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The effect of resveratrol on intimal hyperplasia and endothelial proliferation of rabbit carotid artery anastomosis

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Abstract

OBJECTIVES: We assessed the effect of resveratrol on intimal hyperplasia and endothelial proliferation after its use for carotid artery anastomosis in rabbits.

METHODS: Fourteen New Zealand-type male rabbits, weighing a mean of 2–3 kg were selected randomly. Their right carotid arteries were transected and anastomosed side by side using 8/0 polypropylene. The rabbits were divided into two groups with seven in each group. While the rabbits in the first group were accepted as the Control group, the rabbits in the second group were given resveratrol (1 mg/kg/day) for 14 days intravenously. At the end of the 28th day, all the carotid artery segments that were transected and anastomosed and the left carotid arteries that did not undergo surgery were removed and evaluated histologically.

RESULTS: The results of histological evaluation were as follows: lumen diameter (P <0.001) and lumen area (P <0.05) of the Resveratrol group were larger than those of the Control group, intimal thickness (P <0.05) and media thickness of the Resveratrol group (P = 0.04) were thinner than those of the Control group, and intima/media ratio of the Control group was found to be greater than that of the Resveratrol group (P = 0.002).

CONCLUSIONS: Resveratrol can prevent intimal hyperplasia and endothelial proliferation following surgical anastomosis.

Keywords: Resveratrol • Intimal hyperplasia • Endothelial proliferation

INTRODUCTION

Angioplasty, stenting and bypass graft surgery are common interventions for the treatment of occlusive arterial diseases. However, the success of these interventions is not 100% because of the development of spontaneous thrombosis or stenosis [1]. Iatrogenic trauma and cuts that occur in the vascular endothelium during angioplasty, stenting and bypass graft surgery cause the development of remodelling. Extracellular matrix damage and smooth muscle cell proliferation occur during remodelling.

Neointimal hyperplasia occurs as a result of the migration of proliferated smooth muscle cells from media to intima and is the pathological basis of restenosis [2, 3]. In arterial damage models in animals and humans, it has been demonstrated that the main reason for lumen narrowing is smooth muscle cell proliferation and the accumulation of connective tissue in the intima [2, 4].

After endothelium damage develops, the damaged area is coated with platelets. Following adhesion, platelets release vasoactive and thrombotic factors in their granules (serotonin, ADP, fibrinogen, and Von Willebrand factor) and release growth factors (platelet-derived growth factor, transforming growth factor, and epidermal growth factor) [5]. Mitogenic growth factors initiate the proliferation of smooth muscle cells. Proliferated smooth muscle cells in the media layer migrate to the intima and lead to intimal hyperplasia. According to the response-to-injury hypothesis proposed by Russel Ross and currently widely accepted, the mechanism that initiates intimal thickening is the growth factors that are released from platelets and endothelial cells adhering to the damaged vessel wall and stimulate proliferation of smooth muscle cells [6].

Intimal response to arterial damage occurs in three stages. Smooth muscle cell proliferation occurs in the media within the first 24 h. In the 3rd and 14th days, these smooth muscle cells migrate to the intima, and neointima and neointimal hyperplasia develop. Since neointimal hyperplasia development involves a 14-day process and Bertelli *et al.* [7] have demonstrated that the bioavailability of resveratrol is very good in the first 15 days, we applied resveratrol in the first 14 days of our study.

In the study of More *et al.* [8], they detected that re-endothelization began on the 3rd day following the angioplasty damage in rabbit vessels. Depending on the extracellular matrix accumulation, intimal thickening reached its maximum level after the first month and showed a decrease in 3 months. According to this study, scarification day in our study was determined to be the 28th day when the intimal hyperplasia was at its maximum level.

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In 2006 Gu *et al*. [9] detected that with the use of low-dose resveratrol in rats with intima damage, endothelial nitric oxide (NO) synthase expression with endothelial progenitor cell mobilization increased. Besides this, progenitor cell proliferation increased migration and adhesion activities, and neointima formation decreased with the use of high-dose resveratrol.

In another study, it has been demonstrated that, in endothelium damage of rabbit iliac artery, resveratrol decreased vascular intima hyperplasia, increased lumen area, and significantly decreased the number of smooth muscle cells in the thickened intima. Also, resveratrol added to rabbit smooth muscle cell culture inhibited DNA synthesis dose dependently [10].

Resveratrol inhibits arachidonic acid products through cyclooxygenase and lipooxygenase, which are the source of proinflammatory mediators that play a role in the pathogenesis of cancer and inflammation. The phosphorylation of ATP is inhibited by tyrosine kinase and serine/threonine kinase inhibition. As a result of this, it stops its growth by stimulating apoptosis in various cancer cells [11]. Smooth muscle cell proliferation in the intima reduces transition of the cell cycle from G1 to S phase with antimitotic effects [12–14]. With a similar effect, it has been demonstrated that the development of human aorta vascular smooth muscle cells is blocked by DNA synthesis inhibition [15].

Resveratrol, a red wine polyphenol, is known to exhibit vascular protective effects and reduce vascular smooth muscle cell mitogenesis, and inhibitory effects on proliferation, and migration of vascular smooth muscle cells has been reported [16–18].

Studies in the literature about resveratrol have investigated endothelial damage caused by angioplasty, and there are no studies about damage caused by anastomosis.

For this reason, we planned this experimental study about resveratrol and endothelial damage created by anastomosis, which is believed to be the first, and evaluated the effect of resveratrol on intimal hyperplasia following anastomosis.

We aimed to investigate the effects of resveratrol on smooth muscle cell proliferation and the formation of neointimal hyperplasia in surgical procedures performed on rabbit carotid arteries.

MATERIALS AND METHODS

Our randomized, controlled, experimental study was initiated after approval from Dokuz Eylül University School of Medicine Experimental Animals Ethics Committee on 6 June 2008 with the protocol number 58/2008 and conducted in the Animal Experiments Laboratory.

EXPERIMENT PROTOCOL

Fourteen New Zealand-type male rabbits (mean weight: 2.3–2.9 kg) were used for this study. The right carotid artery of each rabbit was explored for anastomosis. Then, the right carotid arteries were transected full layer, and the layers were closed in the anatomic plane after end-to-end anastomosis with 8/0 polypropylene sutures. Rabbits were randomized into two groups consisting of 7 rabbits each. The rabbits in the first group were given intravenous (IV) saline (Control group) for 14 days following surgery, and the rabbits in the second group were given resveratrol (1 mg/kg/day) IV (Resveratrol group). IV bolus of resveratrol was administered.

Rabbits were euthanized 28 days after surgical intervention. Before euthanizing, the anastomosis area of the right carotid artery and a section from the left carotid artery, for comparison, were removed from each rabbit. All specimens were evaluated with light microscopy and immunohistochemistry.

OPERATION PROCEDURE

A branule was preoperatively inserted into the rabbits from the marginal vein located behind the ear. Anaesthesia was given with intramuscular xylazine (5 mg/kg) and ketamine (50 mg/kg). Also, in order to prevent infections, rabbits were administered IV cefazolin (50 mg/kg) preoperatively. In the study, the same researcher performed all anastomoses. A 3.5 × surgical loop design for vision was used during the operation. The right carotid artery was explored through an oblique incision made at the right side of the neck. Following 100 IU/kg IV heparinization, proximal and distal parts of the right carotid artery were clamped with bulldog clamps, and carotid artery was transected full layer. Then, the artery was anastomosed end-to-end with running monofilament sutures (8.0 polypropylene 6.5 mm 3/8 Circle, Somerville, NJ, US). Layers were closed in the anatomic plane, and the operation was complete.

Rabbits were euthanized on postoperative day 28. Anaesthesia was performed by a standard technique in both groups. First, the anastomosis area in the right carotid artery was explored and excised by an oblique incision performed on the right side of the neck. Then, for the purpose of control, a similar incision was made on the left side of the neck, and the left carotid artery was excised. The excised tissue was put in 10% paraformaldehyde solution and stored at 4°C for histological evaluations. Euthanasia was achieved with high-dose xylazine and ketamine.

HISTOLOGICAL EVALUATION

Obtained samples were fixed in 10% neutral formalin for light microscopy examination. Then, by following routine histological procedures, paraffin blocks were prepared. Serial cross sections of 5 μm were made from the prepared paraffin blocks. Sections were stained with haematoxylin and eosin and Masson trichrome. All the cross-sections were examined with an Olympus BH-2 (Tokyo, Japan) light microscopy. Obtained images were assessed with a digital imaging analysis programme (UTSCSA; Image tool version 3.0 University of Texas, San Antonio, TX, USA). During the vascular tissue assessment, the thickness of tunica intima and tunica media, tunica intima and tunica media areas, vascular lumen diameters and vascular lumen areas were assessed. Differences between the groups for vascular lumen diameter and lumen area, and differences between thickness of intima/media and area were assessed. Also, serial cross-sections were taken from the prepared paraffin tissues.

STATISTICS

Obtained data were expressed as mean ± standard deviation. Data were assessed with SPSS 15.0 evaluation version (SPSS, Chicago, IL, USA) statistical programme with one-way analysis of variance, *post hoc*; and analysed with Bonferroni test for multiple comparisons. $P < 0.05$ was considered significant.

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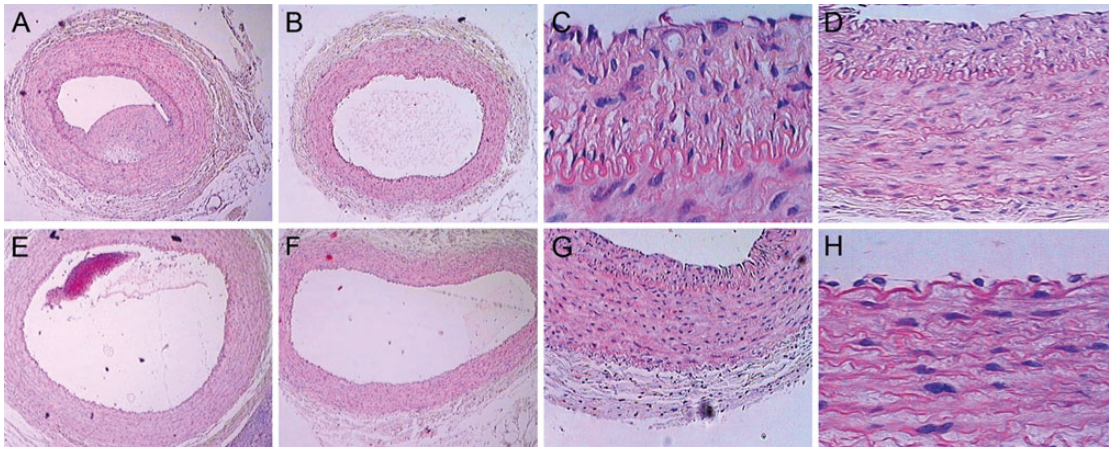


Figure 1: Histological sections of groups, control and resveratrol (haematoxylin-eosin stain). (**A**) The Control group histological section of right carotid artery (40×). (**B**) The Control group histological section of left carotid artery (40×). (**C**) The Control group right carotid artery intimal hyperplasia (40×). (**D**) The Control group right carotid artery media hypertrophy (20×). (**E**) The Resveratrol group histological section of right carotid artery (40×). (**F**) The Resveratrol group histological section of left carotid artery (40×). (**G**) The Resveratrol group right carotid artery intimal hyperplasia (10×). (**H**) The Resveratrol group right carotid artery media hypertrophy (40×).

RESULTS

Specimens were examined pathologically for each anastomosis. Specimens included anastomosis site and the tissue 5 mm away from the anastomosis site (proximal and distal).

In the histological sections obtained from the rabbits not given resveratrol (Control group), when the right carotid artery where anastomosis was performed was compared with the left carotid artery without surgery, the right carotid artery lumen was found narrowed and its smooth circular shape was impaired (Fig. 1A and B). In the intimal area, smooth muscle cell proliferation, disorganized cellular arrangement, intensive connective tissue increase and development of intimal hyperplasia were detected (Fig. 1C).

In the histological sections obtained from the rabbits given resveratrol (Resveratrol group), it was observed that the lumen of the right carotid artery where anastomosis was performed was larger and its geometrical shape was more proper than the right carotid artery lumen of the rabbits where anastomosis was performed but resveratrol was not given (Fig. 1A–E). When the left carotid artery lumens (where anastomosis was not performed) of the resveratrol rabbits were compared with the left carotid artery lumens of the rabbits that did not receive resveratrol, an interesting state was detected. Resveratrol maintains a balance between vasodilators, such as NO, and vasoconstrictors, such as endothelin-1. Resveratrol shows the ability to regulate the production of these vasodilators and vasoconstrictors. Consequently, the vascular lumen of the group that received resveratrol was larger and smoother (Fig. 1B–F) [19–21]. When the right carotid arteries of both groups were compared for intimal hyperplasia and medial hypertrophy, intimal hyperplasia and medial hypertrophy were much more in the group that did not receive resveratrol (Fig. 1C–G; Fig. 1D–H).

When evaluated statistically, the mean diameter of vascular lumen and lumen area of the Resveratrol group were significantly larger on both sides, where anastomosis was performed and where it was not (Tables 1 and 2) (Figs. 2 and 3). Intima thickness and intima/media area ratio were significantly lower in the side where anastomosis was performed, and there was not any significant difference detected in the left side (Tables 3 and 4) (Fig. 4).

Table 1: Comparison of mean lumen diameters

	Resveratrol group ($n = 7$)	Control group ($n = 7$)	*P*-value
Right carotid artery mean lumen diameter (μm)	991 ± 132	663 ± 208	$P < 0.001$
Left carotid artery mean lumen diameter (μm)	1100 ± 168	756 ± 176	$P < 0.001$

Right carotid artery: anastomosis performed; left carotid artery: anastomosis not performed.

Table 2: Comparison of mean lumen area

	Resveratrol group ($n = 7$)	Control group ($n = 7$)	*P*-value
Right carotid artery mean lumen area (μm^2)	451.201 ± 86.116	318.703 ± 116.541	$P < 0.05$
Left carotid artery mean lumen area (μm^2)	507.760 ± 67.121	375.220 ± 154.185	$P = 0.038$

Right carotid artery: anastomosis performed; left carotid artery: anastomosis not performed.

DISCUSSION

Neointimal hyperplasia plays an important role in the early or mid-term occlusions or restenosis following vascular reconstructive interventions such as angioplasty, stenting and bypass graft surgery. Neointimal hyperplasia develops as a result of smooth muscle cell

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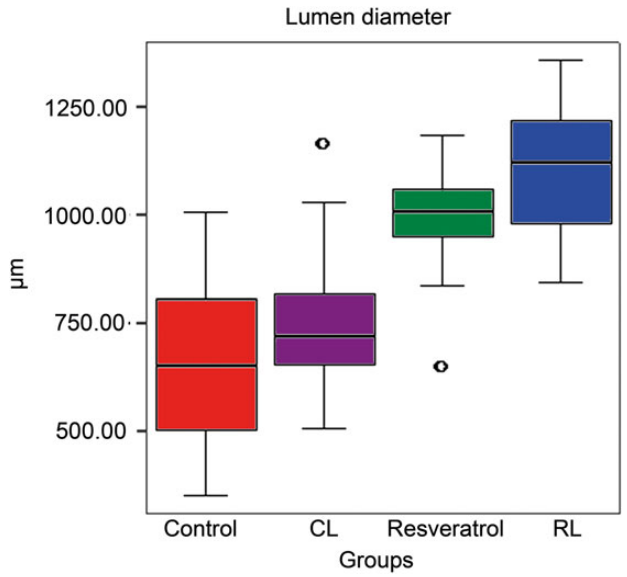


Figure 2: Comparison of mean lumen diameters. Control group: resveratrol not given, anastomosis performed in right carotid artery. CL: anastomosis not performed in left carotid artery from the Control group. Resveratrol group: resveratrol given, anastomosis performed in right carotid artery. RL: anastomosis not performed in left carotid artery from the Resveratrol group.

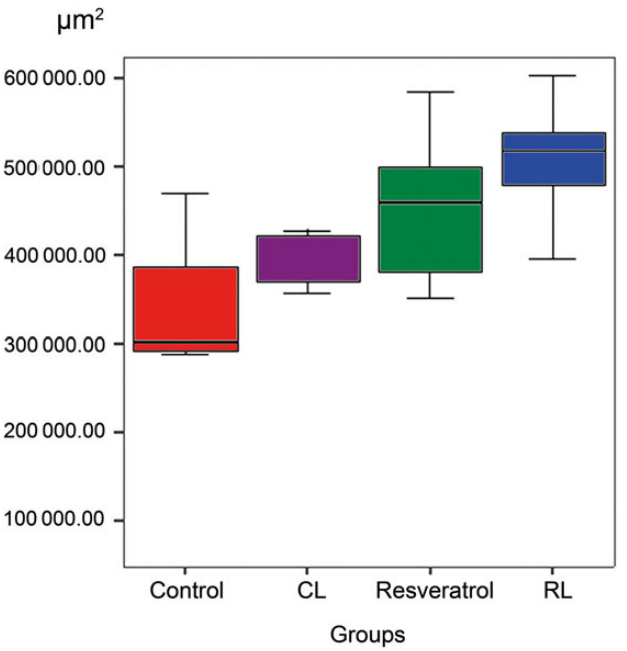


Figure 3: Comparison of mean lumen areas. Control group: resveratrol not given, anastomosis performed in right carotid artery. CL: anastomosis not performed in left carotid artery from the Control group. Resveratrol group: resveratrol given, anastomosis performed in right carotid artery. RL: anastomosis not performed in left carotid artery from the Resveratrol group.

migration and proliferation, and accumulation of extracellular matrix [1, 4]. Intimal hyperplasia is a normal adaptive response of arteries against haemodynamic stress and also a characteristic feature of arterial injury healing [4]. Iatrogenic trauma and cuts of vascular endothelium that develop during the vascular reconstructive interventions cause formation of remodelling [2]. Endothelial cell loss is a factor that is a major contribution to remodelling [3].

Table 3: Comparison of mean intimal thickness

	Resveratrol group (n = 7)	Control group (n = 7)	P-value
Right carotid artery mean intimal thickness (µm)	17 ± 5[a]	58 ± 22[b]	P <0.000
Left carotid artery mean intimal thickness (µm)	6 ± 2[a]	7 ± 3[b]	P <0.214

Right carotid artery: anastomosis performed; left carotid artery: anastomosis not performed.
[a]There was a significant difference between the right carotid artery and the left carotid artery in the Resveratrol group (P <0.000).
[b]There was a significant difference between the right carotid artery and the left carotid artery in the Control group (P <0.000).

Table 4: Comparison of mean intima/media area ratio

	Resveratrol group (n = 7)	Control group (n = 7)	P-value
Right carotid artery mean intimal thickness	0.2131 ± 0.09168	0.4794 ± 0.11139	P = 0.002
Left carotid artery mean intimal thickness	0.1585 ± 0.27876	0.0944 ± 0.04424	P = 0.180

Right carotid artery: anastomosis performed; left carotid artery: anastomosis not performed.

Neointimal hyperplasia develops as a result of remodelling, which is the pathological basis of restenosis [2, 3].

The endothelium is highly sensitive to physical stimuli. Functional changes in the endothelium following physical stimuli are called endothelial cell activation. Vasoconstriction, leukocyte adhesion and smooth muscle cell proliferation occur due to activation. Additionally, neointima develops in intima due to abnormal fibrin proliferative changes. Although this intimal neoplastic response is a part of the post-traumatic repair of blood vessels, sometimes it may be too severe [22].

Prevention of hyperplastic response can be effective in increasing lifespan by significantly extending the duration of patency of the vessel and decreasing loss of organs following vascular reconstructive interventions such as surgical graft bypass or balloon angioplasty [4]. Future studies in the field of vascular biology will positively affect the quality of life of cardiovascular surgery patients by providing better understanding of endothelial vascular tonus regulation, which is primarily responsible for intimal hyperplasia [23].

Excessive neointimal proliferation may cause a decrease in blood flow and cause thrombosis formation by impairing the ability of anticoagulation in the endothelium, leading to narrowing of the lumen [6].

Several studies have been conducted using drugs to prevent intimal hyperplasia and smooth muscle cell proliferation following

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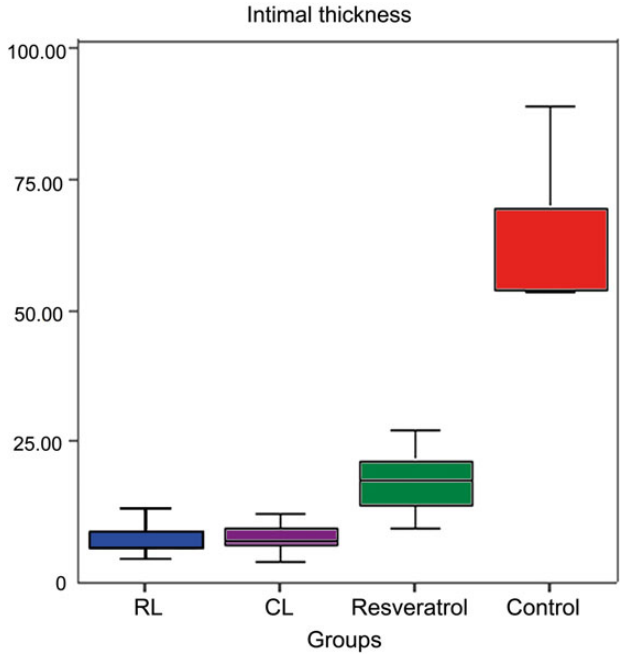


Figure 4: Comparison of mean intimal thickness. Control group: resveratrol not given, anastomosis performed in right carotid artery. CL: anastomosis not performed in left carotid artery from the Control group. Resveratrol group: resveratrol given, anastomosis performed in right carotid artery. RL: anastomosis not performed in left carotid artery from the Resveratrol group.

anastomosis, percutaneous transluminal coronary angioplasty or stenting. Various medications such as growth factor inhibitors, selective adenosine A2a receptor agonists, immunosuppressive agents, calcium channel blockers, statins, aspirin, iloprost, heparin, and angiotensin-converting enzyme inhibitors have been tested for this purpose [24].

Studies about the use of resveratrol for preventing intimal hyperplasia are new and currently at the animal experimental stage [10].

The positive results of resveratrol in preventing intimal hyperplasia that were published previously have been detected in our study too. In the group using resveratrol, both lumen diameter and lumen area were significantly larger than in the group in which resveratrol was not used (Figs. 1A–E, 2 and 3) (Tables 1 and 2). Intimal thickening and intima/media ratio were significantly lower in the Resveratrol group (Figs. 1C–G and 4) (Tables 3 and 4). While the positive results of resveratrol were expected, we detected an interesting state in the histological evaluation of the left carotid arteries of both groups. Lumen diameters and lumen areas of the left carotid arteries of the Resveratrol group were significantly larger than in the other group (Figs. 1B–F, 2 and 3) (Tables 1 and 2). In the study conducted in 1997, Andriambeloson *et al.* [19] detected that polyphenols present in red wine increase the synthesis of NO and lead to endothelial vasodilatation. Since resveratrol has red wine polyphenols, we suggested that the above-mentioned positive effect was due to vasodilatation.

When comparing only the Resveratrol group's left and right carotid arteries, we detected that lumen diameter of the left carotid artery where the endothelia integrity remained intact was significantly larger, and the intima was significantly thinner. (Figs. 1E, 1F and 2–4) (Tables 1–3). Resveratrol decreased the intimal hyperplasia on the anastomotic side and increased lumen diameter because of this. However, this increase was not as significant as the increase of lumen diameter on the stable side. So, resveratrol decreases intimal hyperplasia but never completely prevents it.

Intimal thicknesses of the left carotid arteries (where anastomosis was not performed) for both the Resveratrol group and the group not using resveratrol were found to be similar. According to these results, we may conclude that resveratrol does not have a direct effect on vascular intima if not treated surgically; it only has an effect on decreasing developed intimal hyperplasia.

CONCLUSION

We showed that resveratrol inhibited neointimal smooth vascular cell proliferation, as reported previously. Studies of resveratrol have investigated endothelial damage caused by angioplasty, and there are no studies about damage caused by anastomosis. While damage only develops in the intima layer due to peeling of the vessel following balloon angioplasty, in the case of anastomosis, all the layers of the vessel, intima, media and adventitia, are affected.

When we evaluate present studies about the mechanism of action of resveratrol, we conclude that it reduces neointimal hyperplasia by relying on several factors. Consequently, we suggest that resveratrol can be used for at least 14 days for decreasing the intimal hyperplasia following vascular anastomosis.

Conflict of interest: none declared.

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