

Hydroxytyrosol But Not Resveratrol Ingestion Induced an Acute Increment of Post Exercise Blood Flow in Brachial Artery

Giorgia Sarais¹, Antonio Crisafulli², Daniele Concu³, Andrea Fois⁴, Abdallah Raweh⁵, Alberto Concu^{3,5}

¹Department of Life and Environmental Sciences, University of Cagliari, Cagliari, Italy

²Laboratory of Sports Physiology, University of Cagliari, Cagliari, Italy

³IIC Technologies Ltd., Cagliari, Italy

⁴EventFeel Ltd., Cagliari, Italy

⁵Medical Sciences Faculty, The LUdeS Foundation Higher Education Institution, Kalkara, Malta

Email: aconcu44@gmail.com

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Abstract

The aim of this study was to test if previous ingestion of compounds containing resveratrol or hydroxytyrosol, followed by an exhausting hand grip exercise, could induce an acute post-exercise increase in brachial blood flow. Six healthy subjects (three males and three females, 35 ± 7 years), 60 minutes after ingestion of a capsule containing 200 mg of resveratrol or 30 ml of extra virgin olive oil enriched with tyrosol, oleuropein and hydroxytyrosol, performed a hand grip exercise equal to half of their maximum strength until they were no longer able to express the same force (2-day interval between tests). The nonparametric Wilcoxon signed rank test was used for statistical evaluations. Brachial artery blood flow (Fba) and both blood velocity (Vba) and artery diameter (Db) were assessed immediately after exercise cessation by means of colour Doppler ultrasound. After ingestion of the oil mixture the post-exercise value of Fba median was 2.4 times higher than that after ingestion of the resveratrol compound ($P = 0.03$), and also the Vba median concerning the hydroxytyrosol was 1.9 times higher than that of the resveratrol ($P = 0.03$). Both functional foods did not lead to a significant difference in the Db medians. These results indicate that hydroxytyrosol, but not resveratrol, may be an effective adjuvant of recreational or agonistic, long-lasting sports performances, thanks to the powerful blood flow increment which can be obtained as soon as one hour from its oral intake.

Keywords

Functional Foods, Hydroxytyrosol, Resveratrol, Hand Grip, Blood Flow

1. Introduction

Both resveratrol from peel grapes and hydroxytyrosol from olive leaves are considered functional foods since they are powerful antioxidants [1] [2] [3] [4]. However, there is increasing evidence for their role also on the endothelial function of the vessels. An *in vitro* study of Leikert *et al.* [5] used human umbilical vein endothelial cells treated with increasing concentrations of a polyphenolic extract of red wine and kept in incubation for 20 hours, and they showed that cellular production of nitrogen monoxide (NO) increased due to doubling of the levels of the enzyme nitric oxide synthase (eNOS). From these results, although *in vitro*, it can be assumed that the resveratrol content of red wine extract may induce an increase in NO in these endothelial cells from which a smooth muscle relaxation of the tunica media of these vessels, thus their dilation, could be expected *in vivo* [6] [7]. Reyes *et al.* [8] studied *in vitro* the effects of hydroxytyrosol in human blood samples and they found a concentration-dependent effect of this polyphenol in inhibiting platelet aggregation due to an increase in NO production. Stornio *et al.* [9] in an *in vitro* model that simulates the condition of type 2 diabetes showed a reverted glucose inducing decrease in endothelial eNOS phosphorylation by hydroxytyrosol extract from extra virgin olive oil. These latter experimental results also suggest a possible vasodilator effect of hydroxytyrosol. Nowadays it has been observed that the shear stress on the endothelium of blood vessels due to circulating blood is a powerful stimulus for NO release [10]. Thus the chronic increase in endothelial shear stress induced by the exercise also induces higher levels of gene coding for endothelial eNOS expression, determining in this way an increase in endothelium-dependent muscle relaxation [11]. This occurrence may derive a fall in the vascular resistance of a given vascular district. However, several studies have shown that acute exercise can also have a not negligible impact on endothelial function [12] [13] [14] [15]. Indeed, a review by Padilla *et al.* [16] indicates that acute exercise can be utilized as a model to allow for modulating more efficiently the mode, duration and intensity of exercise on the basis of the endothelial response. In these experiments we wanted to see if the intake of resveratrol or hydroxytyrosol before an acute and exhaustive hand grip exercise could induce a post-exercise blood flow increase in a given vascular district of trained subjects.

2. Materials and Methods

2.1. Subjects

To carry out the experiments with a group of relatively homogenous subjects among graduates in medicine and surgery who were attending postgraduate school in sports medicine at the University of Cagliari (Italy), we found healthy volunteers who were moderately trained. The admission criteria were: no chronic degenerative disease of the cardiovascular and respiratory apparatus, of the nervous-endocrine-metabolic system and of the muscle-skeletal apparatus. Exclusion criteria were: current smoking, the condition of physical inactivity, taking medications, habitual drinking of alcohol, sub-clinical overweight and intolerance to glucose. Eighteen volunteers responded to our

call, each of whom was subjected to a thorough investigation of medical history and to an examination by a sports medicine specialist with detection, at rest, of the ECG, heart rate (R-HR) and mean arterial blood pressure (R-MBP) together with the body mass index (BMI) obtained by dividing body weight by height squared. After these medical controls only six subjects, three males and three females, presented the required characteristics and were engaged in these experiments. **Table 1** shows the socio-demographic and clinical characteristics of these subjects.

2.2. Instrumentation

The device used for the experiments was a hand grip dynamometer (Kern, USA), with settable springs. It displays in real time the produced strength, the maximum strength of a subject's grip and the average strength of several grips.

To assess in a non-invasive way the blood flow in a brachial artery, we employed a widely used technique [17] based on the measurement of the velocity of blood in the vessel, obtained with the ultrasonic Doppler method, and the measurement of the cross-section in the same blood vessel obtained with the ultrasound method. In these experiments, to measure the blood flow in the brachial artery of the hand that performed the exercise, a colour Doppler echocardiograph (M5 Diagnostic Ultrasound System, Mindray Bio-Medical Electronics Co., Shenzhen, China) was utilized with an ultrasound probe type 7L4 suitable for arterial flow measures. The ultrasound probe was positioned in the bend of the elbow at a 60° angle with respect to the plane in which the brachial artery lay.

2.3. Experimental Procedures

The experimental sessions were held at 3 pm at the laboratory of sports physiology of the Department of Medical Sciences, University of Cagliari, Italy. The temperature was stabilized between 20°C and 22°C.

The hand grip exercise consisted of contracting and relaxing the fingers of one hand

Table 1. For each engaged subject are represented the anthropometric variables (age, weight, height and BMI) together with the recreational activities quantified in terms of hours per week and the rest values of heart rate (R-HR) and mean arterial blood pressure (R-MBP).

Socio-demographic and clinical characteristics of subjects									
Subjects	Gender	Age (years)	Weight (kg)	Height (m)	BMI (kg·m ⁻²)	Recreational activities	Exercise volume (hours a week)	R-HR (beats·min ⁻¹)	R-MBP (mmHg)
DA	Female	28	55	1.7	19	Basketball	6	65	90
GG	Female	42	51	1.6	20	Long dist. running	9	58	83
OA	Male	39	82	1.7	28	Football	7	61	93
VS	Male	30	80	1.8	25	Basketball	6	57	87
MS	Female	31	53	1.6	21	Swimming	5	60	87
MR	Male	42	77	1.7	24	Football	8	63	94
Mean values ± SD		35 ± 6	66 ± 15	1.7 ± 0.1	23 ± 3		7 ± 1	61 ± 3	89 ± 4

against a spring resistance equal to half of the maximum force, in kg, expressed with this gesture. The contraction-relaxation cycle of the fingers lasted 2 seconds and was repeated until the subject was no longer able to express the same force. In **Figure 1** are represented mean values of the maximum load developed in a preliminary session of hand gripping in which subjects were invited to release their highest hand contraction, and of the constant load developed throughout the sessions in which the exercise lasted up to exhaustion.

Figure 2 shows one subject while performing a hand grip exercise with the right hand. He was seated with his elbow resting on the surgery cot of the laboratory of sports physiology. Also shown is the ultrasound probe while positioning it in the inner bend of the elbow, being careful to position it at an angle of about 60° with respect to the brachial artery direction.

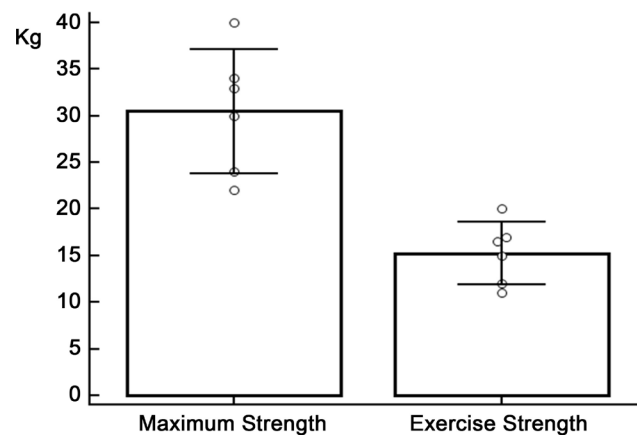


Figure 1. The column on the left represents the mean value, expressed in kg, of the maximum strength delivered by the subjects against the dynamometer by finger contraction; the column on the right corresponds to half the maximum strength that was maintained up to exhaustion. Vertical bars represent the \pm standard deviation while circles along them, respectively for maximum and exercise strengths, show the distribution of each participant.

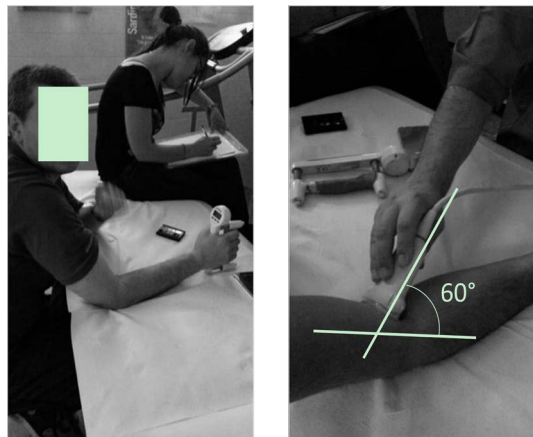


Figure 2. The image on the left shows a subject engaged in the hand grip exercise up to exhaustion. The image on the right shows how the ultrasound probe was positioned in the bend of the subject's elbow at a 60° angle with respect to the plane of the brachial artery.

2.4. Experimental Protocol

The experimental protocol consisted of each subject performing the following tests:

i) Base at Rest (BR)—which consisted of assessing the brachial artery blood flow (Fba) together with Arterial blood velocity (Vba) and arterial diameter (Dbal) with the ultrasound probe while a subject remained seated at rest;

ii) Exercise plus Resveratrol (EXresv)—where subjects assumed orally one capsule containing 200 mg of resveratrol extracted from the roots of *Polygonum cuspidatum* (Resveratrox, produced by Solgar, Italy); they then remained seated at rest for 60 min before performing a hand grip exercise up to exhaustion, after which the Fba, Vba and Dbal in the arm that had worked was again assessed;

iii) Exercise plus Hydroxytyrosol (EXhydr)—where subjects assumed orally 30 ml of extra virgin olive oil enriched with tyrosol (18.8 mg/kg), oleuropein (101.3 mg/kg) and hydroxytyrosol (19.0 mg/kg); they then remained seated at rest for 60 min before performing a hand grip exercise up to exhaustion, after which the Fba, Vba and Dbal in the arm that had worked was again assessed. The oil mixture was prepared by the pharmaceutical laboratory of the Department of Life and Environment Sciences, University of Cagliari, Italy, by extracting these added substances from olive leaves.

Subjects were randomly submitted to two experimental sessions with a 2-day interval between them. In session A they performed a BR test after which they remained seated at rest for 60 min; they then performed the EXresv test. In session B they performed the same tests as previously described, but instead of test EXresv they performed the EXhydr test.

Those participating in the experiments were unaware of the composition of the substances ingested during sessions A and B, nor did they know the experimental hypothesis on which the study was based.

Finally, when both A and B sessions were stopped, we asked to each participant to tell us about possible differences in the perceived sensations during each of these two tests.

2.5. Data Analysis

Due to the asymmetric distribution of the data, the visualization of the assessed values of the hemodynamic variables was made by means of the box and whiskers plots [18] in which we have also included the spread of data. Each box ranged from the 1st quartile (Q1) to the 3rd quartile (Q3) of the distribution, so the box length is the interquartile range (IQR), which contains the central 50% of data, and the line across the box indicates the statistical median, or Q2. The whiskers are lines extending from 1st and 3rd quartile, respectively, to the most extreme data points within $Q1 - 1.5 \times IQR$ and $Q3 + 1.5 \times IQR$ [19]. Moreover, due to the modest sample size of our data, when comparing the Fba, Vba and Dbal post-exercise values between the resveratrol and hydroxytyrosol groups of data, we have chosen the nonparametric Wilcoxon signed rank test. The same test was also applied to compare the differences of the “delta” (Δ) values between the two groups of data as (EXresv – BRresv) versus (EXhydr – BRhydr). In all the compar-

isons the statistical significance was established as a P value < 0.05. Statistical tests were carried out utilizing commercially available software (MedCalc, Belgium).

3. Results

After experimental sessions were finished, no subject reported sensible differences in perceiving sensation from the hand grip exercise when resveratrol or hydroxytyrosol had been ingested before beginning the exercise.

Concerning the test duration, in session A the mean \pm SE value of the EXresv test was 276 ± 72 s while in session B the mean \pm SE value of the EXhydr test was 279 ± 71 s. Comparing these mean duration it was found that the difference between them was not statistically significant. In **Figure 3** the box concerning BRresv values of Fba is smaller than that concerning the BRhydr ones. In fact, the BRresv showed an IQR from 73.2 to 196.8 ml·min⁻¹ while the BRhydr IQR was from 89.6 to 369.5 ml·min⁻¹. However, their respective median lines are very close (BRresv = 142.9 ml·min⁻¹ and BRhydr = 125.9 ml·min⁻¹) with no statistically significant difference between them. The same figure clearly shows that the box of EXhydr data (median = 516.1 ml·min⁻¹ with IQR from 374.3 to 786.1 ml·min⁻¹) is placed totally above the box of EXresv data (median = 211.6 ml·min⁻¹ with IQR from 108.2 to 330.8 ml·min⁻¹), and the statistical comparison between these two groups of data showed a P = 0.03. When Fba Δ was also calculated, the median concerning the hydroxytyrosol group was of 404.5 ml·min⁻¹ while the median concerning the resveratrol group was of 92.1 ml·min⁻¹. The comparison between these two groups of data comes very close to statistical significance (P = 0.06).

Figure 4 concerns the Vba data and shows that the BRresv box data (median = 20.3 cm·s⁻¹ with IQR from 17.6 to 24.9 cm·s⁻¹) could be entirely contained inside the BRhydr

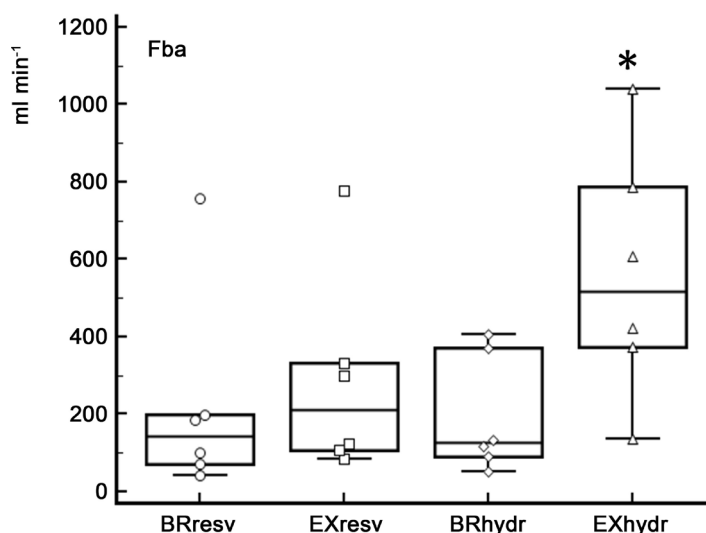


Figure 3. The experimental data concerning the blood flow values in the brachial artery (Fba) in the different experimental conditions are represented as box and whiskers diagrams with markers that reveal the distribution of each participant. Outlier marks are shown outside the whiskers from 1st quartiles of BRresv and EXresv plots. (*) With respect to EXresv: P = 0.03.

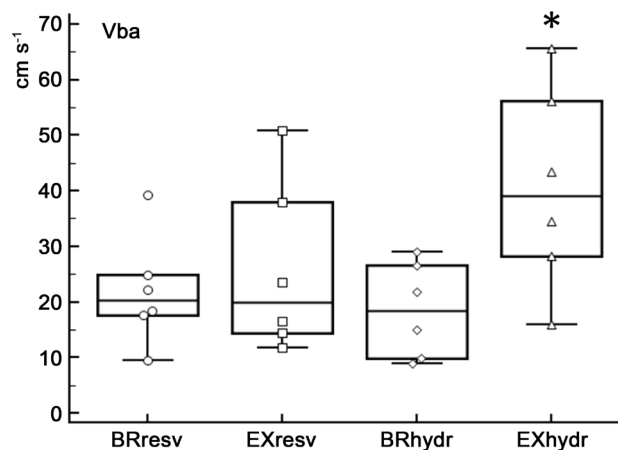


Figure 4. The experimental data concerning the blood velocity values in the brachial artery (V_{ba}) in the different experimental conditions are represented as box and whiskers diagrams with markers that reveal the distribution of each participant. An outlier mark is shown outside the whisker from 1st quartile of BRresv plot. (*) With respect to EXresv: $P = 0.03$.

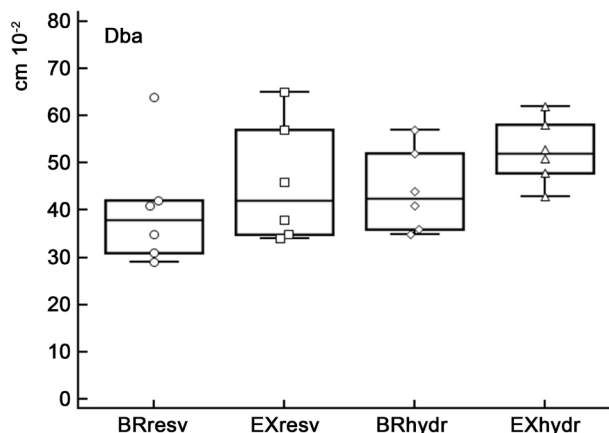


Figure 5. The experimental data concerning the diameter values of the brachial artery (Db) in the different experimental conditions are represented as box and whiskers diagrams with markers that reveal the distribution of each participant. An outlier mark is shown outside the whisker from 1st quartile of BRresv plot.

box (median = $22.9 \text{ cm}\cdot\text{s}^{-1}$ with IQR from 16.4 to $28.4 \text{ cm}\cdot\text{s}^{-1}$). So the comparison between these two groups of data did not reach any statistically significant difference. The figure also shows that despite a practically complete overlap between Q3 of the EXhydr box (IQR: from 28.3 to $56.1 \text{ cm}\cdot\text{s}^{-1}$) and Q1 of the EXresv box (IQR: from 14.4 to $37.9 \text{ cm}\cdot\text{s}^{-1}$), the median in the former box ($39.1 \text{ cm}\cdot\text{s}^{-1}$) was almost doubled compared with that of the second box ($20.1 \text{ cm}\cdot\text{s}^{-1}$). These differences between EXhydr and EXresv data were statistically significant ($P = 0.03$). The comparison between $V_{be} \Delta$ values showed that the median of the hydroxytyrosol group was of $19.7 \text{ cm}\cdot\text{s}^{-1}$ while that of the resveratrol one was of $6.9 \text{ cm}\cdot\text{s}^{-1}$, or nearly three times lower than that concerning hydroxytyrosol, and the comparison between these Δ values reached the statistical significance ($P = 0.03$).

Box and whiskers plots represented in **Figure 5** show that Db values in BRresv (me-

dian = 0.38 cm with IQR from 0.31 to 0.42 cm) and BRhydr (median = 0.42 cm with IQR from 0.36 to 0.52 cm), were quite scattered and their comparison did not reach a significant difference. The same behaviour can be observed when considering post-exercise Db_a measurements. In fact, Db_a median in the EXhydr box was 0.52 cm with IQR from 0.48 to 0.58 cm, and the same variable in the EXresv box was 0.42 cm with IQR from 0.35 to 0.57 cm. Post-exercise Db_a data comparison did not reach the significant difference. As expected, also Db_a Δ values between post-exercise versus base at rest differences for hydroxytyrosol (median = 0.04 cm) did not differ significantly from the same Δ values for resveratrol (median = 0.02 cm).

4. Discussion

The main result from these experiments is the evidence that the pre-exercise ingestion, by moderately trained young subjects, of a hydroxytyrosol enriched extra virgin olive oil, induced a large blood flow post-exercise increase in the brachial artery of the arm that had performed an exhaustive hand grip exercise, mainly due to blood speed increase. A second important result, parallel to the first, is that when the same subjects repeated the hand grip protocol, but with the pre-exercise ingestion of an adequate dose of resveratrol, no increase was found in the blood flow of the brachial artery. Thus, despite these two nutraceutical compounds both being known for playing an important role in the relationships between vessels and blood, only the hydroxytyrosol showed to possess a marked post-exercise activity in increasing the speed of blood flow of the brachial arteries in a small but homogeneous group of trained subjects.

The effect of the hydroxytyrosol in increasing the post-exercise F_{ba}, obtained in the present experiments, agrees with the results of a recent paper of Valls *et al.* [20] in which hypertensive patients who ingested 30 ml of extra virgin olive oil enriched with phenolic compounds containing hydroxytyrosol, were submitted to a brachial ischemic reactive hyperaemia. Five hours after ingestion of the enriched oil, it was found that the reactive hyperaemia had significantly increased with respect to a test in which ischemia was applied with ingestion of non-enriched oil. Since it is known that the test to induce a reactive hyperaemia induces vasodilation [10], the above experiment, which utilized an oil mixture that was qualitatively similar to that used in the present experiment, indirectly reinforces our results of a possible influence of the oil mixtures containing hydroxytyrosol on the modulators of blood flow in the brachial artery. Concerning resveratrol, Wong *et al.* [21] performed a test similar to that of Valls *et al.* [20] in obese individuals after they acutely ingested 270 mg of resveratrol and, compared to a placebo, the flow-mediated dilation of the brachial artery had significantly increased. To explain this experimental divergence between our results and those of Wong *et al.*, it is to be considered that our subjects ingested 200 mg of resveratrol which may be an insufficient dose to induce significant increases in Db_a, and then in F_{ba}. Nevertheless, Posadino *et al.* [22] recently showed that, in endothelial cells, tissue-attainable doses of resveratrol increased the intracellular oxidative state, affecting in this way mitochondrial membrane depolarization which induces death in these cells. Thus, care must be taken

concerning resveratrol dosage. Although the number of participants in these experiments was relatively small, **Table 1** shows that their socio-demographic characteristics can be considered sufficiently homogeneous, so as to ensure a good model for the study of the mechanisms that are the subject of this research. In fact, participants have the same socio-cultural background and all are healthy and relatively young, and all of them perform weekly a considerable and similar amount of physical exercise. Moreover, sports in which they are engaged are characterized by alternating recruitment of energy from aerobic and anaerobic substrates and, in addition, as suggested by the HR and MBP values at rest, they implemented the typical functional adaptations of trained people. Despite this, one could argue that, probably, changes in their vessel endothelial function induced by exercise may differ in male and female subjects [23], thus our mixed experimental group may result in distorted data due to this demographic condition. However, several previous studies [24] [25] [26] [27] have shown that gender differences do not lead to serious differences in the endothelial response to specific stimuli. In these experiments it must be considered that, owing to the type of study protocol, participants were not blinded to the study medication (resveratrol vs. hydroxytyrosol), so there might have been some placebo effect on the research outcomes since subjects self-limited exercise when they became exhausted. Actually this type of risk was greatly limited by the fact that subjects did not know the experimental hypothesis and did not know the composition of the ingested substances.

Possible rebounds of these results concerning exercise physiology and sports medicine are not negligible. This is due to the fact that all engaged subjects could be considered as semi-professional athletes, and this might be an important matter concerning these experiments. In fact, in athletes who perform intermittent muscle efforts, during the interval between two efforts it is advantageous to deliver as much oxygen as possible to the recovering muscles, thus producing aerobic resynthesis of ATP reserves, and pre-race ingestion of extra virgin olive oil, enriched with hydroxytyrosol, might potentiate this need by enhancing the post effort blood flow in the legs vessels.

5. Limitations of the Study

One limitation of this study may arise from the fact that we chose a 2-day interval between the two experimental sessions, and it may be that this time interval was not long enough to wash-out potential effects of the nutraceutical compound assumed in the previous session when, after two days, the subjects assumed the other nutraceutical compound. Indeed, in healthy subjects it was found that after taking 500 mg of resveratrol the half-life of its peak blood concentration was of only 5 hours [28]. On the other hand, hydroxytyrosol blood concentration showed a similar pharmacokinetics in healthy subjects after they had ingested 25 ml of extra virgin olive oil enriched with this nutraceutical compound [29]. Considering the above mentioned experimental results, we are confident that two days could be a long enough period of time to implement the complete wash-out of previously taken nutraceutical compound.

Another limitation of this study may concern some outlier markers which are

present in **Figures 3-5** and, especially for the Vba and thus for Fba, one participant showed excessively high values of these parameters in BRresv, EXresv and EXhydr. This may indicate that the measurements would be highly variable mainly due to the small number of study participants. Therefore, the generalization of our study results needs caution.

In order to overcome these limitations, future experiments with large cohorts of participants and with blood concentration dosage of both resveratrol and hydroxytyrosol during the recovery time after the hand grip exercise, must be programmed.

6. Conclusion

In moderately trained subjects, this study shows a post-exercise nearly doubled increase in blood flow of arms peripheral arteries just 60 min after ingestion of oil enriched with hydroxytyrosol. This physiological adjustment may represent a significant advantage since in the same time span it conveys a larger amount of oxygen to recovering muscles [30]. This condition would be particularly favourable in long-lasting physical performances that exploit aerobic energy sources for the muscles in activity, *i.e.* long distance races. Thus, hydroxytyrosol could satisfy the growing demand of the multitude of individuals engaged in aerobic performances [31] for adjuvants exclusively based on natural foods.

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