Low-Intensity Exercise Training Delays Heart Failure and Improves Survival in Female Hypertensive Heart Failure Rats

Adam J. Chicco, Sylvia A. McCune, Craig A. Emter, Genevieve C. Sparagna, Meredith L. Rees, David A. Bolden, Kurt D. Marshall, Robert C. Murphy, Russell L. Moore

Abstract—Exercise training improves functional capacity and quality of life in patients with heart failure. However, the long-term effects of exercise on mortality associated with hypertensive heart disease have not been well defined. In the present study, we investigated the effect of low-intensity exercise training on disease progression and survival in female spontaneously hypertensive heart failure rats. Animals with severe hypertension (16 months old) were treadmill trained (14.5 m/min, 45 min/d, 3 d/wk) until they developed terminal heart failure or were euthanized because of age-related complications. Exercise delayed mortality resulting from heart failure ($P<0.001$) and all causes ($P<0.05$) and transiently attenuated the systolic hypertension and contractile dysfunction observed in the sedentary animals but had no effect on cardiac morphology or contractile function in end-stage heart failure. Training had no effect on terminal myocardial protein expression of antioxidant enzymes, calcium handling proteins, or myosin heavy chain isoforms but was associated with higher cytochrome oxidase activity in cardiac mitochondria ($P<0.05$) and a greater mitochondrial content of cardiolipin, a phospholipid that is essential for optimal mitochondrial energy metabolism. In conclusion, low-intensity exercise training significantly delays the onset of heart failure and improves survival in female hypertensive heart failure rats without eliciting sustained improvements in blood pressure, cardiac function, or expression of several myocardial proteins associated with the cardiovascular benefits of exercise. The effects of exercise on cytochrome oxidase and cardiolipin provide novel evidence that training may improve prognosis in hypertensive heart disease by preserving mitochondrial energy metabolism. ($Hypertension$. 2008;51:1096-1102.)

Key Words: exercise ■ heart failure ■ hypertrophy ■ mortality ■ rats

Despite long-standing concern over its safety and use in the treatment of heart failure (HF), accumulating evidence suggests that exercise training is a useful adjuvant therapy in stable HF patients, capable of improving functional capacity, attenuating or reversing pathologic remodeling of the heart, and enhancing quality of life.1,2 Although a lack of physical activity has been associated with poor prognosis in HF patients,3,4 whether chronic exercise is an effective means of improving survival has not been clearly established.5 Several studies indicate that exercise training elicits favorable effects on the myocardium in stable HF patients receiving concomitant pharmacotherapy1,6 and in various animal models of genetic and surgically induced cardiac hypertrophy and failure.7–9 However, few studies have examined the independent effect of exercise training on disease progression and mortality in a clinically relevant model of hypertensive HF. The spontaneously hypertensive-HF (SHHF) rat represents a well-characterized congenital model of chronic heart failure progressing to decompensated HF that shares many of the hallmark biochemical and pathophysiological features of dilated cardiomyopathy in aged humans.10 In a previous study, chronic low-intensity aerobic exercise training (LIET) initiated during the late phase of compensated left ventricular hypertrophy delayed the onset of decompensated HF and reduced mortality in male SHHF rats.11 Conversely, Schultz et al12 reported recently that chronic voluntary wheel running accelerated pathologic left ventricular (LV) remodeling and increased HF mortality in female SHHF rats. This deleterious effect of voluntary exercise was attributed to the excessive volume and/or intensity of exercise achieved by animals in running wheels. However, these conflicting results also raise concern over whether males and females respond differently to chronic exercise during the pathogenesis of hypertensive HF.

The present study was conducted to determine the effect of LIET on survival characteristics of hypertensive female rats.
predisposed to dilated HF. We also examined the effect of LIET on blood pressure, cardiac function and morphology, myocardial antioxidant and calcium-handling proteins, and cardioprotin, a mitochondrial phospholipid known to be essential for optimal cardiac bioenergetics that is deficient in the failing heart.13–15

Methods

Animals and Experimental Design
Female SHHF rats (16 months of age, obtained from the breeding colony maintained by S.A.M. at the University of Colorado) were assigned either to the sedentary group (SED; n=11) or to the exercise group (LIET; n=10) that trained on a motorized treadmill at 14.5 m/min at a 10% grade, 45 min/d, 3 d/wk. Animals were monitored daily and euthanized on presentation of signs of overt HF (dramatic weight gain or loss, labored breathing, peripheral edema, piloerection, and/or fractional shortening [FS] <35%) or needed to be euthanized because of severe age-related complications (eg, pituitary or mammary tumors or lack of coordination), referred to hereafter as “censored” animals. The presence of terminal HF was confirmed during necropsy as described in the Results section. All of the animals were treated according to the guidelines conforming to the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health.

Echocardiography
Transtrabecual echocardiography was performed on all of the surviving rats at 23 and 25 months of age and immediately before sacrifice under inhaled isoflurane anesthesia (5% initial and 2% maintenance) using a 12-MHz pediatric transducer connected to a Hewlett Packard Sonos 5500 Ultrasound system. Short-axis M-mode echocardiograms on the left ventricle were obtained for measurement of LV internal diameters at diastole and systole, LV FS, anterior wall thickness, and posterior wall thickness. The individual responsible for obtaining and analyzing echocardiography data were blinded as to the training status of the animals throughout the study to avoid any potential for biased results.

Blood Pressure
Tail-cuff blood pressure measurements were obtained at baseline (16 months of age) and at 20 and 24 months of age by our established method using the Gibson Duograph system with pressure transducers and a photoelectric sensor capable of detecting tail pulses in unheated conscious rats.16

Myocardial Proteins
Relative protein expressions of antioxidant enzymes (Mn-superoxide dismutase, CuZn-superoxide dismutase, and glutathione peroxidase) and calcium handling proteins (Na+/Ca2+ exchanger-1, phospholamban, and sarcoplasmic reticulum Ca2+-ATPase) were determined in LV homogenates obtained from animals euthanized in terminal HF by standard immunoblotting methods using commercially available primary antibodies as described previously.11,14 Blot densities were normalized to calsequestrin to control for potential loading differences, and/or fractional shortening [FS] <35%) or needed to be euthanized because of severe age-related complications (eg, pituitary or mammary tumors or lack of coordination), referred to hereafter as “censored” animals. The presence of terminal HF was confirmed during necropsy as described in the Results section. All of the animals were treated according to the guidelines conforming to the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health.

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Statistical Analyses
All of the data are presented as group means±SEs. Cumulative mortalities because of HF and all causes were plotted on Kaplan-Meier curves using the log-rank statistic for significance. Group means for morphology, age of mortality, echocardiography, and biochemical measures were compared using independent sample t tests. Blood pressure data were analyzed by repeated-measures ANOVA to examine within-group changes over time and by independent sample t tests to determine differences between groups at various time points when appropriate. Pearson correlation analyses were performed to determine the relationships among CL, COx, and survival (age of death) data. Statistical significance is reported at P<0.001, P<0.01, P<0.05, and P<0.10 for all of the analyses.26,27

Results

The training protocol was well tolerated by all of the animals in the LIET group, even in the presence of terminal HF; therefore, no animals were excluded from the study because of noncompliance. However, as is common with any true survival study in an aged population of inbred female rats, several animals developed age-related pathology during the course of the study (eg, mammary and pituitary tumors) that required euthanasia before manifestation of terminal HF. Nevertheless, LIET significantly improved survival compared with SED when analyses were restricted to HF mortality (Figure 1A; P<0.001) and all-cause mortality (Figure 1B; P=0.05).

Table S1 in the online data supplement (please see http://hyper.ahajournals.org) summarizes the animal mortality and morphology data for all of the censored and noncensored (designated “terminal HF”) animals. The presence of HF mortality was confirmed by overt systolic dysfunction on the echocardiogram (FS: <35%) and by postmortem assessments performed by S.A.M., founder and supervisor of the SHHF rat colony at the University of Colorado with >20 years of experience with this model. When possible, all of the individuals were kept blind as to the training status of the animals during necropsy. All of the noncensored animals exhibited cyanosis, labored breathing, overt cardiac hypertrophy, pulmonary and subcutaneous edema, and severe ascites at the time of sacrifice. Censored animals (not in HF) were euthanized because of severe mammary tumor(s), a lack of coordination (often indicating a pituitary tumor), severe lethargy, and/or obvious pain in the absence of the above criteria. Moreover, censored animals exhibited significantly lower mean heart and lung weights (P<0.01) compared with animals euthanized in terminal HF and were excluded from future analyses. The incidence of censorship because of “lethal”
age-related complications was similar between groups but occurred at a significantly older age in the LIET versus SED animals (P<0.05). There were no significant differences in body, heart, or lung weights between SED and LIET in the presence or absence of terminal HF. However, mean age of mortality because of HF, non-HF pathology (censored), and all causes (combined) were significantly greater in the LIET versus SED animals, providing strong evidence for a generalized prosurvival effect of LIET in this model.

All of the animals exhibited severe systolic hypertension characteristic of the SHHF model by 16 months of age.10 There was no difference in systolic blood pressure between the SED and LIET groups at baseline (Figure 2). Blood pressure increased slightly but significantly (P<0.05) in both groups from baseline to 20 months, and this increase was slightly attenuated by LIET compared with SED (P<0.05). Blood pressure decreased significantly from 20 to 25 months in the SED group only (P<0.05), reflecting a decline toward end-stage decompensated HF in the SED but not in the trained animals.

Significant increases in LV ID at end-diastole and systole and a significant decrease in LV FS were evident between 23 months and terminal HF in both groups, but there were no significant differences between SED and LIET animals at either time point (Table 1). Echocardiography performed on all of the surviving noncensored animals at 23 and 25 months revealed a significant attenuation of changes in LVIDs at systole and FS during this period in LIET animals (n=4) compared with SED animals (n=3), suggesting that LIET may preserve LV systolic function during the decompensation phase. There were no differences in final echocardiography data obtained from censored SED and LIET animals at the time of sacrifice. Echocardiography data from censored and 23- to 25-month noncensored animals are available in the online data supplement.

Total CL content in LV mitochondria was 21% greater in LIET versus SED animals (P=0.05; Figure 3A). Absolute levels of Lc,CL were 60% greater in LIET versus SED animals (P<0.05; Figure 3B), whereas the relative quantity of Lc,CL (expressed as a percentage of total CL) increased by 11% (P=0.12; Figure 3C). Enzymatic activity of COx was 76% greater in cardiac mitochondria from LIET compared with SED animals (P<0.01; Figure 3D) and correlated significantly with total mitochondrial CL (r=0.85; P<0.01) and Lc,CL contents (r=0.70; P<0.05) but not relative Lc,CL content (r=0.12; P value not significant). Positive correlations were found between survival (age of death) and COx activity (r=0.663; P<0.05), Lc,CL content (r=0.528; P=0.05), and total CL (r=0.437; P=0.10). LIET had no effect on

Table 1. Echocardiography at 23 Months and Terminal Heart Failure

<table>
<thead>
<tr>
<th>Group</th>
<th>LVIDd</th>
<th>LVIDs</th>
<th>PWtd</th>
<th>AWTd</th>
<th>EF, %</th>
<th>FS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SED</td>
<td>6.2±0.5</td>
<td>3.4±0.5</td>
<td>2.3±0.2</td>
<td>2.5±0.4</td>
<td>80±9</td>
<td>47±3</td>
</tr>
<tr>
<td>LIET</td>
<td>6.4±0.2</td>
<td>3.5±0.3</td>
<td>2.1±0.5</td>
<td>2.7±0.5</td>
<td>83±4</td>
<td>46±4</td>
</tr>
<tr>
<td>HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SED</td>
<td>6.9±0.7†</td>
<td>4.7±0.6†</td>
<td>2.9±0.5</td>
<td>3.1±0.4</td>
<td>68±5†</td>
<td>32±4*</td>
</tr>
<tr>
<td>LIET</td>
<td>7.8±0.6*</td>
<td>5.7±0.7†</td>
<td>3.1±0.5</td>
<td>3.5±0.5</td>
<td>61±5*</td>
<td>28±3*</td>
</tr>
</tbody>
</table>

Data are group means±SEs obtained from all of the noncensored animals at 23 months and in terminal HF immediately before sacrifice (n=6 SED and n=4 LIET). LVIDd indicates LV internal dimension in diastole; LVIDs, LV internal dimension in systole; PWtd, LV posterior (free) wall thickness in diastole; AWTd, LV anterior wall thickness in diastole; EF, ejection fraction.
*P<0.05 vs 23 months within group.
†P<0.1 vs 23 months within group.
myocardial antioxidant enzymes, calcium-handling protein contents, or the α:β MHC isoform ratio in animals euthanized in terminal HF (Table 2).

**Discussion**

The primary finding of this study is that chronic LIET attenuates the development of terminal HF and increases survival in female SHHF rats. These results corroborate the prosurvival effect of LIET reported previously in male SHHF rats but conflict with the deleterious effect of chronic voluntary exercise reported recently in female SHHF rats. Taken together, these studies suggest that the benefit of chronic exercise on long-term prognosis in hypertensive heart disease exists in both males and females but is critically dependent on the volume and/or intensity of the training protocol.

Although the therapeutic value of exercise training in hypertension and HF has become widely accepted, debate remains over the volume and intensity of exercise that provide optimal benefits. Moreover, little is known regarding the long-term effects of exercise training on HF mortality or the extent to which responses vary between males and females. Currently, for stable HF patients, chronic low-to-moderate intensity exercise is recommended and has been reported to attenuate pathologic LV remodeling and improve quality of life. Although high-intensity exercise is known to elicit greater cardiovascular adaptations than low-to-moderate intensity aerobic exercise, the long-term clinical feasibility and adherence to a high-intensity training regimen is questionable in elderly HF patients, where exercise tolerance is severely reduced. However, a recent study by Wisloff et al demonstrated that high-intensity aerobic interval training provided superior cardiovascular benefits to elderly postfart HF patients undergoing moderate-intensity continuous aerobic training. The study duration was only 12 weeks; therefore, it is not known whether these positive effects of high-intensity training would be maintained long term or lead to improved survival. Furthermore, as is the case in most clinical studies, all of the patients received concomitant β-adrenergic and angiotensin-converting enzyme inhibition therapy before and during the course of the study. Because it is unethical to deprive patients of standard pharmacotherapy in studies of this nature, it is necessary to use animal models that closely mimic the pathogenesis of HF in aged humans to examine the independent effect of exercise training during the course of disease progression.

The SHHF rat represents a well-characterized model of chronic hypertension progressing to decompensated dilated HF that shares the hallmark biochemical and pathophysiological features of hypertensive heart disease and dilated cardiomyopathy in aged humans. Previous work in our laboratory demonstrated that chronic LIET identical to the protocol used herein delayed the onset of decompensated HF and improved survival in aged male SHHF rats. It is important to note, however, that initial efforts to increase training intensity in this earlier study dramatically increased mortality, indicating that adherence to the low-intensity training regimen was critical for improved survival. The long-term effects of exercise training in female SHHF rats were recently examined in a study by Schultz et al, where animals were provided free access to running wheels from 6 to 22 months of age. Contrary to the findings of Emter et al, chronic voluntary exercise accelerated HF progression and increased mortality compared with sedentary animals. The authors suggested that this deleterious effect of training may be because of a differential response to exercise training in males and females or the “excessive” volume and intensity of training voluntar-

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**Table 2. Myocardial Protein Contents**

<table>
<thead>
<tr>
<th>Protein</th>
<th>SED</th>
<th>LIET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant enzymes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutathione peroxidase</td>
<td>100±18</td>
<td>83±12</td>
</tr>
<tr>
<td>Mn-superoxide dismutase</td>
<td>100±3</td>
<td>100±4</td>
</tr>
<tr>
<td>CuZn-superoxide dismutase</td>
<td>100±11</td>
<td>115±16</td>
</tr>
<tr>
<td>Calcium-handling proteins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na⁺-Ca²⁺ exchanger</td>
<td>100±14</td>
<td>92±9</td>
</tr>
<tr>
<td>SERCA2</td>
<td>100±14</td>
<td>107±18</td>
</tr>
<tr>
<td>Phospholamban</td>
<td>100±17</td>
<td>105±21</td>
</tr>
<tr>
<td>α-MHC, %</td>
<td>41±6</td>
<td>32±9</td>
</tr>
</tbody>
</table>

Antioxidant and calcium-handling immunoblotting data are expressed as a percentage of SED band density. α-MHC data are expressed as a percentage of total band densities (α+β isoforms). SERCA2 indicates sarco(endo)plasmic reticulum Ca²⁺ ATPase. All of the data represent group means ±SEs.
illy achieved by female rats in the running wheels. Indeed, animals achieved weekly distances ~20-fold greater than rats in the present study, with an average running velocity of 20 m/min and maximal speeds of 74 m/min.12 The marked prosurvival effect of LIET in female SHHF rats in the present study strongly suggests that the conflicting results of the above studies are because of differences in the intensity and/or volume of the exercise training protocol rather than sex-specific differences in the response to exercise training in general. It remains to be determined whether increasing the volume and/or intensity of exercise training would adversely affect survival in male SHHF rats, but the work of Emter et al11 suggests that this may be the case.

It is important to note, however, that the time at which exercise training is initiated may also influence whether exercise is beneficial or deleterious during the pathogenesis of hypertensive heart disease. For instance, it is plausible that lifelong exercise in the presence of severe hypertension may elicit different effects on HF prognosis than if training is initiated during the decompensation phase when pathologic LV remodeling and dysfunction have already ensued. This issue has not been adequately addressed by the present or previous studies and is a clinically relevant concern that merits further investigation. Therefore, future studies should be conducted to determine the extent to which the intensity and timing of an exercise intervention impact its long-term therapeutic value in hypertensive heart disease.

The pathogenesis of HF is a complex, multifactorial syndrome involving cardiovascular alterations at the molecular, cellular, and organ levels. Therefore, there are several mechanisms by which LIET could have contributed to improved survival in the present study. LIET induced only mild transient effects on blood pressure and echocardiographic parameters compared with sedentary animals in the present study. Nevertheless, LIET significantly attenuated the increase in systolic blood pressure observed in sedentary animals between 16 and 20 months of age, indicating that training elicited slight antihypertensive effects not observed previously in this model.11 Training also prevented the decline in blood pressure associated with end-stage HF between 20 and 25 months, as reported previously in male SHHF rats,11 and led to a slight attenuation of systolic dysfunction between 23 and 25 months of age. However there were no significant differences in blood pressure, LV function, or morphology in terminal HF. The extent to which a transient LIET-induced reduction in systolic blood pressure during the early stages of disease progression contributed to improved survival cannot be determined from this study, but the mild effect suggests that other mechanisms may also be involved. Moreover, exercise training has been shown previously to improve survival in models of hypertensive HF independent of any effect on systolic blood pressure.11,32

Among the myriad of cellular disturbances reported in the failing heart, altered intracellular calcium handling,33–35 oxidative stress,33,36 and induction of the fetal gene program, including a downregulation of α-MHC,10,11,37 have all been associated with HF in humans and SHHF rats. Exercise training has been shown previously to increase myocardial antioxidant enzyme expression,38 normalize alterations in calcium-handling protein expression in the failing heart,39,40 and attenuate the downregulation of α-MHC in male SHHF rats.11 However, there were no significant differences in the myocardial content of these proteins between LIET and sedentary animals in the present study. The lack of an LIET-induced effect on antioxidant protein expression may be because of insufficient exercise intensity, because previous studies indicate that similar LIET protocols failed to elicit myocardial superoxide dismutase or glutathione peroxidase protein induction reported after higher intensity training.17,41,42 The extent to which exercise intensity or volume influence the effect of exercise on myocardial calcium handling proteins is not known, but the absence of any effect herein indicates that LIET does not modify at least the protein levels of SERCA2, phospholamban, or NCX1 in the failing female SHHF rat heart. Our previous study in male SHHF rats demonstrated a suppression of α-MHC downregulation in male SHHF rats after 6 months of the LIET protocol used herein11; however, the trained rats in that study were euthanized before they developed terminal HF. The recent study by Schultz et al12 showed no effect on α-MHC in female SHHF rats despite the excessive level of training. Therefore, the MHC isoform shift in the female SHHF rat heart may be less responsive to normalization by exercise training than in males. Taken together, it is clear from this study that sustained effects on the above myocardial proteins are not essential for improved survival in this model.

Mitochondrial respiratory dysfunction may also play an important role in the pathogenesis and progression of HF.43 Exercise training has been reported to prevent an age-associated loss of COx activity in the heart,44 but the present study is the first to demonstrate an exercise-induced improvement of mitochondrial COx activity in the failing heart. The LIET-induced preservation of COx activity correlated closely with improved survival and a greater mitochondrial content of CL, a dimeric mitochondrial phospholipid known to provide essential structural and functional support to several proteins involved in mitochondrial energy metabolism.45 In the healthy mammalian heart, ~77% of CLs contain 4 linoleoyl acyl chains (L4CL),22 which appears to be important for optimal support of COx activity.14,25 Decreases in the content or linoleoyl enrichment of CL have been reported in failing hearts from humans and experimental models13,20,23,46 and have been implicated as the primary causative factor in the lethal x-linked cardiосkeletal myopathy known as Barth syndrome.47 CL deficiency has been specifically associated with impaired mitochondrial enzyme function in a variety of cardiac pathologies,15 including a progressive decline in COx activity observed during the pathogenesis of HF in the SHHF rat heart.14 In the present study, LIET was associated with greater mitochondrial levels of total CL and L4CL, both of which correlated closely with COx activity and improved survival. LIET had no effect on the relative proportion of L4CL, suggesting that exercise increased CL biosynthesis without affecting linoleoyl enrichment of the CL pool. The precise mechanisms by which LIET modulates CL metabolism and respiratory enzyme activity and the extent to which these modifications contribute to improved prognosis in developing HF merit further investigation.
Low-Intensity Exercise in Female SHHF Rats

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Perspectives

Although abundant evidence from animals and clinical trials indicates that chronic exercise is beneficial in HF, recent investigations suggest that this response may vary between males and females and depends on the nature of the training regimen. The present study demonstrates that, as reported previously in males, LIET 3 days per week slows disease progression and improves survival in female SHHF rats. The fact that these findings are diametrically opposed to the accelerated disease progression and mortality induced by excessive exercise reported in the same strain of female rats indicates that the long-term therapeutic value of exercise, at least in females, is critically dependent on the volume and/or intensity of the training regimen. Furthermore, LIET reduced mortality without eliciting sustained improvements in blood pressure, cardiac function, or expression of myocardial proteins typically associated with the cardiovascular benefits of exercise training. However, the favorable effects of LIET on mitochondrial CL and COX activity provide novel preliminary evidence that exercise may improve prognosis in HF by attenuating deficiencies in mitochondrial energy metabolism, which may play a key role in disease progression. Finally, despite evidence that high-intensity exercise generally elicits attenuating deficiencies in mitochondrial energy metabolism, which may play a key role in disease progression. Finally, despite evidence that high-intensity exercise generally elicits greater cellular adaptations to the myocardium and may provide superior short-term benefits to HF patients than low- or moderate-intensity training, care should be taken before assuming that these effects will result in, or are obligatory for, the favorable effects of exercise on the long-term prognosis in hypertensive heart disease.

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Disclosures

None.

References


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Supplemental Data

For

LOW-INTENSITY EXERCISE TRAINING DELAYS HEART FAILURE AND IMPROVES SURVIVAL IN FEMALE HYPERTENSIVE HEART FAILURE RATS

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Table S1. Mortality data and final animal characteristics.

<table>
<thead>
<tr>
<th></th>
<th>SED</th>
<th>LIET</th>
</tr>
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<tbody>
<tr>
<td><strong>Mortality data</strong></td>
<td></td>
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<tr>
<td>Incidence of terminal HF</td>
<td>6/11 (55%)</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td>Mean age of HF mortality, mo</td>
<td>25.3 ± 0.4</td>
<td>29.8 ± 0.5*</td>
</tr>
<tr>
<td>Incidence of non-HF mortality</td>
<td>5/11 (45%)</td>
<td>6/10 (60%)</td>
</tr>
<tr>
<td>Mean age of non-HF mortality, mo</td>
<td>20.6 ± 0.7</td>
<td>23.7 ± 1.2*</td>
</tr>
<tr>
<td>Mean age of all-cause mortality</td>
<td>23.2 ± 0.8</td>
<td>26.1 ± 1.2*</td>
</tr>
<tr>
<td><strong>Morphology: terminal heart failure</strong></td>
<td></td>
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<tr>
<td>Initial body weight, g</td>
<td>239 ± 12</td>
<td>235 ± 2</td>
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<td>Final body weight, g</td>
<td>235 ± 10</td>
<td>244 ± 18</td>
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<td>Heart weight, g</td>
<td>1.77 ± 0.09 †</td>
<td>1.69 ± 0.13 †</td>
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<tr>
<td>Heart / Brain weight, g/g</td>
<td>0.98 ± 0.05 †</td>
<td>0.92 ± 0.07 †</td>
</tr>
<tr>
<td>Lung weight, mg/g</td>
<td>2.52 ± 0.15 †</td>
<td>3.10 ± 0.09 †</td>
</tr>
<tr>
<td>Ascites</td>
<td>6/6</td>
<td>4/4</td>
</tr>
<tr>
<td><strong>Morphology: terminal non-HF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial body weight, g</td>
<td>237 ± 4</td>
<td>250 ± 6</td>
</tr>
<tr>
<td>Final body weight, g</td>
<td>244 ± 18</td>
<td>233 ± 7</td>
</tr>
<tr>
<td>Heart weight, g</td>
<td>1.16 ± 0.07</td>
<td>1.20 ± 0.07</td>
</tr>
<tr>
<td>Heart / Brain weight, g/g</td>
<td>0.61 ± 0.04</td>
<td>0.66 ± 0.04</td>
</tr>
<tr>
<td>Lung weight, mg/g</td>
<td>1.38 ± 0.09</td>
<td>1.61 ± 0.05</td>
</tr>
<tr>
<td>Ascites</td>
<td>0/5</td>
<td>0/6</td>
</tr>
</tbody>
</table>

Data are group means ± SE. Lung weights are presented as mg per gram of body weight. HF, heart failure; * P < 0.05 vs. SED; † P < 0.01 vs. non-failing.
Table S2. Final echocardiography: censored animals

<table>
<thead>
<tr>
<th>Group</th>
<th>LVIDd (cm)</th>
<th>LVIDs (cm)</th>
<th>PWTd (cm)</th>
<th>AWTd (cm)</th>
<th>EF (%)</th>
<th>FS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SED</td>
<td>7.0 ± 0.2</td>
<td>4.2 ± 0.5</td>
<td>2.2 ± 0.2</td>
<td>2.4 ± 0.2</td>
<td>76 ± 6</td>
<td>40 ± 5</td>
</tr>
<tr>
<td>LIET</td>
<td>6.7 ± 0.3</td>
<td>4.1 ± 0.3</td>
<td>2.3 ± 0.2</td>
<td>2.6 ± 0.2</td>
<td>77 ± 4</td>
<td>40 ± 3</td>
</tr>
</tbody>
</table>

Data are group means ± SE obtained from censored animals immediately prior to sacrifice due to non-HF pathology (n = 5 SED, 6 LIET).

Table S3. Absolute echocardiography data at 23 and 25 months of age

<table>
<thead>
<tr>
<th>Group</th>
<th>LVIDd (cm)</th>
<th>LVIDs (cm)</th>
<th>FS (%)</th>
<th>PWTd (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>23 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SED</td>
<td>6.3 ± 0.6</td>
<td>2.7 ± 0.5</td>
<td>58 ± 4</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>LIET</td>
<td>6.4 ± 0.2</td>
<td>3.5 ± 0.3</td>
<td>46 ± 4</td>
<td>2.5 ± 0.2</td>
</tr>
<tr>
<td><strong>25 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SED</td>
<td>7.5 ± 0.5</td>
<td>5.2 ± 0.5</td>
<td>31 ± 6</td>
<td>2.3 ± 0.4</td>
</tr>
<tr>
<td>LIET</td>
<td>7.3 ± 0.5</td>
<td>5.0 ± 0.7</td>
<td>31 ± 3</td>
<td>2.3 ± 0.1</td>
</tr>
</tbody>
</table>

Data are group means ± SE from non-censored animals surviving until 25 months of age, corresponding to the percent change data presented in Figure S1A of the online supplement (n = 3 SED, 4 LIET).
**Figure S1.** Percent changes in LV chamber dimensions, fractional shortening and LV wall thickness determined by echocardiography. A) Data from non-censored animals surviving until 25 months of age, corresponding to data in Table 2, online supplement (N = 3 SED, 4 LIET). B) Data from all non-censored animals between 23 months of age and terminal HF, corresponding to absolute data in Table 1, main text (N = 6 SED, 4 LIET). LVIDd, LV internal diameter in diastole; LVIDs, LV internal diameter in systole; FS, fractional shortening; PWTd, LV posterior wall thickness in diastole. Values are means ± SE. * P < 0.05 vs. SED; † P = 0.06 vs. SED.

Representative calsequestrin blots demonstrating uniform well loading.