RESEARCH ARTICLE

Prolonged QTc Interval in Rat after Long-term High-Intensity Interval Training and Detraining

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Abstract

Long-term exercise induces cardiac remodelling known as exercise-induced ventricle hypertrophy and accompanied by electrical remodelling that can be recorded by ECG. This study aimed at recognizing electrocardiographic changes in rats undergoing long-term high-intensity interval exercise followed by a period of detraining. This study conducted at the Laboratory of the Biochemistry and Molecular Biology Department, FMUI from November 2014-January 2015. Four groups of young adults male wistar rats (100-200gBW) were randomly selected. Group 1 and 2 were assigned as control group for ECG recording on week (4 and 8) and (12 and 16) respectively. Group 3 was given 4 weeks of intensive training, followed by 4 weeks of detraining, while group 4 was given 12 weeks of intensive training followed by 4 weeks of detraining. ECG examination was performed at the end of each period of training or detraining and compared to control group of the same period of age. P wave in the exercising group was significantly increased ($p<0.05$), PR interval was decreased in group 4 after detraining ($p<0.05$). QRS amplitude was increased although not significantly different compared to control group. However, a significant persistent prolonged QTc interval was observed in the exercising group (62.76±4.03 ms and 64.24±3.78 ms) compared to control group (48.88±2.15 ms and 47.33±3.43 ms). Detraining did not restore QTc interval (57.81±1.96 ms and 61.16±5.02 ms) vs (48.93±2.40 ms and 48.13±1.66 ms). In conclusion, cardiac remodelling after long-term high intensity interval training causes ventricular hypertrophy with persistent repolarization disturbances after a period of detraining, indicated by an increase in QRS amplitude and a significant prolonged QTc interval.

Key words: *Long-term exercise; QTc interval*

Pemanjangan Interval QTc pada Tikus setelah Latihan Intensitas Tinggi dengan Interval Jangka Panjang dan Henti Latih

Abstrak

Latihan fisik intensif jangka panjang menyebabkan remodelling jantung yang disebut exercise-induced hipertrofi ventrikel yang disertai perubahan listrik jantung yang dapat direkam melalui EKG. Penelitian ini bertujuan mengamati perubahan pola EKG tikus yang diberi latihan intensitas tinggi dengan interval jangka panjang. Penelitian dilakukan di Laboratorium Departemen Biokimia dan Biologi Molekuler FKUI, sejak November 2014 sampai Januari 2015. Tikus wistar jantan dewasa muda (BB 100-200 gram) dibagi 4 kelompok. Kelompok 1 dan 2 sebagai kelompok kontrol EKG (4 dan 8 minggu) serta (12 dan 16 minggu). Kelompok 3 diberi latihan intensif 4 minggu diikuti henti latih 4 minggu. Kelompok 4 diberi latihan intensif 12 minggu diikuti henti latih 4 minggu. Rekaman EKG dilakukan pada akhir masa latihan dan masa henti latih kemudian dibandingkan dengan kelompok kontrol sesuai usia. Didapatkan peningkatan voltase gelombang P yang bermakna ($p<0,05$) pada kelompok latihan. Interval PR memendek pada kelompok 4 setelah henti latih ($p<0,05$). Amplitudo QRS meningkat meskipun tidak berbeda bermakna dibandingkan kontrol. Didapatkan perpanjangan bermakna pada interval QTc kelompok latih yang menetap (62,76±4,03 ms dan 64,24±3,78 ms) dibandingkan kelompok kontrol (48,88±2,15 ms dan 47,33±3,43 ms). Henti latih tidak memulihkan interval QTc (57,81±1,96 ms dan 61,16±5,02 ms) dibandingkan (48,93±2,40 ms dan 48,13±1,66 ms). Remodelling jantung akibat latihan intensitas tinggi dengan interval jangka panjang menyebabkan hipertrofi ventrikel disertai gangguan repolarisasi menetap meskipun telah dilakukan henti latih, ditandai peningkatan amplitude QRS dan pemanjangan interval QTc yang bermakna.

Kata kunci: *latihan fisik intensif; QTc interval.*

Introduction

It is well established that regular exercise may reduce the risk for cardiovascular disease and is recommended for improving and maintaining health. Despite the knowledge, 'lack of time' seems to be the common cited obstacle in conducting regular exercise, so that sedentary lifestyle has become an expanding problem in modern society. Furthermore, the exact dosage and type of exercise needed to increase physical fitness is still very much debatable.[1,2] Increasing evidence demonstrates that high-intensity interval training (HIIT) may serve as a substitute to endurance training.[1] Moreover, it is perceived to be more enjoyable than moderate continues training.[3] HIIT is also an effective training method in various endurance and sprint/power sports.[4]

Long-term exercise induces cardiovascular remodelling known as exercise-induced ventricle hypertrophy, which include enlargement of the left ventricle cavity dimension, wall thickness and mass. Cardiac remodelling is considered as an important compensatory mechanism in response to volume or pressure overload. Depending on the type and intensity of the exercise, two types of ventricular hypertrophy may develop concentric and eccentric hypertrophy.

Concentric hypertrophy is associated with pressure overload, and is characterized by enlargement in the width of the cardiomyocyte, while eccentric hypertrophy is the result from volume overload, characterized by longitudinal growth of cardiomyocyte. Cardiac hypertrophy due to exercise is associated with an increase in systolic and diastolic function.[5-7] Although, without doubt, regular exercise is beneficial in enhancing physical fitness in general and in prevention of cardiovascular diseases, extreme intense exercise as done by elite athletes puts them in greater risk of developing cardiac arrhythmia.[6]

Changes in cardiomyocyte structure due to high intensity training are accompanied by electrical remodelling, which are reflected on the surface 12 ECG lead recording.[8,7] This recording is a simple non-invasive test that can help to detect disturbances in cardiac rhythm and help to diagnose other cardiac abnormalities such as hypertrophy, ischemia, or infarction.

A few observational studies have shown that intensive heavy exercise is associated with an increase of developing arrhythmia, which may lead to sudden death. Pellicia et al[8] studied abnormal ECG in a population of athletes and found that 60% out of 12% abnormal ECG recordings were associated with "athlete's heart". Most of these athletes with abnormal ECG were young of age. Only 5% of these abnormal ECG recordings in the athletes were associated with abnormal cardiac structure. This study concluded that ECG could reveal abnormal patterns without indication of abnormal cardiac structure. Benito et al[9] on the other hand, showed that long-term intensive exercise in rats caused changes in ventricle functions and increased tendency to develop arrhythmia. Basavarajaiah et al[10] found prolonged QTc interval in 0.4% of the elite athletes with a tendency for developing long QT syndrome.

Long-QT syndrome (LQTS) have been thought to be the underlying reason for polymorphic ventricular tachycardia (VT) during heavy physical activity due to increased adrenergic stimulation.[9,12] VTs have long been associated with exercise related sudden death in young athletes. Therefore, this study aimed at recognizing electrocardiographic changes, specifically QTc interval changes, in rats undergoing long-term high-intensity interval training and whether a period of detraining would restore any disturbances in the ECG findings.

Methods

High Intensity Interval Training and ECG recording were conducted at the Laboratory of the Biochemistry and Molecular Biology Department, FMUI from November 2014-January 2015. This is an *in vivo* experimental study on young male adults wistar rats outbred strain albino *Rattus norvegicus*, aged 8-10 weeks with body weight of 100-200 g. The animals were housed in cages at a room temperature of 23$\pm$1°C and 12-hours cycle of light and dark. Food and drinks were provided *ad libitum*. Acclimatization was done on an animal treadmill for 1 week with increasing duration and speed. The longest duration was for 12 minutes with a maximal speed of 25 m/minute. Intensive exercise was done on an animal treadmill with a speed of 35m/minute for 15 minutes with a resting interval of 90 seconds every 5 minutes of exercise. The exercise regimens were held 5 times/week and conducted for 4 weeks and 12 weeks. The exercise protocol used in this experiment was according to previous study.[11]

Rats were randomly divided into 4 groups. Two groups were selected as controls to minimize the effects of repeated anaesthesia. Group 1 was assigned control group for ECG recordings on week-4 and 8 of the duration of the experiment. Group 2 was also control group for ECG recordings on week-12 and 16. Group 3 was given intensive exercise (training) for 4 weeks followed by cessation of exercise (detraining) for 4 weeks. Group 4 was given training for 12 weeks followed by detraining of 4 weeks.

ECG recordings were done on Fukuda M.E. Cardisuny D300 using filter at 100 Hz, paper speed 50 mm/s and sensitivity of 1 mV = 20 mm. The rats

were anaesthetized with ketamine 75 mg/kg BW and xylazin 5 mg/kg BW. Amplitude and duration of amplitude ECG recordings were analysed by scanner with enlargement of 100x and calculated using paint program. All readings were done on lead II. No rats were sacrificed during this experiment.

Collected data were expressed as mean ± SD. Shapiro-Wilk test was used to ensure normal distribution of sampling ($p>0.05$). Data were analysed using ANOVA followed by post hoc: LSD test to determine difference between groups ($p<0.05$)

Results

Table 1 and Table 2 display ECG analysis results of the control group and exercise group, respectively.

Table 1. Mean ECG Values of the Control Group

Parameters	Control Group			
	4 weeks	8 weeks	12 weeks	16 weeks
Heart rate/min	294±5.99	296±9.23	286±18.35	280±14.88
P wave amplitude (mV)	0.05±0.01	0.06±0.01	0.07±0.01	0.07±0.01
P wave duration (ms)	17.51±0.75	16.92±0.01	15.11±2.25	16.24±1.30
PR interval (ms)	49.86±1.74	50.7±1.28	49.71±0.94	51.69±1.14
R wave amplitude (mV)	0.64±0.04	0.65±0.04	0.63±0.05	0.72±0.06
S wave amplitude (mV)	0.03±0.02	0.06±0.04	0.04±0.01	0.03±0.02
QRS interval (ms)	9.18±0.71	8.48±0.01	9.18±0.71	10.45±1.02
QTc interval (ms)	48.88±2.15	48.93±2.40	47.33±3.43	48.13±1.66
T wave amplitude (mV)	0.10±0.01	0.08±0.01	0.10±0.01	0.11±0.01

Four weeks of exercise did not appear to affect the heart rate of the rats. The effect was more noticeable after 12 weeks of exercise, with a slight and not significant reduction in heart rate compared to control of the same age. Four weeks of detraining was not found to increase heart rate. Analysis of the P wave showed a significant increase in the amplitude of the P wave after 4 weeks and 12 weeks of exercise, which might indicate the development of atrial enlargement. Detraining period in group 3 reduced the amplitude of the P wave, although the amplitude was still significantly higher than control of the same age. Detraining period in group 4 re-established the P wave to near the control or normal values. Although there was an increase in the amplitude of P wave, exercise of 4 weeks, 12 weeks, and the respective detraining periods did not affect the P wave duration indicating a normal conduction spread through the atria.

Four weeks of exercise did not significantly prolong the PR interval when compared to control and 4 weeks of detraining restored the PR interval values. Twelve weeks of exercise slightly increased the PR interval duration, which was not significantly different than control. On the other hand, detraining significantly reduced the PR interval duration compared to control.

Table 2. Mean ECG Values of The Exercise Group and Detrained

Parameters	Exercise Group			
	4 wk	4 wk + detraining	12 wk	12 wk + detraining
Heart Rate/min	294±10.21	300±8.09	273±20.80	270±19.3
P wave amplitude (mV)	0.1±0.01*	0.09±0.02*	0.09±0.01*	0.06±0.01
P wave duration (ms)	17.65±1.23	15.39±1.69	19.06±3.75	14.97±1.32
PR interval (ms)	54.94±1.82	50.98±2.46	51.27±2.22	45.76±1.38*
R wave amplitude (mV)	0.92±0.04*	0.85±0.05*	0.83±0.06*	0.87±0.08
S wave amplitude (mV)	0.13±0.05*	0.11±0.04	0.09±0.04	0.09±0.04
QRS interval (ms)	8.75±0.28	8.33±0.46	8.47±0.22	10.45±1.11
QTc interval (ms)	62.76±4.03*	57.81±1.96	64.24±3.78*	61.16±5.02*
T wave amplitude (mV)	0.16±0.02*	0.10±0.01$^{\varphi}$	0.10±0.01	0.12±0.02

*significant difference compared to control group ($p<0.05$), $^{\varphi}$significant difference compared to the exercising group ($p<0.05$).

Four weeks of exercise and its subsequent detraining period as well as 12 weeks of exercise significantly increased the amplitude of R wave compared to their respective controls. A significant increase in S wave amplitude was only found after four weeks of exercise. Twelve weeks of exercise and detraining also showed an increase, although not significant when compared to control. Training of 4 weeks, 12 weeks, as well as detraining did not affect the duration of the QRS interval.

The T wave amplitude was significantly increased in the 4 weeks exercise, although during the subsequent detraining period, a T wave was significantly reduced compared to its exercise group. No difference was found in the 12 weeks exercise and detraining group when compared to the control group.

The most noticeable change on the ECG patterns caused by intensive training was the change in QTc interval. Four weeks training as well as 12 weeks training showed significant prolonged QTc interval compared to their controls. Although four weeks of detraining reduced the QTc interval, it was still higher than normal. Even after 4 weeks of detraining following 12 weeks of exercise, there was still a significant prolonged QTc interval compared to its control group.

Exercise protocol applied in this study induces ventricle hypertrophy as shown in an increase in QRS voltage (Figure 1).

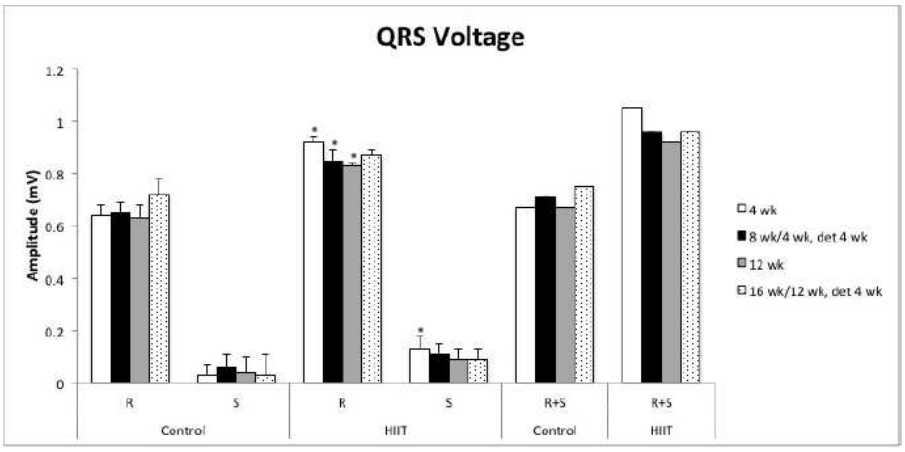

Figure 1. Changes in QRS Amplitude after 4 Weeks, 12 Weeks and Its Subsequent Detraining Periods in Rats. *Significant Difference Compared to Its Control Group Respectively (p<0.05).

As mentioned before, the most noticeable change in the ECG pattern is the persistent prolonged QTc interval in the exercising group and after its detraining period (Figure 2).

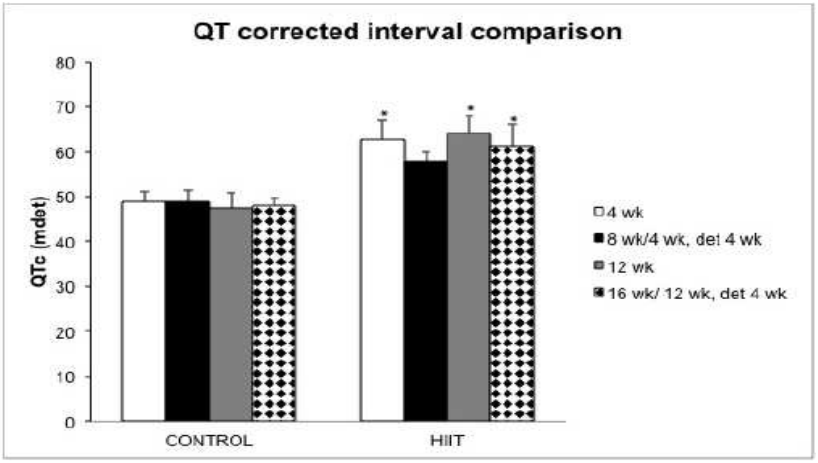

Figure 2. Changes In Qtc Interval after 4 Weeks, 12 Weeks and Its Subsequent Detraining Periods in Rats. *Significant Difference Compared to Its Control Group Respectively (P<0.05).

Discussion

This study describes the resting ECG changes in a rat model after completing 4 weeks and 12 weeks of high-intensity interval training with subsequent detraining period of 4 weeks. The protocol used in this study was proven to have reached an anaerobic state with blood lactate of ≥4.1 mmol/dl.[12]

Although no decrease in heart rate (HR) was observed after 4 weeks of exercise, detraining raises the resting heart rate, which might indicate the recovery of increased vagal activities during exercise. The decrease in HR after 12 weeks of exercise supports the altered vagal activity towards the increased parasympathetic tone. The result of this study is similar to VanHoose et al[13] which assed the effect of aerobic exercise training on diabetic fatty rats. However, while in this study we observed a decrease in HR of the control group with increasing age, all the groups in VanHoose et al[13] experiment showed an increase in HR. Dor-Haim et al[14] observed a significant decrease in normal rat HR undergoing exercise for 8 weeks. The difference in results with this experiment might be due to the difference in the exercise protocol. Dor-Haim et al[14] used a treadmill with inclination and the final duration of exercise lasted for 60 minutes.

In this study we observed a significant increase in P wave amplitude after 4 weeks as well as 12 weeks of exercise. Four weeks of detraining in Group 4 showed a normal P wave amplitude. Multiple studies have noted that P wave amplitude is greater in athletes than in an aged-matched non-athlete population. The exact basis for this finding is still unknown but it may be due to atrial enlargement.[15] A study by Król et al[16] concluded that left atrial enlargement was a common condition in young, healthy rowers. The most often postulated mechanism of physiological LA dilatation in athletes is due to an increase volume load. However, according to a study conducted by Konopka et al[17] enlargement of the left atrium is more prominent in athletes with electrocardiographic changes such as early repolarization. Some theories suggested that enlargement of the left atrium and cardiac remodelling might contribute to paroxysmal supraventricular arrhythmias.[11]

PR interval was slightly prolonged in the exercising group. This might be associated with the increased P wave amplitude. The shortened PR interval in Group 4 after detraining is something that might have to be looked further into.

Intensive exercise is known to induce morphological changes of the heart such as enlargement of cavity dimension, wall thickness, as well as increase in cardiomyocyte length and width.[9,18] Mechanical stress induced by increased haemodynamic load to the heart during intense exercise are translated into pro-hypertrophic intracellular signals. However, the exact mechanisms of how these biomechanical stresses are perceived by the cardiomyocyte are still unknown.[15,19] The QRS duration in all four groups are similar indicating that no ventricular conduction disturbances were present.

The QTc interval in this study was calculated using Bazett's formula, which is commonly used in evaluating patients with long QT syndrome (LQTS).[20] What the significance of an isolated prolonged QTc might indicate has never been studied before.[12] In most forms of underlying structural heart disease associated with sudden death in young athletes, arrhythmia is induced by exercise. A prolonged QT interval indicates repolarization abnormalities, which during intensive exercise, has a high risk of *torsades de points* that can degenerate into ventricular fibrillation. LQTS is a heterogeneous genetic disorder that affects ionic channels of myocardial cells. This study was conducted on normal rats and no reports have been found indicating rats having possible gene disorders causing LQTS. So, the question is whether prolonged QT interval in this study was caused by long intensive exercise, or is there another underlying basis that needs to be looked upon.

Conclusions

The result of this study showed that cardiac remodelling after long-term high-intensity interval training causes atrial and ventricular hypertrophy with persistent repolarization disturbances after a period of detraining, indicated by an increase in P wave amplitude, QRS amplitude and a significant prolonged QTc interval.

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