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Exercise training improves cardiac performance in diabetes: in vivo demonstration with quantitative cine-MRI analyses

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Loganathan R, Bilgen M, Al-Hafez B, Zhero SV, Alenezy MD, Smirnova IV. Exercise training improves cardiac performance in diabetes: in vivo demonstration with quantitative cine-MRI analyses. *J Appl Physiol* 102: 665–672, 2007. First published November 2, 2006; doi:10.1152/japplphysiol.00521.2006.—Diabetic cardiomyopathy is a distinct myocardial complication of the catabolic state of untreated insulin-dependent diabetes mellitus in the streptozotocin-induced diabetic rat. Exercise training has long been utilized as an effective adjunct to pharmacotherapy in the management of the diabetic heart. However, the in vivo functional benefit(s) of the training programs on cardiac cycle events in diabetes are poorly understood. In this study, we used three groups of Sprague-Dawley rats (sedentary control, sedentary diabetic, and exercised diabetic) to assess the effects of endurance training on the left ventricular (LV) cardiac cycle events in diabetes. At the end of 9 wk of exercise training, noninvasive cardiac functional evaluation was performed by using high-resolution magnetic resonance imaging (9.4 T). An ECG-gated cine imaging protocol was used to capture the LV cardiac cycle events through 10 equally incremented phases. The cardiac cycle phase volumetric profiles showed favorable functional changes in exercised diabetic group, including a prevention of decreased end-diastolic volume and attenuation of increased end-systolic volume that accompanies sedentary diabetes. The defects in LV systolic flow velocity, acceleration, and jerk associated with sedentary diabetes were restored toward control levels in the trained diabetic animals. This magnetic resonance imaging study confirms the prevailing evidence from earlier in vitro and in vivo invasive procedures that exercise training benefits cardiac function in this model of diabetic cardiomyopathy despite the extreme catabolic state of the animals.

cardiac cycle; diabetic cardiomyopathy; left ventricle; magnetic resonance imaging

THE DIABETIC HEART IS TARGETED by both coronary and noncoronary pathology that eventually result in cardiac failure (2, 10). The failure to maintain tissue glucose homeostasis compromises cardiac structure and function in humans and experimental animal models of diabetes mellitus (17, 32). The myocardial damage due to chronic hyperglycemia is a key feature of diabetic cardiomyopathy (DCM) and occurs as a result of abnormal metabolic and cell signaling pathways (9, 24, 35). In addition to myocardial damage, DCM is manifested by deposition of interstitial collagen in the myocardial tissue (21, 33). These pathological features compromise the normal contractility and compliance of the diabetic heart (1, 22, 39). DCM is also accompanied by worsening of the recovery of heart function after an ischemic insult (41). Meanwhile, the cardiac dysfunction in diabetes is amenable to therapeutic interventions, for example, pharmacotherapy and exercise therapy (11, 12, 24).

Exercise has long been used as an effective cardioprotective agent in diabetes (19, 28, 34, 37). The structural and functional abnormalities of the diabetic heart respond favorably to exercise training. For example, at the ultrastructural level, benefits of exercise training on the diabetic myocardium manifest as attenuation of *1*) mitochondrial swelling and disruption, *2*) increase in cytoplasmic area, and *3*) increased collagen fiber cross-sectional area (34). Endurance training increases the cardiac output in diabetic rats under high-preload conditions (8). Training prevents the cardiac autonomic nervous dysfunction in diabetes (7) and improves cardiac function in diabetes without benefiting plasma glucose and cholesterol levels (18). Although these results suggest a favorable role for exercise training on the diabetic heart, the exercise-induced benefits on cardiac cycle events are not apparent from earlier in vitro or invasive in vivo studies. The importance of obtaining information on the effects of exercise training on the diabetic cardiac cycle events is underscored by the evidence that DCM is associated with both diastolic and systolic left ventricular (LV) dysfunction, resulting in abnormalities of cardiac cycle events (1, 20).

Thus the primary objective of this study was to characterize the effects of exercise training on the profound cardiac dysfunction noted in the catabolic state of untreated insulin-dependent diabetes. To overcome the interpretive limitations inherent to in vitro and invasive in vivo procedures, and study the cardiac cycle events under the relevant biomechanical constraints of the highly dynamic chest cavity, we utilized high-resolution magnetic resonance imaging (MRI) for the evaluation of exercise-induced effects on the diabetic heart. The use of MRI in our investigation was further motivated by the following advantages: *1*) the confounding effects of thoracotomy and deep anesthesia that often accompany an invasive approach can be avoided (30); *2*) MRI can capture the cardiac pump function in small animals despite their intrinsically high heart rates (40); and *3*) being intrinsically three-dimensional, MRI computations overcome the limitations posed by geometric assumptions that facilitate volumetry in other commonly used noninvasive procedures, for example, echocardiography

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(13). In addition to these unique advantages, the versatility of use and accuracy of measurements made possible by MRI make it ideally suited for cardiac volumetric measurements in heart failure (29). MRI has also been proposed as the technique of choice for the assessment of treatment effects in clinical studies due to its accuracy, low interobserver variability, and the potential to reduce sample size substantially (3).

METHODS

Animal model of diabetes. All procedures on animals were approved by the University of Kansas Medical Center Institutional Animal Care and Use Committee. Twelve male Sprague-Dawley rats (Harlan, Indianapolis, IN), aged 2 mo with an initial mean body mass of 250 g, were used for the study. The rats were randomly assigned to one of the following three groups ($n = 4$ per group): *1*) sedentary nondiabetic control (SC), *2*) sedentary diabetic (SD), and *3*) exercised diabetic (ED). The rats in the diabetic groups were given a single intraperitoneal injection of streptozotocin (65 mg/kg, Sigma, St. Louis, MO) in 10 mM sodium citrate buffer, pH 4.5. The SC group was treated with the same volume of vehicle. Diabetes was confirmed in the SD and ED groups by measuring the nonfasting plasma glucose level (≥300 mg/dl) 2 days following the injection. Body mass and plasma glucose levels were recorded weekly. All rats were given unlimited access to chow and water for the entire duration of the study.

Exercise training protocol. The details of the treadmill endurance training protocol used in this study were presented in a previous report (34). Briefly, the rats in the ED group underwent pretraining for a period of 2 wk before diabetes induction followed by 9 wk of exercise with diabetes. The training intensity and duration began at 15 m/min for 5 min on *day 1* and progressed to 20 m/min for 50 min by the end of *week 2*. After the induction of diabetes, all rats in the ED group maintained the intensity and duration of 20 m/min for 60 min/day for the remaining 9 wk. No electric shock was used to stimulate animals to run. Instead, uncooperative rats were encouraged to run by occasional gentle manual brushing on their backs. To rule out the confounding effects of nontraining factors in the training environment, all animals in the SC and SD groups were handled everyday and subjected to the noise of running treadmill by placing their cages next to the exercising animals. Our laboratory has shown in earlier reports that this training intensity is sufficient to induce favorable structural changes in the diabetic cardiac muscle (34), although it is inadequate to produce an increase in skeletal muscle citrate synthase levels (36).

Physical activity challenge. After 9 wk of training, the efficiency of metabolically active lean tissue (skeletal and cardiac muscles) to sustain a physical challenge was tested in all three groups, by scoring the animals on a 25-min running challenge. The run intensity was increased at the rate of 1 m/min in five steps until the speed of 25 m/min was reached (*step 1*: 5 m/min at *time 0*; *step 2*: 10 m/min at 5 min; *step 3*: 15 m/min at 10 min; *step 4*: 20 m/min at 15 min, *step 5*: 25 m/min at 20 min). The running duration at each step was maintained at 5 min. The following activity capacity scores were assigned: 0, no run; 0.5, complete run for 5 min; 1.0, complete run for 10 min; 1.5, complete run for 15 min; 2.0, complete run for 20 min; 2.5, complete run for 25 min. In case of incomplete runs between any two of the five steps, a full score corresponding to the lower step was assigned. The electrical shocker was used during this procedure and a run was scored incomplete when the animal spent more than 30 s on the shocker.

MRI procedures. At the end of 9 wk of diabetes, cardiac MRI was performed using a 9.4-T horizontal bore scanner (Varian, Palo Alto, CA) and 60-mm radio-frequency volume coil. The anesthetic dose of 1.5% isoflurane in a mixture of air and oxygen (60 and 40%, respectively) was estimated as the minimum amount required to prevent body motion while administered via a nose cone (20). Stable ECG, respiration, and temperature profiles were ensured during scanning sessions via a dedicated small-animal vital signs monitoring system (SA Instruments, New York, NY). Inside the magnet bore, the rats were placed on a custom-built Plexiglas sled designed for optimal imaging of the LV. After confirming heart position with an initial set of scout images, ECG-gated gradient echo-based cine images of LV were captured from a short-axis view of the heart. The LV was spatially resolved into 6 slices (Fig. 1). The cardiac cycle was temporally resolved into 10 equally incremented phases. The following settings were used for image acquisition: repetition time/echo time = 25/2.44 ms, number of averages = 1, field of view = 60 × 60 mm, image matrix = 256 × 256, slice thickness = 2.0 mm.

Image analyses. Images were analyzed with Image J, a freely downloadable Java-based environment (http://rsb.info.nih.gov/ij). For each LV, the phase stereometry was performed by integrating the area of the sliced blood disk (bright region enclosed by the endocardium) with respect to slice thickness from the apex to base using the Cavalieri principle (23) (see Fig. 1). The pixel-to-area conversion factor of 1 pixel/0.11 mm^2 was used for all computations. These computations were repeated for all 10 phases of the cardiac cycle. The phases corresponding to the largest and smallest LV volume were chosen to be representative of end diastole and end systole, respectively (20). The difference between the end-diastolic and end-systolic volume was expressed as the stroke volume. The ratio of stroke volume to the end-diastolic volume was expressed as the ejection fraction (%). The product of stroke volume and heart rate was expressed as the LV output. In addition to the cardiac cycle volumetry, the LV myocardial volume was also estimated in all the three groups from the reconstruction of all six slices from the end-diastolic phase.

The LV volumetric profiles obtained from the MRI analyses were utilized for the evaluation of LV systolic hemodynamics in all the three groups. The systolic component of the LV volumetric curve was approximated by a third-order polynomial fit. The first, second, and third derivatives of LV volume (V) with respect to time (t) were estimated from the polynomial approximation as oblique indexes of LV systolic flow velocity (dV/dt), acceleration (d^2V/dt^2), and jerk (d^3V/dt^3) respectively (38).

Glucometry and gravimetry. Plasma glucose levels were measured using the AccuCheck Active meter (Roche Diagnostics, Indianapolis, IN). Glycated hemoglobin (HbA1c) levels were measured 1 day before MRI scans using antibody-based A1cNow meter (Metrika, Sunnyvale, CA). After the MRI procedures, rats were killed with an overdose of pentobarbital sodium. The hearts were excised, washed in cold phosphate-buffered saline, blotted, and weighed.

Statistical analyses. Statistical analyses were performed with SPSS (version 11.0). Significant differences between the groups on measures of cardiac function were tested with a one-way ANOVA. When

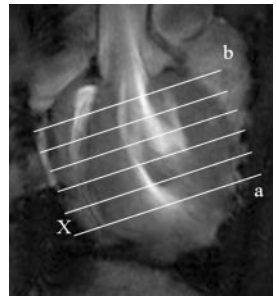

Fig. 1. Illustration of the left ventricular (LV) spatial resolution used for the cine-imaging procedure. LV was spatially resolved into 6 slices. The phase volume (V_p) for each of the 10 cardiac cycle phases was computed by integrating the area [$A(s)$] of the blood disk in each of the slices with respect to slice thickness (X) from the apex (a) to the base (b) of LV as illustrated in this LV sagittal section and given by $V_p = \int_a^b A(s)dX$.

Table 1. *Glucometry and gravimetry*

Rat Group	Plasma Glucose, mg/dl	HbA1c, %	Body Mass, g	Heart-to-Body Mass Ratio, mg/g
Sedentary control	117±5*†	4.8±0.3*†	434±12*†	3.03±0.16*†
Sedentary diabetic	557±18‡	13‡§	265±20‡	3.79±0.17‡
Exercised diabetic	569±30‡	11.5±1.0‡	272±28‡	3.82±0.11‡

Values are means ± SE. *Significantly different from sedentary diabetic group, $P < 0.05$. †Significantly different from exercised diabetic group, $P < 0.05$. ‡Significantly different from sedentary control group, $P < 0.05$. §Because all sedentary diabetic rats had glycated hemoglobin (HbA1c) levels higher than detectable by the method used, we used the highest detectable value (13%) for statistical purposes.

prompted by group differences, post hoc pairwise multiple comparisons were performed using Tukey's honestly significant difference test with the level of significance held at $P \leq 0.05$. All results are presented as means ± SE.

RESULTS

Glucometry, gravimetry, and physical activity challenge. Table 1 summarizes the results of glucometry and gravimetry at 9-wk diabetes duration, before MRI. Glucometric evidence showed uncontrolled hyperglycemia in both diabetic groups, SD and ED. Although there was a decrease in HbA1c levels with exercise training in diabetes, the effect was not significantly different from the SD group. Training did not produce a significant change in body mass of the ED group compared with the SD group. Meanwhile, the heart-to-body mass ratio was significantly increased in both SD (25%) and ED (26%) groups compared with the SC group, indicating cardiac hypertrophy in the former groups.

The mean activity capacity scores were 2.5 for the SC and ED groups. The mean activity capacity score of the SD group was 1.0, thus indicating compromised ability to sustain physical activity due to the diabetic state in the absence of training.

Cardiac cycle events. The mean R-R interval of the three groups was 210.0 ± 10.0 ms for SC, 212.5 ± 12.5 ms for SD, and 235.0 ± 15.0 ms for ED. Although the heart rate in the ED animals showed a trend toward decrease, it was not significantly different from the SC and SD rats.

The cardiac cycle cine image acquisition gated with ECG strong R wave resulted in a maximum LV volume at *phase 1* in all the groups. Hence it was taken as the end diastole (Fig. 2). Meanwhile the minimum LV volume occurred at *phase 6* in all the groups, and it was labeled as end systole (Fig. 2). The cardiac cycle was apportioned into 10 phases of similar duration in all 3 groups, thus allowing comparison of LV volume changes across the cardiac cycle (Fig. 3). For the statistical significance of difference between groups in the specific phase volumes of the LV cardiac cycle phase volumetric profiles, see Table 3. Overall, the time-dependent LV volumetric profile of the ED animals closely followed the profile of SC animals. Diabetes accompanied by a sedentary lifestyle triggered a major shift in the LV volumetric profile compared with the nondiabetic sedentary lifestyle.

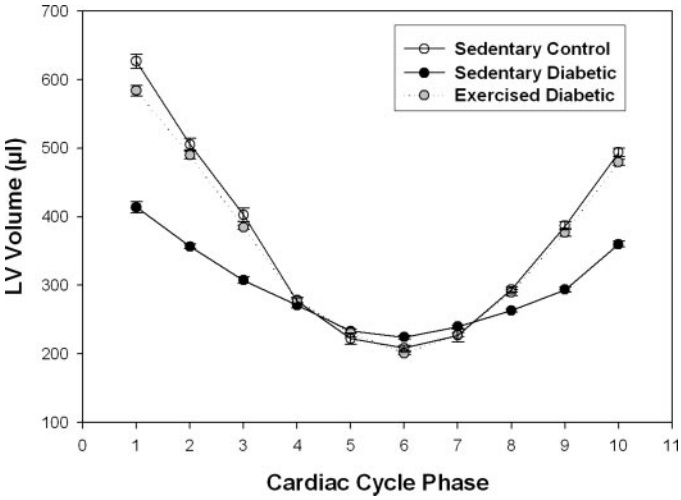

Fig. 3. Cardiac cycle phase volumetric profiles from the SC, SD, and ED groups. Values are means ± SE. See Table 3 for the details of statistical difference in phase volume between the groups for all 10 phases.

There was a 35% decrease in mean LV end-diastolic volume in the SD group compared with the SC group. Exercise training prevented this decrease in diabetes to a considerable extent with only 6% decrease compared with the nondiabetic sedentary lifestyle (Fig. 4*A*). In addition to the decrease in end-diastolic volume, the LV end-systolic volume was increased by 8% in the SD group compared with the SC group. Meanwhile, the end-systolic volume in the ED group was decreased by 4% compared with the SC group (Fig. 4*B*). Accordingly the LV stroke volume and ejection fraction were decreased (55 and 32%, respectively) in the SD group with a decrease (of 8 and 2%, respectively) in the ED compared with the SC group (Fig. 4, *C* and *D*, respectively). The LV output decreased by 58% in

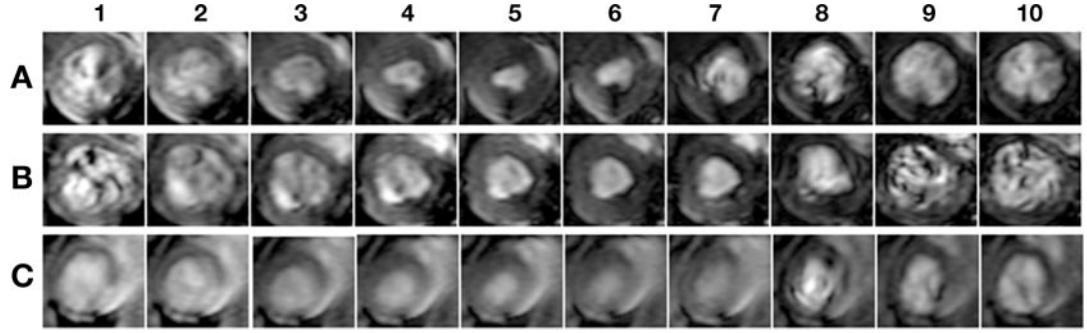

Fig. 2. Representative cardiac cycle phase images of the third LV slice (from apex) from sedentary control (SC; *A*), sedentary diabetic (SD; *B*), and exercised diabetic (ED; *C*) groups. The cardiac cycle was temporally resolved into 10 equally incremented phases indicated by the numbers above the images. End diastole occurred at *phase 1* and end systole occurred at *phase 6* in all 3 groups.

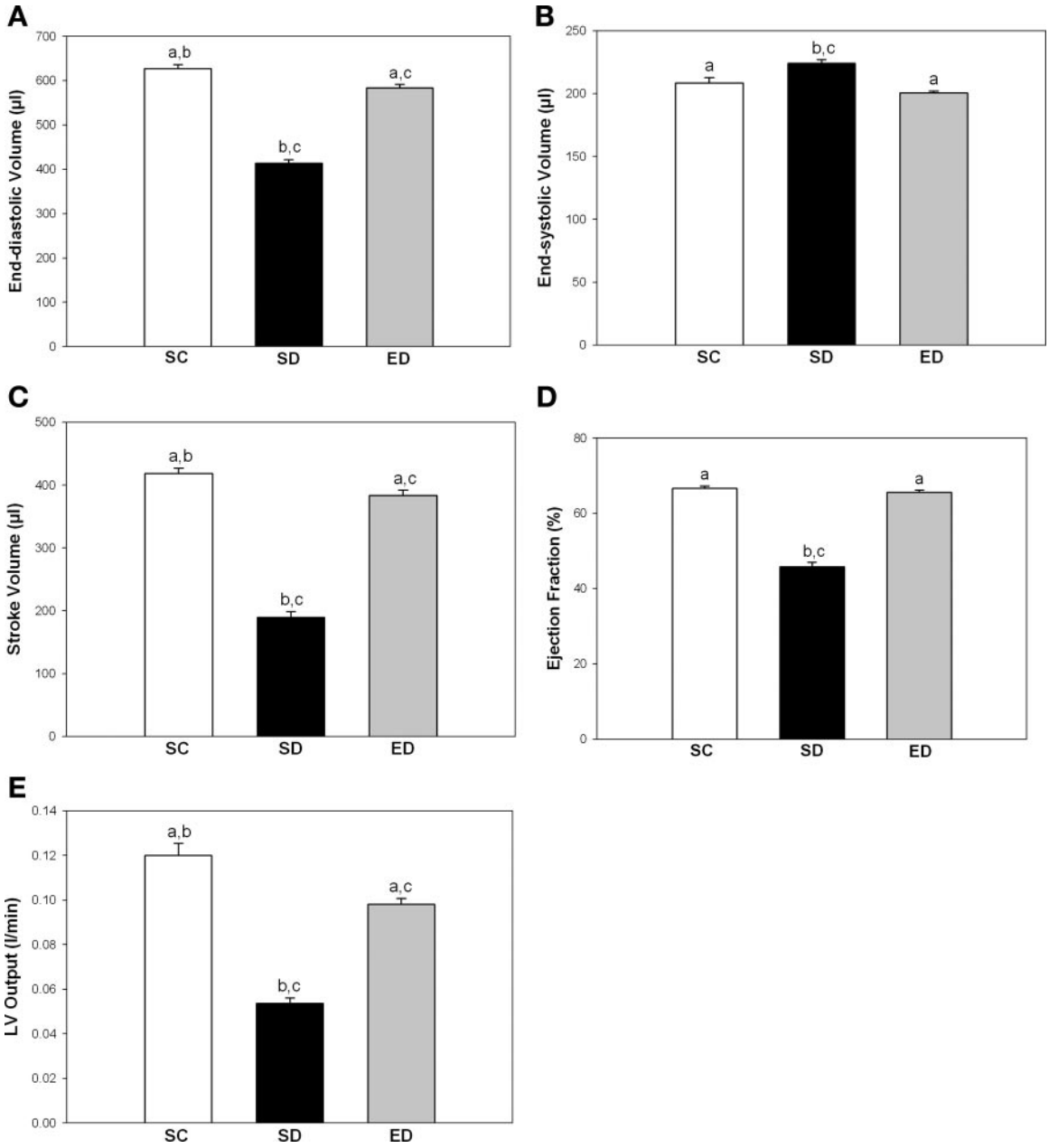

Fig. 4. Volumetric indexes of cardiac cycle events from SC, SD, and ED animals. LV end-diastolic (*A*) and end-systolic (*B*) volumes of all 3 groups were obtained directly from the phase volumetric profiles in Fig. 3. Derived indexes, i.e., LV stroke volume (*C*), LV ejection fraction (*D*), and LV output (*E*) were indicative of cardiac performance differences between groups. Values are means ± SE. [a]Significantly different from SD group, $P < 0.05$. [b]Significantly different from ED group, $P < 0.05$. [c]Significantly different from SC group, $P < 0.05$.

SD group and 25% in the ED group compared with the SC group, indicating that exercise training was able to prevent the decline in LV output that accompanies a sedentary lifestyle in diabetes (Fig. 4*E*). It should be noted that the difference between groups in the LV output was the result of differences in the stroke volume because the heart rate was not different between groups as mentioned earlier.

Table 2 summarizes the body mass-normalized LV cardiac cycle parameters along with myocardial volume for all three groups of animals. The increase in body mass-normalized myocardial volume in both SD and ED groups compared with the SC group corroborates the gravimetric results, suggesting LV hypertrophy in both diabetic groups. The body mass normalization, however, abrogated the difference in all the aforementioned cardiac cycle parameters except the end-systolic volume between the SC and SD groups.

The indexes of the LV systolic hemodynamics from all three groups are presented in Fig. 5. The estimated mean LV systolic flow velocity was decreased in SD group (97%) compared with SC group, whereas it was increased in the ED group (3%) (Fig. 5*A*). The mean LV systolic flow acceleration vector of the SD group showed deficits in both magnitude (97% decrease) and direction compared with the SC group (Fig. 5*B*). The flow acceleration decrease in the ED group was 11% compared with

Table 2. *Body mass-normalized values of LV volume characteristics*

Parameter	Sedentary Control	Sedentary Diabetic	Exercised Diabetic
Myocardial volume, mm^3/g	1.14±0.12*†	2.06±0.30‡	2.05±0.10‡
End-diastolic volume, μl/g	1.49±0.06†	1.59±0.15†	2.19±0.17*‡
End-systolic volume, μl/g	0.48±0.01*†	0.86±0.06‡	0.75±0.05‡
Stroke volume, μl/g	0.97±0.05†	0.73±0.09†	1.44±0.12*‡
LV output, $\mu l \cdot min^{-1} \cdot g^{-1}$	0.28±0.02	0.21±0.02†	0.37±0.03*

Values are means ± SE. LV, left ventricular. *Significantly different from sedentary diabetic group; $P < 0.05$. †Significantly different from exercised diabetic group, $P < 0.05$. ‡Significantly different from sedentary control group, $P < 0.05$.

controls with no directional deficit. Flow jerk was also decreased in the SD group (81%) compared with the SC group (Fig. 5*C*). The identical jerk values observed in both the SC and ED groups were the inevitable consequence of the simple numerical techniques (third-order curve fitting followed by computation of derivatives) utilized in this study. Because the time volumetric profiles of the SC and ED groups were nearly identical for the cardiac cycle systole (Fig. 3, Table 3), the curve-fitting technique produced identical third-order coefficients for both groups that remained the same for the third derivative of LV volume with respect to time, i.e., flow jerk.

DISCUSSION

The major findings of this series of noninvasive cardiac functional evaluation in diabetes are that the deterioration of cardiac cycle events at the subchronic stage of DCM could be prevented (i.e., parameters returning toward control levels yet with a significant difference from controls) and that some aspects of cardiac function could be improved (i.e., parameters indistinguishable from control values) with long-term exercise training. Hence exercise training might prove to be an effective adjunct to other possible modes of prevention and treatment of DCM. Specifically, the decrease in end-diastolic volume that accompanies DCM was prevented by endurance training. In addition, exercise training also improved the increase in end-systolic volume that occurs in sedentary diabetes. Accordingly, the deterioration of stroke volume was prevented and ejection fraction was improved with exercise training in diabetes. The decrease in LV output also improved with exercise training in diabetic animals. These results were suggestive of an overall improvement of the abnormalities of cardiac cycle events in the diabetic animals with exercise training. This first MRI evaluation of exercise-induced benefits also confirms the previous results of other invasive procedures. For instance, cardiac functional deficits, including a reduced cardiac output, under the baseline working mode of an isolated LV working heart preparation attenuated with exercise training in the spontaneously diabetic biobreeding rats (41).

The major advantage offered by the animal model used in this study is that it allows us to study the effect of therapeutic interventions on the diabetic heart disease chiefly due to DCM without the overlapping effects of cardiac macrovascular disease (16). However, we must recognize that, in addition to hyperglycemia, the extreme catabolic state of the animals is likely to contribute to the myocardial dysfunction in this model. Hence the exercise training-induced changes in the diabetic LV in this study can be interpreted as the effects of training on the functional complications of DCM. The insignificant difference in the mean R-R interval between the three groups allowed us to compare their volumetric profiles against a common-phase domain. Thus our results confirm the previous report that an 8-wk endurance training program in the same animal model of diabetes failed to alter the heart rate of trained animals (14). The lack of difference in baseline R-R intervals in SD and ED groups rules out the confounding effects of defective cardiac chronotropism on the cardiac cycle events evaluated in this study.

The body mass and plasma glucose characteristics of the diabetic rats in this study were reminiscent of a model of uncontrolled Type 1 diabetes. The increased heart-to-body mass ratio in the SD and ED groups compared with the SC group was suggestive of cardiac hypertrophy in the former groups. LV hypertrophy in the diabetic groups was confirmed by direct myocardial volumetry (Table 2). The insignificant difference between the SD and ED groups in HbA1c levels reiterated previous results that plasma glucose control cannot be achieved by exercise training alone in Type 1 diabetes (25, 41, 44). Exercise training also failed to significantly alter the body mass in the diabetic rats. These results suggest that the animal model used in this study was able to recapitulate the general features of Type 1 diabetes, however, with extreme catabolic state. Hence these results can be compared with similar intervention studies that utilized in vitro or invasive in vivo methods for cardiac functional assessment in the past (4, 31, 41). Although the moderate-endurance training protocol used in this study was previously shown to attenuate the myocardial structural defects in this rat model of diabetic cardiomyopathy (34), whether the exercise induced structural benefits on the diabetic myocardium were accompanied by improvements in the cardiac cycle events in vivo was not clear until this report.

The defect of cardiac pump function in diabetes has been attributed to the deterioration of function in the active components (for example, myocardial contractile and Ca^{2+} signaling proteins) with questionable changes in the passive components (for example, myocardial collagen) (44). Meanwhile, we speculate that the cardiac pump defects in our SD group might be the result of functional deterioration involving both the passive and active components (20, 21). The attenuation of cardiac pump defects in ED group was suggestive of therapeutic benefits on both the passive and active components in this study. For example, an interesting observation was noted with the exercise-induced benefits on end-diastolic volume in this study that parallel the benefits conferred by the angiotensin-converting enzyme inhibitor captopril in diabetes (1). The similarity between cardiac functional benefits resulting from two different modes of treatment (exercise therapy and captopril therapy) suggests a shared therapeutic mechanism, perhaps

at the level of myocardium at this stage of DCM. The prevention of aberrant LV end-diastolic volume in diabetes with exercise training suggests a role for exercise in improving the compliance of diabetic LV. Confirmation of identical effect on this parameter with a drug (captopril) in diabetes, and the possibility of a shared therapeutic mechanism between drug and training in the form of reduced interstitial fibrosis (1, 34) suggest that the trained group in this study might have benefited from the improvements in the passive components of cardiac pump function. Meanwhile, the exercise-induced conditioning effect might be speculated for the improvement in active components of cardiac pump function in diabetes, chiefly due to the benefits of training in improving the contractility of LV in diabetic animals (26, 42). Exercise training in our study improved the systolic volume dysfunction that occurred with sedentary lifestyle in diabetes. The exercise-induced benefits on systolic function in diabetes have been shown to manifest as efficient contractility of cardiomyocytes (6) and energy mobilization from mitochondria (25, 27). These earlier results interpreted in view of our noninvasive evidence for improved cardiac pump function provide a renewed explanation for the possibility of exercise-induced benefits on both diastolic and systolic cardiac pump function in diabetes. These results also demonstrate the enormously beneficial effect of exercise on this otherwise nearly fatal catabolic condition.

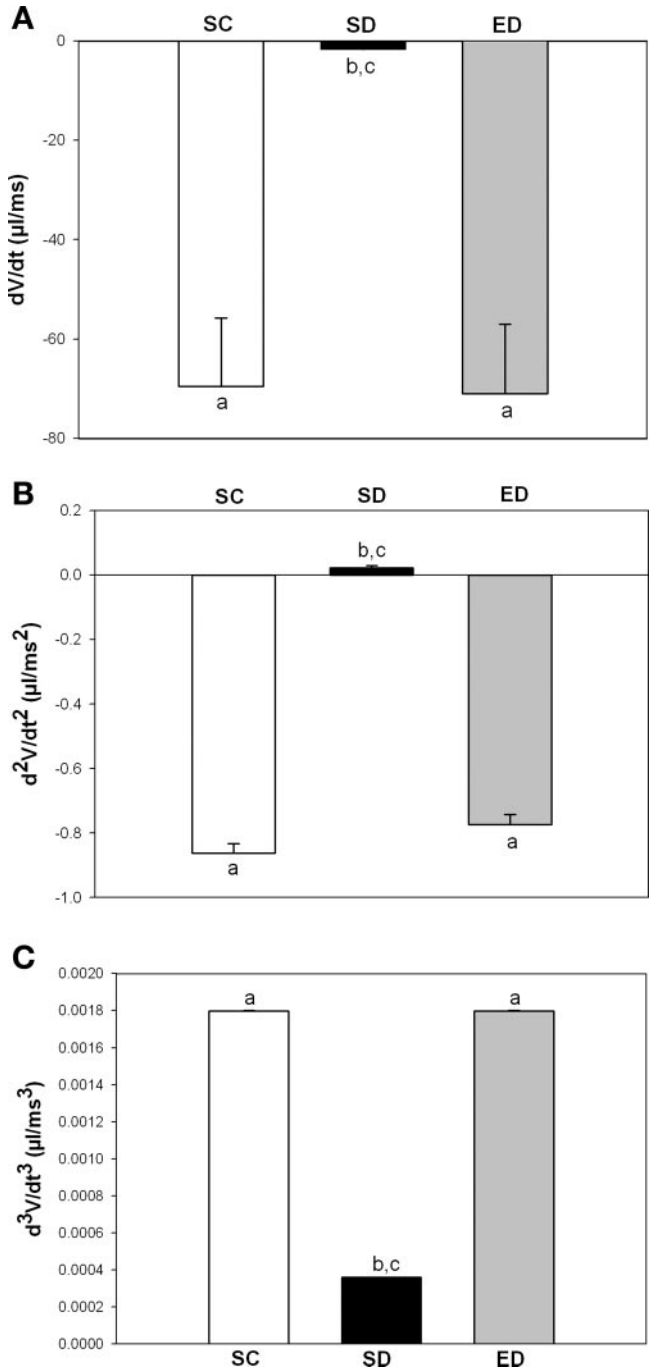

Fig. 5. LV systolic hemodynamic indexes from SC, SD, and ED animals. LV systolic hemodynamic measures were estimated from the derivatives of the third-order polynomial fit of the cardiac cycle systolic phase volume components (*phases 1-6*). Values are means ± SE of the instantaneous rates of change that correspond to the phase domains within the systole. First, second, and third derivatives of LV volume (V) with respect to time (*t*) [i.e., dV/dt (*A*), d^2V/dt^2 (*B*), and d^3V/dt^3 (*C*)] were taken as indexes of systolic ventricular flow velocity, acceleration, and jerk, respectively. [a]Significantly different from SD group, $P < 0.05$. [b]Significantly different from ED group, $P < 0.05$. [c]Significantly different from SC group, $P < 0.05$.

Table 3. *Group differences in cardiac cycle phase volumes*

Cardiac Cycle Phase	Groups		
	Sedentary control	Sedentary diabetic	Exercised diabetic
Phase 1	*†	†‡	*‡
Phase 2	*	†‡	*
Phase 3	*	†‡	*
Phase 4	NS	NS	NS
Phase 5	NS	NS	NS
Phase 6	*	†‡	*
Phase 7	NS	NS	NS
Phase 8	*	†‡	*
Phase 9	*	†‡	*
Phase 10	*	†‡	*

NS, not significant. *Significantly different from sedentary diabetic group, $P < 0.05$. †Significantly different from exercised diabetic group, $P < 0.05$. ‡Significantly different from sedentary control group, $P < 0.05$.

All the body mass-normalized parameters of the cardiac cycle events in the SD group except the end-systolic volume approached control values in our study. This was not unexpected as the SD group used in this study had uncontrolled diabetes along with body wasting. However, body mass-normalized cardiac functional profiles require cautious interpretation because body mass does not satisfy the assumptions of homoscedasticity and hence fails as an appropriate scaling variable for cardiac performance parameters (5). This interpretive limitation on body mass-normalized cardiac performance parameters between groups was overcome however, with the employment of a treadmill running task at the termination of experiments as a means to discern the ability of metabolically active lean tissue to sustain physical challenge. If we assumed that the insignificant difference between the body mass-normalized parameters of our SC and SD groups may not be the optimal indicator of cardiac function, then a challenge that would engage the metabolically active lean tissue of the animal would not be sustained by the presumed suboptimal cardiac performance of the SD group unlike the SC group. The results of physical activity challenge indicated that the SD group (activity capacity score of 1.0) was not able to overcome the

challenge, whereas the SC group (score of 2.5) was successful, although both groups were inexperienced runners. The failure of SD group on the activity challenge in the face of insignificant differences in the body mass-normalized cardiac parameters between the SC and SD group is evidence for a poor overall cardiac performance in the SD group. Exercise training in diabetes was, however, able to overcome the physical activity challenge although the catabolic state and the severity of diabetes in the ED group would have prevented it presumably from exceeding the functional capacity of the SC group had we intensified the challenge further.

Although diastolic dysfunction presents as the early marker of DCM (32), systolic dysfunction is common in diabetic individuals with poor glycemic control during the progression of DCM (15), a feature well demonstrated by the animal model used in this study. The evidence from volumetric profiles obtained in this study along with indications from previous reports (22, 39) for systolic dysfunction in this model of DCM motivated further exploration of the systolic dynamics of the cardiac cycle in diabetes and its response to exercise training. The LV systolic hemodynamic indexes obtained in this study supported the role for exercise in improving cardiac pump function in diabetes. Although oblique, the first, second, and third time derivatives of LV systolic phase volumes nevertheless provided useful indications of ventricular flow velocity, acceleration, and jerk, respectively, for comparison between groups in this study. A spherical coordinate system was perused for LV systolic hemodynamic correlations prompted by the spherical geometry of LV cavities in the SD and ED groups (Loganathan R and Smirnova IV, unpublished observations) due perhaps to the hypertrophic remodeling of the LV. The numerical methods used in our study to obtain the mean ventricular systolic flow velocity (dV/dt) in SC group provided values (70 cm^3/s) comparable to those obtained by direct phase-contrast motion-encoding methods (50 cm/s in-plane flow velocity), the later also noting a maximum in-plane chamber flow velocity of 70 cm/s during systole (43). In our study, the abnormalities of ventricular systolic flow velocity, flow acceleration (both magnitude and directional deficits), and flow jerk in diabetes was improved with exercise training, thus demonstrating the exercise-induced benefits on LV systolic hemodynamics in diabetes.

In summary, the first MRI evaluation, to our knowledge, of exercise-induced benefits on the diabetic heart demonstrates that moderate-endurance training, in addition to attenuating cardiac structural defects (34), also improves cardiac cycle volume and hemodynamic profiles. Interestingly, the functional benefits on the diabetic heart occurred in the absence of plasma glucose control or significant benefits on the body mass of the diabetic animals, confirming the results obtained previously via invasive approaches (4, 18, 31, 41). Taken together, these physiological results nevertheless suggest the possibility of locally occurring molecular correlates of training-induced benefits on cardiac pump function independent of systemic glucose homeostasis in diabetes mellitus. The benefits of training on the efficacy of diabetic cardiac function derived from the use of various animal models, however, are not without translational limitations to human Type 1 diabetes. The major limitation of this study is the acute diabetic state, including the extreme catabolic state of the animals accompanied by permanent hyperglycemia and loss of body mass, which does not represent the current clinical course of long-term diabetes that elicits impaired myocardial function. Hence future experiments will require studies in hyperglycemic animals that have reasonable maintenance of body mass to provide a valid model to address cellular and molecular mechanisms of DCM. This study was, however, able to demonstrate the tremendous beneficial effects of exercise, despite the catabolic state of the rats, and further verified MRI as a promising tool for the noninvasive evaluation of cardiac function.

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