



Effects of acute exercise on atherogenic lipids in untreated mild hypertensive patients

Uticaj akutne fizičke aktivnosti na aterogene lipide kod nelečenih bolesnika sa blagom hipertenzijom

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Abstract

Background/Aim. Exercise can positively influence risk factors associated with cardiovascular disease. The mechanisms by which exercise reduces atherogenic risk remain unknown. The aim of the present study was to investigate the effect of acute exercise (cardiopulmonary exercise cycle ergometer test) on atherogenic lipids in untreated mild hypertensive patients with or without hypercholesterolemia. This testing allows determination of exercise capacity, peak heart rate, and ventilation per minute (VE), peak oxygen uptake (pVO_2) and exercise time (ET). **Methods.** The study group included 85 untreated mild hypertensive patients (according to VII Joint National Committee – JNC 7) divided into two subgroups: hypertensive hypercholesterolemic and hypertensive normocholesterolemic. The control group included 35 normotensive subjects divided into two subgroups: normotensive hypercholesterolemic and normotensive normocholesterolemic. Lipid profiles to determine were oxidized LDL (OxLDL) – a marker of oxidative stress, triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol, which were measured at rest and 30 minutes after the acute bout of cardiopulmonary exercise cycle ergometer test. Lipids profiles were measured by enzymatic methods. Oxidized LDL was determined by a commercially available sandwich ELISA (Mercodia AB, Uppsala, Sweden). C-reactive protein (CRP) was measured using chemiluminiscent methods (Immulin-DPC). **Results.** In our study OxLDL was significantly higher in hypertensive patients with atherogenic lipid profiles in basal condition, compared to the hypertensive patients without atherogenic

lipid profiles and controls. There was a significant difference in CRP ($p < 0.001$) between hypercholesterolemics (hypertensive and normotensive) and normocholesterolemics (hypertensive and normotensive). We found increased OxLDL after exercise in both groups (hypertensive patients and normotensive), but only in the hypertensive hypercholesterolemic patients the difference was statistically significant (90.47 ± 15.31 vs. 105.94 ± 14.17 IU/L, $p < 0.001$). Systolic and diastolic blood pressures were significantly higher during exercise only in the hypertensive patients. There were significantly lower values of pVO_2 only in hypertensive hypercholesterolemic patients. There were no significant differences between hypertensive and normotensive ones for ET and VE. In hypertensive ones we found after exercise a negative correlation between pVO_2 and OxLDL ($r = -0.473$; $p < 0.05$), and pVO_2 and CRP ($r = -0.478$; $p < 0.05$). We also found in normotensive normocholesterolemic patients a positive correlation between VE and systolic blood pressure ($r = 0.420$; $p < 0.05$), a negative correlation between VE and OxLDL ($r = -0.421$; $p < 0.05$), and VE and CRP ($r = -0.561$; $p < 0.05$). **Conclusion.** This study showed that acute exercise induces and increases oxidative stress only in untreated mild hypertensive patients with atherogenic lipid profiles. These results imply the need to normalize atherogenic lipid profile in untreated patients with mild hypertension in order to prevent an increased lipid peroxidation under acute exercise.

Key words:
cardiovascular diseases; risk factors; exercise;
hypertension; hyperlipidemias; cholesterol; spirometry.

Apstrakt

Uvod/Cilj. Fizička aktivnost može pozitivno uticati na faktore rizika koji su udruženi sa kardiovaskularnim oboljenjima. Još uvek su nepoznati mehanizmi koji smanjuju aterogeni rizik. Cilj studije bio je da se ispita uticaj akutne fizičke aktivnosti (kardiopulmonalna vežba uz pomoć ergometarskog testa)

na aterogene lipide kod nelečenih bolesnika sa blagom hipertenzijom i sa ili bez hiperholesterolemije. **Metode.** Grupa ispitanika sastojala se od 85 bolesnika sa blagom hipertenzijom koji su bili podeljeni u dve podgrupe: hipertenzivni bolesnici sa hiperholesterolemijom i hipertenzivni bolesnici sa normocholesterolemijom. U kontrolnoj grupi bilo je 35 normotenzivnih ispitanika podeljenih u dve podgrupe: sa hiperholestero-

lemijom i sa normoholesterolemijom. Određivani su oksidovani LDL (OxLDL) kao marker oksidativnog stresa, trigliceridi, ukupni kolesterol, LDL kolesterol i HDL kolesterol koji su mereni u stanju mirovanja i 30 minuta posle perioda kardiopulmonalne vežbe na ergometarskom testu. Za merenje ovih parametara korišćeni su komercijalni aparati. Vrednost OxLDL određivana je komercijalnim ELISA testom. Vrednost CRP merena je hemiluminescentnim metodama. **Rezultati.** Najveće vrednosti OxLDL nađene su kod hipertenzivnih bolesnika sa aterogenim lipidnim profilom u bazalnim uslovima. Postojala je statistički značajna razlika u vrednostima CRP između bolesnika sa hiperholesterolemijom (hipertenzivni i normotenzivni) i onih sa normoholesterolemijom (hipertenzivni i normotenzivni). Posle fizičke aktivnosti vrednosti OxLDL rasle su u obe grupe (hipertenzivni i normoten-

zivni), ali samo kod bolesnika sa hipertenzijom i hiperholesterolemijom ova razlika je bila statistički značajna. Nađene su statistički značajno niže vrednosti preuzimanja kiseonika samo kod hipertenzivnih bolesnika sa hiperholesterolemijom. **Zaključak.** Fizička aktivnost izaziva i povećava nivo oksidativnog stresa samo kod nelečenih bolesnika sa blagom hipertenzijom i aterogenim lipidnim profilom. Dobijeni rezultati ukazuju na potrebu normalizacije lipidnog profila bolesnika sa netretiranom blagom hipertenzijom u cilju sprečavanja lipidne peroksidacije u uslovima akutnog fizičkog naprezanja.

Ključne reči:
kardiovaskularne bolesti; faktori rizika; vežbanje; hipertenzija; hiperlipidemija; kolesterol; spirometrija.

Introduction

Exercise can positively affect risk factors that are associated with cardiovascular disease such as diabetes mellitus, obesity, increased plasma lipids, hypertension, and endothelial dysfunction¹. However, the mechanisms by which exercise reduces atherogenic risk remain unknown. It is known that acute physical exercise-induced oxidative stress could promote plasma oxidation of circulating LDL and its clearance by the liver²⁻⁴. One notable factor in the development of arteriosclerosis is OxLDL, a marker of oxidative stress⁵. Moreover, studies showed that exercise could also induce antioxidant enzymes in different tissues: heart, liver, blood or muscle^{6,7}. This induction of antioxidant enzymes would not only minimize oxidative damage but also reduce the generation of oxidants *in situ*. Exercise-induced plasma oxidative stress could be responsible for the prevention of arteriosclerosis by stimulating arterial antioxidant response. There is some evidence that adequate physical training may increase antioxidant defenses of the body, which is explained by the adapted response of exercise. These observations alerted us to the possibility that extracellular oxidative stress could be potentially beneficial for arteriosclerosis through the induction of arterial antioxidant response^{8,9}.

Limited information is available on the relationships between physical activity and oxidative status grade in untreated mild hypertensive patients. The aim of this study was to investigate effects of acute exercise (cardiopulmonary exercise cycle ergometer test) on atherogenic lipids in untreated mild hypertensive patients with or without hypercholesterolemia, and normotensive subjects with or without hypercholesterolemia.

Methods

The patients included in the study were selected from an outpatient list of the Endocrinology and Cardiology Department, University Clinical Centre "Dr Dragiša Mišović", Belgrade, Serbia. The study population consisted of 85 untreated mild essential hypertensive patients clinically diagnosed according to the criteria of VII Joint National Com-

mittee¹⁰. The study group was divided into two subgroups: hypertensive hypercholesterolemic (n = 35), and hypertensive normocholesterolemic (n = 50). All the subjects were admitted to the study if they were not on any medication or antioxidant therapy at the time of their participation in the study, they drank alcohol less than once a week but only small amount, they had not been involved in any regular physical activity for at least a year, and they had never smoked or taken birth control pills. Exclusion criteria were previously treated essential hypertension, cardiovascular disease (myocardial infarction, angina pectoris, stroke, intermittent claudication, and aortic disease), body mass index (BMI) > 30 kg/m², diabetes mellitus, chronic obstructive lung disorder, acute or chronic inflammatory disease, immunological disease, history or the presence of neoplastic disease, or severe renal failure. Secondary hypertension was excluded by means of clinical and biochemical assessment. Coronary heart disease was excluded on the basis of clinical history, electrocardiography (ECG), and echocardiography. The control group included 35 normotensive subjects divided into two subgroups: normotensive hypercholesterolemic (n = 20) and normotensive normocholesterolemic (n = 55). The same exclusion criteria were applied to the control group.

The study protocol was approved by the local Ethics Committee. Informed consent was obtained from each subject.

After overnight fasting blood samples were drawn for the determination of serum values of lipids. Blood samples were withdrawn into heparinized tubes from a cubital vein before and 30 minutes after to measure lipid parameters. Triglycerides and total cholesterol were measured by enzymatic colorimetric methods. High-density lipoprotein (HDL) cholesterol was measured after precipitation of LDL and very low-density lipoprotein (VLDL) by phosphotungstic acid (Serbolab). LDL cholesterol was calculated using the Friedewald formula¹¹. C-reactive protein (CRP) was measured using hemiluminiscent methods (Immulite – DPC). OxLDL was determined by a commercially available sandwich ELISA (Mercodia AB, Uppsala, Sweden).

The patients did exercises on a cycle ergometer (Jaeger Oxycon Delta ER - 900) after four minutes of warming-up and then with a progressively increased load (25W increments each three minutes) up to the symptom limitation. Accurate monitoring of clinical signs and electrocardiogram for arrhythmias and ischemic changes such as ST significant depression or T-wave changes were carried out during exercise and recovery time. There was breath by breath gas exchange (O_2 uptake and CO_2 output) and spirometric analysis during exercise and recovery time. This testing allowed determination of exercise capacity, peak heart rate, and ventilation per minute (VE), peak oxygen uptake (pVO_2) and exercise time (ET). Amount of oxygen (VO_2) was defined as the highest VO_2 made at rest and during exercise testing without requirement to reach additional VO_2 .

The obtained values were expressed as means $\pm$ SD. The data were analyzed with Statistical Package for the Social Sciences Program - version 10 (SPSS) or Windows software. Comparisons between groups in clinical, biochemical characteristics were performed using the one-way ANOVA methods. Bivariate analysis of the associations between each risk factor and oxidative parameters was performed with Pearson's correlation coefficient. Statistical significance was considered at $p < 0.05$.

Results

Clinical characteristics of the participants are shown in Table 1. Biochemical parameters of the hypertensive participants of the study before and after the acute exercise test are shown in Table 2. The value of OxLDL was significantly higher in hypertensive patients with atherogenic lipid profiles in basal condition, compared with the hypertensive patients without atherogenic lipid profiles and controls. We showed significantly higher levels of OxLDL after the acute exercise only in hypertensive hypercholesterolemics ($p < 0.001$). In basal condition the levels of CRP were also significantly higher ($p < 0.001$) in hypertensive hypercholesterolemic group. Changes of other lipids after the exercise were not significantly different in the hypertensive group ($p > 0.05$).

Biochemical parameters of the normotensive participants of the study before and after acute exercise test are shown in Table 3. In basal condition the levels of CRP were also significantly higher ($p < 0.001$) in the normotensive hypercholesterolemic group. Changes of other lipids after the exercise were not significantly different in the normotensive group ($p > 0.05$).

Table 1

Clinical characteristics of patients before the exercise

Parameter	Hypertensive patients		Normotensive patients	
	hypercholesterolemics (n = 35)	normocholesterolemics (n = 50)	hypercholesterolemics (n = 20)	normocholesterolemics (n = 35)
Age (years), $\bar{x} \pm SD$	52 $\pm$ 3.5	48 $\pm$ 3.5	49 $\pm$ 5.5	46 $\pm$ 2.5
Female/male (n)	25/10	35/15	15/5	20/15
Body mass index (kg/m ²), $\bar{x} \pm SD$	23.45 $\pm$ 1.8	23.30 $\pm$ 1.5	23.80 $\pm$ 1.3	23.18 $\pm$ 1.4
Systolic blood pressure (mmHg), $\bar{x} \pm SD$	144.3 $\pm$ 8.3* [†]	139.3 $\pm$ 6.7* [†]	116.0 $\pm$ 5.2	113.8 $\pm$ 5.5
Diastolic blood pressure (mmHg), $\bar{x} \pm SD$	94.4 $\pm$ 11.3* [†]	92.9 $\pm$ 11.1* [†]	75.5 $\pm$ 9.0	75.1 $\pm$ 8.3

* $p < 0.001$ values statistically significantly different from normotensive hypercholesterolemic patients; [†] $p < 0.001$ values statistically significantly different from normotensive normocholesterolemic patients

Table 2

Biochemical parameters ($\bar{x} \pm SD$) of hypertensive patients before and after the exercise

Parameters	Hypertensive patients			
	hypercholesterolemics		normocholesterolemics	
	before exercise	after exercise	before exercise	after exercise
TC (mmol/L)	6.48 $\pm$ 0.42	6.66 $\pm$ 0.75	5.76 $\pm$ 0.72	5.89 $\pm$ 0.84
HDL-C (mmol/L)	1.10 $\pm$ 0.23	1.11 $\pm$ 0.24	1.18 $\pm$ 0.37	1.20 $\pm$ 0.39
LDL-C (mmol/L)	4.28 $\pm$ 0.54	4.47 $\pm$ 0.63	3.81 $\pm$ 0.62	3.86 $\pm$ 0.63
TG (mmol/L)	1.80 $\pm$ 0.47	1.92 $\pm$ 0.52	1.37 $\pm$ 0.40	1.57 $\pm$ 0.50
TC: HDL-C ratio	6.19 $\pm$ 1.23	6.35 $\pm$ 1.18	5.26 $\pm$ 1.66	5.37 $\pm$ 1.61
LDL-C: HDL-C ratio	4.14 $\pm$ 1.04	4.09 $\pm$ 0.79	3.44 $\pm$ 1.25	3.42 $\pm$ 1.19
TG: HDL-C ratio	1.75 $\pm$ 0.63	1.87 $\pm$ 0.53	1.33 $\pm$ 0.68	1.49 $\pm$ 0.68
OxLDL (IU/L)	90.47 $\pm$ 15.31	105.94 $\pm$ 14.17*	85.56 $\pm$ 18.19 [†]	87.93 $\pm$ 16.07
CRP (mg/ml)	2.57 $\pm$ 1.23		1.81 $\pm$ 1.06 [‡]	

TC = total cholesterol; HDL-C = HDL cholesterol; LDL-C = LDL cholesterol; TG = triglyceride; OxLDL = oxidized LDL cholesterol; CRP = C-reactive protein; * $p < 0.001$ values statistically significantly different after exercise; [†] $p < 0.001$ values statistically significantly different from hypertensive hypercholesterolemics in basal condition; [‡] $p < 0.001$ values statistically significantly different from hypertensive hypercholesterolemics in basal condition

Table 3

Biochemical parameters ($\bar{x} \pm SD$) of normotensive patients before and after the exercise

Parameters	Normotensive patients			
	hypercholesterolemics		normocholesterolemics	
	before exercise	after exercise	before exercise	after exercise
TC (mmol/L)	6.20 $\pm$ 0.93	6.56 $\pm$ 1.28	5.47 $\pm$ 0.61	5.50 $\pm$ 0.76
HDL-C (mmol/L)	1.11 $\pm$ 0.33	1.18 $\pm$ 0.42	1.21 $\pm$ 0.33	1.24 $\pm$ 0.36
LDL-C (mmol/L)	4.20 $\pm$ 0.67	4.29 $\pm$ 0.96	3.63 $\pm$ 0.65	3.75 $\pm$ 0.84
TG (mmol/L)	1.82 $\pm$ 0.69	1.93 $\pm$ 0.79	1.35 $\pm$ 0.42	1.49 $\pm$ 0.51
TC: HDL-C ratio	5.96 $\pm$ 1.19	5.78 $\pm$ 0.96	4.90 $\pm$ 1.47	4.74 $\pm$ 1.63
LDL-C: HDL-C ratio	4.24 $\pm$ 0.96	3.90 $\pm$ 0.98	3.25 $\pm$ 1.31	3.03 $\pm$ 1.30
TG: HDL-C ratio	1.84 $\pm$ 0.70	1.89 $\pm$ 0.76	1.27 $\pm$ 0.62	1.31 $\pm$ 0.70
OxLDL (IU/L)	86.35 $\pm$ 15.79	87.90 $\pm$ 13.97	77.23 $\pm$ 15.85	80.26 $\pm$ 15.57
CRP (mg/ml)	2.14 $\pm$ 1.16		1.35 $\pm$ 0.71*	

TC = total cholesterol; HDL-C = HDL cholesterol; LDL-C = LDL cholesterol; TG = triglyceride; OxLDL = oxidized LDL cholesterol; CRP = C-reactive protein; * $p < 0.05$ values statistically significantly different from normotensive hypercholesterolemics

Only in the hypertensive patients systolic blood pressure ($p < 0.001$) and diastolic blood pressure ($p < 0.05$) were significantly higher during the exercise (Table 4) but not in the normotensive participants (Table 5).

Table 6 shows a comparison of mean values of cardiopulmonary capacity during exercise between the participants. Hy-

and normotensive normocholesterolemics ($p < 0.001$). There were no significant differences between the hypertensive and normotensive subjects for ET and VE.

A significant positive correlation between CRP and OxLDL was found only in normotensive normocholesterolemics ($r = 0.585$; $p < 0.001$). There was no relationship

Table 4

Blood pressure ($\bar{x} \pm SD$) before and during the exercise for hypertensive patients

Blood pressure (BP)	Hypertensive patients			
	hypercholesterolemics		normocholesterolemics	
	rest	during exercise	rest	during exercise
Systolic BP	144.3 $\pm$ 8.36	206.8 $\pm$ 22.9 [†]	139.3 $\pm$ 6.75	177.6 $\pm$ 13.6 [†]
Diastolic BP	94.4 $\pm$ 11.33	103.75 $\pm$ 11.89*	92.9 $\pm$ 11.15	99.12 $\pm$ 6.18*

* $p < 0.05$; [†] $p < 0.001$

Table 5

Blood pressure ($\bar{x} \pm SD$) before and during the exercise in normotensive patients

Blood pressure (BP)	Normotensive patients			
	hypercholesterolemics		normocholesterolemics	
	rest	during exercise	rest	during exercise
Systolic BP	116.0 $\pm$ 5.28	125.0 $\pm$ 8.64	113.8 $\pm$ 5.56	121.9 $\pm$ 6.90
Diastolic BP	75.5 $\pm$ 9.01	76.6 $\pm$ 8.56	75.1 $\pm$ 8.35	76.2 $\pm$ 5.72

Table 6

Respiratory and cardiovascular post-exercise data ($\bar{x} \pm SD$) in the participants of the study

Variable	Hypertensive patients		Normotensive patients	
	hypercholesterolemics	normocholesterolemics	hypercholesterolemics	normocholesterolemics
pVO ₂ (mL/kg/min)	20.54 $\pm$ 6.72 [†] *	23.20 $\pm$ 6.58	25.55 $\pm$ 5.88	26.84 $\pm$ 6.32
VE (L/min)	53.04 $\pm$ 13.27	52.96 $\pm$ 13.31	52.57 $\pm$ 13.50	52.19 $\pm$ 13.85
ET (min)	13.47 $\pm$ 4.75	13.05 $\pm$ 2.58	11.08 $\pm$ 1.48	11.05 $\pm$ 1.57

pVO₂ - peak oxygen uptake; VE = ventilation per minute; ET-exercise time in minutes; [†] $p < 0.001$ values statistically significantly different from hypertensive normocholesterolemics; * $p < 0.001$ values statistically significantly different from normotensive hypercholesterolemics; [‡] $p < 0.001$ values statistically significantly different from normotensive normocholesterolemics

pertensive hypercholesterolemics had significantly lower values of pVO₂ compared with hypertensive normocholesterolemics ($p < 0.001$), normotensive hypercholesterolemics ($p < 0.001$),

between the blood pressure values and the OxLDL. In the hypertensive hypercholesterolemic patients we found a negative correlation between pVO₂ and OxLDL ($r = -0.473$;

$p < 0.05$). In hypertensive normocholesterolemics pVO_2 was negatively correlated with CRP ($r = -0.478$; $p < 0.05$). In normotensive normocholesterolemics we found a positive correlation between VE and SBP ($r = 0.420$; $p < 0.05$), and a negative correlation between VE and OxLDL ($r = -0.421$; $p < 0.05$), and VE and CRP ($r = -0.561$; $p < 0.05$).

Discussion

Numerous studies documented a relation of increased physical activity with an improved cardiovascular risk factors, especially arterial blood pressure levels¹²⁻¹⁵. It is widely accepted that exercise also affects atherogenic lipid in a positive way, by regulating the metabolism of all lipids in the blood^{16, 17}. In this study we evaluated the effect of acute exercise on lipids in the patients with untreated mild hypertension with or without atherogenic lipid profiles. The results of the present study show that OxLDL and CRP were significantly higher in the hypertensive patients with atherogenic lipid profiles in basal condition, compared to the hypertensive patients without atherogenic lipid profiles and normotensive ones. These results fit into the concept that circulating OxLDL is associated with proinflammatory CRPs which are risk factors for development of arteriosclerosis¹⁸. Elevated high-sensitivity CRP levels have been linked to future cardiovascular events as was shown in several cohort studies around the world¹⁹⁻²³. Finally, there are also data relating CRP levels to prevalent hypertension and incident hypertension^{24, 25}.

We showed that acute exercise slowly increased total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, ratio of total cholesterol: HDL cholesterol, ratio of triglyceride: HDL cholesterol in both hypertensive subgroups, while ratio of LDL cholesterol: HDL cholesterol decreased in study groups and controls. We found that OxLDL was statistically significantly increased ($p < 0.01$) after the exercise test only in hypertensive subjects with atherogenic lipid profiles.

Atherogenic lipids, particularly OxLDL, are responsible for a wide range of cellular dysfunctions within the vessel wall²⁶⁻³². The mechanisms by which elevated levels of OxLDL cause an acceleration of atherogenesis are only incompletely understood. Many animal experiments or *in vitro* studies in humans support the hypothesis that increased oxidative stress may be one of the initial triggers of vascular remodeling and elevated blood pressure³³⁻³⁵. In humans, hypertension is considered a state of oxidative stress that can contribute to the development of arteriosclerosis and other hypertension-induced organ damage³⁶⁻³⁷. Oxidative stress

produces oxidative damage in cells, which is caused by an overabundance of reactive oxygen species or a decline in antioxidant ability against them. Oxidized LDL, as a stimulator of oxidative stress, facilitates monocyte-related atherogenesis. Oxidized LDL has been identified as a potent chemoattractant and oxidative stressor of atherogenesis, typically causing endothelium dysfunction and facilitating monocyte emigration into the subendothelial space. Previous studies indicated that acute exercise increases OxLDL-induced suppression of anti-oxidative capacity of monocyte³⁸. However, mild and moderate exercise likely protect individuals against suppression of antioxidative capacity of monocyte by OxLDL. Whether physical exercise influences oxidant production and antioxidative capacity of monocyte mediated by OxLDL remains unclear. It is probable that exercise impacts OxLDL-mediated redox status of monocytes, with reactions determined by exercise intensity.

This study also showed that untreated mild hypertension without atherogenic lipid profiles are not associated with increased lipid peroxidation after an acute exercise³⁹. A possible explanation for these findings is that oxidative stress is not implicated in the pathogenesis of human essential hypertension alone, at least in the early stages, although this study does not rule out the possibility that lipid peroxidation is increased in later stages of essential hypertension.

As we expected, untreated mild hypertensive patients with atherogenic lipid profile had decreased cardiopulmonary capacity during exercise compared with mild hypertensive patients without lipid disturbances and the control. In mild hypertensive patients pVO_2 was negatively correlated with OxLDL and with CRP. These findings may have important implications for exercise training in rehabilitation programs and future studies on hypertensive patients⁴⁰. Life-style change is the only intervention recommended for most mild hypertensive.

Conclusion

An acute exercise induces an increase of oxidative stress only in untreated mild hypertensive patients with atherogenic lipid profiles. A therapeutic approach to untreated mild hypertension could be pharmacological correction of atherogenic lipid profiles in order to prevent an increased lipid peroxidation during acute exercise. These results should be completed with effects of regular physical activity on atherogenic lipids in untreated mild hypertensive patients to precise our observations.

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