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Original Article

The Effects of High Intensity Exercise to Exhaustion on the Concentrations of Endostatin and VEGF in Plasma.

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ABSTRACT

Endostatin and Vascular Endothelial Growth Factor (VEGF) are important markers driving the angiogenic switch. It is clear that short periods of moderate to high intensity exercise significantly increase the concentration of endostatin and VEGF in plasma. **Objective:** To investigate concentration of circulatory endostatin in plasma and impact of different intensities of exercise encompassing from low to maximum on distribution of endostatin and VEGF concentrations in plasma. **Methods:** Eight healthy male volunteers were recruited through advertisements and personal contacts, after assessing their fitness through two pre-participation health screening questionnaires, PAR-Q and ACSM Health Fitness Facility pre-participation health screening questionnaire for performing maximal exercise to volitional exhaustion. All the volunteers attend the lab on 2 consecutive days. The blood was centrifuged at 1000 RPM for 15 minutes for endostatin and VEGF and at 3000 RPM for 15 minutes for lipid profiles and insulin. Samples were analysed for endostatin and VEGF concentrations using Quantikin® ELISA kit of the R&D systems, while Insulin was measured using ELISA kit (Mercodia, Uppsala Sweden). **Results:** The basal endostatin concentration remained consistent and higher intensity of exercise significantly increased the endostatin concentration for up to 2 hours. Exercise also influenced VEGF concentration transiently and only at 30 minutes' interval increase in VEGF was statistically significant. **Conclusion:** It is worth noting that those participants who showed an immediate decrease in VEGF after exercise, later on exhibited a concentration higher than basal.

INTRODUCTION

Endostatin and Vascular Endothelial Growth Factor (VEGF) are important markers driving the angiogenic switch. An imbalance of which can lead to atherosclerosis. It is clear that short periods of moderate to high intensity exercise significantly increase the concentration of endostatin and VEGF in plasma [1]. These changes are different at different intensities of exercise. However, the changes were observed for 1 hour only without a return to baseline. The possibility of later changes in VEGF or endostatin concentration could not be ruled out completely, as significant changes in endostatin and VEGF concentrations up to 6 hours after exercise has been reported [2]. Moreover, it was thought that factors important in development of atherosclerosis and endothelial functions such as; body fat composition, fasting lipid profile, fasting blood glucose concentration and insulin sensitivity should be explored to determine any possible association with endostatin and VEGF. Endostatin is a part of collagen in the basement membrane. It is in close proximity to the endothelium and other vascular structures. It is known that internal milieu strongly influences the endothelium and other vascular structure's functions. For example, an increase in body fat is associated with activation of renin angiotensin aldosterone system (RAAS), and subsequent increases in angiotensin II affects the vascular stiffness [3]. Moreover, increase in body fat increases the risk type 2 diabetes [4] which in turn increases the risk of atherosclerosis [5]. Similarly, insulin resistance is associated with endothelial dysfunction and impaired vascular relaxation which in turn

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contributes to atherosclerosis and other cardiovascular events [6]. In addition, deranged lipid profile and hyperglycaemias are important determinants of endothelial dysfunction derived health problems, including atherosclerosis and peripheral vascular diseases [7].

Thus, the possibility of an association of endostatin with these metabolic factors could not be ruled out. Therefore, experiment was designed to look for the influence of high intensity exercise on endostatin and VEGF concentration in plasma for a longer duration (24 hours) after exercise and to investigate their correlation with other factors involved directly or indirectly in the pathogenesis and development of atherosclerosis.

METHODS

The Research Ethics Committee of the College of Medical, Veterinary and Life Sciences, University of Glasgow, granted the approval for this study. Eight healthy male volunteers were recruited through advertisements and personal contacts, after assessing their fitness through two pre-participation health screening questionnaires, PAR-Q and ACSM Health Fitness Facility pre-participation health screening questionnaire [8] for performing maximal exercise to volitional exhaustion. Different characteristics of all participants with mean ± SD are illustrated. Ht; Height in m, Wt; Weight in kg, BMI; Body mass index, SBP; Systolic blood pressure, DBP; Diastolic blood pressure, WC; Waist circumference, HC; Hip circumference, W:H ratio; Waist to hip circumference ratio. All the volunteers attend the lab on 2 consecutive days. The total duration of their stay, was 6 to 7 hours on the first day and about 30 minutes on the second day. On initial visit, the participants were requested to visit the lab in fasted. After signing consent forms, their height, weight, blood pressure, heart rate, waist and hip circumference were measured and body fat percentages were estimated using air displacement plethysmography in a Bod Pod. The fasting blood glucose concentrations of the participants were determined using glucometer (Accu-Chek Aviva, Manheim, Germany). After rest 3 blood samples of 5 ml were taken, one each for endostatin, VEGF and fasting blood lipid profile and insulin concentration. The participants were then given isotonic drinking solution to restore some energy. The participants performed maximal exercise test on the tread mill using the modified Taylor protocol [9]. During the test, maximal oxygen uptake of the participant was measured with breath by breath analyser (Medical Graphics Corporation, Borngasse, Germany). The test was completed by all the volunteers and they were encouraged to make a maximum effort. The effort was considered maximum, if most of the following criteria were observed, as per ACSM guidelines [8]: Achieved heart rate during the test was in the range of age predicted maximum heart rate ± 10 bpm. A respiratory exchange ratio of more than 1.10. A post exercise lactate concentration of 8 mmol. A plateau in oxygen consumption (VO2) or failure in oxygen uptake by 150ml.min-1, beside increase in work rate, as shown in the figure 6-1 from the data of one participant. A rating of >17 on Borg scale of perceived exertion. At the end of the test all the participants walked slowly for 5 minutes till the heart rate dropped to 120 bpm. Blood was taken by a finger prick at 0, 3, and 5 minutes at the end of running to measure the lactate concentrations. The participants then relaxed in a quiet room and more blood samples were taken at 10, 30, 60, 120, and 240 minutes after the exercise. During this time, they watched movies or videos as per choice, while sitting on a chair. They were given biscuits and isotonic drinks during this time. After the final blood sample, cannula was removed and a full meal was served. They were asked to attend the lab on next day for a 24-hour sample. On day 2 the participants attended the lab for two blood samples, one each for VEGF and endostatin.

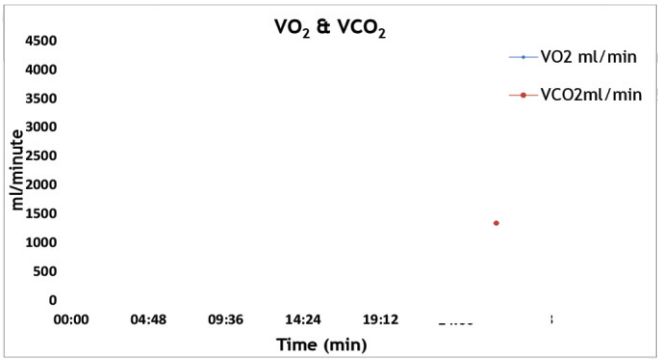

Figure 1: Breath by breath oxygen consumption and carbon dioxide production.

Show oxygen consumption (VO2) and carbon dioxide production (VCO2) from one of the participant during exercise. The initial 3 minutes are the resting period and the maximum effort was noticed at 22 minutes. The dotted line on the horizontal axis shows the maximum effort period during which the plateau in oxygen consumption can be seen. The blood was centrifuged at 1000 RPM for 15 minutes for endostatin and VEGF and at 3000 RPM for 15 minutes for lipid profiles and insulin. Plasma was separated into 3 aliquots each for endostatin, VEGF and lipid profile into 1ml Eppendorf tube using disposable plastic pipettes (Wilford Ind. Nottingham, UK). Samples were analysed for endostatin and VEGF concentrations using QuantikinR ELISA kit of the R&D systems, while Insulin was measured using ELISA kit (Mercodia, Uppsala Sweden). Plasma glucose, total and high density lipoprotein, triglyceride and non- esterified fatty acid (NEFA) were determined using commercially available enzymatic kits. Friedewald equation was used for the determination of low density lipoprotein (LDL), as follow

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[10]; LDL mmol l-1 = (Total cholesterol – HDL cholesterol) – (TG /2.2) Insulin resistance was determined using the QUICKI equation as follow; QUICKI = 1/ (log G0 + logI0). Where G0 is the fasting blood glucose concentration in mg/dl, I0 is the fasting insulin concentration in Mu/l. SPSS version 17.0 and Minitab version 16.0 were used for the statistical analyses. The normalities of all variables were determined and where necessary log transformations were carried out. Summary statistics were carried out for data and presented as mean ± SD. ANOVA with repeated measures was used for checking the difference between the mean in pre and post exercise blood samples. Correlations between endostatin, VEGF and other variables were determined using person correlation. Box plot were produced to graphically present the data, where necessary.

RESULTS

Anthropometric data and are physical characteristics of the participants shown in the Table 1 below.

S. no	Age (Yrs.)	Ht. (m)	Wt. (kg)	BMI (kg/m2)	SBP (mmhg)	DBP (mmhg)	WC (cm)	HC (cm)	W:H ratio
1	34	1.68	75.1	26.6	112	76	79	93	0.85
2	25	1.85	69.9	20.4	116	76	80	99	0.81
3	36	1.61	61.3	23.6	123	76	75	79	0.95
4	27	1.82	72.2	21.8	123	82	88	99	0.89
5	30	1.91	70.1	19.2	118	81	74	95	0.78
6	34	1.71	67.2	22.9	130	80	83	99	0.84
7	22	1.75	69.7	22.8	118	62	81	96	0.84
8	40	1.80	88.9	27.4	126	76	85	94	0.90
Mean ±SD	31± 6.1	1.77 ± 0.1	71.8± 7.9	23.1 ± 2.8	121 ± 6	76 ± 6	81 ± 5	94 ± 7	0.86 ±0.05

Table 1: Anthropometric and physical Characteristics of the participants

All the volunteers performed exercise without any complications. The mean duration for the test was 17.04 ± 2.6 minutes (ranging 12 to 19 minutes) during which the participants covered a mean distance of 2.1 ± 0.34 Km. All the participants run at fixed speed of 8 km/hr with a mean maximum gradient of 11 ± 2%. The mean maximum heart rate achieved during the test was 191 ± 10 bpm which increased by 167% from the mean basal heart rate of 72 bpm ($p < 0.001$). A mean increase of 38 ml/kg/min in oxygen consumption (VO2) was observed with the maximum oxygen consumption (VO2max) of 42 ml/kg/min achieved during the test ($P < 0.001$). Mean lactate concentration post exercise was 7.4 mmol (ranging 5.4 to 9.8 mmol). The individual values and mean ± standard deviations of the parameters of exercise are given in Table below 2.

S. no	BHR	Max HR	Duration	distance	Max Grad	BVO2	Vo_2 Max	RER	RR
1	68	180	12.04	1.45	7.5	3.3	33	1.20	62
2	71	194	19.25	2.40	12.5	4.3	45	1.44	48
3	68	184	18.04	2.20	10.0	4.8	44	1.29	39
4	70	210	18.16	2.25	12.5	4.3	39	1.59	49
5	82	184	19.10	2.38	12.5	3.9	45	1.17	35
6	82	194	15.07	1.84	10.0	4.8	39	1.23	48
7	76	196	19.28	2.43	12.5	5.4	47	1.34	47
8	63	184	15.44	1.93	10.0	4.0	44	1.30	41
Mean ±SD	72 ± 9	191 ± 10	17.04 ± 2.6	2.1± 0.34	11± 1.9	4.3± 0.6	42± 5	1.3± 0.6	46 ± 8

Table 2: Different parameters of exercise at base levels and during exercise

The individual values for components of exercise and mean ± standard deviation are shown. These indicate a maximal effort by all participants according to ACSM guidelines. BHR; Basal heart rate (beats per minute), Max HR; Maximum heart rate, Max Grad; Maximum gradient (%), BVO2; Resting oxygen consumption (ml/kg/min), VO2Max; Maximum oxygen consumption (ml/kg/min), RER; Respiratory exchange ratio, RR; Respiratory rate (breaths per minutes). Mean concentrations of endostatin in plasma before and after exercise are shown in figure 2. It is clear, that single bout of short period of high intensity exercise increased the mean endostatin concentration as confirmed by ANOVA with Bonferroni corrections ($P < 0.001$). The mean values were: 126 ± 16, 139 ± 15, 132 ± 12, 129 ± 12, 120± 23 and 107 ± 15 ng/ml respectively, at 10 minutes, 30 minutes, 1 hour, 2 hours, 4 hours and 24 hours after the exercise. These changes correspond to increases of 21% ($P = 0.003$), 34% ($P < 0.001$), 27% ($P < 0.001$), 24% ($P = 0.001$), 15% ($P = 0.07$), and 3% ($P = 0.883$) compared to resting endostatin concentration. The changes at points 1-4 i.e. up to 2 hours post exercise were statistically significant. The highest increase was observed at 30-minute interval after the exercise as shown in Figure 2.

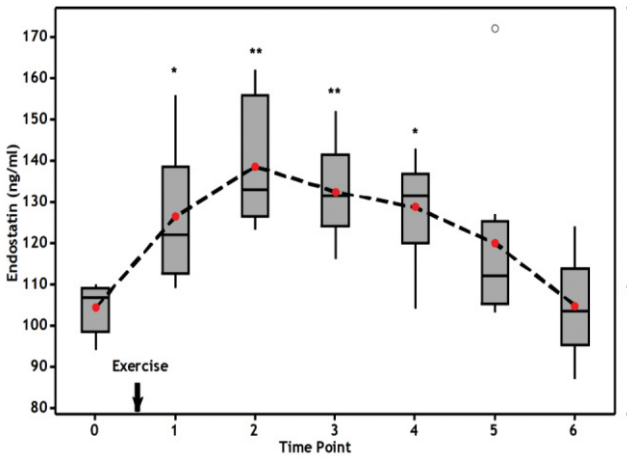

Figure 2: Endostatin concentration before and different intervals after maximal exercise

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Endostatin concentration before and different intervals after exercise (0 = before exercise, 1= 10 minutes, 2 = 30 minutes, 3 = 1 hour, 4 = 2 hours, 5 = 4 hours and 6 = 24 hours after exercise). Significant changes in mean endostatin concentrations were observed after exercise at 10 minutes, 30 minutes, 1 hour and 2 hour intervals. (* = P value <0.05 between basal and time point, ** = P value <0.001 between basal and time point). Clear circle represent outlier. The effect of exercise on VEGF concentration was also investigated. The mean VEGF concentrations were: 102 ± 46, 115 ± 35, 109 ± 40, 113 ± 38, 108 ± 53 and 99 ± 23 pg/ml at 10 minutes, 30 minutes, 1hour, 2 hours, 4 hours and 24 hours respectively, after the exercise. These changes are equal to 12% (P = 0.43), 26% (P = 0.04), 19% (P = 0.32), 24% (P = 0.067), 19% (P = 0.077) and 9% (P = 0.36), respectively. The increase in VEGF concentration was only significant at 30-minute interval (P = 0.04). The VEGF concentration remained higher than basal at all-time points up to 24 hours after exercise, as shown in Figure 3.

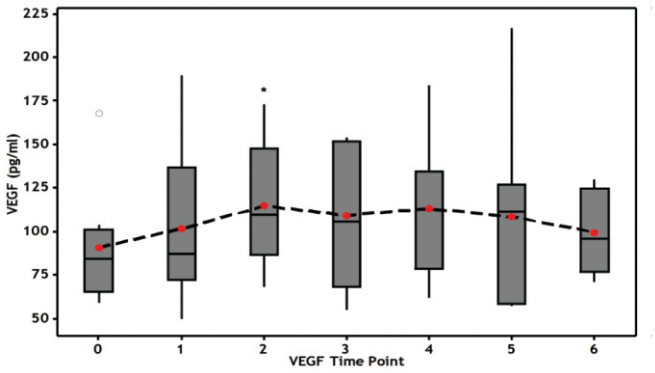

Figure 3: VEGF concentrations before and different intervals after maximal exercise test

Figure shows the VEGF concentrations before and at different time points after exercise (0 = before exercise, 1= 10 minutes, 2 = 30 minutes, 3 = 1 hour, 4 = 2 hours, 5 = 4 hours and 6 = 24 hours after exercise). The significant change in VEGF concentration was only observed at 30 minutes after exercise (P = 0.04). Clear circle shows outlier in basal VEGF. Correlations of changes in endostatin and VEGF with anthropometric lipid profile and exercise parameters. Finally, the changes in endostatin and VEGF concentrations were extensively correlated with anthropometric parameters (age, weight, height etch) lipid profile (Cholesterol, TG, LDL, HDL) and exercise parameters (maximal heart rate, RER, VO2 max etc.), however, no significant correlations of statistical importance were observed.

DISCUSSION

This study was aimed to determine the effect of maximal intensity exercise to volitional exhaustion (VO2max) on plasma concentration of endostatin and VEGF in young healthy participants. Additional aims include the correlation of basal endostatin and VEGF with anthropometric, physical and metabolic characteristics of the individuals. Moreover, the effects of changes in endostatin concentration on the respective changes in VEGF were also aimed. This study provided more conclusive results in terms of effect of exercise on endostatin concentration. The change in endostatin concentration was clear and more pronounced [1]. Moreover, this study also verified the results in the previous studies i.e. the basal endostatin concentration remained consistent and higher intensity of exercise significantly increase the endostatin concentration for up to 2 hours. Additionally, no correlations of statistical significance between anthropometric characteristics including body fat percentages and metabolic parameters including fasting lipid profile, fasting blood glucose and insulin with endostatin and VEGF were observed. Exercise also influenced VEGF concentration transiently and only at 30-minute interval increase in VEGF was statistically significant. The participants showed the increase in VEGF concentration at different time points after exercise. Due to this variation in person to person response after exercise, quantification of VEGF is difficult. However, it is worth noting that even those participants who showed an immediate decrease in VEGF after exercise, later on exhibited a concentration higher than basal. High intensity exercise showed significant increase in endostatin. Although the endostatin concentration after exercise in plasma was higher than basal, up to 4 hours but significantly high concentrations were observed up to 2 hours. The results in this study confirm the previous results, when the volunteers exercised at 70% and 80% predicted maximum heart rate. Moreover, these results are also consistent with previous published studies carried out by many researchers [2;11; 12; 13; 14]. It seems that short bouts of relatively high intensity exercise increase the endostatin concentration transiently for duration up to 2 hours. The extent of change in endostatin concentration was, however, different and can be attributed to the difference in mode, intensity and physical characteristics of the participants. Gu and his colleagues has reported a significant increase up to 6 hours after exercise [2]. Physical fitness seems to affect the degree of increase in endostatin concentration after exercising [13]. This also implies that many other reasons, such as easy fatigability, presences of co-morbid conditions and age of the participants could cause the difference in the extent of changes. This could be true as one study reported increase in endostatin concentration only in healthy and young individuals and not in old age individuals [14]. However, our results can be compared with study done by Suhr, who also

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found significant increase lasting for two hours after exercise [11]. The effects of long term physical activity on the basal endostatin concentration are contradictory. Sponder and his colleagues reported significantly high basal endostatin concentration in athlete males and females compared to their controls. It was assumed, that high basal endostatin concentration is due to the regular physical training of the athletes [13]. In contrast, decrease in basal endostatin concentration after 6 months of regular physical training in 50 – 60 years old individuals [15], as well as in long and short track elite runners have been reported [16]. The mechanism behind these differences is not clear and needs further studies. The other aim of the study was to correlate the basal endostatin concentration with anthropometric and metabolic parameters of the participants. Good metabolic profile indicates healthy endothelial status and well-being of the individual. It was hypothesised, that they might affect basal endostatin concentration, as well as the change in it after exercise. No correlations of significant importance were observed either with the basal endostatin concentration or the change in it at any time point after the exercise. To the author's knowledge this is a complete novel finding. It is interesting due to the fact that deranged lipid profile, glucose intolerance or insulin insufficiency play important roles in early endothelial events leading to atherosclerosis. Despite endostatin being present in blood and basement membrane, did not show any interactions with these parameters. However, sample size is small to appreciate any such associations and study with a bigger sample size will be required to draw solid conclusion. Finally, no correlation of statistical significance was observed between endostatin concentration and anthropometric measurements. The exercise intensity in this series of experiments was higher than used previously. The duration of near maximal exercise was shorter and the use of breath by breath measurement allowed the gas exchange to be monitored in real time. Different features of exercise showed no statistically significant correlations with the changes in endostatin concentrations, at different time points after the exercise. These results are different from Gu who reported a strong linear correlation between change in exercise and peak oxygen consumption [2]. In author's opinion, the results in our study are more reliable because the values for the peak oxygen consumption, in Gu's study, were estimated by calculation rather than measured. Moreover, Gu's findings could not be confirmed in later studies [12; 13]. It was observed consistently that moderate to high intensity exercise increase the endostatin concentration without direct correlations with any exercise feature. From this it can be assumed, that exercise does change the endostatin concentration by altering different mechanisms indirectly including increasing expression of enzymes involved in endostatin release [16]. Mean basal VEGF concentration of 91 + 34 pg/ml in this study group is higher than that seen chapter 4, which was 75 + 36 pg/ml. It is clear from the broad confidence intervals, shown in figure 6-6, that there is substantial variation in basal VEGF concentrations. A wide range of basal concentrations, between 98 to 485 pg/ml, has been reported and this is attributed to the differences in genetic regulation and makeup of these individuals [17]. Such variations make it difficult to quantify the increase in VEGF after exercise. The Mean VEGF concentration increased initially after exercise until 30 minutes. After this time point, a pattern of increase and decrease can be observed, as shown in figure 6. It can also be seen that mean VEGF concentration was never found to be lower than basal during this experiment. These results confirm our earlier results that increase in mean VEGF concentration after exercise with no specific pattern. The literature about exercise as a regulator of VEGF is conflicting and limited. On one hand, increases in VEGF concentrations after exercise have been reported [18; 19; 20; 21]. The extent of increase in mean VEGF after exercise reported, varies from as low as 30% [19] to as high as 240% [20] and as acutely as 30-minute post exercise to as long as 5 days' post exercise. These changes may reflect different exercise modalities. On the other hand, a decrease in mean VEGF concentration after acute exercise has also been reported by [22; 2]. Again the modes of exercise in the above studies were completely different. In Gustafsson study, the participants performed one knee extension for 7 sessions of 45 minutes over a period of 10 days. Timings of the blood sample collection are crucial, as the first sample was taken before 1st exercise session and the last sample was taken 24 hours after the 7th exercise session. In our study it was observed that exercise affect VEGF concentration transiently. The VEGF concentration tends to drop back towards normal at about 1 hour after exercise. So it is possible, that VEGF concentration 24 hours after exercise may be more or less the same as basal VEGF concentration. Similar results to Gustafsson have also been reported in another study, where long term endurance exercise programme for 6 months, showed no alteration in VEGF concentration. Interestingly, post intervention plasma samples were taken, on next day after the last exercise session [15]. However, the study done by Gu, has shown the decrease in mean VEGF concentration significantly up to 6 hours, a finding which could not be confirmed by published literature or this study. There is convincing evidence in the literature, that acute exercise bouts increase VEGF concentration in skeletal muscles and its subsequent release to venous circulation [19; 18; 23] but not to arterial

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circulation [18]. It is plausible that after release from the stretched muscles during exercise into the venous system, the VEGF is taken by other tissues, not directly involved in the exercise. However, the possibility of increase in VEGF from cells like platelets and myocytes cannot be overruled, as electrical stimulations of cardiac myocytes has been shown to increase VEGF release [24]. Finally, correlation between endostatin and VEGF concentrations before and at all-time points after exercise were carried out. Concurrently the correlations between the changes in both mediators at each time point were also checked, as shown in table 5. No correlations of statistical importance at any time point were observed. It is established from the literature that endostatin antagonises the signalling mechanisms of VEGF [25; 26]. However, it is clear from the results, that increase in endostatin concentration after high intensity exercise has no negative effect on the plasma VEGF concentration, a finding which is in dispute with the results published by Gu and his co-workers [2]. An increase in VEGF concentration after exercise seems more logical as exercise increase the expression of mRNA in skeletal muscle [18], which enhances the production of VEGF in skeletal muscles and favours the release of VEGF from tissue to circulation [21].

CONCLUSIONS

In conclusion, the high intensity exercise increases the mean endostatin more prominently and for a longer duration than VEGF without any important interaction between the two mediators.

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