Moderate Exercise Training Improves Survival and Ventricular Remodeling in an Animal Model of Left Ventricular Volume Overload

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Background—Exercise training has beneficial effects in patients with heart failure, although there is still no clear evidence that it may impact on their survival. There are no data regarding the effects of exercise in subjects with chronic left ventricular (LV) volume overload. Using a rat model of severe aortic valve regurgitation (AR), we studied the effects of long-term exercise training on survival, development of heart failure, and LV myocardial remodeling.

Methods and Results—One hundred sixty male adult rats were divided in 3 groups: sham sedentary (n=40), AR sedentary (n=80), and AR trained (n=40). Training consisted in treadmill running for up to 30 minutes, 5 times per week for 9 months, at a maximal speed of 20 m/minute. All sham-operated animals survived the entire course of the protocol. After 9 months, 65% of trained animals were alive compared with 46% of sedentary ones (P<0.05). Ejection fractions remained in the normal range (all above 60%) and LV masses between AR groups were similar. There was significantly less LV fibrosis in the trained group and lower LV filling pressures and improved echocardiographic diastolic parameters. Heart rate variability was also improved by exercise.

Conclusion—Our data show that moderate endurance training is safe, does not increase the rate of developing heart failure, and most importantly, improves survival in this animal model of chronic LV volume overload. Exercise improved LV diastolic function, heart rate variability, and reduced myocardial fibrosis. (Circ Heart Fail. 2009;2:437-445.)

Key Words: survival ■ exercise ■ hypertrophy ■ valves ■ collagen

Regular exercise seems to be beneficial in most patients with stable cardiac diseases. In patients with heart failure, current evidence suggests that exercise can improve functional capacity and quality of life. However, the impact of exercise on mortality in patients with heart failure has not yet been clearly established.1 The ability of exercise to prevent or delay the occurrence of heart failure in high-risk subjects also remains unclear. Chronic left ventricular (LV) volume overload diseases such as aortic valve regurgitation (AR) are well tolerated for many years before heart failure occurs. There is currently no treatment proven effective to decrease morbidity, mortality, delay evolution toward heart failure or the need of surgery in this category of patients.2 The potential benefits of exercise have never been evaluated in subjects with chronic LV volume overload, dilated ventricles but preserved LV systolic function. The body of evidence suggests that aerobic exercise can improve cardiac performance by several mechanisms such as improvement of contractility, increased myocardial perfusion and angiogenesis, normalization of the sympathetic-parasympathetic balance, improvement of myocardial energetic metabolism, decreasing oxidative stress, better myocardial calcium handling, and improvement of peripheral arterial compliance.3–8 We have previously shown in a pilot study that exercise can be well tolerated in female rats with volume overload and that it may improve LV remodeling. However, that study was not designed to assess survival and was clearly underpowered to evaluate the impact of exercise on cardiac tissue.9 Considering these encouraging preliminary data and the potential benefits of exercise on cardiac physiology, we designed this study to assess the effects of a regular exercise program on cardiac remodeling, occurrence of systolic and diastolic dysfunction, and survival in male rats suffering from chronic LV volume overload caused by severe AR.

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Methods

Animals
One hundred sixty adult male Wistar rats were purchased from Charles River (Saint-Constant, Quebec, Canada) and divided in 3

Received December 18, 2008; accepted May 13, 2009.
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Circ Heart Fail is available at http://circheartfailure.ahajournals.org DOI: 10.1161/CIRCHEARTFAILURE.108.845487
groups as follows: (1) sham sedentary (SS; n=40); (2) AR sedentary (ARS; n=80), and (3) AR trained (ART; n=40). Six additional groups of male rats (n=8 to 10 per group) underwent the same protocol but for shorter periods to obtain intermediate tissue data after 3 months (SS3, ARS3, and ART3) and 6 months (SS6, ARS6, and ART6).

Exercise Protocol
Animals in the trained groups were exercised 5 days/week for 9 months on a motorized treadmill with a slope of 10°. The duration and the intensity increased progressively during the first 8 weeks until the animals were running for 30 minutes at 20 m/minute. This protocol was approved by the Université Laval’s animal protection committee and was consistent with the recommendations of the Canadian Council on animal care.

Aortic Regurgitation
Severe AR induced by retrograde puncture of the aortic valve leaflets under 1.5% inhaled isoflurane anesthesia, as described previously.10–12 Sham animals had their right carotid artery cannulated under anesthesia without puncture of the aortic valve. Animals were clinically evaluated daily by experienced animal laboratory technicians for the presence of signs of heart failure (increased respiratory rate/distress and/or peripheral edema) and were weighed weekly. At the end of the protocols (3, 6, or 9 months), surviving animals were euthanized, hearts were quickly dissected, and all cardiac chambers were weighed. LV were snap frozen in liquid nitrogen and kept at −80° Celsius for further analysis.

Echocardiography
A complete M-Mode, 2D, and Doppler ECG was performed on the animals under 1.5% inhaled isoflurane anesthesia using a 12 MHz probe with a Sonos 5500 echograph (Philips Medical Imaging, Andover, Mass) immediately before and during surgery, after 2 weeks, 3 months, 6 months, and 9 months. The ECG after 2 weeks was performed to quantify AR before starting the training program to ensure all animals still met the entry criteria. LV dimensions, wall thickness, ejection fraction, diastolic function, cardiac output, and myocardial performance index were evaluated, as reported previously.13–15

Heart Rate and Heart Rate Variability in Conscious Animals
Heart rate, heart rate variability and low to high frequency in conscious animals were measured using the ECGenie system and eMouse ECG analyses software from Mouse Specifics Inc (Quincy, Mass). A 20-minute adaptation period was allowed before recordings were made. The animals were freely moving on the recording platform, and the ECG was recorded through the contact of their paws with the electrodes. Several ECG stretches (mean of 10) of at least 30 seconds were then recorded for analysis.

Hemodynamic Measurements
LV and aortic pressures and dP/dt (positive and negative) were measured invasively in 15 animals per group using a Millar 2F pressure volume catheter under 1.5% isoflurane anesthesia at the end of the protocol.15

Cardiomyocyte Cross-Sectional Area and Evaluation of LV Fibrosis
Sections from paraffin-embedded mid-LV portions were stained using trichrome-Masson coloration. Three subendocardial sections or slides from all surviving animals were analyzed for the evaluation of cross-sectional area of the cardiomyocytes, as described previously16,17 and for the evaluation of the proportion of LV subendocardial fibrosis as the blue (fibrosis)/red (myocytes) ratio using a computerized image analysis system (Image-Pro Plus version 4.5, Media Cybernetics, Silver Spring, Md). The subendocardial sections were defined as the inner third of the LV wall facing the LV cavity.15,16 Determination of LV perivascular fibrosis was performed, as described previously.17

LV Collagen Content
LV hydroxyproline content was determined by using a modified Stegemann procedure.18 LV midsection pieces were homogenized and then hydrolyzed in a solution of 6N HCl for 24 hours at 100°C. Samples were then dried overnight under vacuum and resuspended in 1 mL of water. Hydroxyproline standards were also made in water. Five hundred micro liters of standard solutions or LV samples were used for the determination. One milliliter of isopropanol was then added to the tubes before being vortexed. To this solution, 500 µL of oxidant (0.35 g of chloramine-T dissolved in a solution of 5 mL of water plus 20 µL citrate buffer) was added. After 4 minutes of incubation at room temperature, 3.25 mL of Ehrlich reagent were added, and the mix was let to incubate at 25°C overnight. The intensity of red coloration was measured using a spectrophotometer (350 nm). The amount of hydroxyproline per milligram of LV tissue was calculated, and the collagen content was estimated by multiplying the hydroxyproline content by a factor of 8.2.

Analysis of mRNA Accumulation by Quantitative Real-Time Polymerase Chain Reaction
The analysis of LV mRNA levels by quantitative real-time polymerase chain reaction has been described in details elsewhere.15 Briefly, 1 µL RNA (500 ng) was converted to cDNA using the QuantiTect Reverse Transcription kit (Qiagen, Valencia, Calif). The cDNA obtained was further diluted 11-fold with water before amplification. Five micro liters of diluted cDNA were amplified in duplicate by quantitative polymerase chain reaction in a Rotor-Gene thermal cycler (Corbett Life Science, Sydney, Australia), using QuantiTect Primer Assays (preoptimized specific primer pairs from Qiagen) and QuantiFast SYBR Green polymerase chain reaction kits (Qiagen). The quantification of gene expression was based on the −ΔΔCt method,16 using the cyclophilin A as a housekeeping gene and as a control.

Statistical Analysis
Results are presented as mean±SEM unless specified otherwise. Intergroup comparisons were done using 1-way ANOVA and Tukey post test or Student t test. Survival was analyzed by standard Kaplan-Meier analysis with log-rank test. Statistical significance was set at a P<0.05. Data and statistical analysis were performed using Graph Pad Prism version 5.01 for Windows (Graph Pad Software, San Diego, Calif). Sample sizes were calculated based on a previous survival study11 to ensure a 0.80 power to detect a mean of 30 days benefit of survival in trained animals with an α value of 0.05 using a 2:1 ratio of untreated and treated animals.

Statement of Responsibility
The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results
Clinical Data and Animal Characteristics
Exercise training was well tolerated. Figure 1 shows the survival curves of sedentary (sed) or trained (tr) AR animals during a period of 270 days. All sham-operated animals were alive at the end of the protocol (not shown). Ninety percent of trained animals were alive after 6 months compared with only
74% in the sedentary group. After 9 months, the survival of trained animals was significantly better with a survival rate of 65% compared with 46% for the untreated group \( (P<0.05) \).

No animals developed signs of overt heart failure defined as excessive weight gain, labored breathing, peripheral edema, or decrease of ejection fraction below 50%. Most deaths were sudden, unexpected, and unwitnessed (occurring overnight). One death occurred suddenly during the exercise on the treadmill.

**Tissue Weights**

After 9 months (3 and 6 months for the shorter protocols), surviving animals were euthanized and results for tissue weights are summarized in Figure 2. Total heart weight was smaller in trained animals. This difference in total heart weight was mainly due to a reduction in right ventricular and left atrial hypertrophy in the trained animals, whereas LV weight was not statistically different. Lung weight was similar in both groups. After 9 months, surviving trained animals were leaner than the sedentary ones as shown in Figure 2 by their smaller weight, weight gain, and retroperitoneal fat content. Overall growth however was similar between groups (tibial length; not shown).

**Hemodynamic Measurements**

Hemodynamic measurements were made at the end of the 9-month protocol in surviving animals and the results are summarized in Table 1. All measurements were made under isoflurane anesthesia. There were no differences between groups in resting heart rate, stroke volume, and systolic and diastolic pressures. The dP/dtmax was also similar in both groups. However, LV end-diastolic pressures were significantly lower in the trained animals and the values of dP/dtmin. Heart rate and heart rate variability were evaluated by telemetry in conscious animals and results are shown in Figure 3. Conscious resting heart rates were similar between the groups. However, heart rate variability decreased in sedentary AR animals was normalized by exercise in trained animals.
Echocardiographic Data

As shown in Figure 4, exercise training reduced LV dilatation both in diastole and in systole. This protective effect was detectable as early as 12 weeks after the beginning of the protocol. LV wall thickness remained similar between groups. Despite a slow steady decrease in ejection fraction throughout the protocol, calculated ejection fraction remained >60% in all the animals of both groups. Trained animals had

<table>
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</table>

Measurements obtained under inhaled 1.5% isoflurane anesthesia in surviving animals. Values are mean ± SEM of the indicated number of animals, with the exception of for the dP/dt and LVEDP values (n=15). Sed indicates AR sedentary group; tr, AR trained group; HR, heart rate; SV, stroke volume in left ventricular outflow tract by pulsed Doppler; SBP, systolic blood pressure; DBP, diastolic blood pressure; dP/dt_{min}, minimal derivative of pressure/time; dP/dt_{max}, maximal derivative of pressure/time; LVEDP, left ventricular end-diastolic pressure.

Table 1. Hemodynamic Data

Echocardiographic Data

As shown in Figure 4, exercise training reduced LV dilatation both in diastole and in systole. This protective effect was detectable as early as 12 weeks after the beginning of the protocol. LV wall thickness remained similar between groups. Despite a slow steady decrease in ejection fraction throughout the protocol, calculated ejection fraction remained >60% in all the animals of both groups. Trained animals had
higher ejection fractions after 12 and 26 weeks than sedentary animals. However, after 40 weeks, only a trend for a better ejection fraction was present in trained animals but that difference did not reach statistical significance.

Diastolic echocardiographic parameters were also measured throughout the protocol (Figure 4). Trained animals had lower E and A wave velocities and E wave slopes than sedentary ones. The E/Ea ratio was significantly lower in trained animals correlating well with the invasive LV end-diastolic pressures measurements and left atrial weights. Figure 4 also depicts the longitudinal measurements of diastole-related parameters during the protocol. Marked differences in E wave and A wave velocities were detectable as early as 12 weeks after the beginning of the training protocol. Similar differences were noted after 12 weeks for the E wave slope, left atrial diameter, and E/Ea ratios. E/A ratios remained similar between groups.

Subanalysis of the Characteristics of Survivors Versus Deceased Animals

Tables 2 and 3 summarize comparative data obtained in the animals that survived the entire protocol (n = 58) and animals that died during the protocol (n = 62). Table 2 compares the necropsic data in those animals. These data clearly show that animals that would not survive the entire protocol had significantly larger hearts than late survivors. The left and right ventricles, left atria, lungs, and livers were all significantly larger in those animals compared with the survivors. Table 3 summarizes the 6-month echocardiographic data in the survivors and in the animals, which would later die before the end of the protocol (death occurring between 6 and 9 months). These data clearly show that after 6 months, animals that would die prematurely had larger left ventricles, more LV hypertrophy (LV mass), larger left atria, and some abnormal diastolic filling parameters (E wave slope and E/Ea ratio). LV ejection fraction, however, was still normal in both groups after 6 months (>60%) even though animals that would die prematurely had a slightly lower LV ejection fraction that can be considered clinically nonsignificant (65% versus 67%).

Tissue Analysis

Results obtained from tissue analysis of explanted hearts at the end of the 9-month protocol are shown in Figures 5 and 6. Data for total collagen content from 3 to 6 months trained animals are shown as comparative data in Figure 5. Trained animals had significantly less myocardial fibrosis than sedentary animals. Fibrosis content evaluated by trichrome-
Masson staining was significantly lower in trained animals compared with sedentary ones (Figure 5). This finding was confirmed by total collagen content measurement. Perivascular fibrosis was also normalized in trained animals compared with sedentary ones. Myocyte cross-sectional area was increased compared with healthy rats in both AR groups but this parameter was unaffected by exercise. Gene expression of various extracellular matrix components related to fibrosis was measured and results are summarized in the top panel of Figure 6. Collagen I, collagen 3, and fibronectin mRNA levels were all increased in both AR groups compared with normal sham animals. Both collagens 1 and 3 expressions were significantly reduced by training, whereas fibronectin expression was unaffected. Lysyl oxidase mRNA expression was also unaffected by training. Matrix metalloproteinase 2 and tissue inhibitor of metalloproteinase 1 mRNA expressions were significantly increased in AR animals compared with sham animals and exercise training successfully reduced both overexpressions. The mRNA expression of profibrotic transforming growth factor β1, transforming growth factor β2, and connective tissue growth factor were also assessed. Again, AR animals displayed a significant overexpression of all 3 components with a reduction of that expression in trained animals. The expression status of genes encoding for 3 secreted cardio-protective factors namely the atrial and the brain natriuretic peptides as well as follistatin-like 1 (Fstl1) were measured. Gene expression was increased for all 3 of them in AR animals but only the levels of Fstl were reduced by exercise training. β1-adrenergic receptor gene expression was reduced by AR, whereas the β2-adrenergic receptor mRNA levels remained stable. β1/β2 receptor ratio was improved by exercise. Finally, we also evaluated the regulation of 3 genes implicated in myocardial calcium handling namely SERCA2a, phospholamban, and S100a1 protein. mRNA levels encoding for phospholamban and S100a1 in AR were decreased compared with normal animals, whereas those of SERCA2a were unchanged. Exercise had no effect on the mRNA levels of these genes.

### Discussion

The main and most important finding of this study is that a moderate-intensity aerobic exercise program improves survival in the setting of experimental LV volume overload. Using this model of chronic AR, we have also demonstrated that exercise is well tolerated and helps reduce myocardial fibrosis. Diastolic filling parameters were improved by exercise and heart rate variability. To our knowledge, these data are the first to be reported in the setting of chronic volume overload. The impact of regular exercise on subjects with chronic LV overload has never been evaluated before.

The benefits of exercise in animal models of preheart failure and heart failure have been demonstrated in the context of systemic hypertension, after myocardial infarction, and transgenic dilated or hypertrophic cardiomyopathies. Few of them assessed the impact of exercise on survival. None of these studies were related to chronic volume overload. There are no human clinical trials evaluating exercise and survival in chronic volume overload or any other type of valvular disease.

In contrast to other models of volume overload such as aortocaval fistulae, which result in rapid heart failure involving right and left ventricles, our model of severe AR is well tolerated for a long period of time during which the ventricle progressively dilates and hypertrophies but still retains a normal LV ejection fraction. This model is therefore more relevant and closer to human disease than more aggressive models such as aortocaval fistula, which are virtually never encountered in real life. Although the aortocaval fistula model is very useful for the study of heart failure and the acute response to volume overload, it cannot be used for longer chronic studies because reported mortality rates are as high as 50% after just 12 weeks and close to 80% after 20 weeks. Rats with severe AR can survive up to 1 year and few will develop clinical heart failure. This model is therefore more appropriate for chronic studies and evaluation of long-term therapies.

The exercise protocol, we chose in this study is of moderate intensity. Considering the severe volume overload imposed on the animals and the severe LV dilatation to be expected, we voluntarily excluded an intense training program in fear that it would not be tolerated by the animals. Based on published data by other groups, it could also be suspected that intense exercise could increase mortality. On
the other hand, we did not want to test a low intensity exercise protocol that might have little if any physiological impact. The moderate intensity exercise protocol we chose was therefore selected based on preliminary data and on our pilot study that confirmed a significant physiological impact of the protocol in normal animals and also that this exercise intensity was accepted and tolerated by the AR animals.\(^9\) Oxygen consumption was not measured in our animals but based on other publications, it can be estimated that our protocol corresponded roughly to 50% of maximal Vo\(_2\) consumption.\(^{28}\)

Exercise improved survival in our animals. The survival curves started to diverge between 120 and 150 days after the training program started and remained different until the end of the protocol. Interestingly, most deaths were sudden and unexpected. Clinical heart failure was of rare occurrence, and we suppose as in previous studies that deaths must have been arrhythmic in nature. Because the animals were not constantly monitored, arrhythmias were unfortunately not documented. However, considering that the animals did not develop clinical signs of heart failure and that ejection fractions remained in the normal range after 6 months in the animals, which would decease prematurely, it would be very surprising that heart failure was the cause of death.

The risk of sudden death and arrhythmia in heart failure\(^{20,30}\) and AR\(^{2,31}\) has been correlated to the severity of LV dilatation and hypertrophy. The subgroup analysis of survivors versus deceased animal in our study definitively showed that animals that would eventually die had significantly larger left ventricles after 6 months than survivors. Exercise attenuated LV dilatation. It is therefore logical to suggest that less LV dilatation in exercising animals protected against sudden death.

Myocardial fibrosis is also known to be proarrhythmic. Fibrosis promotes electric heterogeneity and arrhythmias by various electrophysiological mechanisms.\(^{32–36}\) In our protocol, trained animals had significantly less myocardial fibrosis. This could be another factor influencing the risk of sudden death. Finally, we have also shown that heart rate variability was improved in the trained animals. A decrease in heart rate variability is another risk factor for sudden death that may have been favorably influenced by exercise training in our animals.\(^{37,38}\)

Exercise was clearly beneficial in trained animals, despite a lack of difference in any of the hemodynamic parameters that were measured. Indeed, both trained and sedentary animals had similar resting heart rates, systolic pressures, diastolic pressures, and pulse pressure. Stroke volume, cardiac output, and AR severity were also similar in both groups. The benefits induced by exercise cannot therefore be attributed to significant hemodynamic improvements or reduction in volume overload. Peripheral arterial compliance does not seem to be affected either. We have to acknowledge, however, that these hemodynamic parameters were measured under general anesthesia and that significant differences might have been present in awake animals. Improved heart rate variability in the trained animals suggests that there might have been such a difference.

Systolic function was similar in both groups as shown by the similar values of dP/dt\(_{\text{max}}\) and normal ejection fraction. However, most diastole-related echocardiographic parameters were improved by exercise and these improvements are corroborated by lower LV filling pressures (LV end-diastolic pressures), higher dP/dt\(_{\text{min}}\), smaller left atria, lungs, and right ventricles all suggesting lower diastolic filling pressures and improved LV compliance. Diastolic properties may be influenced by numerous factors, one of these being the amount of myocardial fibrosis. Our results clearly show that exercise reduced myocardial fibrosis in AR rats and that profibrotic gene expressions were clearly decreased by exercise. This decrease in interstitial fibrosis must have helped improve diastolic function.

Intense exercise can result in physiological volume overload and consequent physiological hypertrophy. Even a moderate exercise program such as the one used in our study can impose some volume overload on the heart and induce mild LV dilatation and hypertrophy.\(^9\) Therefore, there was a theoretical risk of increasing LV dilatation and hypertrophy by combining exercise and AR (physiological-pathological volume overload). The fear remained that the combination of both volume overloads may have additive or even synergistic effects, cause worse LV dilatation or even accelerate the heart failure process. Not only did we find that exercise did not worsen LV remodeling and function but also that it had protective effects against dilatation and fibrosis.

Considering all these data, it seems reasonable to think that moderate aerobic exercise is safe and probably beneficial in subjects with chronic LV volume overload. We, however, need to keep in mind that high-intensity exercise training might not have given similar results and that we must remain cautious in that regard.

**Limitations**

Our animal model has limitations like any animal models, and we must keep those limitations in mind before transposing this data to humans. Rodent cardiovascular physiology differs from humans in many aspects. Oxygen consumption was not measured during our exercise protocol and therefore exercise intensity was not precisely quantified. Exercise was started rather early in the course of the disease, and it is not known if the beneficial effects would have been found if training had been started later or in older animals with comorbidities. However, we have previously reported in our model that significant LV dilatation is already established in the first month of the protocol and that most acute adaptive mechanisms have receded after 2 weeks.\(^{17}\) The effects of long-term training in males versus females were not evaluated, although we have shown in our pilot study that exercise seems to be beneficial in females also.\(^9\)

Despite these limitations, we found no deleterious effects of exercise on any of the measured clinical, hemodynamic, and echocardiographic or tissue analysis parameters in our animals after 9 months. Survival was improved by exercise. Diastolic parameters and filling pressures were also improved and myocardial fibrosis decreased. Therefore, we can reasonably conclude that a moderate supervised aerobic exercise training program is beneficial in rats with chronic volume overload.
40. Bower GL, Gardner JD, Janicki JS. Gender mediated cardiac protection from adverse ventricular remodeling is abolished by ovariecotom}. Mol Cell Biochem. 2003;251:89–95.
CLINICAL PERSPECTIVE

Chronic left ventricular volume overload as seen in patients with aortic valve regurgitation results in severe left ventricular dilatation, hypertrophy, and eventually to heart failure if surgical valve replacement is not performed at the appropriate time. No pharmacological treatment has been clearly shown to be effective to protect the myocardium against the deleterious effects of chronic volume overload. Regular aerobic exercise has been shown to be beneficial in various cardiac diseases but its effects in chronic volume overload have never been evaluated. On the basis of the promising preliminary data, we designed a protocol to evaluate the long-term (9 months) effects of a moderate regular treadmill aerobic exercise program in rats with severe aortic valve regurgitation. Our results show that exercise decreases left ventricular remodeling, improves diastolic properties, and decreases myocardial fibrosis. But most importantly, exercise also improves survival in those animals in comparison with sedentary ones. These results suggest that moderate aerobic exercise is not only safe but also helps preserve normal myocardial properties and integrity. It may also improve survival in subjects with chronic volume overload. Although animal studies must always be interpreted with caution, these exciting results suggest that the impact of regular aerobic exercise should be addressed in carefully designed clinical trials in humans.
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Circ Heart Fail. 2009;2:437-445; originally published online June 15, 2009;
doi: 10.1161/CIRCHEARTFAILURE.108.845487
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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