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Effects of streptozotocin-induced diabetes and noradrenaline infusion on cardiac output and its regional distribution in pithed rats

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Summary. ^{46}Sc-and ^{99m}Tc-labelled microspheres were used to measure the effects of noradrenaline infusion on cardiac output and its regional distribution in 10 control and 10 streptozotocin-diabetic pithed rats. Plasma noradrenaline concentrations during the infusion were similar in both groups. Pressor responses were significantly smaller in the diabetic animals (controls: +79, diabetic: +44 mmHg; $p < 0.001$). Cardiac output remained similar in both groups before and during the noradrenaline infusion. Total peripheral resistance was similar in both groups before noradrenaline but the noradrenaline-mediated increase was significantly smaller in the diabetic animals (controls: +150%, diabetic: +76%; $p < 0.05$). Noradrenaline-mediated resistance increases were significantly reduced in several tissues of the diabetic rats including the small intestine (controls: +132%, diabetic: −4%; $p < 0.005$), the large intestine (controls: +150%, diabetic: +39%; $p < 0.05$) and the kidneys (controls: +180%, diabetic: +27%; $p < 0.05$), but were very similar in other areas, e.g. in the hindlimbs and tails.

Key words: Streptozotocin diabetes, pithed rat, cardiac output, regional blood flow, noradrenaline infusion.

Several studies in tissues isolated from made diabetic with alloxan or streptozotocin have found increased vascular reactivity to noradrenaline (NA), for example, in rat aorta [1], perfused hindquarters [2] and perfused mesentery [3, 4]. However, diabetic pithed rats, have been found to be less sensitive to the pressor effects of NA [5]. Possible explanations of this contrast include decreased NA sensitivity in vascular beds other than those which have been examined in vitro, the influence of factors such as changed plasma composition present in pithed rats but not in vitro or a relatively low cardiac output in NA-stimulated pithed diabetic rats. It was decided to investigate these possibilities by measuring cardiac output and its regional distribution before and during a NA infusion using the radiolabelled microsphere technique.

Materials and methods

Streptozotocin diabetes

Wistar rats (200–300 g) were used. Animals to be rendered diabetic received 1 ml/kg of a freshly prepared solution of streptozotocin (55 mg/ml; pH 4.5, citrate buffer) via a tail vein. Control rats received 1 ml/kg of buffer only. Diabetes was confirmed in the streptozotocin-treated animals by their reduced growth rates and raised blood glucose levels (> 20 mmol/l). At no time were the rats denied access to food or water.

Cardiac output and blood flow

Fourteen days after streptozotocin or vehicle administration, the rats were pithed under ether and respired with O_2 ($1\,ml \cdot 100\,g^{-1} \cdot 0.8\,Hz^{-1}$). Cannulae were placed in the left ventricle of the heart via the right carotid artery for microsphere injection, in the right femoral artery for withdrawal of blood and blood pressure recording and in the right femoral vein for NA infusion. In three diabetic and three control rats, pressure was also recorded from size 19G hypodermic needles placed in the hepatic portal and inferior vena cava veins. All cannulae contained heparin in saline (0.154 mol/l). Cardiac output and its regional distribution were estimated before and 5 min after beginning an infusion of 11.6 nmol NA. $kg^{-1} \cdot min^{-1}$, using ^{46}Sc-labelled polystyrene microspheres (approximately 150,000 in 0.15 ml, mean diameter 15 μm; New England Nuclear Chemicals, Dreieich, FRG) and ^{99m}Tc-labelled albumin microspheres (approximatley 90,000 in 0.15 ml, mean diameter 22 μm; Riker Laboratories, Loughborough, UK). Because of the differences between the two types of microsphere used, five animals in each group received the ^{46}Sc-labelled microspheres before and the ^{99m}Tc-labelled microspheres during the NA infusion, the order being reversed in the remaining five animals of each group. Blood withdrawal (0.43 ml/min) from the femoral artery cannula was begun approximately 5 s before each microsphere injection. Microsphere suspensions were injected slowly over about 10 s and arterial withdrawal was continued for a further 20 s. The NA solution was infused at a rate of 0.02 ml/min, the NA concentration be-

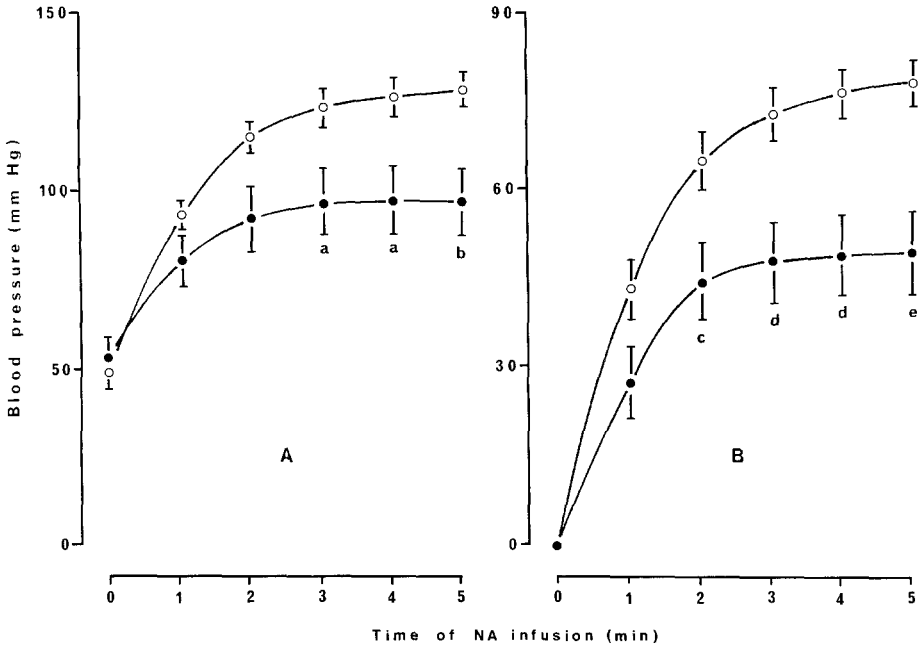

Fig. 1. **A** Blood pressure and **B** net pressor responses to noradrenaline (NA) infusion in control (○) and diabetic (●) pithed rats ($n = 10$ in both cases). Data are mean ± SEM. [a] < 0.05, [b] < 0.025, [c] < 0.01, [d] < 0.005 and [e] < 0.001; significance of differences between control and diabetic groups

Table 1. Blood glucose and plasma noradrenaline concentrations during noradrenaline infusion and growth in control and 14-day-streptozotocin-diabetic rats

	Control rats ($n = 10$)	Diabetic rats ($n = 10$)	p
Growth in 14 days (g)	40.8 ± 4.7	−5.5 ± 6.3	< 0.001
Blood glucose (mmol/l)	10.0 ± 1.1	47.7 ± 6.4	< 0.001
Plasma NA (nmol/l)	105 ± 11	114 ± 13	NS

Results are given as mean ± SEM

Table 2. Hepatic portal and inferior vena cava pressures in control and diabetic rats before and during noradrenaline infusion

		Pressure (mmHg)		
		Control rats ($n = 9$)	Diabetic rats ($n = 9$)	p
Hepatic portal vein	Before NA	6.2 ± 1.0	6.8 ± 0.9	NS
	During NA	11.0 ± 0.9[b]	10.1 ± 0.6[a]	NS
Inferior vena cava	Before NA	2.4 ± 0.4	2.4 ± 0.4	NS
	During NA	2.4 ± 0.3	2.5 ± 0.6	NS
Femoral artery	Before NA	53 ± 4	55 ± 4	NS
	During NA	126 ± 10[c]	96 ± 4[c]	< 0.02

Results are given as mean ± SEM. Arterial pressures are included for comparison with Figure 1. [a] $p < 0.02$, [b] $p < 0.001$; significance of differences in values obtained with and without NA

ing adjusted according to the weight of the rat. Arterial, hepatic portal and femoral vein pressures were recorded using a PT 400 transducer and an MD4 four channel oscillograph (both from BioScience, Sheerness, Kent, UK). Thirty seconds after the second microsphere injection, while the NA infusion continued, an arterial blood sample was taken from the ventricular cannula for blood glucose and plasma NA estimations. Removal of tissues to be counted was completed within 20 min of the second microsphere injection. The methods for estimation of cardiac output and tissue blood flow from counts obtained have been described previously [6]. Resistance to blood flow was obtained by dividing mean perfusion pressure (mean arterial – venous or mean arterial – hepatic portal vein pressure) by blood flow. Resistance units were $mmHg \cdot 100\,g \cdot min \cdot ml^{-1}$.

Six additional diabetic and control pithed rats were used to assess the effects of the NA infusion on blood glucose concentrations. Blood glucose was determined in 0.05 ml samples of blood taken before and 5.5 min after beginning the infusion. Arterial, hepatic portal vein and inferior vena cava blood pressures were also monitored in these animals.

Arterial blood samples were taken from six additional diabetic and control pithed rats which did not recieve an NA infusion. These samples were for the assessment of NA concentrations at rest and were taken from the descending aorta. The blood vessels supplying the adrenal glands were ligated immediately before sampling to prevent discharge of catecholamines into the circulation during the procedure.

Glucose and noradrenaline measurements

Blood glucose levels were determined in 0.05 ml or 0.1 ml samples of whole blood by a micro-colorimetric copper reduction method [7]. Plasma NA was determined by high performance liquid chromatography with electrochemical detection [8]. The equipment used consisted of a pump (Pye Unicam, model LC XPS, Cambridge, UK) operating at a flow rate of 1 ml/min, a sample injector (Rheodyne 7125, Rheodyne, Contati, California, USA), a 10 cm column (Shandon Scientific, London, UK) packed with 5 µm diameter reverse phase particles (ODS hypersil, Bioanalytical Systems, West Lafayette, Indiana, USA) and a glassy carbon thin layer electrochemical detector (Kipp, model 9205, Kipp Analytica, Emmen, The Netherlands) with an applied voltage of 0.7 V. The mobile phase contained NaH_2PO_4 (0.1 mol/l), NaCl (2 mmol/l), EDTA (0.1 mmol/l) and 10% methanol with octyl-sulphonate (1.2 mmol/l) added as the ion-pairing agent. The solution was degassed under vacuum before use. All solutions were prepared in distilled deionized water. Samples were prepared as follows: to 1 ml of plasma was added dihydroxybenzylamine (50 pmol) as the internal standard, followed by acidified alumina (15 mg). The mixture was then shaken vigorously for 15 min using a mechanical shaker (Griffin & George, London, UK). The supernatant was removed and the alumina was washed with distilled deionized water (2 × 1 ml). The supernatant was removed as completely as possible after the second wash and 40 µl of 0.1 mol/l perchloric acid was

Table 3. Effects of diabetes, noradrenaline infusion and the type of microspheres used on the percentage of microspheres detected in the lungs

	Percentage microspheres detected in lungs	
	Control rats ($n=5$)	Diabetic rats ($n=5$)
Before NA		
^{46}Sc-polystyrene	2.06 ± 0.44	3.47 ± 0.31^{a}
^{99m}Tc-albumin	2.02 ± 0.46	2.35 ± 0.47
Total	2.05 ± 0.30	2.91 ± 0.36
During NA Infusion		
^{99m}Tc-albumin	8.61 ± 0.44^{e}	11.50 ± 2.28^{c}
^{46}Sc-polystyrene	9.82 ± 1.11^{e}	6.79 ± 1.64^{b}
Total	9.22 ± 0.60^{e}	9.15 ± 1.75^{d}

Results are expressed as mean ± SEM.
[a] $p < 0.02$ versus controls, [b] $p < 0.05$, [c] $p < 0.025$, [d] $p < 0.005$ and [e] $p < 0.001$ versus the same group of rats before the NA infusion

then added and the sample shaken to desorb the catecholamines. Aliquots (10 µl) of this solution were injected onto the column. Retention times were, NA 3.75 min, adrenaline 5.3 min and dihydroxybenzylamine 6.7 min.

Statistical analysis

All results are expressed as mean ± SEM. The significance of differences between groups were assessed using the two-tailed Student's t-test. Differences were considered significant when their probability according to the null hypothesis was less than 0.05.

Results

Growth rate, blood glucose and plasma NA concentrations

Diabetes was confirmed in all animals which received streptozotocin by a greatly reduced growth rate and raised blood glucose concentrations (Table 1). Blood glucose concentrations were higher than had been observed previously in our laboratory in similar control and diabetic animals. The same NA infusion was subsequently found to raise blood glucose concentrations in control pithed rats from 4.6 ± 1.0 to 9.6 ± 1.7 mmol/l ($n=6$, $p<0.05$) and in diabetic pithed rats from 24.4 ± 2.7 to 39.4 ± 6.0 mmol/l ($n=6$, $p<0.05$).

Plasma NA concentrations 5.5 min after beginning the NA infusion were similar in control and diabetic animals. Resting NA concentrations in arterial blood of six additional control and diabetic pithed rats were found to be 1.46 ± 0.19 and 1.63 ± 0.22 nmol/l, respectively.

Pressor responses to NA

Mean arterial pressure rose to significantly higher levels in the control rats within 3 min of starting the NA infusion (Fig. 1a). When pre-NA mean blood pressures were subtracted to give the net pressor response (Fig. 1b), the differences between the two groups were more significant and were evident after 2 min of infusion. The pressor response to NA reached a plateau in the diabetic animals within 5 min of the infusion. This was not the case in the control rats.

Venous pressure results are from three control and diabetic rats of the blood flow study and six additional control and diabetic animals (Table 2).

Mean hepatic portal vein pressures were significantly higher in both groups during the NA infusion than they were before the infusion started ($p<0.05$). Mean vena cava blood pressures were not significantly changed by the NA infusion in either group. The mean pressures recorded from both veins were very similar in the diabetic and control rats. Mean arterial pressures were similar to the results presented in Figure 1, a significantly reduced pressor response to NA in the diabetic group being observed ($p<0.02$).

Lung counts

Before NA infusion, a significantly increased proportion of spheres, as estimated from lung counts, were observed in the diabetic compared with the control rats in those animals receiving ^{46}Sc-labelled microspheres ($p<0.02$). There was no such significant difference in those animals receiving ^{99}Tc-labelled microspheres or when the results from both the microsphere types were pooled (Table 3). The NA infusion resulted in an approximately fourfold increase in the proportion of microspheres found in the lungs of both control and diabetic rats ($p<0.005$ and $p<0.001$, respectively). No significant differences were observed between the proportions of each of the two types of microsphere detected in the lungs either before or during the NA infusion.

Cardiac output, tissue blood flow and resistance to blood flow

Cardiac output was similar in both groups before and during the NA infusion (Table 4). Peripheral resistance was similar in both groups before NA but was lower in the diabetic group during the infusion ($p<0.025$). The NA-mediated increase in peripheral resistance was smaller in the diabetic group ($p<0.05$).

Blood flow before NA infusion in the small intestines of the diabetic rats was only approximately half that of the control animals ($p<0.001$). During the infusion blood flow was similar in both groups, there being a greater increase in flow in the diabetic group (115% compared with 7% in the controls, $p<0.005$). Since this occurred in the presence of pressor responses which were much greater in the control animals, mean values for resistance responses to NA showed an even greater difference between the two groups (+132% for control, −5% for diabetic rats, $p<0.005$). Similar results were

Table 4. Cardiac output, total peripheral resistance and blood flow and resistance to blood flow before and during NA infusion in control and diabetic pithed rats

		Before NA		During NA infusion		Change with NA	
		Control rats ($n=10$)	Diabetic rats ($n=10$)	Control rats ($n=10$)	Diabetic rats ($n=10$)	Control rats ($n=10$)	Diabetic rats ($n=10$)
Cardiac output		26 ± 2	28 ± 4	25 ± 2	27 ± 2	+1.0 ± 3.1	+0.7 ± 4.5
Peripheral resistance		2.2 ± 0.2	2.1 ± 0.3	5.4 ± 0.5	3.7 ± 0.5[b]	+3.3 ± 0.6	+1.6 ± 0.5[a]
Small intestine:	Flow	214 ±28	109 ±11[e]	230 ±23	234 ±25	+16 ± 35	+125 ±26[b]
	Resistance	0.25± 0.01	0.44± 0.05[d]	0.58± 0.07	0.42± 0.05	+0.33± 0.07	−0.02± 0.06[d]
Large intestine:	Flow	201 ±35	143 ±27	178 ±20	184 ±23	−22 ± 29	+41 ±21
	Resistance	0.30± 0.04	0.41± 0.06	0.75± 0.09	0.57± 0.1	+0.45± 0.08	+0.16± 0.1[a]
Stomach:	Flow	134 ±16	91 ±18	115 ±17	116 ±18	−19 ± 25	+25 ±24
	Resistance	0.45± 0.12	0.71± 0.17	0.91± 0.16	0.91± 0.16	+0.80± 0.19	+0.20± 0.19[a]
Spleen:	Flow	258 ±57	195 ±63	326 ±91	373 ±91	+68 ±101	+179 ±70
	Resistance	0.25± 0.05	0.53± 0.16	0.72± 0.18	0.39± 0.10	+0.48± 0.15	−0.14± 0.19[b]
Kidneys:	Flow	240 ±29	155 ±26[a]	215 ±27	190 ±24	−25 ± 25	+34 ±24
	Resistance	0.25± 0.03	0.44± 0.09	0.70± 0.11	0.56± 0.05	+0.45± 0.09	+0.12± 0.11[a]
Liver (arterial):	Flow	15 ± 2.1	12 ± 2.3	25 ± 2.3	19 ± 3	+10 ± 2.7	+7 ± 4.2
	Resistance	4.3 ± 8.9	7.2 ± 2.3	5.3 ± 0.4	8.1 ± 2.6	+0.9 ± 0.7	+0.9 ± 3.6
Heart:	Flow	259 ±65	180 ±41	600 ±85	364 ±81	+341 ± 72	+184 ±78
	Resistance	0.30± 0.05	0.46± 0.13	0.27± 0.05	0.47± 0.10	−0.03± 0.07	+0.01± 0.14
Skeletal muscle (abdominal):	Flow	9.4 ± 1.1	15.6 ± 3.2	5.1 ± 0.6	8.3 ± 1.0	−4.3 ± 1.2	−7.3 ± 3.2
	Resistance	6.2 ± 0.7	3.5 ± 0.6	27.7 ± 2.9	14.5 ± 3.0[d]	+21.5 ± 3.0	+11.2 ± 2.4[b]
Skeletal muscle (hindleg):	Flow	23 ± 4.9	31 ± 5.4	11.9 ± 1.9	10.6 ± 1.0	−11.1 ± 5.8	−21 ± 5.2
	Resistance	2.9 ± 1.4	2.0 ± 0.3	12.5 ± 1.4	10.6 ± 1.8	+9.6 ± 1.6	+8.6 ± 1.8
Skin (abdominal):	Flow	8.8 ± 2.0	5.0 ± 0.9	7.0 ± 0.6	6.8 ± 1.1	−1.8 ± 1.6	+1.8 ± 0.8
	Resistance	7.4 ± 1.1	13.0 ± 2.8	18.9 ± 1.3	17.2 ± 2.6	+11.5 ± 1.4	+4.2 ± 2.6[a]
Skin (hind leg):	Flow	20 ± 2.3	18 ± 3.5	15 ± 2.1	17 ± 3.5	−5 ± 3.2	−1 ± 2.1
	Resistance	2.9 ± 0.3	3.7 ± 0.7	10.5 ± 1.8	3.8 ± 1.7	+7.6 ± 1.8	+4.1 ± 1.1
Bone (tibia):	Flow	34 ± 3.1	20 ± 3.2[c]	28 ± 3.1	14 ± 2.8[d]	−6 ± 4.1	−6 ± 3.3
	Resistance	1.7 ± 0.2	2.9 ± 0.4[c]	5.2 ± 0.7	8.8 ± 1.6[a]	+3.5 ± 0.7	+5.9 ± 1.7
Hind paw:	Flow	61 ± 8.0	58 ± 8.3	64 ± 5.9	49 ± 6.2	+2.7 ± 7.1	−8.4 ± 7.1
	Resistance	0.9 ± 0.1	1.1 ± 0.2	2.1 ± 0.2	2.3 ± 0.4	+1.2 ± 0.2	+1.2 ± 0.5
Tail:	Flow	27 ± 3.7	23 ± 4.5	14 ± 1.9	12 ± 1.3	−13 ± 3.2	−11 ± 5.0
	Resistance	2.5 ± 0.5	2.6 ± 0.3	10.7 ± 1.3	8.6 ± 1.2	+8.2 ± 1.1	+6.0 ± 1.3
Testes:	Flow	25 ± 3.5	20 ± 2.8	18 ± 2.2	17 ± 2.5	−7.3 ± 3.7	−2.8 ± 3.7
	Resistance	2.5 ± 0.4	3.0 ± 0.4	8.0 ± 1.0	7.3 ± 1.6	+5.5 ± 0.9	+4.3 ± 1.5

Results are given as mean ± SEM, [a] <0.05, [b] <0.025, [c] <0.01, [d] <0.005 and [e] <0.001; significance of difference between control and diabetic groups. Cardiac output and tissue blood flow units are ml·100 g^{-1}; min^{-1}. Peripheral resistance and tissue resistance units are mmHg·min·100g·ml^{-1}

obtained in the large intestine, stomach, spleen, kidneys and abdominal skin where resistance increased by between 150 and 192% in the controls and by less than 40% in the diabetic animals. In each case the difference between the two groups in their resistance response was significant ($p<0.05$). In abdominal skeletal muscle the resistance mean response to NA was also smaller in the diabetic group, being about half that in the controls ($p<0.025$). Blood flow in bone (tibia) of the diabetic rats was only 59% of control values before NA ($p<0.01$) and 50% of control values during the infusion ($p<0.005$). Resistance values were correspondingly greater. NA-mediated decreases in blood flow and increases in resistance values did not differ significantly between the two groups.

Increases in resistance to blood flow during the NA infusion were similar in control and diabetic rats in the hind paw, hind leg muscle, the tail and the liver arterial vascular bed.

Discussion

Plasma NA concentrations 5.5 min after beginning the NA infusion were very similar in control and diabetic animals and were about 70 times those occurring in the absence of exogenous NA. These concentrations, although well above the physiological range for plasma, are probably comparable with those attained in the region of vascular α-receptors during sympathetic stimulation. Studies in isolated aorta have reported that noradrenaline concentrations of between 10 and 20 nmol/l are required to produce 50 maximal contractions [9, 10]. The smaller pressor responses of the pithed diabetic rats to similar NA concentrations agrees with previous results [5] and appear to be due to lower overall vascular sensitivity rather than to an effect on cardiac output.

Vascular sensitivity as estimated by resistance responses was considerably reduced in several tissues of the diabetic rats including the intestines. This contrasts

with previous reports [3, 4] of greater NA sensitivity of perfused mesenteries isolated from diabetic rats than in preparations obtained from controls. This contrast could be due to one or more of a number of differences between the pithed rat and the isolated perfused mesentery preparation. For example, changes in the sensitivity to NA of resistance vessels within the intestinal wall or changes in the distribution of blood between capillaries and arteriovenous shunts would affect the results of the present study but not those obtained using isolated mesenteries (15–22 μm diameter microspheres are likely to pass through arteriovenous shunts so that only capillary flow is measured). Another possibility is that endogenous factors present at higher levels in diabetic than in control animals may oppose the vasoconstriction mediated by NA. Possible candidates for this effect are glucose and glucagon, both of which have been reported to inhibit responses of isolated mesenteric vessels to NA [11, 12].

Similar resistance responses were observed in control and diabetic groups in several areas including the hind leg and tail. Pressure-flow autoregulation plays an important role in the regulation of blood flow in these areas. The occurrence of similar resistance increases in the diabetic rats in the presence of smaller pressor responses, therefore, indicates either more sensitive autoregulatory mechanisms or greater NA sensitivity. The latter conclusion is supported by a report of increased sensitivity to the vasoconstrictor effects of NA in the hindquarters of diabetic compared with control rats when perfused with blood at a constant rate [2].

The occurrence of similar or increased sensitivity to NA in the hindquarters and decreased sensitivity in the major vascular beds of the mesentery and kidneys may explain the altered distribution of blood flow demonstrated in anaesthetised diabetic rats with markedly decreased tail and hind limb blood flow and raised splanchnic flow [6]. Such an effect might be expected to be exaggerated when sympathetic tone and/or plasma catecholamines are high. This may explain an early report on an increased incidence of tail gangrene in cold-stressed diabetic rats [13]. Such an effect may be of interest in view of the evidence of circulatory insufficiency in the legs and feet of long-term diabetic patients. Although plethysmographic and ultrasound studies have generally found arterial flow to the feet of such patients to be increased [14, 15], there is evidence that sensitivity to NA is increased [14] and that a higher proportion of arterial flow passes through arteriovenous shunts [16]. The microspheres used in this study are, as mentioned above, likely to pass through such shunts so that only capillary flow is measured. The finding of an increased proportion of the 15 μm diameter microspheres which were injected before NA in the lungs of the diabetic rats may indicate that such shunting was increased in these animals.

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