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Effects of Excessive Long-Term Exercise on Cardiac Function and Myocyte Remodeling in Hypertensive Heart Failure Rats

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Abstract—The long-term effects of exercise on cardiac function and myocyte remodeling in hypertension/progression of heart failure are poorly understood. We investigated whether exercise can attenuate pathological remodeling under hypertensive conditions. Fifteen female Spontaneously Hypertensive Heart Failure rats and 10 control rats were housed with running wheels beginning at 6 months of age. At 22 months of age, heart function of the trained rats was compared with heart function of age-matched sedentary hypertensive and control rats. Heart function was measured using echocardiography and left ventricular catheterization. Cardiac myocytes were isolated to measure cellular dimensions. Fetal gene expression was determined using Western blots. Exercise did not significantly impact myocyte remodeling or ventricular function in control animals. Sedentary hypertensive rats had significant chamber dilatation and cardiac dysfunction. In exercised hypertensive rats, however, exercise time was excessive and resulted in a 21% increase in left ventricular diastolic dimension ($P<0.001$), a 24% increase in heart to body weight ratio ($P<0.05$), a 27% increase in left ventricular myocyte volume ($P<0.01$), a 13% reduction in ejection fraction ($P<0.001$), and a 22% reduction in fractional shortening ($P<0.01$) compared with sedentary hypertensive rats. Exercise resulted in greater fibrosis and did not prevent activation of the fetal gene program in hypertensive rats. We conclude that excessive exercise, in the untreated hypertensive state can have deleterious effects on cardiac remodeling and may actually accelerate the progression to heart failure. (Hypertension. 2007;50:410-416.)

Key Words: hypertension ■ heart failure ■ exercise ■ hypertrophy ■ myocytes ■ voluntary wheel running ■ SHHF

Research has shown a predictable remodeling of cardiac myocyte shape underlying progression to heart failure (HF). Initially, under hypertensive conditions, there is a marked increase in myocyte cross-sectional area (CSA) whereas cell length remains normal. Between the ages of 6 and 12 months in female spontaneously hypertensive heart failure (SHHF) rats, after a period of compensated hypertrophy, myocyte length begins to increase without further increase in CSA. This excessive addition of sarcomeres in series continues until the development of overt signs of HF at 24 months. In the healthy heart, aerobic exercise training has been shown to increase myocardial mass, left ventricle (LV) chamber dimensions, and stroke volume. In LV dysfunction and in HF patients, exercise has been shown to improve exercise tolerance and symptoms. This benefit has traditionally been attributed to peripheral adaptations. More recent studies, however, indicate that beneficial changes may be occurring centrally as well. As in the healthy heart, these adaptations include increased LV wall thickness and LV function, and enhanced myocardial β-adrenergic responsiveness. Recent studies by Iemitsu et al and Emter et al showed that regular exercise training results in reversal of the fetal gene expression pattern observed in aging and attenuation of the progression to HF. An encouraging recent study by Konhilas et al found that voluntary wheel running (VWR) resulted in reduced myocyte disruption, beneficial changes in apoptotic markers, and reversal of fetal genes in hypertrophic cardiomyopathic mice. These findings suggest that exercise may offset the deleterious effects of hypertension in the development of HF. The primary goal of this study was to determine whether long-term voluntary wheel running ameliorates negative remodeling observed in hypertensive animals.

Methods

Experimental Design

The SHHF rat provides a model that mimics human progression of hypertension from hypertrophy to HF. SHHF rats develop hyperten-
sion and HF in a consistent and predictable manner. Lean female SHHF rats were purchased from Charles River Laboratories (Indianapolis, Ind). SHHF female rats were given access to running wheels beginning at 6 months of age. They were housed with running wheels for 16 months. At 22 months of age, heart function of the trained SHHF (SHHFex, n=15) rats was compared with the heart function of age- and size-matched SHHF (SHHFsed, n=14) rats that were housed similarly but without access to running wheels. For comparison purposes, age-matched female Wistar-Furth (WF; Charles River Laboratories; Wilmington, Mass) rats served as both exercise (WFex, n=6) and sedentary (WFsed, n=10) normotensive controls. Animals were randomly distributed to groups at the beginning of the study. All animals were maintained in the same environment including temperature and humidity and free access to food and water. At termination, echocardiography, hemodynamics, isolated myocytes, and whole heart tissue were collected from each animal group. All procedures in this study were approved by the University of South Dakota Animal Care and Use Committee and followed institutional guidelines for animals. All studies have been conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Wheel Running Quantification
Running wheels were connected to a Minimitter system that used a magnetic sensor to record wheel rotations. This system was interfaced with a computer, and recorded using VitalView software at 1 minute intervals 24 hours/d for the duration of the 16-month experiment. Only days that had a complete 24 hours of data were included in the data analysis. Thus, running data from 10 of the 16 months were included for SHHF (months 3 to 9, 12 to 13, 15). For WF rats, running data from 8 of the 16 months were included (months 1 to 6, 12 to 13, 15).

Because the circumference of the running wheels used was 1 m, the number of revolutions recorded for each animal is equivalent to total number of meters run by that individual rat. VitalView software (Mini Mitter Co Inc) was set to store the number of revolutions in 1 minute bins. From this, the number of meters run each minute was determined, and each rat’s running speed in meters per minute was calculated. The number of bins with non-zero values were recorded as 1 minute running values and used to ascertain the total amount of time each rat spent running.

Echocardiography and Hemodynamics
Animals were anesthetized with 1.5% isofluorane gas, weighed, and given an echocardiogram to measure functional changes in chamber dimensions and wall thickness both pre- and postintervention. Standard echocardiography techniques10 were used to obtain M-mode echocardiograms from short-axis views of the left ventricle below the tip of the mitral valve leaflets with a General Electric RT5000 echo machine with a 7-MHz transducer. Measurements included left ventricle chamber (left ventricular internal dimension [LVID]), anterior wall thickness (AWT), posterior wall thickness (PWT), ejection fraction (EF), and fractional shortening (FS). LV hemodynamics were obtained by catheterization of the right common carotid artery using a Millar Mikro-tip catheter (Millar Instruments). LV pressure and dP/dT were recorded after 5 minutes of stabilization. LV end systolic and end diastolic (meridional) wall stresses were calculated from chamber dimensions and pressures as described by Litwin et al.10

Myocyte Isolation and Morphology
After hemodynamic data were collected, hearts were removed, blotted, weighed, and cannulated through the aorta for perfusion with collagenase for isolation of myocytes as described previously.11 Freshly isolated cardiac myocytes were fixed immediately in 2% gluteraldehyde in 80 mmol/L phosphate buffer for subsequent determination of myocyte length (microscopy), volume (Coulter Channelizer, Beckman Coulter, Fullerton, CA), and cross-sectional area as described previously.11

<table>
<thead>
<tr>
<th>Table 1. Body Weight and Heart Weight</th>
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<td>Group</td>
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<td>WFsed</td>
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<tr>
<td>WFex</td>
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<tr>
<td>SHHFsed</td>
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<td>SHHFex</td>
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</table>

WF indicates Wistar Furth rats; SHHF, spontaneously hypertensive heart failure rats; sed, sedentary; ex, exercise. Values are means±SD.

Whole Heart Preparation
Hearts were trimmed, blotted, and ventricular weights determined. Hearts were then cannulated and flushed with cold Joklik media to remove blood. From the middle third of the ventricles, a transverse slice of approximately 1 to 2 mm thickness was taken and fixed in 10% formalin (n=5 for SHHFex; n=6 for SHHFsed; and n=4 for WFsed; no whole heart data were collected from WFex because of limitations of wheel availability). The remaining basal and apical portions of the ventricles were flash frozen.

Histopathology and Morphometry
Formalin-fixed transverse sections of the LV and septum were stained with collagen-specific picrosirius red. Collagen volume percent was quantitated by point counting morphometry (points on collagen/points on solid tissue).

Western Blot Analysis
As previously described,12 Western blotting was used to determine α-myosin heavy chain (α-MHC) and β-myosin heavy chain (β-MHC) expression.

Determination of T4 and T3 Concentrations
T4 and T3 concentrations were measured in serum by specific and highly sensitive RIA and in LV tissues after extraction and purification of iodothyronines as detailed previously.13

Statistical Analyses
All data are presented as means±SD. One-way ANOVA was used to compare data between groups. The Bonferroni post hoc test was used to examine statistically significant differences. Results were considered significant when P<0.05. Statistical analysis was performed using SPSS (Version 13.0).

Results
BW did not differ between any of the groups at 22 months (Table 1). Both SHHF groups had significantly greater heart weight (HW) and heart weight-to-body weight ratios (HW:BW) than both WF groups. Exercise in the SHHF, but not WF, rats resulted in additional increases in HW and HW:BW. Five of the SHHFex presented with ascites on termination. Three rats from each of the SHHF groups expired prior to completion of the study.

The SHHF rats ran an average of 6752±911 (mean±SD) m/d whereas the WF rats ran 4243±2.556 m/d (Figure 1). Analysis of the data indicates that, over the 16 months, the SHHF ran an average of 336±24 minutes/d, 20.0±2.4 m/min, and maximum speed of 74.4±11.9 m/min. The WF ran an average of 155±70 minutes/d, 21.0±11.8 m/min, and maximum speed of 91.5±60 m/min. The SHHF ran significantly farther (P<0.01) and spent more time exercising...
(P<0.001) daily than the WF. There were no differences in average or maximum running speeds.

At baseline, echocardiograms showed that SHHF rats had increased wall thickness compared with WF (data not shown). At 22 months of age, SHHF animals had significantly larger LV internal dimensions during systole (LVIDd) and diastole (LVIDd), significantly increased LV anterior wall thickness in systole (AWTs) and diastole (AWTd), and significantly decreased EF and FS compared with WF animals (Table 2). Exercise resulted in greater chamber dilation and greater reduction in cardiac function in SHHF rats (Table 2, Figure 2). Exercise in the WF rats resulted in no significant echocardiographic changes.

The SHHFsed had significantly lower heart rates (HR) than the WFsed, and the SHHFex had significantly lower HR than both WF groups (Table 3). The maximum rate of pressure rise (+dP/dT) was decreased in SHHFex compared with WFex. The maximum rate of pressure decline (−dP/dT) was significantly reduced in both SHHF groups compared with the WFex animals. Although neither obtained statistical significance, exercise resulted in 27% and 16% increases in +dP/dT and −dP/dT, respectively, in WF animals suggesting a tendency for improved cardiac function. In addition, there was a 45% increase in end-diastolic pressure (LVPed) in the SHHFex rats compared with the SHHFsed, which appears to be an important stimulus for progressive chamber dilatation in HF.14 There were no significant differences in LV end systolic or end diastolic wall stresses between WFsed and WFex. LV end systolic wall stress was increased in hypertensive SHHF groups versus normotensive WF groups. In SHHF rats, exercise led to a 42% increase in LV end systolic wall stress and an 80% increase in end diastolic wall stress. As with the echo data, hemodynamic and wall stress changes indicate greater impairment of cardiac function in the SHHFex animals.

There was a tendency for myocyte length (L), volume (V), and cross sectional area (CSA) to increase in WFex versus WFsed, but none of these changes reached statistical significance (Table 4). SHHF animals had significantly greater L, V, and CSA compared with the WFsed rats. Compared with SHHFsed, exercise resulted in greater V (27% increase) and CSA (15% increase) in SHHF rats. Exercise also resulted in a 10% increase in L in the SHHF rats, although this did not obtain significance.

Representative histological sections showing collagen distribution are shown in Figure 3. Collagen content was increased 44% in SHHFsed and 338% in SHHFex versus WFsed. In each case, collagen increases were interstitial and perivascular in nature.

Compared with WF animals, α-MHC was significantly lower in both SHHFsed and SHHFex animals (Figure 4).

Preliminary data were collected for serum and LV tissue T3 and T4 from SHHFex and SHHFsed. The mean values for serum T4 (11.9±3.7 ng T4/mL) and T3 (0.44±0.14 ng T3/mL) of SHHFex animals were lower than those of SHHFsed rats, that were, respectively, 16.9±3.3 ng T4/mL

Table 2. Echocardiography (22 months)

<table>
<thead>
<tr>
<th>Group</th>
<th>LVIDd</th>
<th>LVIDs</th>
<th>AWTd</th>
<th>AWTs</th>
<th>PWtd</th>
<th>PWTs</th>
<th>EF (%)</th>
<th>FS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WFsed</td>
<td>7.3±0.2</td>
<td>3.7±0.4</td>
<td>1.5±0.2</td>
<td>2.9±0.4</td>
<td>1.5±0.2</td>
<td>2.7±0.2</td>
<td>85±4</td>
<td>49±5</td>
</tr>
<tr>
<td>WFex</td>
<td>7.4±0.3</td>
<td>3.6±0.4</td>
<td>1.5±0.1</td>
<td>2.6±0.3</td>
<td>1.5±0.2</td>
<td>2.8±0.2</td>
<td>86±3</td>
<td>51±4</td>
</tr>
<tr>
<td>SHHFsed</td>
<td>8.1±0.7*</td>
<td>4.8±0.8†</td>
<td>2.1±0.2‡</td>
<td>3.4±0.2*</td>
<td>1.8±0.3</td>
<td>2.8±0.4</td>
<td>76±6§</td>
<td>41±6†</td>
</tr>
<tr>
<td>SHHFex</td>
<td>9.8±0.6¶**</td>
<td>6.6±0.9¶**</td>
<td>2.1±0.2¶</td>
<td>3.4±0.3¶</td>
<td>2.0±0.2†</td>
<td>2.9±0.3</td>
<td>66±8¶**</td>
<td>32±5¶†</td>
</tr>
</tbody>
</table>

LVIDd indicates left ventricular internal dimension in diastole; LVIDs, LV internal dimension in systole; AWTd, anterior wall thickness in diastole; AWTs, anterior wall thickness in systole; PWtd, posterior wall thickness in diastole; PWTs, posterior wall thickness in systole; EF, ejection fraction; FS, fractional shortening. Values are means±SD.

*P<0.05 vs WFsed; †P<0.01 vs WFsed; ‡P<0.001 vs WFsed; §P<0.05 vs WFex; ¶P<0.01 vs WFex; ||P<0.001 vs WFex; #P<0.01 vs SHHFsed; **P<0.001 vs SHHFsed.
HF is characterized by decreased cardiac function and is associated with pathological LV remodeling with excessive myocyte lengthening and little or no change in myocyte transverse area during the transition to failure. Aerobic exercise, in addition to its numerous peripheral adaptations, is known to cause physiological remodeling of the LV which is characterized by fairly proportional increases in LV chamber diameter and wall thickness, as well as enhanced cardiac performance. As such, we had hypothesized that long-term exercise in the SHHF rats would result in a more physiological pattern of cardiac remodeling and better preservation of cardiac function.

Historically, there have been concerns regarding exercise with HF, but recent studies examining the effects of exercise on the progression of HF have found that exercise may result in beneficial adaptations even in the presence of this pathological condition. Of particular interest to our study, Emter et al. examined the effects of 6 months of low-intensity treadmill exercise in young and old male SHHF rats. They found that trained rats were healthier, lived longer, and demonstrated a more physiological pattern of cardiac remodeling.

The results of our study indicate that, although some beneficial remodeling occurred, exercise actually accelerated the progression of HF. Compared with sedentary controls, exercising SHHF rats demonstrated an accelerated pattern of progression toward HF as evidenced by greater LV dilatation and decreased cardiac function. In addition, exercising SHHF rats were more cachexic in appearance and more frequently presented with ascites on termination, indicating many of these animals had symptomatic HF.

Exercise did not significantly impact wall thickness in either group of animals, although there was an 11% increase in PWTd in the SHHFex compared with SHHFsed. In SHHF, exercise resulted in 10% and 14% increases in myocyte L and CSA, respectively, whereas cell V increased 27%. These changes are indicative of a more physiological remodeling pattern and are consistent with anatomic changes seen in the aforementioned study by Emter et al. The increase in CSA explains the tendency for greater wall thickening observed with echocardiography. Surprisingly, this physiological pattern of myocyte growth in the SHHFex did not translate into improved, or even maintained, cardiac function. The tendency for aerobic training to produce a concomitant increase in chamber diameter and wall thickness has been reported previously and suggests both series and parallel addition of sarcomeres, consistent with eccentric hypertrophy.

**Discussion**

The major finding of this study is that although long-term VWR tended to promote a physiological pattern of myocyte growth, it also led to significant additional chamber dilatation, worsening of LV function, increased myocardial fibrosis, and accelerated signs of heart failure in aging SHHF rats. This study used methods of documented reliability to provide the first comprehensive data on LV myocyte shape changes in response to lifespan exercise in normal and hypertensive animals.

<table>
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<th>TABLE 3. Hemodynamics</th>
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<td><strong>Group</strong></td>
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<td>SHHFsed</td>
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<td>SHHFex</td>
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HR indicates heart rate; LVPes, LV end-systolic pressure; LVPed, LV end-diastolic pressure; dP/dT, maximum rate of pressure rise; (−) dP/dT, maximum rate of pressure decline; LV-SWS, LV end systolic wall stress; LV-DWS, LV end diastolic wall stress. Values are means±SD.

*P<0.05 vs WFsed; †P<0.001 vs WFsed; ‡P<0.05 vs WFex; §P<0.01 vs WFex; ¶P<0.001 vs WFex; ††P<0.05 vs SHHFsed.
Collagen changes. Picrosirius red staining demonstrates minimal interstitial collagen (black) in WFsed, increases in SHHFsed, and more pronounced and diffuse increases in SHHFex. Quantitative changes in collagen percentage are shown in the final panel. *P<0.05 vs WFsed; †P<0.01 vs WFsed.

Histologically, the progression to heart failure is typically associated with increased fibrosis and disruption of normal cellular organization.20 Compared with WFsed, SHHFsed rats demonstrated some increased fibrosis, whereas exercise in the SHHF resulted in widespread fibrosis. This abnormal increase in interstitial fibrosis in the SHHFex suggests the level of physical activity was stressful on the heart. Increased collagen content is commonly observed with pressure overload and can negatively impact both diastolic and systolic function as well as increase the risk for cardiac arrhythmias.21,22 Although the mechanism for collagen increase in SHHFex is not clear, we have recently become interested in the role of thyroid hormones in the regulation of myocardial collagen content. We found that thyroid hormone treatment of cardiomyopathic hamsters with subclinical hypothyroidism had a powerful antifibrotic effect on ventricular myocardium. It has also been shown that low thyroid function stimulates myocardial collagen synthesis and that thyroid hormones inhibit collagen synthesis.23,24 Preliminary data for serum and myocardial tissue T3 and T4 collected from SHHFex in these experiments suggest the presence of reduced thyroid hormone function. When considering the 59% decrease in tissue T3 in SHHFex, a study by Wassen and colleagues25 is of interest. In their rat model of hypertension and failure, a 5-fold increase in the D3 deiodinase was noted in the affected ventricle. Because this deiodinase converts T4 to deactivated rT3, it is possible that a similar change occurred here. Although more work is clearly needed to confirm the potential relationship of low thyroid conditions and myocardial fibrosis in hypertension, the potential clinical importance of this finding certainly merits further study.

HF is associated with a shift in the fetal gene profile.26 Specifically, there tends to be an upregulation in the expression of the β-MHC isoform with a reciprocal downregulation of the α-MHC isoform and reductions in PLB and SERCA expression.27,28 We have previously demonstrated, however, that changes in fetal gene expression are not required to see changes in cardiac function.29 Although previous studies have shown exercise suppresses the fetal gene pattern changes observed with aging7 and progression to HF,8 our results indicate exercise did not positively impact α- or β-MHC expression in either the SHHF or WF rats.
Understanding why this exercise protocol accelerated progression to HF is of both theoretical and practical importance, particularly in light of the fact that the treadmill protocol employed by Emter et al. had the opposite effect. When comparing the exercise regimen of our animals with that used by Emter et al., it is clear that our SHHF rats ran vastly greater daily (6.8 km) and weekly (48 km) distances voluntarily on the wheels than their animals did on the treadmills (0.6 km/d and 1.89 km/week). The intensity at which our animals exercised was also a great deal higher. SHHF rats in our study ran at an average speed of 20 m/min whereas their rats ran at an average of 14 m/min. In fact, our SHHF rats recorded an average maximum speed of 74 m/min, with several animals attaining over 100 m/min. Significantly, Emter and colleagues initially trained their animals at 17.5 m/min but reduced the intensity after 3 of their animals died of sudden death while exercising. Training intensity may, therefore, play a role in determining a pathological or physiological response of the hypertensive heart to endurance training. In addition, the SHHF rats in our study exercised for a remarkable average of almost 6 hours/d. As a result of this excessive pattern, it is likely exercise became a pathologic overloading stimulus rather than the physiological stimulus that has been observed in other studies. Although there was a more physiological growth pattern in cardiac myocytes, it was clearly not enough to compensate for this level of stress. Finally, in should be recognized that gender may have contributed to the study outcome differences because females were employed in our study whereas Emter used males.

Although it appears there was an increase in LV mass in the SHHFex, there was an even greater increase in LV chamber size. This relationship resulted in increased end diastolic and end systolic wall stress which are associated with decreased cardiac performance and a poor prognosis. It has been proposed that the degree of LV dilatation, and its corresponding effect on wall stress, may have a more significant impact than contractile dysfunction on cardiac performance. Furthermore, it may be that LV dilatation is a self-propagating process which serves to further increase chamber size. As such, it may be reasonable to conclude that the relatively sustained preload stimulus from frequent bouts of VWR resulted in a chronic volume overload superimposed on hypertension which, cumulatively, led to a worsened outcome.

Limitations of the Study
The study was limited by the availability of running wheels. Consequently, 2 decisions were made at the beginning of the study. We wanted to ensure that adequate information was obtained from SHHFex animals and that sufficient animals were available for isolated myocyte determination of cell remodeling. Consequently, we did not have sufficient WFex rats to allow comprehensive assessment of both whole tissue and isolated myocytes. In retrospect, it would have been interesting to contrast differences between the outcome of exercise in the SHHF (detrimental) versus WF (beneficial) groups using whole tissue assessment of collagen (eg, collagen types, matrix metalloproteinases, TIMPs) and other changes.

Perspectives
Because of evidence of both central and peripheral beneficial adaptations to exercise, it has become widely accepted that exercise should be prescribed, with caution, in HF patients.33 The findings of this study support the need for continued caution when recommending exercise in cardiomyopathy or HF. This study indicates that excessive exercise, in the untreated, hypertensive state, can have deleterious effects on cardiac remodeling and may actually accelerate the progression to HF. Declines in cardiac function and general health of the animals occurred despite the apparent beneficial adaptations in myocyte shape. Although the mechanisms of such findings are unclear, it is likely the SHHF rats simply exercised too much. Perhaps the frequent acute stress of repeated bouts of high-intensity exercise, in their already chronically-stressed, hypertensive condition, only served to exacerbate LV dilatation and, thus, the decline in function and progression to failure. This model may prove useful in defining the optimum level of exercise in hypertension-induced HF by establishing the threshold between beneficial and detrimental levels of exercise.

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Disclosures
None.

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