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Impaired autoregulation of GFR in hypertensive non-insulin dependent diabetic patients

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Impaired autoregulation of GFR in hypertensive non-insulin dependent diabetic patients. We investigated the effect of acute lowering of blood pressure (BP) upon glomerular filtration rate (GFR) in hypertensive non-insulin-dependent diabetes mellitus (NIDDM) patients, 14 with diabetic nephropathy and 12 with normoalbuminuria. The study was performed twice with the subjects receiving an intravenous injection of either clonidine (150 to 225 μg) or saline (0.154 mmol/liter). We assessed GFR, albuminuria, and BP. The two groups were well matched with respect to demographic data, baseline GFR and BP. Clonidine induced similar reductions in mean arterial blood pressure 19 (SE ± 4) and 21 (SE ± 3) mm Hg in patients with and without nephropathy, respectively. In the nephropathy group GFR diminished in average from 90 (SE ± 6) to 81 (SE ± 7) ml/min/1.73 m^2 ($P = 0.006$), fractional clearance of albumin ($\times 10^{-6}$) declined from a geometric mean of 219 (antilog SE ·/÷ 1.3) to 186 (antilog SE ·/÷ 1.3) ($P = 0.04$), and four patients had a complete pressure-passive vasculature, defined as ΔGFR% = ΔMABP%. A significant correlation between relative reductions in MABP and GFR ($r = 0.78$, $P < 0.001$) was demonstrated in albuminuric patients. None of the normoalbuminuric patients had a complete pressure-passive vasculature and there were no significant differences in GFR between the two examinations, but five had abnormal autoregulation of GFR. Mean difference between changes in GFR (95% confidence interval) between the nephropathic and normoalbuminuric group was 5.5 (÷ 2.7 to 13.7) ml/min/1.73 m^2 ($P = 0.18$). Our study suggests that hypertensive NIDDM patients, particularly patients with nephropathy, frequently suffer from impaired or abolished autoregulation of GFR.

Initiation of antihypertensive treatment induces a faster initial and slower subsequent decline in glomerular filtration rate (GFR) in hypertensive insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) patients with incipient or overt diabetic nephropathy [1–3]. The faster initial decline in GFR may be due to a functional (hemodynamic) effect of antihypertensive treatment in patients with diabetic nephropathy [4, 5]. Furthermore, studies suggest that the normal autoregulation in GFR, that is, the maintenance of GFR within normal limits during changes in perfusion pressure induced by changing arterial blood pressure (BP), is defective in IDDM patients with diabetic nephropathy [6]. No information on this important servo mechanism is available in hypertensive NIDDM patients with diabetic nephropathy.

Therefore, the aim of our study was to investigate the effect of acute blood pressure reduction upon GFR in hypertensive NIDDM patients with diabetic nephropathy.

Key words: diabetes, autoregulation of GFR, glomerular filtration rate, hypertension, non-insulin dependent diabetes mellitus.

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METHODS

All 131 NIDDM patients with diabetic nephropathy (biopsy verified $N = 28$, or clinical criteria $N = 103$) attending the outpatients clinic at Steno Diabetes Center during 1995 were identified. Diabetic nephropathy was diagnosed clinically if the following criteria were fulfilled: persistent albuminuria (> 300 mg/24 hr in at least two out of three consecutive, sterile, nonketotic, 24-hour urine samples), presence of diabetic retinopathy, and no clinical or laboratory evidence of other kidney or renal tract disease [7]. The patients were considered to have NIDDM if they fulfilled the WHO definition of NIDDM [8].

Inclusion criteria were the following: NIDDM with diabetic nephropathy, age at entry ≥ 18 and ≤ 70 years, and GFR ≥ 25 ml/min/173 m^2. One-hundred and five patients were excluded because of the following reasons: age > 70 years ($N = 24$), GFR < 25 ml/min/173 m^2 ($N = 8$), treatment with more than two antihypertensive drugs or systolic blood pressure > 190 mm Hg despite treatment with two antihypertensive drugs ($N = 32$), severe cardiovascular disease ($N = 29$), blindness ($N = 4$), superimposed non-diabetic kidney disease ($N = 3$), cancer ($N = 1$), mental disease ($N = 4$). Twenty-six patients were eligible for the study, 9 were unwilling to participate, 3 patients dropped out after inclusion. Fourteen hypertensive (repeated office BP recording > 140/90 mm Hg) patients with NIDDM and diabetic nephropathy ($N = 4$ with biopsy-verified diabetic glomerulosclerosis) completed the study.

All NIDDM patients without known diabetic nephropathy ($N = 817$) attending the outpatients clinic at Steno Diabetes Center during 1995 were identified. Three hundred and fifty-six patients had normoalbuminuria. Thirty-six hypertensive NIDDM patients with normoalbuminuria (albuminuria < 30 mg/24 hr) were eligible for the study, since they matched the NIDDM patients with diabetic nephropathy with respect to sex, age and arterial blood pressure level. Twenty were unwilling to participate and four patients dropped out after inclusion. Twelve hypertensive patients with NIDDM and normoalbuminuria completed the study. Four weeks before the first examination, all antihypertensive treatment was withdrawn in both patients groups, but two patients in each group received furosemide (40 to 80 mg/day)

because of edema formation. All subjects included in the study gave informed consent to participate in the study. The study was approved by the local ethics committee and conducted according to the principles expressed in the Declaration of Helsinki.

We performed a randomized single-blind crossover study. The study was performed twice within two weeks, with the subjects receiving a slow intravenous injection (10 min) at 8:20 a.m. of either clonidine (150 to 225 μg; Boehringer, Ingelheim, Germany) or saline (0.154 mmol/liter), in random order. The patients had their normal breakfast and antidiabetic treatment.

The GFR was measured in a four hour period after a single intravenous injection of 3.7 MBq of Na ^{51}Cr-labeled edetic acid ([^{51}Cr] EDTA) at 8.30 a.m., by determining the radioactivity in venous blood samples taken at 180, 200, 220, and 240 minutes after the injection [9, 10]. The small underestimation (10%) of ^{51}Cr EDTA clearance versus clearance of inulin was corrected for by multiplying EDTA clearance by 1.10 [9]. The results were standardized for 1.73 m^2 body surface area, using the patients' surface area at the start of the study. The mean coefficient of variation in GFR rate of each patient from day to day was 4%. Patients rested supine during the entire investigation and drank approximately 200 ml of tap water per hour.

Blood pressure and heart rate was measured with the Takeda TM2420 device (A&D, Tokyo, Japan) using right arm, appropriate cuff sizes [25 × 12 cm (upper arm circumference ≤ 35 cm) and 30 × 15 cm (upper arm circumference > 35 cm)] at baseline after at least 10 minutes rest in the supine position (average of 3 measurements) at 8.10 a.m. and every 10 minutes during the GFR measurements. Mean arterial blood pressure (MABP) was calculated as diastolic blood pressure plus one third of the pulse amplitude.

Blood glucose concentration was measured every hour during the four hour period by a glucose-oxidase method on an autoanalyzer (one touch 2; Lifescan, Milpitas, CA, USA).

Urinary albumin excretion (UAE) during the four hour period was determined by using an enzyme-linked immunoadsorbent assay, intra-assay variation 2.1% and interassay variation 8.3% [11]. Fractional clearance of albumin was obtained by dividing the clearance of albumin (calculated as UV/P, where U is urine albumin concentration, V is urine flow, and P is plasma albumin concentration) with the simultaneously measured GFR. Residual urine was determined by an ultrasonic diagnosis apparatus (Toshiba Sonolayergraph SAL-20A; Tokyo Shibaura Electric Co., Ltd., Tokyo, Japan). Urinary sodium excretion was measured during the four-hour GFR measurement. Morning urine was tested for bladder infection by a stix (Nephur-Test; Boehringer Mannheim, Mannheim, Germany).

Hemoglobin A_{1c} (HbA_{1c}) was measured by high performance liquid chromatography (VARIANT analyzer; BIO-RAD, CA, USA). The normal range of HbA_{1c} in our laboratory is 4.1 to 6.4%.

Statistical analysis

Normally distributed data are expressed as mean and SD or SE. Values for albuminuria and fractional albumin clearance were logarithmically transformed and expressed as geometric mean and antilog SE, because of their positively skewed distribution. All comparisons of normally distributed parameters were done with a Student's *t*-test, and intergroup comparisons were done with unpaired and intragroup comparisons using paired design. Wilcoxon's non-parametric test for paired comparison was used for analysis of urinary albumin excretion. All blood pressure measurements during the four hour period were used to calculate the mean values and SD during each examination in each patient. The differences between the two examination was transformed into relative changes and linear regression analysis was used to analyze for correlations between relative change in MABP (%) and relative change in GFR (%) in patients with and without nephropathy. Spearman rho was estimated for the correlations between change in MABP and changes in albuminuria and fractional clearance of albumin. All calculations were made using SPSS for Windows (SPSS Inc., Chicago, IL, USA). A P value of < 0.05 was considered significant (two-tailed).

RESULTS

The two groups were well matched regarding arterial blood pressure, age, sex, and body mass index (BMI). Patients with nephropathy had a significantly higher HbA_{1c} and a longer known duration of diabetes. All patients in both groups had hypertension defined as repeated arterial blood pressure > 140/90 mm Hg. Two patients with nephropathy versus 5 without nephropathy had never received antihypertensive treatment (Table 1). Intravenous clonidine injection induced an equal and significantly reduction in MABP of 19 mm Hg and 21 mm Hg in patients with and without nephropathy, respectively ($P < 0.001$). MABP was not reduced below 80 mm Hg in any patients. Arterial blood pressure reduction for each patient are shown in Table 2 and Figure 1, demonstrating a more variable BP response in patients with nephropathy.

Twelve out of 14 patients with nephropathy had a reduction in GFR (mean difference 9 ml/min per 1.73 m^2; $P = 0.006$) versus the control group where only 7 out of 12 patients had a reduction (mean difference 4 ml/min per 1.73 m^2; NS) after clonidine injection. Mean difference between changes in GFR (95% confidence interval) between the nephropathic and normoalbuminuric patients group was 5.5 (÷ 2.7 to 13.7) ml/min/1.73 m^2, $P = 0.18$. Their was no significant difference in GFR (ml/min per 1.73 m^2) before clonidine injection between the two groups (90 ± 23 in the nephropathy group vs. 93 ± 15 in the control group; NS; Table 2).

Ten out of 14 patients with nephropathy had a reduction in albuminuria ($P < 0.05$) and in fractional clearance of albumin ($P < 0.05$) as shown in Table 2. A significant correlation between the reduction in MABP and the reduction in albuminuria (rho = 0.55, $P = 0.04$) as well as fractional clearance of albumin (rho = 0.55, $P = 0.04$) was demonstrated in patients with diabetic nephropathy.

We found a significant correlation between the percent of relative change in MABP and relative change in GFR ($r = 0.78$, $P < 0.001$) in patients with nephropathy, while no correlation was found in the control group ($r = 0.41$, $P = 0.19$; Fig. 1). Four patients with nephropathy had a nearly equal relative change in MABP and GFR (Fig. 1). In the control group no patients had a complete pressure-passive vasculature, but 5 out of the 12 patients investigated had an abnormal autoregulation of GFR, that is, > 10% reduction in relative GFR.

No correlation was found between the autoregulation index [relative change in GFR (%)/relative change in MABP (%)] and baseline albuminuria or GFR in any of the groups.

Intravenous clonidine injection induced a significant mean reduction in natriuresis in the albuminuric and normoalbuminuric

Table 1. Clinical data of NIDDM patients with and without diabetic nephropathy

Subjects	Sex	Age *years*	BMI *kg/m²*	Known duration of diabetes *years*	HbA_{1c} %	Baseline BP *mm Hg*	Previous antihypertensiv treatment	Antidiabetic treatment	Diabetic retinopathy
NIDDM patients with diabetic nephropathy									
1	M	47	28	8	10.0	142/86	Nil	Tablet	Nil
2	M	66	26	18	9.5	163/76	Yes	Tablet	Proliferativ
3	M	63	33	4	8.4	146/84	Yes	Tablet	Proliferativ
4	M	63	25	25	9.5	192/97	Yes	Insulin	Simplex
5	M	63	35	21	7.8	155/81	Yes	Tablet	Simplex
6	M	59	31	34	9.7	152/89	Yes	Insulin	Proliferativ
7	M	69	32	27	9.1	167/91	Yes	Insulin	Proliferativ
8	M	66	26	9	8.1	185/75	Yes	Insulin	Nil
9	F	42	26	9	5.5	144/77	Nil	Insulin	Proliferativ
10	F	46	34	16	11.0	172/86	Yes	Insulin	Simplex
11	M	63	26	6	7.2	184/71	Yes	Tablet	Nil
12	M	68	31	21	11.1	177/96	Yes	Insulin	Proliferativ
13	M	46	38	11	12.2	148/88	Yes	Insulin	Simplex
14	M	42	33	1	7.3	163/99	Yes	Tablet	Nil
Mean ± SD		57 ± 10	30 ± 4	15 ± 10	9 ± 2	164/85 ± 17/9			
NIDDM patients with normoalbuminuria									
1	M	50	29	1	7.4	144/91	Nil	Diet alone	Nil
2	M	66	24	10	6.9	174/105	Nil	Insulin	Nil
3	M	66	34	10	7.2	148/76	Yes	Tablet	Simplex
4	M	61	31	12	7.5	186/79	Yes	Insulin	Simplex
5	M	68	27	6	9.4	162/98	Nil	Tablet	Nil
6	M	63	33	4	7.2	192/87	Yes	Insulin	Simplex
7	F	56	32	11	7.5	151/89	Yes	Insulin	Proliferativ
8	F	65	40	10	6.7	200/109	Yes	Tablet	Simplex
9	M	62	31	20	8.6	166/88	Yes	Insulin	Proliferativ
10	M	69	20	11	7.7	156/85	Nil	Insulin	Simplex
11	M	55	28	6	7.9	164/92	Yes	Insulin	Simplex
12	M	60	36	1	7.1	156/104	Nil	Diet alone	Nil
Mean ± SD		62 ± 6	30 ± 5	8 ± 5	7.6 ± 1	167/92 ± 19/10			
P value (intergroup comparisons)		NS	NS	= 0.048	= 0.016	NS			

groups, 4.7 (95% confidence interval, 0.2 to 9.1) mmol/hr, $P = 0.04$, and 8.1 (1.5 to 14.7) mmol/hr, $P = 0.02$, respectively. The mean difference between the changes in natriuresis (95% confidence interval) in the nephropathic and the normoalbuminuric groups was −3.4 (−10.7 to 3.9) mmol/liter, NS.

No patients had blood glucose concentration below 3 mmol/liter (average of 5 measurements) during the four-hour clearance period. There were no significant difference in blood glucose concentration (mmol/liter) between the two groups during the two examinations: 7.8 ± 2.9 versus 9.2 ± 3.8, NS (before and after clonidine injection), and 6.4 ± 1.6 versus 7.4 ± 1.7, $P = 0.022$ (before and after clonidine injection) in patients with and without nephropathy, respectively. There were no significant correlations between blood glucose changes and GFR changes. Furthermore, the response of patients receiving insulin treatment did not differ from those on tablets.

Apart from a dry mouth and sleepiness, no serious side-effects were observed after clonidine injection.

DISCUSSION

Our randomized single-blinded crossover study shows that acute lowering of BP following intravenous injection of clonidine reduces GFR, albuminuria, and fractional clearance of albumin in hypertensive NIDDM patients with diabetic nephropathy. It should be mentioned that a wide variation in responses to acute blood pressure reduction (ranging from normal to severely impaired autoregulation) was demonstrated, despite that no patients had a MABP below the lower normal limit of autoregulation that is, 80 mm Hg [12–16]. A complete pressure-passive vasculature was found in 4 out of 14 patients with nephropathy [Δ MABP (%) = Δ GFR (%)]. In the control group no patients had complete pressure-passive vasculature and there were no significant difference in GFR between the two examinations; however, 5 out of the 12 patients investigated had an abnormal autoregulation of GFR, that is, > 10% reduction in relative GFR. A significant correlation between Δ MABP (%) and Δ GFR (%) was demonstrated in patients with nephropathy, while this correlation was insignificant in the control group. The two groups had nearly the same BP before intravenous injection of clonidine and equal average reduction in blood pressure after intravenous injection of clonidine.

Omitting the two patients in each group receiving a small dose of furosemide did not alter the observed differences within and between the two groups. This is in agreement with previous studies reporting that autoregulation of renal blood flow and GFR are maintained after administration of loop diuretics [17, 18].

There was no significant difference in blood glucose concentration during the renal clearance studies between the two groups. Furthermore, a glycemic effect on GFR and albuminuria is lacking in diabetic nephropathy [19, 20]. Thus, it seems highly unlikely that the present small difference in metabolic control had any impact on the measured kidney function variables.

Since for safety reasons we excluded hypertensive proteinuric

Table 2. Blood pressure (BP), glomerular filtration rate (GFR) and urinary albumin excretion (UAE) before and during acute blood pressure reduction in NIDDM patients with and without diabetic nephropathy

	BP *mm Hg*		GFR *ml/min per 1.73 m²*		UAE *μg/min*		Fractional clearance of albumin ($\times 10^{-6}$)	
Subject	Before clonidin	After clonidin	Before clonidin	After clonidin	Before clonidin	After clonidin	Before clonidin	After clonidin
NIDDM patients with diabetic nephropathy								
1	147/94 ± 7/12	144/85 ± 7/3	98	103	277	286	71	71
2	181/95 ± 12/8	126/71 ± 17/13	92	65	1391	630	360	255
3	151/84 ± 11/6	137/80 ± 10/7	105	94	178	134	40	37
4	201/88 ± 13/8	163/78 ± 16/11	92	84	2925	1426	1060	566
5	154/86 ± 4/3	124/78 ± 11/5	54	47	280	615	126	319
6	176/100 ± 16/5	121/76 ± 15/12	76	66	2607	2102	1107	910
7	192/100 ± 19/11	111/70 ± 29/14	91	55	1553	495	474	257
8	203/92 ± 16/10	137/80 ± 20/15	98	90	222	177	63	55
9	149/81 ± 10/4	128/75 ± 17/5	77	71	221	276	78	100
10	166/82 ± 14/5	159/82 ± 8/4	54	53	517	455	266	232
11	185/81 ± 21/7	141/73 ± 11/5	112	112	681	626	156	140
12	176/95 ± 10/10	153/82 ± 10/6	62	57	2080	678	932	350
13	159/92 ± 10/6	157/88 ± 9/5	133	125	668	676	136	142
14	152/94 ± 7/3	122/82 ± 8/3	112	106	1457	1026	310	236
Mean ± SD	171/90 ± 20/7	138/79 ± 16/5	90 ± 23	81 ± 25	708 (1.3)[a]	532 (1.2)[a]	219 (1.3)[a]	186 (1.3)[a]
P	< 0.001		= 0.006		= 0.02		= 0.04	
NIDDM patients with normoalbuminuria								
1	148/93 ± 3/3	123/83 ± 5/5	119	136	7	6	1.3	1.1
2	165/89 ± 12/12	117/75 ± 13/12	97	87	4	5	1.0	1.4
3	156/81 ± 11/5	120/79 ± 5/4	73	78	9	5	2.9	1.5
4	173/86 ± 12/6	126/77 ± 8/9	96	97	7	5	1.9	1.4
5	171/106 ± 8/4	142/89 ± 7/6	83	75	19	6	6.2	2.4
6	194/99 ± 7/4	144/82 ± 23/12	97	81	7	3	1.9	1.0
7	160/93 ± 9/4	122/82 ± 5/4	107	99	5	4	1.3	1.1
8	189/105 ± 10/6	121/79 ± 12/5	90	77	12	4	3.3	1.3
9	158/86 ± 27/10	121/72 ± 7/3	91	95	4	9	1.2	2.6
10	141/81 ± 6/4	112/70 ± 7/6	106	93	4	11	1.0	3.1
11	149/85 ± 9/6	152/90 ± 9/6	64	65	10	7	4.3	2.9
12	166/107 ± 11/6	121/88 ± 8/6	93	89	30[b]	12	8.3	3.6
Mean ± SD	164/93 ± 16/10	127/80 ± 12/7	93 ± 15	89 ± 18	8 (1.2)[a]	6 (1.1)[a]	2.2 (1.2)[a]	1.8 (1.1)[a]
P	< 0.001		NS		NS		NS	

[a] Geometric mean (antilog SE)
[b] All ($N = 4$) previous UAE < 30 mg/24 hr during the last 6 months before the study

NIDDM patients with severe vascular and hemodynamic abnormalities, the present study may well underestimate the acute impact of blood pressure reduction on kidney function.

We have used the plasma clearance of ^{51}Cr-EDTA for GFR determination during the last 25 years, because this method is accurate, precise (coefficient of variation 4%), and does not require frequent timed urine collections as do classical renal clearance procedures [9, 10]. The coefficient of variation for renal clearance of ^{51}Cr-EDTA, calculated from four urine collection periods of 40 minutes each, was as high as 20% in patients with diabetic nephropathy [21]. This is mainly due to residual urine that is frequently found in long-standing diabetic patients due to diabetic cystopathy [22]. We have demonstrated that correction for residual urine reduces the coefficient of variation in renal clearance in NIDDM patients from 23% to 6% [23]. Finally, subjects receiving intravenous clonidine cannot stand up and void for four to five hours because of an orthostatic blood pressure drop.

Originally, we reported defective GFR autoregulation in IDDM patients with diabetic nephropathy using clonidine as a blood pressure lowering drug [6]. Our reasons for selecting clonidine as a hypotensive drug, in the past and the present study, were its lack of direct pharmacological effects on the renal vessels [24–26], its predictable effectiveness, and its safety in inducing a prolonged fall in arterial pressure lasting five to seven hours after intravenous injection. An intravenous bolus injection of clonidine has a brief direct alpha-adrenergic stimulating effect lasting a few minutes (hypertension), followed by a prolonged suppression of the central nervous system sympathetic centers (hypotension) [24, 25]. No peripheral sympathetic inhibition has been demonstrated. In an attempt to avoid the initial rise in blood pressure, we intravenously injected clonidine slowly (10 min). Intravenous injection of clonidine in normo- and hypertensive subjects induces a slight but insignificant reduction in peripheral and renal vein renin concentration [24, 26]. The decrease in the blood pressure is due to diminished cardiac output and not to effects on total peripheral resistance [25, 26]. Intravenous injection of clonidine (150 to 300 μg) to normo- and hypertensive nondiabetic subjects induces no significant change in renal plasma flow and GFR [6, 24, 26]. The average reduction in mean arterial blood pressure ranged from 17 to 27 mm Hg in the three studies. Since the relative reduction in GFR did not exceed 10% of the baseline value, this level was used as the cut off for normal autoregulation. Autoregulation of GFR, that is, the maintenance of relative constancy of GFR despite variations in MABP above 80 mm Hg, is present in innovated, denervated and isolated kidney [16, 27, 28]. Experimental studies suggest that autoregulation of GFR is

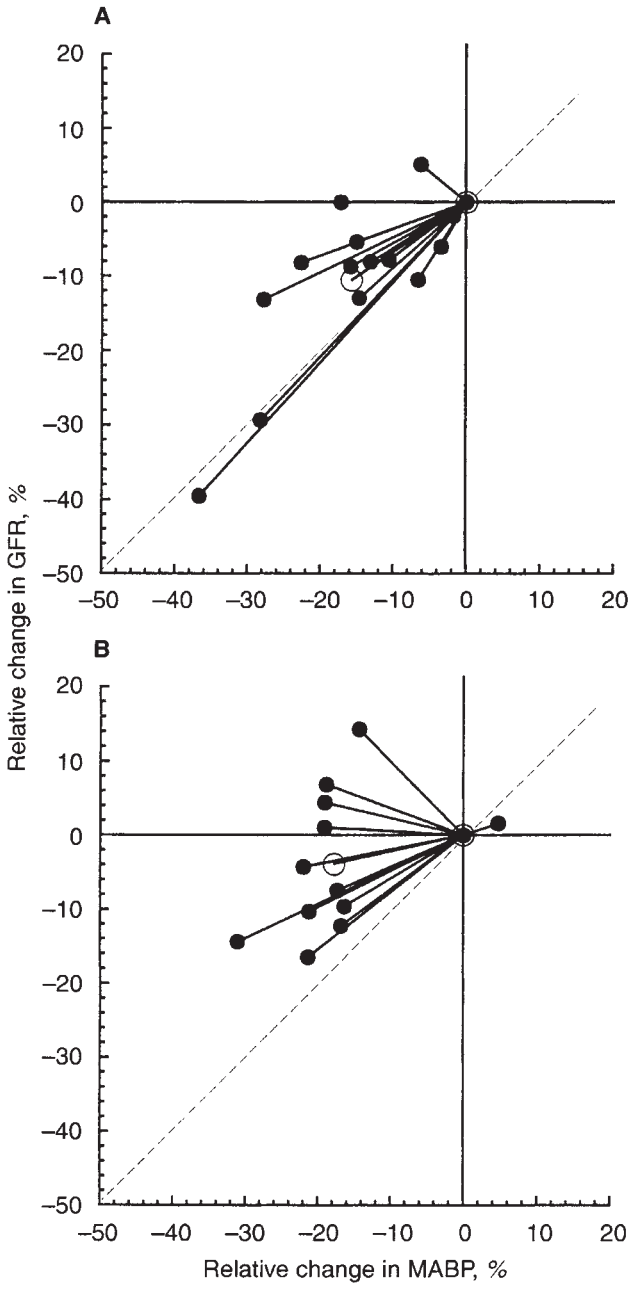

Fig. 1. Relative change in GFR (percentage change of control GFR) and relative change in MABP (percentage change of control MABP) induced by intravenous injection of clonidine. (*A*) Fourteen NIDDM patients with nephropathy (●) and the mean response (○). (*B*) Twelve NIDDM patients with normoalbuminuria (●) and the mean response (○).

due to autoregulation of two of the main GFR determinants, that is, renal plasma flow and glomerular capillary pressure [16, 27].

The afferent arteriole plays a pivotal role in regulating glomerular capillary pressure, renal plasma flow, and consequently GFR [16, 29–33]. As the ability of the afferent arteriole to dilate or constrict is a critical component of the kidney's defense against changes in renal perfusion pressure, failure of the afferent arteriole to constrict in the setting of elevated blood pressure can lead to enhanced transmission of the systemic pressure into the glomerular capillary network, and glomerular hypertension [28, 34]. This hemodynamic alteration is associated with an increase in proteinuria and acceleration of glomerular sclerosis [27]. Conversely, we found a decrease in albuminuria and fractional clearance of albumin (particularly gross albuminuria) induced by acute blood pressure reduction, suggesting that albuminuria is pressure dependent, probably due to diminished glomerular capillary hydrostatic pressure. The impaired myogenic responses to pressure changes might be caused by arteriolar hyalinosis, which has been seen in biopsy specimens from kidneys with hypertensive lesions and/or diabetic glomerulosclerosis [35, 36], or metabolic disturbance of the preglomerular vessels, or a combination of both of these factors [32, 33]. Furthermore, it has been suggested that autoregulation of GFR in general could be governed by various humoral substances, such as prostaglandins and the renin-angiotensin system. However, postaglandins synthetase inhibitors and angiotensin II antagonists failed to interfere with autoregulation in the majority of studies performed [37, 38].

Regardless of the precise mechanisms for the failure of autoregulation, the clinical significance of impaired autoregulation of GFR in hypertensive diabetic patients with and without nephropathy is the lack or diminished protection against hyper- or hypoperfusion induced by alteration in blood pressure. In other words, there is increased vulnerability to hypertension or ischemic injuries of glomerular capillaries in diabetic patients with nephropathy [39–41]. This finding may in part explain the beneficial effect of aggressive antihypertensive treatment on progression of diabetic nephropathy.

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APPENDIX

Abbreviations used in this article are: BP, blood pressure; GFR, glomerular filtration rate; NIDDM, non-insulin dependent diabetes mellitus; IDDM, insulin dependent diabetes mellitus; UAE, urinary albumin excretion; MABP, mean arterial blood pressure; HbA_{1c}, hemoglobin A_{1c}; BMI, body mass index.

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