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Characterization of the dynamic changes in left ventricular morphology and function induced by exercise training and detraining

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ABSTRACT

Background: Although exercise-induced cardiac hypertrophy has been intensively investigated, its development and regression dynamics have not been comprehensively described. In the current study, we aimed to characterize the effects of regular exercise training and detraining on left ventricular (LV) morphology and function.
Methods: Rats were divided into exercised (n = 12) and control (n = 12) groups. Exercised rats swam 200 min/day for 12 weeks. After completion of the training protocol, rats remained sedentary for 8 weeks (detraining period). Echocardiographic follow-up was performed regularly to obtain LV long- and short-axis recordings for speckle-tracking echocardiography analysis. Global longitudinal and circumferential strain and systolic strain rate were measured. LV pressure-volume analysis was performed using additional groups of rats to obtain haemodynamic data.
Results: Echocardiographic examinations showed the development of LV hypertrophy in the exercised group. These differences disappeared during the detraining period. Strain and strain rate values were all increased after the training period, whereas supernormal values rapidly reversed to the control level after training cessation. Load-independent haemodynamic indices, e.g., preload recruitable stroke work, confirmed the exercise-induced systolic improvement and complete regression after detraining.
Conclusions and translational aspect: Our results provide the first comprehensive data to describe the development and regression dynamics of morphological and functional aspects of physiological hypertrophy in detail. Speckle-tracking echocardiography has been proven to be feasible to follow-up changes induced by exercise training and detraining and might provide an early possibility to differentiate between physiological and pathological conditions.

1. Introduction

Long-term, regular physical training results in structural and functional alterations in the heart that are adaptive responses to the increased haemodynamic demands during exercise sessions. This complex adaptive cardiac remodelling has been referred to as "athlete's heart" and includes a balanced enlargement of ventricular cavity dimensions and myocardial mass, accompanied by increased stroke volume and lower resting heart rate [1,2]. The recognition of training-induced physiological hypertrophy has attracted numerous experimental and clinical projects.

These left ventricular (LV) structural adaptations in response to exercise training and alterations after cessation of training (detraining) have been confirmed utilizing echocardiography several decades ago [3]. Since then, several experimental and human studies reflected that after inducing myocardial hypertrophy by exercise training, short- and long-term deconditioning results in progressive regression of exercise-induced cardiac morphological remodelling [4–6]. This phenomenon might be especially valuable to distinguish between athlete's heart and structurally similar forms of pathological hypertrophy in case of challenging clinical cases, the so-called grey-zone hypertrophy [7].

Currently, the impact of exercise training on LV myocardial mechanics is less clear. In the 20th century, the echocardiographic studies suggested unchanged resting LV systolic function using traditional parameters, which was confirmed by cardiac magnetic resonance imaging [8,9]. These non-invasive techniques have an essential role in describing the morphological characteristics of the athlete's heart; however, they are not able to characterize cardiac intrinsic LV systolic

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mechanics. Thus, novel imaging techniques have been required in sports cardiology [10].

In the last few decades, tissue Doppler imaging and speckle-tracking echocardiography have been introduced to understand the myocardial mechanics in exercise-induced hypertrophy more deeply. Furthermore, these advanced techniques were suggested to be able to distinguish between physiological and pathological myocardial conditions [11,12]. However, previous publications provided inconsistent results on myocardial mechanics in the context of athlete's heart and reported unchanged, increased and even decreased strain values at rest. Invasive experimental investigations using reliable indices of intrinsic myocardial inotropy clearly indicated enhanced contractility in a small animal model of exercise-induced left ventricular hypertrophy [13]. Moreover, in a cross-sectional study, our research group found strong correlation between invasive, load-independent contractility parameters and systolic strain values by speckle-tracking echocardiography after inducing physiological hypertrophy [14].

In the current project, we aimed to characterize the effects of regular exercise training and detraining on LV morphology and function using conventional and speckle-tracking echocardiography in a rat model.

2. Methods

2.1. Animals

All experimental procedures were reviewed and approved by the Ethical Committee of Hungary for Animal Experimentation. This investigation conformed to the Guide for the Care and Use of Laboratory Animals provided by the National Institute of Health (NIH Publication No. 86–23, revised 1996.) and to the EU Directive 2010/63/EU. All animals received humane care.

Young adult, male Wistar rats (n = 48, m = 275–325 g) were housed in standard rat cages at a constant room temperature (22 ± 2 °C) and humidity with a 12:12-h light-dark cycle. Rats were fed standard laboratory rodent chow and water ad libitum.

2.2. Study design

After acclimation, twenty-four rats were randomly divided into control (Co, n = 12) and exercised groups (Ex, n = 12). These rats completed a 12-week-long training and also an 8-week-long detraining period, and during this period, they underwent regular echocardiographic measurements at weeks 0, 4, 8, 12, 14, 16, 18 and 20. At week 20, these animals underwent LV pressure-volume (P—V) analysis.

Additionally, to obtain haemodynamic data at weeks 0 (baseline) and 12 (end of training period), twelve rats were assigned to groups (Co_0, n = 6 and Ex_0, n = 6), and pressure-volume analysis was performed at week 0. Further, twelve rats were used to perform invasive haemodynamic measurements (Co_{12}, n = 6 and Ex_{12}, n = 6) after completion of training protocol (Suppl. Fig. 1).

Body weight (BW) was measured three times a week during the 20-week-long period. The rats were euthanized after completion of in vivo experiments (P—V analysis); the heart was excised, and heart weight (HW) was measured immediately and was indexed to BW values.

2.3. Training and detraining protocol

Swim training was performed in a container divided into six lanes filled with tap water (45 cm deep) maintained at 30–32 °C. Rats of exercised groups were exposed to 200 min/day swimming 5 days/week for 12 weeks to induce physiological LV hypertrophy, as described previously [13].

Thereafter, during the detraining period, animals from both groups remained sedentary for 8 weeks. The duration of the detraining period was chosen according to pilot study and corresponding literature data.

2.4. Echocardiography

Regular echocardiographic assessments were performed under pentobarbital anaesthesia, as described previously [14]. Further information is provided in Data Supplement.

2.5. Speckle-tracking echocardiography

Strain analysis was carried out in accordance with our internal protocol, as described previously [14]. Briefly, two-dimensional acquisitions of long- and short-axis views of the LV dedicated for speckle-tracking analysis were recorded at least three times by a constant frame rate of 218 Hz. Speckle-tracking analysis was performed by a blinded operator with expertise in the software environment (EchoPAC v113). To quantify global longitudinal strain (GLS) and longitudinal systolic strain rate (LSr), three different long-axis recordings from each animal and three cardiac cycles from each recording were analysed. To measure global circumferential strain (GCS) and circumferential systolic strain rate (CSr), the same sequence was performed using short-axis loops. After manual contouring of the endocardial border, the software automatically separated the region of interest into six segments and calculated strain and strain rate values, correspondingly. In case of low tracking fidelity, the contour was further corrected manually, and the analysis was repeated. Acceptance of a segment to be included in further analysis was guided by the recommendation of the software. Ideally, for each parameter (3 × 3 × 6), 54 segmental values were available. Based on our protocol, animals with <36 values did not enter into statistical analysis (none).

2.6. Haemodynamic measurements – left ventricular pressure-volume analysis

After completion of the training and detraining protocol (at week 20) and in the additional groups (at week 0 and 12), in vivo haemodynamic measurements were performed, as described previously [15,16]. Further details are available in Data Supplement.

2.7. Histology

The hearts were removed and were fixed in buffered paraformaldehyde solution (4%) and embedded in paraffin. Transverse, transmural, ~5 μm thick slices of the ventricles were cut and placed on adhesive slides.

Hematoxylin and eosin staining was performed to measure cardiomyocyte diameter as a cellular marker of myocardial hypertrophy. In each sample, 100 longitudinally oriented cardiomyocytes from the LV were examined, and the diameters at transnuclear position were defined. The mean value of 100 measurements represented one sample.

The extent of myocardial fibrosis was assessed on picrosirius-stained sections. ImageJ software (National Institutes of Health, Bethesda, MD) was used to identify the picrosirius-red positive area. Three transmural images (magnification 50×) were randomly taken from the free LV wall on each sections. The fibrosis area (picrosirius red positive area-to-total area ratio) was determined on each image, and the mean value of three images represents each animal.

2.8. Statistics

The results are expressed as the mean ± SEM. After confirming normal distribution of data, data were analysed using two-way analysis of variance (ANOVA) and mixed ANOVA. Training (p_{iT}) and detraining (p_{iD}) interaction p values were used to interpret our results. To assess reproducibility of STE measurements, Lin's concordance correlation coefficient was calculated. A p value <0.05 was the criterion of significance.

Further details are available in Data Supplement.

3. Results

3.1. Heart weight data

HW/BW ratio did not differ between our baseline groups (3.42 ± 0.06 g/kg Ex_0 vs. 3.39 ± 0.03 g/kg Co_0). A marked increase in the HW/BW ratio confirmed cardiac hypertrophy in trained animals (p_{iT} = 0.0051; 3.67 ± 0.14 g/kg Ex_{12} vs. 2.96 ± 0.16 g/kg Co_{12}), which regressed to control values after the detraining period (p_{iD} = 0.0012; 2.72 ± 0.04 g/kg Ex vs. 2.73 ± 0.10 g/kg Co).

3.2. Data from LV pressure-volume analysis

Heart rate and pressure values did not differ between control and exercised animals, either after completing the training plan (at week 12) or after the detraining period (at week 20) (Table 1). The volume values corresponded to the echocardiographic data: as a result of 12-week-long swim training, unaltered LV end-diastolic volume (LVEDV) was associated with decreased LV end-systolic volume (LVESV), resulting in increased SV, EF, cardiac index (CI) and stroke work (SW) compared to control animals.

Load-independent indices of myocardial contractility [preload recruitable stroke work (PRSW); end-systolic P—V relationship ($ESPVR_q$) and maximal dP/dt – end-diastolic volume relationship (dP/dt_{max}-EDV)] were increased as a result of long-term exercise-training (Table 1, Fig. 1).

Both conventional and load-independent parameters of systolic function and contractility did not show any difference at week 20, confirming the complete morphological and functional reversibility of exercised-induced alterations (Fig. 1).

Table 1
Haemodynamic data.

	Week 0		Week 12		p_{iT}	Week 20		p_{iD}
	Co_0 (n = 6)	Ex_0 (n = 6)	Co_{12} (n = 6)	Ex_{12} (n = 6)		Co (n = 12)	Ex (n = 12)	
HR, beats/min	272 ± 11	273 ± 5	224 ± 6	243 ± 14	0.3836	244 ± 8	239 ± 10	0.2276
MAP, mmHg	77.4 ± 1.4	77.0 ± 1.8	81.6 ± 3.8	85.3 ± 2.8	0.4370	85.9 ± 3.9	80.9 ± 2.3	0.6121
LVESP, mmHg	85.0 ± 4.1	85.5 ± 1.1	100.4 ± 2.8	96.3 ± 2.6	0.4405	101.1 ± 4.2	100.5 ± 3.4	0.6696
LVEDP, mmHg	5.0 ± 0.2	4.5 ± 0.3	4.9 ± 0.4	5.6 ± 0.5	0.1208	4.3 ± 0.2	4.2 ± 0.2	0.2043
dP/dt_{max}, mmHg/s	6453 ± 429	5880 ± 309	7305 ± 345	7585 ± 227	0.2101	6979 ± 284	6775 ± 304	0.4518
dP/dt_{min}, mmHg/s	−6570 ± 441	−6167 ± 228	−7509 ± 583	−7552 ± 398	0.6116	−7539 ± 365	−7176 ± 239	0.6128
LVEDV, μl	212.8 ± 8.3	224.4 ± 7.9	261.6 ± 7.6	258.3 ± 8.3	0.3637	276.4 ± 8.5	269.0 ± 7.4	0.8177
LVESV, μl	65.8 ± 5.0	69.1 ± 6.1	110.4 ± 8.2	85.3 ± 3.4*	0.0271	123.4 ± 4.3	118.2 ± 3.7	0.0545
SV, μl	147.0 ± 4.0	155.3 ± 3.0	151.3 ± 6.3	173.0 ± 7.3*	0.0240	153.0 ± 5.2	150.8 ± 5.8	**0.0496**
EF, %	69.3 ± 1.3	69.5 ± 1.8	58.8 ± 2.4	66.9 ± 1.1*	0.0213	55.4 ± 0.7	56.0 ± 1.1	**0.0044**
CI, (ml/min)/100 g BW	127.4 ± 4.7	136.2 ± 4.9	72.9 ± 3.3	98.2 ± 9.7*	0.1931	64.7 ± 2.7	67.4 ± 3.6	**0.0234**
SW, mmHg·ml	11,798 ± 536	11,735 ± 253	12,612 ± 844	15,012 ± 649*	0.0568	12,615 ± 594	12,226 ± 360	**0.0317**
ESPVR	1.78 ± 0.09	1.84 ± 0.12	1.76 ± 0.05	2.23 ± 0.10*	0.0411	1.73 ± 0.13	1.74 ± 0.08	**0.0282**
PRSW	97.9 ± 4.9	98.3 ± 2.8	85.2 ± 4.1	107.4 ± 3.9*	0.0128	80.7 ± 5.2	80.8 ± 3.1	**0.0126**
dP/dt_{max}-EDV	35.4 ± 1.0	33.6 ± 1.1	35.2 ± 1.5	44.4 ± 1.1*	0.0002	34.6 ± 1.6	34.5 ± 1.7	**0.0101**

Values are the mean ± SEM. Haemodynamic parameters were measured by the Millar pressure-volume conductance catheter system. HR, heart rate; MAP, mean arterial pressure; LVESP, left ventricular (LV) end-systolic pressure; LVEDP, LV end-diastolic pressure; dP/dt_{max} and dP/dt_{min} maximal slope of the systolic pressure increment and the diastolic pressure decrement, respectively; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; SV, stroke volume; EF, ejection fraction; CI, cardiac index; BW, body weight; SW, stroke work; ESPVR, slope of end-systolic pressure-volume relationship; PRSW, preload recruitable stroke work; dP/dt_{max}-EDV, slope of dP/dt_{max} – end-diastolic volume relationship. *$p < 0.05$ vs. Co at week 12. p_{iT} and p_{iD}: interaction value of two-way analysis of variance (ANOVA) during training and detraining, respectively.

3.3. Echocardiography

Our results during the training period indicate that LV wall thickness values and calculated LV mass index were significantly increased after one month of swim training (Fig. 2, Suppl. Table 1). While end-diastolic dimensions (LVEDD, LVEDV) remained unaltered compared to control animals, end-systolic dimensions (LVESD, LVESV) significantly decreased in swimming animals, resulting in increased SV and CO as well as improved FS and EF (Suppl. Table 1). RWT clearly increased in the training period, suggesting the appearance of a concentric hypertrophy in our trained rats (Fig. 2). HR did not differ between groups at any time points (Suppl. Table 1).

Cessation of swim training resulted in a rapid, complete regression of wall thickness, LV mass index and RWT values (Fig. 2): just

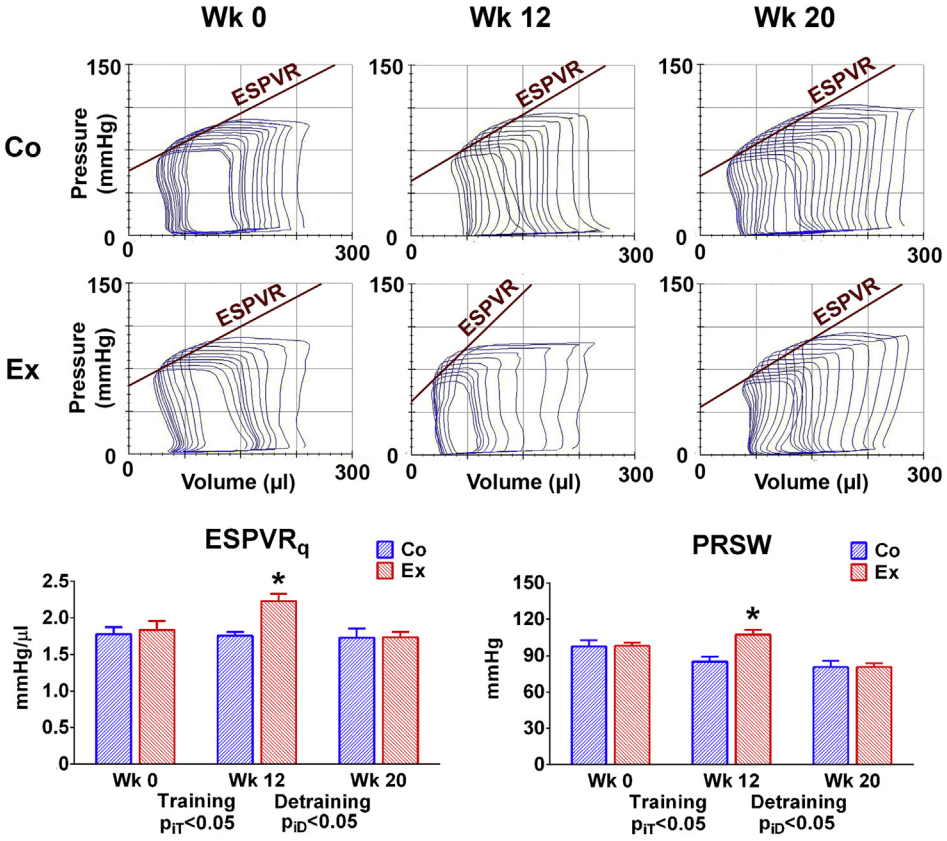

Fig. 1. Load-independent contractility parameters measured by left ventricular pressure-volume analysis. Upper panel: representative original recordings of one control (Co) and exercised (Ex) rat during transient occlusion of the inferior vena cava at weeks (Wk) 0, 12 and 20. The slope of end-systolic pressure-volume relationship (ESPVR) reflects alterations of cardiac contractility. Lower panel: alterations of sensitive contractility parameters [ESPVR and preload recruitable stroke work (PRSW)] during training and detraining. *$p < 0.05$ vs. Co. p_{iT} and p_{iD}: interaction value of two-way analysis of variance (ANOVA) during training and detraining, respectively.

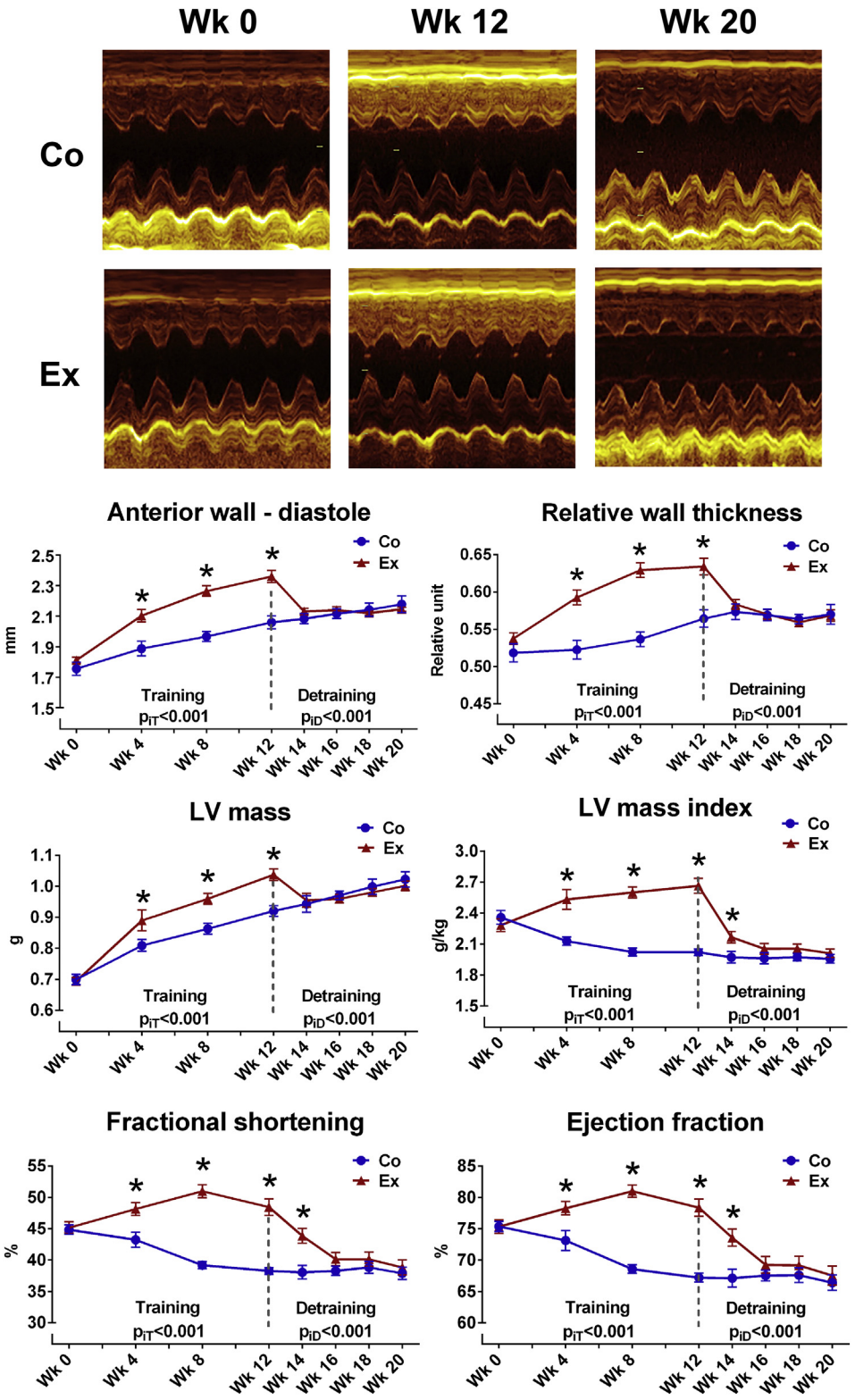

Fig. 2. Consecutive standard echocardiographic measurements. Upper panel: representative left ventricular (LV) M-mode images from one control (Co) and exercised (Ex) rat at weeks (Wk) 0, 12 and 20. Note the increased wall thickness and decreased end-systolic dimensions in Ex rats compared to Co rats after completion of the training programme (Wk 12) and the reversibility of the observed structural alterations (Wk 20). Lower panel: Echocardiographic data of consecutive LV measurements: end-diastolic anterior wall thickness, relative wall thickness and LV mass values showed rapid development and regression of exercise-induced morphological alterations, which were followed by changes in fractional shortening and ejection fraction. Data: the mean ± SEM. *$p < 0.05$ Co vs. Ex. p_{iT} and p_{iD}: interaction value of mixed analysis of variance (ANOVA) during training and detraining, respectively.

two weeks after discontinuation of swim training (at week 14), there was no difference between control and exercised groups. This morphological regression was followed by reversion of alterations in cavital dimensions and systolic parameters (FS and EF), which did not differ after 4 weeks of detraining. The values between these two groups did not differ in the remaining six weeks of our protocol suggesting complete rapid regression of exercise-induced hypertrophy.

3.4. Speckle-tracking echocardiography

After initiation of the training period, a slight, non-significant decrease could be observed regarding longitudinal and circumferential strain and strain rate parameters in both control and exercise groups (Fig. 3). This finding could be a consequence of body mass gain, while the continuous increase in EDV refers to this phenomenon. At week 8, and even more prominently at week 12, in the trained group, both longitudinal and circumferential strain and strain rate parameters showed a significant increase in systolic function compared to control animals. Consistently with morphological data, an immediate drop in STE-derived parameters could be observed in the trained group after cessation of training. There was no difference between the two groups from week 14 to week 20.

Concordance correlation coefficient values were the highest in terms of strain rate parameters (intra-reader and inter-reader; LSr: 0.973 and 0.970, CSr: 0.974 and 0.961, respectively). Reproducibility of GLS and GCS showed comparably lower coefficient values (GLS: 0.917 and 0.917, GCS: 0.942 and 0.936).

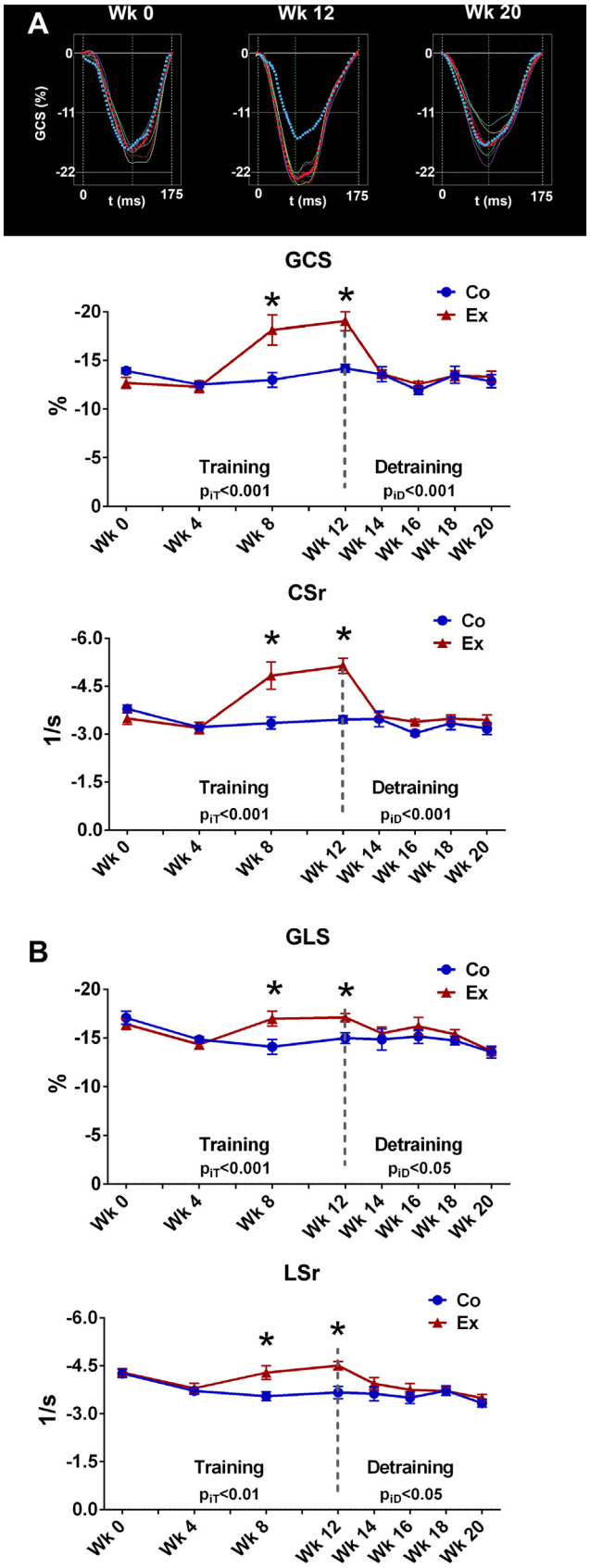

Fig. 3. Layout and results of speckle-tracking analysis. A: Representative speckle-tracking analysis images to determine global circumferential strain (GCS) and circumferential strain rate (CSr) on left ventricular mid-papillary short-axis original recordings of an exercised (Ex) rat at weeks (Wk) 0, 12 and 20. Each continuous curve represents a given segment of echocardiographic image. Average values of the 6 segments are delineated with the red dotted line and compared to an original recording from a control (Co) rat (blue dotted line). Results of consecutively measured GCS and CSr during training and detraining periods are depicted below. B: Results of consecutively measured global longitudinal strain (GLS) and longitudinal strain rate (LSr) during training and detraining periods *$p < 0.05$ Co vs. Ex. p_{iT} and p_{iD}: interaction value of mixed analysis of variance (ANOVA) during training and detraining, respectively.

3.5. Histology

Increased cardiomyocyte width values were observed in exercised rats compared to control ones after completion of training program (Suppl. Fig. 2.A). This exercise-induced alteration showed complete regression after the 8-week long resting period.

Picrosirius staining revealed no collagen deposition in the myocardium of exercise trained rats, that confirms the physiological nature of the observed hypertrophy (Suppl. Fig. 2.B).

4. Discussion

The current study aimed at providing a detailed characterization of LV morphological and functional changes induced by long-term, intense exercise training and detraining in a rodent model using consecutive evaluation by advanced echocardiography. Our results would also serve as the first comprehensive data to describe the development and regression dynamics of morphological and functional aspects of physiologic hypertrophy in detail. Invasive haemodynamic measurements were used to prove training-induced systolic enhancement and its reversibility.

Intense and chronic exercise training leads to complex remodelling of the structure and function of the heart to enhance cardiovascular performance. Although the increase in myocardial mass has been unequivocally shown in different athletes, the degree and type of hypertrophy vary considerably with well-established factors, such as sport type, training session length, age, sex or ethnicity [3,17–19]. Although morphological cardiac alterations have been widely described in several cross-sectional studies in a non-invasive manner [8,9], the dynamics of hypertrophy development are less characterized [20]. According to our echocardiographic data, LV hypertrophic response was observed even after 4 weeks of exercise training, and during the remaining weeks of training period, further development of ventricular hypertrophy could be observed (Fig. 2). Swim-training—a prototype of dynamic, aerobic sports—has been proposed as a stimulus leading to eccentric LV hypertrophy according to the dichotomous concept of Morganroth [21–23]. However, increased RWT values and unaltered end-diastolic dimensions suggest that concentric hypertrophy has been developed

by long-term swim training in our animals (Fig. 2). Our data might show similarity with valuable research that followed sedentary young subjects after intensive endurance training and showed a biphasic response with an initial concentric hypertrophy in the first six-month-long period [24]. Along with similar heart rate values during anaesthesia, end-diastolic chamber sizes did not differ between the control and exercised groups, while end-systolic dimensions were markedly decreased after exercise training (Suppl. Table 1). In addition to the heterogeneous response of myocardial structure to exercise training [8], the role of differences in scale of cardiac dimensions and heart rate between rodents and humans could not be excluded.

The cessation of regular exercise (detraining) in athletes leads to the reversion of cardiovascular adaptation. This phenomenon can be used to aid the differential diagnosis between athlete's heart and primary forms of pathological hypertrophy [25]. Previous echocardiographic studies in trained athletes and small animals also showed rapid changes (within 2–4 weeks) in response to deconditioning [4,6]. Consistently, the consecutive data of wall thickness and LV mass values showed complete morphological regression after 2 weeks of cessation of swim training (Fig. 2). These results suggest a rapid reversion of training-induced myocardial growth after discontinuation of biomechanical stress caused by exercise sessions. The exercise-induced cavity dimensions also regressed to control values after the detraining period, however, with a slight delay compared to the alterations in myocardial mass. This complete regression after deconditioning was demonstrated in most of the healthy individuals participating in different sports [5,26]. The development and regression of physiological hypertrophy was also underlined by histological analysis in according with our previous results (Suppl. Fig. 2.) [13,15].

While increased cardiac mass is a clear and essential feature of exercise-induced cardiovascular adaptation, the follow-up of training-induced alterations in LV myocardial mechanics are still ambiguous. The traditionally used systolic indices are highly sensitive to alterations of preload and heart rate, which showed to be altered in athletes [27]. Contractility has been defined as the intrinsic ability of the myocardium to generate force and to shorten, independently of changes in preload, afterload or heart rate, and is mainly determined by the relation of myofilament system and cellular calcium homeostasis [28]. Because myocardial contractility is a major determinant of LV function, in the last decades, efforts have been made to describe myocardial inotropy in vivo, which led to the development of novel invasive methods [16]. Particular attention has been paid to exercise-induced physiological hypertrophy because this state is associated with “supernormal” myocardial contractility. This remarkable attribution has been observed in both in vitro (isolated cardiomyocyte, papillary muscle) and in vivo experimental investigations with the development of different techniques [29,30]. Our haemodynamic data, utilizing load-independent parameters (ESPVR, PRSW), underpin the “supernormal” contractility in our animals after completing a 12-week-long training plan and indicate total reversion after the detraining period (Fig. 1). Although these parameters can describe myocardial inotropy in detail, pressure-volume analysis requires the sacrifice of experimental animals; thus, this method cannot be applied in longitudinal experimental sports cardiology projects.

Speckle tracking has emerged as an advanced semi-automated echocardiographic technique to better characterize ventricular segmental and global function by also being sensitive on subtle changes compared to conventional measurements (i.e., ejection fraction). Nevertheless, the detection of supernormal LV systolic function of athlete's heart by speckle-tracking echocardiography is a matter of debate according to human studies. There are studies that confirm the increased systolic function even during resting conditions [31–33]; however, some part of the literature suggests a slight decrease in terms of strain parameters [19,34]. Several underlying factors may be hypothesised behind these conflicting results. First and foremost, the investigated populations are different (sport disciplines, level of training, ethnicity, age and gender of the athletes, etc.). Furthermore, training often results in a considerable LV dilation, a scenario where less myocardial deformation is sufficient to achieve similar stroke volume at rest compared to a smaller LV cavity.

In our previous cross-sectional study and in the current animal experiments, strain and strain rate parameters were able to demonstrate the supernormal systolic function of the LV in the context of exercise-induced hypertrophy. We have recently shown that these parameters correlate well with the gold standard pressure-volume analysis-derived measurements of cardiac contractility, highlighting the usefulness of speckle tracking-derived deformation parameters [14]. Of note, our rat model of an athlete's heart is characterized by a concentric type of LV hypertrophy, and the lack of the abovementioned prominent LV dilation may have prevented the “pseudonormalisation” or even decrease of strain parameters.

To date, there have been no comprehensive longitudinal studies performed to characterize the changes in myocardial deformation during exercise training and detraining. The dynamic nature of the development and regression of LV structural versus functional remodelling is of pivotal interest. Since the regression of LV morphological remodelling (hypertrophy) is a principal feature of an athlete's heart, used even in clinical decision-making, the potential presence of an instant reversal of the characteristic functional changes may hold additive value.

Several works suggested a temporal disparity regarding the development of characteristic changes in LV volume, mass and function in the athlete's heart. The initial response to exercise training is suggested to be concentric hypertrophy, while LV dilation appears later [24]. Weiner and colleagues performed an elegant longitudinal study and found that eccentric remodelling appears in response to training augmentation, and a chronic maintenance phase is better characterized by an increase in LV mass [35]. These results could be falsely interpreted as conflicting; however, the latter subjects were not sedentary before undergoing intensification of training. In accordance with the aforementioned results, the training period of our rat model was accompanied by a significant and continuous increase in LV mass resulting in a concentric hypertrophy.

Despite the differing types of LV remodelling, the increase in LV systolic function was present in these two studies. According to our data, there is a constant gain of function during the training period as assessed by global longitudinal and circumferential strain and systolic strain rate. However, the drop back to the control level in systolic function seems a much more instant phenomenon after the cessation of training.

Development dynamics of athlete's heart are far better investigated compared to its reversibility. In line with our results, even the first publications suggested quite an instant morphological drop [4,36]. Thus, the time until the development of athlete's heart markedly exceeds the time until its complete morphological and functional regression. Our study is the first to characterize the effects of detraining on LV myocardial mechanics confirming an instantaneous normalization of systolic deformation. The experiments with a prompt cessation of training may refer to a real-life scenario, where the athlete is forced to stop exercise, i.e., due to an injury.

We would like to emphasize that speckle tracking-derived deformation parameters show an immediate reduction in response to deconditioning in previously exercised animals (Fig. 3), which is more instant compared to conventional echocardiographic measurements of systolic function. This phenomenon might provide another useful aspect of reversibility, which might support an early differential diagnosis between an athlete's heart and pathological cardiac hypertrophy in doubtful situations.

4.1. Study limitations

In our rat model of athlete's heart, a concentric type LV hypertrophy developed. However, in everyday clinical practice, eccentric LV

hypertrophy is the common finding in endurance athletes. This discrepancy may be attributable to the nature and also the longevity of training, beyond inherent differences between the species.

We should also mention that during our in vivo investigations heart rate did not differ between trained and control animals, which might be related to the anaesthetic status that might influence the autonomic balance and mask exercise-induced bradycardia and the consequent chamber dilatation. Although this phenomenon could be a limitation of the study, the similar heart rate values might offer the advantage to obtain more comparable parameters of ventricular dimensions and mechanics.

Furthermore, the echocardiographic hardware and software environment is not dedicated to animal models. Nevertheless, previous correlations with pressure-volume analysis derived sensitive measurements, and the reported intra- and interobserver variability (Suppl. Table 1) suggest that both the sensitivity and the reproducibility of our experimental setup are comparable to dedicated systems [37,38].

4.2. Conclusions and translational aspect of the work

The reversibility of an athlete's heart is a well-established phenomenon representing an important feature of physiological hypertrophy in differential diagnostical issues. Our experiments provide the first comprehensive analysis on development and regression dynamics of morphological and functional aspects of exercise-induced LV hypertrophy. According to our results, it is imperative to characterize the effects of training along with detraining by advanced echocardiographic methods in human settings of various sport disciplines. Speckle-tracking echocardiography might be the method of choice to follow-up changes induced by exercise training and detraining. Theoretically, this approach might be used to monitor the training process to optimize performance. Most of all, in-depth characterization of the dynamic nature of LV morphological and functional changes induced by exercise training and detraining may allow for a more sensitive and expeditious recognition of overlapping pathological conditions with an athlete's heart.

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Conflict of interest

No conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.092.

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