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RESEARCH ARTICLE

Short-Term Resveratrol Pretreatment Suppresses Noradrenaline-Induced Contractions in Human Saphenous Vein and Internal Mammary Artery Rings

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Short-Term Resveratrol Pretreatment Suppresses Noradrenaline-Induced Contractions in Human Saphenous Vein and Internal Mammary Artery Rings

SUMMARY

The aim of the present study was to investigate whether short-term resveratrol pretreatment has a suppressive effect on the contraction to noradrenaline and whether this changes between human saphenous vein (SV) and internal mammary artery (IMA). The effects of endothelium removal and pretreatments with nitric oxide synthase inhibitor (L-NOARG) and cyclooxygenase inhibitor (indomethacin) were studied to explain the mechanism of action of resveratrol. SV and IMA samples were obtained from 38 patients undergoing coronary artery bypass operation. The contractile response-curves for noradrenaline (10-8-10-4 M) were obtained in SV and IMA rings. Pretreatment with resveratrol (10 and 30 μM) for 20 min significantly suppressed the contractions to noradrenaline in both vessel rings with endothelium. L-NOARG pretreatment completely abolished resveratrol-induced suppression on the contractions in SV, but not in IMA. Moreover, resveratrol has also inhibitory effect on the contractions in endothelium denuded rings from IMA. Resveratrol of 30 μM suppressed noradrenaline-induced maximal contractions by 40 % in both SV and IMA rings. This effect of resveratrol was mainly endothelium-dependent and mediated by nitric oxide in SV as different from that of IMA. The pretreatment with resveratrol could be a new method for preparation of grafts and prevention of vasospasm.

Key Words: *Short-term resveratrol pretreatment, noradrenaline, contraction, human vessels*

Kısa süreli resveratrol tedavisi noradrenalinin safen ven ve internal meme arteri preparatlarında oluşturduğu kontraktil etkiyi baskılar

ÖZET

Sunulan çalışmanın amacı; kısa süreli resveratrol tedavisinin noradrenalinin safen ven (SV) ve internal meme arterinde (IMA) oluşturduğu kontraktil etkiyi baskılayıp baskılamadığı ve bu etkinin iki damar preparatı arasında farklılık gösterip göstermediğini incelemektir. Resveratrolün etki mekanizmasını açıklamak için, endotel tabakası kazınması, nitrik oksit sentaz inhibitörü (L-NOARG) and siklooksijenaz inhibitor (indometazin) kullanılmıştır. SV ve IMA örnekleri koroner bypass operasyonuna giren 38 hastadan elde edilmiştir. Noradrenalin (10-8-10-4 M) kontraktil doz-cevap eğrisi SV ve IMA halkaları üzerinde oluşturulmuştur. Resveratrol (10 ve 30 μM) ile 20 dakikalık ön tedavi, endotel tabakası sağlam her iki tür damar halkasında da noradrenalinin neden olduğu kontraktil etkiyi belirgin şekilde inhibe etti. L-NOARG ile yapılan ön tedavi, kontraktil cevapta resveratrolün oluşturduğu inhibisyonu SV preparatlarında tümüyle ortadan kaldırdı, fakat IMA'da bu etkiyi göstermedi. Ayrıca, resveratrolün endotel tabakası kazınmış IMA preparatlarında kontraktil cevabı inhibe ettiğini de tespit ettik. Resveratrol (30 μM) ile inkübasyon, noradrenalinin oluşturduğu maksimal kontraktil etkiyi SV ve IMA preparatlarında % 40 varan ölçüde baskılamıştır. Resveratrolün ortaya çıkardığı etkinin SV preparatlarında, IMA'dan farklı olarak, endotel-bağımlı ve nitrik oksit aracılı olduğu görülmektedir. Resveratrol ile ön tedavi, bypass materyallerinde ortaya çıkan spazmların önlenmesinde yeni bir yöntem olarak kullanılabilir.

Anahtar Kelimeler: *Kısa süreli resveratrol ön tedavisi, noradrenalin, kontraksiyon, insan damarları*

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Introduction

Epidemiologic studies indicate that moderate consumption of red wine may decrease risk of cardiovascular diseases (Lorgeril et al., 2002). The polyphenolic compounds from red wine have various favourable effects such as promotion of endothelium-dependent relaxation, activation of nitric oxide synthase, inhibition of platelet and neutrophil function and reduction of oxidation of LDL-cholesterol (Bradamante et al., 2004). Resveratrol could be the main effective polyphenolic compound of red wine, because it has all above mentioned beneficial cardiovascular effects (King et al., 2006). Additionally, in various experimental models, resveratrol was shown to have reducing effect on the infarct size in ischemia-reperfusion injury of heart, kidney, brain and spinal cord which is correlated with its inhibitory effect on several enzymes generating reactive oxygen species (Ray et al., 1999; Giovanni et al., 2001; Sinha et al., 2002; Kiziltepe et al., 2004).

Previously, it has been shown that preincubation with resveratrol suppressed noradrenaline-induced contraction in rat aorta and its acute application produced mainly endothelium-dependent relaxation in animal arteries (Bradamante et al., 2004; Chen & Pace-Asciak 1996; Orallo et al., 2002). In long-term studies, resveratrol was reported to improve flow-mediated vasodilation (Zou et al., 2003) and endothelium-dependent relaxations to acetylcholine and estrogen (Rush et al., 2007; Soylemez et al., 2008). However, relatively little is known about the vascular effects of resveratrol in humans (Rakici et al., 2005; Coskun et al., 2006; Novakovic et al., 2006). These studies, which are performed in the samples obtained from coronary revascularization vessels, demonstrated that resveratrol increases endothelial reactivity and elicites endothelium-dependent and independent relaxations. The endothelium-dependent relaxing effect of resveratrol observed in small peripheral arteries from healthy men was not apparent in those from men with coronary heart diseases (Cruz et al., 2006). To our knowledge, it is not studied possible preventive effect of resveratrol against spasm of human vessels. The vasospam that causes temporary reduction of blood flow is important problem in the maintenance of circulation in many vascular beds including bypass conduits. The current vasodilators used for prevention of graft spasm have some limitations requiring safe treatment confirmation (Sivalingam et al., 2005). The functional characteristics of arterial graft (IMA) and venous graft (SV), the most widely used conduits in coronary revascularization, show diversity that changes to the approach to management of spastic vascular disorders. Therefore, in this study we investigated whether short-term resveratrol pretreatment has a suppressive effect on contractions to noradrenaline of human saphenous vein and internal mammary artery. Additionally, we have sought the mechanism of its possible preventive effect and compared the responsiveness between arterial and venous grafts.

Materials and Methods

Sampling and preparation of the vessels

SV and IMA samples were obtained from 38 randomized patients undergoing coronary artery bypass operations. The use of the discarded vessels was approved by the Institutional Review Board of Baskent University and conform to the principles outlined in the Declaration of Helsinki. Clinical characteristics of the patients and their drug therapies are given in Table 1. In this study, diabetic patients were excluded. The vessel segments, which are not exposed to any preparatory drugs, were placed immediately into cold (4 ^{0}C) Krebs Ringer-bicarbonate solution of the following composition (mM): NaCl 118, KCl 4.7, KH_2PO_4 1.2, $NaHCO_3$ 25, $MgSO_4.7H_2O$ 1.2, $CaCl_2$ 2.5, glucose 11.1, and disodium EDTA 0.026. Care was taken during harvesting of the vessels in order not to stretch and touch the endothelial surface. After removing fat and connective tissues from the vessels, the obtained segments were cut into rings of 3-4 mm in length and mounted in a 10 ml organ bath containing Krebs Ringer-bicarbonate solution at 37 ^{0}C and aerated with 95 % O_2 and 5% CO_2. The force displacement transducers (Grass model FT 03 and May Com model FDT 10-A) were used for the measurement of isometric force. In our preliminary experiments with SV and IMA, resting tension of 2 g was determined to be optimal for maximal noradrenaline responsiveness. The endothelium of some vessels was removed by gently rubbing the luminal surface of the ring with a roughened polyethylene tube. The vessels were allowed to equilibrate for approximately 2 h with exchange of bathing solution every 15 min. One to four rings were obtained from each vessel segment and each ring was subjected to only one study.

Experimental protocol

The viabilities of the vessel rings were tested by noradrenaline (3 x 10^{-6} M) and preparations which developed a tension of less than 1 g were not further processed. The reproducible contractions to noradrenaline (3 x 10^{-6} M) and 40 mM KCl were obtained two times to see the vessel standardization.

The completeness of endothelium removal was confirmed by the lack of relaxation to acetylcholine (10^{-6} M) on noradrenaline precontracted rubbed rings. The cumulative concentration-response curves to noradrenaline (10^{-8}- 10^{-4} M), which are reproducible two times, were constructed in SV and IMA rings with and without endothelium. The concentration-response curves for contractile effects of noradrenaline were assessed in each vessel before and after administration of resveratrol (10 and 30 μM) or resveratrol (30 μM) in combination with L-NOARG (10^{-4}M), or with indomethacin (10^{-5} M), which were added into bathing medium 20-30 min before the second concentration-response curve of noradrenaline. In some experiments, cumulative concentration-response curves for noradrenaline were repeated in the absence of the antagonists as time-match control to verify the effects of the antagonists. The concentrations of resveratrol of 10 and 30 μM did not show any effect on the quiescent rings of SV and IMA. These resveratrol concentrations were chosen on the basis of our preliminary studies, in which 1 μM resveratrol did not modify noradrenaline concentration-response curves in SV and IMA.

Drugs

The drugs used were purchased from Sigma Chemical Co. (St. Louis, MO). A stock solution of noradrenaline was prepared in 0.001N HCl and ascorbic acid was added to prevent oxidation. Acetylcholine was dissolved in 0.001 N HCl. Resveratrol was dissolved in absolute ethanol. Indomethacin was dissolved in 5% (w/v) sodium bicarbonate. Further dilutions were prepared in Krebs solution and kept in a cold dark medium. The volume of ethanol of 10-40 μl, that is used as vehicle, was found to have no effect on the contractions to noradrenaline

Statistical analysis

The results are given as mean ± SEM. The contractile responses to noradrenaline were expressed according to KCl (40 mM) induced contraction in that vessel ring. The maximal response (E_{max}) and potency (EC_{50}) of noradrenaline were calculated separately for each dose-response by nonlinear curve fitting using the Prism 3 GraphPad program. EC_{50} values were expressed as negative log M. In this study, n is represented the number of patients. Statistical analysis was determined by Student's paired or unpaired t-test and analysis of variance. Values were considered to be significantly different when p value is less than 0.05.

Results

Patients characteristics

Table 1 shows the clinical characteristics and drug therapy of the patients undergoing coronary revascularization.

Table 1. Clinical characteristics of the patients undergoing coronary bypass

Parameters	
Number of patients, n	38
Sex	
Female	7
Male	31
Age (years)	54.6 ± 4.3
Hypertension	19
Hypercholesterolemia	21
Drugs	
Calcium antagonists	12
ACE inhibitors	12
Antihyperlipidemics	14
β-adrenoceptor antagonists	11
Nitrovasodilators	16

ACE: Angiotensin converting enzyme

Concentration–response curves to noradrenaline in endothelium-intact and removed SV and IMA rings

Noradrenaline (10^{-8}- 10^{-4} M) produced concentration-dependent contractions in human SV and IMA rings with endothelium (Figures 1, 5). The maximal contraction and sensitivity to noradrenaline were higher in the endothelium-intact rings of SV than those of IMA (Table 2). Removal of endothelium increased the maximal contraction and sensitivity to noradrenaline in IMA but not in SV rings (Figures 2, 6; Table 2). In endothelium-intact and removed SV and IMA rings**: SV,** E_{max}: 160 ± 8 vs 159 ± 14, n=7-23, p>0.05; EC_{50}: 6.29 ± 0.09 vs 6.27 ± 0.11, n=7-23, p>0.05; **IMA,** E_{max}: 106 ± 5 vs 127 ± 8, n= 9-19, p< 0.05; EC_{50}: 5.67 ± 0.08 vs 5.98 ± 0.05, n= 9-19, p< 0.05, respectively).

Effects of resveratrol pretreatment on contractile responses of SV and IMA to noradrenaline

Pretreatment with resveratrol of 10 and 30 mM of human SV and IMA rings markedly decreased the maximal contractions (E_{max}) to noradrenaline in both vessels rings with endothelium (Figures 1, 5 and Table 2). Mechanical removal of the endothelium or pretreatment with L-nitroarginine (L-NOARG, 10^{-4}M), a nitric oxide synthase inhibitor, completely abolished the suppressive effect of resveratrol on noradrenaline contraction in SV (Figures 2, 3). However in IMA,

the effect of resveratrol on noradrenaline contraction was decreased, but not disappeared, after the same procedures (Figures 6, 7). In regard to EC_{50} values, the sensitivity to noradrenaline was significantly decreased after pretreatment with 30 mM resveratrol only in SV rings with endothelium indicating a shift of noradrenaline response-curves to the right in SV. In the absence of resveratrol no change was observed in the second concentration-response curves to noradrenaline in either vessels rings. Moreover, the addition of resveratrol of 10 and 30 mM did not alter the resting tension of the vessels. The suppressive effects of resveratrol on noradrenaline-induced contractions were slightly modified following the incubation of the vessels rings with 10^{-5} M indomethacin, used to inhibit prostaglandin synthesis, in both vessels (Table 2, Figures 4, 8).

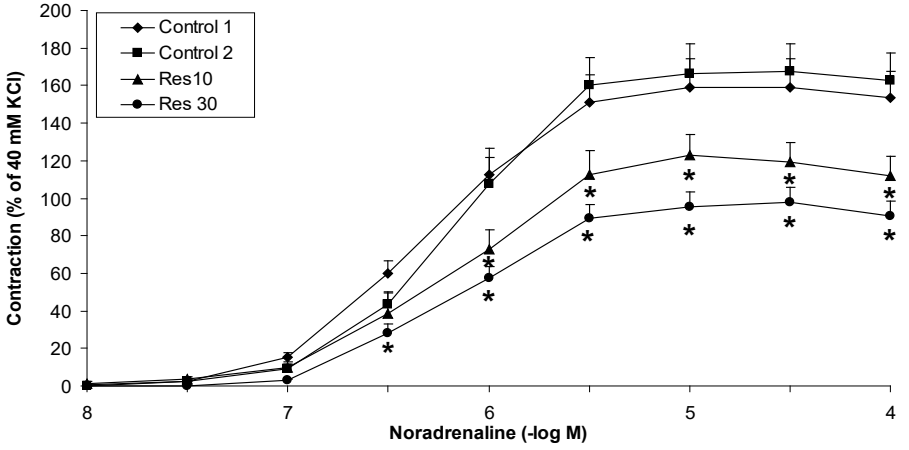

Fig. 1. Cumulative concentration-response curves for contractile effect of noradrenaline (10^{-8} - 10^{-4} M) in SV rings with endothelium in control (Control 1, ◆), the second control as time match (Control 2, ■) and presence of 10 (Res 10, ▲) and 30 mM resveratrol (Res 30, ●). Values are expressed as mean ± SEM from at least 6 experiments. *Significantly different from the respective control value, $p<0.05$.

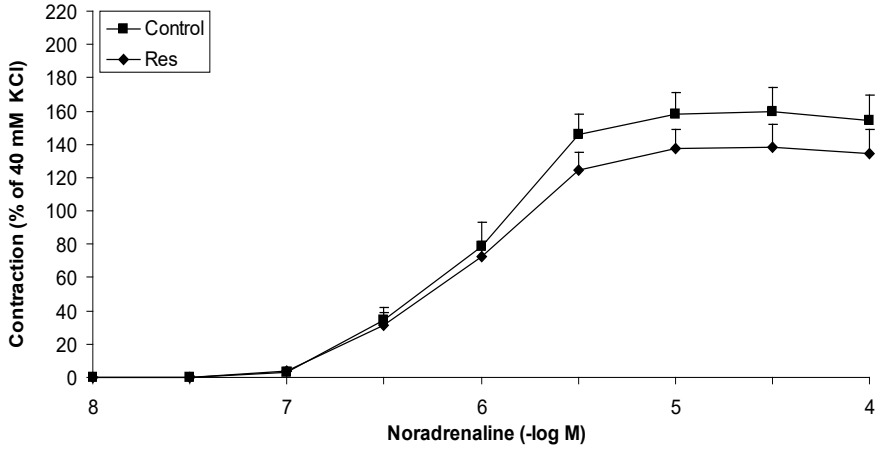

Fig. 2. Cumulative concentration-response curves for contractile effect of noradrenaline (10^{-8} - 10^{-4} M) in SV rings without endothelium in absence (Control,■) and presence of 30 mM resveratrol (Res, ◆). Values are expressed as mean ± SEM from 7 experiments.

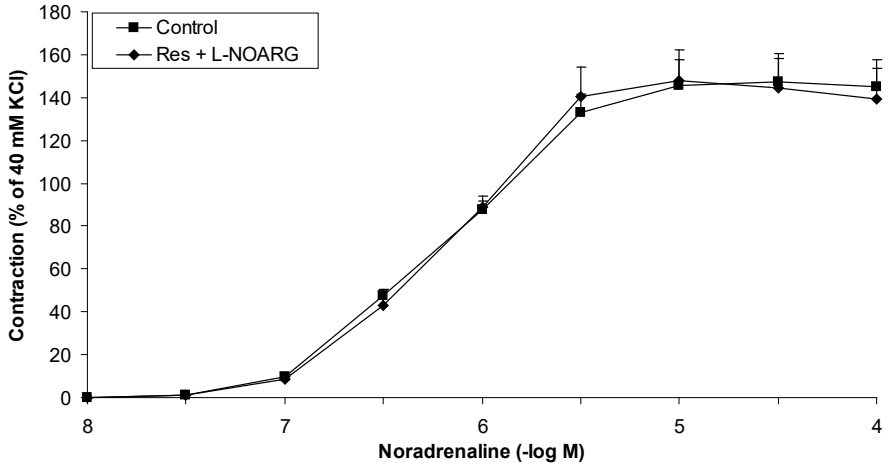

Fig. 3. Cumulative concentration-response curves for contractile effect of noradrenaline (10^{-8}- 10^{-4} M) in SV rings with endothelium in absence (Control, ■) and presence of combination of 30 mM resveratrol and 10^{-4} M L-NOARG (Res+L-NOARG, ◆). Values are expressed as mean±SEM from 7 experiments.

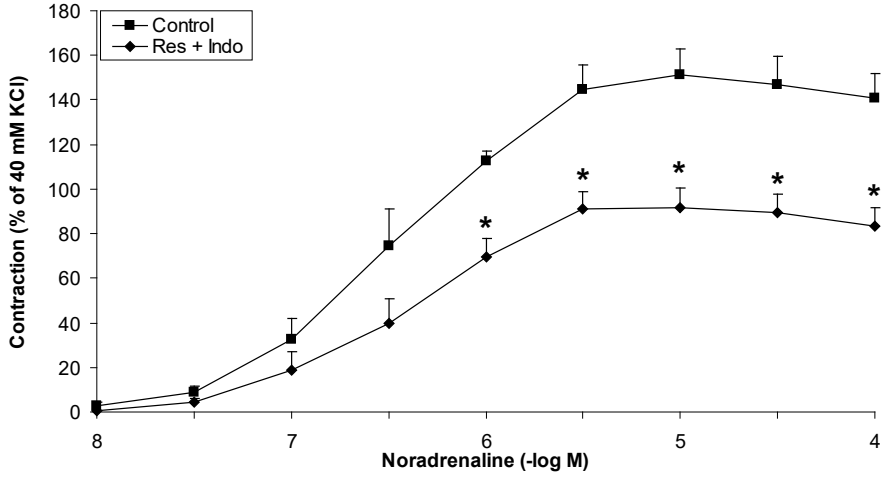

Fig. 4. Cumulative concentration-response curves for contractile effect of noradrenaline (10^{-8}-10^{-4} M) in SV rings with endothelium in absence (Control, ■) and presence of combination of 30 mM resveratrol and 10^{-5} M indomethacin (Res+Indo, ◆). Values are expressed as mean±SEM from 5 experiments. *Significantly different from the respective control value, $p<0.05$.

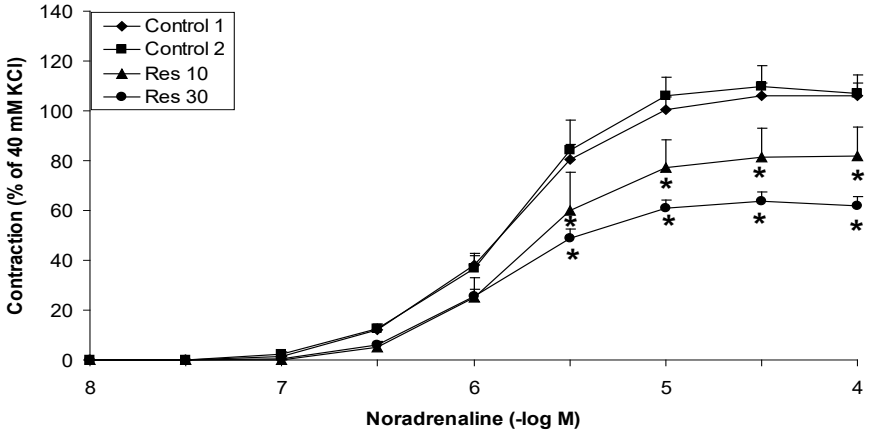

Fig. 5. Cumulative concentration-response curves for contractile effect of noradrenaline (10^{-8}- 10^{-4} M) in IMA rings with endothelium in absence (Control 1, ◆) and the second control as time match (Control 2, ■) and presence of 10 (Res 10, ▲) and 30 mM resveratrol (Res 30, ●). Values are expressed as mean±SEM from at least 5 experiments. *Significantly different from the respective control value, $p<0.05$.

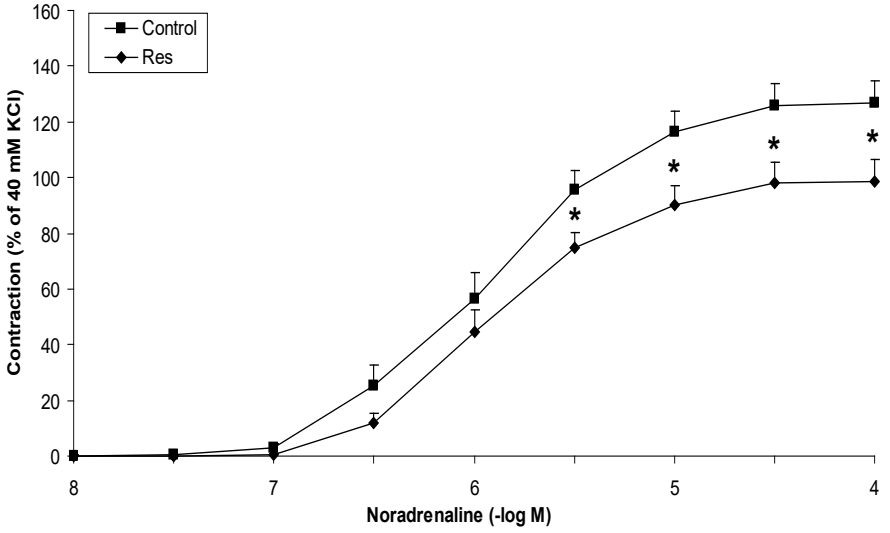

Fig. 6. Cumulative concentration-response curves for contractile effect of noradrenaline (10^{-8}- 10^{-4} M) in IMA rings without endothelium in absence (Control, ■) and presence of 30 mM resveratrol (Res, ◆). Values are expressed as mean±SEM from 9 experiments. *Significantly different from the respective control value, $p<0.05$.

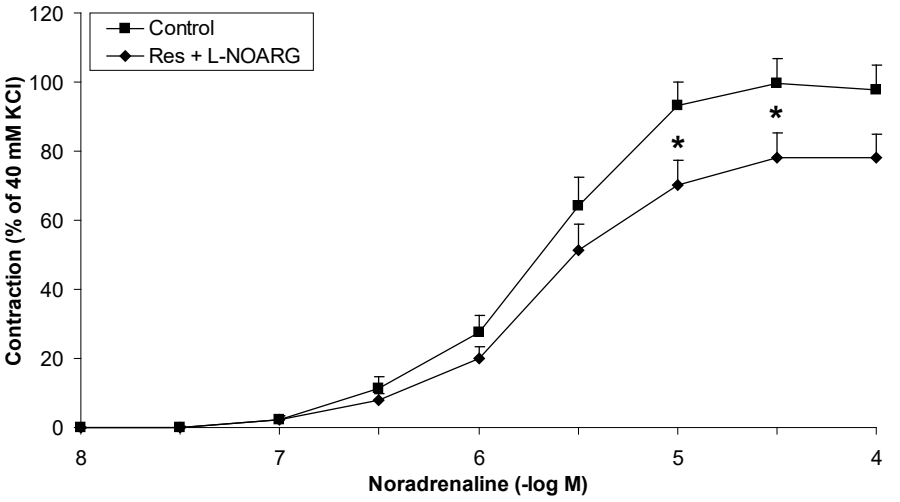

Fig.7. Cumulative concentration-response curves for contractile effect of noradrenaline (10^{-8}- 10^{-4} M) in IMA rings with endothelium in absence (Control, ■) and presence of combination of 30 mM resveratrol and 10^{-4} M L-NOARG (Res+L-NOARG, ◆). Values are expressed as mean±SEM from 9 experiments. *Significantly different from the respective control value, $p<0.05$.

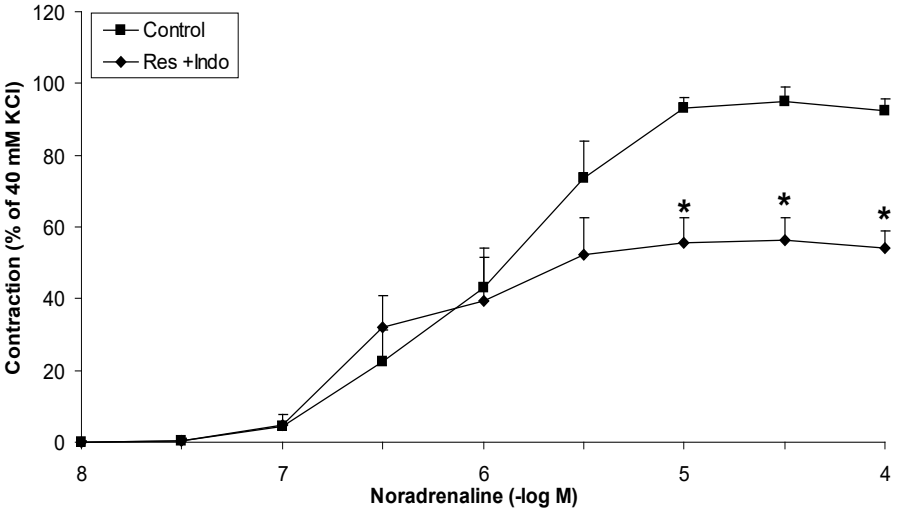

Fig. 8. Cumulative concentration-response curves for contractile effect of noradrenaline (10^{-8} - 10^{-4} M) in IMA rings with endothelium in absence (Control, ■) and presence of combination of 30 mM resveratrol and 10^{-5} M indomethacin (Res+Indo, ◆). Values are expressed as mean±SEM from 5 experiments. *Significantly different from the respective control value, $p<0.05$.

Table 2. The potency (EC_{50}, - log M) and maximum contraction (E_{max}) values to noradrenaline (NA) in endothelium-intact SV and IMA rings from control, 10 and 30 mM resveratrol-pretreated (Res 10, Res 30), resveratrol-pretreated in combination with L-NOARG (Res30 + L-NOARG) or indomethacin (Res30 + Indo) vessels.

	EC_{50}	E_{max}	n
SV			
NA (control)	6.29 ± 0.09	160 ± 8	23
NA + Res10	6.25 ± 0.19	122 ± 11*	6
NA + Res30	5.92 ± 0.13*	98 ± 8*	11
NA + Res30 + L-NOARG	6.15 ± 0.17	140 ± 12#	7
NA + Res30 + Indo	6.43 ± 0.20#	94± 9*	5
IMA			
NA (control)	5.67 ± 0.08#	106 ± 5#	19
NA + Res10	5.62 ± 0.15	81 ± 10*	5
NA + Res30	5.76 ± 0.11	64 ± 5*	9
NA + Res30 + L-NOARG	5.76 ± 0.14	76 ± 8*	9
NA + Res30 + Indo	5.96 ± 0.17	55 ± 7*	5

Values are expressed as mean±SEM. * $p<0.05$, significantly different from control; # significantly different from SV,#significantly different from Res 30 pretreatment in SV.

Discussion

Our results showed that pretreatment with resveratrol (30 mM for 20 min) suppressed noradrenaline-induced maximal contractions by 40 % in both SV and IMA rings. However, mechanism of the suppressive action of resveratrol in SV was different from that of IMA, which was mainly endothelium-dependent and mediated by NO. This showed that resveratrol has a changing action characteristic through the vasculature. The pretreatment with resveratrol indicates a potential for prevention of vascular spasm.

The contraction to noradrenaline, in terms of maximal contraction and sensitivity, is modulated by endothelium in IMA but not in SV reflecting its weak endothelial reactivity in accordance with our previous studies (Rakıcı et al., 2005; Akar et al., 1994). However, short-term resveratrol pretreatment (10 and 30 μM) made functionally visible the potential endothelial reactivity of SV as shown by the inhibition of the contraction to noradrenaline in the presence of endothelium. This finding demonstrated that some factors may blunt actual endothelial capacity of SV. In support of this suggestion, it has been shown that pretreatment with tetrahydrobiopterin, an obligatory cofactor for nitric oxide synthase, promotes endothelial relaxation to acetylcholine in SV indicating shortage of cofactor (Verma et al., 2000). In the other study, NAD(P)H oxidase inhibition causes higher endothelial relaxation in SV in comparison to that of IMA showing a decline in nitric oxide bioavailability by superoxide especially in SV (Hamilton et al., 2002).

Noradrenaline-induced contractions in the samples of bypass conduits were markedly suppressed after short-term treatment with resveratrol, in a concentration-dependent manner. Pretreatment with resveratrol, at concentration of 30 mM, inhibited noradrenaline-induced maximal contractions by 40 % in both SV and IMA rings. This ratio is very impressive because many vasodilators, at concentrations corresponding to their EC_{50} values, could not have achieved this inhibition degree in bypass conduits contracted with noradrenaline (Akar et al., 1994; He et al., 1992; He et al., 1994; Akar et al., 1997; Medina et al., 1998; Akar et al., 2007). In a previous study, we have found that concentration of resveratrol of 30 mM is very close to its EC_{50} values in both SV and IMA precontracted with noradrenaline. However, in that sudy, resveratrol, at a maximally effective concentration of 70 μM, is unable to fully reverse noradrenaline-induced precontraction in both conduits (Rakıcı et al., 2005). This indicated that resveratrol presented in the medium before precontraction may cause the timely activation of anticontractile pathways.

The removal of endothelium and preincubation with L-NOARG almost completely abolished the suppressive effect of resveratrol on concentration-response curve to noradrenaline in SV but partially in IMA. In a very recent study, we have shown resveratrol treatment improves the endothelial reactivity of rat aorta by increasing of nitric oxide and/or by suppressing of superoxide generation (Soylemez et al., 2008). These findings indicate that resveratrol pretreatment may suppress noradrenaline-induced contractions mainly by promoting the endothelial reactivities of grafts. However, some of its effects in IMA may be due to additional mechanisms such as increased cGMP formation, potassium channels

activation, calcium desensitization, as proposed in some studies (Novakovic et al., 2006; El-Mowafy, 2002; Buluc et al., 2006). Previously, we have found that resveratrol-induced relaxation was mostly dependent on presence of endothelium in IMA but partially in SV (Rakıcı et al., 2005). Our two studies with bypass grafts showed that effect of resveratrol changes depend on its incubation and vessel contraction times. These findings are partly compatible with the results of in rat aorta, in which was found that inhibition of nitric oxide synthesis completely reversed resveratrol-induced suppression on dose-response curve to noradrenaline (Chen & Pace-Asciak, 1996). The effect of resveratrol on noradrenaline-induced contractions was not mediated by the relaxant prostaglandins because indomethacin slightly modified the contractions to noradrenaline showing little possible prostaglandins participation. The effect was specific to resveratrol because there was no inhibition in repeating of noradrenaline concentration-response curves in the absence of resveratrol. All these data reported here proposed that, the effect of resveratrol on bypass conduits could be primarly related to improvoment of endothelial reactivity.

A pharmacokinetic study performed in human showed that systemic bioavailability of resveratrol is very low due to rapid metabolism as evidenced by plasma levels of 5 ng/ml of its unchanged form after oral dose of 25 mg. In the same study, resveratrol metabolites were measured as 490 ng/ml (about 2 M) with plasma half-life of 9 h (Walle et al., 2004). The oral dose of 25 mg of resveratrol is higher than that ingested with moderate consumption of red wine in humans when considered resveratrol concentrations ranged from approximately 0.3 to12 mg /l in regular red wines. The concentration of resveratrol achieving with moderate consumption of red wine is not sufficient to produce biological effects which has been reported at concentrations ranging from 10 to 100 μM (Bradamante et al., 2004). These findings raise some doubts about the beneficial effects of red wine and resveratrol consumption. In this context, if resveratrol is tested during preparation of grafts for revascularization its short half-life may limit its efficiency into intra-operative period only. However, it has been proposed that potentially active metabolites of resveratrol may be responsible for beneficial effects of resveratrol and red wine (Walle et al., 2004; Wenzel et al., 2005). Future studies elucidating biological effects of resveratrol and its metabolits or their interactions will provide a better understanding of the health effects of resveratrol.

The limitation of our study was use only noradrenaline to mimic the spasm among the many potential agents such as thromboxane A_2, serotonin, endothelin-1. However, noradrenaline may be the most important endogenous mediator of vasospasm as evidenced by effectively use of alpha-adrenoceptor antagonist phenoxybenzamine for prevention of graft spasm in the clinical setting (Mussa et al., 2003). In supporting this, the levels of catecholamines have been reported to increase during bypass operation and postoperative period (Minami et al., 1990). Additionally, noradrenaline can be used in order to adjust hemodynamic state during the operation. In this study, therefore, we focused on noradrenaline-induced spasm to test the effect of resveratrol. Although not investigated in this study, resveratrol may have a potential against other possible vasospastic agents over phenoxybenzamine. Moreover, phenoxybenzamine which is an irreversible alpha-adrenoceptor antagonist may produce a refractory state to supportive treatment with noradrenaline or adrenaline after operation. There is no entirely acceptable antispasmodic for prevention of graft spasm due to some limitations such as low efficiency, short duration, harmful effect on endothelium, tolerance and some side effects (Sivalingam et al., 2005). The use of resveratrol during preparation of SV and IMA conduits, in addition to its other possible therapeutic relevancies (Akar et al., 2012; Pektaş et al., 2015; Sadi et al., 2015) can be an alternative option for prevention of graft spasm following some assessments.

In conclusion, the present study in human vessels has shown that resveratrol effectivelly suppressed the contractions to noradrenaline and its action characteristic may change between artery and vein. The short-term pretreatment of bypass conduits with resveratrol could be a new method for their preparation as grafts. Additionally, these findings may be useful for prediction of benefit from resveratrol in other spastic vascular diseases. Resveratrol is accepted as a nontoxic phytoestrogen because several foods contain substantial quantities of resveratrol. Therefore, nutritional intake of resveratrol may be recommended for prevention of vasospastic disorders. Little information concerning effect of resveratrol on human cardiovascular system needs to perform more studies to explaine mechanism of potential health benefits of red wine because it is not known whether in humans, resveratrol will have health effects similar to those seen in animals.

Conflict of interest

The authors state no conflict of interest

References

Akar, F., Uydes, B.S., Ayrancioglu, K., Yener, A., Aslamaci, S., Arsan, M. & Kanzik, I. (1994). Endothelial function of human gastroepiploic artery in comparison with saphenous vein. Cardiovascular Research, 28, 500–504.

Akar, F., Uydes-Dogan, B. S., Tufan, H., Aslamacı, S., Koksoy, C. & Kanzik, I. (1997). The comparison of the responsiveness of human isolated internal mammary and gastroepiploic arteries to levcromakalim: an alternative approach to the management of graft spasm. British Journal of Clinical Pharmacology, 44, 49 –56.

Akar, F., Manavbasi, Y., Parlar, A. I., Ulus, A. T. & Katircioglu, S. F. (2007). The gender differences in the relaxation to levosimendan of human internal mammary artery. Cardiovascular Drugs and Therapy, 21(5), 331-338.

Akar, F., Uludag, O., Aydın, A., Aytekin, Y. A., Elbeg, S., Tuzcu, M. & Sahin, K. (2012). High-fructose corn syrup causes vascular dysfunction associated with metabolic disturbance in rats: Protective effect of resveratrol. Food Chemistry and Toxicology, 50, 2135–2141.

Bradamante, S., Barenghi, L. & Villa, A. (2004). Cardiovascular protective effects of resveratrol. Cardiovascular Drug Reviews, 22,169-188.

Buluc, M. & Demirel-Yilmaz, E. (2006). Resveratrol decreases calcium sensitivity of vascular smooth muscle and enhances cytosolic calcium increase in endothelium. Vascular Pharmacology, 44, 231–237.

Chen, C.K.& Pace-Asciak, C. R. (1996). Vasorelaxing activity of resveratrol and quercetin in isolated rat aorta. General Pharmacology, 27, 363-366.

Coskun, B., Soylemez, S., Parlar, A. I., Ulus, A.T., Katircioglu, S. F. & Akar F. (2006). Effect of resveratrol on nitrate tolerance in isolated human internal mammary artery. J Cardiovascular Pharmacology, 47, 437-445.

Cruz, M. N., Luksha, L., Logman, H., Poston, L., Agewall, S. & Kublickiene, K. (2006). Acute responses to phytoestrogens in small arteries from men with coronary heart disease. American Journal of Physiology, 290(5), H1969–1975.

El-Mowafy AM. (2002). Resveratrol activates membrane-bound guanylyl cyclase in coronary arterial smooth muscle: a novel signaling mechanism in support of coronary protection. Biochemical Biophysical Research Communication, 291, 1218–1224.

Giovanni, L., Migliori, M., Longoni, B. M., Das, D. K., Bertelli, A. A. E., Panichi, V., Bertelli A. (2001). Resveratrol, a polyphenol found in wine, reduces ischemia reperfusion injury in rat kidneys. Journal Cardiovascular Pharmacology, 37, 1-9.

Hamilton, C. A., Brosnan, M. J., Al-Benna, S., Berg, G. & Dominiczak, A. F. (2002). NAD(P)H oxidase inhibition improves endothelial function in rat and human blood vessels. Hypertension, 40, 755– 762.

He, G. W., Shaw, J., Yang, C. Q., Hughes, C., Thomson, D., Baird, D. K. (1992). Inhibitory effects of glyceryl trinitrate on alpha-adrenoceptor mediated contraction in the human internal mammary artery. British Journal of Clinical Pharmacology, 34(3), 236–243.

He, G. W., Acuff, T. E., Ryan, W. H., Yang, C. Q., Douthit, M. B., Bowman, R. T. & Mack, M. J. (1994). Inhibitory effects of calcium antagonists on alpha-adrenoceptor-mediated contraction in the human internal mammary artery. British Journal of Clinical Pharmacology, 37(2), 173–179.

Lorgeril, M., Salen, P., Paillard, F., Laporte, F., Boucher, F. & de Leiris, J. (2002). Mediterranean diet and the French paradox: Two distinct biogeographic concepts for one consolidated scientific theory on the role of nutrition in coronary heart disease. Cardiovascular Research, 54, 503-515.

King, R. E., Bomser, J. A. & Min, D. B. (2006). Bioactivity of Resveratrol. Comprehensive Reviews. Food Science Food Safety, 5,65-70.

Kiziltepe, U., Turan, N. D., Han, H.& Akar F. (2004). Resveratrol, a red wine polyphenol, protects spinal cord from ischemia-reperfusion injury. Journal Vascular Surgery, 40, 138-145.

Medina, P., Acuna, A. & Martınez-Leon, J. B. (1998). Arginine vasopressin enhances sympathetic constriction through the V vasopressin receptor in human saphenous vein. Circulation, 97, 865–870.

Minami, K., Korner, M. M., Vyska, K., Kleesiek, K., Knobl, H. & Korfer, R. (1990). Effects of pulsatile perfusion on plasma catecholamine levels and hemodynamics during and after cardiac operations with cardiopulmonary bypass. Journal Thoracic and Cardiovascular Surgery, 99, 82–91.

Mussa, S., Guzik, T. J., Black, E., Wood, K., Keith, M., Channon, K. M. & Taggart, D. P. (2003). Comparative efficacies and durations of action of phenoxybenzamine, verapamil/nitroglycerin solution and papaverinenas topical antispasmodics for radial artery coronary bypass grafting. Journal Thoracic and Cardiovascular Surgery, 126,1798–1805.

Novakovic, A., Gojkovic-Bukarica, L., Peric, M., Nezic, D., Djukanovic, B. & Markovic-Lipkovski J. (2006). The mechanism of endothelium-independent relaxation induced by the wine polyphenol resveratrol in human internal mammary artery. Journal of Pharmacological Science, 101, 85-90.

Orallo, F., Alvarez, E., Camina, M., Leiro, J. M., Gomez, E. & Fernandez, P. (2002). The possible implication of *trans*-resveratrol in the cardioprotective effects of long-term moderate wine consumption. Molecular Pharmacology, 61, 294–302.

Pektaş, M. B., Sadi, G. & Akar, F. (2015). Long-term dietary fructose causes gender-different metabolic and vascular dysfunction in rats: modulatory effects of resveratrol. Cell Physiology and Biochemistry, 37(4), 1407–1420.

Rakici, O., Kiziltepe, U., Coskun, B., Aslamacı, S. & Akar F. (2005). Effects of resveratrol on vascular tone and endothelial function of human saphenous vein and internal mammary artery. International Journal of Cardiology, 105, 209-215.

Ray, P. S., Maulik, G., Cordis, G. A., Bertelli, A. A. E., Bertelli, A. & Das, D. K. (1999). The red wine antioxidant resveratrol protects isolated rat hearts from ischemia reperfusion injury. Free Radical Biology & Medicine, 27,160-169.

Rush, J. W. E., Quadrilatero, J., Levy, A. S. & Ford, R. J. (2007). Chronic resveratrol enhances endothelium-dependent relaxation but does not alter eNOS levels in aorta of spontaneously hypertensive rats. Experimental Biology and Medicine, 232, 814–822.

Sadi, G., Ergin, V., Yilmaz, G., Pektas, M. B., Yildirim, O. G., Akar, F. (2015). High-fructose corn syrup-induced hepatic dysfunction in rats: improving effect of resveratrol. European Journal of Nutrition, 54(6), 895-904.

Sinha, K., Chaudhary, G. & Gupta, Y. K. (2002). Protective effects of resveratrol against oxidative stree in middle cerebral artery occlusion model of stroke in rats. Life Science, 71, 655-665.

Sivalingam, S., Levine, A. & Dunning J. (2005). What is the optimal vasodilator for preventing spasm in the left internal mammary artery during coronary arterial bypass grafting? Interactive CardioVascular and Thoracic Surgery, 4, 365–371.

Soylemez, S., Gurdal, H., Sepici, A. & Akar F. (2008). The effect of long-term resveratrol treatment on relaxation to estrogen in aortae from male and female rats: role of nitric oxide and superoxide. Vascular Pharmacology, 49, 97-105.

Verma, S., Lovren, F., Dumont, A. S., Mather, K. J., Maitland, A. Keiser, T.M., Anderson, T. J. (2000). Tetrahydrobiopterin improves endothelial function in human saphenous veins. Journal Thoracic and Cardiovascular Surgery, 120, 668–671.

Walle, T., Hsieh, F., DeLegge, M. H., Oatis, J. E. & Walle, U. K. (2004). High absorption but very low bioavailability of oral resveratrol in humans. Drug Metabolism and Disposition, 32(12), 1377–1382.

Wenzel, E. & Somoza, V. (2005). Metabolism and bioavailability of trans-resveratrol. Molecular Nutrition and Food Research, 49, 472 – 481.

Zou, J-G., Wang, Z-R., Huang, Y-Z., Cao, K-J. & Wu, J. M. (2003). Effect of red wine and wine polyphenol resveratrol on endothelial function in hypercholesterolemic rabbits. International Journal of Molecular Medicine, 11, 317-320.