ORIGINAL ARTICLES

Impaired Arteriolar Myogenic Reactivity in Early Experimental Diabetes

MICHAEL A. HILL AND GERALD A. MEININGER

Hyperperfusion and an increase in capillary pressure has been implicated in the pathogenesis of diabetic microangiopathy. The existence of such alterations suggests that the myogenic response to increased intravascular pressure may be altered in diabetes. To examine this, in vivo studies were performed on the rat cremaster muscle microcirculation of age-matched control and STZ-induced (65 mg/kg) diabetic rats (3–4 wk of diabetes). Anesthetized rats were enclosed in an airtight Plexiglas box with the cremaster muscle exteriorized into an organ bath containing Krebs' solution. To study myogenic responsiveness, box pressure was increased in steps of 10 mmHg from 0 to 30 mmHg for 2 min. Third-order arterioles of the control animals (lumen diameter 18 ± 2 μm) responded to increased pressure with a rapid onset vasoconstriction. In contrast, the rate of development of the constriction was markedly attenuated in similar vessels (15 ± 1 μm) of the diabetic animals, despite their ability to exhibit a similar maximal arteriolar constriction to that of the control animals. When 20 mmHg pressure steps were applied for only 10 s, arterioles of the diabetic animals constricted minimally, whereas those of the control animals constricted to 75% of the maximal response expected for that pressure increase ($P < 0.01$). Second-order arterioles of both groups of animals responded with a primarily passive distension to increased intravascular pressure suggesting that the impaired responsiveness of the third-order arterioles is not compensated for by an increase in the myogenic responsiveness of upstream vessels. Basal intravascular pressures, measured in first-, second-, and third-order arterioles, were similar in control and diabetic animals. These data suggest that experimental diabetes is associated with an impairment in the rate of development of myogenic vasoconstriction in precapillary arterioles that may predispose the capillary bed to transient episodes of elevated pressure. *Diabetes* 42:1226–32, 1993

Studies have suggested that structural microvascular abnormalities associated with long-term diabetes are secondary to hemodynamic disturbances that exist very early in the course of the disorder (1–3). It has been proposed that the initiating factor is a generalized peripheral vasodilatation with a resultant increase in capillary pressure and blood flow. Subsequently, the elevated hydrostatic pressure is suggested to contribute to increased vessel wall permeability and the stimulation of proliferative changes that lead to basement membrane thickening and eventually narrowing of the vessel lumen. The hemodynamic hypothesis has been supported by the observation of increased blood flow in several tissues of short-term diabetic subjects, including kidney (4), retina (5), and limbs (6). Additional support for this hypothesis has been provided by studies of experimental animals that have demonstrated elevated blood flow in the kidney of STZ-induced mildly diabetic rats (7–9) and the retina of acutely hyperglycemic cats (10). Collectively, these studies indicate the presence of altered microvascular blood flow and pressure but do not identify the possible functional defects that contribute to such alterations.

The existence of chronically increased capillary pressure and blood flow in diabetes could be a result of an impairment or inhibition of normal autoregulatory function of precapillary arterioles. Of particular importance to

From the Microcirculation Research Institute, Department of Medical Physiology, College of Medicine, Texas A&M University, College Station, Texas; and the Department of Physiology, Eastern Virginia Medical School, Norfolk, Virginia.

Address correspondence and reprint requests to Dr. Michael A. Hill, Department of Physiology, Eastern Virginia Medical School, P.O. Box 1980, Norfolk, VA 23501.

Received for publication 30 January 1990 and accepted in revised form 6 May 1993.

STZ, streptozocin; pO_2, partial pressure oxygen; pCO_2, partial pressure carbon dioxide; ANOVA, analysis of variance; ANG II, angiotensin II; NE, norepinephrine; type I diabetes, insulin-dependent diabetes mellitus; MAP, mean arterial pressure.

diabetes may be alterations in the myogenic mechanism of autoregulation that is considered to play a major role in the regulation of vascular tone and the local control of microvascular blood flow and capillary pressure (11–13). The major goal of these studies, therefore, was to examine the effect of short-term experimental diabetes on the myogenic response of rat skeletal muscle arterioles to acute increases in intravascular pressure. A defect in the myogenic mechanism could predispose sensitive elements of the microvasculature to elevated pressure. An additional goal was to provide direct quantitative measurements of the effect of STZ-induced diabetes on the arteriolar pressure distribution within the cremaster muscle.

RESEARCH DESIGN AND METHODS

We studied 56 male Sprague-Dawley rats. Diabetes was induced in the rats ($n = 34$) at age 3–5 wk by a single intraperitoneal injection of STZ (65 mg/kg) dissolved in citrate buffer (100 mM, pH 4.0). Age-matched control animals received a similar injection of buffer alone ($n = 22$). All animals were then studied 3–4 wk after administration of either STZ or citrate buffer. Diabetes induction was confirmed by the presence of glycosuria, weight loss, and elevated blood glucose concentrations (>15 mM). Additional groups of diabetic animals were treated daily with subcutaneous Ultralente insulin: 2 $U \cdot kg^{-1} \cdot day^{-1}$ ($n = 7$) or 12 $U \cdot kg^{-1} \cdot day^{-1}$ ($n = 3$) given as a divided dose of 3 U in the morning and 9 U in the evening. The low insulin dose treatment protocol provided a group of animals with sustained hyperglycemia but without the marked weight loss associated with untreated STZ-induced diabetes. Rats were housed in pairs in a temperature controlled facility with a 12-h light-dark cycle. All animals were allowed free access to a standard rat chow and drinking water before the study.

Cremaster muscle microcirculatory preparation. Rats were anesthetized with a mixture of urethane (425 mg/kg) and α-chloralose (100 mg/kg) administered intramuscularly; anesthesia was thereafter maintained with 20–40% supplementary doses given intraperitoneally when indicated. Body temperature was maintained at 37°C by an overhead heating lamp and a circulating water heating pad placed under the back of the rat. To ensure a patent airway, rats were intubated with polyethylene cannulas appropriate to the size of the animal (PE205–PE240). The left femoral artery was cannulated (PE50) for measurement of MAP.

For observation of skeletal muscle microvasculature, the right cremaster muscle was prepared using a modification (14) of the method of Baez (15). In brief, a midline incision was made in the scrotal skin to expose the testis with surrounding cremaster muscle. Connective tissue overlying the muscle was gently dissected away before opening the cremaster sac with a microcautery. The ligament joining the cremaster muscle to the testis was disrupted followed by ligation of the spermatic cord and removal of the testis. The muscle was then secured as a flat sheet over an optical port in a custom-made tissue bath. The static tissue bath (volume 45 ml) was filled with a modified Krebs-Ringer bicarbonate solution with controlled pH (7.35–7.45), temperature (34°C), pO_2 (<40 mmHg), and pO_2 (<50 mmHg) (7). The bath solution was changed between experimental manipulations.

For those studies involving measurement of myogenic activity, an airtight Plexiglas box was placed over the body of the rat with the cremaster muscle exteriorized into the bath chamber. The muscle was exteriorized through a small slot in the box, without impairing the circulation, and the box sealed with silicone grease. Pressure in the box was increased by connecting an inlet port to a compressed air supply. This technique, described in detail elsewhere (12), allows intravascular pressure to be increased to selectively stimulate the myogenic mechanism without altering the pressure gradient for blood flow, which could stimulate metabolic mechanisms of local blood flow regulation.

The microvasculature was observed through an intravital microscope coupled to a closed-circuit video system at a final magnification of ×1000–2000. Arterioles of the cremaster muscle were classified according to branching order with the major arteriole supplying the tissue being designated the first-order arteriole and subsequent branches being numbered consecutively. Vessel lumen diameters were measured with a calibrated electronic video caliper (16). Intravascular pressure was measured with the servonull micropressure system (IPM, California) using glass micropipettes (Omega Dot, Frederick Haer, Brunswick, MN) pulled and beveled to an outer tip diameter of ~2 μm. Plasma glucose concentrations were determined using a standard glucose oxidase method.

Effect of STZ-induced diabetes on arteriolar myogenic responsiveness. Studies were performed on second- and third-order cremaster muscle arterioles. These vessels were selected on the basis of previous studies demonstrating that second-order arterioles respond with a largely passive distension to increased intravascular pressure, whereas third-order arterioles respond with active vasoconstriction (12). Thus, we were able to examine vessels that were normally myogenically responsive as well as nonresponsive vessels to determine whether experimental diabetes results in a change in the extent and/or site of myogenic activity. Basal arteriolar diameter was measured for 1 min after which intravascular pressure was rapidly elevated from 0 to 10, 20, or 30 mmHg for 2 min. At the completion of each pressure step, the pressure in the box was rapidly returned to atmospheric conditions, and the recovery phase of the vessel followed for 3 min. The protocol was applied to vessels in both the resting and maximally dilated (10^{-4} M adenosine) states. A second series of experiments, performed in both control and untreated diabetic rats, examined the effect of a sequence of six 10-s periods of increased pressure (20 mmHg): each increase in box pressure was separated by a 60-s recovery. These experiments were performed on third-order arterioles. The rationale for this series of experiments was based on the assumption that, under normal in vivo conditions, many myogenic stimuli would be more transient or episodic in nature rather than occur as a sustained increase

TABLE 1
Clinical characteristics of the animal groups

	n	Body weight (g)	MAP (mmHg)	Blood glucose (mM)
Control rats	22	170 ± 5	109 ± 3	6.7 ± 0.5
STZ-induced diabetic rats	24	141 ± 5*	112 ± 2	35.7 ± 1.4*
STZ-induced diabetic plus insulin rats ($2\ U \cdot kg^{-1} \cdot day^{-1}$)	7	169 ± 4	105 ± 1	28.1 ± 3.0*

Data are means ± SE; *n*, number of rats.
*$P < 0.001$ significantly different from control.

in intravascular pressure (e.g., constantly changing posture).

Intravascular pressure measurements. Basal intravascular pressure was measured in first-, second-, and third-order arterioles of control and diabetic animals. These studies were performed to document any differences in skeletal muscle arteriolar pressure distribution between the two experimental groups. In addition, this allowed us to establish whether the initial starting pressures were similar in the diabetic and control animals and whether any differences could possibly complicate the comparison of myogenic responsiveness.

Statistical analysis. Where simple comparisons have been made between diabetic and control animals, levels of significance have been calculated using a two-tailed Student's *t* test. Where multiple comparisons have been performed, for example, for the effect of insulin treatment on myogenic responsiveness, levels of significance were determined by ANOVA in conjunction with Fisher's protected least squares difference. Data are means ± SE. Statistical significance has been assumed at the $2P < 0.05$ level.

RESULTS

Animal characteristics. Blood glucose levels, body weights, and MAPs for all control, diabetic, and insulin-treated diabetic animals used in the studies are summarized in Table 1. In brief, both untreated and insulin-treated ($2\ U \cdot kg^{-1} \cdot day^{-1}$) diabetic animals were significantly hyperglycemic compared with control animals. Body weight was significantly ($P < 0.001$) decreased in the untreated diabetic group compared with control animals. Despite continued hyperglycemia, body weight of the insulin-treated diabetic group was similar to that of control animals. No significant differences were detected in MAPs between the groups of animals.

Arteriolar response to increased intravascular pressure. Third-order arterioles of both the control and diabetic animals responded to acute increases in intravascular pressure with vasoconstriction. At each pressure step studied, however, the diabetic animals exhibited an impairment in the rate of development of vasoconstriction. Thus, the time taken to reach 25, 50, and 100% of maximal constriction was significantly increased in the arterioles of the diabetic animals regardless of the magnitude of the applied pressure stimulus.

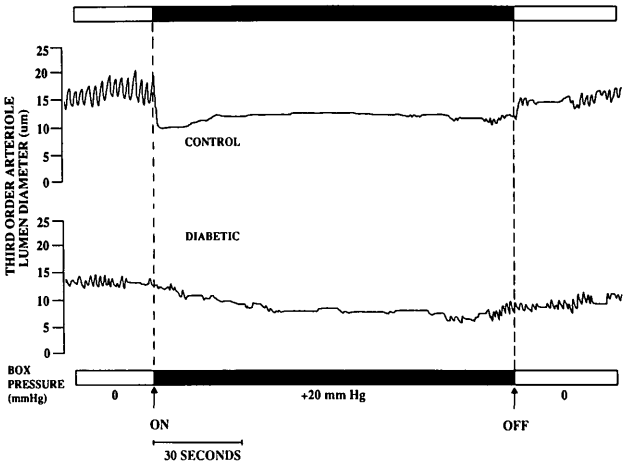

FIG. 1. Contractile response of a third-order cremaster muscle arteriole from a control and a diabetic animal to an acute increase in intravascular pressure of 20 mmHg. Cyclical changes in basal diameter, evident in both tracings, represent spontaneous vasomotor activity that is characteristic of these small arterioles.

Example arteriolar responses for a control and a diabetic animal are illustrated in Fig. 1 and the group data detailed in Fig. 2. The slower response was not a consequence of the diabetic animals showing a greater maximal vasoconstriction to the increased intravascular pressure (Table 2) nor was it a reflection of an impaired contractile activity in general (Fig. 3). In addition, the decreased rate of response could not be explained by a nonspecific effect related to the marked weight loss in the untreated diabetic animals, as diabetic animals treated with a dose of insulin aimed at preventing weight loss but maintaining hyperglycemia also showed an impaired myogenic response (Fig. 2). No significant differences existed in the rates of response for the treated and untreated groups of animals. Treatment of diabetic animals with the high dose of insulin ($12\ U \cdot kg^{-1} \cdot day^{-1}$) prevented the abnormality in myogenic reactivity. For example, for a 20 mmHg increase in intravascular pressure, the time taken to reach 50% of the maximal pressure-induced arteriolar constriction was 7.5 ± 1.8 s in the diabetic animals ($n = 3$) compared with 6.8 ± 1.9 s (not significantly different) in the control animals.

The decreased myogenic responsiveness of the small arterioles in the diabetic animals was even more apparent when the pressure steps were applied as a series of pulses. Figure 4 contrasts the response of a third-order arteriole from both a control and a diabetic animal to a series of six 10-s increases in intravascular pressure (20 mmHg). A 60-s recovery was interposed between each pressure step. In control animals ($n = 5$; basal diameter 16 ± 2 μm), this protocol resulted in a series of reproducible vasoconstrictions (59 ± 8% of basal diameter). The magnitude of each response was ~75% of the maximal constriction observed for a maintained (2 min) 20 mmHg increase in intravascular pressure. In contrast, diabetic animals exhibited minimal constrictor responses to each of the 10-s pressure pulses; with third-order arterioles ($n = 6$; basal diameter 18 ± 1 μm) constricting to only 93 ± 1% of basal diameter ($P < 0.01$ compared with that of control animals).

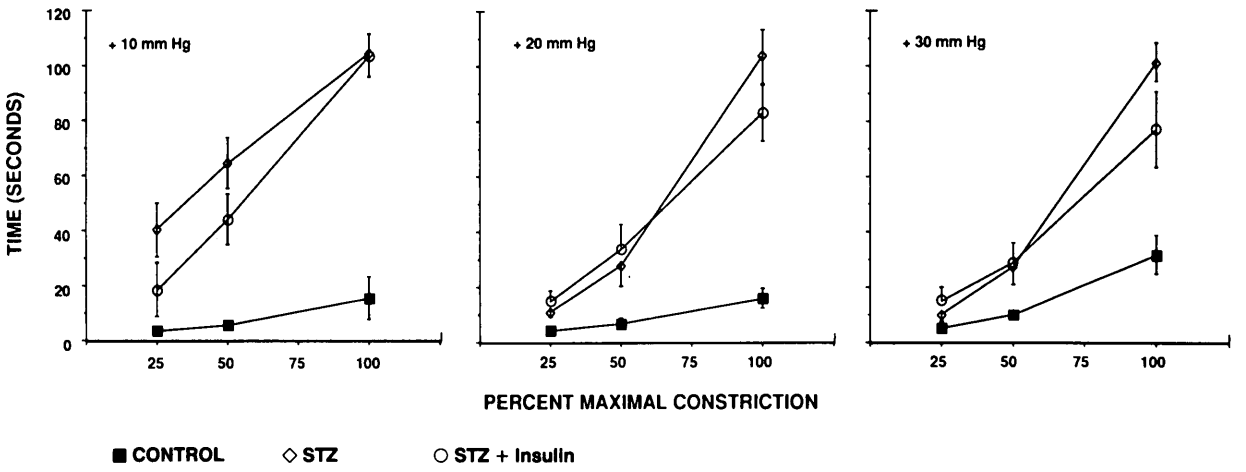

FIG. 2. Rate of third-order arteriolar response to intravascular pressure increases of 10, 20, and 30 mmHg. Rate of response (*seconds*) is plotted with respect to the percentage of maximal vasoconstriction. Data are given for control (n = 8), untreated STZ-induced diabetic (n = 8), and insulin-treated (2 U · kg^{-1} · day^{-1}) (n = 7) animals. Data are mean ± SE. Untreated and insulin-treated diabetic animals exhibited impaired rates of myogenic constriction compared with control animals at each pressure step studied (P < 0.05, ANOVA).

Second-order arterioles in both control (n = 5; basal diameter 60 ± 2 μm) and diabetic animals (n = 7; basal diameter 55 ± 5 μm) responded to an increase in intravascular pressure with a largely passive distension. No significant differences between the two groups were detected in the extent of distension after intravascular pressure increases of 10, 20, or 30 mmHg. For example, in response to a 20 mmHg pressure increase, second-order vessels of the control animals distended to 110 ± 3% of basal diameter compared with 107 ± 1% in the untreated diabetic animals. These data suggest that the sites of active myogenic constriction are similar in both experimental groups and that the impaired responsiveness of the third-order arterioles in the diabetic animals was not compensated for by an increase in the myogenic responsiveness of upstream vessels.

In the presence of maximally dilating concentrations of adenosine (10^{-4} M), third-order arterioles from both control and diabetic animals demonstrated a passive distension to increased intravascular pressure. No significant differences between the control and diabetic groups were detected in the extent of distension after pressure increases of 10, 20, or 30 mmHg. For example, in response to a pressure increase of 20 mmHg, third-order arterioles of control animals (n = 5) distended to 109 ± 4% of basal diameter compared with 114 ± 2% in the untreated diabetic group (n = 4; not significantly different). These data, together with that of the second-order vessels, suggest that the arterioles of control and diabetic animals exhibit a similar degree of distensibility.

TABLE 2
Maximal decrease in third-order arteriolar diameter in response to a 2-min increase in intravascular pressure

	n	Basal diameter (μm)	Δ Decrease in diameter (μm)		
			10 mmHg	20 mmHg	30 mmHg
Control rats	8	18 ± 2	4 ± 2	9 ± 2	10 ± 1
STZ-induced diabetic rats	8	15 ± 1	5 ± 1	8 ± 1	10 ± 1

Data are means ± SE; n, number of vessels studied from number of rats (1 vessel/animal).

Microvascular pressure distribution. Basal intravascular pressures, measured in the first-, second-, and third-order arterioles, were similar in the control and diabetic animals (Fig. 5). In addition, no detectable differences occurred when the results were normalized with respect to the MAP of each animal. These data therefore indicate that the impaired acute myogenic response of the third-order arterioles of the diabetic animals is not the result of differences in basal intravascular pressure. In a previous study, measurements of intravascular pressure taken at the level of first- and third-order arterioles, during acute increases in box pressure, confirmed that the pressure steps were quantitatively transmitted from the box to the cremaster muscle microvasculature (12). Studies performed in 3 rats verified that this also occurred in diabetic animals and showed that the rate of the intravascular pressure rise paralleled that of the box pressure.

DISCUSSION

This study demonstrates that short-term STZ-induced diabetes in the rat is associated with an impaired arteriolar myogenic response to increased intravascular pressure. The altered response was manifest as a decreased rate of myogenic vasoconstriction despite subsequent development of a maximal constrictor response similar to that of the control animals. This alteration in myogenic responsiveness would appear to represent a functional vascular abnormality as a result of its presence in the early stages of experimental diabetes before the appearance of obvious structural defects. The impaired myogenic responsiveness appears selective in that the same vessels are capable of demonstrating rapid-onset vasoconstriction to other stimuli such as ANG II (17) and NE (18).

The experimental approach used in this study allows us to be reasonably confident that the arteriolar response

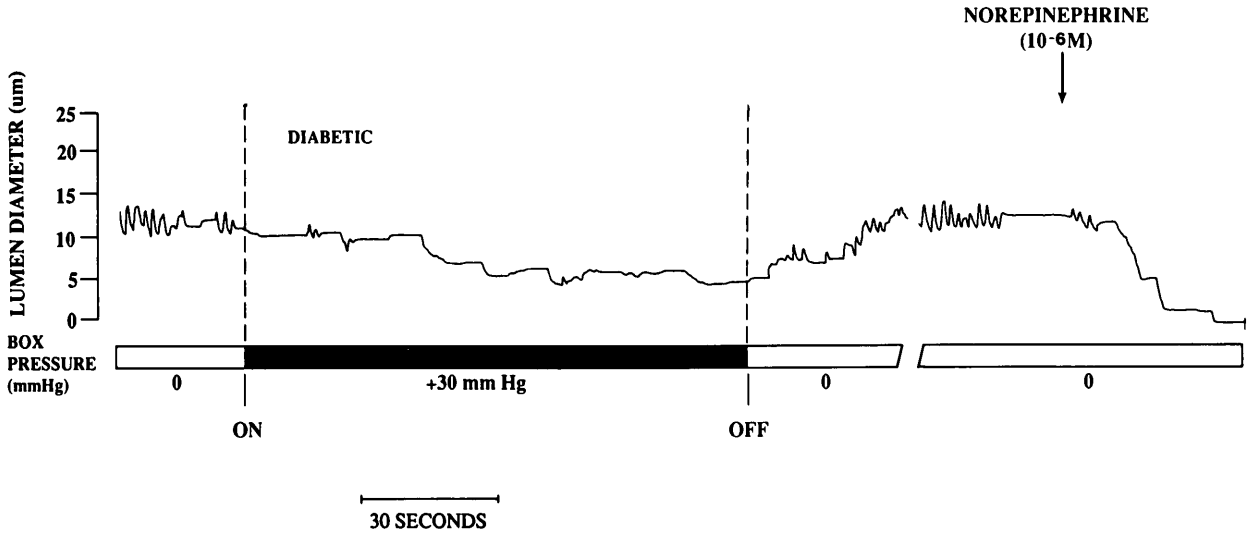

FIG. 3. Example tracing illustrating that third-order arteriole from a diabetic animal can exhibit rapid constrictor response to topically applied NE despite showing an impaired rate of response to a 30 mmHg increase in intravascular pressure.

to increased intravascular pressure represents a local myogenic mechanism. The use of the box technique to increase intravascular pressure avoids altering the pressure gradient for blood flow, as occurs in studies where vessels are occluded to alter the perfusion pressure, and thus would not be expected to stimulate metabolic mechanisms of flow regulation. In addition, previous studies have demonstrated that, in cremaster muscle, this pressure-induced constrictor response is not mediated by a local sympathetic axon reflex nor does the technique activate neurohumoral pathways of blood pressure regulation (12). Apparently, the impaired arteriolar myogenic response in the diabetic animals represents a local vascular abnormality.

Studies examining the effects of diabetes on the ability of tissues to autoregulate blood flow are relatively few in number. Rubin and Bohlen (19) found normal cerebral vascular autoregulation in STZ-induced diabetic rats; however, they only reported data obtained after pressure had stabilized for ~90 s. Hashimoto et al. (20) reported that, in uncontrolled STZ-induced diabetes in the rat, renal blood flow fluctuates with blood pressure to a greater degree than that in control animals. This study, however, only examined the renal blood flow response to pressures <100 mmHg. In addition, those authors used graded aortic occlusion to alter intravascular pressure, which would be expected to invoke both metabolic and myogenic stimuli. Thus, it is not possible to determine the mechanism for the altered autoregulatory responses and the methodological differences make comparison with this study difficult.

Whether the findings of this study are of direct relevance to human diabetes is not clear. Note that, consistent with this experimental study, young diabetic subjects without nephropathy have been reported to show a decreased precapillary vasoconstriction in the feet after

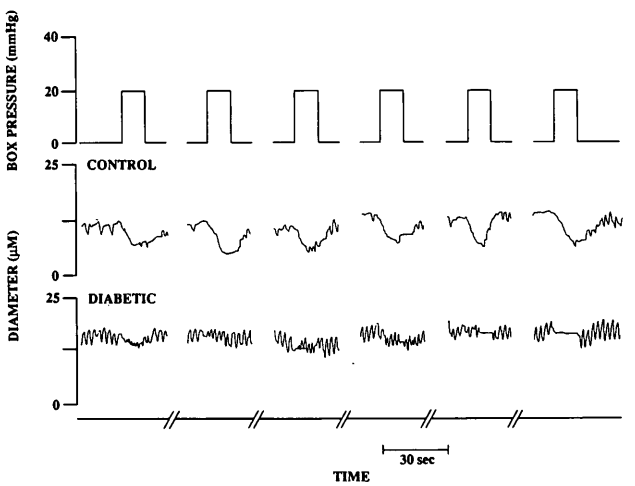

FIG. 4. Example recordings demonstrating response of third-order arterioles from a control and a diabetic animal to a series of six 10-s increases in intravascular pressure (20 mmHg). Recovery periods of 60 s were allowed between application of pressure steps. Recording has been split during recovery periods for illustrative purposes.

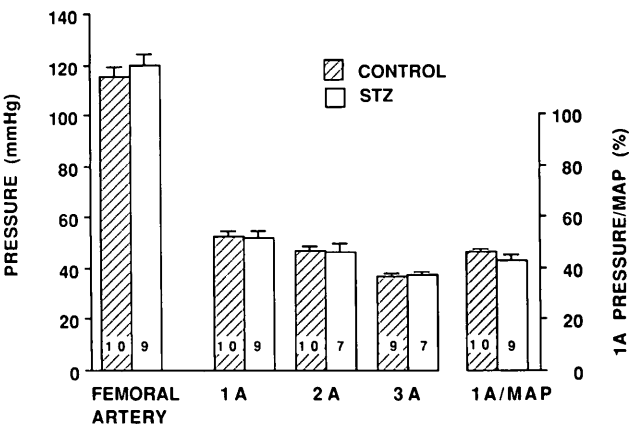

FIG. 5. Systemic and arteriolar pressure measurements for control and diabetic animals. At right, first-order arteriole intravascular pressure normalized with respect to the systemic pressure of each animal is shown. Data are means ± SE, and numbers within the data bars represent the number of vessels studied.

changes in posture (2). Although these authors favor an impairment in a local neurogenic reflex, the later studies of Hassan and Tooke (21) have indicated that local myogenic mechanisms do contribute to posture-induced vasoconstriction. Previous studies demonstrating impaired autoregulatory responses in skeletal muscle and subcutaneous tissues of human diabetic subjects have suggested that the altered function relates to structural vascular abnormalities such as arteriolar hyalinosis (22,23). However, in one of those studies, 3 of 6 short-term diabetic subjects, without evidence of arteriolar hyalinosis, showed an impaired autoregulation at pressures >140 mmHg. Breakthrough in the autoregulatory response at this pressure level was not evident in any of the control subjects. Thus their study and these data are consistent with a functional component to the impaired autoregulatory response.

Studies examining the mechanism underlying myogenic vasoconstriction have suggested that the response may be triggered by an initial vessel distension subsequent to an acute increase in intravascular pressure. As such, alterations in connective tissue that result in decreased vascular distensibility, or increased vessel stiffness, might be expected to impair the myogenic response. Although a number of alterations in connective tissue (24), some associated with an increase in vessel stiffness (25), have been reported in human type I diabetes and STZ-induced diabetes in the rat, it is unlikely that such changes are significant as early as 3 wk after the induction of experimental diabetes. The results of this study do not appear to be consistent with this possibility. Indeed for a given increase in intravascular pressure, the arterioles of the diabetic animals were capable of a similar extent of vasoconstriction as that of control animals despite showing a marked impairment in the rate of response. Furthermore, in the passive state, a similar degree of arteriolar distension was observed in both groups of animals for each of the pressure steps.

The demonstration of an impaired myogenic constrictor response of small cremaster muscle arterioles in short-term STZ-induced diabetes is somewhat in contrast with our previous studies indicating an enhanced response of such vessels to topically applied constrictor agents (17,18). In support of a stimulus-specific constrictor defect, third-order vessels with an impaired myogenic response appeared to show rapid vasoconstriction in response to exogenous NE. This apparent anomaly may relate to the differing signal transduction mechanisms that couple the constrictor stimulus with the contractile apparatus of the vascular smooth muscle. Furthermore, the methodology used in this study provides a defined endogenous myogenic stimulus for vasoconstriction, whereas the response to exogenously applied agonists may be complicated by factors other than those directly determining contractile activity. For example, the enhanced reactivity of skeletal muscle arterioles in STZ-induced diabetes to ANG II may reflect upregulation at the receptor level as a result of a depressed endogenous system, as demonstrated by decreased plasma renin activity (17), rather than contractile activity.

The mechanism underlying the decreased rate of myogenic vasoconstriction in the diabetic animals is, at present, unclear. Conceivably, increased microvascular levels of humoral factors that alter vascular smooth muscle cyclic nucleotide levels, such as prostaglandins, could oppose the myogenic vasoconstriction. This is supported by reports of increased prostaglandin production in predominantly microvascular beds of diabetic animals (17,26,27) and studies from our laboratory that demonstrate potentiation of arteriolar myogenic reactivity after exposure to cyclooxygenase inhibitors (28). Hyperglycemia may impair autoregulatory responses as studies in experimental animals have shown that acute hyperglycemia increases retinal blood flow (10) and impairs the autoregulatory constriction of retinal vessels after inspiration of 100% oxygen (29). Another possibility is that the impaired myogenic response relates to the degree of diabetes in the animals studied. In this regard, Hostetter et al. (8) demonstrated decreased glomerular filtration rate in severely diabetic rats, whereas filtration rate was increased in animals that were less severely diabetic. That ketoacidosis could explain the results of this study is unlikely as both untreated diabetic rats and those given a low dose of insulin (2 $U \cdot kg^{-1} \cdot day^{-1}$) exhibited the impaired myogenic response. In support of this, previous studies in our laboratory demonstrated that diabetic animals treated with this dose of insulin show increased renal blood flow (7) and furthermore, an additional group of insulin-treated diabetic animals was found to exhibit plasma ketone levels similar to control rats (data not shown). Additional studies, however, will be required to determine whether the impairment in myogenic reactivity results from an interaction with metabolic factors or occurs as a result of alterations within the vessel wall.

The existence of a chronic elevation of pressure in the small arterioles and capillaries of diabetic animals has been somewhat controversial. Detection of increased capillary pressure has been limited mostly to studies of the superficial glomeruli of moderately diabetic Munich-Wistar rats, whereas studies that used a similar methodology in Sprague-Dawley and Wistar animals have found unchanged or decreased capillary pressure, depending on the severity of experimental diabetes (30). Direct microvascular pressure measurements in vascular beds other than glomeruli have been limited to that of the small intestine of STZ-induced diabetic rates (31). The study of Lash and Bohlen (31) did not support the existence of chronically elevated arteriolar pressures in early experimental diabetes. Although pressure in this study was only measured in precapillary vessels, it would appear unlikely, given that systemic and arteriolar pressures were similar in both the control and diabetic groups, that capillary pressure is raised at this early stage of experimental diabetes.

In summary, this study suggests that short-term experimental diabetes leads to an impairment in the local arteriolar response to acute alterations in intravascular pressure. The relevance of these observations relates to the hemodynamic theory for microangiopathy, which assumes that increased capillary pressure, consequent on hyperperfusion, acts to initiate pathological changes

in the microcirculation. Although these results are not consistent with a chronic increase in intravascular pressure in experimental diabetes, the demonstrated decreased rate of myogenic vasoconstriction provides a potential mechanism whereby the capillary bed could be exposed to transient episodes of increased intravascular pressure.

ACKNOWLEDGMENTS

This study was supported, in part, by the Juvenile Diabetes Foundation International and National Institutes of Health Grant HL-33324.

Thanks are extended to Mary Beth Thompson for assisting in the preparation of this manuscript.

Portions of this work are contained in *Endothelial Cell Function in Diabetic Microangiopathy: Problems in Methodology and Clinical Aspects*. Molinatti GM, Bar RS, Belfiore F, Porta M, Eds. Basel, Karger, 1990, p. 118–26.

REFERENCES

1. Parving HH, Viberti GC, Keen JS, Christiansen JS, Lassen NA: Hemodynamic factors in the genesis of diabetic microangiopathy. *Metabolism* 32:943–49, 1983
2. Tooke JE: Microvascular hemodynamics in diabetes mellitus. *Clin Sci* 70:119–25, 1986
3. Zatz R, Brenner BM: Pathogenesis of diabetic microangiopathy, the hemodynamic view. *Am J Med* 80:443–53, 1986
4. Mogensen CE: Glomerular filtration rate and renal plasma flow in normal and diabetic man during elevation of blood sugar levels. *Scand J Clin Lab Invest* 28:177–82, 1971
5. Kohner EM, Hamilton AM, Saunders SJ, Sutcliffe BA, Bulpitt CJ: The retinal blood flow in diabetes. *Diabetologia* 11:27–33, 1975
6. Christensen NJ: A reversible vascular abnormality associated with diabetic ketosis. *Clin Sci* 39:539–48, 1970
7. Hill MA, Larkins RG: Alterations in distribution of cardiac output in experimental diabetes in rats. *Am J Physiol* 257:H571–80, 1989
8. Hostetter JH, Troy JL, Brenner BM: Glomerular hemodynamics in experimental diabetes mellitus. *Kidney Int* 19:410–15, 1981
9. Jensen PK, Christiansen JS, Steven K, Parving HH: Renal function in streptozotocin diabetic rats. *Diabetologia* 21:409–14, 1981
10. Atherton A, Hill DW, Keen H, Young S, Edwards EJ: The effect of acute hyperglycaemia on the retinal circulation of the normal cat. *Diabetologia* 18:233–37, 1980
11. Davis MJ: Microvascular control of capillary pressure during increases in local arterial and venous pressure. *Am J Physiol* 254: H772–84, 1988
12. Meininger GA, Mack CK, Fehr KL, Bohlen HG: Myogenic vasoregulation overrides local metabolic control in resting rat skeletal muscle. *Circ Res* 60:861–70, 1987
13. Mellander S: Myogenic mechanisms in local vascular control. *Acta Physiol Scand* 133 (Suppl. 571):25–41, 1981
14. Harris PD, Longnecker DE, Greenwald EK, Miller FN: Small vessel constriction in the rat cremaster during the early phase of moderate hemorrhagic hypotension. *Microvasc Res* 10:29–37, 1975
15. Baez S: An open cremaster muscle preparation for the study of blood vessels by in vitro microscopy. *Microvasc Res* 5:384–94, 1973
16. Goodman AH: Un calibreur video simple pour l'utillsation en microscopie. *Innovation Technol Biol Med* 9:350–56, 1988
17. Hill MA, Larkins RG: Altered microvascular reactivity in streptozotocin-induced diabetes in rats. *Am J Physiol* 257:H1438–45, 1989
18. Hill MA: *Microvascular Haemodynamics and Reactivity in Experimental Diabetes in the Rat*. PhD thesis. Melbourne, Australia, University of Melbourne, 1987
19. Rubin MJ, Bohlen HG: Cerebral vascular autoregulation of blood flow and tissue PO_2 in diabetic rats. *Am J Physiol* 249:H540–46, 1985
20. Hashimoto Y, Ideura T, Yoshimura A, Koshikawa S: Autoregulation of renal blood flow in streptozotocin-induced diabetic rats. *Diabetes* 38:1109–13, 1989
21. Hassan AK, Tooke JE: Mechanism of the postural vasoconstrictor response in the human foot. *Clin Sci* 75:379–87, 1988
22. Faris I, Nielsen HV, Parving HH, Lassen NA: Impaired autoregulation of blood flow in skeletal muscle and subcutaneous tissue in long-term type I (insulin-dependent) diabetic patients with microangiopathy. *Diabetologia* 25:486–88, 1983
23. Kastrup J, Norgaard T, Parving HH, Henriksen O, Lassen NA: Impaired autoregulation of blood flow in subcutaneous tissue of long-term type I (insulin-dependent) diabetic patients with microangiopathy: an index of arteriolar dysfunction. *Diabetologia* 28:711–17, 1985
24. Oxlund H, Rasmussen LM, Andreassen TT, Heickendorff L: Increased aortic stiffness in patients with type I (insulin-dependent) diabetes mellitus. *Diabetologia* 32:748–52, 1989
25. Andreassen TT, Oxlund H: Changes in collagen and elastin of the rat aorta induced by experimental diabetes and food restriction. *Acta Endocrinol* 115:338–44, 1987
26. Fujii K, Soma M, Huang Y-S, Manku MS, Horrobin DF: Increased release of prostaglandins from the mesenteric vascular bed of diabetic animals: the effects of glucose and insulin. *Prostaglandins Leukotrienes Med* 24:151–61, 1986
27. Schambelan M, Blake S, Sraer BM, Nivez MP, Wahbe F: Increased prostaglandin production by glomeruli isolated from rats with streptozotocin induced diabetes. *J Clin Invest* 75:404–12, 1985
28. Hill MA, Davis MJ, Meininger GA: Cyclooxygenase inhibition potentiates myogenic activity in skeletal muscle arterioles. *Am J Physiol* 258:H127–33, 1990
29. Ernest JT, Goldstick TK, Engerman RL: Hyperglycemia impairs retinal oxygen autoregulation in normal and diabetic dogs. *Invest Ophthalomol Vis Sci* 24:985–89, 1983
30. O'Donnell MP, Kasiske BL, Keane WF: Glomerular hemodynamic and structural alterations in experimental diabetes mellitus. *FASEB J* 2:2339–47, 1988
31. Lash JM, Bohlen HG: Structural and functional origins of suppressed acetylcholine vasodilation in diabetic rat intestinal arterioles. *Circ Res* 69:1259–68, 1991