Differential Pulmonary Vascular Effects of Streptozotocin Diabetes in Male and Female Rats (44207)

ROY D. RUSS[1] AND BRIAN W. TOBIN

Division of Basic Medical Sciences and Department of Pediatrics, Mercer University School of Medicine, Macon, Georgia 31207

Abstract. **We examined the effect of streptozotocin (STZ) diabetes on pulmonary pressor responses and segmental pulmonary vascular resistance in male and female Wistar-Furth rats. Pulmonary vascular reactivity was studied using isolated, salt-perfused lungs at a constant flow rate of 30 ml/min/kg body weight. Following STZ administration, pressor responsiveness to 1.0 μg of U-46619 (9,11 dideoxy-9α, 11α-methanoepoxy Prostaglandin $F_{2\alpha}$) was diminished ($p < 0.05$) in lungs obtained from male diabetic rats when compared to sham treated controls (7.87 ± 1.67 vs. 13.59 ± 1.67 mmHg). In contrast, diabetes failed to affect pressor responsiveness in lungs from female animals. In another set of animals, segmental pulmonary vascular resistance was determined in lungs isolated from male and female diabetic or sham-treated (STZ carrier vehicle) animals. Total pulmonary vascular resistance was significantly elevated in male diabetic animals as compared to controls. This elevation was attributable to significant increases in resistance at the level of small pulmonary veins. In addition, diabetes was associated with a shift in the primary site of resistance from small arteries to small veins in male animals. We were unable to detect any effect of short-term diabetes on the segmental resistance profile in lungs obtained from female animals. These data indicate that both the pulmonary segmental resistance profile and pulmonary vascular reactivity are altered by short-term diabetes in male rats. Additionally, these studies demonstrate gender-related effects of short-term diabetes, which may suggest a more favorable pulmonary response to diabetes in female animals.** [P.S.E.B.M. 1998, Vol 217]

Secondary complications of diabetes involve a number of organ systems, but none is more detrimentally affected than the cardiovascular system. Overall, 66% of all morbidity and mortality in diabetes is due to cardiovascular disease (1). While these effects are traditionally attributed primarily to atherosclerotic processes, a portion of this pathophysiology may be directly modulated by vascular mediators. Insulin-dependent diabetes mellitus (IDDM) has been shown to produce profound effects on vascular tone and its control by endogenous and exogenous mediators. Depending upon the vascular bed and the vasoconstrictor agent studied, IDDM has been associated with increased (2–4), decreased (5–7),or no alteration (3) in pressor responses.

In spite of clinical evidence of pulmonary vascular derangements in diabetic patients (8, 9), there is a paucity of data on the influence of diabetes and hyperglycemia upon the pulmonary vascular complications of IDDM. The reasons for this omission are unclear but may relate to the unsubstantiated notion that pulmonary vascular complications of diabetes are uncommon and of minor clinical importance. However, several studies illustrate detrimental effects of altered glucose and/or insulin concentration on pressor responses in the pulmonary vasculature. Elevated glucose concentrations in nondiabetic animals have been shown to reduce pressor responses to hypoxia or anoxia in isolated-perfused rat lungs (10, 11) and isolated-perfused ferret lungs (12, 13). Only one study to date has directly

[1] To whom requests for reprints should be addressed at Division of Basic Medical Sciences, Mercer University School of Medicine, 1550 College St., Macon, Ga 31207.
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assessed the effects of short-term diabetes on the rat pulmonary vasculature (14). In this study, we reported that short-term diabetes in male rats was associated with a shift in the primary site of pulmonary vascular resistance from the arterial to the venous side of the circulation.

No published reports examine alterations in pulmonary vascular responsiveness in diabetes or the gender specificity of any such changes. However, a growing body of evidence clearly illustrates a need for such investigations. In clinical studies conducted between 1980 and 1989, the age-adjusted incidence for diabetes in Caucasian females was 33% greater than in Caucasian males (1). In addition, the incidence of peripheral vascular disease was nearly double in women with diabetes than in men (1).

Thus, the goal of the present study was to determine the effect of the diabetic state upon pulmonary vascular reactivity and segmental vascular resistances in Wistar-Furth rats. Specifically, we chose to delineate: 1) any alterations in baseline pulmonary hemodynamic status, and/or 2) any alterations in pressor responsiveness to the synthetic thromboxane analogue 9,11-didexoy-9α,11α-methanoepoxy Prostaglandin $F_{2\alpha}$ (U-46619). Finally, since no information exists regarding the gender specificity of any pulmonary vascular effects of short-term diabetes, we wished to examine this phenomenon in both male and female animals.

Materials and Methods

All protocols and surgical procedures were reviewed and approved by the Institutional Animal Care and Use Committee of the Mercer University School of Medicine. Wistar-Furth rats (9–10 weeks old at the beginning of the study) were used for all experiments. All animals were allowed at least one week to acclimate to the research facilities prior to the beginning of the study.

Induction of Diabetes. After acclimation to the animal facility, animals were assigned randomly to treatment groups. Streptozotocin (55 mg/kg) dissolved in acetate buffer (pH 4.3) was administered intravenously into either the penile or the tail vein of animals assigned to the diabetic group. Sham control animals were given intravenous acetate buffer only. Diabetes was allowed to develop for a 2–3-week period.

Isolated Lung Preparation and Protocol. The surgical procedure for lung isolation has been described previously (15, 16). Briefly, animals were anesthetized with pentobarbital sodium (100 mg/kg, ip.). The trachea was isolated and cannulated with a 17-gauge needle stub. A midsternal incision was made to expose the heart, and heparin sodium (100 U) was injected directly into the right ventricle. The pulmonary artery was cannulated with a 17-gauge needle stub via an incision in the right ventricle, and the preparation was rapidly connected to a perfusion system containing a physiological saline solution (126 mM NaCl, 5.4 mM KCl, 0.83 mM $MgSO_4$, 19 mM $NaHCO_3$, 1.8 mM $CaCl_2$, 5.5 mM glucose and 4% albumin; wt/vol; 290 ± 5 mOsm/kg H_2O). The left ventricle was then cannulated with a 4 mm plastic tube, and the heart and lungs were removed *en bloc*. After removal, the heart and lungs were suspended in a humidified chamber maintained at 38°C and perfused initially at 1.0 ml/min/kg body weight. The perfusion rate was gradually increased to 30 ml/min/kg body weight, and it remained at this flow rate throughout the experiment. Because diabetic animals undergo significant weight loss without similar reductions in blood volume and cardiac output (17), all flow rates were based upon the body weights of animals in the control group.

The lungs were ventilated at a frequency of 55 breaths/min (tidal volume approximately 2.5 ml) with a gas mixture containing 5% CO_2 in room air for the duration of the experiment. The gas mixture was humidified prior to entering the trachea. Inspiratory pressure was set at 9 cm H_2O and end-expiratory pressure at 2 cm H_2O. All experiments were initiated with the lungs under zone two conditions (pulmonary arterial pressure > alveolar pressure > pulmonary venous pressure). Once suspended, lungs were allowed 20 minutes to stabilize before any experiments were begun. After stabilization, lungs were tested using the protocol outlined below. Pulmonary arterial pressure was measured using a Gould Statham P23ID pressure transducer connected to a Grass Model 7P122B low-level DC amplifier and recorded on one channel of a Grass Model 7D chart recorder. Because of the possibility of tachyphylaxis (18), each lung was studied using only one protocol. Following the equilibration period, the pulmonary vasculature was preconstricted using U-46619. U-46619 was chosen as the pressor agent because, unlike hypoxia and other common vasoconstrictor agents, it results in consistently stable and long-lasting pressor responses in the isolated-perfused rat lung. In order to achieve an index of pressor responsiveness, a small initial dose of U-46619 (1.0 μg) was added to the perfusate reservoir (40 ml total volume) to elicit vasoconstriction. In the isolated lung, excess pressure is associated with edema formation that also serves to elevate pulmonary arterial pressure and thus complicates data interpretation. To avoid this potential problem, only one index dose of U-46619 was used to compare responsiveness of the vasculature, and total pressor responses in the preparation were not allowed to exceed 15 mmHg. This technique allowed us to achieve a reliable index of responsiveness without causing the edema that would have been associated with construction of a full dose-response curve and allowed each lung to be used for further study. Following stabilization of the initial pressor response, additional U-46619 was added (1.0–3.0 μg total) as needed to achieve a maximal stable pressor response between 10 and 15 mmHg that did not differ significantly between groups.

Determination of Segmental Resistances. Segmental vascular resistances across the pulmonary circulation were assessed in a separate group of animals using vascular occlusion techniques as previously described (19, 20). Total pulmonary vascular resistance (R_T) was calculated by subtracting pulmonary arterial pressure (P_{PA}) from

left atrial pressure (P_{LAT}) and dividing by the flow rate (Q). Prior to vascular occlusions, lungs were placed in Zone 3 conditions (pulmonary arterial pressure > pulmonary venous pressure > alveolar pressure). We then simultaneously occluded the arterial and venous outflow cannulae for 3 sec and allowed pressure within the pulmonary circulation to equilibrate with pulmonary capillary pressure (P_{PC}). A representative double occlusion is depicted in Figure 1. Pulmonary arterial resistance (R_{ART}), was calculated as the difference between P_{PA} and P_{PC} divided by Q. Similarly, pulmonary venous resistance (R_{VEN}) was calculated as the difference between P_{PC} and P_{LAT} divided by Q.

The contribution of large and small pulmonary arteries to overall pulmonary vascular resistance (PVR) was assessed by occluding the pulmonary inflow cannula for 3 sec. Pulmonary arterial occlusion pressure ($P_{PA,O}$) was identified from the inflection point of the P_{PA} tracing as described previously (19). Resistance due to large pulmonary arteries (R_{LA}) was calculated by subtracting $P_{PA,O}$ from P_{PA} and dividing by Q. Resistance due to small pulmonary arteries (R_{SA}) was calculated by subtracting P_{PC} from $P_{PA,O}$ and dividing by Q. Resistance due to large and small pulmonary veins was calculated in a similar manner. The pulmonary outflow cannula was occluded for 3 sec and the pulmonary venous occlusion pressure ($P_{PV,O}$) was identified from the inflection point of the P_{PV} tracing as described previously (19). Resistance due to large pulmonary veins (R_{LV}) was calculated by subtracting P_{PV} from $P_{PV,O}$ and dividing by Q. Resistance due to small pulmonary veins (R_{SV}) was calculated by subtracting $P_{PV,O}$ from P_{PC} and dividing by Q. Representative tracings of arterial and venous occlusions are presented in Figure 2. This technique for determining pulmonary vascular resistances has been extensively published and found to be reliable (19–21). One potential disadvantage in the present study was the presence of the left atrium and left ventricle in the perfusion system, which could have altered the compliance of the circuit. However, we did not feel this was a problem as pressure tracings from our studies were qualitatively similar to those from published studies where the cardiac chambers were not included in the perfusion system (20, 21; Figures 1 and 2).

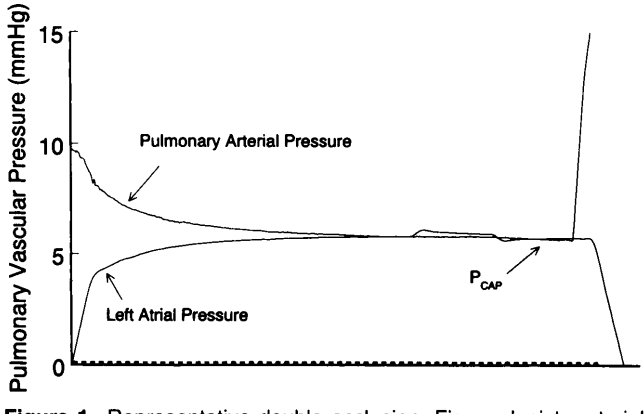

Figure 1. Representative double occlusion. Figure depicts arterial and venous pressure tracings following simultaneous occlusion of arterial and venous cannulae in isolated lungs. Dashed line represents duration of occlusion. P_{CAP} indicates site where pulmonary capillary pressure was determined.

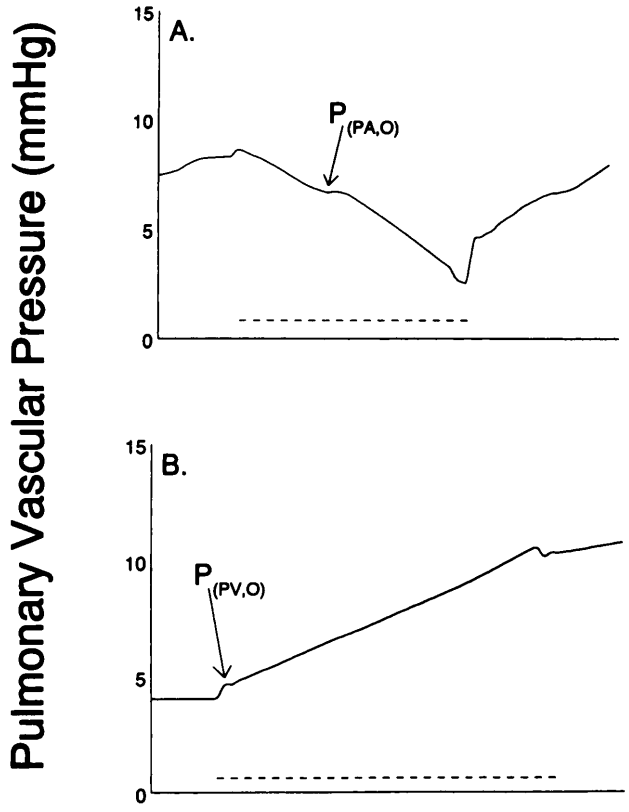

Figure 2. Representative arterial and venous occlusions. Figure A depicts a pulmonary arterial pressure tracing following occlusion of pulmonary arterial cannula (venous tracing removed for clarity). Dashed line represents duration of occlusion. $P_{(PA,O)}$ indicates site where pulmonary arterial occlusion pressure was determined. Figure B depicts pulmonary venous pressure tracing following occlusion of pulmonary venous outflow cannula (arterial tracing removed for clarity). Dashed line represents duration of occlusion. $P_{(PV,O)}$ indicates site where pulmonary venous occlusion pressure was determined.

Calculations and Statistics. Data on diabetic versus control pulmonary vessels were analyzed by two-way analysis of variance where appropriate using a *t*-test with Bonferonni correction as the post-hoc analysis for individual comparisons. All other comparisons were made using a one-way analysis of variance, again using a *t*-test with Bonferroni correction for post-hoc comparisons. $P < 0.05$ was accepted as statistically significant for all comparisons.

Results

Metabolic Data Following Short-term Diabetes. In both male and female diabetic animals, 2–3 weeks of diabetes was associated with significantly elevated plasma glucose concentrations (Table I.) In addition, diabetic animals attained a body weight significantly less than sham-treated controls (Table I), regardless of gender and despite pronounced hyperphagia in the diabetic rats. Body weight was significantly decreased and plasma glucose significantly increased in diabetic animals. Two-way analysis

Table I. Body Weight and Plasma Glucose of Short-term Diabetic and Sham Animals Used in Isolated, Perfused Lung Experiments

Gender	Male		Female	
Treatment group	Diabetic	Sham	Diabetic	Sham
n =	6	6	7	7
Body weight (grams)	234 ± 3.7*	294 ± 6.9	176 ± 3.2*	190 ± 3.1
Plasma glucose (mmol/L)	29.7 ± 5.24*	7.5 ± 0.31	27.4 ± 1.1*	6.8 ± 0.2

All values are mean ± SEM. * indicates $p < 0.05$ versus appropriate sham control.

of variance indicated that these effects were due to the diabetes and not the initial randomization. In addition, female animals weighed significantly less than their age-matched male counterparts.

Hemodynamic Values Following Short-term Diabetes. Baseline pulmonary arterial pressure and total pressor response obtained from lungs isolated following 2–3 weeks of diabetes are depicted in Table II. Baseline pulmonary arterial pressure did not differ among the groups tested following diabetes. The total pressor response exhibited by lungs isolated from male sham-treated animals was significantly greater than that noted in female sham-treated rats, although the dose of U-46619 used to obtain these responses was not the same, which makes this comparison suspect. More importantly, there was no difference in the within-gender, total-pressor responses of diabetic or sham-treated animals.

Lungs from male diabetic animals exhibited significantly reduced pressor responsiveness to 1.0 μg of U-46619 when compared to male sham-treated controls (Figure 3). In contrast, diabetes had no effect on pressor responsiveness in lungs isolated from female rats. Likewise, there were no significant differences in responses of male or female animals, regardless of treatment condition (Figure 3).

Figure 4 shows the baseline segmental resistance profile in lungs isolated from male sham-treated and diabetic animals. The sham-treated animals exhibited the expected pattern of resistance whereby the primary site of resistance was located in the small arteries. Resistance at this site was found to be significantly greater than that noted in any other vascular segment. In contrast, lungs isolated from diabetic animals had significantly greater total resistance than that exhibited in control lungs, and this increase was attributable to increased resistance in small veins. In diabetic animals,

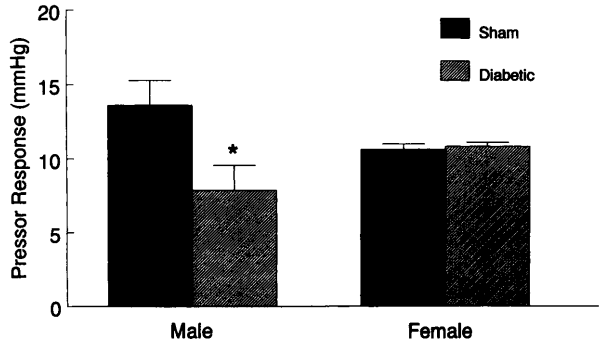

Figure 3. Pressor responsiveness to 1.0 μg U-46619 in isolated lungs obtained from male sham (n = 9), male diabetic (n = 6), female sham (n = 7) and female diabetic (n = 6) animals. * indicates $p < 0.05$ versus male sham group.

the small venules were the primary site of resistance. Further, in addition to total resistance, small venous resistance was significantly elevated in diabetic lungs compared to controls.

The baseline segmental resistance profile of female animals is depicted in Figure 5. In contrast to males, lungs isolated from female control animals failed to show any significant difference in the resistances of large arteries, small arteries, or large veins. Resistance attributable to large veins was significantly lower than that due to small veins. Unlike the case with males, lungs obtained from diabetic female animals exhibited a similar pattern of resistance when compared to female control animals. Again, there was no significant difference in resistances attributable to large arteries, small arteries, or small veins. Resistance due to small arteries was significantly increased in diabetic animals compared to sham-treated animals, but the overall pattern of resistance within each group was not different.

Table II. Hemodynamic Values in Isolated, Perfused Lungs Obtained from Male and Female Diabetic and Sham Treated Animals

Gender	Male		Female	
Treatment condition	Diabetic	Sham	Diabetic	Sham
n =	6	9	6	7
Baseline pressure (mmHg)	8.83 ± 0.24	8.22 ± 0.23	8.86 ± 0.63	8.42 ± 0.26
Total pressor response (mmHg)	13.00 ± 0.84	14.61 ± 0.53*	10.79 ± 0.28	11.50 ± 0.18

All values are mean ± SEM. * indicates $p < 0.05$ versus female sham animals.

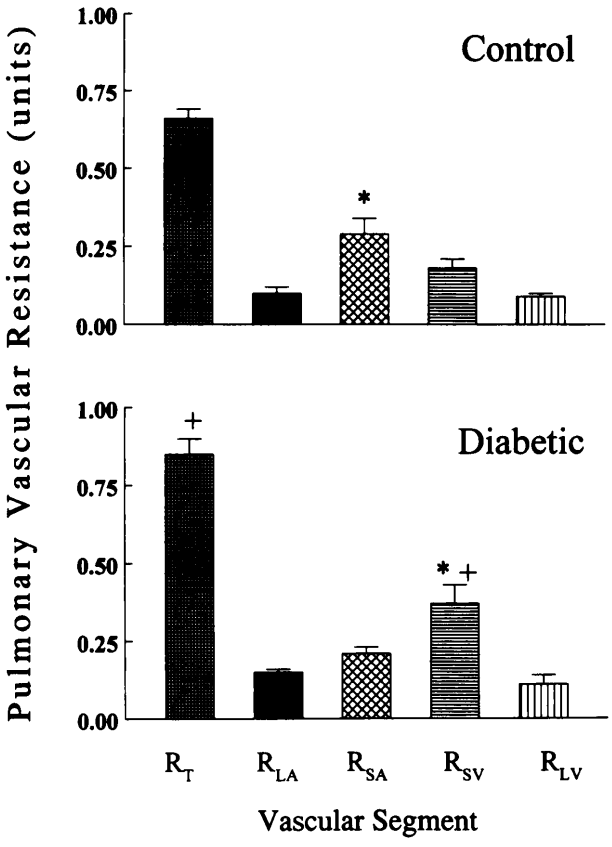

Figure 4. Pulmonary vascular segmental resistance profile in isolated lungs obtained from male sham and diabetic animals. n = 6 per group. Abbreviations are explained in the text. * indicates $p < 0.05$ versus other vascular segments within treatment group. + indicates $p < 0.05$ versus same vascular segment in control animals.

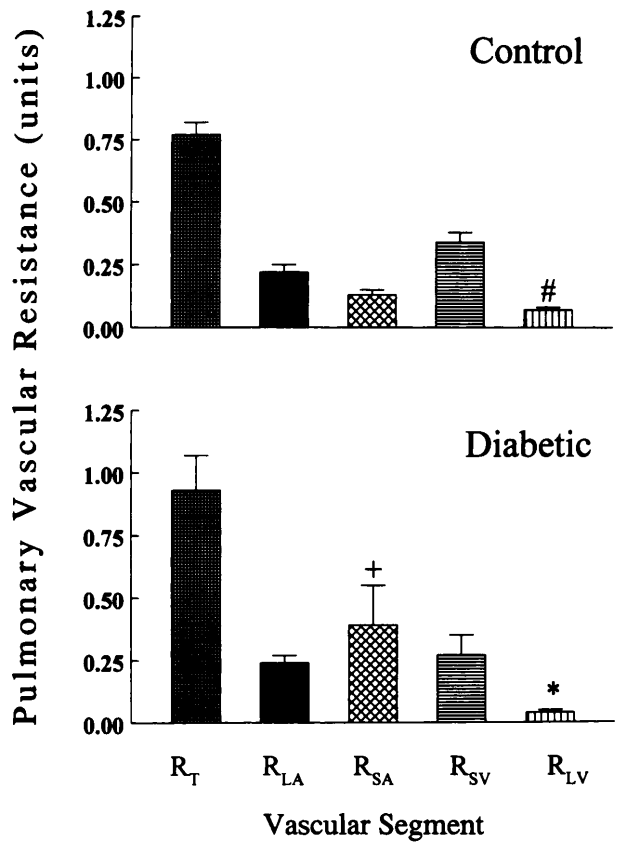

Figure 5. Pulmonary vascular segmental resistance profile in isolated lungs obtained from female sham and diabetic animals. n = 6 per group. Abbreviations are explained in the text. * indicates $p < 0.05$ versus other vascular segments within treatment group. # indicates $p < 0.05$ versus R_{SV} of control animals. + indicates $p < 0.05$ versus same vascular segment in control animals.

Discussion

The major findings of this study are: 1) short-term diabetes significantly reduces pressor responsiveness to the synthetic thromboxane analogue U-46619 in the pulmonary vasculature of male, but not female, animals; 2) short-term diabetes is associated with a shift in the primary site of resistance from small pulmonary arteries to small pulmonary veins in male, but not female, rats; and 3) female animals appear to be protected against the pulmonary vascular effects of 2–3 weeks of STZ-induced diabetes.

We are aware of no reports that examine the effects of diabetes *per se* on pulmonary vascular reactivity. Rounds *et al.* (10) studied the effects of glucose and glucose metabolism on hypoxic pulmonary vasoconstriction (HPV) in isolated, blood-perfused lungs. Addition of glucose or pyruvate to the blood significantly accelerated the rate of decline of HPV. This effect was not apparent when a nonmetabolizable analog of glucose was added to the perfusate. Further, addition of an inhibitor of glucose metabolism significantly augmented and prolonged HPV in their study. The same laboratory later reported (11) that it is not glucose *per se,* but the metabolism of glucose to pyruvate that is responsible for attenuating HPV. Using isolated, perfused ferret lungs, Wiener and Sylvester (12) also failed to demonstrate any alterations in the early phase of HPV. However, they did report significant augmentation of the HPV at 90–180 min following induction of hypoxic exposure in lungs perfused with hyperglycemic medium. In a subsequent report (13), the authors demonstrated that this response was not altered by the addition of insulin, nonmetabolizable analogues of glucose, or pyruvate to the perfusate. Similar to the reports described above, these studies did not examine the effects of diabetes on pulmonary vascular reactivity; rather they examined the effects of hyperglycemia alone.

Our finding that short-term diabetes reduces pulmonary pressor responsiveness in male rats is consistent with the preponderance of data examining the effects of diabetes on systemic vascular reactivity. Jackson and Carrier (22) reported diminished pressor responses to norepinephrine and angiotensin II (ANGII) in conscious, freely moving rats as early as 4 weeks after induction of diabetes with streptozotocin. Hebden *et al.* (23) studied the effects of 3 weeks of diabetes on the pressor responses to vasopressin, ANGII, and methoxamine in streptozotocin-treated conscious rats, both in the intact state and following ganglionic blockade. These authors failed to demonstrate significant differences in pressor responsiveness to any of the agents tested in the intact animal. However, ganglionic blockade unmasked sig-

nificant reductions in the pressor response to the endogenous agents vasopressin and ANGII. Further, the same authors in a separate report (24), demonstrated diminished blood pressure recovery from pentolinium-induced ganglionic blockade in conscious rats. They report that this impaired recovery is most likely secondary to diminished responsiveness of the systemic vasculature to ANGII and vasopressin. More recently, Sikorski *et al.* (25) reported diminished contractile responses in rat aortic rings exposed to norepinephrine as early as 2 weeks following induction of diabetes with streptozotocin. Wilkes *et al.* (7) demonstrated reductions in renal vasoconstrictor responses to U-46619 following streptozotocin-induced diabetes in rats. They reported that this reduction was at least partially secondary to reduced numbers of thromboxane receptors in their animals. This last report may be particularly relevant to the current study where U-46619 was used as a vasopressor agent.

The inability of short-term diabetes to alter pulmonary vascular reactivity in female animals was unexpected, but it is consistent with other gender-related effects of diabetes that are more severe in males than in females. Bell *et al.* (26) reported greater decrements in body weight of male rats given streptozotocin than in their female counterparts, a finding corroborated in the current study. In addition, diabetic male animals have been reported to have higher fed plasma glucose levels than diabetic females (27). The reason(s) for this differential effect of diabetes on male and female animals is not readily apparent, although postulated explanations include increased insulin sensitivity in female animals (28), a detrimental effect of androgenic hormones in males (27), or a combination of the two. A further explanation may be that the adverse effects of diabetes do occur in females but take longer to become manifest. It has already been documented that the vascular effects of diabetes in males develop rather slowly and get progressively more severe with the duration of diabetes. It is conceivable that it merely takes longer for females to exhibit these changes. Another possible explanation for the relative lack of effect of diabetes in female animals could relate to estrogenic modulation of dihydropyridine calcium channels. Several recent reports have documented diminished activity of L-type calcium channels by 17β-estradiol in both vascular (29, 30) and neural (31) tissues. In the current study, pulmonary pressor responses are diminished in female control animals compared to their male control counterparts. This finding is consistent with a role for circulating estrogens in female animals.

Diabetes was also associated with profound effects on the pattern of segmental vascular resistance across the pulmonary vascular bed of male animals. Sham-treated male rats exhibited the expected pattern of resistance whereby small arterial resistance exceeded that of all other vascular segments. In contrast, the primary site of resistance in diabetic male animals was located at the level of the small pulmonary veins. Further, lungs isolated from diabetic male rats demonstrated significantly elevated total pulmonary vascular resistance compared to controls, and this increase was solely attributable to the selective increase in small pulmonary venous resistance.

One possibility for these changes is an underlying change in compliance of the pulmonary microvasculature with or without any real change in resistance. However, we are aware of no reports that document a change in vascular compliance following the induction of diabetes, suggesting that our findings are indeed secondary to alterations in vascular resistance. Further, we have previously demonstrated elevated pulmonary venous resistance in the lungs of male diabetic rats (18) using the double occlusion technique that uses the properties of highly compliant alveolar vessels only. The present study extends these findings and demonstrates this effect at the level of small pulmonary veins. This finding may be particularly salient in light of recent clinical reports (8, 9) that demonstrated altered lung function, including disturbances in ventilation/perfusion matching in diabetic subjects. Indeed, in our experience we have found that lungs isolated from diabetic male animals seem to result in a much more "fragile" preparation than those isolated from control animals and are more likely to fail due to excessive edema formation. This would seem logical in light of altered Starling forces and increased capillary hydrostatic pressure concurrent with the current finding of increased resistance in small pulmonary veins.

The cellular basis underlying alterations in segmental vascular resistance of diabetic animals is not readily apparent, but it may relate to altered cellular calcium handling in the pulmonary veins of male diabetic animals. Abnormal intracellular calcium handling has been documented in cardiac muscle (32), aorta (33), coronary arteries (34), and mesenteric arteries (35) of diabetic animals. Pieper and Gross (34) reported augmented vasorelaxant effects of calcium channel-blockers in coronary resistance vessels obtained from the hearts of diabetic rats, suggesting that altered expression and/or function of calcium channels may play a role in deranged control of myocardial vessels in diabetes. Ganguly *et al.* (36) reported increased sarcoplasmic reticulum calcium-pump activity in tissues obtained from streptozotocin diabetic rats. More recently, Lee and Dhalla (37) demonstrated increased density of calcium channels associated with diabetes. Finally, Walker (38) provided evidence that the L-type or dihydropyridine calcium channel is either not present or not functional on the venous side of the rat pulmonary circulation. It is possible, in light of the present findings, that diabetes somehow upregulates these channels in the pulmonary venous circulation, thereby enhancing myocyte calcium availability and basal tone in this portion of the pulmonary circulation.

In conclusion, we have demonstrated diminished pulmonary pressor responsiveness to the synthetic thromboxane analogue U-46619 following 2 weeks of streptozotocin-induced diabetes in male, but not female, animals. However, most notably, the current investigations have demonstrated selective increases in resistance attributable to

small pulmonary veins in lungs isolated from male, but not female, diabetic animals. These data suggest that diabetes exerts complex actions on the pulmonary vasculature.

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