. The MDA levels of R10 were significantly lower than those of the group C (55 ± 12.9 nmol/mg protein vs 83.9 ± 15.1 nmol/mg protein, respectively; *P = .001*) (Fig 2). The difference between groups S and R10 was not significant (*P = .065*).

Nitrite/nitrate levels. The time courses of the nitrite/nitrate levels throughout the experiment are depicted in Fig 3. The control group had decreased NO release during the ischemia period (*P < .01* vs preischemia) while near to complete recovery occurred during reperfusion phase. In contrast, group R10 had increased NO release (*P < .05*) during ischemia, which decreased to baseline during reperfusion. The time courses of groups R1 and R10 were also significantly different compared with those of group C at the ischemia period (when calculated changes between consecutive data points were compared: group C vs group R1, *P < .05*; group C vs group R10, *P < .01*) and reperfusion period (group C vs group R1, *P < .01*; group C vs group R10, *P < .01*).

DISCUSSION

Our findings revealed that preischemic infusion of 10 mg/kg resveratrol protected spinal cord from I/R injury as evidenced by improved neurologic function and near normal histopathologic appearance. This protective effect was not prominent in animals that received 1 mg/kg resveratrol. The time course of the nitrite/nitrate levels demonstrated significantly increased NO release after resveratrol infusion and return of NO levels to baseline in time. However, NO release of the control group decreased during ischemia and recovered during reperfusion.

Reperfusion injury is one of the most important components in the pathogenesis of neurologic dysfunction following SCI. Reoxygenation of the energy-depleted cells causes massive production of FOR. Peroxidation of membrane lipids and loss of membrane functions result in cell
Inflammatory response with production of cytokines by microglia and activated neutrophils also contributes to generation of these radicals. Another mechanism of neuronal death is excitotoxicity. Following SCI, release of the excitotoxic transmitter glutamate and activation of N-methyl D-aspartate receptors cause excessive Ca"<sup>2+</sup> influx and trigger a chain of reactions that lead to neuronal death.

Resveratrol-induced brain protection has been demonstrated by several authors, although we did not find any report that investigated its effect against SCI. Its neuroprotective effect was attributed mainly to the protection membranes with neutralization of FOR generated by both neutrophils and endothelium. Some reports indicate that NO is the mediator of resveratrol-induced protection against I/R injury in kidney and heart. Resveratrol increases NO production by upregulation of endothelial NOS (eNOS) mRNA expression, and slows its degradation. It produces both NO-mediated and NO-independent vasorelaxation to improve perfusion of tissues during reperfusion.

Effects of NO on neural tissue is controversial: it has potent anti-inflammatory property and may contribute to neuroprotection. Potent in vivo antioxidant properties of resveratrol were explained by its stimulation of NO formation as well as its role as a potent scavenger for FOR generated by both neutrophils and endothelium. Some reports indicate that NO is the mediator of resveratrol-induced protection against I/R injury in kidney and heart. Resveratrol increases NO production by upregulation of endothelial NOS (eNOS) mRNA expression, and slows its degradation. It produces both NO-mediated and NO-independent vasorelaxation to improve perfusion of tissues during reperfusion.

Table II. Neurologic status 48 hours after reperfusion as evaluated by the Tarlov neurologic recovery scale

<table>
<thead>
<tr>
<th>Tarlov score*</th>
<th>Group S (n = 7)</th>
<th>Group C (n = 7)</th>
<th>Group R1 (n = 7)</th>
<th>Group R10 (n = 7)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td>1</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Mean ± SD
0.03 ± 2.2 2.9 ± 1.95 4.1 ± 1.2

Median 5 0 3 5

*Number of viable neurons divided by the total neuron count within the ventral spinal cord (quantitative).

Table III. Quantitative and qualitative histopathologic analysis of spinal cord specimens at the 48th hour of reperfusion

<table>
<thead>
<tr>
<th>Neuronal viability index*</th>
<th>Group S (n = 7)</th>
<th>Group C (n = 7)</th>
<th>Group R1 (n = 7)</th>
<th>Group R10 (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1</td>
<td>0.46 ± 0.34</td>
<td>0.45 ± 0.28</td>
<td>0.82 ± 0.24†</td>
</tr>
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</table>

Histopathologic score‡

Histopathologic score (qualitative): 1, normal histologic appearance; 2, mild cellular damage; 3, moderate cellular damage; 4, severe cellular damage; 5, frank necrosis.

†P = .014, vs group C (Kruskal-Wallis 1-way ANOVA followed by Multiple Comparison Test).

‡P = .015 group C vs group R1. †P = .0005, groups R1 and R10 vs group S.
protects cell membranes from oxidative stress. NO that originates from eNOS is required for mediation of ischemic preconditioning–induced neuroprotection against I/R injury, as documented in cerebral ischemia by Gidday et al. It has also been shown that NO-related S-nitrosylation causes decreased N-methyl D-aspartate receptor activity and caspase enzyme activity, thus providing neuroprotection from excitotoxic insults. In support of this hypothesis, it has been shown that inhibition of NO synthesis causes a decrease in cerebral blood flow, and an increase in cerebral infarction volume.

The data of Matsumoto et al revealed the importance of NO in SCI as evidenced by aggravation of spinal cord injury with nonselective NOS blockage by using L-NAME (N\textsuperscript{G}-nitro-L-arginine-methyl ester, a nonspecific nitric oxide synthase inhibitor) in rabbits subjected to SCI. Our results are in agreement with these findings and show association of improved neurologic status and elevated NO release in animals receiving 10 mg/kg resveratrol whereas decreased levels of NO were associated with severe neurologic deficit after SCI. Although not included in this study, we attempted to neutralize the resveratrol-induced spinal cord protection with L-NAME in 10 rabbits. These animals received an L-NAME infusion (10 mg/kg) before resveratrol infusion (10 mg/kg). Unfortunately, all but 2 animals unexplainably died in the early postoperative period due to significant hemodynamic instability; thus we could not demonstrate loss of the spinal cord protection with combined use of L-NAME and resveratrol. However, nitrite/nitrate data showed that L-NAME infusion suppressed resveratrol-induced NO release and formed a parallel time course to the control group.

The present study is probably one of the first to demonstrate the effects of resveratrol in attenuating the I/R-induced neurologic injury to the rabbit spinal cord. MDA data suggest decreased oxidative stress as one of the most possible mechanisms. Elevated NO release may also cause decreased excitotoxicity and improved perfusion due to vasodilation. This neuroprotection could be a form of pharmacologic preconditioning that was induced by activation of eNOS, as suggested by Gidday et al. We also propose that decrease of NO release to baseline, approximately 1.5 hours after resveratrol infusion, indicates the need for a continuous infusion or another bolus dose before reperfusion to further potentiate its protection against ischemic spinal cord injury. Another conclusion would be the inadequacy of the 1 mg/kg dose of resveratrol. Future studies investigating the abrogation of resveratrol-induced spinal cord protection with nonselective and selective inhibitors of NOS may reveal the underlying mechanism of this protection. The protection of resveratrol against apoptosis may also be an important future research interest. Further studies using different doses and timing of resveratrol infusion are necessary to clarify the detailed mechanism responsible for the beneficial effects of resveratrol infusion on SCI.

In this study, although we proved the protective role of resveratrol, we could not fully explain the underlying mechanism. Our failure to document possible abrogation of the effects of resveratrol by L-NAME is probably the major limitation of this study. To explain the mortality of these animals, different dose combinations of resveratrol and L-NAME should be tried. We believe the higher mortality of study groups (which is related to surgical complications in almost half of the animals) is not related to SCI and did not affect our results.

In conclusion, preischemic infusion of 10 mg/kg resveratrol protects the spinal cord from I/R injury in rabbits. This protection is related to decreased oxidative stress and can be a form of NO-mediated pharmacologic preconditioning. L-NAME infusion may abrogate this protection.
Following clarification of the underlying mechanism of this protection, correct dose, and timing of resveratrol, studies of this red wine polyphenol in the prevention of neurologic deficits associated with surgical procedures of the descending aorta in humans may be useful.

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REFERENCES


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