

Cardioprotection by resveratrol: A human clinical trial in patients with stable coronary artery disease

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Abstract. Several beneficial effects of resveratrol (RES), a natural antioxidant present in red wine have already been described. The aim of our study was to investigate if RES had a clinically measurable cardioprotective effect in patients after myocardial infarction.

In this double-blind, placebo controlled trial 40 post-infarction Caucasian patients were randomized into two groups. One group received 10 mg RES capsule daily for 3 months. Systolic and diastolic left ventricular function, flow-mediated vasodilation (FMD), several laboratory and hemorheological parameters were measured before and after the treatment. Left ventricular ejection fraction showed an increasing tendency (ns) by RES treatment. However, left ventricular diastolic function was improved significantly ($p < 0.01$) by RES. A significant improvement in endothelial function measured by FMD was also observed ($p < 0.05$). Low-density lipoprotein (LDL) level significantly decreased ($p < 0.05$) in the RES treated group. Red blood cell deformability decreased and platelet aggregation increased significantly in the placebo group ($p < 0.05$), while resveratrol treatment has prevented these unfavourable changes. Concerning other measured parameters no significant changes were observed neither in placebo nor in RES group.

Our results show that resveratrol improved left ventricle diastolic function, endothelial function, lowered LDL-cholesterol level and protected against unfavourable hemorheological changes measured in patients with coronary artery disease (CAD).

Keywords: Resveratrol, cardioprotection, endothelial dysfunction, platelet aggregation, red blood cell deformability, left ventricular diastolic function

1. Introduction

French people tend to have a lower incidence of cardiovascular diseases despite having similar coronary risk factors as people in other industrialized countries, which phenomenon is known as the French paradox and attributed to the higher red wine intake by the French [17]. Red wine contains high amount of polyphenolic compounds like resveratrol (RES) (trans-3,4,5-trihydroxystilbene), epicatechin, catechin, gallic acid, quercetin. Primarily RES is thought to be responsible for the cardioprotective effect of red wine.

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Several studies supported its antioxidant activity, its ability to decrease low-density lipoprotein (LDL) oxidation [1], and function as a direct free radical scavenger [1]. RES improves endothelial function, and has numerous beneficial effects on vascular tone and vessels in human and animal models. It has been shown that RES improves the release of nitric oxide (NO) and prostacyclin (PGI) which play a prominent role in the maintenance of endothelial function [16]. In endothelial cells obtained from human umbilical vein, RES enhanced the activity of endothelial nitric oxide synthase (eNOS) promoter [23]. In other *in vitro* human investigations RES resulted in NO depending relaxation of vascular rings of saphenous vein and internal mammary artery [16]. Furthermore RES plays an important role in the mitigation of platelet aggregation [14, 28]. The protective effect of RES against thrombosis can be explained by the regulation of prostaglandin synthesis with reversible cyclooxygenase 2 (COX2) and irreversible cyclooxygenase 1 (COX1) inhibition. On thromboxane A2 (TXA2), which is produced by COX1 in platelets and enhances aggregation, RES also has an inhibitory effect [5].

It has already been shown that RES reduces serum cholesterol and triglyceride levels in rats [1]. It has also been observed that the size, and the density of atherosclerotic lesions in the thoracic aorta as well as the thickness of intima were lowered and flow mediated dilatation (FMD) was improved by RES [20]. Several experiments have been carried out on FMD of the brachial artery, showing the ability of endothelium dependent dilatation of a vessel, which was further increased by red grape polyphenol extract [10].

The aim of our study was to reveal whether RES has any favourable effects on endothelium dependent vasodilatation, on systolic and diastolic left ventricular function as well as on hemorheological parameters, like red blood cell deformability and platelet aggregation and on certain laboratory parameters in patients after myocardial infarction.

2. Materials and methods

2.1. Resveratrol

Resveratrol (trans-3,4,5-trihydroxystilbene) was a kind gift from Admarc Med Diagnostics and Nutraceuticals (Fót, Hungary). Ten mg RES capsule was applied orally once daily which is in commercial use and possesses official permission for being marketed. Admarc Med Diagnostics and Nutraceuticals has also provided the matching placebo.

2.2. Subjects and protocol

Fourty patients were enrolled into our double blind, placebo controlled, randomized study (42–80 year old, mean age 66.3 ± 8.9 years, 26 men, 14 women). All patients had a history of myocardial infarction (at least 6 months prior to randomisation) and angiographically verified coronary artery disease. They were randomized into two groups, 13 males and 7 females were in both groups. In one group 10 mg resveratrol, in the other group 10 mg placebo was administered orally for 3 months. Patients received 90 tablettts at the beginning of the study and they were asked to return unused tablets at the final follow-up visit. Concomittant medical therapy of the patients remained unchanged for 3 months before randomization and during the study period. Patients received a medical therapy recommended by the current guidelines for secondary prevention of myocardial infarction including platelet aggregation inhibitors, statins, β -blockers and ACE-inhibitors.

At baseline and after the 3-month treatment period the following examinations were performed: physical examination, blood pressure measurement, clinical chemistry and hemorheological measurements, 12 lead electrocardiography, echocardiography and determination of FMD. The protocol of our study was approved by the Regional Ethics Committee of the University of Pecs and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients to participate in the study.

2.3. Clinical chemistry

From blood samples drawn from the cubital vein after 12-hour fasting white blood cell count, C-reactive protein, TNF- α , glucose, glycosylated hemoglobin-HgA_{1c}, fasting lipid levels (total cholesterol, triglyceride, high-density lipoprotein (HDL), LDL-cholesterol) were measured in the Department of Laboratory Medicine, University of Pecs.

2.4. Hemorheological parameters

From blood samples drawn from the cubital vein after 12-hour fasting hematocrit, plasma fibrinogen level, plasma and whole blood viscosity, red blood cell (RBC) deformability, aggregation and platelet aggregation were determined. Hematocrit was measured in a microhematocrit centrifuge (Hemofuge, Heraeus Instr., Germany), plasma fibrinogen concentration was determined by Clauss' method. Plasma and whole blood viscosities were determined in Hevimet 40 capillary viscosimeter (Hemorex Ltd., Hungary). In this viscosimeter the flow of the fluid is detected optoelectronically along a capillary tube and a flow curve is drawn. Shear rate and shear stress are calculated from this curve. Viscosity values are determined as a function of these parameters according to Casson's principle. RBC aggregation was measured in Myrenne aggregometer (MA-1 Aggregometer, Myrenne Ltd., Germany), applying the light transmission method of Schmid-Schönbein et al. The principle of this technique is based on the increase of light transmission through a red cell suspension. The extent of aggregation is characterized by the aggregation index (AI), calculated from the surface area below the light intensity curve in a 10 s measurement period. Red blood cell filterability was measured in Carat FT-1 filtrometer (Carat Diagnostics Ltd., Hungary) using St. George's technique. In this filtrometer RBC suspension was measured at four pairs of light sources and detectors. The apparatus is interfaced to a computer, which automatically analyzes sequential flow rates and thus distinguishes the relative cell transit time (RCTT) and the pore clogging rate. In our experiments filtration pressure was set for 4 cm of water. All measurements were repeated three times with each sample. Collagen-induced platelet aggregation (2 μ g/ml collagen) was measured using a Carat TX4 optical platelet aggregometer (Carat Diagnostics Ltd., Hungary) [12].

2.5. Brachial artery flow-mediated dilatation

Determination of FMD was executed using the modified method described by Celermajer [2]. Patients were studied in fasting state, exposure to caffeine and smoking were prohibited for 12 hours before the measurements. FMD was measured on the right brachial artery after 10 minutes resting in a supine position. Images were acquired and saved in digital format using a Technus MPX ultrasound System (ESAOTE, Italy) with a linear vascular transducer. Arterial flow velocity was measured using pulsed wave Doppler signals at a 70° angle to the vessel 5 cm above the antecubital fossa. A pneumatic cuff was then inflated to suprasystolic pressure (250 mmHg) on the forearm for 4 min and a second scan was

taken 15 sec after the cuff deflation and arterial lumen diameter was measured 90 sec after cuff deflation. FMD was determined as the percentage change in vessel diameter measured at rest and at 90 sec after cuff release [2, 3].

2.6. Echocardiography

Echocardiographic measurements were performed with a Vivid 7 Pro (GE, USA) equipment with 3S transducer according to international guidelines. Systolic [8] and diastolic left ventricular function [8, 22] were determined at baseline and at the end of the study period.

2.7. Statistical analysis

Data are expressed as means \pm SEM. The changes of parameters after treatment were assessed by two-sample Student's t-test. Differences in mean values between groups were assessed using the Pearson khi-square test using the statistical program for Social Sciences 13.0 Software for Windows (SPSS, Chicago, IL, USA). *P* values <0.05 were considered to be significant.

3. Results

3.1. Subjects

There were no significant differences in baseline patient characteristics of the placebo and RES treated group (Table 1).

3.2. The effect of RES on hemorheological, laboratory and blood pressure parameters

In both placebo and RES groups hematocrit, fibrinogen level and whole blood viscosity did not show significant changes during the 3-month follow up. Red blood cell deformability decreased and platelet aggregation increased significantly in the placebo group, which had been prevented by RES treatment ($p < 0.05$) (Table 2). Plasma viscosity elevated significantly in both groups during the 3-month follow up period. Routine laboratory and inflammatory parameters (white cell count, platelet count, CRP, HgbA_{1c}, TNF α , total cholesterol, triglyceride, HDL-cholesterol) did not show any significant changes after 3 months of treatment with RES (Table 2). The treatment was associated without any significant changes in blood pressure.

3.3. The effect of RES treatment on the flow-mediated dilatation of the brachial artery

Flow-mediated dilatation of the brachial artery increased significantly in the RES treated group ($p < 0.05$) (Fig. 1). In contrast, in the placebo group no significant changes could be observed.

3.4. The effect of Resveratrol treatment on left ventricular function

After 3 months of RES treatment left ventricular ejection fraction (EF) showed a slight improving tendency compared to placebo group (RES treated group: baseline $54.77 \pm 1.64\%$, 3rd month $55.83 \pm 1.94\%$;

Table 1

The table shows baseline characteristics of patients. Values are expressed as mean \pm SEM

	Resveratrol-treated group (n = 20)	Placebo-treated group (n = 20)	P-value
Male gender	13	13	
Age, year (mean \pm SEM)	65.3 \pm 9.7	67.4 \pm 7.7	ns
Major CV risk factors			
Diabetes	7 (35%)	8 (40%)	ns
Hypertension	20 (100%)	19 (95%)	ns
Dyslipidemia	13 (65%)	14 (70%)	ns
Smoking	3 (15%)	4 (20%)	ns
Obesity (BMI > 30)	8 (40%)	7 (35%)	ns
BMI (kg/m ²)	29.3 \pm 2.1	28.1 \pm 3.2	ns
Secondary prevention drug treatment			
Antiplatelet drugs	17 (85%)	18 (90%)	ns
Salicylate	15 (75%)	17 (85%)	ns
Thienopyridine	5 (25%)	7 (35%)	ns
ACEI/ARB	18 (90%)	18 (90%)	ns
Beta-blockers	18 (90%)	17 (85%)	ns
Statins	15 (75%)	16 (80%)	ns

ns = non significant.

Table 2

Hemorheological and laboratory parameters. Values are represented as mean value \pm SEM

	Placebo baseline	Resveratrol baseline	Placebo 3rd month	Resveratrol 3rd month
Hemorheological parameters				
Hematocrit (%)	43.9 \pm 1.22	44.4 \pm 0.98	43.47 \pm 0.86	44.11 \pm 0.91
Fibrinogen (g/l)	3.22 \pm 0.12	3.46 \pm 0.17	3.38 \pm 0.15	3.7 \pm 0.21
Red blood cell aggregation (%)	12.8 \pm 0.76	11.57 \pm 0.33	13.1 \pm 0.53	11.32 \pm 0.59
Collagen Induced platelet aggregation (%)	43.22 \pm 6.57	42.61 \pm 6.22	47.95 \pm 6.74*	32.89 \pm 4.81*
Plasma viscosity (mPas)	1.26 \pm 0.02	1.26 \pm 0.02	1.31 \pm 0.02	1.34 \pm 0.02
Whole blood viscosity at 90 s ⁻¹ shear rate (mPas)	4.37 \pm 0.18	4.5 \pm 0.13	4.49 \pm 0.17	4.6 \pm 0.1
Red blood cell transit time (RCTT)	6.9 \pm 0.13 [#]	7.1 \pm 0.14	7.5 \pm 0.14 [#]	7.03 \pm 0.1
Laboratory parameters				
White blood cell ($\times 10^9/l$)	6.11 \pm 0.37	6.81 \pm 0.49	6.53 \pm 0.37	7.08 \pm 0.38
CRP (mg/l)	3.27 \pm 0.35	3.64 \pm 0.57	7.03 \pm 3.31	6.51 \pm 2.97
HgA1C%	6.47 \pm 0.26	6.33 \pm 0.19	6.18 \pm 0.25	6.04 \pm 0.23
TNF α (pg/ml)	5.95 \pm 0.59	6.13 \pm 0.51	10.12 \pm 0.99	10.1 \pm 1.01
Platelet count ($\times 10^9/l$)	195.42 \pm 10.9	197.82 \pm 8.43	210 \pm 11.9	205 \pm 8.48
Serum cholesterol level (mmol/l)	4.5 \pm 0.25	5.1 \pm 0.5	4.5 \pm 0.26	4.74 \pm 0.26
Serum triglyceride level (mmol/l)	1.94 \pm 0.24	1.67 \pm 0.21	2.04 \pm 0.25	1.84 \pm 0.26
Serum LDL-cholesterol level (mmol/l)	2.6 \pm 0.24	3.15 \pm 0.35 ⁰	2.51 \pm 0.21	2.7 \pm 0.15 ⁰
Serum HDL-cholesterol level (mmol/l)	1.02 \pm 0.06	1.2 \pm 0.06	1.1 \pm 0.08	1.2 \pm 0.06

* $p < 0.05$ Res 3rd month versus placebo 3rd month. [#]Placebo baseline versus placebo 3rd month ⁰RES baseline versus RES 3rd month.

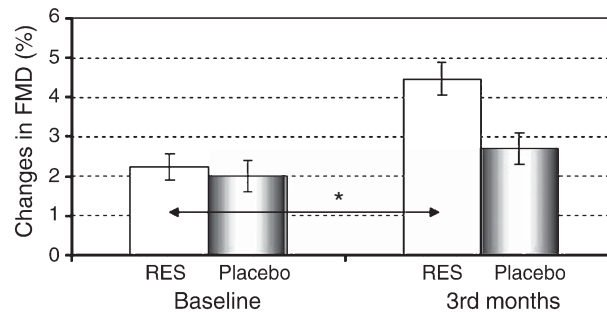


Fig. 1. Flow-mediated vasodilatation before and after three-months follow-up period. The endothelial function showed a significant improvement in RES-treated group compared to baseline values. In placebo-treated group flow-mediated vasodilatation has not changed. The results were expressed as mean \pm SEM, * $p < 0.05$: FMD was defined as the percentage change in vessel diameter measured at rest and 90 sec after cuff release.

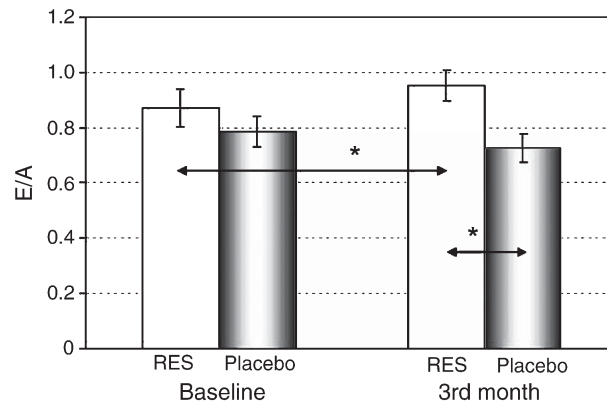


Fig. 2. Left ventricular diastolic function (expressed as E/A ratio) of patients at baseline and after three months. The diastolic function in RES-treated group improved significantly. The results were expressed as mean \pm SEM. * $p < 0.05$.

placebo group: baseline $52.42 \pm 1.55\%$, 3rd month $51.33 \pm 1.84\%$). In LV diastolic function however, significant increase of E/A ratio was observed in the resveratrol group after three months compared to baseline values ($p < 0.01$). In the placebo group diastolic function showed a deteriorating tendency during the 3-month follow up (Fig. 2).

4. Discussion

In this study the possible cardioprotective effects of RES were examined in patients after myocardial infarction. According to previous studies the cardiovascular benefits of RES presumably includes vasorelaxation, antioxidant, antiplatelet and cholesterol lowering effects.

The decreased vasorelaxation response – observed in patients with atherosclerosis – was due to impaired endothelial function. Endothelial dysfunction induces atheromatous plaque formation and it is considered to be an important factor for the development of CAD [19]. Several studies have shown the favourable effects of RES on endothelial function [4, 10, 16, 20, 23] but these investigations were carried out on

animal models, *in vitro* human vessels [16] or examined only the acute intake of RES [10]. In our study endothelial function was measured by FMD and a significant improvement ($p < 0.05$) was detected in vasorelaxation in RES treated group. According to previous studies these effects are presumably due to an increase in NO level and signalling [16, 19, 23] and the stimulation of Ca^{2+} activated K^+ channels [20].

The importance of hemorheological processes in the progression of atherosclerosis is well known [12, 19]. Previous studies have proved the inhibitory effect of RES on platelet aggregation *in vitro*. The inhibition of platelet aggregation is presumably due to the enhancement of the activity of endogenous antiplatelet substances like prostaglandins [26]. In addition, under *in vitro* circumstances it was shown that RES inhibits type I collagen mRNA expression, and the adhesion of platelets to collagen in a concentration dependent manner [24]. RBC deformability has an important role in coronary microcirculation since the average capillary diameter is below the diameter of RBC. Decreased RBC deformability reduces the coronary microcirculation. According to previous studies certain unfavourable changes in hemorheological parameters can be observed in patients after myocardial infarction [12]. In our investigation a significant decrease of RBC deformability and an increase of platelet aggregation was also experienced in the placebo group but RES treatment prevented these disadvantageous changes ($p < 0.05$). The majority of patients (80%) were on ASA therapy. Increasing collagen-induced platelet aggregation during the 3 month follow-up period in the placebo group may represent developing aspirin insensitivity which was prevented by RES administration. It also appears that RES increased platelet sensitivity to aspirin. These findings may have significant importance on the prevention of aspirin insensitivity (which could be observed many times during ASA therapy) and finally on the treatment of CAD.

High level of LDL-cholesterol is very harmful to endothelial cells and has an important role in the development of atherosclerosis [21]. According to the literature the effects of RES on lipid parameters are rather conflicting [1, 25]. Some investigations have proved that RES lowered total cholesterol [9], increased HDL level and reduced formation of atherosclerotic plaques [21]. In our research a favourable effect of RES was discovered on plasma LDL level ($p < 0.05$), but no significant effect was detected on other lipid parameters, like total cholesterol, HDL cholesterol and on triglyceride levels.

During our study no significant changes could be measured in white blood cell count, plasma fibrinogen and C-reactive protein levels.

RES possesses direct protective effect on cardiomyocytes which was demonstrated in several animal studies [6, 11, 18, 27]. In a myocardial remodeling model cardiac fibrosis was inhibited with RES [13], furthermore RES protected cardiomyocytes from ischemia-reperfusion injury with a suppression of superoxide levels and activation of potassium channels in animal models [1]. In our study RES treatment resulted in a slight improvement of left ventricular systolic function. On the other hand diastolic function of the left ventricle was significantly improved which might be based on the inhibitory effect of RES on myocardial fibrosis through the inhibition of phosphorylation of PKC α/β and activation of Akt pathways described in animal models [15].

In conclusion, our clinical trial provided evidences that RES exerts multiple protective effects on the cardiovascular system in patient with CAD developing its beneficial effect in addition to the routine medical therapy used in the secondary prevention of myocardial infarction. Three-month of RES treatment improved FMD, increased red blood cell deformability, inhibited platelet aggregation presumably with increasing platelet sensitivity to aspirin, decreased LDL cholesterol level and improved left ventricular diastolic function.

Despite epidemiological data suggesting the beneficial effects of red wine on the cardiovascular system we can not encourage patients to drink more red wine to protect against atherosclerosis, because of the

potential risks of higher alcohol consumption. On the other hand – on the bases of previous data and our observations – RES administration (without alcohol intake) might be recommended in patients with CAD to slow down progression of atherosclerosis.

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