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Impaired *in Vivo* Myocardial Reactivity to Norepinephrine in Diabetic Rats (42403)

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Abstract. The effects of long-term diabetes with and without insulin treatment on *in vivo* myocardial contractile activity were studied under basal conditions and as a function of intravenously infused norepinephrine. Diabetes was induced by iv injection of streptozotocin (50 mg/kg). Insulin-treated diabetic rats received 5 units per day of isophane insulin suspension. The duration of the study was 8 weeks. *In vivo* myocardial contractility measurements were performed in ketamine–xylazine-anesthetized rats using a miniature catheter-tip pressure transducer advanced through the right carotid artery into the left ventricle. Peak positive dP/dt and intraventricular developed pressure were comparable among the groups when measured under basal conditions; however, the magnitude of the response to variable doses of norepinephrine (6×10^{-12} to 6×10^{-8} mole/kg body wt) were significantly diminished in diabetic rats, but the sensitivity was unchanged. Negative dP/dt was decreased under basal conditions and in response to norepinephrine in diabetic rats. Insulin treatment to diabetic rats prevented these changes, but heart rate was elevated. These results demonstrate that the *in vivo* cardiovascular reactivity of diabetic rats to norepinephrine is significantly attenuated.

There is a growing body of evidence that diabetes mellitus is associated with myocardial dysfunction that is not attributable to preexisting coronary artery disease. The Framingham epidemiologic study has revealed an increased risk for congestive heart failure in diabetics as compared with nondiabetics (1). No correlation, however, was found in this study between the increased incidence of congestive heart failure and coronary heart disease. Intracardiac catheterization studies on diabetic patients have demonstrated a significant elevation in left ventricular end-diastolic pressure with reduced end-diastolic and stroke volumes (2). Again, no evidence of coronary occlusion was detected. More recently Mildenberger and co-workers have reported that one-third of diabetic patients studied who were managed with anti-hyperglycemic therapy and who lacked clinical evidence of heart disease, atherosclerosis risk factors, or other diabetic complications nevertheless exhibited a decreased ejection fraction during supine bicycle exercise (3). In view of this evidence, there is a growing awareness that a significant portion of the diabetic population is prone to developing primary myocardial abnormalities. Long-term diabetes has also been associated with autonomic neuropathy and changes in cardiovascular reactivity to vasoactive compounds (4, 5). The underlying biochemical mechanism(s) responsible for diabetic cardiomyopathy is unknown.

Studies on the diabetic heart from experimental animals have demonstrated significant alterations in cardiac performance in response to changes in pre- and afterloads and β-adrenergic receptor stimulation. Except for a few studies on large animals (6, 7), these studies have been performed in isolated papillary muscles or perfused hearts from alloxan or streptozotocin-induced diabetic rats (8–16). Although there are many advantages to this experimental approach, there are also problems. For example, there is the possibility that *in vitro* cardiac performance measurements may be altered by the transient period of ischemia that occurs when the heart is excised from the chest. The functional recovery of contractile activity may be different in hearts from control and diabetic rats. Moreover, the perfusion medium used in *in vitro* procedures may not approximate the true *in vivo* condition. Indeed, preliminary studies obtained in our laboratories indicate that the functional status of the diabetic heart is significantly and preferentially influenced by the substrate used in the perfusion medium. Thus, functional

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and metabolic analyses of the diabetic heart performed under these conditions cannot be assumed to unequivocally represent the *in vivo* status of the diabetic heart. Previously, the size disparity between commercially available intravascular cardiac catheters and the diameter of surgically accessible arteries in the rat prevented the performance of *in vivo* studies of cardiac performance in closed-chested diabetic rats. However, these technical constraints have been eliminated by the recent demonstration that such measurements are feasible in the rat using the technique developed by Kopp (17) which involves the intravascular insertion of a miniature solid-state catheter-tip pressure transducer into the left ventricle of anesthetized rats. Although this technique does not have the inherent questions associated with *in vitro* methods, there are other experimental considerations introduced with the *in vivo* approach. Anesthetic effects and the inability to precisely regulate preload, afterload, and heart rate may influence the assessments of myocardial performance in control and diabetic animals. Since both *in vitro* and *in vivo* methods of assessing cardiac performance introduce potentially significant but different methodologic variables, it is important to demonstrate a congruency between these two experimental approaches. In the present study the effects of long-term streptozotocin-induced diabetes with and without insulin treatment on *in vivo* cardiac contractile activity were assessed. Myocardial performance was measured at basal levels and as a function of intravenously infused norepinephrine.

Methods. *Induction of diabetes mellitus.* Diabetes was produced in 24 male rats of the Sprague–Dawley strain (250–275 g body wt, Sasco/King Animal Laboratories) by iv injection of streptozotocin, 50 mg/kg. Fourteen control rats were injected with an equal volume of vehicle, 0.01 *M* citrate buffer, pH 4.5. Seventy-two hours later the induction of diabetes was confirmed by the detection of urine glucose with Ames Keto-Diastix. Subcutaneous injection of 5 units/day of isophane insulin suspension was initiated in 12 of the diabetic animals 72 hr after induction of diabetes. The remaining 12 animals were untreated. All animals had free access to commercial chow and water throughout the 8-week duration of diabetes. The insulin-treated diabetic rats received their last injection of insulin approximately 6 hr prior to surgery.

In vivo assessment of cardiac contractile activity (17). Rats were anesthetized with ketamine (80 mg/kg) and xylazine (8 mg/kg) and placed dorsal side down on a styrofoam interfacing sheet on a 37°C Deltaphase isothermal pad to maintain body temperature during surgery. Needle electrodes were inserted into each limb for recording of ECG. A medial incision was made into the ventral surface of the neck and the right and left external jugular veins were isolated. An insulated silver wire electrode was inserted into the right atrium via the right jugular for recording the intracardiac electrogram. A reference electrode was inserted under the skin. The left jugular vein was catheterized with a saline-filled open-lumen catheter. Prior to insertion of this cannula, approximately 1 ml of blood was taken for measuring hematocrit and plasma glucose (18). The right common carotid artery was isolated and cannulated with a calibrated catheter-tip pressure transducer (Model PR-249, Millar Instruments). The catheter was advanced into the left ventricle. The intracardiac electrogram, left intraventricular pressure, positive and negative dP/dt, and heart rate were recorded with an Electronics for Medicine AR-6 simultrace recording system. These parameters were measured at basal levels following a 10-min postsurgical stabilization period, and following intravenous norepinephrine administration (6×10^{-12} to 10^{-8} mole/kg body wt).

Assessments of myocardial responsiveness to various doses of norepinephrine were performed in each animal in triplicate for each dose. Doses were injected as a single bolus at 2-min intervals following restoration of basal heart rate and left intraventricular pressure. For each animal, maximal electrical and mechanical responses to each norepinephrine dose were determined by analyzing peak effects that occurred in conjunction with a sinus electrical rhythm, and averaging the triplicate values obtained for each of the measured functional parameters. At the end of the experiment, the chest was opened and the heart excised and weighed.

Statistical methods. Group means and standard errors were calculated for each of the measured indices using the average values obtained from each animal. The data were eval-

uated for statistical significance by the one-way analysis of variance method and the Schéffé comparison procedure. A probability value of $P < 0.05$ was accepted as significant. The ED_{50} values for each group were calculated as described by Fleming *et al.* (19).

Results. At the end of 8 weeks, the induction of diabetes was again confirmed by measuring body weight and plasma glucose. One streptozotocin-treated rat was found to have normal plasma glucose and body weight and was dropped from the study. Diabetic rats had significantly lower body weight and elevated plasma glucose (Table I). Hematocrit was not affected. Heart weight was not changed, but the heart weight:body weight ratio was significantly increased in diabetic rats. Insulin treatment of diabetic rats prevented these changes.

In vivo myocardial contractile characteristics at basal levels and in response to intravenous norepinephrine are shown in Figs. 1 and 2. No differences in left ventricular peak positive dP/dt were found at basal levels among the three groups (Fig. 1a). Changes in positive peak dP/dt in response to all doses of intravenous norepinephrine were significantly attenuated in diabetic rats as compared to controls and insulin-treated diabetic rats. At the highest dose of norepinephrine, 6×10^{-8} mole/kg body weight, the control rats had a 32% greater increase in positive dP/dt than diabetic rats. Higher doses of norepinephrine usually were fatal. The average dose that produced 50% maximal effect (ED_{50}) in control, diabetic, and insulin-treated diabetic was calculated to be 1.7×10^{-9}, 2.88×10^{-9}, and 1.51×10^{-9} (mole/kg body wt), respectively; however, the values were not significantly different.

The rate of ventricular relaxation was assessed by measuring negative dP/dt, which corresponds to the maximum rate of left ventricular pressure dissipation, (Fig. 1b). Diabetic rats had significantly lower maximum negative dP/dt at basal levels and in response to each dose of norepinephrine. Values for control and insulin-treated diabetic groups were comparable.

Changes in peak left ventricular pressure in response to norepinephrine showed a similar intergroup pattern as that observed for positive and negative dP/dt (Fig. 2a). No differences were detected under basal conditions and at the lowest norepinephrine dose, but at the higher doses, diabetic rats exhibited significantly diminished responses. Insulin treatment of diabetic rats prevented this decline.

The effects of norepinephrine on heart rate in each of the three groups are shown in Fig. 2b. The recorded heart rate was measured when dP/dt was maximal. Norepinephrine infusion did not produce any significant increase in heart rate except at the largest dose. The lack of an increase at lower doses is most likely due to activation of the baroreceptor reflex. No significant differences were detected between control and diabetic rats, except for the last dose where the positive chronotropic response of control rats was significantly greater. The insulin-treated diabetic group was characterized by a significantly greater heart rate at basal levels and after the first three doses of norepinephrine as compared to the control or diabetic groups. The explanation for the more rapid heart rate is uncertain, but may be re-

TABLE I. EFFECTS OF STREPTOZOTOCIN-INDUCED DIABETES AND INSULIN TREATMENT ON PLASMA GLUCOSE, HEMATOCRIT, AND BODY AND HEART WEIGHTS

Group (n)	Plasma glucose (mg/dl)	Hematocrit (vol %)	Body wt (g)	Heart wt (g)	Heart wt/ Body wt (mg/g)
Control (14)	256 ± 25	49 ± 1	442 ± 11	1.02 ± 0.04	2.27 ± 0.09
Diabetic (11)	$601 \pm 18^{a,b}$	48 ± 2	$300 \pm 13^{a,b}$	0.96 ± 0.07	$3.22 \pm 0.22^{a,b}$
Insulin (12)	130 ± 31^{a}	51 ± 1	445 ± 9	1.12 ± 0.07	2.44 ± 0.13

Note. All values are means ± SE for n shown in parentheses.
[a] Significance from control, $P < 0.05$.
[b] Significance relative to insulin-treated diabetic group, $P < 0.05$.

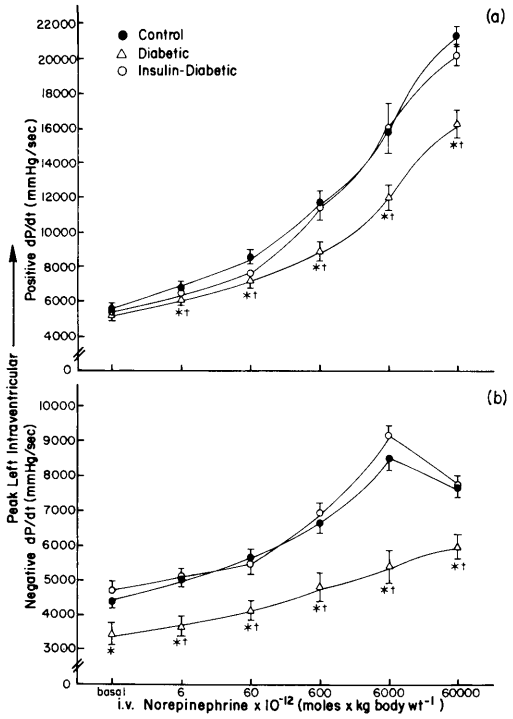

FIG. 1. (a) *In vivo* left ventricular peak positive and (b) negative dP/dt in response to norepinephrine infusion in control, diabetic, and insulin-treated diabetic rats. All values are means ± SEM for $n = 11$ to 14. *Significance from control group, $P < 0.05$. †Significance from insulin-treated diabetic group, $P < 0.05$.

lated to the positive chronotropic effect of insulin observed in diabetic patients (20).

Discussion. Intravenous injection of streptozotocin, 50 mg/kg, induced a relatively moderate state of diabetes which was tolerated for 8 weeks without insulin treatment or significant loss of body weight. The diabetic group, however, failed to gain weight appreciably, and maintained a relatively constant body weight throughout the 8-week period of the study. Control and insulin-treated diabetic rats gained weight at comparable rates and had no notable growth abnormalities. Diabetic rats exhibited the common characteristics of diabetes: polyuria, glucosuria, polydypsia, and polyphagia. At the end of 8 weeks plasma glucose was elevated approximately twofold. Cardiac enlargement, as evidenced by the increased heart-to-body weight ratio, was also manifested in the diabetic animals.

The principle purpose of this study was to determine whether this model of diabetes produced significant alterations in myocardial contractility when assessed *in vivo* and whether these alterations could be reversed by insulin treatment. A number of studies have demonstrated impaired contractile activity and altered myocardial responsiveness to norepinephrine of *in vitro* perfused hearts or muscle strips using this model of diabetes (8–16). However, the extent to which these abnormalities occur *in vivo* has not been previously determined, and the possibility that the tissue isolation procedures may have contributed inadvertently to the reported results cannot be discounted.

The method used to assess *in vivo* myocardial contractility was an intracardiac catheterization procedure described by Kopp (17). The primary index of myocardial contractility

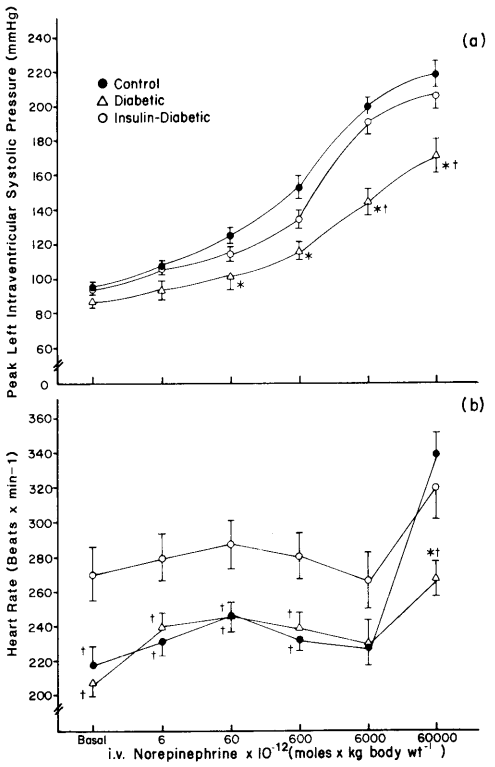

FIG. 2. (a) *In vivo* intraventricular pressure development and (b) heart rate in response to norepinephrine infusion in control, diabetic, and insulin-treated diabetic rats. All values are means ± SEM for $n = 11$ to 14. *Significance from control group, $P < 0.05$. †Significance from insulin-treated diabetic group, $P < 0.05$.

employed in this study was left intraventricular peak-positive dP/dt. Positive dP/dt serves as a valid index for detecting changes in myocardial contractility in response to increased inotropic demand, provided that peak dP/dt occurs before aortic valve opening and preload does not vary appreciably (21). These criteria were met in the present study. The peak-positive dP/dt measurements were always made prior to aortic valve opening. There were no significant differences in left intraventricular end-diastolic pressure among the three groups, which suggests that preload was not appreciably different. This index of contractility, however, is not always sensitive enough to detect absolute changes in basal myocardial contractility. Thus, the absence of discernable differences in peak-positive dP/dt between control and diabetic rats at basal levels may not necessarily reflect any absolute discrepancy with published *in vitro* findings (9–16). These findings do suggest, however, that the magnitude of the contractile dysfunction in the diabetic heart may be accentuated by *ex vivo* perfusion conditions. Norepinephrine was infused at concentrations bracketing a 10^4-fold dose range to induce minimal and near maximal positive inotropic responses. The changes in peak-positive dP/dt in response to norepinephrine were significantly attenuated in diabetic rats, but the sensitivity to norepinephrine was not significantly decreased as indicated by similar ED_{50} values. Peak pressure development and negative dP/dt were also significantly depressed in diabetic rats. Insulin treatment of diabetic rats prevented these alterations during this relatively short-term period of diabetes.

These results are similar qualitatively to most previous reported *in vitro* (10–13, 16, 23–27) and *in situ* (8, 22) studies, but some important differences were found. Consistent with our results are the studies by Foy and Lucas (10, 22) which showed a reduction in the inotropic and chronotropic responses to exogenous norepinephrine and isoproterenol in pithed diabetic rats and isolated diabetic rat atria. Another study involving open chest, anesthetized rats has demonstrated that the left ventricular-positive dP/dt response to isoproterenol stimulation was depressed in 4-week diabetic rats (8). However, Ingebretsen *et al.* (11) have reported no change in the dose-dependent inotropic effect of isoproterenol on isolated working hearts from acutely diabetic rats. A study by Vadlamudi and McNeill (16) found no change in the magnitude of the response or dose for positive dP/dt of isolated working hearts from 180-day diabetic rats, but the responsiveness of negative dP/dt was significantly diminished. Fein *et al.* (23) reported similar results in isolated papillary muscles from 3- to 4-month alloxan diabetic rabbits. Ramanadham and Tenner (13) found that the chronotropic and inotropic effects of isoproterenol on isolated atria from diabetic rats were lowered in 4-week diabetic rats. Ventricular tissue from diabetic rats had greater basal developed tension but the sensitivity to isoproterenol was not significantly affected. Collectively most of the above *in vitro* studies demonstrate that at least some aspect of the cardiac response to catecholamines was diminished in hearts of diabetic animals, but sensitivity was unchanged. Although, there are some focal inconsistencies the results obtained in the present study are in general agreement with previous findings.

The attenuated effects of norepinephrine on left ventricular positive dP/dt with no change in sensitivity indicate that myocardial contractile activity is depressed in this model of diabetes and/or the number of β-adrenergic receptors is decreased but the affinity is unchanged. Several studies have shown that cardiac actomyosin and myosin ATPase activities are diminished with diabetes (9, 14). Other studies (8, 13, 25) have reported a significant reduction in β-adrenergic receptor density in diabetic hearts with no change in receptor affinity. Ingebretsen *et al.* (26) have also shown that the isoproterenol-induced increase in cyclic AMP content and activation of cyclic AMP-dependent protein kinase is depressed in diabetic hearts. In addition, Atkins *et al.* (8) have reported that the sensitivity of adenylate cylase to isoproterenol-induced stimulation was depressed in diabetic hearts. Finally, Gøtzsche (27) has shown that the isoproterenol-induced stimulation of ^{45}Ca uptake by hearts of diabetic rats was diminished.

The other major finding of the present study was that the rate of ventricular relaxation, as indicated by left intraventricular negative dP/dt, was significantly diminished in diabetic rats at basal levels and in response to norepineph-

rine. This result is similar to the effect described in previous *in vitro* studies (9, 16, 28). Although the mechanism responsible for this alteration in relaxation is unknown, various defects involving impaired myocardial calcium metabolism have been described. Fein *et al.* (9) have shown that calcium binding and uptake were depressed in sarcoplasmic reticulum fractions isolated from diabetic hearts. Lopaschuk *et al.* (28) have reported that the inhibition of calcium transport was associated with an accumulation of long chain acylcarnitine esters by the diabetic heart. However, in a subsequent study, Lopaschuk *et al.* (29) found that treating diabetic rats with insulin or oral D,L-carnitine produced conflicting results. Insulin treatment prevented the accumulation of long chain acylcarnitine, inhibition of sarcoplasmic-reticulum calcium transport, and depression of both positive and negative left ventricular dP/dt of perfused hearts in response to changes in preload. Carnitine therapy also decreased the long chain acylcarnitine level and prevented the depression of sarcoplasmic reticulum calcium transport, but it did not improve myocardial hemodynamic function. These findings suggest that alterations in sarcoplasmic reticulum regulation of intracellular ionized calcium may not be the major cause of impaired ventricular relaxation.

Overall, the result obtained in the present study indicates that the *in vivo* myocardial reactivity to norepinephrine is significantly diminished in diabetic animals. This diminished reactivity may contribute to impaired cardiac responsiveness of diabetic patients to exercise, ischemia, and hypertension. Insulin treatment of 8-week diabetic rats prevented these alterations in cardiac function. The contractile characteristics exhibited by the diabetic heart under basal and catecholamine stress conditions *in vivo* generally were qualitatively similar to those reported in previous *in vitro* studies. There are indications, however, that the magnitude of the contractile dysfunction exhibited by the diabetic heart may be accentuated by *ex vivo* and *in vitro* perfusion and superfusion conditions. This observation emphasizes the importance of employing multiple procedural approaches in evaluating the functional performance of the diabetic heart. In this manner potential, intrinsic methodologic biases can be recognized, which will facilitate more accurate appraisal of the diabetic cardiomyopathy.

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