Prevention of Ischemic Heart Failure by Exercise in Spontaneously Diabetic BB Wor Rats Subjected To Insulin Withdrawal

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Poor metabolic control resulting from insulin withdrawal in chronic type 1 diabetic rats results in ischemic heart failure. In the present study, we determined whether heart failure occurs in acute type 1 diabetic rats following insulin withdrawal and if prior exercise training can prevent this dysfunction. Four-week-old diabetic prone BB Wor rats were either sedentary or moderately exercised by daily treadmill running. Training was discontinued at the onset of diabetes. Isolated working rat heart function was then assessed in the following groups: diabetic resistant, uncontrolled sedentary diabetic (USD), controlled sedentary diabetic (CSD), uncontrolled trained diabetic (UTD), and controlled trained diabetic (CTD) rats. To induce an uncontrolled state, insulin treatment was withheld for 24 hours. During increased metabolic demand and reperfusion following ischemia, heart rate, contractility, and cardiac output were depressed in hearts from USD animals. Treatment with insulin prevented the depressions in cardiac performance from occurring. Hearts from UTD rats perfused under these conditions showed comparable cardiac function to that seen in the controlled state. This occurred despite poor metabolic control, reflected by elevated levels of plasma glucose and free fatty acids. Our results indicate that metabolic deteriorations in acute diabetes result in ischemic heart failure. However, this cardiac dysfunction can be prevented with exercise training.

EPIDEMIOLOGICAL STUDIES indicate diabetes as a major risk factor for developing cardiovascular disease.[1-3] Individuals with diabetes are prone to coronary artery disease, myocardial infarction (MI), and congestive heart failure.[4] In addition, diabetic individuals have a higher incidence of complications following an acute coronary syndrome compared to nondiabetic individuals, as evidenced by higher morbidity and mortality rates post-MI.[1,5,6] Indeed, diabetes and ischemic heart disease interact to accelerate the progression of myocardial dysfunction.[7] Moreover, recent epidemiological data support the important role of glycemic control in the prevention of heart failure in diabetic individuals.[8,9]

In addition to diet and pharmacological therapy, exercise training is an important adjunct in the treatment of type 1 and type 2 diabetes. Regular exercise reduces the risk of cardiovascular disease,[10-12] decreases the severity and complications of ischemic events,[13-14] and can prevent the onset of type 2 diabetes.[15] Experimental studies in diabetic animals clearly demonstrate that exercise improves cardiac performance[16,17] and reduces ischemic failure,[14] and in doing so improves heart function during postischemic recovery.[18] These benefits of exercise can be attributed, in part, to enhanced energy metabolism at the cellular level. In fact, exercise increases insulin sensitivity,[19-21] lowers plasma lipid levels,[22] and increases heart carnitine content.[23] As a result, exercise can prevent the suppression of glucose metabolism that not only normally occurs in diabetes, but also is considered a contributing factor to the development of cardiac dysfunction.[18,24]

Experimental studies using a model of type 1 diabetes have demonstrated that poor metabolic control, resulting from acute insulin withdrawal, accelerates ischemic heart failure.[25] In hearts from chronically diabetic rats, heart failure was associated with increased plasma levels of free fatty acids and a concomitant suppression in myocardial glucose utilization.[26] Taken together, these studies indicate that acute changes in the metabolic status of type 1 diabetic rats significantly affect the severity of myocardial ischemia. To date, no studies have addressed whether poor metabolic control, resulting from insulin withdrawal, contributes to ischemic heart failure in early onset type 1 diabetes. In addition, it is not known if exercise training can prevent ischemic injury that may occur under these conditions. Therefore, this study was designed to determine if acute insulin withdrawal contributes to ischemic failure in newly diagnosed type 1 diabetic rats, and if so, whether exercise training suppresses this heart failure response. Our results indicate that insulin withdrawal is associated with ischemic heart failure in newly diagnosed type 1 diabetic rats. Prior exercise training is clearly of benefit and protects these hearts from ischemic injury, regardless of metabolic control.

MATERIALS AND METHODS

Animal Model of Diabetes

Diabetic resistant and diabetic prone male BB Wor rats, 21 to 30 days old, were purchased from Biomedical Research Models (Worcester, MA). The diabetic resistant BB Wor rat is a strain genetically engineered to not develop type 1 diabetes during their lifespan. Conversely, the diabetic prone BB Wor rat is characterized by spontaneous development of autoimmune pancreatic islet cell destruction and insulitis, which occurs when rats are approximately 70 days old.[27] As a model of diabetes, the BB prone rat is representative of type 1 diabetes seen in humans. Diabetic prone rats were examined daily for the signs of diabetes, which included increased food/water consumption and increased urine output. The diagnosis of diabetes was confirmed by assessing urine for the presence of glucose and ketone bodies using test strips (Keto-Diastix, Bayer, Elkhart, IN). Following the onset of diabetes, rats were given twice daily intrperitoneal protamine zinc insulin (Blue Ridge Pharmaceuticals, Greensboro, NC) injections dosed at 0.6

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to 0.8 U/100 g body weight. All animals used in this study were cared for in accordance to the recommendations in The Guide for the Care and Use of Laboratory Animals, National Institute of Health, Publ. No. 85-23, 1986.

Exercise Training Protocol

All diabetic prone rats underwent a 7-day adaptation period to mild treadmill running. Rats not willing to run were assigned into a sedentary group. Training was performed until the onset of diabetes, which occurred when animals were 9 to 10 weeks old. Training was performed on a compact electric treadmill (Columbus Instruments, Columbus, OH) using a modification of the exercise training protocol previously described.[14] Briefly, rats were subjected to 5 to 6 weeks of moderate-intensity exercise training 5 days per week, 20 minutes per day, starting at 17 m/min for the first 2 weeks. The intensity was then increased to 22 m/min for the remaining 3 to 4 weeks. Throughout the entire training protocol, the grade of the treadmill was maintained at 5 degrees.

Induction of Acute Change in Metabolic Control

Following confirmation of diabetes, animals were removed from the exercise protocol and allowed to rest for 72 hours before experimentation. This rest period was selected to eliminate the effects of acute bouts of training that occur during a program of regular exercise. Twenty-four hours prior to experimentation, controlled trained diabetic rats (CTD) received insulin treatment, while uncontrolled trained diabetic rats (UTD) had insulin withheld for 24 hours. Withholding insulin for this period, as expected, produces deteriorations in metabolic control exemplified by hyperglycemia and elevated plasma levels of free fatty acids. This acute change in metabolic control is known to contribute to ischemic heart failure in the BB Wistar rat.[25,26] Rats in the sedentary groups underwent the same 72-hour protocol following confirmation of diabetes; controlled sedentary diabetic rats (CSD) received insulin and uncontrolled sedentary diabetic rats (USD) had insulin withheld 24 hours before experimentation. On the day of experimentation, all rats that had insulin administered during the previous 24-hour period received insulin 2 hours before their hearts were excised and mounted on a perfusion apparatus. A group of nontrained age-matched diabetic resistant rats (DR) served as the control group.

Heart Perfusions

The isolated left ventricular working heart preparation was used to assess the effects of exercise training and acute changes in metabolic control on heart function. On the day of experimentation, rats were euthanized with CO_2 gas followed by decapitation. After the hearts were excised, the aortas were cannulated and perfused retrogradely in Langendorff mode with Krebs-Henseleit buffer (pH 7.4, 37°C) containing 1.75 mmol/L calcium, 11 mmol/L glucose, and oxygenated with 95% O_2–5% CO_2 gas. In the Langendorff mode, excess tissue was trimmed and the opening of left atrium was cannulated. Hearts were then switched to working mode and perfused with Krebs-Henseleit buffer (pH 7.4, 37°C) containing 11 mmol/L glucose and 1.2 mmol/L palmitate bound to 3% bovine serum albumin. The working mode buffer contained concentrations of fatty acids commonly found during myocardial ischemia,[28] as well as in uncontrolled diabetes.[25] Hearts were aerobically perfused for 15 minutes at 15 cm H_2O preload and 100 cm H_2O afterload. The afterload was then raised to 140 cm H_2O for 15 minutes to increase the workload placed on the heart prior to ischemia. After this period, the afterload was reduced back to 100 cm H_2O for a 10-minute stabilization period. Hearts were then subjected to 20 minutes of global, no-flow ischemia by clamping the preload and afterload line. Following ischemia, flow was abruptly restored and hearts were reperfused for 30 minutes. Throughout the entire perfusion, cardiac function was measured using a Digi-Med Heart Performance Analyzer (Louisville, KT) interfaced with a Pentium computer. In-line flow probes (Transonic Systems, Ithaca, NY) in the preload and afterload lines measured cardiac output.

Table 1. Body Weight and Serum Metabolite Concentrations

Group	Body Weight (g)	Glucose (mmol/L)	Free Fatty Acids (mmol/L)
DR	335 ± 14	8.8 ± 0.3	0.23 ± 0.03
CSD	285 ± 7	8.8 ± 2.4	0.22 ± 0.14
USD	257 ± 17	26.8 ± 2.0*†	0.81 ± 0.13*†
CTD	258 ± 15	5.5 ± 0.6‡	0.14 ± 0.03‡
UTD	287 ± 18	24.7 ± 2.9*†§	0.81 ± 0.27*†§

NOTE. Values are mean ± SEM for 4 to 6 animals each group.

Abbreviations: DR, diabetic resistant; CSD, controlled sedentary diabetic; USD, uncontrolled sedentary diabetic; CTD, controlled trained diabetic; UTD, uncontrolled trained diabetic.

*Significantly different from DR, $P < .05$.

†Significantly different from CSD, $P < .05$.

‡Significantly different from USD, $P < .05$.

§Significantly different from CTD, $P < .05$.

Metabolite Assays

Blood samples were collected in chilled heparinized tubes following decapitation and centrifuged for 3 minutes at 3,000 rpm. The plasma was collected, stored at −20°C, and later analyzed for glucose and free fatty acids using commercially available kits from Sigma Diagnostics (St Louis, MO) and Roche Diagnostics (Basel, Switzerland), respectively.

Statistical Analysis

All values are reported as the mean ± SEM. Statistical significance between group means was determined by an analysis of variance (ANOVA) followed by a Student-Newman-Keuls test. A P value less than .05 was considered statistically significant.

RESULTS

Plasma Metabolites

Plasma levels of glucose and free fatty acids are shown in Table 1. As expected, reflecting acute insulin withdrawal, plasma levels of glucose and free fatty acids were elevated in USD and UTD rats compared to all other groups. Exercise training was not beneficial in lowering glucose or free fatty acid levels in the UTD group, which is consistent with the observation that glycemic control cannot be achieved with exercise alone in type 1 diabetes.

Baseline Left Ventricular Function

The effects of exercise training and insulin withdrawal on left ventricular function during the initial 15-minute aerobic perfusion are shown in Fig 1. A significant depression in heart rate (Fig 1A) and cardiac output (Fig 1B) was seen in hearts from USD rats. However, these depressions in cardiac function were prevented with insulin treatment and with prior exercise training. In fact, no deterioration in function was observed in the UTD group, despite the presence of poor metabolic control.

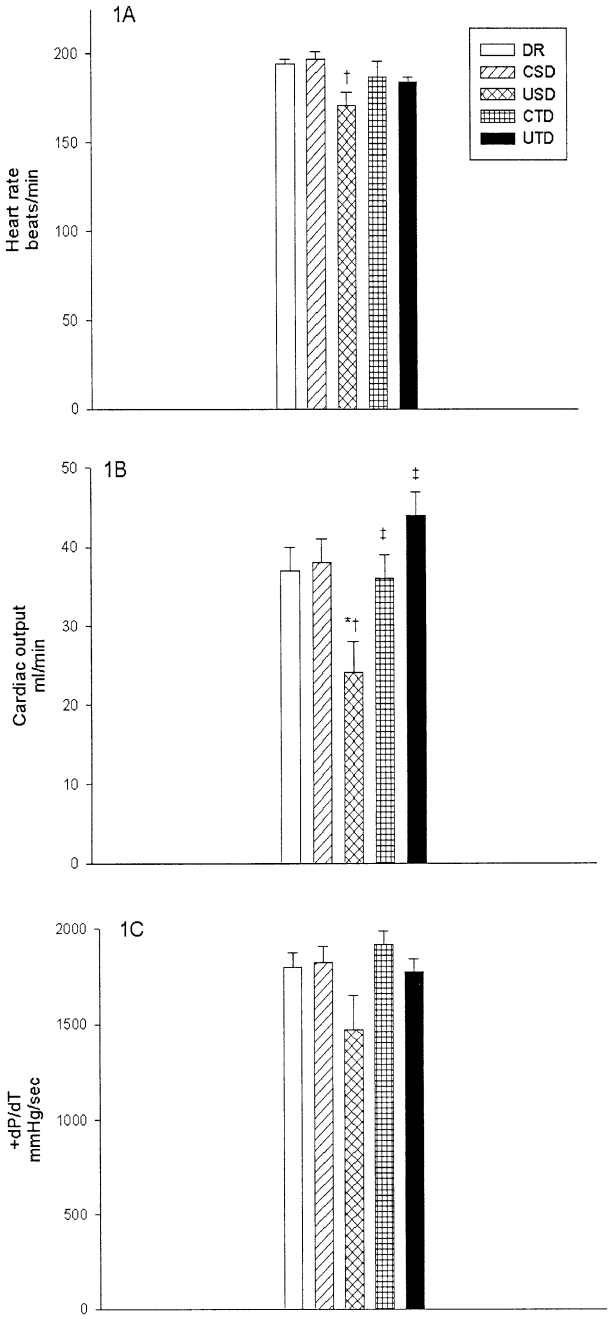

Fig 1. (A) Heart rate, (B) cardiac output, and (C) +dP/dt during the initial 15-minute aerobic perfusion at a constant workload of 15 cm H_2O left atrial filling pressure and 100 cm H_2O afterload. Values are mean ± SEM for 6 hearts in each group. *Significantly different from DR, $P < .05$. †Significantly different from CSD, $P < .05$. ‡Significantly different from USD, $P < .05$.

Increased Afterload Challenge

Following the initial 15-minute aerobic perfusion, the aortic afterload resistance was changed to 140 cm H_2O to increase metabolic demand on the hearts. At this workload, function expressed as heart rate (Fig 2A), cardiac output (Fig 2B), and contractility (+dP/dt) (Fig 2C) was depressed in USD hearts. These depressions were prevented by insulin treatment. Under these conditions of increased workload, exercise training was beneficial on heart function. Even with insulin withdrawal,

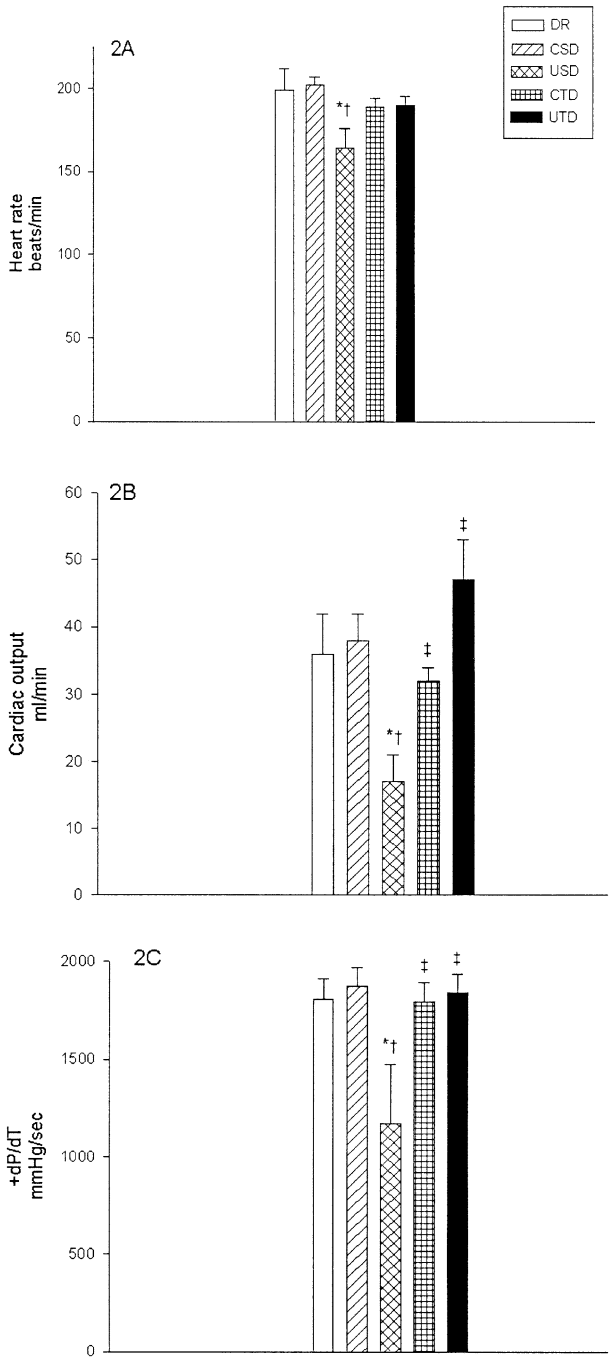

Fig 2. (A) Heart rate, (B) cardiac output, and (C) +dP/dt during increased metabolic demand at 15 cm H_2O left atrial filling pressure and 140 cm H_2O afterload resistance. Values are mean ± SEM for 6 hearts in each group. *Significantly different from DR, $P < .05$. †Significantly different from CSD, $P < .05$. ‡Significantly different from USD, $P < .05$.

Table 2. Cardiac Parameters During the Equilibration Period Prior to Ischemia

Group	HR (beats/min)	PSP (mmHg)	EDP (mm Hg)	CO (mL/min)	+dP/dt (mm Hg/s)
DR	209 ± 9	109 ± 3	46 ± 2	43 ± 5	1,917 ± 132
CSD	210 ± 6	110 ± 3	46 ± 2	46 ± 6	1,974 ± 128
USD	173 ± 14†	102 ± 6	53 ± 2	23 ± 6*†	1,323 ± 282
CTD	193 ± 6	114 ± 4	49 ± 2	39 ± 3‡	1,920 ± 97
UTD	199 ± 4	115 ± 3	44 ± 2‡	55 ± 6‡	2,074 ± 141‡

NOTE. Values are mean ± SEM for 6 hearts in each group.

Abbreviations: DR, diabetic resistant; CSD, controlled sedentary diabetic; USD, uncontrolled sedentary diabetic; CTD, controlled trained diabetic; UTD, uncontrolled trained diabetic. HR, heart rate; PSP, peak systolic pressure; EDP, end diastolic pressure; CO, cardiac output; +dP/dt, positive pressure development per unit time.

*Significantly different from DR, $P < .05$.

†Significantly different from CSD, $P < .05$.

‡Significantly different from USD, $P < .05$.

§Significantly different from CTD, $P < .05$.

hearts from trained rats were able to maintain function at this increased workload challenge.

Equilibration Period Prior to Ischemia

Following the workload challenge, the aortic afterload was returned to 100 cm H_2O for 10 minutes prior to ischemia. The results are shown in Table 2. USD rats displayed the same depressions in heart function seen throughout the perfusion compared to all other groups, with the exception of +dP/dt. These depressions were prevented with either insulin treatment, or prior exercise training irrespective of metabolic control.

Recovery of Function During Reperfusion

The effects of insulin withdrawal and exercise training on recovery of left ventricular function following ischemia are shown in Table 3 and Fig 3. Recovery of heart rate, cardiac output, and +dP/dt in hearts from USD rats was significantly depressed compared to all other groups (Fig 3). However, this was clearly not the case in hearts from UTD rats. In fact, recovery of function following ischemia in these hearts was similar to the DR, CSD, and CTD groups. When recovery of mechanical of function following ischemia is expressed as percent recovery, cardiac output and +dP/dt were depressed in hearts from USD animals compared to all other groups (Table 3).

DISCUSSION

This study has highlighted the importance of metabolic control and underlined the role of exercise training as an adjuvant in the management of diabetes and prevention of diabetes-related sequelae. Our results indicate that changes in metabolic control, resulting from insulin withdrawal, are associated with depressed myocardial function in early-onset insulin-dependent diabetic rats. Mechanical function of uncontrolled sedentary diabetic hearts under normoxic conditions and during increased workload displayed reduced chronotropism, contractility, and cardiac output. When these hearts were subjected to global ischemia, significant postischemic mechanical dysfunction was observed. Another important finding was that exercise training before the onset of diabetes prevented ischemic heart failure, even in poorly controlled diabetic rats. In fact, there were no significant differences in function between hearts from uncontrolled trained diabetic and controlled trained diabetic hearts under normoxic conditions and following ischemia. Our findings provide further support to the notion that diabetic individuals are susceptible to a specific cardiomyopathy prior to the

Table 3. Percent Recovery Following 30-Minute Reperfusion

Group	HR (beats/min)	PSP (mm Hg)	EDP (mm Hg)	CO (mL/min)	+dP/dt (mm Hg/s)
DR	106 ± 5	93 ± 2	110 ± 2	97 ± 10	98 ± 5
CSD	109 ± 4	94 ± 1	103 ± 2	113 ± 9	102 ± 6
USD	87 ± 8	83 ± 4	101 ± 7	44 ± 8*†	44 ± 10*†
CTD	115 ± 4‡	90 ± 2	116 ± 5†	99 ± 7‡	90 ± 5‡
UTD	103 ± 7	90 ± 5	92 ± 4	100 ± 18‡	98 ± 17‡

NOTE. Values are mean ± SEM for 6 hearts in each group.

Abbreviations: DR, diabetic resistant; CSD, controlled sedentary diabetic; USD, uncontrolled sedentary diabetic; CTD, controlled trained diabetic; UTD, uncontrolled trained diabetic. HR, heart rate; PSP, peak systolic pressure; EDP, end diastolic pressure; CO, cardiac output; +dP/dt, positive pressure development per unit time.

*Significantly different from DR, $P < .05$.

†Significantly different from CSD, $P < .05$.

‡Significantly different from USD, $P < .05$.

§Significantly different from CTD, $P < .05$.

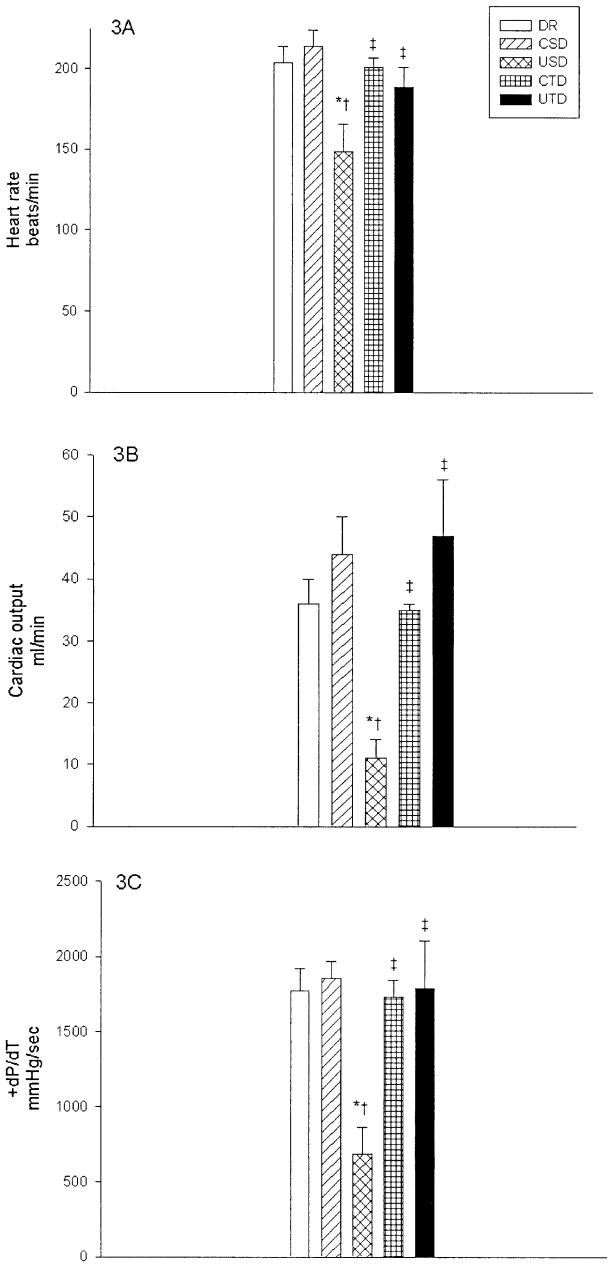

Fig 3. (A) Heart rate, (B) cardiac output, and (C) +dP/dt following 30-minute reperfusion at 15 cm H_2O left atrial filling pressure and 100 cm H_2O afterload resistance. Values are mean ± SEM for 6 hearts in each group. *Significantly different from DR, $P < .05$. †Significantly different from CSD, $P < .05$. ‡Significantly different from USD, $P < .05$.

onset of the complications of diabetes, such as coronary artery disease and cardiovascular disease.[29,30]

While many experimental studies have determined the effects of ischemia on heart function in chronic diabetes, relatively few studies have investigated cardiac dysfunction and ischemic injury in acute diabetes. Studies in rats treated 48 hours before experimentation with either streptozotocin[31,32] or alloxan[33] have demonstrated increased myocardial sensitivity to ischemia and depressed postischemic recovery of cardiac function. The results of studies using an acute model of diabetes are not attributed to the biochemical changes that occur during myocardial ischemia in chronically diabetic rats.[34] It was hypothesized that the mechanical failure seen in acute diabetes is caused by an accumulation in myocardial levels of fatty acid metabolites and depressed rates of myocardial glucose utilization.[25,26,33,35] Supporting the importance of glucose utilization is the observation that ischemic heart failure in diabetic rats subjected to poor metabolic control is associated with a reduction in myocardial glucose metabolism.[26,36]

A possible explanation for the increased susceptibility of uncontrolled diabetic hearts to ischemic injury is the increased reliance on fatty acid. In poorly controlled diabetes, glucose uptake and oxidation are impaired, causing the heart to rely almost exclusively on fatty acid metabolism for energy production.[37] Perfusing hearts from poorly controlled diabetic rats with 1.2 mmol/L palmitate abolishes myocardial glucose oxidation,[37,38] whereas hearts from well-controlled diabetic rats perfused under identical conditions maintain glucose oxidation capacity.[26] As shown in Table 1, plasma from uncontrolled sedendary diabetic rats contained concentrations of free fatty acids capable of inhibiting glucose utilization.[38] This concentration of fatty acids is similar to the concentration used in the perfusate for this study, and known to contribute to cardiac dysfunction in diabetic animals. Interestingly, exercise training conferred protection against cardiac dysfunction and ischemic injury despite poor metabolic control in trained diabetic rats, implicating an endogenous mechanism contributing to the beneficial effect of exercise.

Considerable evidence indicates that exercise training can retard or prevent the cardiac dysfunction that occurs in diabetes. Epidemiological studies have shown that exercise not only decreases the risk of cardiovascular disease[10-12] and complications following ischemic events,[13,14] but can also prevent the onset of type 2 diabetes.[15] In experimental studies, exercise training prevents the attenuation of contractile dysfunction associated with diabetes and benefits reperfusion recovery following ischemia.[14-18,39] The present findings are consistent with the benefits of exercise training in diabetes and this is the first study to clearly demonstrate that exercise training, prior to the onset of diabetes, confers protection against ischemic heart failure after the onset of diabetes occurs, regardless of metabolic control. Although the actual mechanism by which exercise exerts this beneficial effect was not determined, a possible mechanism may be enhanced myocardial glucose utilization.[22] It is well established that regular exercise training can prevent the decline in glucose transporter proteins and glucose oxidation in heart muscle that normally occurs in sedentary diabetic rats.[20,21] Preventing the decline in glucose metabolism would allow for glucose uptake and metabolism to occur under conditions of increased metabolic demand.[21,22]

In conclusion, clinical studies indicate diabetes as an independent risk factor for developing cardiovascular disease.[1-3] Diabetic individuals are also more susceptible to myocardial ischemic injury and have higher morbidity and mortality rates post-MI compared to the nondiabetic population.[1,5,6] These observations may be partly explained by clinical studies show-

ing a relationship between plasma free fatty acid levels and death after infarct.[40] If myocardial substrate utilization is shifted towards glucose use post-MI, by using a glucose-insulin-potassium infusion, a significant reduction in arrhythmias and morbidity is seen in diabetic persons. The findings of the present study corroborate these clinical observations. It was demonstrated that poor metabolic control, as a result of 24 hours of insulin withdrawal, causes elevated plasma free fatty acids and accelerates ischemic heart failure in sedentary diabetic rats. In contrast, insulin treatment prevented this heart failure. Moreover, exercise training confers protection against ischemic heart failure in diabetic rats, regardless of metabolic control. This study further emphasizes the deleterious impact of acute metabolic disturbances on ischemic injury in diabetes, and underlines the importance of exercise training in this population prone to heart disease.

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