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Training/detraining-induced gender specific functional adaptations of isolated rat heart

Polno specifične funkcionalne adaptacije izolovanog srca pacova uzrokovane treningom/prekidom treninga

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Abstract

Background/Aim. Mechanisms responsible for the beneficial effects of aerobic exercise training on cardiovascular function are well known, but detraining effects on myocardial parameters have not been adequately elucidated. Therefore, the study aimed to determine the occurrence and speed of cardiac adaptation reversibility after the cessation of aerobic exercise and to reveal gender differences in achieved effects of training/detraining. **Methods.** Female and male Wistar albino rats were divided into the following groups: control, trained, and two detrained groups. Hearts were perfused according to the Langendorff technique and the following cardiodynamic parameters were determined: the maximum and minimum rate of pressure development in the left ventricle (dp/dt max and dp/dt min, respectively), systolic and diastolic left ventricular pressure (SLVP and DLVP, respectively), heart rate (HR), and coronary flow. **Results.** Training significantly reduced values of dp/dt max, dp/dt min, and SLVP in males and females, and coronary flow in males. Detraining caused a reversion of those changes, which was gender-specific. In females, levels of SLVP were higher after 4 weeks of detraining compred to training, and after 2 weeks of detraining. Values of SLVP were lower in both detraining periods compared to training in males. Males had higher coronary flow after 2 weeks of detraining. Simultaneously, coronary flow was reduced in the 4th week of detraining in females. **Conclusion.** By using a model of the isolated rat heart, the present study confirmed the existence of training-induced changes in cardiac function. Cessation of training was followed by the loss of those adaptations, faster in males than females.

Key words:
adaptation, physiological; exercise; rats; heart; gender.

Apstrakt

Uvod/Cilj. Mehanizmi odgovorni za blagotvorno dejstvo aerobnog treninga na funkciju kardiovaskularnog sistema su dobro poznati, ali efekti prekida treninga na parametre srčane funkcije nisu dovoljno razjašnjeni. Studija je imala za cilj da utvrdi pojavu i brzinu reverzibilnosti srčane adaptacije nakon prestanka aerobnog treninga, kao i da otkrije postojanje razlike među polovima postignute delovanjem treninga/prekida treninga. **Metode.** Pacovi soja Wistar (ženke i mužjaci) su bili podeljeni u sledeće grupe: kontrolnu grupu, grupu podvrgnutu treningu i dve grupe kod kojih je trening prekinut. Izolovana srca su perfundovana prema Langendorff-ovoj metodi, a praćeni su sledeći kardiodinamski parametri: maksimalna i minimalna stopa razvoja pritiska u levoj komori (dp/dt max i dp/dt min), sistolni i dijastolni pritisak u levoj komori (SLVP i DLVP), frekvenca otkucaja srca (HR) i koronarni protok. **Rezultati.** Trening je značajno smanjio vrednosti dp/dt max, dp/dt min i SLVP i kod mužjaka i kod ženki, kao i koronarni protok kod mužjaka. Prekid treninga je doveo do vraćanja vrednosti postignutih tokom treninga na vrednos

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ti pre treninga kod ženki pacova, nivo SLVP je bio viši nakon 4 nedelje od prekida treninga u poredjenu sa vrednostima tokom treninga i 2 nedelje nakon prekida treninga. Vrednosti SLVP su kod mužjaka bile niže u periodima prekida treninga u poređenju sa periodom treninga. Mužjaci su imali veće vrednosti koronarnog protoka nakon 2 nedelje od prekida treninga. Istovremeno, koronarni protok se smanjio u 4. nedelji od prekida treninga kod ženki. **Zaključak.** Na modelu izolovanog srca pacova, je potvrđeno postojanje promena srčane funkcije pod uticajem treninga. Prestanak treninga je bio praćen gubitkom detektovanih adaptacija, koji je bio brži kod mužjaka nego kod ženki pacova.

Ključne reči:
adaptacija, fiziološka; vežbanje; pacovi; srce; pol.

Introduction

Regular physical activity brings numerous benefits which are associated with reduced risk of cardiovascular diseases. These benefits of regular physical activity (exercise) were also noticed in patients with established cardiovascular disease [1–4]. Regular exercise induces changes in hemodynamic and loading conditions of the heart, which can lead to a series of positive changes in the heart's structure and function [5]. Improved oxygen supply and myocardial contractility, both in health and disease, represent exercise-related cardiac adaptations [6]. In addition, the amelioration of cardiovascular capacity due to aerobic exercise training is associated with increased left ventricular (LV) mass and volume, myocyte hypertrophy, increased LV stroke volume, and lower resting and submaximal heart rate (HR) [1, 6–10].

These training-induced anatomical and physiological cardiovascular adaptations are partially or completely lost as a result of reduction or cessation of training. Significant changes in cardiovascular function occur after detraining and it is related to decreased peak oxygen uptake (peak VO_2) and cardiomyocyte length [11, 12]. Previous studies pointed out that exercise training induced myocardial remodeling and improved myocardial contractile state, but these changes disappeared after a short period of detraining [12-14]. While the mechanisms responsible for the beneficial effects of aerobic exercise training on cardiovascular function and dimensions of cardiomyocytes are well known [6, 10], detraining effects on myocardial parameters has not been adequately elucidated.

Another important variable in training/detraining responses is gender. Recently, it has been reported that cardiovascular response to exercise is sex-dependent [15–17]. Investigations in rodents have shown that females have a more pronounced hypertrophic response to exercise than males. Furthermore, there are differences in the pathways leading to cardiac hypertrophy between the sexes. It is certain that the genetic and hormonal differences modify cardiac adaptations and improve cardiovascular capacity [18–20].

Despite the growing number of studies investigating the gender differences in the exercise-induced response of the cardiovascular system, data are still inconsistent and not sufficiently reliable. Moreover, detraining effects on heart function between males and females are almost unknown and remain to be elucidated as well. Therefore, the present study aimed to assess the presence and speed of reversibility of cardiac adaptation after the cessation of aerobic exercise as well as to determine gender differences in achieved effects of training/detraining on isolated rat heart.

Methods

Ethical approval

The study was performed in the Laboratory for Cardiovascular Physiology of the Faculty of Medical Sciences, University of Kragujevac, Serbia. The experimental protocol was approved by the Faculty of Medical Sciences Ethics Committee for the welfare of experimental animals, University of Kragujevac, number 01-275916, and by the Ministry of Agriculture, Forestry, and Water Management, Authority for Veterinary of Serbia number 323-07-02882/2014-05. All experiments were also performed according to the European Union Directive for the welfare of laboratory animals (86/609/EEC) and principles of Good Laboratory Practice (GLP).

Animals

Sixty-four Wistar albino rats (32 males and 32 females, eight weeks old at the beginning of the experiment, body weight 180–200 g, obtained from the Military Medical Academy, Belgrade, Serbia) were subjected to the study's protocol. Rats were housed with a temperature adjusted to 22 ± 1 °C with a 12:12 light/dark cycle and free access to food and water (*ad libitum)*.

Exercise training protocol

Rats were subjected to swimming according to the training protocol described below. Rats were divided into 4 groups, while each group consisted of 2 subgroups, males (M) and females (F). The first group was the control group (C), containing subgroups CM and CF (n = 8 for each subgroup). The second group was the trained group (T), containing subgroups TM and TF (n = 8 for each subgroup). The third group included 2 weeks detrained animals (D2), i.e., animals subjected to training, followed by 2 weeks of detraining period, subgroups DM2 and DF2 (n = 8 for each subgroup). The fourth group consisted of 4 weeks detrained animals (D4), ie., animals subjected to training followed by 4 weeks of detraining, subgroups DM4 and DF4 (n = 8 for each subgroup). Rats from the control group were placed in the pool 5 times a week for 3 minutes to achieve water induced-stress [21]. Rats from the groups T, D2 and D4 were subjected to moderate-intensity exercises, such as swimming training (8 weeks, 5 days/week, 60 min/day). A week before the experiment, rats were gradually exposed to

swimming training from 5 to 15 minutes in order to familiarize them with the swimming exercise. Subsequently, they started with 8 weeks training process. Rats from the group T (TM and TF) were sacrificed a day after accomplishing the training process. On the same day, rats (the same age as in the T group) from the C group were sacrificed as well. Animals from the DM2, DF2, DM4 and DF4 groups were sacrificed after 2 and 4 weeks of training cessation, respectively.

Rats swam in a specially constructed swimming pool made of glass (80 × 60 × 100 cm). Water temperature (34 °C) was maintained by an electric heater, and a pump continuously made waves in order to prevent rats from floating. The swimming was continuously supervised.

Preparation of isolated rat hearts

The hearts of male and female Wistar albino rats (n = 64, 8 in each experimental subgroup) were excised and retrogradely perfused according to the Langendorff technique (Experimetria Ltd, 1062 Budapest, Hungary). After short-term narcosis induced by intraperitoneal application of ketamine (10 mg/kg) and xylazine (5 mg/kg), the animals were sacrificed by cervical dislocation (Schedule 1 of the Animals/ Scientific Procedures, Act 1986, UK), and premedicated with heparin as an anticoagulant. After emergency thoracotomy and rapid cardiac arrest by superfusion with ice-cold isotonic saline, hearts were rapidly excised, the aortas were cannulated and retrogradely perfused at gradually increased coronary perfusion pressure (CPP) from 40 to 120 cm H_2O in order to establish coronary autoregulation.

The composition of the non-recirculating Krebs-Henseleit perfusate was as follows (mM): NaCl 118, KCl 4.7, $CaCl_2x2H_2O$ 2.5, $MgSO_4x7H_2O$ 1.7, $NaHCO_3$ 25, KH_2PO_4 1.2, glucose 11, pyruvate 2, equilibrated with 95% O_2 plus 5% CO_2, and warmed to 37 °C (pH 7.4).

Immediately after the restoration of normal heart rhythm, through the created entrance to the left atrium of the heart and damaged mitral valve, the sensor (transducer BS473-0184, Experimetria Ltd, Budapest, Hungary) was inserted into the left ventricle for continuous monitoring of cardiac function.

After placing the sensor in the left ventricle, the following parameters of myocardial function have been continuously registered: maximum rate of pressure development in the left ventricle (dp/dt max); minimum rate of pressure development in the left ventricle (dp/dt min); systolic left ventricular pressure (SLVP); diastolic left ventricular pressure (DLVP); heart rate (HR).

The above-mentioned cardiodynamic parameters were recorded during every CPP. Furthermore, during every CPP, the coronary flow was measured by flowmetry.

Statistical analysis

IBM SPSS Statistics 20.0 for Windows was used for statistical analysis. Descriptive statistics were used to calculate the arithmetic mean with dispersion measures (standard deviation – SD and standard error – SE). The distribution of data was checked by the Shapiro-Wilk test. Where distribution between groups was normal, statistical comparisons were performed using the one-way ANOVA tests with a Tukey's post hoc test for multiple comparisons. Kruskal-Wallis test was used for comparison between groups where the distribution of data was different than normal. Values of $p < 0.05$ were considered to be statistically significant.

Results

Maximum rate of pressure development in the left ventricle (dp/dt max)

Trained groups (TM, TF) had significantly decreased levels of this parameter compared to their controls (CM, CF). This difference was observed only when CPP was high (80, 100, and 120 cm H_2O). Significantly higher values of dp/dt max were noticed in the DF4 group compared to the DM4 group during CPP of 80 and 100 cm H_2O (Figure 1, A–D).

Minimum rate of pressure development in the left ventricle (dp/dt min)

Values of dp/dt min were also lower in trained groups (TM, TF) compared to their controls (CM, CF). Statistical significance was observed during high CPP (80, 100, and 120 cm H_2O). Significantly higher values of dp/dt min were noticed in the DF4 group compared to the DM4 group during CPP of 80, 100, and 120 cm H_2O (Figure 2, A–D).

Systolic left ventricular pressure (SLVP)

Lower levels of SLVP were noticed in trained groups (TM, TF) compared to their controls (CM, CF) at CPP of 80, 100, and 120 cm H_2O. The TM group had higher levels of SLVP compared to the DM2 at all CPP values. A significant increase of SLVP in the DF4 group was found compared to the TF group, while the DM4 group had lower levels of SLVP than the TM group (CPP 80, 100, and 120 cm H_2O). Significantly higher values of SLVP in the DF4 group were noticed compared to the DM4 group during all CPP values. When comparing the DF2 group with DF4, the DF4 group had significantly higher levels of SLVP at all CPP values (Figure 3, A–D).

Diastolic left ventricular pressure (DLVP)

There were no significant changes in values of this parameter in any group (Figure 4, A–D).

Heart rate (HR)

TM group had lower HR than CM group during CPP 40 and 120 cm H_2O. HR in the TM group was significantly lower compared to DM2 and DM4 groups at CPP between 40 and 120 cm H_2O (Figure 5, A–D).

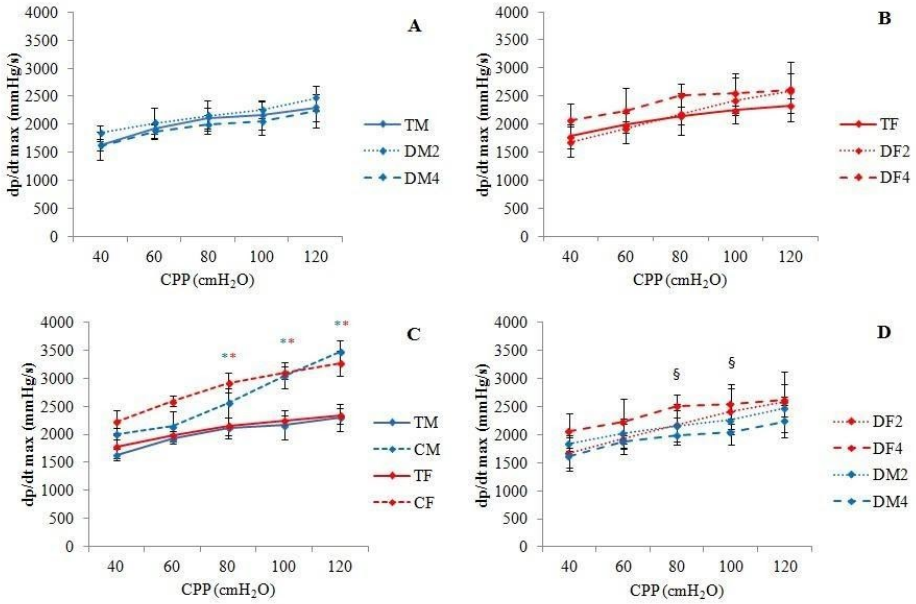

Fig. 1 – Effects of training/detraining on maximum rate of left ventricular pressure development (dp/dt max): A) TM vs. DM2 vs. DM4; B) TF vs. DF2 vs. DF4; C) CF vs. TF vs. CM vs. TM; D) DF2 vs. DF4 vs. DM2 vs. DM4.

Statistical significance at the level of $p < 0.05$: **TM (TF) vs. CM (CF); §DM4 vs. DF4. Data are presented as means ± SD.
CPP – coronary perfusion pressure; TM – trained males; DM2 – 2 weeks detrained males; DM4 – 4 weeks detrained males; CM – control males; TF – trained females; DF2 – 2 weeks detrained females; DF4 – 4 weeks detrained females; CF – control females.

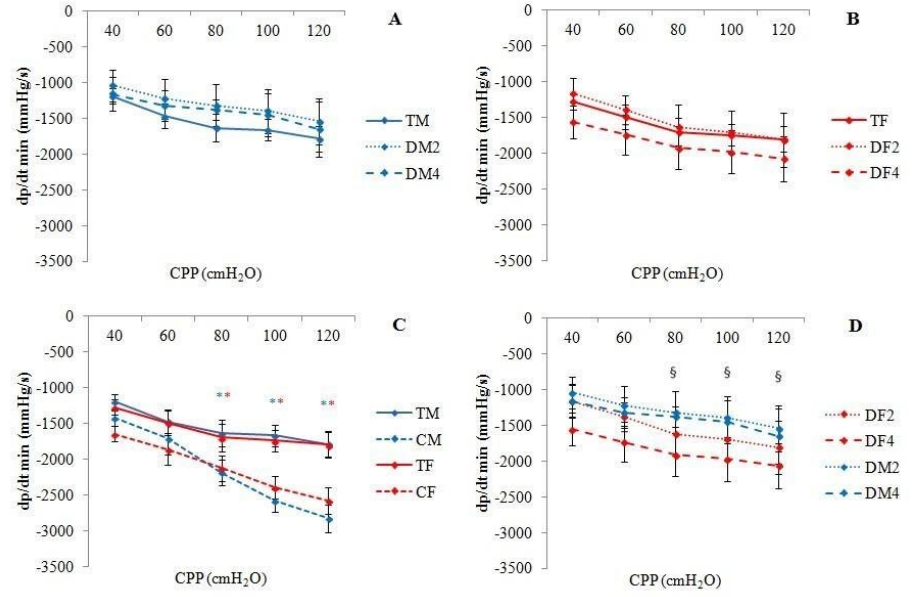

Fig. 2 – Effects of training/detraining on minimum rate of left ventricular pressure development (dp/dt min): A) TM vs. DM2 vs. DM4; B) TF vs. DF2 vs. DF4; C) CF vs. TF vs. CM vs. TM; D) DF2 vs. DF4 vs. DM2 vs. DM4.

Statistical significance at the level of $p < 0.05$: **TM(TF) vs. CM(CF); §DM4 vs. DF4. Data are presented as means ± SD.
CPP – coronary perfusion pressure; TM – trained males; DM2 – 2 weeks detrained males; DM4 – 4 weeks detrained males; CM – control males; TF – trained females; DF2 – 2 weeks detrained females; DF4 – 4 weeks detrained females; CF – control females.

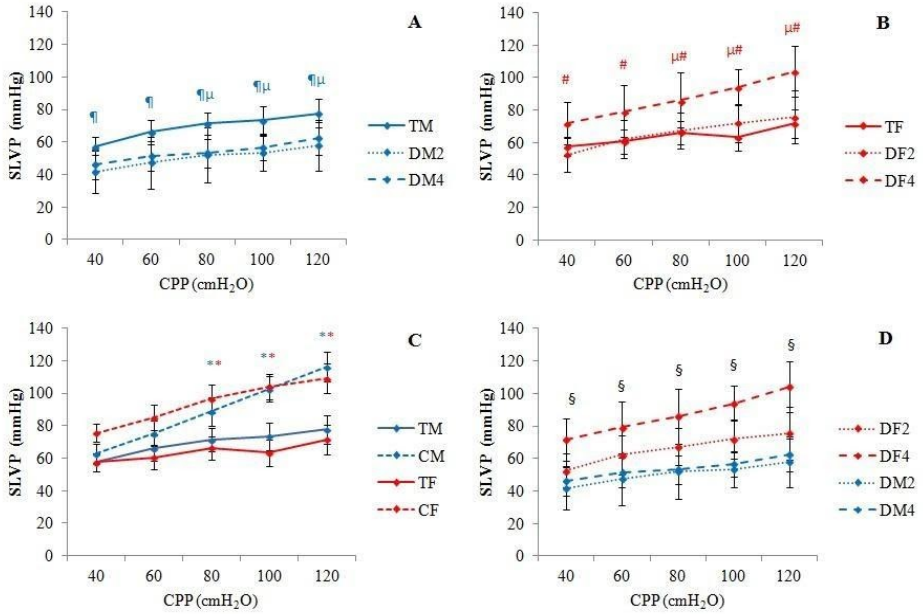

Fig. 3 – Effects of training/detraining on systolic left ventricular pressure (SLVP): A) TM vs. DM2 vs. DM4; B) TF vs. DF2 vs. DF4; C) CF vs. TF vs. CM vs. TM; D) DF2 vs. DF4 vs. DM2 vs. DM4.

Statistical significance at the level of $p < 0.05$: *TM(TF) vs. CM(CF); #DM2 (DF2) vs. DM4(DF4); ¶ TM(TF) vs. DM2(DF2); µTM(TF) vs. DM4 (DF4); £DM2 vs. DF2; §DM4 vs. DF4.

Data are presented as means ± SD.

CPP – coronary perfusion pressure; TM – trained males; DM2 – 2 weeks detrained males; DM4 – 4 weeks detrained males; CM – control males; TF – trained females; DF2 – 2 weeks detrained females; DF4 – 4 weeks detrained females; CF – control females.

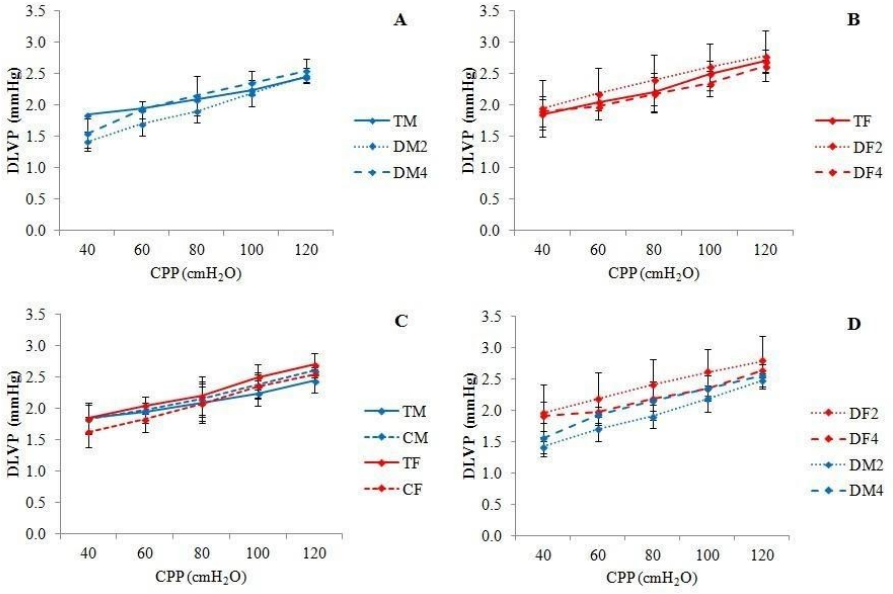

Fig. 4 – Effects of training/detraining on diastolic left ventricular pressure (DLVP). A) TM vs. DM2 vs. DM4; B) TF vs. DF2 vs. DF4; C) CF vs. TF vs. CM vs. TM; D) DF2 vs. DF4 vs. DM2 vs. DM4.

Statistical significance at the level of $p < 0.05$: **TM(TF) vs. CM(CF); #DM2 (DF2) vs. DM4(DF4); ¶ TM(TF) vs. DM2(DF2); µTM(TF) vs. DM4 (DF4); £DM2 vs. DF2; §DM4 vs. DF4.

Data are presented as means ± SD.

CPP – coronary perfusion pressure; TM – trained males; DM2 – 2 weeks detrained males; DM4 – 4 weeks detrained males; CM – control males; TF – trained females; DF2 – 2 weeks detrained females; DF4 – 4 weeks detrained females; CF – control females.

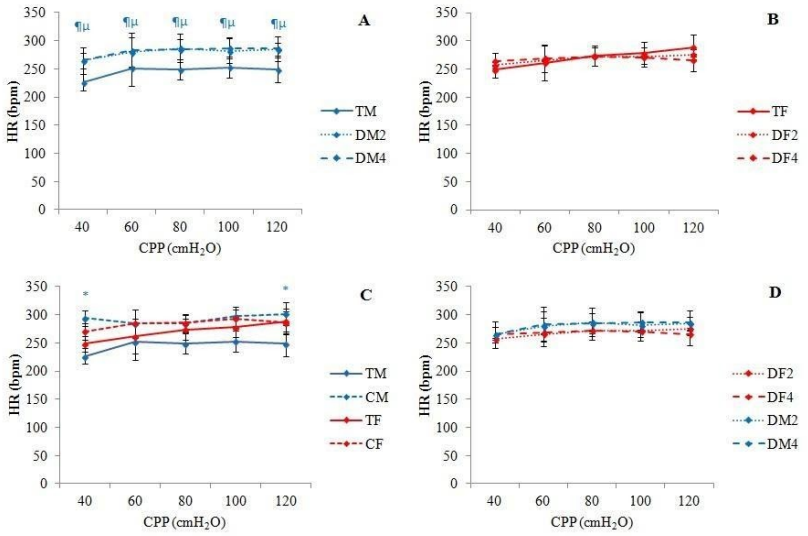

Fig. 5 – Effects of training/detraining on heart rate (HR): A) TM vs. DM2 vs. DM4; B) TF vs. DF2 vs. DF4; C) CF vs. TF vs. CM vs. TM; D) DF2 vs. DF4 vs. DM2 vs. DM4. Statistical significance at the level of $p < 0.05$: *TM(TF) vs. CM(CF); ¶ TM(TF) vs. DM2(DF2); ᵻTM(TF) vs. DM4 (DF4).
Data are presented as means ± SD.
CPP- coronary perfusion pressure; TM – trained males; DM2 – 2 weeks detrained males; DM4 – 4 weeks detrained males; CM – control males; TF – trained females; DF2 – 2 weeks detrained females; DF4 – 4 weeks detrained females; CF – control females.

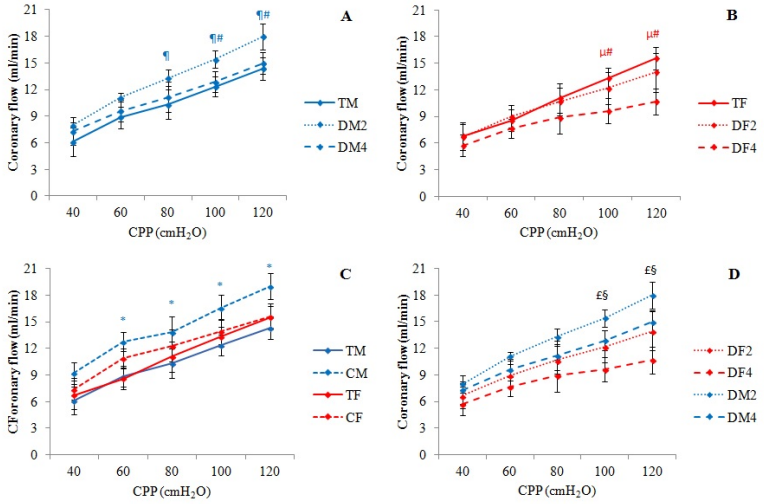

Fig. 6 – Effects of training/detraining on coronary flow (CF): A) TM vs. DM2 vs. DM4; B) TF vs. DF2 vs. DF4; C) CF vs. TF vs. CM vs. TM; D) DF2 vs. DF4 vs. DM2 vs. DM4. Statistical significance at the level of $p < 0.05$: **TM(TF) vs. CM(CF); #DM2 (DF2) vs. DM4(DF4); ¶ TM(TF) vs. DM2(DF2); ᵻ TM(TF) vs. DM4 (DF4); £DM2 vs. DF2; §DM4 vs. DF4.
Data are presented as means ± SD.
CPP- coronary perfusion pressure; TM – trained males; DM2 – 2 weeks detrained males; DM4 – 4 weeks detrained males; CM – control males; TF – trained females; DF2 – 2 weeks detrained females; DF4 – 4 weeks detrained females; CF – control females.

Coronary flow

The TM group had significantly lower levels of coronary flow than the CM group at CPP 60–120 cm H_2O. Coronary flow was significantly higher in the DM2 group compared to the TM at CPP 80–120 cm H_2O. The DF4 group had significantly lower levels of coronary flow than the TF group at CPP 100 and 120 cm H_2O. Comparing the DF2 with DM2 group, females had lower coronary flow than males at CPP 100 and 120 cm H_2O. The same results were recorded after 4 weeks of detraining between males and females. Coronary flow was higher in the DM2 group than in the DM4 and in the DF2 group than in the DF4 at 100 and 120 cm H_2O CPP (Figure 6, A–D).

Discussion

The magnitude of cardiovascular training-induced adaptations depends on mode, intensity, duration, and frequency of exercise. The best way to ensure a good training program is to ensure a gradual increase of load and enough time between exercise sessions for muscle regeneration, but not for regression of supercompensation [13, 21, 22]. Those adaptations are associated with the promotion of physiological cardiac hypertrophy (PCH), which is linked to less cardiac fibrosis and better systolic and diastolic function when compared to pathological hypertrophy. Ventricular dilatation represents a short-term adaptive response, while hypertrophy of the cardiac muscle fibers appears after a long time of regular physical activity [8, 9, 12, 23, 24].

In our experimental model, the heart was retrogradely perfused through the aorta, thus normal cardiac output and ejection fraction were not present. SLVP and dp/dt max describe systolic function in our research, while the diastolic function is described by dp/dt min and DLVP parameters. Our results show that 8 weeks of exercise induce slight depression of coronary function (lower SLVP and dp/dt max) in both males and females, keeping heart function within physiological limits. The reason for this might be the adaptation of the myocardium in terms of the rationality of its work at rest, proving its better response when exposed to physical effort. wIn our previous study, 12 weeks of training improved heart function, which could be related to the duration and intensity of the training program in this experimental protocol [21]. Values of HR in our study were significantly lower in the TM group compared to the control. This sinus bradycardia is in correlation with other cardiodynamic parameters and the abovementioned hypothesis and represents another physiological response of cardiac muscle to exercise, recently proved by D'Souza et al. [25] on a mice model.

Ishida et al. [26] investigated the influence of electrical stimulation on contractile parameters of the triceps during training and detraining and showed that 8 weeks of strength training did not induce significant changes in contractile properties, while during detraining, the muscles contracted faster. It was suggested that the release of Ca^{2+} and sarcoplasmic reticulum (SR) response during the strength training could be deferred and these effects might improve after strength training. This could be in agreement with our results which showed that levels of SLVP were higher after 4 weeks of detraining compared to training, and 2 weeks of detraining in females. On the contrary, values of this parameter in males were lower in both detraining periods than after the training period. HR in males was higher after both 2 and 4 detraining weeks compared to HR after regular training. Evangelista et al. [27] demonstrated that lower intrinsic HR is associated with low resting HR in trained rats. Detraining increased resting HR, approaching the basal values, as well as intrinsic HR. This bradycardia at rest tends to be associated with increased vagal activity and decreased sympathetic activity [28–30].

Furthermore, our results indicate that training-induced adaptations were lost after detraining in males and that value of tested parameters returned to the value similar to the control. Achieved adaptations persisted longer in females. The mechanism underlying the increased contractility in training has been reported as higher activity of Ca^{2+} ATPase and of Na^{+}/Ca^{2+} exchange [31, 32], therefore, the activity of this enzyme is probably lower in detraining. Opposite to our results, Bocalini et al. [13] found that the training-induced improvement in females was abolished after 2 weeks of detraining and returned to the values observed in the untrained group. A possible explanation for disproportion with the present investigation may be a different experimental protocol (investigation on isolated papillary muscle). In that sense, other authors determined that reduction of myocardial remodeling after detraining in rats and humans may be due to the duration of detraining [33]. For instance, a group of authors showed that after about 3 weeks of physical inactivity, the cardiac mass in rats regressed to baseline [34]. This is in correlation with the results of Kemi et al. [35], who determined that fractional shortening regressed with only 2 weeks of detraining. It was also proved that training-induced ventricular adaptation decline after detraining in humans [36].

Results regarding coronary flow showed that training protocol induced a decrease in heart perfusion which is in accordance with depression of myocardial function. In addition, this drop in coronary flow did not compromise the working capacity of the heart, allowing it to work in a lower physiological manner, as described above. On the other hand, detraining effects were gender-specific. While males had higher coronary flow after 2 weeks of detraining, in females, the reduction of coronary flow occurred in the 4th week of detraining. Based on this, we assume that training had a longer effect on females than males.

We did not find any significant differences in cardiodynamics between males and females who trained. Nevertheless, after 4 weeks of detraining, the heart function improved more in females than in males. An explanation for this might be a more pronounced hypertrophic response in females than in males, which was proved by many investigations [19, 37]. Ogawa et al. [38] noticed that gender difference is a result of a greater percentage of body fat in women. Some authors demonstrated that lipolytic activity in white adipose tissue, as well as plasma free fatty acid (FFA) levels, were higher in women after training than in men [39]. Furthermore, increased catecholamine-induced cardiac FFA uptake which leads to PCH in women is exercise-dependent. Investigations on rodents also identified pathways that may contribute to sexual dimorphism in exercise and cardiac adaptation to exercise. That mechanism underlying the development of PCH in females involves Ca^{2+}/calmodulin-dependent kinase (CaMK) and Akt/glycogen synthase kinase-3 (GSK-3) pathways [37]. Recent investigations proved that sex hormones could affect cardiac function and training-induced cardiac adaptations in rats [17, 40, 41]. Furthermore, since both estrogen receptors are expressed in the heart, female cardiac tissue activation of these receptors could lead to increased adaptive lipolytic activity. Moreover, it has been shown that reduction of cardiomyocytes contractility may be due to reduction of circulating testosterone which is in correlation with our results [14, 16, 19].

As expected, our study possesses some limitations. They are reflected in absence of the determination of histological and biochemical parameters within the heart muscle which could confirm obtained functional changes.

Conclusion

Findings of the present study pointed out that applied type of physical load induced functioning of the heart at a lower level of its cardiodynamic parameters, thus improving the rationality of heart work at rest. While training-induced cardiac responses were similar in males and females, cessation of training caused a reversion of those changes, which was gender-specific. Achieved adaptations were lost faster in males than in females. Results of the present study may be of practical interest in terms of obtaining an excellent basis for future reliable investigations on humans.

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