# **Originals**

# Reduced transcapillary escape of albumin during acute blood pressure-lowering in Type 1 (insulin-dependent) diabetic patients with nephropathy

H.-H. Parving<sup>1,2</sup>, J. Kastrup<sup>1,2</sup> and U. M. Smidt<sup>2</sup>

<sup>1</sup>Hvidöre Hospital, Klampenborg, and <sup>2</sup>Department of Clinical Physiology, Bispebjerg Hospital, Copenhagen, Denmark

Summary. The effect of acute arterial blood pressure lowering upon albumin extravasation was studied in 10 patients with nephropathy and retinopathy due to long-standing Type 1 (insulin-dependent) diabetes. The following variables were measured: transcapillary escape rate of albumin (initial disappearance of intravenously injected <sup>125</sup>I-labelled human serum albumin), and urinary albumin excretion rate (radial immuno-diffusion). The study was performed twice within 2 weeks, with the patients receiving an intravenous injection of either clonidine (225 µg) or saline (0.154 mmol/l). The clonidine injection induced the following changes: arterial blood pressure decreased from 134/87 to 107/73 mmHg (p < 0.01), transcapillary escape rate of albumin declined from 8.1 to 6.7% of

Transcapillary escape rate of albumin (TERalb, defined as the fraction of intravascular mass of albumin that passes to the extravascular space per unit of time) is elevated in newly diagnosed and short-term Type 1 (insulin-dependent) diabetic patients with poor metabolic control [1, 2]. This abnormality is normalized during strict metabolic control [1, 2]. Elevated hydraulic pressure in the microcirculation has been suggested as an explanation for this reversible phenomenon [1]. The enhanced TERalb characteristically found in long-term Type 1 diabetic patients with clinical microangiopathy is not affected by metabolic control, suggesting a per se effect of the microvascular lesions on albumin extravasation [2-4]. In addition, haemodynamic factors, e.g. elevated capillary hydrostatic pressure, may be involved. It is well documented that acute and chronic arterial and venous hypertension enhance TERalb [5-8]. Recent studies have suggested a link between capillary hypertension, increased extravasation of plasma proteins and the development and progression of diabetic microangiopathy [9-11].

To elucidate this haemodynamic concept, we investigated the effect of acute blood pressure reduction on TERalb and albuminuria in Type 1 diabetic patients with nephropathy. the intravascular mass of albumin/h (p < 0.01), albuminuria diminished from 1434 to 815 µg/min (p < 0.01), and plasma volume raised slightly from 2916 to 2995 ml (p < 0.05). Our findings demonstrate that the enhanced albumin passage through the wall of the microvasculature characteristically found in long-term Type 1 diabetic patients with clinical microangiopathy is pressure-dependent to a large extent. This may be due to elevated hydrostatic pressure in the microcirculation.

**Key words:** Albuminuria, arterial blood pressure, glomerular filtration, diabetic nephropathy, microvascular permeability, transport kinetics, Type 1 diabetes.

#### Subjects

Ten Type 1 diabetic patients with nephropathy were investigated (Table 1). The present and a previous study dealing with autoregulation of glomerular filtration rate [12] were carried out during the same series of experiments. All patients were insulin-dependent from the time of diagnosis, and all received two daily injections of insulin. Apart from insulin, none of the patients were taking any other drugs. Diabetic nephropathy was diagnosed clinically according to previously described criteria [13]. Furthermore, a kidney biopsy had been performed in all patients except patient 1. Nodular diabetic glomerulosclerosis was found in two patients, while diffuse diabetic glomerulosclerosis was demonstrated in the remaining seven patients.

All patients gave their informed consent, and the experimental design was approved by the local Ethical Committee.

### Methods

The study was performed twice within 2 weeks, with the patients receiving a slow intravenous injection (10 min) at 8.40 hours of either clonidine (225µg, Boehringer, Ingelheim, FRG) or saline (0.154 mmol/l), in random order. Measurements were taken in the morning following an overnight fast. The study was carried out from 09.00 to 13.00 hours. The patients had their last injection of insulin at 17.00 hours the day before the study. The patients drank 200 ml of tapwater per hour during the study. Measurements were performed in the supine position.

Patient no.	Sex	Age (year)	Duration of diabetes (year)	HbA <sub>1c</sub> (%)	Insulin dose (U/kg per day)	Albumin- uria ) (µg/min)	GFR (ml/min per 1.73 m <sup>2</sup> )	Retinopathy	Biopsy proven diabetic glomerulosclerosis <sup>1</sup>
1	F	29	17	10.7	0.70	1674	39	Background	
2	Μ	33	18	8.4	0.52	474	112	Background	Diffuse
3	Μ	25	17	9.4	0.65	824	84	Background	Nodular
4	М	39	17	10.3	0.52	1486	82	Background	Diffuse
5	Μ	40	27	11.1	0.51	368	102	Proliferative	Diffuse
6	М	39	18	9.3	0.58	1204	83	Background	Diffuse
7	Μ	34	22	9.0	0.61	2244	78	Proliferative	Diffuse
8	Μ	34	32	8.4	0.59	2979	74	Proliferative	Diffuse
9	F	34	21		0.45	1983	57	Proliferative	Nodular
10	Μ	36	21	9.7	0.57	1108	96	Proliferative	Diffuse
Mean		34	18	9.6	0.57	1434	81		
$\pm$ SD		5	6	1.0	0.07	816	21		

Table 1. Clinical data in 10 Type 1 diabetic patients with nephropathy

<sup>1</sup> Kidney biopsy was not performed in patient 1

Table 2. Arterial blood pressure, transcapillary escape rate of albumin, plasma volume and intravascular mass of albumin before and after acute blood pressure reduction in 10 Type 1 diabetic patients with nephropathy

Patient no.	Arterial blood p (mmHg)	pressure <sup>1</sup>	Transcapillary escape rate of albumin (% intravascular mass of albumin/h)		Plasma volume (ml)		Plasma albumin (µmol/l)		Intravascular mass of albumin (µmol)	
	Before clonidine	After clonidine	Before clonidine	After clonidine	Before clonidine	After clonidine	Before clonidine	After clonidine	Before clonidine	After clonidine
1	$126/87 \pm 2/1$	$98/68 \pm 3/1$	8.2	6.7	2531	2506	490	612	1240	1533
2	$128/87 \pm 5/4$	$110/80 \pm 4/3$	8.2	5.9	3041	3149	570	560	1733	1763
3	$126/82 \pm 1/4$	$108/73 \pm 5/5$	7.1	5.5	2959	3062	598	674	1769	2064
4	$121/83 \pm 5/2$	$110/74 \pm 2/2$	8.2	5.9	2894	2834	451	503	1305	1425
5	$140/87 \pm 2/1$	$126/83 \pm 8/4$	9.6	8.3	3133	3368	578	579	1811	1950
6	$135/88 \pm 1/2$	$96/69 \pm 1/1$	5.3	4.1	3457	3637	568	550	1964	2000
7	$147/92 \pm 3/1$	$119/70 \pm 2/2$	9.4	8.2	3153	3311	510	500	1608	1655
8	$143/91 \pm 3/1$	$95/71 \pm 4/3$	8.0	6.7	2956	3054	397	414	1174	1264
9	$139/91 \pm 1/2$	$112/76 \pm 8/4$	6.8	5.9	2591	2670	520	466	1347	1244
10	$136/89 \pm 10/7$	$96/66 \pm 3/3$	10.1	9.4	2444	2360	576	509	1407	1201
Mean	134/87	107/73	8.1	6.7	2916	2995	526	537	1536	1610
± SD	8/3	11/5	1.4	1.6	314	402	65	74	275	326
	<i>p</i> < 0.01		<i>p</i> < 0.01		<i>p</i> < 0.05		NS		NS	

<sup>1</sup> Values obtained during the TERalb measurements (12.00 to 13.00 hours)

Glomerular filtration rate (GFR) was measured after a single intravenous injection of  ${}^{51}$ Cr-EDTA (09.00 hours) by studying the plasma disappearance for 4 h, as described by Bröchner-Mortensen et al. [14]. Urinary albumin excretion was measured during the 4-h clearance period using the radial immunodiffusion technique [15].

Transcapillary escape rate of albumin is defined as the fraction of intravascular mass of albumin that passes to the extravascular space per unit of time. It is determined as the rate constant of the practically monoexponential decrease in plasma radioactivity over the first 60 min after injection of tracer albumin (initial slope method), as calculated by the least squares method. We have described this procedure and the theoretical basis for the calculation of TERalb in detail previously [5, 16]. Briefly, human serum albumin labelled with <sup>125</sup>I (code MIAK, Institute of Atomic Energy, Kjeller, Norway) was injected intravenously at 12.00 hours. The tracer preparation contains less than 1.0% of free radioactive iodide and has by metabolic studies been demonstrated to behave like endogenous albumin [17]. About 6 µCi of the tracer was injected into one arm vein, and 9 venous blood samples of 6 ml each were drawn from the other arm, 10, 15, 20, 30, 35, 40, 50, 55, 60 min after the injection. Plasma protein concentration was read refractometrically in duplicate with a total solid-meter (American Optical Corp., Scientific Instrument Div., Buffalo, NY). None of the patients had interfering hyperlipemia. The plasma radioactivity was expressed as cpm/g total plasma protein to cancel out the effects of small plasma volume change during the 1-h sampling period.

The mean intra-individual coefficient of variation for TERalb is 8.5% [6]. The normal value of TERalb (adults) in our laboratory is  $5.4 \pm 1.1\%$  of the intravascular albumin mass (mean  $\pm$  SD) [16].

Plasma volume was determined by extrapolation of the disappearance curve of tracer albumin to injection time, and from the injected amount of tracer measured by weighing. The mean intra-individual coefficient of variation for plasma volume in our laboratory is 1.5% [6].

Plasma albumin concentration was measured at the start of each TER determination by the method of Laurell [18]. Intravascular mass of albumin (IVMalb) equals plasma volume × plasma concentration of albumin. Blood glucose was measured every hour during the 4-h investigation period by a glucoseoxidase method on an autoanalyzer (Model II, Technicon, Tarrytown, New York, USA). Stable haemo-globin  $A_{1c}$  was measured at the first investigation (normal range 4.1 to 6.1% of total haemoglobin) [19]. Blood pressure was measured with a

		Time course (min)						
		0-60	60-120	120-180	180-240			
Arterial blood pressure (mmHg)	Saline Clonidine	$\frac{137/89 \pm 10/6}{110/75 \pm 14/5}$	$\frac{134/86 \pm 7/6}{105/73 \pm 13/6}$	$\frac{132/86 \pm 8/5}{108/74 \pm 13/3}$	$\frac{134/87 \pm 8/3}{107/73 \pm 11/5}$			
Blood glucose (mmol/l)	Saline Clonidine	$13.6 \pm 5/4$ $11.7 \pm 5.1$	$13.2 \pm 5.6$ $11.2 \pm 6.1$	$13.0 \pm 4.3$ $10.7 \pm 6.3$	$12.8 \pm 4.6$ $10.6 \pm 6.2$			

 Table 3. Time course of arterial blood pressure and blood glucose concentration after intravenous injection of saline or clonidine in Type 1 diabetic patients with nephropathy

Results expressed as mean  $\pm$  SD

standard clinical sphygmomanometer (cuff  $25 \times 12$  cm) on the right arm. Blood pressure was measured every 15 min after the clonidine injection and at least every hour during the control experiments (median 12, range 5 to 17 measurements).

#### Statistical analysis

The paired (diabetic patients) and the unpaired (diabetic patients and control subjects) Student's t-test (two-tailed) was used. A two-way analysis of variance was used for analysis of the blood pressure values.

#### Results

None of our patients had frank hypertension, but borderline hypertension was present in 3 patients (nos. 7, 8, 9). The clonidine injection reduced arterial blood pressure from  $134/87 \pm 8/3$  to  $107/73 \pm 11/5$  mmHg (Table 2, p < 0.01). The blood pressure reduction remained stable during the 4-h clearance procedure (Table 3). TERalb declined in all patients following the clonidine injection, from  $8.1 \pm 1.4$  to  $6.7 \pm 1.6\%$ IVMalb/h (Table 2, p < 0.01). The TERalb values before and after clonidine injection are elevated compared to healthy adults (n=28), mean  $5.4\pm1.1\%$ IVMalb/h (p < 0.05) [16]. There were no significant changes in total plasma protein concentration during the TERalb determination (60 min), either before, mean  $60.1 \pm 6.1 \text{ g/l}$  (10-15 min) and  $60.2 \pm 6.2 \text{ g/l}$  (55-60 min), or after the clonidine injection, mean  $58.4 \pm 6.2$ g/l (10–15 min) and 57.5 ± 5.4 g/l (55–60 min). Plasma volume increased in 8 out of the 10 patients (mean 2.7%) after clonidine (Table 2, p < 0.05). Plasma albumin concentration remained practically unaltered. A slight, but statistically insignificant, increase in IVMalb was found after clonidine (mean 4.8%).

Albuminuria diminished in all patients from a mean of  $1434 \pm 816$  to  $815 \pm 459 \,\mu\text{g/min}$  after clonidine (p < 0.01). The blood pressure reduction following clonidine induced a decline in GFR from  $81 \pm 21$  to  $73 \pm 21$  ml/min/1.73 m<sup>2</sup> (p < 0.01).

Blood glucose during the TERalb measurements, was slightly higher during the control studies (mean  $12.8 \pm 4.6 \text{ mmol/l}$ ) compared with the clonidine studies (mean  $10.6 \pm 6.2 \text{ mmol/l}$ ), (p > 0.1). Blood glucose con-

centration decreased slightly during the course of the 4 h investigation period (Table 3). Apart from a dry mouth and sleepiness, no serious side-effects were observed after clonidine.

# Discussion

Our study has demonstrated diminished transcapillary escape rate of albumin and albuminuria during acute arterial blood pressure reduction in normotensive and in borderline hypertensive Type 1 diabetic patients with nephropathy. Since the transglomerular fraction of the overall albumin extravasation rate constitutes maximally a few percent, our study demonstrates that the reduced extravasation of albumin, as measured by TERalb, occurs mainly in the microvasculature of the extrarenal organs.

Poor metabolic control enhances TERalb and urinary albumin excretion in short-term Type 1 diabetic patients without clinical microangiopathy [1]. Strict metabolic control normalizes these abnormalities [1]. Neither short-term nor long-term strict metabolic control induces a reduction in albuminuria in Type 1 diabetic patients with diabetic nephropathy [20, 21]. O'Hare et al. [2] found no relation between the elevated TERalb and mean blood glucose or HbA<sub>1</sub> levels in Type 1 and Type 2 diabetic patients with microangiopathy. Furthermore, one year of strict metabolic control obtained by continuous subcutaneous insulin infusion has failed to influence the abnormally elevated TERalb found in 18 Type 1 diabetic patients with microangiopathy (Bo Feldt-Rasmussen, personal communication).

Finally, insulin has no effect on TERalb in Type 1 diabetic patients [22]. Thus, it seems highly unlikely that the present small difference in metabolic control in our study had any impact on TERalb and albuminuria measured during the 4-h clearance procedure.

The mechanisms involved in the abnormally elevated microvascular passage of albumin characteristically found in long-term Type 1 diabetic patients with microangiopathy can either be an increase in the permeability (charge-size selective filter properties) and/or a raised hydrostatic pressure gradient across the microvascular wall. A loss of the charge selective properties and increased pore size of the glomerular capillary wall contribute to albuminuria in diabetic nephropathy [23, 24]. Studies in diabetic animals have suggested a decreased rate of synthesis of acid glycosaminoglycans in the renal and extra-renal microvasculature [25–27].

Direct measurements of nail fold capillary pressure revealed normal values in a group of Type 1 diabetic patients with and without clinical microangiopathy [28]. Direct determination of glomerular pressure in insulintreated streptozotocin diabetic rats has revealed glomerular hypertension [29, 30]. A marked elevation in glomerular capillary hydrostatic pressure, 52.6 versus 43.8 mmHg, has been found in spontaneous hypertensive diabetic rats compared to non-diabetic hypertensive rats (mean arterial blood pressure 160 mmHg) [31].

Our study suggests that the enhanced albumin passage through the wall of the microvasculature is pressure-dependent to a large extent. The most simple explanation of our findings may therefore be the correct one: a reduction of the hydrostatic pressure in the microcirculation induced by acute lowering of systemic blood pressure. If elevated hydrostatic pressure is present in the microcirculation as suggested, it is not a consequence of arterial hypertension, since seven of our patients were normotensive and only three had borderline hypertension. Furthermore, moderate blood pressure elevation (mean 144/98 mmHg) does not enhance TERalb (mean 5.7% IVMalb/h) in patients with essential hypertension [32].

Normally, glomerular filtration rate and blood flow to various organs and tissues are kept relatively constant in response to rather wider variations in perfusion pressure; this phenomenon is termed autoregulation of blood flow to the brain, eyes, skeletal muscle and subcutaneous tissue in long-term Type 1 diabetic patients with clinical microangiopathy [33–36]. We have previously demonstrated impaired autoregulation of GFR in the presently studied patients [12]. Impaired autoregulation, particularly in case of a complete pressure-passive vasculature, will contribute significantly to the present findings due to hypoperfusion and hypotension in the microcirculation.

The slight increase in plasma volume and in intravascular albumin mass is probably due to reduced filtration from the intra- to the extravascular space. In this context, it should be mentioned that acute hypertension induced by intravenous infusion of angiotensin II causes exactly the opposite effects: increased TERalb, reduced plasma volume and intravascular albumin mass [6]. Elevated TERalb and urinary albumin excretion rate are present in essential hypertension, and both variables can be normalized during antihypertensive treatment [16, 37]. Acute reduction in mean arterial blood pressure of 16 to 18 mmHg, induced by intravenous injection of clonidine, has no effect on the normal urinary albumin excretion rate in short-term Type 1 diabetic patients and in control subjects [12]. This suggests that the albumin leakage found during normal conditions is not pressure-dependent.

From the present observations it is suggested that the rapidly reversible part of the elevated TERalb and albuminuria cannot be explained by concomitment changes in the permeability (morphological origin, microangiopathy) but is probably due to a reduction in the hydrostatic pressure of the microcirculation (haemodynamic origin). If a link between capillary hypertension, increased extravasation of plasma proteins and the development and progression of diabetic microangiopathy exists, as previously suggested [9–11], our results support the case for an early and effective treatment of arterial blood pressure elevation.

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Received: 20 May 1985 and in revised form: 9 September 1985

Dr. H.-H. Parving Hvidöre Hospital Emiliekildevej 1 DK-2930 Klampenborg Denmark