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Effects of erythropoietin on cardiac morphometry in exercised male and female adolescent rats

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Abstract

Erythropoietin (EPO) is a glycoprotein hormone predominantly produced in the kidneys, primarily stimulating erythroid cell proliferation in the bone marrow. The present study investigated the impact of EPO combined with swimming exercise on cardiac morphometry in adolescent male and female rats. The 4-week study involved 48 rats (24 males and 24 females), which were divided into four main groups of six males and six females each. The control group was administered intraperitoneal saline four times a week. The swimming exercise group also received intraperitoneal saline, followed by 30 min of swimming exercise, four times a week. The drug control group was given 50.00 IU kg^{-1} epoetin alfa intraperitoneally, four times a week. Lastly, the Swimming + Drug group received 50.00 IU kg^{-1} epoetin alfa intraperitoneally, four times a week, followed by 30 min of swimming exercise. The post-study measurements demonstrated that EPO administration did not result in notable alterations in crucial parameters, including the left ventricular mass index, left ventricular mass, and left ventricular posterior wall in the context of left ventricular hypertrophy in both genders. However, in female rats, EPO-only group and the combined EPO and exercise group showed significant thinning of the right ventricular wall and interventricular septum indicating potential cardiac dilatation. The results highlight the necessity of considering gender-specific responses when evaluating EPO's cardiovascular effects, particularly concerning the right ventricle, and suggest further investigation into the long-term consequences of these observed changes.

Introduction

Erythropoietin (EPO) is legally used to treat anemia in clinical settings. Administering this hormone to those with anemia increases the number of red blood cells by 35.00%, alters their shape, and enhances their oxygen-carrying capacity. Erythropoietin is a crucial hematopoietic growth factor necessary for erythropoiesis. It is a glycoprotein hormone composed of 165 amino acids and four carbohydrate chains, with a molecular weight of 30,400 kD.[1,2].

The EPO gene locus is located on the seventh chromosome.[3] The majority of EPO is synthesised in the kidney (90.00%), with the remaining 10.00% produced in the liver.[2,4,5] The serum EPO concentration in healthy individuals without anemia ranges from 4.00 – 48.00 U mL^{-1}. There is no difference in serum EPO concentration between healthy men and women, despite differences in blood hemoglobin levels. Erythropoietin levels are not affected by age.[6,7]

Tissue hypoxia is the primary physiological stimulus for EPO production, which is directly related to the number of circulating erythrocytes.[8] Therefore, the body attempts to maintain tissue oxygenation within certain limits by regulating the number of erythrocytes in circulation. A negative feedback mechanism exists between EPO production and erythropoiesis. In hypoplastic anemias, EPO activity increases in proportion to the degree of anemia. In cases of chronic inflammation or malignant diseases, EPO activity is low. Acute hemorrhage increases EPO secretion in both humans and animals.[9,10] When erythrocyte levels and tissue oxygenation decrease, prompting increased EPO production in the kidney and liver.[2,4,6]

Erythropoietin enhances erythroblast development in the bone marrow. The EPO binds to receptors on the

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surface of erythroid colony forming unit and erythroid burst forming unit cells in the bone marrow, promoting their transformation into proerythroblasts. It also facilitates the proliferation of proerythroblasts and basophilic erythroblasts and their transformation into mature normoblasts and regulating the number of circulating erythrocytes within physiological limits.[8,11]

Erythropoietin is a hormone that stimulates the production of red blood cells and is used medically to treat anemia and other conditions. Unfortunately, some athletes use EPO as a performance-enhancing drug, despite it being a banned substance.[12] This is a serious issue, particularly among young athletes who may be tempted to use it to improve their physical appearance and athletic performance. The aim of this study was to investigate the morphometric changes of EPO in male and female rat hearts during puberty, as they are frequently consumed as a form of doping. Additionally, we aimed to determine the potential of EPO to cause cardiac hypertrophy.

Materials and Methods

Animals and diets. The study used a total of 48 Sprague-Dawley rats, 24 males and 24 females, aged 40 days and weighing between 150-220 g. The rats were provided with normal rat food and water ad libitum, and were kept in a controlled environment with a 12/12 hr light/dark cycle at 22.00 ± 2.00 ˚C.

Drugs. The EPO alfa used in the experimental study was procured from Gürel Pharmaceutical Trading Inc. (Istanbul, Türkiye). Thiopental sodium (0.50 g mL^{-1}) used for euthanasia was supplied by İ.E Ulagay Pharmaceutical Inc. (Istanbul, Türkiye). The organ samples were fixed in a 37.00% formaldehyde solution (Tekkim Kimya, Istanbul, Türkiye).

Experimental design. The study used rats, which were divided into four main groups and eight subgroups based on gender. Table 1 presents the details of the groups, which were formed with the same number and conditions for both males (n = 6) and females (n = 6). The control group rats were administered intraperitoneal physiological saline four times a week. The swimming exercise group rats were given intraperitoneal saline application four times a week and 30 min of swimming exercise after each application. Erythropoietin alfa was administered intraperitoneally at a dose of 50.00 IU kg^{-1} four times a week to the drug control group. The rats in the swimming and drug trial group received the same dose of EPO and were subjected to 30 min of swimming exercises after each application. The study duration was 4 weeks. The study was approved by the Selçuk University Faculty of Veterinary Medicine Ethics Committee (Approval Date: 26.08.2011, Decision no: 2011/080-081).

Table 1. Experimental design.

Groups	Saline	Erythropoietin	Swimming exercise
Control			
Male (MC)	+	-	-
Female (FC)	+	-	-
Swimming exercise			
Male (MS)	+	-	+
Female (FS)	+	-	+
Drug control			
Male (MD)	-	+	-
Female (FD)	-	+	-
Swimming + Drug			
Male (MSD)	-	+	+
Female (FSD)	-	+	+

MC: Male control group; FC: Female control group; MS: Male swimming exercise group, FS: Female swimming exercise group; MD: Male drug control group; FD: Female drug control group; MSD: Male swimming and drug group; FSD: Female swimming and drug group.

Method of sampling and relative organ weights. At the end of the study period, all rats were anesthetized with sodium thiopental (40.00 mg kg^{-1}, intraperitoneally) for euthanasia. Following the measurement of their live body weights (BW), euthanasia was performed by cervical dislocation. In systemic necropsy, the liver, heart, kidneys and spleen were dissected. The organs were weighed after being freed from surrounding tissues. The relative organ weight for each organ was then calculated using the following formula:[13]

Relative organ weight (g) = Organ weight (g) × 100 / BW (g)

Heart morphometrical method. The hearts were fixed whole in 10.00% formaldehyde solution and cut at the level of the musculus papillaris. Paraffin blocks were obtained after routine pathological tissue processing, and the surfaces of the blocks were shaved with a microtome (TP1020; Leica Biosystems, Nussloch, Germany). Images were captured and thickness, diameter, and area were measured using Image Analysis Software (version 2.2; Digital Life Science Imaging, analySIS® LS Starter, Olympus, Münster, Germany). Thickness was measured at three different points and averaged, while area and diameter were each measured three times and averaged.[14] For this purpose, we measured the left ventricular posterior wall (LVPT), interventricular septum thickness (IVST), left ventricular lumen diameter (LVLD), right ventricular wall thickness (RVT), cross-sectional area (CSA), and the cranio-caudal (CCD) and latero-lateral diameters (LLD) of the cross-section (two measurement lines forming right angles) as illustrated in Fig. 1. Following the measurements, we calculated the left ventricular mass (LVM), LVM index (LVMI) and left ventricular internal dimension Penn convention (LVIDp) according to Devereux and Reichek method.[15] Also, we calculated the body surface area (BSA) using Erer and Kiran formula.[16]

$$LVM\ (g) = 1.04\ ([LVPT + LVLD + IVST]^3\text{-}[LVIDp]^3) - 14\ g$$

$$LVMI\ (g\ per\ m^2) = LVM / BSA$$

$$BSA\ (m^2) = (BW\ (kg))^{2/3} \times K/100$$

where, K is a species-specific factor and is used as 9.00 for mice and rats, 10 for cats, 10.10 for dogs and 10.60 for a human weighing 70.00 kg.[16]

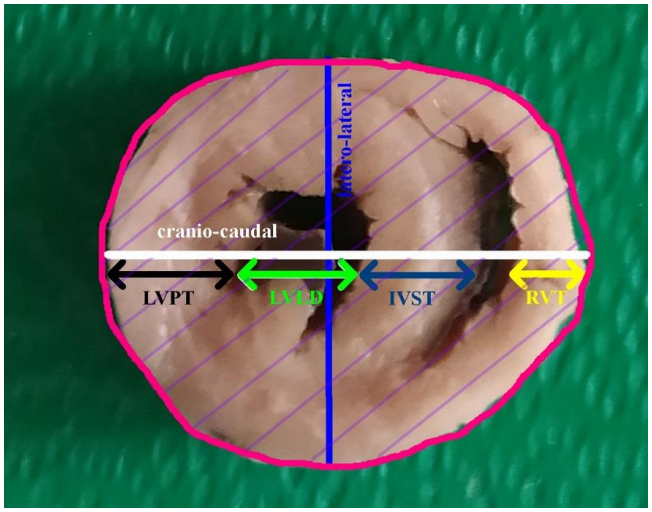

Fig. 1. Measurements on the cross-sectional area of the heart. LVPT: Left ventricular posterior wall thickness; IVST: Interventricular septal thickness; LVLD: Left ventricular lumen diameter; RVT: Right ventricular thickness; Cranio-caudal: Cranio-caudal diameter; Latero-lateral: Latero-lateral diameter; Cross-sectional area (Striped area outlined in red).

Statistical analysis. Statistical evaluation of the data was performed using the SPSS Software (version 13.0; SPSS Inc., Chicago, USA). The results are presented as Mean ± SD. The ANOVA and Duncan's test were used to compare data between groups, while independent *t*-test was used to compare data between genders. Results were considered statistically significant when *p*-value was below 0.05.

Results

The results of the heart morphometry study are presented in Table 2, with separate for male and female rats (Fig. 2). Table 3 provides the relative weights of the liver, heart, kidney, and spleen.

In male rats, the LVLD value was found to be significantly higher in the male swimming (MS) group (3.04 ± 0.94 mm) than in the other groups as male control group (MC): 1.90 ± 0.94 mm, male drug group (MD): 2.17 ± 0.41 mm, and male swimming and drug group (MSD): 2.34 ± 0.66 mm; $p < 0.05$, Table 2). The BSA and BW values were found to be significantly lower in the MSD group compared to the other groups (BSA, MSD: 0.034 ± 0.003 m^2; MC, MD, MS: 0.036 ± 0.001 - 0.002 m^2, BW, MSD: 228.83 ± 26.06 g; MC: 258.50 ± 15.04 g, MD: 255.20 ± 13.77 g, MS: 261.83 ± 18.92 g; $p < 0.05$, Table 2). No significant alteration was discerned in the relative organ weights of the liver, heart, kidney, and spleen in the male groups ($p > 0.05$, Table 3).

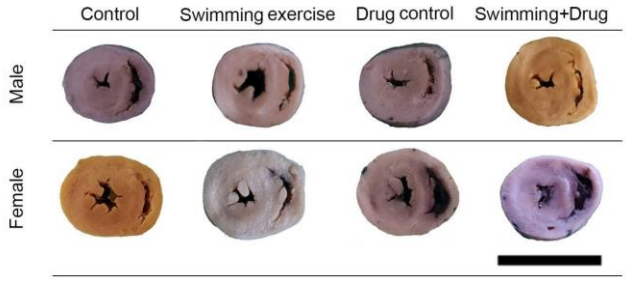

Fig. 2. The cross-sectional surfaces of hearts according to experimental groups (Scale bar: 10.00 mm).

Table 2. Morphometric measurements of the heart. The results are presented as mean ± SD.

Items	Male				Female			
	MC	MD	MS	MSD	FC	FD	FS	FSD
LVPT (mm)	1.58 ± 0.17	1.38 ± 0.30	1.38 ± 0.23	1.34 ± 0.18	1.57 ± 0.32	1.36 ± 0.30	1.33 ± 0.17	1.34 ± 0.25
IVST (mm)	2.90 ± 0.30	2.75 ± 0.10	2.70 ± 0.34	2.60 ± 0.18	2.58 ± 0.43^{ab}	2.42 ± 0.37^{b}	2.86 ± 0.23^{a}	2.63 ± 0.21^{ab}
RVT (mm)	3.30 ± 0.58	3.52 ± 0.52	3.07 ± 0.36	3.18 ± 0.54	3.16 ± 0.25^{ab}	3.05 ± 0.36^{ab}	3.40 ± 0.35^{a}	2.93 ± 0.36^{b}
CCD (mm)	10.65 ± 0.61	10.80 ± 0.36	10.85 ± 0.96	10.57 ± 0.89	9.89 ± 0.43^{ab}	10.35 ± 0.43^{a}	10.11 ± 0.80^{ab}	9.61 ± 0.40^{b}
LLD (mm)	8.75 ± 0.66	8.76 ± 0.62	9.24 ± 0.55	9.26 ± 0.39	8.55 ± 0.75	8.88 ± 0.26	8.85 ± 0.44	8.36 ± 0.24
CSA(mm^2)	79.00 ± 5.52	77.27 ± 6.53	82.29 ± 10.53	81.87 ± 6.80	70.90 ± 4.58^{ab}	76.27 ± 6.26^{a}	72.60 ± 6.89^{a}	64.89 ± 4.12^{b}
LVLD	1.90 ± 0.94^{b}	2.17 ± 0.41^{ab}	3.04 ± 0.94^{a}	2.34 ± 0.66^{ab}	1.92 ± 0,51^{b}	2.75 ± 0.58^{a}	1.87 ± 0.52^{b}	2.22 ± 0.52^{ab}
LVM	253.61 ± 79.88	243.91 ± 93.84	336.89 ± 95.32	234.30 ± 61.84	213.67 ± 49.78	259.73 ± 75.01	214.39 ± 57.72	227.29 ± 67.66
LVMI	6.92 ± 2.05	6.70 ± 2.40	9.09 ± 2.27	7.02 ± 1.91	6.53 ± 1.47	8.12 ± 2.21	6.72 ± 1.63	7.04 ±2.07
BSA(m^2)	0.036 ± 0.001^{a}	0.036 ± 0.001^{a}	0.036 ± 0.002^{a}	0.034 ± 0.003^{b}	0.,033 ± 0.001	0.032 ± 0.001	0.032 ± 0.001	0.032 ± 0.002
BW (g)	258.50 ± 15.04^{a}	255.20 ± 13.77^{a}	261.83 ± 18.92^{a}	228.83 ± 26.06^{b}	219.00 ± 9.41	211.00 ± 9.21	209.5 ± 14.90	215.17 ± 21.57

MC: Male control group; FC: Female control group; MS: Male swimming exercise group, FS: Female swimming exercise group; MD: Male drug control group; FD: Female drug control group; MSD: Male swimming and drug group; FSD: Female swimming and drug group; LVPT: Left ventricular posterior wall thickness; IVST: Interventricular septum thickness; LVLD: Left ventricular lumen diameter; RVT: Right ventricular wall thickness, CSA: Cross-sectional area; CCD: Cranio-caudal diameter; LLD: Latero-lateral diameter; LVM: Left ventricular mass; LVMI: Left ventricular mass index; BSA: Body surface area; BW: Body weight.
^{ab} indicate statistically significant difference in each row ($p < 0.05$).

Table 3. Relative organ weights. The results are presented as mean ± SD.

Items	Male				Female			
	MC	MD	MS	MSD	FC	FD	FS	FSD
Liver	4.44 ± 0.71	5.03 ± 0.84	4.46 ± 0.62	4.78 ± 0.92	4.77 ± 0.37	4.98 ± 0.44	4.93 ± 0.55	5.04 ± 0.46
Heart	0.37 ± 0.04	0.36 ± 0.04	0.41 ± 0.03	0.40 ± 0.03	0.39 ± 0.03	0.40 ± 0.04	0.40 ± 0.03	0.41 ± 0.04
Spleen	0.50 ± 0.14	0.50 ± 0.15	0.40 ± 0.06	0.51 ± 0.26	0.43 ± 0.10[b]	0.56 ± 0.15[a]	0.44 ± 0.04[b]	0.45 ± 0.06[ab]
Kidney	0.46 ± 0.04	0.50 ± 0.06	0.47 ± 0.03	0.45 ± 0.06	0.51 ± 0.06	0.53 ± 0.05	0.48 ± 0.09	0.49 ± 0.08

MC: Male control group; FC: Female control group; MS: Male swimming exercise group, FS: Female swimming exercise group; MD: Male drug control group; FD: Female drug control group; MSD: Male swimming and drug group; FSD: Female swimming and drug group.
[ab] indicate statistically significant difference in each row ($p < 0.05$).

In female rats, the IVS was found to be significantly lower in the female drug (FD) group (2.42 ± 0.37 mm) in comparison to the other groups as female control group (FC): 2.58 ± 0.43 mm, female swimming group (FS): 2.86 ± 0.23 mm, female swimming and drug group (FSD): 2.63 ± 0.21 mm; $p < 0.05$, Table 2). The RVT was observed to be decreased in the FSD (2.93 ± 0.36 mm) and FD (3.05 ± 0.36 mm) groups in relationship to the other groups (FC: 3.16 ± 0.25 mm, FS: 3.40 ± 0.35 mm; $p < 0.05$, Table 2). Likewise, CCD was increased in the FD group (FD: 10.35 ± 0.43 mm, FC: 9.89 ± 0.43 mm, FS: 10.11 ± 0.80 mm, FSD: 9.61 ± 0.40 mm). The CSA was found to be significantly higher in the FD (76.27 ± 6.26 mm^2) and FS groups (72.60 ± 6.89 mm^2) in contrast to the other groups (FC: 70.90 ± 4.58 mm^2, FSD: 64.89 ± 4.12 mm; $p < 0.05$, Table 2). Furthermore, the LVLD was noted to increase in the FD group (2.75 ± 0.58 mm), in comparison to the other groups (FC: 1.92 ± 0.51 mm, FS: 1.87 ± 0.52 mm, FSD: 2.22 ± 0.52). No change was observed in the relative weights of the liver, heart, and kidneys in the female groups. However, a significant increase in spleen weight was found in the FD group ($p < 0.05$, Table 3).

Significant differences were observed in some parameters when comparing male and female subjects. In males, the drug control group showed a significant increase in BSA and BW ($p < 0.001$), and the swimming exercise group showed a significant increase in LVM ($p < 0.05$), BSA and BW ($p < 0.01$). The male swimming and drug trial group had a significant increase in CCD ($p < 0.05$), LLD and CSA ($p < 0.001$). No significant changes were observed in other parameters.

Discussion

Erythropoietin is a glycoprotein hormone synthesized predominantly in the kidneys and stimulates the proliferation and maturation of erythroid cells in the bone marrow. The EPO has recently become very popular with their anti-inflammatory, antioxidant, anti-apoptotic and angiogenic effects, as well as the treatment of anemia due to chronic renal failure, where they are frequently used.[17] However, the number of studies investigating the cardiac effects of EPO, which is known to be used by athletes for doping purposes from time to time, especially in the pubertal period, is quite limited. Thus, the current study aimed to determine the cardiac hypertrophy potential of EPO by making morphometric measurements in the hearts of pubertal male and female rats.

This study examined the impact of EPO and exercise on left ventricular parameters in both male and female rats during the pubertal period. Despite the anticipated impact of EPO on increasing hematocrit levels and potentially contributing to left ventricular hyper-trophy, the findings did not demonstrate statistically significant differences in LVPT, LVM, and LVMI across both genders, irrespective of the treatment or exercise regimen. This lack of significant difference indicates that the short-term administration of EPO in conjunction with moderate exercise does not induce hypertrophic changes in the left ventricle, particularly in comparison to the longer-term or chronic EPO usage reported in previous studies.[18,19] However, the physiological differences between genders, such as baseline ventricular size and response to hypertrophic stimuli, may be a contributing factor to the overall outcome. Therefore, while this study did not observe significant hypertrophic changes, it emphasises the importance of considering both gender differences and the duration of EPO exposure when evaluating its effects on cardiac morphology.

The study also evaluated the influence of EPO and exercise on right ventricular parameters. Significant differences were observed in RVT and IVST between different treatment groups in female rats, indicating a gender-specific response to EPO and exercise. In the FS group, the observed increase in IVST, RVT and CCD levels, which is thought to occur as a result of exercise-induced pulmonary hypertension, indicates a hypertrophic response that was less pronounced in the male groups. Conversely, in the FSD group, the decline in RVT, IVST, CCD and CSA levels was regarded as indicative of acute cardiac dilatation. A similar trend was observed in the FD group, with declines in RVT, IVST and CSA accompanied by increases in LVDL and CCD. The alterations observed in the FSD and FD groups indicate that female rats exhibit heightened sensitivity to the thinning of the right heart wall and interventricular septum in response to EPO and physical exertion. This phenomenon may be attributed to the existence of differences in hormonal regulation and cardiovascular physiology between the sexes. These outcomes emphasise the necessity of considering gender-specific differences in the cardiovascular effects of EPO, particularly with regard to the right ventricle.

A comparative analysis of the relative organ weights reveals that the effects of EPO and exercise on different organs vary according to gender. In particular, the spleen is one of the organs in which these differences are most evident. In female rats, a significant increase in spleen weight was observed in the EPO-only group (FD), while this increase was more limited in the EPO-and-exercise-combined group (FSD). This indicates that the stimulatory impact of EPO on the hematopoietic system can be mitigated when combined with exercise. The minor alterations in other organs are likely attributable to inherent variations in body weight and sex hormones. These findings suggest that the effects of EPO on cardiac morphometry cannot be directly correlated with organ weights.

Moreover, a significant decrease in BW and BSA parameters was observed in the EPO and exercise combined group (MSD) in male rats, whereas no alteration was evident in the EPO-only group (MD) and in the female groups (Table 2). A study by Caillaud *et al.*,[20] reported that EPO increased body lipid oxidation during exercise in men. The data presented here suggest that the combined administration of EPO and exercise may exert gender-specific effects on body weight.

While the present study offers valuable insights into the cardiac morphometric changes induced by EPO in combination with exercise, it is important to acknowledge certain limitations. Notably, the study did not measure blood-related parameters such as hematocrit, hemoglobin levels, and red blood cell count. These parameters are essential for comprehending the full scope of EPO's effects, particularly its role in enhancing oxygen-carrying capacity and the potential contribution of this to the observed cardiac alterations. Incorporating these hematological assessments would have enabled a more comprehensive analysis of the physiological mechanisms underlying the cardiac outcomes observed in this study. It would be beneficial for future research to include these measurements in order to gain a more comprehensive understanding of the systemic effects of EPO, particularly in the context of cardiovascular adaptations and potential gender-specific responses.

In conclusion, the findings of the present study demonstrated that short-term EPO administration in conjunction with moderate exercise did not result in the development of left ventricular hypertrophy in both male and female rats. However, a reduction in the thickness of the right ventricular wall and the interventricular septum was observed in female groups administered EPO, indicating acute cardiac dilatation. These results emphasise the necessity to consider gender differences in the cardiovascular effects of EPO, particularly regarding the right ventricle. Moreover, further research is required to gain insight into the long-term effects of these changes on female subjects.

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None.

Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose.

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