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RESEARCH ARTICLE

ANGIOGENIC REGULATORS DURING ALPINE SKIING TRAINING

Metin Polat[1], Inayet Gunturk[2], Duran Demiryurek[3]

[1] Sivas Cumhuriyet University, Faculty of Sport Sciences, Sivas, Turkey
[2] Nigde Omer Halisdemir University, Faculty of Health Sciences, Department of Midwifery, Nigde, Turkey
[3] Erciyes University, Institute of Health Sciences, Kayseri, Turkey

ORCID: M.P. 0000-0001-7299-0531; I.G. 0000-0002-8299-1359; D.D. 0000-0003-3545-1082

Corresponding author: Metin Polat, **E-mail:** polat.metin@gmail.com
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ABSTRACT

Purpose: The present study evaluates angiogenesis response through the determination of acute changes in hypoxia inducible factor 1 alpha, vascular endothelial growth factor, erythropoietin and endostatin levels measured after a single-session slalom and giant slalom trainings.
Material and Methods: A total of 20 volunteer male athletes average age of 22.16 ± 4.86 years with no health problems, and with international alpine skiing competition experience were included in the study. At the outset, the height, body weight and VO_2max values of the volunteers was measured, and a giant slalom training lasting 2.5 hours was performed after a week on a giant slalom course. The volunteers were then asked not to exercise for a week, and slalom training was performed lasting 2.5 hours on a slalom course. The endostatin, erythropoietin, hypoxia inducible factor 1 alpha, and vascular endothelial growth factor levels of the volunteers were examined from 5 ml venous blood samples drawn into biochemistry tubes 20 minutes before and as soon as trainings over both the giant slalom and slalom trainings.
Results: A significant increase was determined in the hypoxia inducible factor 1 alpha, vascular endothelial growth factor, erythropoietin and endostatin levels after both the giant slalom and slalom trainings ($p < 0.05$).
Conclusion: These increases observed in the angiogenesis markers suggests that a single-session giant slalom and slalom trainings induces angiogenesis responses.

Keywords: Capillarization, Alpine Skiing, Performance, Ischemia

INTRODUCTION

Alpine Skiing competitions comprise two speed and two technical categories, differentiated by the turning radius, speed and course length. The speed category includes downhill and super giant slalom (super G) (1), while the technique category includes slalom (SL) and giant slalom (GS) (2). Although a high level of anaerobic power is required, aerobic power is also substantially important in alpine skiing (3). In addition, the use of explosive power has also been reported during skiing activities (4), and eccentric movements have been reported to be widely used during alpine skiing competitions (5). Significant intramuscular pressure increases have been reported during the turning phase, resulting in a more anaerobic load (2). All such activities result in metabolic processes, including muscle ischemia, hypoxia and changes in ion concentrations in the body (6). In addition, the high degree of knee flexion and the continuous muscle contractions, typically experienced during skiing competitions contribute to a decrease in oxygen delivery to the active muscles. In conclusion, the blood perfusion of active muscle is decreased due to a greater decrease in the blood volume, increased lactate accumulation and an unproportionally high heartbeat (7). Hereby, muscle ischemia and a greater

dependency on the anaerobic metabolism is experienced (2).

Capillarization resulting from adaptation due to training can help the athlete cope with the metabolic and mechanical conditions that cause fatigue resulting from eccentric contractions, while providing an increase in the amount of blood delivered to the active muscles during exercise and a positive effect on performance (8). Muscle capillarization is important for the delivery of nutrients and oxygen to the exercise muscles. A higher capillary density may increase the muscle-blood exchange surface and decrease the oxygen diffusion distance and increase the erythrocyte mean transit time (9).

Hypoxic conditions trigger a series of physiological and pathophysiological responses and adaptations such as vasculogenesis, angiogenesis and erythropoiesis to protect the organism (10). Angiogenesis refers to the growth of new capillary vessels from the previously present vessels (11) and is stimulated by the metabolic cycle and hypoxia (12) as well as by the mechanical factors such as shear stress and the passive stretching of muscle fiber (13,14). High-intensity training has been considered a powerful stimulus for angiogenesis, since metabolic demand, blood deoxygenation and blood flow are increased together with the increased workload (15). High-intensity interval training and low intensity endurance training have been shown to exert equal effects on angiogenesis in those who are untrained (16).

Regulating proteins such as hypoxia inducible factor 1 alpha (HIF-1α), vascular endothelial growth factor (VEGF), erythropoietin (EPO) and endostatin are known to play a key role in the proangiogenetic process. HIF-1α, VEGF and EPO support angiogenesis, while endostatin has a tendency to halt the angiogenetic process (17). Previous studies have investigated the chronic angiogenesis response to training, while studies of acute angiogenesis response are limited. To our best of our knowledge, there has been no study to date on angiogenesis as a response to alpine skiing competition or training.

The present study, therefore, investigates the acute changes in HIF-1α, VEGF, EPO and endostatin levels in post-training for both slalom and giant slalom, which are included in the alpine skiing technical category, and also to evaluate the angiogenesis response that is considered to have a positive effect on skiing performance.

MATERIAL AND METHODS

Volunteer groups and ethical approval

Included in the study were 20 volunteers male athletes average age of 22.16 ± 4.86 years with no health problems, and with international alpine skiing competition experience. Approval for the study was obtained from the Clinical Investigations Ethics Board of Erciyes University (Decision Date: 20.01.2017, Number: 2017/32) prior to the start of the study. All testing and training procedures were fully explained, and written informed consent was obtained for each participant. The study was supported by the Erciyes University Scientific Research Projects Coordination Unit, project number TYL-2017-7493.

Experimental Design

At the outset of the study the height, body weight and VO_2max values of the volunteers were measured. A giant slalom training session lasting 2.5 hours was completed a week later on a giant slalom course homologated by the International Ski Federation (FIS). The volunteers were then asked not to exercise for a week, and a further slalom training session was performed lasting 2.5 hours on a slalom course that was also homologated by the FIS. The study participants all provided a 5 ml venous blood sample 20 minutes before and as soon as trainings over both the giant slalom and slalom training sessions, drawn into biochemistry tubes, and the obtained samples were sent immediately to the Department of Medical Biochemistry of the Faculty of Medicine of the Erciyes University.

Measurements

The height of the volunteers was measured while standing against the wall using a height scale with 0.01 cm sensitivity, and the body weight was measured using an electronic scale with 0.1 kg sensitivity. An exercise protocol with incremental running test was applied on a motorized treadmill (h/p/Cosmos Quasar med, Nussdorf-Traunstein, Germany) to determine the VO_2max of the athletes. Throughout the VO_2max test, breath-by-breath gas measurements were taken using an indirect calorimetric system (Quark PFT Ergo, Cosmed Srl, Rome, Italy) which was calibrated before the test to the manufacturer's instructions. The test started with running at a 0% incline at a speed of 7 km/hour, and the speed was increased by 1 km/hour every minute. The athletes were asked to continue the exercise until they were exhausted. The criteria for having reached

the VO_2max for the athletes were accepted as reaching the maximal heart rate (220-age), a respiratory exchange ratio (RER) greater than 1.10 and a plateauing of oxygen intake despite increased exercise intensity (18). The highest 15 second oxygen intake value at the time when at least these two of the criteria were met was accepted as the VO_2max value (ml/kg/min).

Blood Analyses

The blood samples sent to the biochemistry laboratory were centrifuged at +4°C at 1500 g for 15 minutes, and the separated serum samples were stored at -80 °C in small pieces until the study date. The levels of HIF-1α (Cusabio Technology LLC, Cat No: CSB-E12112h), VEGF (ThermoFisher Scientific, Cat No: KHG0111), EPO (ThermoFisher Scientific, Cat No: BMS2035-2) and endostatin (Cusabio Technology LLC, Cat No: CSB-E07973h) in the serum samples were determined using the ELISA technique.

Training Applications for Giant Slalom and Slalom

The giant slalom training course was prepared by the national Turkish alpine skiing team coach using a giant slalom course that was homologated by the FIS. A total of 36 giant slalom gates, 28 meters apart were laid out on the course, which had a 300-meter altitude difference. The volunteers trained for 2.5 hours on the prepared giant slalom course.

The slalom training course was also prepared by the national Turkish alpine skiing team coach on a slalom course homologated by the FIS. A total of 42 slalom gates, 10 meters apart were laid out on the course, which had a 120-meter altitude difference. The volunteers trained for 2.5 hours on the prepared slalom course.

Table 1. Descriptive Information of the Volunteers

	n	$\overline{X}$ ±SD	Min.	Max.
Age (years)	20	22.16±4.86	18	27
Height (cm)		178.07±3.42	169	182
Body weight (kg)		80.69±8.46	67	98
VO_2max ($ml/kg^{1}/min^{-1}$)		50.71±2.87	45.41	54.22

Statistical Analysis

The data obtained in the study were analyzed using IBM SPSS Statistics (Version 25.0. Armonk, NY: IBM Corp.). After conducting descriptive analyses, the data were evaluated to determine the normality of distribution using a Shapiro-Wilk test, skewness and kurtosis levels and histogram and Q-Q and P-P graphics and were found to be non-normally distributed. A Wilcoxon Signed Ranks Test was used to compare the blood analyses before and after the training sessions. The level of significance was set at $p < 0.05$.

RESULTS

The age, height, body weight and VO_2max levels of the volunteers participating in the study are presented in Table 1.

The pre- and post-giant slalom training Endostatin, EPO, HIF-1α and VEGF levels are presented in Table 2, in which the Endostatin, EPO, HIF-1α and VEGF levels can be seen to be significantly increased following giant slalom training ($p<0.05$).

The pre- and post-slalom training Endostatin, EPO, HIF-1α , and VEGF levels are presented in Table 3, where Endostatin, EPO, HIF-1α and VEGF levels can be seen to be significantly increased after slalom training ($p<0.05$).

Table 2. Comparison of the Pre-and Post- Giant Slalom Training Values

		n	Median (25-75%)	z	p
Endostatin (ng/mL)	Pre-training	20	15.33 (9.92-21.25)	-2.156	0.031*
	Post-training		17.49 (10.63-25.40)		
EPO (mIU/mL)	Pre-training		6.07 (5.40-6.85)	-3.288	0.001*
	Post-training		8.95 (7.13-10.25)		
HIF-1α (pg/mL)	Pre-training		292.39 (203.57-372.55)	-3.724	< 0.001*
	Post-training		331.84 (251.11-415.24)		
VEGF (pg/mL)	Pre-training		125.09 (94.23-155.32)	-2.373	0.018*
	Post-training		130.39 (96.15-172.20)		

*$p < 0.05$

DISCUSSION

HIF-1α has been reported to be a transcription factor mediating adaptive responses to low cellular oxygen levels (19) and has also been reported to transcriptionally activate hundreds of genes associated with angiogenesis in cancer, exercise and ischemia, energy metabolism, nutrient transport and cell migration (20). Furthermore, HIF-1α gene transfer has been demonstrated to increase muscle perfusion and collateral vessel formation in the ischemic rabbit hind limbs (21). Decreased arterial O2 saturation and PiO2 of exercise origin has been reported to activate HIF-1, and HIF-1α to independently stimulate angiogenesis and thus facilitate muscle oxygen extraction (22).

The increased O2 consumption during exercise leads to a decrease in PiO2 levels, while the addition of environmental hypoxia to exercise further decreases the already lowered PiO2 (22). Exercise in hypoxia or normoxia has been reported to increase muscle HIF-1α mRNA (23), protein content, and also the degree of nucleus translocation of HIF-1α and DNA binding activity (24). These observations, independent of the arterial O2 saturation, suggest that any decrease in PiO2 of exercise origin is likely sufficient to completely activate HIF-1α (22).

The increased intramuscular pressure resulting from the high intensity contractions during alpine skiing may limit blood flow to the working skeletal muscle and may even stop it altogether (25). This condition results in decreased tissue oxygenation and the muscle becomes ischemic due to the decrease in oxygen supplied to the functioning muscles. A decrease in oxygen saturation in the quadriceps muscle has been reported in young well-trained skiers during GS and SL (2).

HIF-1α levels were found to be significantly increased after both slalom and giant slalom training in the present study ($p < 0.05$), suggesting that the level of hypoxemia to which skeletal muscles are exposed during a single unit alpine skiing training session increases HIF-1α production and triggers angiogenesis.

HIF-1 activation has been reported to be important in VEGF release in skeletal muscle angiogenesis upon exercise (26), and VEGF release has also been reported to occur through HIF-1α transcription (19). Additionally, VEGF has been reported to be of vital importance for training originated angiogenesis (27).

VEGF has been identified as a key regulator of physiological angiogenesis (11,28), and has been shown to increase during exercise (29). An inadequate level of O2 in skeletal muscle tissue has been shown during exercise, and this has been demonstrated to cause an increase in VEGF mRNA and protein levels in skeletal muscle tissue (30,31). Such an increase in VEGF mRNA and protein levels, it has been suggested, may cause new capillary vessels along the chemical gradient of VEGF (32). On the other hand, increased physical exercise has been reported to increase total skeletal muscle blood flow, while emergent mechanical stress has been reported to play a very important role in angiogenesis through increased VEGF production (33).

Nevertheless, interval training has been suggested to be as equally effective as endurance training in increasing capillarization (16). Repeated exercise is reported to have the potential to complicate muscle oxygen homeostasis, since a single exercise session is associated with muscle hypoxia (34). Increased VEGF levels have been recorded after a single unit of exercise (35). It has also been reported that higher intensity exercise produces a higher venous plasma VEGF level than lower intensity exercise (36).

Loading intensity may be high during alpine skiing training. Heartrate, VO2 and blood lactate levels have been recorded at 201.7 + 2 bpm, 38.50 + 2.34 ml/kg/min, and 10.13 + 0.43 mmol/L, respectively

Table 3. Comparison of the Pre-and Post- Slalom Training Values

		n	Median (25-75%)	z	p
Endostatin (ng/mL)	Pre-training	20	24.71 (15.20-37.07)	-3.527	< 0.001*
	Post-training		33.35 (26.15-44.46)		
EPO (mIU/mL)	Pre-training		6.97 (5.40-8.62)	-3.516	< 0.001*
	Post-training		10.47 (7.63-12.50)		
HIF-1α (pg/mL)	Pre-training		328.18 (213.92-399.96)	-2.722	0.006*
	Post-training		365.74 (328.91-447.85)		
VEGF (pg/mL)	Pre-training		118.01 (94.69-172.80)	-3.154	0.002*
	Post-training		137.40 (99.51-196.32)		

*$p < 0.05$

during a single giant slalom running (37). In addition, alpine skiing training sessions include consecutive interval loadings. Athletes reach the start point using the mechanical plant after completing the training run on a course, and approximately 15 minutes pass between the two loading periods.

The present study also revealed significantly increased VEGF levels after both GS and SL, concurring with the results of the studies mentioned above ($p < 0.05$). The obtained data suggest that a single unit alpine skiing training increases VEGF release and stimulates angiogenesis.

One of genes that HIF-1α regulates its transcriptions to produce cellular adaptation against low PO2 is EPO (38). It is well known that the primary function of EPO is to stimulate erythropoiesis and to increase the oxygen transfer to working muscles during exercise (39). Furthermore, it has been suggested that EPO leads to a decrease in lactate production during submaximal exercise (40), affecting also local vascular and skeletal muscle properties by stimulating localized angiogenesis and slow oxidative fibril-type changes, respectively (41,42).

There is evidence that EPO may stimulate an increase in mitochondrial activity, and thus increase the oxidative metabolic properties of human muscle fibers (43). EPO may possibly stimulate, whether directly or indirectly, an increase in muscle oxidative capacity, although this has yet to be confirmed. Erythropoietin also has been suggested to exert angiogenic effects on growing or repairing tissues (41). Taking these findings in consideration together, it can be suggested that EPO has an effect similar to endurance training, which is known to induce muscle mitochondrial biogenesis and growth, and to increase oxidative enzymatic activity, angiogenesis induction and the transition to muscle fiber type (39).

After the GS and SL trainings EPO levels were found to be significantly increased in the present study ($p < 0.05$). In the light of the above information, the elevated EPO levels after skiing training suggest that EPO induces the physiological adaptations required by both angiogenesis and alpine skiing.

Endostatin has been shown to inhibit angiogenesis by preventing the proliferation and migration of endothelial cells (10). Endostatin prevents the progression of atherosclerosis (44), and the primary growth of tumors and metastasis (45) by inhibiting angiogenesis. A significant increase was observed in endostatin levels after both giant slalom and slalom training in the present study ($p<0.05$), and this increase is thought to be an anti-angiogenic effect against the angiogenic effect originating from the increased HIF-1α, VEGF and EPO levels.

That said, several authors have reported that endostatin may function as an angiogenic modulator rather than an anti-angiogenic agent (46,47). Schmidt et al. (46,48) determined both the proangiogenic and anti-angiogenic dose-dependent effects of endostatin, although further studies are required to definitively determine the angiogenic modulator effect of endostatin.

In parallel to the findings of the present study, Gu et al. (49) reported an increase in plasma endostatin levels in circulation after a treadmill exercise test due to exercise proportionate to the intensity of the exercise. Suhr et al. (10) reported a significant increase in the plasma concentration of endostatin following physical exercise, independent of such exogenously induced stimuli as normobaric hypoxia and mechanical loading. Sponder et al. (50), in their study of healthy young male and female volunteers, reported a significant increase in serum endostatin levels, by 23.6% and 26.92% in females and males, respectively during a maximal cycling exercise test.

In addition, endostatin has been reported to lead to vasorelaxation by increasing in vitro cytosolic nitric oxide (NO) production (47), and it is therefore considered to be one of the mechanisms regulating blood flow during high intensity physical activity (10). It has been stated that vasorelaxation provides more O2 and metabolites to the tissue, which is an advantage during exercise (50). The increase in endostatin levels reported in the present study suggests that endostatin release may be induced due to the increased requirement for vasodilation in the active tissues during exercise, in addition to the anti-angiogenic effects of endostatin.

CONCLUSION

In conclusion, a significant increase was observed in HIF-1α, VEGF, EPO and Endostatin levels after a single-session slalom and giant slalom trainings in the present study. This increase observed in angiogenesis markers supports that a single unit alpine skiing training induces the production of angiogenesis. An increase in the amount of capillarization in response to alpine skiing training will result in an increased capacity of blood flow in the active muscles. Thus, it will be possible to contribute to optimal performance by providing more oxygen and substrates to the active muscles during loading

and more efficient removal of accumulated metabolic wastes.

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