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Original

Efectos agudos del ejercicio de resistencia y aeróbico sobre los niveles de HIF-1α, eritropoyetina y VEGF en mujeres con un estilo de vida sedentario: un ensayo controlado aleatorizado

Acute Effects of Resistance and Aerobic Exercise on HIF-1α Erythropoietin, and VEGF Levels in Women with a Sedentary Lifestyle: A Randomized Controlled Trial

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EFECTOS AGUDOS DEL EJERCICIO DE RESISTENCIA Y AERÓBICO SOBRE LOS NIVELES DE HIF-1A, ERITROPOYETINA Y VEGF EN MUJERES CON UN ESTILO DE VIDA SEDENTARIO: UN ENSAYO CONTROLADO ALEATORIZADO

RESUMEN

Objetivo. La prevalencia mundial de las enfermedades cardiovasculares constituye un problema significativo que requiere medidas preventivas inmediatas. Uno de los factores desencadenantes de estas enfermedades es el sedentarismo. El factor inducible por hipoxia 1 alfa (HIF-1α) desempeña un papel fundamental en la adaptación celular al estrés hipóxico y regula dianas clave como la eritropoyetina (EPO) y el factor de crecimiento endotelial vascular (VEGF). Tanto la EPO como el VEGF contribuyen a la eritropoyesis y la angiogénesis, adaptaciones fisiológicas esenciales al ejercicio. Investigaciones previas confirman que el entrenamiento físico mejora estas vías, pero las respuestas moleculares agudas tras las distintas modalidades de ejercicio aún no se comprenden del todo, especialmente en mujeres menos activas. Por lo tanto, el objetivo de este estudio fue determinar los efectos del ejercicio de resistencia y aeróbico sobre los niveles de HIF-1α, EPO y VEGF en mujeres con un estilo de vida sedentario. Material y métodos. En este estudio experimental se utilizaron grupos experimentales y de control antes y después del ejercicio. Las participantes fueron seleccionadas mediante muestreo aleatorio y, tras su selección, se formaron tres grupos: el grupo de tratamiento (GT), n=10, recibió una intervención de ejercicio de resistencia; el grupo de tratamiento (GT), n=10, recibió una intervención de ejercicio aeróbico; y el grupo de control (GC), n=10, permaneció sentado sin realizar ninguna actividad. Este estudio incluyó a treinta mujeres sanas con un estilo de vida sedentario, con edades comprendidas entre los 18 y los 26 años. La recolección de datos se llevó a cabo durante dos días, comenzando con la obtención de información sobre las características de las participantes. Posteriormente, antes del ejercicio, se les extrajo sangre como dato previo a la prueba. A continuación, se les pidió a las participantes que realizaran un calentamiento. Después, realizaron ejercicios físicos según su grupo, incluyendo ejercicios de resistencia y aeróbicos. Tras la intervención, se tomaron muestras de sangre como dato posterior a la prueba. Resultados. Los resultados mostraron que el entrenamiento de resistencia incrementó significativamente los niveles de HIF-1α (IC 95%; p=0,000; Tamaño del efecto: 3,13; p<0,05) y el entrenamiento aeróbico también incrementó significativamente los niveles de HIF-1α (IC 95%; p=0,005; Tamaño del efecto: 0,94; p<0,05) en comparación con el grupo control. Sin embargo, los niveles de HIF-1α fueron significativamente mayores en el grupo de entrenamiento de resistencia que en el grupo de entrenamiento aeróbico (IC 95%; p=0,002; Tamaño del efecto: 1,25; p<0,05). En cuanto a los niveles de EPO, el entrenamiento de resistencia incrementó significativamente los niveles de EPO (IC 95%; p=0,000; Tamaño del efecto: 1,52; p<0,05), al igual que el entrenamiento aeróbico (IC 95%; p=0,005; Tamaño del efecto: 3,15; p<0,05) en comparación con el grupo control. No se observaron diferencias significativas entre el entrenamiento de resistencia y el entrenamiento aeróbico en el aumento de los niveles de EPO (p > 0,05). El entrenamiento aeróbico incrementó significativamente los niveles de VEGF (IC del 95%; p = 0,040; Tamaño del efecto: 1,13) (p < 0,05) en comparación con el grupo control. Sin embargo, no se encontraron diferencias significativas entre el grupo de entrenamiento de resistencia y el de entrenamiento aeróbico, ni entre el grupo de entrenamiento de resistencia y el grupo control (p > 0,05). Conclusiones: El ejercicio físico aumenta los niveles de HIF-1α, EPO y VEGF. Por lo tanto, puede ser una alternativa para incrementar la angiogénesis, especialmente en mujeres sedentarias, lo que podría tener un impacto en la prevención de enfermedades cardiovasculares.

Palabras clave: Buena salud; Bienestar; Ejercicio físico; HIF-1α; EPO; VEGF.

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

ACUTE EFFECTS OF RESISTANCE AND AEROBIC EXERCISE ON HIF-1A ERYTHROPOIETIN, AND VEGF LEVELS IN WOMEN WITH A SEDENTARY LIFESTYLE: A RANDOMIZED CONTROLLED TRIAL

ABSTRACT

Purpose. The prevalence of cardiovascular disease worldwide is a significant problem requiring immediate preventive measures. One of the triggers for cardiovascular disease is a sedentary lifestyle. Hypoxia-inducible factor 1-alpha (HIF-1α) plays a central role in cellular adaptation to hypoxic stress and regulates key downstream targets such as erythropoietin (EPO) and vascular endothelial growth factor (VEGF). Both EPO and VEGF contribute to erythropoiesis and angiogenesis, essential physiological adaptations to exercise. Previous research confirms that exercise training is known to enhance these pathways, but the acute molecular responses after various exercise modalities remain poorly understood, particularly in less active women. Therefore, the aim of this study was to determine the effects of resistance and aerobic exercise on HIF-1α, EPO, and VEGF levels in women with a sedentary lifestyle. Material & Methods. Experimental and control groups before and after were used in this experimental study. People were selected through random sampling, and after they were selected, three groups were formed: the treatment group (RT) n=10 received resistance exercise intervention, the aerobic exercise intervention was given to the treatment group (AT) n=10, while the control group (CO) n=10 did not do any activity, just sitting. This study involved thirty healthy women with a sedentary lifestyle. Women aged 18 to 26 years participated as respondents in this study. Data collection took place over two days, starting with collecting information regarding the characteristics of the subjects. Then, before the exercise, the subjects had their blood drawn as pre- test data. After that, the participants were asked to warm up. Then, the subjects did physical exercises according to their groups. The exercises performed included resistance and aerobic exercises. After the exercise intervention, blood samples were taken as post-test data. Results. The results showed that resistance training was proven to significantly increase HIF-1α (CI 95%; p=0.000; Effect Size: 3.13) $p<0.05$ and aerobic training was proven to significantly increase HIF-1α levels (CI 95%; p = 0.005; Effect Size: 0.94) $p<0.05$ compared to the control group. However, the resistance training group was significantly higher than the aerobic group (CI 95%; p=0.002; Effect Size: 1.25) $p<0.05$. In EPO levels, resistance training significantly increased EPO levels (CI 95%; p=0.000; Effect Size: 1.52) $p<0.05$, aerobic training also significantly increased EPO levels (CI 95%; p=0.005; Effect Size: 3.15) $p<0.05$ compared to the control group. There was no difference between resistance training and aerobic training in increasing EPO levels $p>0.05$. Aerobic training significantly increased VEGF levels (95% CI; p=0.040; Effect Size: 1.13) $p<0.05$ compared to the control group. Meanwhile, there was no significant difference between the resistance training group and aerobic training or resistance training and the control group ($p>0.05$). Conclusions. Physical exercise increases levels of HIF-1α, EPO, and VEGF. Therefore, it can be an alternative exercise to increase angiogenesis, especially in sedentary women, which can have an impact on preventing cardiovascular disease.

Keywords: Good health; Wellbeing; Physical Exercise; HIF-1α; EPO; VEGF.

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

INTRODUCTION

According to earlier research, ischemic heart disease and stroke are the main causes of the global increase in cardiovascular disease mortality, which rose from 12.1 million in 1990 to 18.6 million in 2019 (Brodmann et al., 2020). During this time, dietary hazards, high LDL cholesterol, and high systolic blood pressure have all been found to be important cardiovascular risk factors (Chan et al., 2025). Globally, cardiovascular disease is a major cause of death and high medical expenses (Brodmann et al., 2020). Over the past 30 years, the overall number of deaths from cardiovascular disease has continued to rise despite numerous preventative measures and advances in treatment, which have been impacted by unfavorable health behaviors and environmental variables (Brodmann et al., 2020). Thus, it can be considered an epidemic of metabolic diseases worldwide (Chin et al., 2023). Asia is especially affected by the epidemic of cardiovascular disease, which accounted for 60% of the 18.6 million cardiovascular deaths that were reported worldwide in 2019. The predicted slowdown in global progress toward increasing life expectancy between 2016 and 2040, despite multinational and multifaceted cardiovascular prevention strategies, is primarily due to growing trends in metabolic risk factors such as high body mass index (BMI) and stagnant increases in cardiovascular disease (Sze et al., 2025). Sedentary lifestyles are the root cause of cardiovascular disease (Petersen et al., 2014).

Sedentary behavior is often defined as standing, sitting, or lying down with minimal energy expenditure, usually less than 1.5 metabolic equivalent units (MEUs) (Tremblay et al., 2017). Adults are sedentary for 50–60% of the day on average (Healy et al., 2011). Adults are sedentary for 50–60% of the day on average (Healy et al., 2011). Sedentary behavior rates continue to rise among schoolchildren in most countries worldwide, becoming a serious public health concern. Previous data shows that 81% of adolescents worldwide do not meet the World Health Organization's (WHO) minimum requirement of 60 minutes of moderate to vigorous physical activity per day. Consequently, rates of overweight and obesity have increased exponentially in recent years, leading to an increase in problems such as diabetes and hypertension. (Vázquez Moreno, V, Guzmán, 2025). Patients who sat for ten hours a day had a 34 percent higher risk of dying, according to their self-reported total sitting time (Chau et al., 2013). It will make cardiovascular disease more likely (Guo & Wang, 2025). Cardiovascular diseases include heart and blood vessel conditions such as coronary heart disease, cerebrovascular disease, rheumatic heart disease, and others. The primary risk factor for death is high blood pressure, or hypertension, which also increases the risk of cardiovascular disease (Guo & Wang, 2025). Additionally, the prevalence of hypertension is still rising worldwide (Forouzanfar et al., 2017). Furthermore, atherosclerosis is an important pathophysiological basis for cardiovascular disease. Subendothelial lipid deposition, which causes the development of atherosclerotic plaques, is its primary feature (Yan et al., 2025). Therefore, different approaches are required to stop the rising number of cardiovascular illnesses brought on by a sedentary lifestyle.

One important aspect of preventing cardiovascular disease is vascular enhancement. Particularly in the context of chronic ischemic disorders such as cardiovascular and cerebrovascular diseases, neurodegenerative disorders, hypertension, and osteoporosis, where increased vascularization is essential for restoring tissue function and slowing the progression of disease, angiogenesis plays a critical role in promoting wound healing, tissue repair, and improving regional blood flow (Jiang et al., 2025). By forming a network of new blood vessels, angiogenesis enhances blood circulation and guarantees that wounded tissues receive enough oxygen and vital nutrients. Angiogenesis necessitates the coordinated cooperation of several cellular elements and molecular cues (Jiang et al., 2025). Exercise is an alternative treatment that uses angiogenesis to prevent cardiovascular disease. The cornerstones of a healthy lifestyle and the prevention of cardiovascular disease are getting enough exercise and cutting back on idle time (Sallis et al., 2018). Promoting physical activity in people and populations has emerged as a key global public health priority as evidence of the benefits of physical activity in preserving general and cardiovascular health has grown over the past several decades (Mi et al., 2025).

A crucial component of the hypoxic response to exercise, the transcription factor HIF-1α regulates the expression of target genes linked to angiogenesis, erythropoiesis, energy consumption, and cell survival

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

(Soori et al., 2020). One important modulator of angiogenesis that encourages the formation of vascular endothelial cells is vascular endothelial growth factor (VEGF). One of the main causes of morbidity and mortality in clinical settings is the angiogenic response, which is characterized by increased VEGF expression, especially in ischemic tissues and organs. Increased vascular permeability and capillary development are facilitated by elevated VEGF levels, which also reduce ischemia damage and encourage vascular recovery (Karamysheva, 2008). In addition, erythropoietin is in charge of carrying out erythropoiesis and increasing hemoglobin mass, which increases the capacity to store oxygen (Ayubi et al., 2024). Thus, to promote angiogenesis, HIF-1α, EPO, and VEGF are intimately related. Exercise has been proven to increase VEGF, EPO, and HIF-1α (Yulfadinata et al., 2025; Ayubi et al., 2024; Kim et al., 2023). Nevertheless, the impact of different forms of physical activity on raising HIF-1α, EPO, and VEGF has not yet been examined in these studies. Additionally, respondents did not provide particular information regarding sedentary lifestyles. Thus, the purpose of this study was to investigate how aerobic and resistance exercise affected the levels of VEGF, EPO, and HIF-1α in inactive women.

RESEARCH METHODS

Study Design

After being randomly selected, thirty female respondents were divided into three groups. There were three groups: n=10 for resistance training (RT), n=10 for aerobic training (AT), and n=10 for control (CO). While the control group did nothing, the RT group followed a program involving weight training, and the AT group followed a program involving aerobic exercise on a treadmill. The following exercise interventions will discuss these exercise programs in more detail.

Subjects

The ethics committee of the State Polytechnic of Health of Malang approved this experimental study, which was conducted in accordance with the Declaration of Helsinki. The study involved thirty healthy women (Table 1 displays subject characteristics). The researchers established inclusion and exclusion criteria to assess whether the volunteers met the study requirements. Subjects were required to be between 18 and 26 years old, have a normal body mass index (BMI), lead a sedentary lifestyle, be non-smokers, have no history of cancer, cardiovascular disease, or musculoskeletal disorders, not be taking dietary supplements or ergogenics, and be willing to participate in the study. As a shortened version of the International Physical Activity Questionnaire (IPAQ), a sedentary lifestyle is defined as a physical activity level of less than 600 MET minutes per week (Moghaddam et al., 2012). Furthermore, respondents were not required to exercise regularly. Participants under eighteen years of age were not permitted to participate in this study. Our study also excluded respondents with hypertension, those with very high blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) before the activity. Furthermore, subjects were disqualified if they were currently taking nonsteroidal anti-inflammatory drugs (NSAIDs).

Pregnancy, starting a specific diet, using medications, and not wanting to continue the recommended exercise intervention (not attending all sessions) were reasons for exclusion. A formal consent form was read and signed by each selected participant. Three groups of 30 female volunteers participated in this study: n=10 were assigned to the resistance training (RT) group, n=10 to the aerobic training (AT) group, and n=10 to the control (CO) group. The study was conducted at a Fitness Center in Tulungagung City, East Java Province. In addition, all participants were guided by a certified professional fitness trainer during the exercise intervention.

Research Instruments

The following instruments we used include measurements of weight, height, and blood pressure, data collection sheets, stationery, blood drawing equipment, treadmills, and gym equipment used for weight training.

Procedure

There were multiple steps in the data collection process for this study. Before the study started, the subjects went through a screening procedure. This method was predicated on particular criteria that let

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

data to be added to or removed from the study. Additionally, after being educated about the research protocols, individuals provided their informed consent in order to participate in the research. Out of the trial participants, three groups were chosen at random and split into treatment groups receiving resistance training and aerobic training interventions and a control group receiving no intervention.

Data collection was conducted over two days, beginning with information on the subjects' characteristics. Before the investigation, subjects were not allowed to eat anything. The day before the study, subjects were instructed to maintain a regular diet and rest patterns. They were then instructed to warm up before exercising. Afterward, they engaged in physical activity, consisting of resistance training and moderate-intensity aerobic exercise.

Before the exercise, 3cc of blood was taken as pretest data, and after the exercise, 3cc of blood was taken as posttest data. After that, the blood samples were centrifuged to separate the serum. After centrifugation was complete, the blood serum was taken for laboratory analysis to check the levels of HIF-1α, EPO, and VEGF. This analysis was carried out in a laboratory at the Physiological Sciences Laboratory Installation, Faculty of Medicine, University of Brawijaya, Malang. The method for examining HIF-1α, EPO, and VEGF levels used the ELISA (Enzyme-linked immunosorbent assay) method with reagents for human HIF-1α, EPO, and VEGF levels. After analyzing the data, the researchers finally wrote a written report outlining the findings as a form of accountability.

Exercise Intervention

Resistance Training (RT) consists of group training sessions where participants receive instruction on exercise techniques and have their performance evaluated by trained professional trainers. Each training session lasts 60 minutes and is delivered acutely. Targeting both the upper and lower body, the 40-minute strength training session consists of three sets of ten exercises, such as the triceps pushdown, seated row, shoulder press, chest press, lateral pull-down, abdominal crunch, leg press, leg extension, and sitting bicep curl. Every resistance exercise is carried out in compliance with the National Strength and Conditioning Association's criteria, which have been applied in earlier research (Amanat et al., 2020). Each exercise involved 8–10 repetitions in 3 sets, with 5–10 minutes of recovery in between sets. The intensity of the exercise was 75–80% of 1RM. Participants were assessed using seated leg presses and upper and lower body bicep curls to determine their 1RM. Participants were placed with their knees bent at a 90-degree angle following their leg press warm-up. After applying a conservative load to the machine, participants were told to bend their knees completely and do so again until they became fatigued. The weight was raised for sitting bicep curl participants in a range of 100 degrees, from full extension to fatigue. Due to the participants' inexperience and potential for harm, 1RM was calculated for each participant using a formula rather than being measured directly Brzycki, 1993: 1RM = (Total weight lifted (kg)/(102.78 - (002.78 × number of repetitions)).

Aerobic Training (AT) consists of brisk walking on a treadmill for 30 minutes at a pace of 5–6 km/h. The following formula is used to measure each participant's maximal heart rate (HRmax), which determines the exercise's intensity: HRmax is equal to 208 - (0.7 × age) (Tanaka et al., 2001). During a single training session, the exercise's intensity progressively increases from 65% of HRmax to 75% of HRmax.

The control group (CO) was asked to just sit and lie down at the designated research location. The only activities allowed were playing with cell phones, sitting, and walking to the bathroom in the designated area. Participants in this group were allowed to play with their cell phones and communicate with their groupmates to overcome boredom while waiting in line to have their blood drawn.

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

CONSORT flowchart

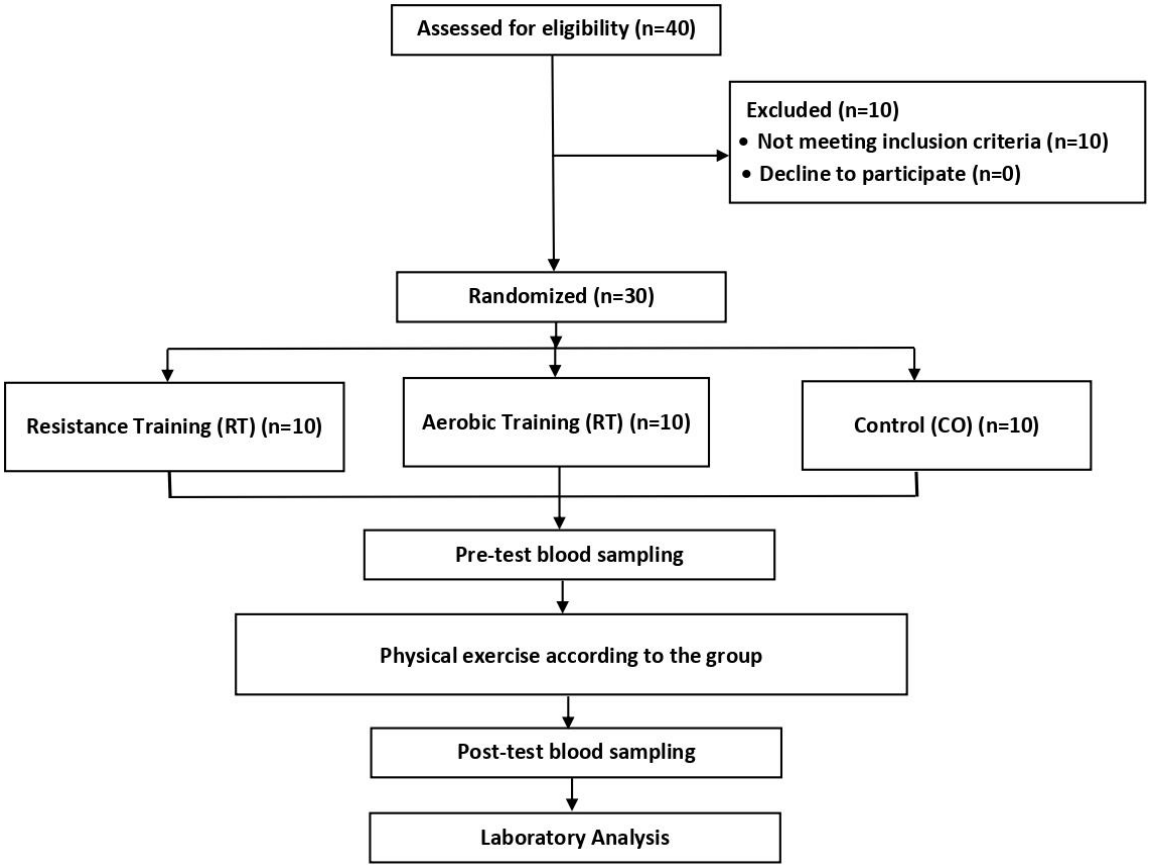

Figure 1. The CONSORT flowchart

Statistical analysis

After data collection, statistical analysis was performed using SPSS Version 16.00 software. The data were then analyzed descriptively to determine the mean and standard deviation. This study also used the Shapiro-Wilk test to test for normality. An ANCOVA test was used to determine the influence and differences between groups controlled by the pretest. We also examined the effect size to determine the extent of the change.

Ethics

With registration number DP.04.03/F.XXI.30/01077/2025, we received ethical approval from the Malang Health Polytechnic Ethics Committee prior to data collection.

RESULTS

Statistics and details regarding the general description of the participants in Table 1 are presented in this section. These statistics provide information about the characteristics of each group. Mean ± standard deviation is used to display the data. There were no significant differences between the resistance training, aerobic training, and control groups, based on the ANOVA test results ($p>0.05$).

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

Table 1. Characteristics of research subjects

Data	Group	N	Mean ± SD	p-value
Age (y)	Resistance Training	10	20.50±1.08	0.973
	Aerobic Training	10	20.60±2.27	
	Control	10	20.70±2.11	
Height (cm)	Resistance Training	10	157.00±5.88	0.874
	Aerobic Training	10	155.80±5.99	
	Control	10	155.70±6.73	
Weight (kg)	Resistance Training	10	54.30±8.21	0.367
	Aerobic Training	10	53.50±8.44	
	Control	10	49.90±4.40	
BMI (kg/m^2)	Resistance Training	10	22.20±2.98	0.539
	Aerobic Training	10	22.02±3.12	
	Control	10	20.71±2.81	
Systolic (mmHg)	Resistance Training	10	119.40±15.63	0.447
	Aerobic Training	10	111.60±8.90	
	Control	10	113.00±17.37	
Diastolic (mmHg)	Resistance Training	10	76.80±10.22	0.254
	Aerobic Training	10	70.40±4.88	
	Control	10	74.20±9.33	

Table 2. Results of Normality Tests

Data	Group	Normality	
		N	p-value
HIF-1α	Resistance Training	10	0.728
	Aerobic Training	10	0.588
	Control	10	0.746
EPO	Resistance Training	10	0.702
	Aerobic Training	10	0.513
	Control	10	0.785
VEGF	Resistance Training	10	0.702
	Aerobic Training	10	0.400
	Control	10	0.282

The HIF-1α, EPO, and VEGF data of all groups were normally distributed ($p>0.05$), based on the normality test in Table 2.

Figure 2 displays the HIF-1α analysis findings for each group.

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

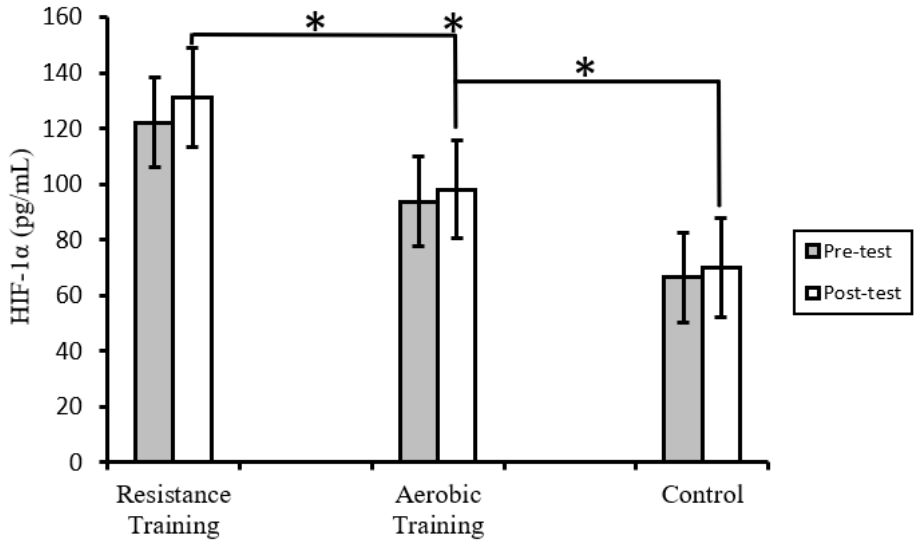

Figure 2 shows a significant difference in HIF-1α levels between the resistance training and aerobic training, the resistance training and control, and the aerobic training and control groups ($p<0.05$).

Figure 3 displays the EPO analysis findings for each group.

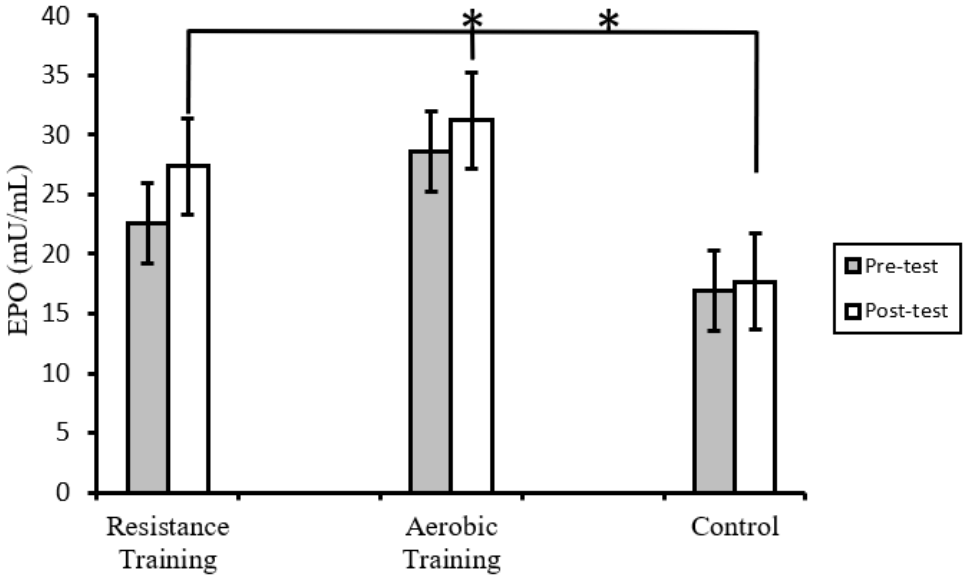

Figure 3 shows a significant difference in EPO levels between the resistance training and control, and the aerobic training and control groups ($p<0.05$).

Figure 4 displays the VEGF analysis findings for each group.

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

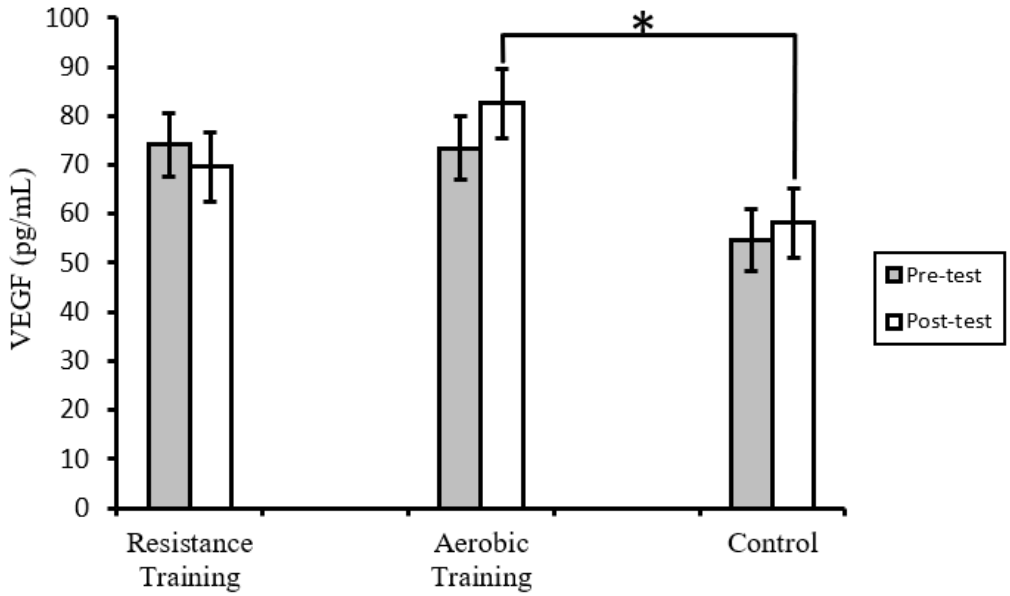

Figure 4 shows a significant difference in VEGF levels between aerobic training and control group ($p<0.05$).

Table 3. Results of Differences in HIF-1α, EPO, and VEGF Levels in Each Group

Data	Group	ANCOVA	
		Mean ± SD	p-value
HIF-1α	Resistance Training	131.28 ± 14.40	*0.000
	Aerobic Training	98.14 ± 34.60	
	Control	70.07 ± 23.54	
EPO	Resistance Training	27.37 ± 7.32	*0.001
	Aerobic Training	31.22 ± 3.13	
	Control	17.66 ± 5.21	
VEGF	Resistance Training	69.59 ± 23.32	*0.044
	Aerobic Training	82.59 ± 10.24	
	Control	58.13 ± 28.84	

Information:
The results of the study showed significant differences between groups in HIF-1α levels (p=0.000), EPO (p=0.001), and VEGF (p=0.44) $p<0.05$.

Table 4. Pairwise Comparison Results of HIF-1α, EPO, and VEGF Levels in Each Group

Data	Group	ANCOVA	
		Mean Difference ± Std. Error	p-value
HIF-1α	Resistance Training with Aerobic Training	46.98 ± 11.82	*0.002
	Resistance Training with Control	88.41± 15.06	*0.000

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

	Aerobic Training with Control	41.42 ± 11.73	*0.005
EPO	Resistance Training with Aerobic Training	-4.16 ± 2.83	0.462
	Resistance Training with Control	10.00 ± 2.79	*0.004
	Aerobic Training with Control	14.17 ± 3.59	*0.002
VEGF	Resistance Training with Aerobic Training	-12.84 ± 9.93	0.623
	Resistance Training with Control	16.18 ± 11.01	0.461
	Aerobic Training with Control	29.03 ± 10.94	*0.040

Information:
The results of the HIF-1α level study proved that there was a significant difference in HIF-1α levels between resistance training and aerobic training (CI 95%; p=0.002; Effect Size: 1.25) p<0.05, resistance training and control (CI 95%; p=0.000; Effect Size: 3.13) p<0.05, and aerobic training and control (CI 95%; p=0.005; Effect Size: 0.94) p<0.05. The results of the EPO level study proved that there was a significant difference in EPO levels between resistance training and control (CI 95%; p=0.000; Effect Size: 1.52) p<0.05, and aerobic training and control (CI 95%; p=0.005; Effect Size: 3.15) p <0.05. While between resistance training and aerobic training there was no significant difference p>0.05. The results of the VEGF level study showed that there was a significant difference in VEGF levels between aerobic training and control (CI 95%; p=0.040; Effect Size: 1.13) p<0.05. Meanwhile, there was no significant difference between resistance training and control or between resistance training and aerobic training (p>0.05).

DISCUSSION

This study sought to ascertain how aerobic and resistance training affected the levels of VEGF, EPO, and HIF-1α in inactive women. The study's findings demonstrated that, in comparison to the control group, resistance training significantly raised HIF-1α and EPO levels (p<0.05) but had no significant effect on VEGF levels (p>0.05). In contrast to the control group, aerobic exercise significantly raised the levels of HIF-1α, EPO, and VEGF (p<0.05). Four training sessions were carried out with the study sample, according to additional research findings. The first session involved rest; the second included thirty minutes of exercise at 50% VO2max; the third included seventy-five minutes of exercise at 75% VO2max; and the fourth session involved training at 100% VO2max until exhaustion. The results of the investigation demonstrated an increase in HIF-1α levels, with the maximum expression occurring at 75% VO2max (Baygutalp et al., 2021). Thus, HIF-1α increases are influenced by exercise intensity. According to other studies, runners who trained for three weeks at sea level and four weeks at high altitude had higher levels of HIF-1α. The runners trained for sixteen hours a week (two or three sessions each day at 6:00 AM, 10:00 AM, and 4:00 PM) (Soori et al., 2020). Resistance and aerobic training both markedly raised HIF-1α levels in this study (p<0.05). As a result, both forms of exercise help raise HIF-1α levels. Hypoxia is linked to HIF-1α levels. The body is in a hypoxic condition during physical activity, which increases the requirement for oxygen to create and transmit energy, such as ATP, throughout the body.

Insulin sensitivity, cardiovascular health, bone density, muscle mass, and metabolic health have all been demonstrated to improve with strength training in particular (Mukund & Subramaniam, 2020). Hypoxia inducible factor (HIF-1), a transcription factor that regulates metabolism and aids in the body's adaptation to hypoxic conditions, is activated when exercise causes the body to enter a hypoxic phase (Yu et al., 2020). Another study revealed that HIF-1α expression was elevated in mice that underwent an eight-week regular physical exercise intervention at moderate intensity (about 60% of their maximal aerobic speed) on a treadmill (Tian et al., 2020). Male mice exhibited elevated HIF-1α expression following HIIT therapy and strength training (Tryfonos et al., 2021). This supports our findings that exercise raises HIF-1α levels. Additionally, the kidneys' interstitial cells secrete erythropoietin, or EPO, a hormone that is often created when oxygen levels drop. For example, low oxygen levels are linked to HIF-1α expression when the body is hypoxic or at high elevations; this stimulates the production of erythropoietin, which makes more red blood cells to carry oxygen to the

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

tissues (Mairbäurl, 2013). Therefore, raising HIF-1α levels during exercise is crucial for raising the body's EPO levels.

An essential hematopoietic growth factor for erythropoiesis, or the production of blood cells, is erythropoietin. With a molecular weight of 30,400 kDa, it is a glycoprotein hormone made up of four carbohydrate chains and 165 amino acids (Burak et al., 2025). The primary physiological stimulus for EPO generation is tissue hypoxia, which is correlated with the quantity of erythrocytes in circulation (Weiss et al., 2020). Thus, by controlling the quantity of erythrocytes in circulation, the body attempts to keep tissue oxygenation within specific bounds (Burak et al., 2025). EPO is a naturally occurring glycoprotein hormone that promotes oxygen-carrying erythrocyte maturation and proliferation in addition to erythropoiesis (Trinh et al., 2020). In order to maintain tissue oxygen delivery levels within a specific range, the body uses EPO to regulate the quantity of red blood cells in circulation (Trinh et al., 2020). Exercise under hypoxic conditions has been shown to significantly raise EPO levels following physical exercise intervention, according to the findings of earlier research (Yatsutani et al., 2020). According to the findings of other studies, runners who had finished a 21-kilometer race had higher EPO levels (Ventura, 2007). Exercise has been shown to raise blood levels of EPO, which is good for erythropoiesis. In addition to EPO, HIF-1α signaling causes levels of VEGF, a signaling protein that encourages the growth of new blood vessels (angiogenesis), to rise during exercise (Mehran & Zeinab, 2020).

Angiogenesis lowers the risk of myocardial infarction, stroke, and hypertension while simultaneously improving oxygenation to skeletal muscles and providing an effective framework (Ventura, 2007); It is one of the primary requirements for competing successfully in sports, particularly endurance exercises and raising maximum oxygen consumption (VO2max). The arterial-venous blood oxygen difference and VO2max are increased when capillary density is increased by increasing the diffusion rate, lengthening the blood-tissue exchange time, and decreasing the oxygen diffusion distance (Gavin et al., 2025). According to earlier research, participants were senior individuals between the ages of 65 and 75 who underwent 16 weeks of aerobic and resistance training three times a week to compare VEGF expression. Exercise-induced positional hypoxia is one of the initial triggers for conditions like elevated concentration density and oxidative capacity, as well as mechanisms like mitochondrial activity that are very sensitive to oxygen supply and respond to the changes that take place (Ohno et al., 2012). Conversely, increased oxygen intake during physical activity results in increased reactive oxygen species (ROS), which is implicated in the control of HIF-1α (Trisciuoglio et al., 2005). Additionally, the results of this study show that pregnant rats' heart tissue significantly increased in VEGF after three weeks of resistance and endurance exercise. Both aerobic and non-aerobic exercise were shown to raise VEGF levels, which is consistent with this study (Flora et al., 2012). These results are in line with earlier studies demonstrating that hypoxia significantly increases VEGF in a variety of tissues, despite the lack of direct evidence (Xu et al., 2021) and that a VEGF-mediated route is one way that mixed aerobic-endurance training enhances endothelial function (Tao et al., 2023).

Resistance training dramatically increases VEGF expression, according to other studies (Kim et al., 2023). VEGF levels are influenced by environmental factors in addition to the type of exercise. The data that follows contrasts elevated VEGF expression with altitude. At normoxic elevations of 2,000, 3,000, and 4,000 meters above sea level, subjects received physical activity interventions. According to the findings, VEGF expression significantly increased at 4,000 meters above sea level (Suhr et al., 2021). Supporting evidence that VEGF expression is increased by both moderate and high-intensity physical activity (Huang et al., 2025). In a later study, older persons were given a combination of low- and moderate-intensity exercise four times a week for three weeks, totaling twelve 30-minute sessions on a cycle ergometer. The findings demonstrated that VEGF expression was significantly elevated by moderate-intensity exercise (Górna et al., 2025). These investigations thus corroborate our findings, which demonstrated a considerable increase in VEGF levels following physical activity. But this kind of activity also has a big impact on raising VEGF levels. In contrast to the resistance training group, which did not exhibit any significant rise in VEGF levels, our data demonstrated that only aerobic exercise significantly raised these levels. However, more investigation into the causes of this negligible rise is

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

needed in subsequent studies. Additionally, a variety of elements play a role because every individual's physiological reaction to physical activity is different, which makes it difficult for researchers to carry out thorough investigation.

Molecular Mechanisms of Physical Exercise Trigger Angiogenesis Through HIF-1α, EPO, and VEGF Levels

Exercise is frequently advised to enhance performance and health as well as to prevent and treat a variety of harmful medical disorders (Hawley et al., 2014). In cells and tissues, angiogenesis is a common response to hypoxia (Zimna & Kurpisz, 2015). Hypoxia-inducible transcription factors mediate the majority of the transcriptional response to hypoxia (Zimna & Kurpisz, 2015), such as HIF-1α and HIF-2α. HIF has been shown to increase the pro-angiogenic factor ANGPT-1 regulation and decrease the ANGPT-2 regulation (Brian D. Kelly et al., 2003). According to a prior study, HIF-1α controls VEGF more than HIF-2α does in response to hypoxia (Carroll & Ashcroft, 2006). According to recent research, adult organisms' hypoxia and HIF-1 expression may stimulate angiogenesis in the following ways: initially turning on angiogenic genes and their receptors, like VEGF (Greijer et al., 2005), the second controls proangiogenic receptors and chemokines (Ceradini et al., 2004), and the third boosts endothelial cells and controls DNA replication and cell cycle genes (Manalo et al., 2005). All of these results demonstrate how HIF-1 affects angiogenesis (Zimna & Kurpisz, 2015). Another gene that adapts to hypoxia is VEGF, which stimulates the growth of endothelial cells. Angiogenesis is significantly impacted by the translocation of proliferating endothelial cells into the extracellular matrix.

By promoting capillary formation, VEGF and EPO react to sudden increases in oxygen demand in human skeletal muscle, indicating that oxygen-sensitive pathways may be important for adaptation to physical activity (Ohno et al., 2012). Indeed, PGC-1α protein not only controls mitochondrial biogenesis but also boosts the expression of VEGF mRNA and consequent angiogenesis (Zhang et al., 2011). However, in response to hypoxia, the transcription factors HIF-1α and HIF-2α also control the expression of VEGF (Arany et al., 2008). Most of the evidence regarding hypoxia and angiogenesis comes from studies of cancer and angiogenesis. These studies have found that acute hypoxia can lead to dysregulation of the tumor vascular system. In chronic hypoxia, HIF-1α regulates the proangiogenic activity of VEGF, which controls the expression of various genes that induce angiogenesis (Lee et al., 2020). Vascular endothelial growth factor (VEGF), which affects multiple stages of angiogenesis, including endothelial cell activation, proliferation, and migration, is the most well-known proangiogenic factor that is essential to skeletal muscle (Ferrara, 1999). Skeletal muscle myofibers, pericytes, and other muscle cells all contain VEGF protein (Hoier et al., 2013), and endothelial cells (Ross et al., 2023) and has both autocrine and paracrine actions. Because muscle myofibers contain vesicular storage of VEGF and release considerable amounts of VEGF in response to muscle contraction, evidence points to a primary paracrine role for VEGF in muscle myofibers (Gavin et al., 2007).

Additionally, research using genetically altered mice has demonstrated the significance of myocyte VEGF for both baseline capillarization and exercise-induced capillary development (Olfert et al., 2010). Exercise and enhanced angiogenesis are related. Aerobic exercise has been demonstrated to improve cardiac function in myocardial infarction models (Ellison et al., 2012). Exercise has been demonstrated to promote angiogenesis and cardiac repair by increasing levels of follistatin-like protein 1 (FSTL1) and VEGF, activating the transforming growth factor-β (TGF-β)/Smad2/3 and PI3K/eNOS pathways, and reducing the expression of microRNAs linked to myocardial fibrosis (such as miR-15a and miR-146a) (Saati et al., 2023). It has been demonstrated that in aged rats (20–24 months), an 8-week training program that combines aerobic and resistance training dramatically increases angiogenesis in cardiac tissue. Increased aerobic endurance and elevated levels of certain proteins linked to blood vessel creation, such as eNOS, VEGF, and HIF-1α, are the causes of this rise (Shen et al., 2021). In male patients with stable heart failure, both HIIT and HIIT in conjunction with strength training (such as leg curls and extensions) improved diastolic function. Additionally, both exercises elevated HIF-1α in heart failure patients and signals that support angiogenesis (angiopoeitin-2, VEGFR-2, and VEGF) in skeletal muscle (Tryfonos

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

et al., 2021). Citric acid synthetase activity and exercise capacity rose in heart failure patients after eight weeks of exercise, as did VEGF levels (Gordon et al., 2001).

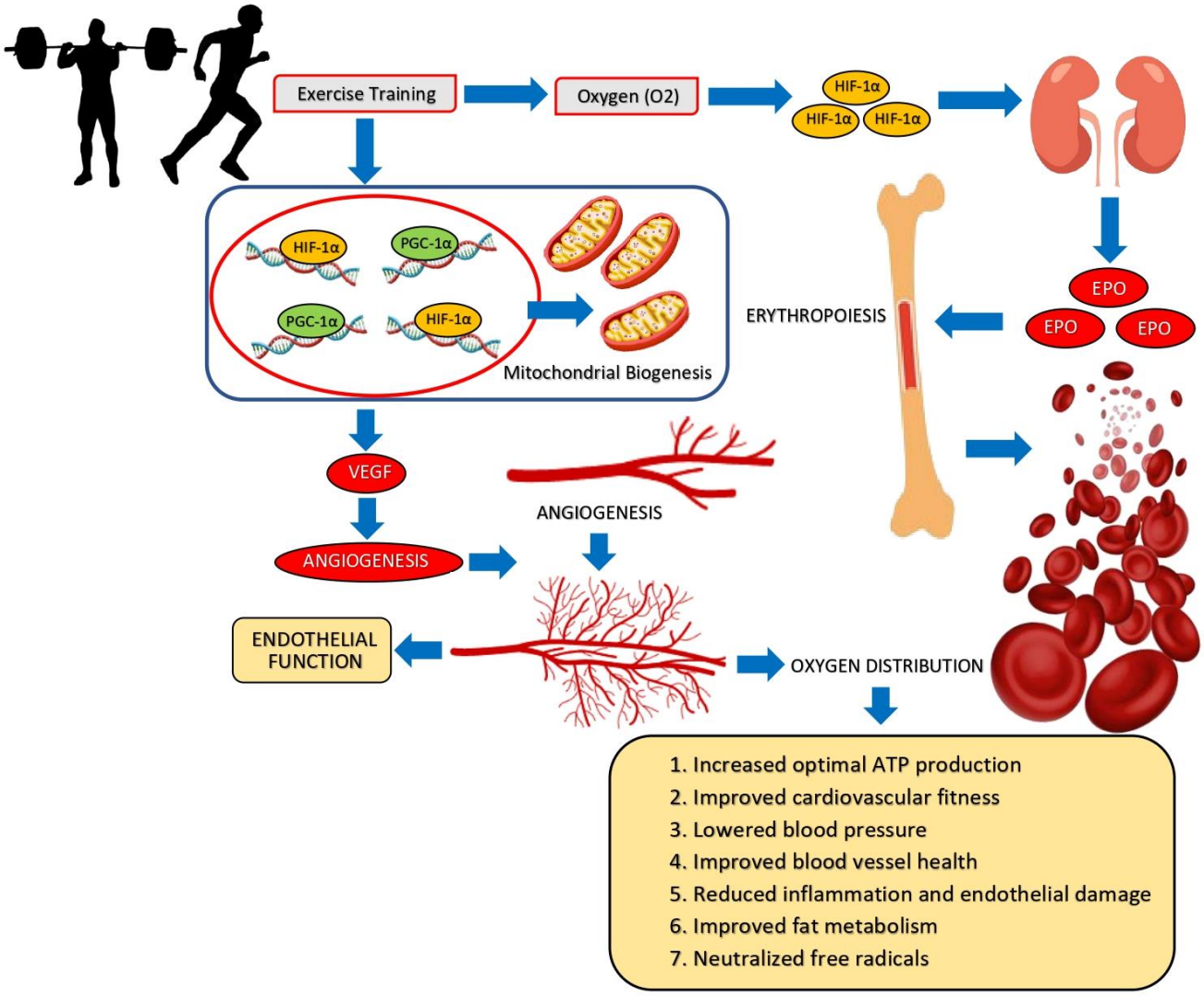

Figure 5. Molecular mechanism of physical exercise triggers angiogenesis and increases oxygen consumption through HIF-1α, EPO, and VEGF level

The oxygen requirement of muscle tissue increases significantly during vigorous physical activity, especially resistance or aerobic training. Relative hypoxia, or a drop in local oxygen tension, is the result of the blood circulation's oxygen supply failing to instantly offset this increased consumption. This situation is a physiological signal that activates HIF-1α. The study's findings support the physiological theory that physical activity can promote angiogenesis by activating the VEGF and HIF-1α pathways. Local hypoxia occurs in muscle tissue as a result of an imbalance between oxygen supply and demand brought on by increased muscular activity during exercise. The main signal that stabilizes and activates HIF-1α at the cellular level is this hypoxic state. One significant response to exercise is changes in blood volume.

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

Red blood cell volume and plasma volume add up to blood volume. Blood volume can be altered independently of plasma volume and red blood cell volume (Lin, 2012). While erythrocyte volume expansion often occurs gradually over weeks to months, plasma volume expansion can occur quickly over hours to days with endurance exercise (Sawka et al., 2000). By activating EPO receptors on endothelial cells and initiating the JAK2/STAT5 and PI3K/Akt signaling pathways, which promote endothelial proliferation and migration, increased EPO expression not only boosts erythropoiesis and blood oxygen transport capacity but also directly contributes to angiogenesis (Chen & Liang, 2025). In the interim, HIF-1α-induced angiogenesis is largely mediated by VEGF. By binding to VEGFR-2 on the surface of endothelial cells, VEGF activates the ERK1/2 and Akt pathways, which promote the growth and elongation of new capillaries (Haas & Nwadozi, 2018). All things considered, elevated HIF-1α expression during exercise initiates an adaptive response in the form of elevated EPO and VEGF levels, which cooperate to support muscle tissue angiogenesis and capillaryization. During repeated exercise, this adaptation enhances oxygen transport, boosts oxidative capacity, and supports muscular efficiency. These results further reinforce the evidence that a crucial molecular mechanism in exercise-induced vascular adaptation is HIF-1α activation.

Strength and Limitations

The strength of this study lies in its randomized controlled experiment, the most reliable scientific method, which eliminates the possibility of ambiguous cause-and-effect relationships. Furthermore, we discuss the limitations of our study, such as the limited sample size. We acknowledge that a larger sample size would provide a better understanding of the results. This is indeed a limitation of our study. Furthermore, our intervention focused only on resistance training and aerobic exercise. Perhaps in the future, we could examine how increases in HIF-1α, EPO, and VEGF levels are affected by a combination of aerobic exercise and different forms of resistance training. This will be important to determine which type of exercise is effective in increasing HIF-1α, EPO, and VEGF levels. Furthermore, our age justification focused only on those aged 18 to 26. Future research might examine increases in HIF-1α, EPO, and VEGF levels after exercise in those aged 30 and older, or those approaching old age. Furthermore, it is also important to examine how exercise affects individuals with cardiovascular disease or metabolic syndrome. This will allow for a more concrete understanding of how the actual effects of exercise influence the adverse effects resulting from metabolic syndrome. Furthermore, the chronic effects of exercise should also be further explored.

CONCLUSION

Acute physical exercise has different effects on HIF-1α, EPO, and VEGF levels. Resistance training and aerobic exercise significantly increased HIF-1α levels compared to the control group. However, between the two types of exercise, resistance training significantly outperformed the aerobic group in increasing HIF-1α levels. Resistance training and aerobic training significantly increased EPO levels compared to the control group. VEGF levels were only significantly increased in the aerobic group. Nevertheless, physical exercise is a real recommendation for increasing angiogenesis by increasing HIF-1α, EPO, and VEGF levels, which results in increased oxygen supply to tissues to produce ATP, which has a significant effect on improving metabolism and blood circulation.

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Journal of Sport and Health Research 2025, 17(Supl 2):117-140

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

Journal of Sport and Health Research 2025, 17(Supl 2):117-140

Journal of Sport and Health Research 2025, 17(Supl 2):117-140