

Endothelial function in athletes in the process of adaptation to various training exercise modes

S. M. Kanyhina^{ID}*^{B,D,F}, V. V. Syvolap^{ID}^{A,C,E}, M. S. Potapenko^{D,E}

Zaporizhzhia State Medical University, Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Key words:

endothelial function, endurance, strength, speed.

Zaporozhye
medical journal
2021; 23 (1), 52-59

*E-mail:
malakhova_sn@ukr.net

Studies on endothelial dysfunction and its relationship with adaptive disorders in highly skilled athletes are few in number and mainly carried out in cyclic kinds of sports due to larger volumes and higher intensities of training loads associated with endurance performance gain. Stress and sex hormones and growth hormone play an important role in the regulation of endothelial function, but factors, which can stimulate negative vascular changes, remain a matter of debate. It is also unclear, whether changes in the vascular system depend on the type, mode or intensity of physical activity.

The aim of the work was to perform a comparative assessment of endothelial function and to study the role of some hormones in its regulation in highly qualified athletes in the process of adaptation to various training loads.

Material and methods. After signing a written informed consent, the study involved 104 athletes (80 men and 24 women) qualifying from the First-Class athletes to Masters of Sports of International Class (MSIC): 63 – athletes, who mainly trained endurance performance (triathletes, swimmers, long-distance runners, rowers), 31 – strength performance (weightlifters, powerlifters, kettlebell lifters), 10 – speed performance (sprinters). The mean age of the examined athletes was 21.75 ± 3.32 years. Among them, there were Masters of Sports of International Class (MSIC) – 2 athletes, Masters of Sports (MS) – 25, Candidates Master of Sports (CMS) – 48, First-Class athletes – 29.

Plasma levels of endothelin-1, 6-keto-PG, erythropoietin, growth hormone, testosterone, free testosterone were determined by enzyme-linked immunoassay on a Seac ELISA-Reader Sirio S (Seac Radim Company, Italy).

Results. There was no statistically significant difference in endothelin-1 levels between the endurance and strength athletes, but the strength-trained athletes showed a tendency towards endothelin-1 level predominance (0.77 ± 0.04 fmol/ml vs. 0.72 ± 0.06 fmol/ml; $P = 0.176$) and 2 times ($P = 0.017$) higher levels of 6-keto-PG. The endothelin-1 and 6-keto-PG levels did not differ significantly between the endurance and speed athletes. The strength-trained athletes exhibited 5.2 % ($P = 0.016$) higher endothelin-1 levels than speed-trained athletes. However, these athletes did not differ statistically in the 6-keto-PG (292.30 ± 70.38 pg/ml against 106.92 ± 74.44 pg/ml; $P = 0.834$) level. A positive correlation was found between the levels of erythropoietin and 6-keto-PG in the endurance-trained ($r = 0.57$; $P = 0.00001$) and strength-trained ($r = 0.46$; $P = 0.013$) athletes.

Analysis of testosterone and free testosterone levels did not reveal statistically significant differences between endurance-, strength- or speed-trained athletes. At the same time, there was a trend towards higher levels of testosterone and free testosterone in the strength-trained athletes as compared to those in the endurance- or speed-trained athletes. The strength athletes showed a positive correlation ($r = 0.46$; $P = 0.013$) between the levels of free testosterone and endothelin-1. The highest level of somatotrophic hormone was in the speed-trained athletes (11.74 ± 3.13 mIU/l), 2 times less – in the endurance-trained athletes (5.69 ± 1.19 mIU/l), and the lowest one – in the strength-trained athletes (2.66 ± 1.32 mIU/l). A positive correlation between the growth hormone and erythropoietin levels ($r = 0.29$; $P = 0.038$) was revealed in the endurance athletes.

Conclusions. The endurance and speed athletes did not differ in the levels of endothelin-1, 6-keto-PG, erythropoietin, and testosterone. The strength-trained athletes showed signs of endothelial dysfunction: higher endothelin-1 levels with significantly reduced growth hormone and a tendency of increase in the serum testosterone level, as well as a compensatory increase in 6-keto-PG to maintain the balance between vasoconstrictors and vasodilators.

Ключові слова:

функція ендотелію, витривалість, сила, швидкість.

Запорізький
медичний журнал.
2021. Т. 23, № 1(124).
С. 52-59

Функція ендотелію у спортсменів у процесі адаптації до тренувальних навантажень різної спрямованості

С. М. Канигіна, В. В. Сиволап, М. С. Потапенко

Дослідження ендотеліальної дисфункції та її зв'язку з адаптаційними порушеннями у висококваліфікованих спортсменів нечисленні. Здебільшого їх здійснюють у циклічних видах спорту, що зумовлено інтенсивнішими та більшими за обсягом тренувальними навантаженнями, які спрямовані на розвиток витривалості. Важливу роль у регуляції функцій ендотелію відіграють гормони стресу, статеві гормони та гормони росту, але питання про те, які фактори можуть стимулювати негативні судинні зміни, залишається дискусійним. Також неясно, чи залежать зміни судинної системи від виду, спрямованості й інтенсивності фізичних навантажень.

Мета роботи – порівняльне оцінювання показників функції ендотелію та вивчення ролі окремих гормонів в її регуляції у висококваліфікованих спортсменів у процесі адаптації до тренувальних навантажень різної спрямованості.

Матеріали та методи. Після підписання письмової інформованої згоди в дослідження залучили 104 спортсмени (80 чоловіків і 24 жінки) рівня майстерності від 1 розряду до МСМК: 63 – атлети, які розвивали переважно якість витривалості (тріатлоністи, плавці, бігуни на довгі дистанції, академічна гребля), 31 – якість сили (важкоатлети, паверліфтинг, гирьовий спорт),

10 –якість швидкості (бігуни-спринтери). Середній вік становив $21,75 \pm 3,32$ року. Обстежили майстрів спорту міжнародного класу (МСМК) – 2 спортсмени, майстрів спорту (МС) – 25, кандидатів у майстри спорту – 48, першорозрядників – 29. Методом ІФА визначили рівні ендотеліну-1, 6-кето-ПГ, еритропоетину, гормону росту, тестостерону, вільного тестостерону.

Результати. У спортсменів, які удосконалювали якості витривалості або сили, відсутня статистично вірогідна різниця за вмістом ендотеліну-1, проте у спортсменів, які розвивали якість сили, встановлена тенденція до переважання вмісту ендотеліну-1 ($0,77 \pm 0,04$ фмоль/мл проти $0,72 \pm 0,06$ фмоль/мл; $p = 0,176$) та вдвічі ($p = 0,017$) більший вміст 6-кето-ПГ. За вмістом ендотеліну-1 і 6-кето-ПГ спортсмени, які розвивали якості витривалості або швидкості, вірогідно не відрізнялися. У спортсменів, які розвивали якість сили, вміст ендотеліну-1 більший, ніж у спортсменів, які розвивали якість швидкості, на $5,2\%$ ($p = 0,016$). Але ці спортсмени статистично не відрізнялися за вмістом 6-кето-ПГ ($292,30 \pm 70,38$ пг/мл проти $106,92 \pm 74,44$ пг/мл; $p = 0,834$). Між вмістом еритропоетину та 6-кето-ПГ встановили позитивний кореляційний зв'язок у спортсменів, які удосконалювали якість витривалості ($r = 0,57$; $p = 0,00001$), та спортсменів, які розвивали якість сили ($r = 0,46$; $p = 0,013$).

Аналіз вмісту тестостерону та вільного тестостерону не показав статистично вірогідну різницю між групами спортсменів, які розвивали якості витривалості, сили або швидкості. Але визначили тенденцію до переважання вмісту тестостерону та вільного тестостерону у спортсменів, які удосконалювали якість сили, над аналогічними показниками у спортсменів, які розвивали якості витривалості або швидкості. У спортсменів, які розвивали якість сили, між вмістом вільного тестостерону та ендотеліну-1 виявили позитивний кореляційний зв'язок ($r = 0,46$; $p = 0,013$). Найбільший вміст соматотропного гормону визначили у спортсменів, які розвивали якість швидкості ($11,74 \pm 3,13$ мкМОд/мл), удвічі менший – у спортсменів, які удосконалювали якість витривалості ($5,69 \pm 1,19$ мкМОд/мл), найменший – у силових атлетів ($2,66 \pm 1,32$ мкМОд/мл). У спортсменів, які удосконалювали якість витривалості, виявили позитивний кореляційний зв'язок між вмістом гормону росту та еритропоетину ($r = 0,29$; $p = 0,038$).

Висновки. Спортсмени, які розвивали якості витривалості або швидкості, не відрізнялися за вмістом ендотеліну-1, 6-кето-ПГ, еритропоетину, тестостерону. У спортсменів, які розвивали якість сили, виявили ознаки ендотеліальної дисфункції: більший вміст ендотеліну-1 на тлі істотного пригнічення гормону росту й тенденції до збільшення тестостерону, компенсаторне збільшення вмісту 6-кето-ПГ, яке підтримало рівновагу вазоконстрикторів і вазодиліляторів судинного ендотелію.

Функция эндотелия у спортсменов в процессе адаптации к тренировочным нагрузкам различной направленности

С. Н. Каныгина, В. В. Сыволап, М. С. Потапенко

Исследование эндотелиальной дисфункции и ее связи с адаптационными нарушениями у высококвалифицированных спортсменов немногочисленны. В основном их проводят в циклических видах спорта, что обусловлено более интенсивными и объемными тренировочными нагрузками, направленными на развитие выносливости. Важную роль в регуляции функции эндотелия играют гормоны стресса, половые гормоны и гормон роста, но вопрос о том, какие факторы могут стимулировать негативные сосудистые изменения, остается дискуссионным. Также неясно, зависят ли изменения сосудистой системы от вида, направленности и интенсивности физических нагрузок.

Цель работы – проведение сравнительной оценки показателей функции эндотелия и изучение роли некоторых гормонов в ее регуляции у высококвалифицированных спортсменов в процессе адаптации к тренировочным нагрузкам различной направленности.

Материалы и методы. После подписания письменного информированного соглашения в исследование включены 104 спортсмена (80 мужчин и 24 женщины) уровня мастерства от 1 разряда до МСМК: 63 – атлеты, которые развивали преимущественно качество выносливости (триатлонисты, пловцы, бегуны на длинные дистанции, академическая гребля), 31 – качество силы (тяжеловесы, пауэрлифтинг, гиревой спорт), 10 – качество скорости (бегуны-спринтеры). Средний возраст составил $21,75 \pm 3,32$ года. Обследовали мастеров спорта международного класса (МСМК) – 2 спортсмена, мастеров спорта (МС) – 25, кандидатов в мастера спорта – 48, перворазрядников – 29. Методом ИФА определили уровни эндотелина-1, 6-кето-ПГ, эритропоэтина, гормона роста, тестостерона, свободного тестостерона.

Результаты. У спортсменов, которые совершенствовали качества выносливости или силы, не установлена статистически достоверная разница по содержанию эндотелина-1, однако у спортсменов, развивающих качество силы, отмечена тенденция к преобладанию содержания эндотелина-1 ($0,77 \pm 0,04$ фмоль/мл против $0,72 \pm 0,06$ фмоль/мл, $p = 0,176$) и в 2 раза ($p = 0,017$) большее содержание 6-кето-ПГ. По содержанию эндотелина-1 и 6-кето-ПГ спортсмены, развивающие качества выносливости или скорости, достоверно не отличались. У спортсменов, которые развивали качество силы, содержание эндотелина-1 больше, чем у спортсменов, которые развивали качество скорости, на $5,2\%$ ($p = 0,016$). Однако эти спортсмены статистически не отличались по содержанию 6-кето-ПГ ($292,30 \pm 70,38$ пг/мл против $106,92 \pm 74,44$ пг/мл, $p = 0,834$). Между содержанием эритропоэтина и 6-кето-ПГ установлена положительная корреляционная связь у спортсменов, совершенствовавших качество выносливости ($r = 0,57$; $p = 0,00001$), и спортсменов, которые развивали качество силы ($r = 0,46$; $p = 0,013$).

Анализ содержания тестостерона и свободного тестостерона не показал статистически достоверную разницу между группами спортсменов, которые развивали качества выносливости, силы или скорости. Тем не менее отмечена тенденция к преобладанию содержания тестостерона и свободного тестостерона у спортсменов, совершенствовавших качество силы, над аналогичными показателями у спортсменов, развивающих качества выносливости или скорости. У спортсменов, которые развивали качество силы, между содержанием свободного тестостерона и эндотелина-1 установлена положительная корреляционная связь ($r = 0,46$; $p = 0,013$). Наибольшее содержание соматотропного гормона отмечено у спортсменов, развивающих качество скорости ($11,74 \pm 3,13$ мкМЕд/мл), в 2 раза меньше – у спортсменов, совершенствовавших качество

Ключевые слова:
функция эндотелия,
выносливость,
сила, скорость.

Запорожский
медицинский журнал.
2021. Т. 23, № 1(124).
С. 52-59

выносливости ($5,69 \pm 1,19$ мкМЕд/мл), наименьшее – у силовых атлетов ($2,66 \pm 1,32$ мкМЕд/мл). У спортсменов, которые совершенствовали качество выносливости, обнаружена положительная корреляционная связь между содержанием гормона роста и эритропоэтина ($r = 0,29$; $p = 0,038$).

Выводы. Спортсмены, развивающие качества выносливости или скорости, не отличались по содержанию эндотелина-1, 6-кето-ПГ, эритропоэтина, тестостерона. У спортсменов, которые развивали качество силы, отмечены признаки эндотелиальной дисфункции: большее содержание эндотелина-1 на фоне значительного угнетения гормона роста и тенденции к увеличению тестостерона, компенсаторное увеличение содержания 6-кето-ПГ, которое сохранило равновесие вазоконстрикторов и вазодилаторов сосудистого эндотелия.

Special attention is now being paid to studying vascular endothelial dysfunction as its biological role in the development of pre-pathological and pathological conditions remains poorly known, and the prevention of endothelial dysfunction can be important for achieving performance benefits.

Higher volumes of exercise can accelerate the development of endothelial dysfunction, and high-intensity exercise can increase the risk of cardiovascular disease (CVD). The severity of vascular damage depends on training volumes, undertaken by an athlete throughout life. CVD risk is likely to be associated with the type of sports discipline practiced [9].

However, there was evidence of no differences in endothelial function in athletes, who performed different intensity and duration of exercise [15].

In modern high-achievement sports, intense physical activity leads to multidirectional changes in the body, in particular, contributes to the development of universal biochemical and physiological phenomena – chronic oxidative stress and associated tissue hypoxia [4], which is one of the components of vascular endothelial dysfunction [8].

Endothelial cells are less sensitive to hypoxia and are damaged by ischemia much less than other cells due to their ability to switch to anaerobic energy metabolism, as well as to synthesize heat shock proteins, glucose-regulated proteins, enzymes involved in glycolysis (glyceraldehyde 3-phosphate dehydrogenase and non-neuronal enolase), that increases the resistance of cells to damage [23]. Stress hormones, sex hormones and growth hormone (GH) play an important role in the regulation of endothelial function, but what kind of factors can stimulate negative vascular changes, remains a matter of debate. It is also unclear, whether changes in the vascular system depend on the type, mode or intensity of physical activity [7].

Endothelial dysfunction is recognized as a universal mechanism modulated by all risk factors associated with cardiovascular disorders. To assess the adaptation level to training loads in athletes, the dynamics of changes in the vascular endothelium regulators is used [1]. However, studies on endothelial dysfunction and its relationship with adaptive disorders in highly skilled athletes are few in number [13] and mainly carried out in cyclic kinds of sports due to larger volumes and higher intensities of training loads associated with endurance performance gain.

Aim

Therefore, the aim of the work was to perform a comparative assessment of endothelial function and to study the role of some hormones in its regulation in highly qualified athletes in the process of adaptation to various training loads.

Material and methods

After signing a written informed consent, the study involved 104 athletes (80 men and 24 women) qualifying from the First-Class athletes to Masters of Sports of International Class (MSIC): 63 – athletes, who mainly trained endurance performance (triathletes, swimmers, long-distance runners, rowers), 31 – strength performance (weightlifters, powerlifters, kettlebell lifters), 10 – speed performance (sprinters). The mean age of the examined athletes was 21.75 ± 3.32 years. The mean age of the examined athletes was 21.75 ± 3.32 years. Among them, there were Masters of Sports of International Class (MSIC) – 2 athletes, masters of sports (MS) – 25, candidates masters of sports – 48, athletes of the 1 category – 29.

Plasma levels of endothelin-1, erythropoietin, 6-keto-prostaglandin, testosterone, free testosterone and GH were determined by enzyme-linked immunoassay on a Seac ELISA-Reader Sirio S (Seac Radim Company, Italy).

The results were processed by methods of variation statistics using the software package Statistica 13.0 (Stat-Soft, USA), license number JPZ8041382130ARCN10-J). The Shapiro–Wilk test was used to test the hypothesis of normal distribution of quantitative indicators. The quantitative indicators were presented in the form of arithmetic mean and standard error ($M \pm m$), Me (Q25; Q75) taking into account the normality of the data distribution; qualitative indicators – in the form of absolute and relative frequency. The quantitative indicators of independent groups were compared by the method of parametric statistics using the two-sample Student's t-test with a two-sided test index for a statistical significance value, and the non-parametric Mann–Whitney U test. The differences were considered statistically significant at a value of $P < 0.05$.

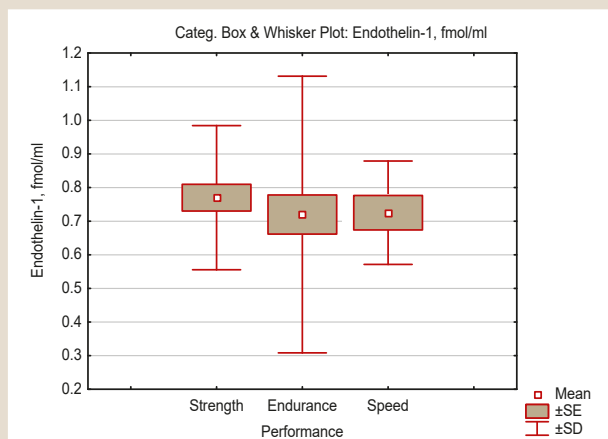
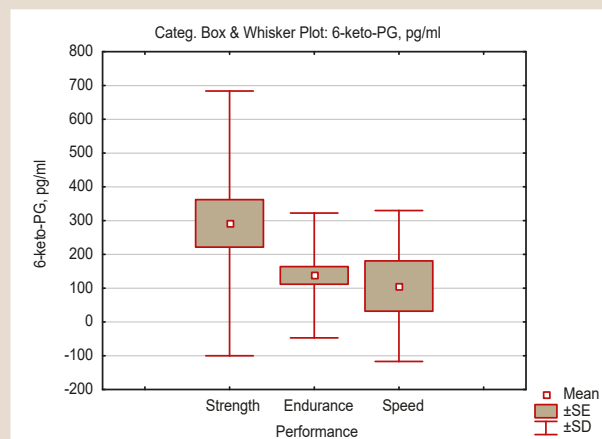
Results

Endothelial function in athletes was assessed by the levels of endothelin-1 and 6-keto-prostaglandin (6-keto-PG). There was no statistically significant difference in endothelin-1 levels between the endurance and strength athletes (Table 1, Fig. 1), but the strength-trained athletes showed a tendency towards endothelin-1 level predominance (0.77 ± 0.04 fmol/ml vs. 0.72 ± 0.06 fmol/ml; $P = 0.176$) and 2 times ($P = 0.017$) higher levels of 6-keto-PG (Table 1, Fig. 2). The levels of endothelin-1 and 6-keto-PG in the endurance- and speed-trained athletes did not differ significantly (0.72 ± 0.06 fmol/ml vs. 0.73 ± 0.05 fmol/ml; $P = 0.176$) and (138.24 ± 26.12 pg/ml vs. 106.92 ± 74.44 pg/ml; $P = 0.834$), respectively.

A comparison of endothelin-1 level between the strength and speed athletes showed significantly 5.2 % higher its concentrations in strength-trained athletes (0.77 ± 0.04 fmol/ml

Table 1. The levels of endothelin-1, 6-keto-PG, erythropoietin, growth hormone, testosterone, free testosterone in endurance-, strength- and speed-trained athletes, M ± m, Me (Q25; Q75)

Value, units of measure	Performance			P _{1,2} Endurance – Strength Mann–Whitney U Test	P _{1,3} Endurance – Speed Mann–Whitney U Test	P _{2,3} Strength – Speed Mann–Whitney U Test
	Endurance (n = 63)	Strength (n = 31)	Speed (n = 10)			
Erythropoietin, mIU/ml	7.66 ± 0.63 6.12 (4.94; 8.82)	8.52 ± 1.47 6.47 (4.94; 10.23)	10.57 ± 4.95 5.53 (4.59; 9.69)	0.803	0.460	0.304
Endothelin-1, fmol/ml	0.72 ± 0.06 0.72 (0.64; 0.79)	0.77 ± 0.04 0.74 (0.68; 0.82)	0.73 ± 0.05 0.76 (0.75; 0.79)	0.176	0.160	0.016
Testosterone, ng/ml	7.78 ± 0.59 7.93 (4.04; 11.8)	8.14 ± 0.68 8.69 (4.90; 11.80)	5.83 ± 1.55 5.64 (2.07; 10.6)	0.792	0.126	0.873
Testosterone free, pg/ml	11.37 ± 1.18 9.04 (2.98; 17.39)	13.00 ± 1.59 11.77 (7.40; 16.84)	6.78 ± 2.05 6.75 (2.10; 8.14)	0.459	0.071	0.873
Growth hormone, mIU/l	5.69 ± 1.19 1.02 (0.09; 10.70)	2.66 ± 1.32 0.09 (0.05; 1.5)	11.74 ± 3.13 8.26 (4.47; 18.7)	0.014	0.021	0.011
6-keto-PG, pg/ml	138.24 ± 26.12 67.34 (27.96; 198.06)	292.30 ± 70.38 132.82 (46.95; 353.19)	106.92 ± 74.44 20.22 (10.09; 54.68)	0.017	0.065	0.834

**Fig. 1.** The level of endothelin-1 in the endurance-, strength- and speed-trained athletes.**Fig. 2.** The level of 6-keto-PG in the endurance-, strength- and speed-trained athletes.

vs. 0.73 ± 0.05 fmol/ml; $P = 0.016$). Although the content of 6-keto-PG did not differ statistically between these athletes, there was a tendency to a predominance of 6-keto-PG in the strength-trained athletes compared with the speed-trained athletes (292.30 ± 70.38 pg/ml against 106.92 ± 74.44 pg/ml, $P = 0.834$).

Thus, the levels of endothelin-1 and 6-keto-PG did not differ between the endurance and speed athletes, who shared the same pattern of endothelial function. At the same time, the strength athletes showed signs of endothelial dysfunction because they had higher levels of endothelin-1. However, this increase in vasoconstrictor was compensated by a 2-fold increase in the level of 6-keto-PG – a biologically active substance with vasodilating properties.

An analysis of erythropoietin level (Table 1, Fig. 3) revealed an upward trend in its concentration in the speed-trained athletes. The lowest level of erythropoietin was observed in the endurance athletes. However, the difference in erythropoietin levels between the groups of endurance-, strength- and speed-trained athletes was not statistically significant.

A positive correlation was found between the levels of erythropoietin and 6-keto-PG (Fig. 4) in the endurance-trained athletes ($r = 0.57$; $P = 0.00001$) and in the strength-trained athletes ($r = 0.46$; $P = 0.013$).

An analysis of testosterone and free testosterone (Table 1, Fig. 5, 6), despite the expectations, did not reveal a statistically significant difference between the groups of endurance-, strength- and speed-trained athletes. But even so, there was a trend towards higher levels of testosterone and free testosterone in the strength-trained athletes as compared to those in the endurance- or speed-trained athletes.

In the strength-trained athletes (Fig. 7), a positive correlation was found between the levels of free testosterone and endothelin-1 ($r = 0.46$; $P = 0.013$), which may indicate the ability of the active fraction of testosterone to induce endothelin-1 synthesis in the vascular endothelium.

The athletes of all three studied groups differed significantly in GH level (Table 1, Fig. 8). The highest level of somatotrophic hormone was in the speed-trained athletes (11.74 ± 3.13 mIU/l), 2 times less – in the endurance-trained athletes (5.69 ± 1.19 mIU/l), and the lowest one – in the strength-trained athletes (2.66 ± 1.32 mIU/l).

A positive correlation between the GH and erythropoietin levels ($r = 0.29$; $P = 0.038$) was revealed in the endurance-trained athletes ($r = 0.29$; $P = 0.038$).

Thus, the endurance and speed training in the athletes was associated with a significant increase in the somatotrophic hormone level, due to the need to ensure an adequate level of aerobic energy metabolism during muscular exercise.

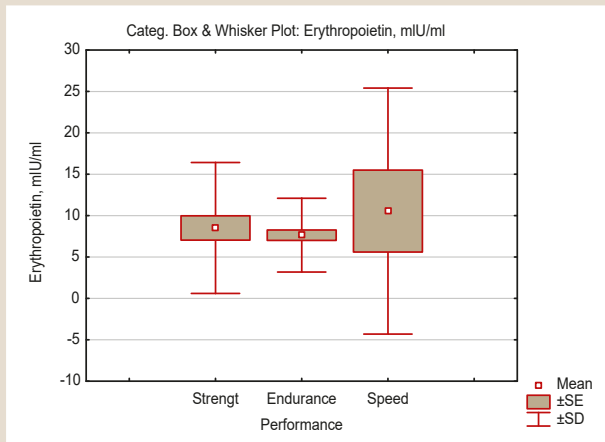


Fig. 3. The level of erythropoietin in the endurance-, strength- and speed-trained athletes.

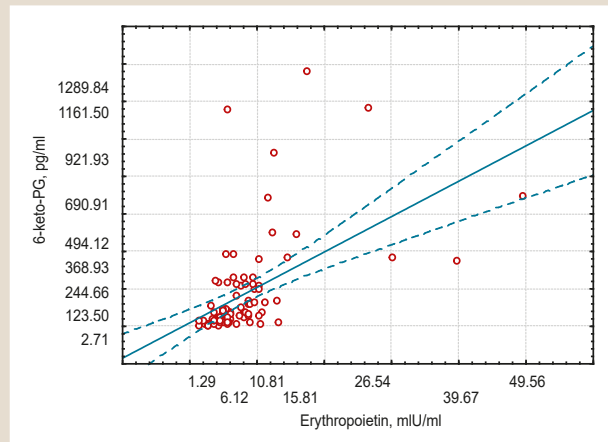


Fig. 4. Correlation between erythropoietin and 6-keto-PG levels in the endurance-trained athletes.

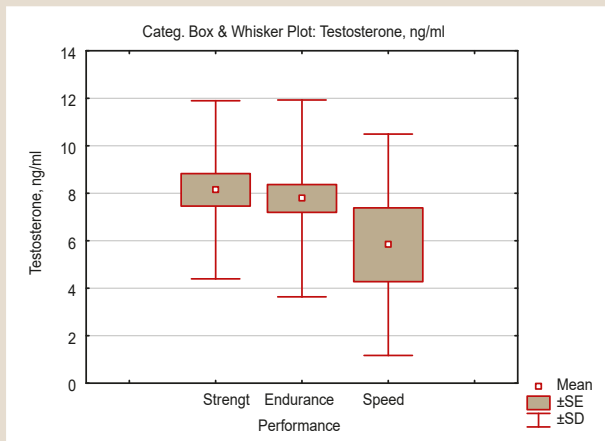


Fig. 5. The level of testosterone in the endurance-, strength- and speed-trained athletes.

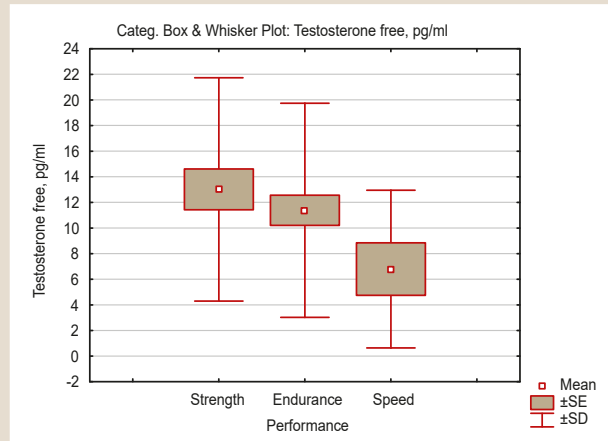


Fig. 6. The level of free testosterone in the endurance-, strength- and speed-trained athletes.

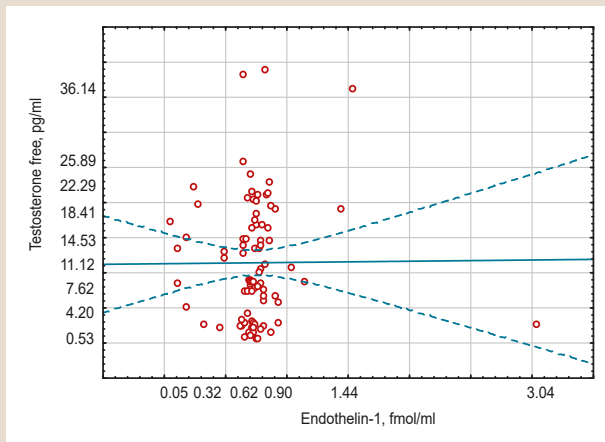


Fig. 7. Correlation between free testosterone and endothelin-1 in the strength-trained athletes.

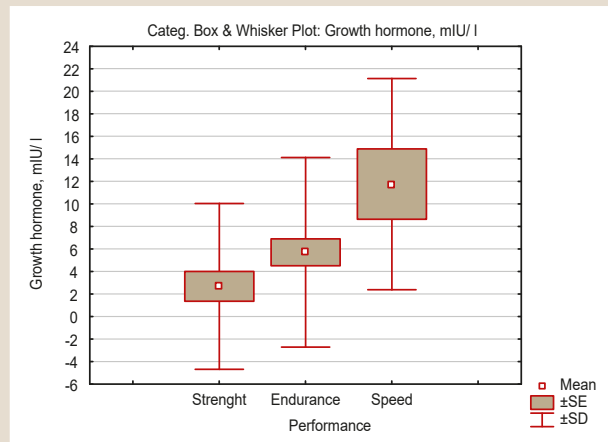


Fig. 8. The level of growth hormone in the endurance-, strength- and speed-trained athletes.

Discussion

Endothelial dysfunction is characterized by a shift in the endothelium towards a pro-inflammatory and prothrombotic state with a decrease in vasodilation or paradoxical vasoconstriction. Paradoxical vasoconstriction and impaired NO-dependent vasodilation are of particular clinical signi-

ficance in conditions of mental and physical stress. Some studies have proven a decreased endothelial response and endothelial dysfunction presence in athletes [7,13].

In the work of Smirnov I.E. it has been shown that young swimmers of both sexes had the most significant increase in plasma endothelin-1 concentrations: 3 times – in female swimmers, 3.4 times – in male swimmers compared with

the reference group levels. However, the serum nitric oxide content in all the examined young swimmers was not different from the control group. Derangements in endogenous production of nitric oxide and endothelin-1 in the examined swimmers was accompanied by a significant decrease (1.4 times) in the plasma concentration ratio of these bioregulators in both boys and girls, indicating a shifted balance towards higher endothelin-1 production [13].

In the study of V. V. Kologrivova et al. among weightlifters during the reactive hyperemia test before exercise, there was no change in the brachial artery diameter, and after exercise it decreased by 5.3 %. In the group of athletes before exercise, the brachial artery diameter increased by 2.9 %, after exercise there was the vessel dilation by 4.1 %. That is, there was an increase in endothelial function in response to exercise training. According to the researchers, the endothelial functional state in strength sports athletes should be considered as an adaptive factor to regular exercise, as there was a temporary cessation of blood flow due to compression of blood vessels by muscle tensing. Significant endothelium-dependent vasodilation in such conditions may result in steal syndrome [7].

Athletes trained in cyclic sports also showed a decrease in endothelial activity [7]. According to D. J. Green and co-authors, signs of early atherosclerosis and a tendency to thrombosis were revealed in 60.5 % of athletes in cyclic kinds of sports (rowing, skiing and cycling). The researchers believe, that constant exposure of endothelium to shear stress, increased blood pressure and production of endothelium-dependent factors may stimulate the development of atherosclerosis [19].

The researchers attributed different responses to the reactive hyperemia test before and after exercise among athletes in cyclic and strength kinds of sports to variations in the endothelial nitric oxide synthase (eNOS) expression. Strength athletes demonstrated a sharp decrease in plasma eNOS after exercise training, while its contrasting increase was found in track-and-field athletes. In addition, the studies showed that the reactive hyperemia test induced NO-mediated brachial artery dilation [19].

Our study has shown no statistically significant differences in endothelin-1 and 6-keto-PG levels in the endurance- and speed-trained athletes. Meanwhile, the strength-trained athletes showed signs of endothelial dysfunction. They exhibited higher levels of endothelin-1, but the increased vasoconstrictor level was compensated by significantly increased level of 6-keto-PG.

When analyzing the levels of hormones with a potential effect on endothelial function, the significant difference only in somatotropic hormone has been found.

It is known, that one of the most permanent biological effects of GH is the dilation of peripheral blood vessels. This effect is thought to be mediated by insulin-like growth factor-1 (IGF-1), for which there are high-affinity binding sites on the endothelial cells. IGF-1 directly stimulates the release of NO, which is a known mediator of vasodilation, inhibitor of platelet aggregation, leukocyte adhesion and smooth muscle cell growth. In healthy volunteers, infusions of IGF-1 caused a pronounced dilation of the forearm blood vessels, which was prevented by the administration of L-NG-monomethylarginine [2]. Recombinant growth hormone (rGR) replacement therapy had a positive effect

on the vascular parameters: improvements of endothelial function, vascular elasticity, a reduction in total cholesterol, LDL cholesterol and an increase in HDL cholesterol. In GH-deficient adults, rGR treatment reversed early atherosclerotic changes in major arteries. In a small number of GH-deficient adults, rGR replacement therapy for 6-24 months reduced the intima-media complex thickness of the common carotid artery to normal [16]. Discontinuation of rGR therapy in adults (but not in adolescents) with severe GH deficiency led to an increase in the intima-media complex thickness and cardiovascular risk [17].

We have found the highest levels of GH in the speed-trained athletes, the endurance-trained athletes have shown half of this level, and the lowest levels of the hormone have been revealed in the strength-trained athletes.

Changes in GH level in athletes were also obtained in another study [12]. An increase in GH and a decrease in insulin levels after muscle work (30-minute ergometric cycling load with an intensity of 75 % of ischemic preconditioning (IPC)) were observed in endurance-trained athletes. These changes occurred due to the need to ensure proper muscle energy metabolism, as enforced by somatotropin – an insulin antagonist. In individuals with muscle adaptations to the load effect, there was a significant increase in insulin at constant levels of somatotropin. Athletes, who developed anaerobic capacity through graduated ergometric loads, were characterized by high stability of GH and insulin. According to the researchers, such changes in the plasma GH and insulin concentrations at rest and after graduated ergometric loads indicated the presence of specific shifts in hormonal and metabolic status due to the level and peculiarity of daily physical activity [12].

Although the erythropoietin levels showed no significant differences between the endurance-, strength- and speed-trained athletes, it exhibited a clear upward trend in the speed-trained athletes as compared to this hormone levels in the strength athletes, and the lowest levels of erythropoietin were determined in the endurance athletes. The most interesting fact was the positive correlation between the levels of 6-keto-PG and erythropoietin that we thought was indicative of the endothelioprotective properties of the latter. The association between the erythropoietin and 6-keto-PG levels was observed in both the endurance- and strength-trained athletes, i.e. regardless of the training mode. The data obtained suggest the positive effect of erythropoietin on endothelium-independent vasodilation. A possible pathophysiological mechanism of this erythropoietin action should be considered as its ability to increase circulating plasma titer of endothelial progenitor cells, which effectively help to maintain the vascular endothelium integrity. The process of endothelial progenitor cells homing or recruitment of circulating ones to endothelial injury or ischemic sites is regulated by key angiogenic chemokine stromal cell-derived factor-1 (SDF-1). In conditions of ischemia, inflammation, discrete regions of hypoxia in the bone marrow undergo an increase in the hypoxia inducible factor-1 (HIF-1) transcriptional activity, which is responsible for an expression of SDF-1. Nitric oxide, estrogens, high-density lipoproteins, vascular endothelial growth factor and erythropoietin also increase the plasma titer of endothelial progenitor cells and recruit them to the site of injury through activating the phosphatidylinositol-3-phosphate

(PIP3)/Akt pathway. Cell adhesion molecules, such as P/E-selectin and ICAM-1, mediate the binding of endothelial progenitor cells to the injured endothelium. Subsequently, under the influence of the laminar shear stress of the blood, the attached endothelial progenitor cells differentiate into endothelial cells [5].

We have not obtained the statistically significant association between testosterone or free testosterone and exercise training mode in our study. However, there was a trend towards higher levels of testosterone and free testosterone in the strength-trained athletes as compared to those in the endurance- or speed-trained athletes.

The study [10] has proved a significant impact of sports specialization and sports experience, as well as the amounts and types of food intake and daily physical activity on the plasma levels of sex hormones, such as testosterone, progesterone, estradiol, follicle-stimulating and luteinizing hormone. Performing a 30-minute ergometric bicycle load with an intensity of 75 % of the IPC led to a decrease in the serum concentration of sex hormones in persons with different levels and specifics of daily physical activity compared to baseline values. The combined use of muscular loading and nutritional supplementation was accompanied by a pronounced gradual recovery of serum hormone levels in both athletes training in different exercise modes and non-athletes relative to the baseline values. The serum concentration of sex hormones in the athletes, who trained in different modes of energy expenditure, was highly resistant to muscular load in contrast to the control group [10].

The literature data on the effects of male sex hormones on the cardiovascular system and endothelial function are contradictory. The negative effect of androgens on the course of cardiovascular pathology is confirmed by a decrease in HDL cholesterol during puberty-related surge of androgens in boys and in the testosterone esters treatment for adolescents with delayed puberty [11], early onset CVD in athletes who used anabolic androgenic steroids. The monograph [6] presents 17 cases of anabolic androgenic steroid-related CVD (11 acute myocardial infarctions, 2 strokes and 4 cases of cardiomyopathy) in young athletes engaged in bodybuilding.

However, according to C. B. Severo (2013), anabolic androgenic steroid-users athletes and non-users did not differ regarding endothelium-independent function, but the brachial artery flow-mediated dilation was significantly reduced in anabolic androgenic steroid-users athletes compared to non-users ($P = 0.03$). In addition, flow-mediated dilation was positively associated with high-density lipoprotein cholesterol levels ($r = 0.49$, $P = 0.03$) [22].

Despite the prevailing ideas about the negative effects of testosterone and the cardioprotective effect of estrogens, such a dichotomy is conditional. Callou de Sa E. Q. et al. found an association between estradiol (E2), rather than testosterone, and coronary heart disease, confirmed by coronography, in young and middle-aged men [14]. Approximately 30–40 μg of E2, the most active estrogen, is synthesized per day in men. About 20 % of this hormone is secreted directly from the testes by Leydig cells, the remaining 80 % is derived from peripheral aromatization of circulating androgen precursors, mainly testosterone, in different tissues (fat, prostate, endothelium and other tissues).

Meanwhile, in clinical observations, androgen therapy in men with coronary heart disease has been found to increase ST-segment depression [3]; conversely, other studies have shown improvements in coronary blood flow and the functional class of chronic heart failure, a decrease in blood pressure and left ventricular myocardial mass [20]. Testosterone replacement therapy stimulates stem cells-derived endothelial progenitor cells via androgen receptors, contributing to myocardial healing and reduction in necrotic lesion size [18].

The reason given by the vast majority of studies for the protective effect of endogenous androgens on the heart and blood vessels is the conversion of the hormones into estrogens, but in the work of D. Liu et al., the protective effect of dehydroepiandrosterone sulfate on the endothelium was not prevented by estrogen receptor inhibition [21].

Thus, in the strength-trained athletes, we have found the highest level of endothelin-1, which was associated with elevated testosterone levels, as evidenced by the direct correlation, and the lowest growth hormone concentration. However, the increase in endothelin-1 level in strength-trained athletes was accompanied by the significant increase in the level of 6-keto-PG. It is clear that shear stress, induced by strength exercise, on endothelial cells is caused by an increase in vasoconstrictors, which contributes to changes in testosterone and growth hormone levels, but the balance is restored by a compensatory increase in the vasodilator 6-keto-PG synthesis.

Conclusions

The endurance and speed athletes did not differ in the levels of endothelin-1, 6-keto-PG, erythropoietin, and testosterone. The strength-trained athletes showed signs of endothelial dysfunction: higher endothelin-1 levels with significantly reduced growth hormone and a tendency of increase in the serum testosterone level, as well as a compensatory increase in 6-keto-PG to maintain the balance between vasoconstrictors and vasodilators.

Conflict of interest: authors have no conflict of interest to declare.
Конфлікт інтересів: відсутній.

Надійшла до редакції / Received: 29.09.2020
Після доопрацювання / Revised: 20.10.2020
Прийнято до друку / Accepted: 30.10.2020

Information about authors:

Kanyhina S. M., MD, PhD, Associate Professor of the Department of Physical Rehabilitation, Sports Medicine, Physical Education and Health, Zaporizhzhia State Medical University, Ukraine.
ORCID ID: [0000-0002-8197-299X](https://orcid.org/0000-0002-8197-299X)

Syvolap V. V., MD, PhD, DSc, Professor, Head of the Department of Propaedeutic to Internal Medicine, Radiation Diagnostics and Radiation Treatment, Zaporizhzhia State Medical University, Ukraine.
ORCID ID: [0000-0001-9865-4325](https://orcid.org/0000-0001-9865-4325)

Potapenko M. S., MD, PhD, Assistant of the Department of Anesthesiology and Intensive Care, Zaporizhzhia State Medical University, Ukraine.

Відомості про авторів:

Канигіна С. М., канд. мед. наук, доцент каф. фізичної реабілітації, спортивної медицини, фізичного виховання і здоров'я, Запорізький державний медичний університет, Україна.

Сиволап В. В., д-р мед. наук, профессор, зав. каф. пропедевтики внутрішньої медицини, променевої діагностики та променевої терапії, Запорізький державний медичний університет, Україна. Потапенко М. С., канд. мед. наук, асистент каф. анестезіології та інтенсивної терапії, Запорізький державний медичний університет, Україна.

Сведения об авторах:

Каныгина С. Н., канд. мед. наук, доцент каф. физической реабилитации, спортивной медицины, физического воспитания и здоровья, Запорожский государственный медицинский университет, Украина.

Сиволап В. В., д-р мед. наук, профессор, зав. каф. пропедевтики внутренней медицины, лучевой диагностики и лучевой терапии, Запорожский государственный медицинский университет, Украина.

Потапенко М. С., канд. мед. наук, ассистент каф. анестезиологии и интенсивной терапии, Запорожский государственный медицинский университет, Украина.

References

- Bershova, T. V., Bakanov, M. I., Smirnov, I. E., Sanfirova, V. M., Korneva, I. T., Polyakov, S. D., & Soloveva, Yu. V. (2016). Izmeneniya funktsional'nogo sostoyaniya sosudistogo endoteliiya u yunyh sportsmenov razlichnoi kvalifikatsii [Changes in the functional state of the vascular endothelium in young athletes of varying skill levels]. *Rossiiskii pediatricheskii zhurnal*, 19(1), 14-19. [https://doi.org/10.18821/1560-9561-2016-19\(1\)-14-19](https://doi.org/10.18821/1560-9561-2016-19(1)-14-19) [in Russian].
- Volevodz, N. N. (2011). Gormon rosta i serdechno-sosudistaya sistema [Growth hormone and the cardiovascular system]. *Problemy endokrinologii*, 57(4), 37-47. [in Russian].
- Gamidov, S. I., Tazhetdinov, O. Kh., Pavlovichev, A. A., Popova, A. Yu., & Tkhatapsoeva, R. A. (2010). Osobennosti patogeneza, diagnostiki i lecheniya erektil'noi disfunktsii u bol'nykh s gipogonadizmom [Peculiarities of pathogenesis, diagnostics and treatment of erectile dysfunction in patients presenting with hypogonadism]. *Problemy endokrinologii*, 56(5), 33-42. [in Russian].
- Gumina, L. M., Lisnjak, I. A., & Burmac, V. O. (2013). Fiziologicheskii angiogenez kak faktor adaptatsii sportsmenov k fizicheskim nagruzkam s razlichnym mekhanizmom energoobespecheniya [Physiological angiogenesis as factor of adaptation of sportsmen to physical activities with different mechanism of energy's providing]. *Vestnik sportivnoi nauki*, (3), 34-38. [in Russian].
- Gureyev, S. A., Zinovkin, D. A., & Shebushev, N. G. (2013). Endotelial'nye progenitornye kletki: uchastie v angiogeneze i perspektivy ispol'zovaniya v autologicheskoi kletchnoi terapii ateroskleroticheskikh porazhenii osudov [Endothelial progenitor cells: their role in angiogenesis and prospects of application in autologous cell therapy of atherosclerotic vascular disease]. *Problemy zdorov'ya i ekologii*, (1), 7-11. [in Russian].
- Dedov, I. I., & Kalinchenko, S. Yu. (2006). *Vozrastnoi androgennyi defitsit u muzhchin [Age androgen deficiency in men]*. Prakticheskaya meditsina. [in Russian].
- Kologrivova, V. V., Zakharova, A. N., Pakhomova, E. V., Vasilyev, V. N., & Kapilevich, L. V. (2018). Kharakteristika endotelii-zavisimoi vazodilatsii u sportsmenov i netrenirovannykh muzhchin [The characteristic of endothelium-dependent vasodilatation in athletes and untrained volunteers]. *Byulleten' sibirskoi meditsiny*, 17(4), 42-46. <https://doi.org/10.20538/1682-0363-2018-4-42-46> [in Russian].
- Loktionova, I. L., Pokrovskiy, M. V., Ragulina, V. A., Titareva, L. V., Denisuk, T. A., Stupakova, E. V., Sytnik, M. V., Saroyan, K. V., & Losenok, S. A. (2012). Sostoyanie funktsii sosudistogo endoteliiya pri infektsionnoi patologii razlichnoi etiologii [The status of vascular endotheliumfunction in infectious diseases of various etiologies]. *Nauchnye vedomosti Belgorodskogo gosudarstvennogo universiteta. Seriya: Meditsina. Farmatsiya*, 17(1)(4), 20-31. [in Russian].
- Markin, A. M., Markina, Yu. V., Sukhorukov, V. N., Khaylov, A. M., & Orekhov, A. N. (2019). Rol' fizicheskikh nagruzkov v razvitii ateroskleroticheskikh porazhenii sosudistoi stenki [The role of physical activity in the development of atherosclerotic lesions of the vascular wall]. *Klinicheskaya i eksperimental'naya morfologiya*, 8(4), 25-31. <https://doi.org/10.31088/CEM2019.8.4.25-31> [in Russian].
- Medvedeva, S. V., & Rechkalov, A. V. (2015). Izmenenie kontsentratsii polovyykh gormonov v syvorotke krovi u sportsmenov raznoi spetsializatsii i lits, ne zanimayushchikhsya sportom, pod vliyaniem fizicheskoi i pishchevoi nagruzkov [The change of concentration of sexual hormones in blood serum in athletes of different specializations and in individuals not engaged in sports activities under the influence of physical and food load]. *Vestnik Kurganskogo gosudarstvennogo universiteta. Seriya: Fiziologiya, psikhologiya i meditsina*, (2), 6-11. [in Russian].
- Mirskii, V. E., & Rishchuk, S. V. (2008). *Rukovodstvo po detskoj i podrostkovo andrologii: (organizatsionno-klinicheskie aspekty) [Guidelines for child and adolescent andrology (organizational and clinical aspects)]*. SpetsLit. [in Russian].
- Rechkalov, A. V., Kargapol'tsev, A. V., Shimchenko, M. V., Shubin, M. G., & Medvedeva, S. V. (2012). Uroven' gastrina, insulina i somatotropnogo gormona u sportsmenov pri sovmestnom primenenii myshechnoi nagruзки i probnogo zhirovogo zavtraka [The level of sportsmen's gastrin, insulin and somatotrophic hormone when physical load was combined with a fatty breakfast]. *Vestnik Kurganskogo gosudarstvennogo universiteta. Seriya: Fiziologiya, psikhologiya i meditsina*, (1), 8-13. [in Russian].
- Smirnov, I. E., Kucherenko, A. G., Polyakov, S. D., Sorokina, T. E., Bershova, T. V., & Bakanov, M. I. (2015). Mediatory endotelial'noi disfunktsii pri fizicheskom perenapryazhenii miokarda u yunyh sportsmenov [Mediators of endothelial dysfunction in physical myocardial overexertion in young athletes]. *Rossiiskii pediatricheskii zhurnal*, 18(5), 21-25. [in Russian].
- Callou de Sá, E. Q., Feijó de Sá, F. C., e Silva, R., de Oliveira, K. C., Guedes, A. D., Feres, F., & Verreschi, I. T. (2011). Endogenous oestradiol but not testosterone is related to coronary artery disease in men. *Clinical Endocrinology*, 75(2), 177-183. <https://doi.org/10.1111/j.1365-2265.2011.04017.x>
- Cipryan, L., Tschakert, G., & Hofmann, P. (2017). Acute and Post-Exercise Physiological Responses to High-Intensity Interval Training in Endurance and Sprint Athletes. *Journal of Sports Science and Medicine*, 16(2), 219-229.
- Colao, A., Di Somma, C., Filippella, M., Rota, F., Pivonello, R., Orio, F., Vitale, G., & Lombardi, G. (2004). Insulin-like growth factor-1 deficiency determines increased intima-media thickness at common carotid arteries in adult patients with growth hormone deficiency. *Clinical Endocrinology*, 61(3), 360-366. <https://doi.org/10.1111/j.1365-2265.2004.02105.x>
- Colao, A., Di Somma, C., Rota, F., Pivonello, R., Savanelli, M. C., Spiezia, S., & Lombardi, G. (2005). Short-Term Effects of Growth Hormone (GH) Treatment or Deprivation on Cardiovascular Risk Parameters and Intima-Media Thickness at Carotid Arteries in Patients with Severe GH Deficiency. *The Journal of Clinical Endocrinology & Metabolism*, 90(4), 2056-2062. <https://doi.org/10.1210/jc.2004-2247>
- Foresta, C., Zuccarello, D., De Toni, L., Garolla, A., Caretta, N., & Ferlin, A. (2008). Androgens stimulate endothelial progenitor cells through an androgen receptor-mediated pathway. *Clinical Endocrinology*, 68(2), 284-289. <https://doi.org/10.1111/j.1365-2265.2007.03036.x>
- Green, D. J., Hopman, M. T., Padilla, J., Laughlin, M. H., & Thijsen, D. H. (2017). Vascular Adaptation to Exercise in Humans: Role of Hemodynamic Stimuli. *Physiological Reviews*, 97(2), 495-528. <https://doi.org/10.1152/physrev.00014.2016>
- Jones, R. D., Nettleship, J. E., Kapoor, D., Jones, H. T., & Chaner, K. S. (2005). Testosterone and Atherosclerosis in Aging Men. *American Journal of Cardiovascular Drugs*, 5(3), 141-154. <https://doi.org/10.2165/00129784-200505030-00001>
- Liu, D., Si, H., Reynolds, K. A., Zhen, W., Jia, Z., & Dillon, J. S. (2007). Dehydroepiandrosterone Protects Vascular Endothelial Cells against Apoptosis through a Gai Protein-Dependent Activation of Phosphatidylinositol 3-Kinase/Akt and Regulation of Antiapoptotic Bcl-2 Expression. *Endocrinology*, 148(7), 3068-3076. <https://doi.org/10.1210/en.2006-1378>
- Severo, C. B., Ribeiro, J. P., Umpierrez, D., Da Silveira, A. D., Padilha, M. C., De Aquino Neto, F. R., & Stein, R. (2013). Increased atherothrombotic markers and endothelial dysfunction in steroid users. *European Journal of Preventive Cardiology*, 20(2), 195-201. <https://doi.org/10.1177/2047487312437062>
- Sullivan, D. C., Huminiecki, L., Moore, J. W., Boyle, J. J., Poulos, R., Creamer, D., Barker, J., & Bicknell, R. (2003). EndoPDI, a Novel Protein-disulfide Isomerase-like Protein That Is Preferentially Expressed in Endothelial Cells Acts as a Stress Survival Factor. *The Journal of Biological Chemistry*, 278(47), 47079-47088. <https://doi.org/10.1074/jbc.M308124200>