ORIGINAL RESEARCH

# Intensive Exercise Training Improves Cardiac Electrical Stability in Myocardial-Infarcted Rats

Horesh Dor-Haim, PhD; Chaim Lotan, MD; Michal Horowitz, PhD; Moshe Swissa, MD

***Background*—**Moderate exercise training has been shown to decrease sudden cardiac death post myocardial infarction. However, the effects of intensive exercise are still controversial.

***Methods and Results*—**Fourteen myocardial-infarcted rats were divided into sedentary (n=8) and intensive training groups (n=6) and 18 sham control rats to sedentary (n=10) and intensive training groups (n=8). Heart rate variability was obtained at weeks 1 and 8. The inducibility of ventricular tachycardia/fibrillation was assessed in a Langendorff system. Fast Fourier transforms were applied on the recorded ventricular tachycardia/fibrillations. Training reduces low to high frequency ratio of heart rate variability at week 8 compared with that at week 1 ($P<0.05$). In isolated hearts, the probability for ventricular tachycardia/fibrillation was decreased from 4.5±0.8% in sedentary controls to 1.56±0.2% in intensive training controls ($P<0.05$) and from 13.5±2.1% in the sedentary group to 5.4±1.2% in the intensive training group ($P<0.01$). Moreover, the pacing current required for ventricular fibrillation induction in the trained groups was increased following exercise ($P<0.05$). Fast Fourier transform analysis of ECG findings revealed an exercise-induced ventricular fibrillation transition from a narrow, single-peak spectrum at 17 Hz in sedentary controls to a broader range of peaks ranging from 13 to 22 Hz in the intensive training controls.

***Conclusions*—**Intensive exercise in infarcted rats leads to reduced ventricular fibrillation propensity and is associated with normalization of refractoriness and intrinsic spatiotemporal electrical variations. **(*J Am Heart Assoc*. 2017;6:e005989. DOI: 10.1161/JAHA.117.005989.)**

**Key Words:** electrophysiology test • exercise training • myocardial infarction • remodeling • ventricular fibrillation

Many clinical and epidemiological studies support the concept that physical fitness correlates with reduced cardiovascular and overall mortality in a wide-ranging population[1–4] and prevents sudden cardiac death in patients with established ischemic heart disease.[5–7] While regular cardiovascular programs that include moderate-intensity aerobic training[5,6] are considered safe, strenuous activity can be described as having variable safety concerns, depending on the patient population and the setting of exertion.[7] Recently, an intensive aerobic program was superior to a moderate program (80–90% versus 50–70% of peak aerobic capacity) in patients with cardiovascular disease.[8,9] In addition, while the risk of cardiovascular events is decreased following many episodes of exercise, the risk of a cardiovascular event (eg, myocardial infarction [MI], stroke, ventricular tachycardia/ventricular fibrillation [VT/VF], and sudden death) has been studied to be transiently elevated during the actual episode of exertion.[10,11]

Both animal and clinical studies on athletes who perform intensive exercise have demonstrated enhanced left ventricular wall fibrosis and dyssynchrony leading to electrical instability and arrhythmia.[12–14] However, it has been shown in animal models that exercise training protects against VF induced by ischemia.[15,16] In addition, it was shown that moderately intense aerobic training can normalize autonomic dysfunction post MI, and thus reduce the risk of sudden cardiac death.[17] Recently, we showed that a continuous intense exercise program in normal rats is associated with increased resistance to VF and is characterized by intrinsic alterations in the properties of VF.[18]

The electrophysiological consequences of cardiac adaptation to intensive exercise training are still controversial. Furthermore, the manner in which intensive exercise training intrinsically affects the heart's susceptibility to arrhythmias remains inadequately defined. Thus, the aim of this study was to characterize the effect of intensive aerobic exercise

*From the Heart Institute (H.D.-H., C.L.) and Department of Physiology (M.H.), Hadassah-Hebrew University Medical Center, Jerusalem, Israel; Kaplan Medical Center, Rehovot, Israel (M.S.); Hadassah-Hebrew University Medical Center, Jerusalem, Israel (M.S.).*

**Correspondence to:** Moshe Swissa, MD, Heart Institute, Kaplan Medical Center, PO Box 1, Rehovot 76100, Israel. E-mail: swissam@mail.huji.ac.il

Received February 28, 2017; accepted June 6, 2017.

## Clinical Perspective

### What Is New?

- Intensive aerobic training reduces susceptibility to malignant arrhythmia in normal and infarcted hearts.
- This reduced susceptibility is linked to intrinsic exercise-induced normalization of refractoriness in the hypertrophied infarcted heart.
- Although both myocardial infarction and intensive training induce myocardial hypertrophy, the trained animals were more resistant to induction of ventricular arrhythmias.

### What Are the Clinical Implications?

- In this study, we showed that a relatively intermediate-term (8 weeks) intensive training program reduces arrhythmias in both normal and infarcted hearts.
- In contrast, it was shown that a long-term (16 weeks) intensive exercise training program in normal rats was associated with changes in cardiac function, fibrous tissue content, fibrotic markers, and arrhythmia susceptibility.
- Clinical implication attributable to the observed discrepancy is to recommend intermittent rather than continuous intensive exercise, especially for a long-term program.
- However, this clinical implication should be further confirmed with human heart adaptation to an intensive exercise regimen, which may not be the same as the regimen for a rat.

training on cardiac electrical properties in normal and infarcted hearts.

## Methods

Forty male rats (Sprague–Dawley, weight 250–300 g) were used for this study. The study protocol was approved by the ethics committee of the Hebrew University Hadassah Medical School, Jerusalem, in compliance with the American Heart Association guidelines. Twenty of 40 rats underwent left anterior descending (LAD) ligation to achieve MI (n=14, survived) and the remaining 20 had a sham operation (n=18, survived). The MI group was further divided into a sedentary group (SMI, n=8) and an intensive training group (TMI, n=6) that exercised for 8 weeks. The sham-operated control group was also divided into a sedentary group (SCN, n=10) and an intensive training group (TN, n=8) that exercised for 8 weeks.

## In Vivo Monitoring

Aerobic exercise capacity was defined as the duration of the exercise in minutes, while the speed and elevation of the slope were increased gradually up to exhaustion. Aerobic exercise capacity was measured 3 times. The first exercise test for baseline capacity was performed at the beginning of the study before the sham or the LAD ligation operation. The second exercise test was performed 1 week later after the sham or LAD ligation operation to determine the effects of MI induction on the exercise capacity. The third exercise test was performed at the end of the study at week 8 to test the effect of the exercise program on the exercise capacity. A 20-minute ECG recording was collected (at weeks 1 and 8) for heart rate and heart rate variability (HRV) measurements.[18] An echocardiography was performed for all rats at day 1 (n=40) and at day 7 after the procedures for all survivors (sham group, n=18; LAD ligation group, n=14).

## Exercise Protocol

A progressive intensive exercise protocol was designed to achieve 90% of maximal exercise capacity evaluated in aerobic gradual testing. Because of the variability of the exercise capacity between the rats, the exercise protocol used in this study was individualized for each rat as performed in a human rehabilitation program. Meaning that for each rat the speed and elevation of the slope were increased until the rat reached 90% of its own exercise capacity. In detail, rats were trained 5 days a week for 8 weeks on a rodent treadmill. The treadmill had different lanes to serve as corridors for each animal and had a grid in the back that administered a small electric shock on contact to ensure that animals ran effectively. The electric shock was of constant intensity (0.3–2 mA), sufficient to encourage the animal to run without being harmful. The speed and elevation of the slope were increased to gradually increase the exercise intensity. Exercise intensity was gradually increased during the first 10 minutes of each session until rats reached 90% of their exercise capacity and then continued running at a steady state at the same level until the animal showed signs of exhaustion.

## MI Induction

Rats (250–300 g) were anesthetized with ketamine 85 mg/kg and xylazine 15 mg/kg and ventilated with a respirator (Model SN-480-7, Astec) to keep $P_{O_2}$, $P_{CO_2}$, and pH levels within a physiological range. Thoracotomy in the fourth intercostal space was obtained, the heart was suspended on the pericardial cradle, and the LAD artery was ligated for 45 minutes. Myocardial ischemia was confirmed by regional cyanosis, bulging of the relevant segment of the left ventricle, an increase in the left ventricular end-diastolic pressure, and elevation of the ST segment on ECG. In the sham group, the same procedure was performed without the LAD occlusion.

## Langendorff Perfusion System and Isolated Heart Monitoring

On day 75, the hearts were excised for mechanical and electrophysiological measurements. The animals were anesthetized and the heart was removed and connected to a Langendorff system and perfused within 120 seconds with a modified Krebs solution[18] at a temperature of 37°C.

Two platinum electrodes were placed on the left ventricle apex and the right atrial appendage to obtain an ECG. Left ventricular pressure (LVp) was recorded using a pressure transducer inserted into the left ventricle. ECG and pressure were acquired in a PowerLab data acquisition system (ADInstruments Inc). The cardiac output was indirectly determined based on the LVp time integral. Systolic function was determined as dLVp/dt(max) and diastolic function as dLVp/dt(min).[18]

## Electrophysiological Protocol

Two additional electrodes were placed on the free wall of the right ventricle for pacing and stimulation using a programmable stimulator (Master-8, A.M.P. Instruments, LTD). The pacing threshold was determined at 5 Hz. Two stimulation protocols were used to determine the effective refractory period (ERP) and VT/VF induction threshold. VT was defined as a rapid rate with changed QRS morphology compared with the basic rate but with a new monomorphic pattern. VF was defined as a rapid rate with randomly changed complex morphology. ERP was measured using the standard S1 and S2 protocol at twice the pacing threshold intensity. A set of 16 sequences, each containing 8 beats at a cycle length of 260 ms (S1), and a ninth beat (S2) with a coupling interval (CI) of 100, 90, 80, 70, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, and 5 ms was used for induction of tachyarrhythmia (VT/VF). The initial pacing intensity was set at twice the pacing threshold and a pulse width of 1 ms. The S1 and S2 sequences were applied until induction of VT/VF or loss of capture was detected. If the index set did not induce VT/VF, a new set of 16 sequences was repeatedly applied (after a rest period of 60 seconds) with an increased pacing intensity of S2 only (0.2 mA up to 10 mA). The VT/VF thresholds were defined as the minimum pacing intensity that induced arrhythmias. The VT/VF CIs were defined as the S1 and S2 time intervals that induced arrhythmias. Once an induced arrhythmia was sustained for more than 60 seconds, intracoronary lidocaine hydrochloride (0.25 mg) was used for chemical defibrillation. A washout period of 15 minutes was applied before introducing the next stimulation protocol. Probability of arrhythmia was determined as the number of induced VT/VF per 1000 attempts.

## Spectral Analysis of VF

All ECG recordings of sustained VF (>2.5 seconds, with the first 0.5 seconds ignored) were spectrally analyzed to determine their frequency content using fast Fourier transform (Power Lab Chart 5 software). Accordingly, 10- to 20-second episodes of contiguous VF were segmented into sequential sections of 1 second each. Subsequently, the 1-second sections were zero padded and their power spectra calculated separately using a 0.24-Hz resolution fast Fourier transform. Finally, the individual power spectra were averaged via the Welch method[18] for each animal and for all the animals in their respective groups to obtain an overall frequency content characterization. The dominant frequency (DF) was defined as the frequency with maximal power in the spectrum.

## Heart Morphometric and Infarct Size Measurements

At the end of the study, the atria of the heart were removed and the heart was weighed. Infarct size was measured in 3 hearts from each of the MI groups. Transverse 5-μm-thick sections were cut at 500-μm distances, stained with hematoxylin-eosin and azan, and morphological analysis was performed using an Axioplan microscope (Zeiss) and NIH Image software.

## Statistical Analysis

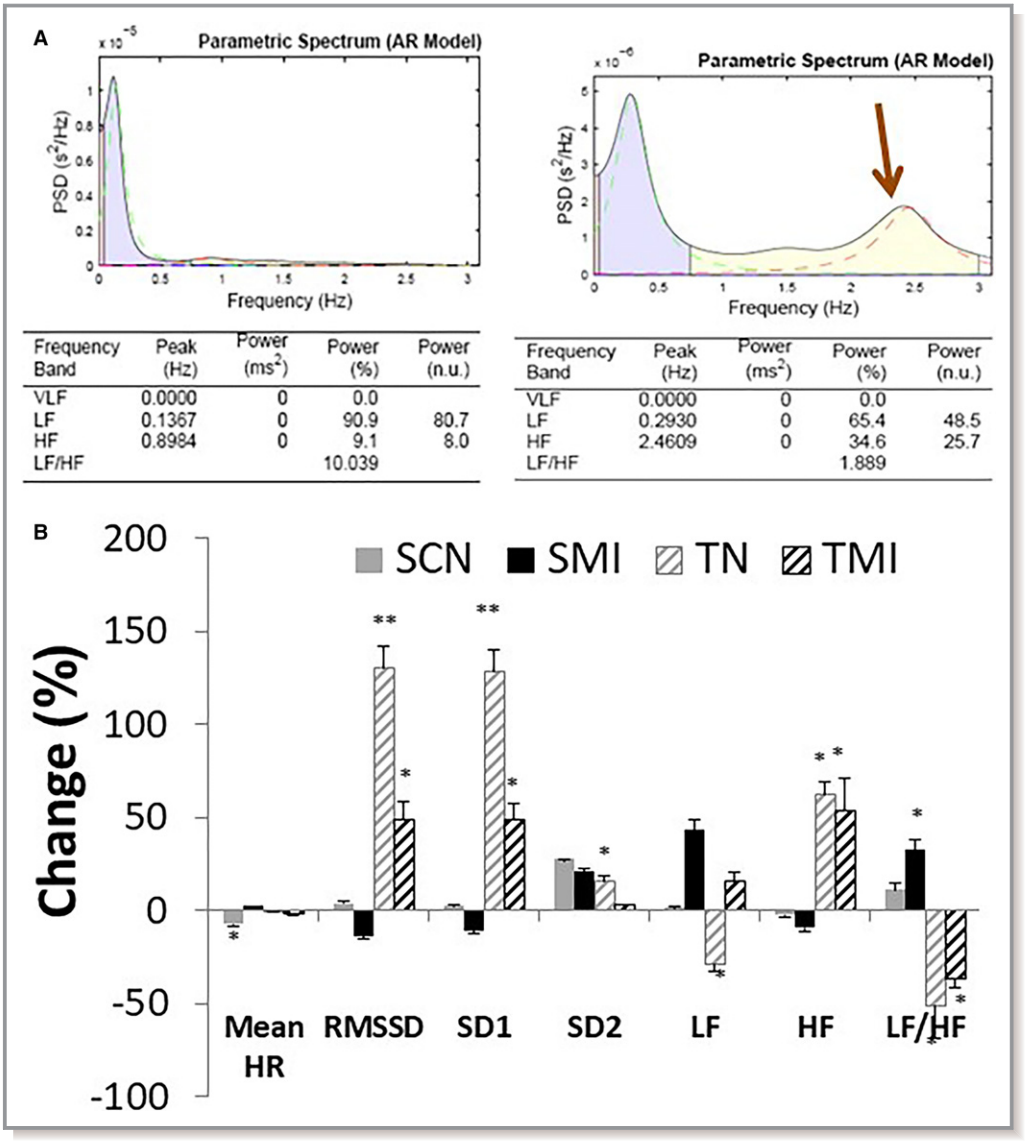
Values are expressed as mean±SD. Categorical data were compared using chi-square test. Categorical data and the effectiveness of the training programs comparing the percentage of change and differences between the 4 groups (such as VFP [ventricular fibrillation probability], VTP [ventricular tachycardia probability], ventricular fibrillation threshold, and others) were examined via multivariate ANOVA using the accurate assumptions. ANOVA repeated measures (HRV measures) (Figure 1) were used to compare pretest and posttest values. The $\alpha$ level was set to $P<0.05$.

## Results

The mortality rate of rats caused by the MI procedure was 36%: 5 of 22 rats died during the ligation of the LAD and another 3 rats died in the next 24 hours (leaving 14). None of the rats died during the sham operation.

## Aerobic Exercise Capacity

While the exercise capacity in the first gradual aerobic test at baseline was comparable, a significant decrease in exercise capacity was observed in the second exercise test in both MI




| Frequency Band | Peak (Hz) | Power ($ms^2$) | Power (%) | Power (n.u.) |
|---|---|---|---|---|
| VLF | 0.0000 | 0 | 0.0 | |
| LF | 0.1367 | 0 | 90.9 | 80.7 |
| HF | 0.8984 | 0 | 9.1 | 8.0 |
| LF/HF | | | 10.039 | |

| Frequency Band | Peak (Hz) | Power ($ms^2$) | Power (%) | Power (n.u.) |
|---|---|---|---|---|
| VLF | 0.0000 | 0 | 0.0 | |
| LF | 0.2930 | 0 | 65.4 | 48.5 |
| HF | 2.4609 | 0 | 34.6 | 25.7 |
| LF/HF | | | 1.889 | |

**Figure 1.** Intensive training increases heart rate variability (HRV). A, Increased high-frequency domain in the intensive training myocardial infarction group; left panel before exercise, right panel after 8 weeks of intensive training. B, HRV parameters relative to normalized value at week 1 in percentage. Values are expressed as mean±SD. AR indicates autoregressive; HF, high-frequency power; HR, heart rate; LF, low-frequency power; PSD, power spectral density; RMSSD, root mean square of successive differences; SD1, short-term HRV; SD2, long-term HRV; VLF, very low frequency. **P*<0.05; ***P*<0.01.

groups (SMI and TMI) compared with both sham groups (TN and SCN, *P*<0.05) (Table 1). Gradually increased exercise intensity was achieved (see protocol) for both exercised groups (TN and TMI). The TN group achieved a higher absolute training level compared with the TMI group (higher average training speed and slope 17±1.8 m/min and 4.2±0.4° versus 15.2±2 m/min and 2.8±1°, respectively; *P*<0.05). In addition, the trained groups (TN and TMI) showed a gradual increase in the time to exhaustion during the 8 weeks of exercise up to 53±4 and 30±5, respectively. In parallel, a significant increase in exercise capacity was observed during the third exercise test (at week 8) in both trained groups (TN and TMI) (Table 1).

## Echocardiography

While the mean ejection fraction was comparable for the presham and postsham operation rats (77±5.3% versus 76.5±4.9%, respectively; *P*=0.4 [n=18]), a significant reduction (17%) in EF was observed in the post-LAD ligation rats compared with the pre-LAD ligation rats (60.2±5.1% versus 77.3±5.6%, respectively; *P*<0.001 [n=14]) caused by the induced MI.

**Table 1.** Aerobic Capacity in the Gradual Exercise Test and 8 Weeks of Training

| Group | ET1, min | ET2, min | ET3, min | Week 1, min | Week 2, min | Week 3, min | Week 4, min | Week 5, min | Week 6, min | Week 7, min | Week 8, min |
|---|---|---|---|---|---|---|---|---|---|---|---|
| SCN | 10.6±0.2 | 10.2±0.4 | 9.6±0.1* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| TN | 9.3±0.4 | 9.8±0.6 | 12.2±0.6† | 10 | 26±3 | 31±3 | 36±4 | 41±3 | 47±4 | 51±3 | 53±4 |
| SMI | 9.5±0.3 | 7.1±1.8* | 7.9±1.3* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| TMI | 10.2±0.7 | 7.6±1.5* | 9.3±0.6† | 10 | 20±4 | 22±5 | 23±5 | 25±4 | 30±5 | 30±4 | 30±5 |

ET1, ET2, and ET3 represent baseline, pretraining, and posttraining gradual exercise tests. Rats ran on a rodent treadmill, acclimating during week 1 (5 minutes of light training). Intensive exercise training was established from week 2 to week 8, in which rats trained to failure. SCN indicates sedentary control group; SMI, sedentary myocardial infarction group; TMI, intensive training myocardial infarction group; TN, intensive training group.
*$P$<0.05.
†$P$<0.01.

## Heart Rate Variability

The mean heart rate change (weeks 1–8) was comparable in all groups except the SCN group (−7%, $P$<0.05) (Figure 1A). HRV data are presented in Figure 1. In both trained groups (TN and TMI), the high-frequency domain, the SD1 (which represents the dispersion of rapid R-R changes), and the root mean square of successive differences (RMSSDs) representing time-domain variability increased (63±7% and 54±17%, 130±12% and 49±9%, and 130±12% and 50±9%, respectively; $P$<0.05) (Figure 1A). In addition, a decreased low-frequency/high-frequency ratio was observed in the TN and TMI groups (−51±5% and 37±7%, respectively; $P$<0.05) (Figure 1A), which is compatible with an increased ratio of parasympathetic over sympathetic tones for the trained groups. Figure 1B shows the increased HRV frequency and time-domain variables from pretraining to posttraining measurements in the trained groups.

## In Vitro Mechanical Function

Cardiac mechanical function was reduced in both infarcted groups (SMI and TMI) compared with the noninfarcted groups (SCN and TN) (Table 2). However, in both trained groups (TN and TMI), an increase in cardiac mechanical function was observed ($P$<0.05, Table 2). In addition, training increased the dP/dt(max) and decreased the dP/dt(min) in both the TN and TMI groups compared with the SCN and SMI groups, respectively ($P$<0.05, Table 2).

## Refractoriness and Ventricular Arrhythmia Inducibility

The ERP was comparable in both intact groups (50±2.8 ms versus 50±2.9 ms for SCN and TN, respectively). However, the ERP significantly increased (68±3.8 ms) in the SMI group compared with the intact group ($P$<0.05). Training normalized the ERP in the TMI group (50±12 ms). Ventricular arrhythmias (VT/VF) were induced by programmed stimulation in 10 of 10 of the SCN, 8 of 8 of the SMI, and 6 of 6 of the TMI rats as compared with 6 of 10 in the TN group ($P$<0.05 by contingency chi-square test for TN compared with SCN and SMI). Exercise training decreased the probability of all VT/VF in the trained groups (Figure 2A). VF and VT probabilities decreased from 4.5±0.8% in SCN to 1.56±0.2% in TN ($P$<0.05), while in MI groups, the probability decreased from 13.5±2.1% in SMI to 5.4±1.2% in TMI ($P$<0.01). The threshold for VF induction was 5- and 2-fold higher in the trained groups compared with the intact groups (9.6±0.3 mA versus 1.8±0.4 mA in SCN versus TN, respectively, and 5.73±1.89 mA versus 2.39±0.6 mA in SMI versus TMI,

**Table 2.** Measurements of Isolated Heart Mechanical Function

| Group | HR, bpm | LVp, mm Hg | LVp×HR, mm Hg×bpm | dP/dt Min, mm Hg/s | dP/dt Max, mm Hg/s |
|---|---|---|---|---|---|
| SCN | 8±245 | 5±117 | 117±28 457 | −103±2713 | 145±4230 |
| TN | 6±260 | 5±123* | 84±31 094* | −134±3392* | 136±4770* |
| SMI | 8±205 | 7±80 | 157±16 189 | −140±2415 | 179±3100 |
| TMI | 10±225 | 9±88* | 210±19 772* | −148±2753* | 193±3314 |

dP/dt minimum and maximum reflect the rate of left ventricular pressure decrease/rise in early diastole/systole. bpm indicates beats per minute; dP/dt, delta pressure/delta time; HR, heart rate; LVp, left ventricular pressure; SCN, sedentary control group; SMI, sedentary myocardial infarction group; TMI, intensive training myocardial infarction group; TN, intensive training group.
*$P$<0.05.

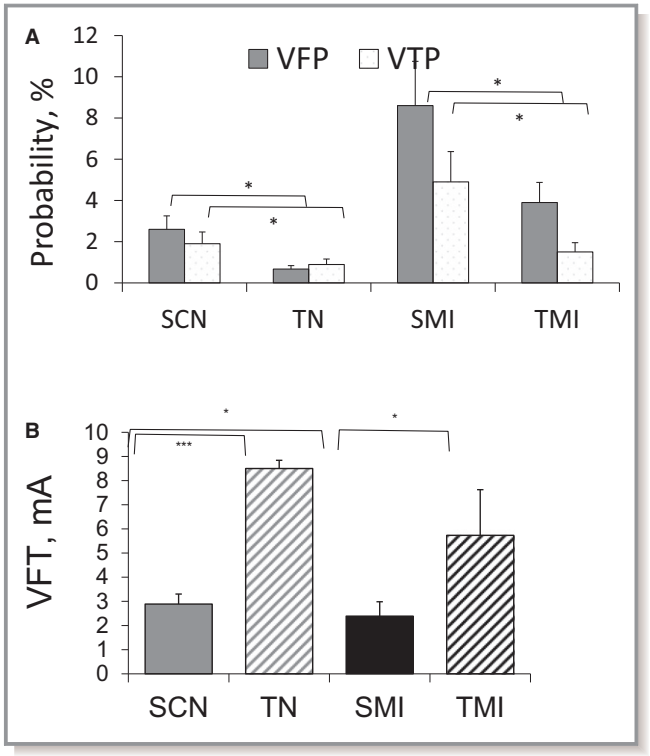



**Figure 2.** Ventricular electrical stability. A, Reduced probability of ventricular tachycardia/ventricular fibrillation (VT/VF) induction in trained groups (percentage of events per 1000 stimuli). B, Increased VF threshold (VFT) in trained groups. *$P$<0.05; ***$P$<0.001. Values are expressed as mean±SD. SCN indicates sedentary control group; SMI, sedentary myocardial infarction group; TMI, trained myocardial infarction group; TN, trained group; VFP, ventricular fibrillation probability; VTP, ventricular tachycardia probability.

respectively [$P$<0.05]). While the average CI was significantly longer in the MI groups compared with the intact groups (58.2±18 ms versus 42.5±16.5 ms, respectively [$P$<0.01]), the training did not show significant differences between groups. However, training decreased the CI dispersion (SD of CI) in both trained groups (13.1±6 versus 20±5 in TN and SCN, respectively, and 17.1±7 versus 20.6±5 in TMI and SMI, respectively [$P$<0.05]). The scatter plot in Figure 3 illustrates that tachyarrhythmias were activated in a narrower window in the trained animals.

## VF Spectral Analysis

ECG recordings of sustained VF were spectrally analyzed to determine their DF. Figure 4 shows the distinct averaged power spectra of the pseudo-ECG for all VF events lasting at least 2 seconds recorded in all animals. In accordance with our previous study, characterization of the VF in the frequency domain revealed a distinct profile for VF in SCN versus TN rats. The sequential control power spectra (for the SCN group) are mostly single peaked around 17 Hz (Figure 4). In

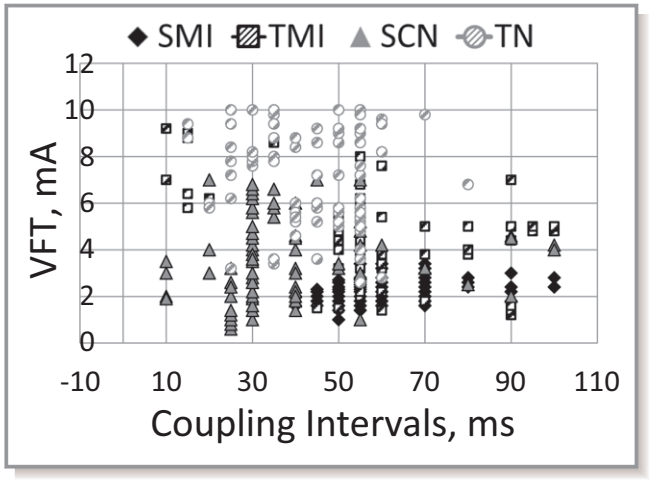



**Figure 3.** Current amplitude and $S_2$ interval for ventricular fibrillation (VF) induction in individual experiments for the 4 groups. It can be seen that for the trained group (TN), a shorter coupling interval and/or higher voltage pacing were needed to induce VF. SCN indicates sedentary control group; SMI, sedentary myocardial infarction group; TMI, trained myocardial infarction group; VFT, VF threshold.

comparison, the power spectra for the animals in the TN group were visibly more complex. Instead of a single and narrow spectral peak as observed in the SCN animal, the TN animals had, at any given moment, multiple spectral peaks spanning a wider band between a lower frequency of 13 Hz and a higher frequency of 22 Hz as compared with the control sample. The SMI groups also demonstrated narrow peaked spectrum patterns (Figure 4), but with an average slower DF of 13.5 Hz (compared with 17 Hz for SCN). Training (TMI) did not differentiate the DF pattern in the MI groups except for a weaker average power spectrum in the main DF (15 Hz) in the

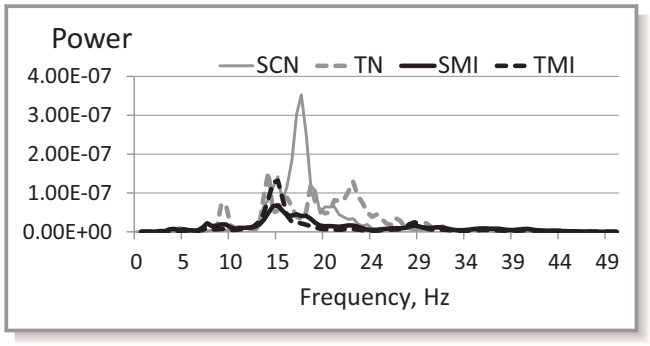



**Figure 4.** Ventricular fibrillation (VF) spectral analysis of pseudo-ECG recordings. Averaged power spectra of 1-second-long pseudo-ECG segments for 69 VF events lasting more than 2 seconds in the sedentary control group (SCN), for 18 VF events in the trained group (TN), for 223 VF events in the sedentary myocardial infarction group (SMI), and 104 VF events in the trained myocardial infarction group (TMI).

sedentary group (SMI=$0.85\times10^{-7}$ versus TMI=$1.3\times10^{-7}$, $P<0.05$).

## Infarct Size and Anatomic Remodeling

Images of heart slices (Figure 5A) show a transmural infarct of the left ventricle with a calculated average infarct size of 17±6% for both MI groups (SMI and TMI) consistent with the echocardiography reduction of ejection fraction (−17%) in the infarcted hearts. Exercise training and MI both induced significant concentric myocardial hypertrophy (Figure 5A). Heart weight increased significantly in the TN, SMI, and TMI groups relative to the SCN group (1.5±0.1 g, 1.71±0.1 g, and 1.93±0.25 g versus 1.42±0.3 g, respectively; $P<0.05$) (Figure 5B). The ratio of heart to body weight demonstrated a moderate level of hypertrophy in the TN, SMI, and TMI groups relative to SCN (114.7±6.8%, 117.6±3%, and 120.1±6.5%, respectively; $P<0.05$) (Figure 5C).

## Discussion

The present study sheds a positive light on the controversial influence of an intensive aerobic training protocol in normal and infarcted rat hearts. This report shows that intensive aerobic training reduces susceptibility to malignant arrhythmia and that this reduced susceptibility is linked to intrinsic exercise-induced normalization of refractoriness in the hypertrophied infarcted heart, exercise-induced increase in electrical organization of excitation (CI dispersion), and increased complexity of spatiotemporal patterns (spectral analysis of VF-dominant frequencies), independent of the nervous system function.

## Exercise-Induced Structural Remodeling

MI structural remodeling increased heterogeneity that creates areas of slow conduction that contributes to the generation of arrhythmias.[19,20] Moreover, structural remodeling and hypertrophy of the ventricle creates a predisposition to temporal dispersion of repolarization and refractoriness and promotes reentry mechanisms.[21] Furthermore, it was shown that intensive exercise enhanced left ventricular wall fibrosis and dyssynchrony and created a predisposition to arrhythmia because of electrical instability.[12,13] Recently it was shown that long-term (16 weeks), intensive exercise training in normal rats was associated with changes in cardiac function, fibrous tissue content, fibrotic markers, and arrhythmia susceptibility.[14] In contrast, we showed a linear protective

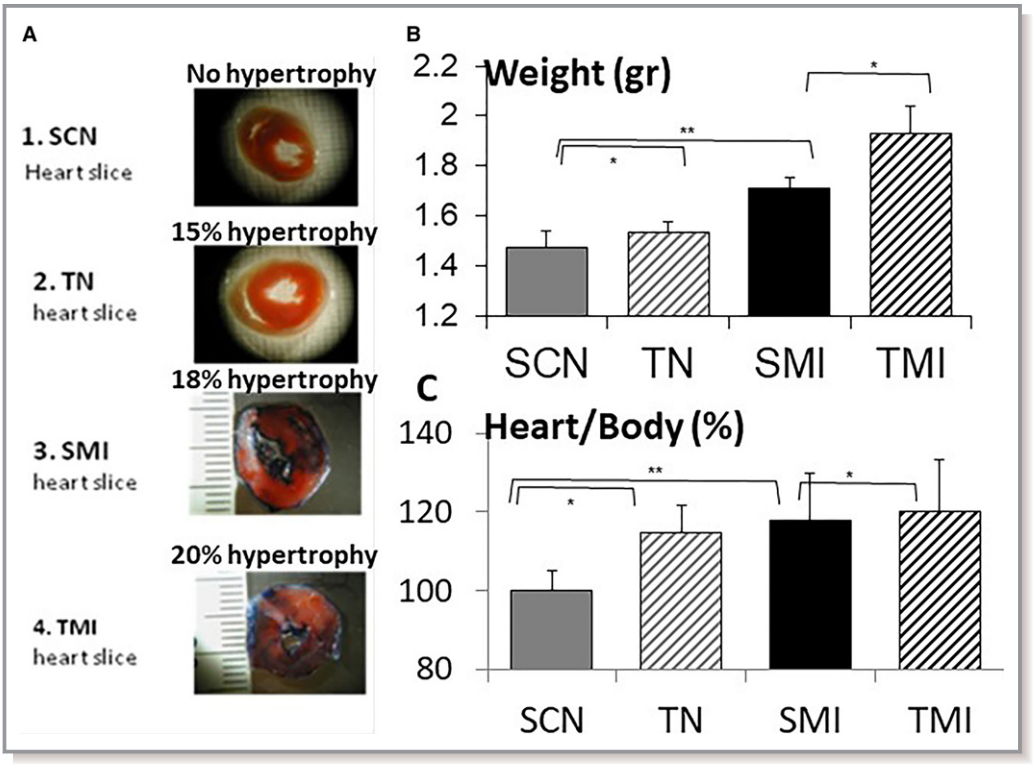



**Figure 5.** Remodeling of left ventricular wall and morphometric measurements. A, Heart slices from the sedentary control (SCN), trained (TN), sedentary myocardial infarction (SMI), and trained myocardial infarction (TMI) groups, demonstrating concentric hypertrophy as a result of training and myocardial infarction. B, Average heart weight of 4 groups. C, Relative increase (%) in heart to body ratio compared with SCN. *$P<0.05$; **$P<0.01$. Values are expressed as mean±SD.

effect of exercise training in normal rat related to increased intrinsic cardiac remodeling, but with a short-term training period (8 weeks).[18] It might be that prolonged compared with short-period intensive exercise is associated with more intrinsic changes such as induction of fibrosis. In addition, the observed discrepancy may be related to differences of the exercise protocol. Furthermore, it possible that intensive exercise should be intermittent especially for a long-term program. In addition, in human participants (52 755 men) in a long-distance (90-km) cross-country skiing event, a faster finishing time and a high number of completed races were associated with bradyarrhythmia and atrial fibrillation but not VT/VF.[22] Furthermore, cardiac rehabilitation participation is associated with a markedly reduced risk of readmission and death after incident MI.[23] In this study, we showed that although both MI and intensive training induce myocardial hypertrophy (about 20% increase), the trained animals were more resistant to induction of ventricular arrhythmias.

## Role of the Autonomic System

It has been shown that remodeling of the autonomic system and increase in HRV caused by moderate aerobic exercise training protects against ventricular arrhythmia.[15,16,18] In the present study, it was shown that an intensive training program increases the in vivo–measured HRV frequency and time-domain variables in the normal and infarcted heart (Figure 1). La Rovere et al[17] demonstrated that an exercise-induced increase in baroreflex sensitivity predicts improved prognosis after MI. Nevertheless, in our study, the arrhythmia threshold and probability were examined on an isolated heart perfusion system, separated from neurohumoral influence. However, the autonomic system signature on the cellular myocardial cyclic AMP level in isolated heart was previously demonstrated.

## Normalization of Cardiac Electrical Properties

Our findings suggest that exercise-induced resistance to arrhythmia may relate to intrinsic electrophysiological cardioadaptive mechanisms. The correlation between MI-induced mechanical and structural remodeling and the prolongation of the ERP and the tendency to develop malignant arrhythmias is well established.[24,25] Similar trends representing ventricular electromechanical relationships were demonstrated in our sedentary MI group and involve asymmetrical hypertrophy (Table 2). However, mechanical function was improved significantly in the TMI group in conjunction with normalization of cardiac electrical properties, and while the MI significantly extended the ERP duration in the SMI group (68±3.8), training normalized it to the level of an intact healthy heart in the TMI group (50±12).

In the 1960s, Han and Moe[26] concluded that the development of VF is related to variations in the refractory period. Post-MI electrical heterogeneity is related to transmural and apex-to-base heterogeneities in action potential durations.[27] In our trained rats, decreased CI dispersion and increased fibrillation threshold were observed (Figures 2 and 3) and expressed as reduced transmural electrical heterogeneity in both MI and normal hearts caused by training. We propose that intensive exercise-induced intrinsic antiarrhythmic mechanisms are related to the transmural regional effect of exercise on the mechanical and electrical properties of cardiac myocytes. Those changes were confirmed by Natali et al,[28] who demonstrated a decreased action potential duration gradient between the epicardial and the endocardial cells in response to training. In addition, they showed an expression of enlargement of the endocardial cells as well as sharper amplitude of the stretch–force relationship in the trained myocytes, which is comparable to the global concentric hypertrophy and increased dP/dt(max) in our trained isolated heart. Those electromechanical modifications may represent the athletic heart adaptation to the increased hemodynamic load driven by exercise, which involves faster and more efficient mechanical activation, followed by the resynchronization of the temporal electrophysiological properties of cardiac myocytes.

## VF Dominant Frequencies

The spectral analysis of electrical activity and its activation rate as measured by the DF have been used to gain insight into mechanisms underlying fibrillation. Regional heterogeneity in the DF of local electrical activity has been attributed to the presence of a driving reentrant source localized to the region with the highest DF and a particular ionic makeup.[29] The hierarchy of decreasing DFs at the periphery of the highest DF is said to result from frequency-dependent conduction impairments, whereby the acceleration of a driver (ie, higher DF) would increase the complexity of the global patterns of activity with an increased number of frequency components in the global ECGs.[30] Our spectral analysis of pseudo-ECG in Figure 4 shows that VF in the sedentary control group is characterized by a narrow power spectrum with a DF at about 17 Hz that was stable over the course of the recordings. In contrast, multiple peaks with higher DFs up to 22 Hz were found in the power spectra of the normal trained group during VF. We suggest that the sources of the VF in the trained intact animals accelerate to produce higher DF values, which, in turn, give rise to additional frequency components corresponding to an intermittent blockade of impulses as well as alterations in the direction and velocity of their propagation across the ventricles of the trained animals.[18] We advocate that this hyperdynamic mechanism

represents the difficulty in stabilization of re-entry currents, which may also explain the increased resistance to VF propagation.

The MI groups also demonstrated a central, dominant, peaked-spectrum pattern, but with an average slower DF of 13.5 Hz in comparison to the 17-Hz DF of the sedentary control animals ($P<0.05$). Training did not differentiate the DF pattern in the MI groups except for a weaker average power spectrum in the main DF in the sedentary group. Thus, we suggest that the sources of VF in the MI animals propagate to produce slower DF values, which, in turn, give rise to a focal DF component corresponding to a blockade of impulses characterized by slower conduction velocity and longer refractoriness.

## Limitations

The main limitation of our study is that our electrical recordings during sinus rhythm and arrhythmia are global and cannot give high-resolution information on spatial patterns of excitation. Second, despite the obvious intrinsic remodeling inferred by our global results in the isolated heart experiments, no structural and cellular mechanisms underlying our observations were explored in the present study and will have to be considered in the future. Finally, because only male rats were used, the effect modification by sex could not be assessed.

## Conclusions

The clinical implications of this study should be further confirmed with human heart adaptation to an intensive exercise regimen, which may not be the same as the regimen for a rat.

## Disclosures

None.

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