Autoregulation of Glomerular Filtration Rate in Patients With Type 2 Diabetes During Isradipine Therapy

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OBJECTIVE — Calcium-channel blockade impairs renal autoregulation in animals. Impaired renal autoregulation leads to transmission of the systemic blood pressure (BP) into the glomerulus, resulting in capillary hypertension. Information on the impact of calcium antagonist treatment on renal autoregulation in humans is lacking. This study examines the effect of isradipine treatment on the autoregulation of the glomerular filtration rate (GFR).

RESEARCH DESIGN AND METHODS — We performed a randomized double-blind crossover study with 5 mg o.d. isradipine retard and matching placebo in 16 hypertensive patients with type 2 diabetes. Each treatment arm lasted 4 weeks. On the last day of each treatment period, GFR (single-shot ^{51}Cr-EDTA plasma clearance technique for 4 h) was measured twice between 8:00 A.M. and 5:00 P.M., first without clonidine and then after intravenous injection of 75 μg clonidine. BP was measured every 10 min (Takeda TM2420; A&D, Tokyo).

RESULTS — Clonidine reduced mean arterial BP (MABP) by 15 ± 1 vs. 11 ± 1 mmHg (means ± SE) during placebo and isradipine treatment, respectively ($P < 0.05$). GFR was reduced from 102 ± 4 to 99 ± 4 ml · min^{-1} · 1.73 m^{-2} with placebo ($P < 0.01$) and from 106 ± 5 to 98 ± 5 ml · min^{-1} · 1.73 m^{-2} during treatment with isradipine ($P < 0.01$). Mean difference (95% CI) between changes in GFR with placebo and isradipine was −4.6 ml · min^{-1} · 1.73 m^{-2} (−10.0 to 0.6) ($P = 0.08$). Six patients had a reduction in GFR >13% (exceeding the normal limit of autoregulation) combined with a complete pressure-passive vasculature (defined as ΔMABP% ≤ ΔGFR%) during isradipine treatment versus none during the placebo treatment ($P < 0.05$).

CONCLUSIONS — Isradipine impairs GFR autoregulation in a sizeable proportion of hypertensive type 2 diabetic patients.

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The ability of the kidney to maintain constancy of the glomerular filtration rate (GFR) over a wide range of renal perfusion pressures is termed autoregulation. In the normal kidney, autoregulatory mechanisms are efficient for controlling and stabilizing GFR during changes in systemic blood pressure (BP) by changes in the renal vascular resistance (1). Changes in arterial BP induce alterations in intracellular calcium in the resistant vessels. The intracellular calcium level in the afferent arteriolar is regulated by an influx of calcium through voltage-dependent calcium channels. In vivo and in vitro studies have shown that calcium-channel blockers dilate the afferent arteriolar and impair renal autoregulation in animals with (2,3) and without (4,5) diabetes. Unfortunately, no information is available on the effects of treatment with calcium-channel blockers on autoregulation of GFR in humans.

Impaired autoregulation leads to capillary hypertension or hypotension depending on the level of systemic BP. Increased glomerular capillary pressure is an important factor in the development and progression of experimental diabetic and nondiabetic glomerulopathies (6).

Therefore, the aim of our randomized double-blind crossover study was to investigate the effect of a dihydropyridine calcium-channel blocker, isradipine, on the autoregulation of GFR in hypertensive patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects

A total of 19 hypertensive patients with type 2 diabetes without overt nephropathy were included in the study. Patients with previous macrovascular events such as myocardial infarction, heart failure, angina pectoris, stroke or leg amputations, or vascular bypass surgery were excluded from the study. All patients gave informed consent to participate, and the study was approved by the local ethics committee and conducted according to the principles expressed in the Declaration of Helsinki.

One patient was excluded before randomization because of angina pectoris, and two patients withdrew consent after randomization (one because of lack of time [during placebo treatment] and one because of severe headache [during isradipine treatment]). The remaining 16 patients completed the study.

We selected hypertensive patients with type 2 diabetes without overt nephropathy to have a group in need of antihypertensive treatment with normal or only slightly impaired autoregulation (7). The patients were regarded as suffering from type 2 diabetes if they were treated by diet alone or diet combined with oral hypoglycemic agents, or if they were treated with insulin and had an onset of

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Abbreviations: BP, blood pressure; GFR, glomerular filtration rate; MABP, mean arterial BP; UAER, urinary albumin excretion rate.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

diabetes after the age of 40 years and a BMI above normal (≥25 kg/m^2 in women and ≥27 kg/m^2 in men) at the time of diagnosis (8). Insulin-treated lean patients (BMI <25 kg/m^2 in women and <27 kg/m^2 in men) were given a glucagon test, and type 2 diabetes was diagnosed if a stimulated C-peptide value was ≥0.60 pmol/ml (8). The glucagon/C-peptide test was carried out after an overnight fast. The patients were considered to have arterial hypertension if they were treated with antihypertensive drugs or had a systolic BP >140 mmHg and/or diastolic BP >90 mmHg, in accordance with the 1999 World Health Organization/International Society of Hypertension guidelines. Patients 1, 2, 6, and 7 had never received antihypertensive treatment. Eleven patients (patients 3, 4, 5, 8, 10, 11, 12, 13, 14, 15, and 16) received an ACE inhibitor or an angiotensin II receptor blocker, half of these in combination with diuretics (patients 4, 11, 12, 13, and 16), and one patient (patient 9) was treated with amlodipine in combination with diuretics. All patients had various degrees of peripheral polyneuropathy, as determined by an increased vibration perception threshold. Before the study, none of the patients had persistent microalbuminuria, defined as an urinary albumin excretion rate (UAER) 30–300 mg/24 h in at least two of three consecutive sterile 24-h urine collections. However, four patients had UAER levels >20 μg/min during the placebo evaluation.

Methods

Before conducting the present study, we evaluated the reproducibility of the GFR and UAER by measuring them twice during the same day (8:00 A.M. to 12:00 P.M. vs. 12:30 P.M. to 4:30 P.M.). This evaluation was carried out in 13 type 2 diabetic patients (6 women/7 men) using exactly the same methods described later in this article, but without clonidine. The mean coefficient of variation in GFR was 3.9%, compared with the mean coefficient of variation in day-to-day GFR of 4.5%. The variation coefficient was 19.9% for UAER during the GFR measurement, compared with a day-to-day variation of 23–58%, with the lowest variation between nighttime collections. No systematic alterations were demonstrated in GFR or UAER, thus ruling out time-dependent changes within the period from 8:00 A.M. to 4:30 P.M. Furthermore, no difference was found in mean arterial BP (MABP) during the two GFR measurements.

All antihypertensive treatment was stopped at least 14 days before randomization. A randomized double-blind crossover study was performed in which each arm lasted 4 weeks, with no washout periods between the two arms. Patients were randomized to treatment with 5 mg o.d. isradipine retard (Novartis A/S, Copenhagen, Denmark) or matching placebo, and each treatment lasted 4 weeks. Tablet counting assessed compliance. GFR was measured twice on the same day at the end of each treatment period: first without clonidine (baseline) and second after intravenous injection of 75 μg clonidine (Boehringer, Ingelheim, Germany).

The GFR measurements were performed during two 4-h periods: one from 8:00 A.M. to 12:00 P.M. after a single intravenous injection of 1.5 MBq of Na ^{51}Cr-labeled eidetic acid (^{51}Cr-EDTA) and the other from 12:30 P.M. to 4:30 P.M. after a single intravenous injection of 8.0 MBq of ^{51}Cr-EDTA by determination of the radioactivity in venous blood samples taken at 180, 200, 220, and 240 min after each injection (9,10). To correct for baseline radioactivity, a venous blood sample was taken at the first and second GFR measurements before injection of ^{51}Cr-EDTA. The residual radioactivity from the first measurement was subtracted from the measured radioactivity at 180, 200, 220, and 240 min after the second injection of 8.0 MBq ^{51}Cr-EDTA. The small underestimation (10%) of ^{51}Cr-EDTA clearance versus clearance of inulin was adjusted for by multiplying EDTA clearance by 1.10 (11). Extra renal loss was adjusted for by subtracting 3.7 ml/min (11). The results were standardized for 1.73 m^2 body surface area using the patient's surface area at the start of the study. The patients rested in a supine position during the entire investigation.

BP and heart rate were measured in the supine position with the Takeda TM2420 device (A&D) using the left arm and appropriate cuff sizes (25 × 12 cm [upper arm circumference ≤35 cm] and 30 × 15 cm [upper arm circumference >35 cm]) at baseline and every 10 min during the GFR measurements. MABP was calculated as diastolic BP plus one-third of the pulse amplitude. UAER was determined during each 4-h period by DAKO turbidimetry.

Blood glucose was measured by a glucose oxidase method on an autoanalyzer (One Touch 2, LifeScan, Milpitas, CA) every hour during the investigation. HbA_{1c} was measured by high-performance liquid chromatography (Variant; Bio-Rad, Hercules, CA). The normal range of HbA_{1c} in our laboratory is 4.1–6.4%.

The lower BP limit of normal autoregulation was defined as an MABP of 80 mmHg (the lower limit of normal autoregulation of GFR in animals [12–14]). A relative reduction induced by clonidine in GFR >13% (exceeding the normal limit of autoregulation of GFR in healthy humans [15]) was defined as impaired autoregulation. Abolished autoregulation was defined as a clonidine-induced relative change in GFR of >13% combined with a relative reduction in GFR greater than or equal to the relative reduction in MABP (ΔMABP% ≤ ΔGFR%).

Statistical analysis

Normally distributed data are expressed as means and SD or SE. All comparisons of normally distributed parameters were carried out with a Student's *t* test using paired design. A Mann-Whitney test was used for nonparametric data. All BP measurements during the 4-h period were used to calculate mean values and SE during each examination in each patient. Spearman's and linear regression analysis were used to analyze correlations between the absolute as well as the relative differences between the two examinations. Values for UAER were logarithmically transformed before inclusion in the analysis because of the positive skewed distribution. Data were tested for a period effect and a treatment–period interaction with a two-sample *t* test. Fisher's exact test was performed on dichotomous variables.

The number of patients needed (n = 16) was calculated using a power of 80%, a significant level of 5%, and a mean difference in GFR of 25%. We included 19 patients.

All calculations were made using SPSS for Windows (SPSS, Chicago, IL). A P value <0.05 was considered significant (two-tailed).

RESULTS — Clinical and demographic data for the 16 hypertensive type 2 diabetic patients without overt nephropathy are shown in Table 1. There were no significant differences in BP be-

Table 1—*Baseline clinical data of 16 type 2 diabetic hypertensive patients without overt nephropathy*

	Sex	Age (years)	Known duration of diabetes (years)	BMI (kg/m^2)	BP (mmHg)	Retinopathy	Antidiabetic treatment
Subject							
1	M	50	9	28	137/92	Nil	2
2	F	63	12	25	148/76	Simplex	3
3	M	52	10	30	152/84	Simplex	4
4	F	56	16	43	151/82	Nil	4
5	F	69	10	38	165/91	Nil	3
6	M	56	6	25	168/91	Nil	3
7	M	55	20	27	141/81	Proliferative	3
8	M	59	21	27	160/82	Simplex	3
9	M	64	16	30	168/90	Simplex	3
10	F	66	4	26	161/90	Nil	3
11	F	60	10	19	169/83	Nil	3
12	M	62	20	27	152/82	Proliferative	2
13	F	56	14	39	152/87	Simplex	3
14	M	62	14	31	163/90	Proliferative	3
15	F	50	20	31	156/71	Simplex	2
16	F	61	19	39	159/83	Nil	3
Mean ± SD		59 ± 6	14 ± 5	30 ± 6	156 ± 10/ 85 ± 6	—	—

1, Diet; 2, oral hypoglycemic treatment; 3, insulin treatment; 4, insulin and oral hypoglycemic treatment.

tween the screening visit and the randomization visit in patients previously treated with antihypertensives (mean difference in MABP −0.3 mmHg [95% CI −4.9 to 4.3]). All patients had normal GFR.

Half of the patients received isradipine during the first treatment period. The patients took 101% (range 94–105) of the tablets during the placebo period and 98% (range 86–104) of the tablets during the isradipine period (NS).

The individual changes in BP, GFR, and UAER induced by intravenous injection of 75 μg clonidine during the placebo and isradipine treatments are shown in Table 2. Intravenous injection of 75 μg clonidine induced a reduction in MABP of 15 ± 1 mmHg ($P < 0.01$) and 11 ± 1 mmHg ($P < 0.05$) during the placebo and isradipine treatment, respectively (Table 3). The mean difference in changes of MABP between placebo and isradipine treatment was 3.5 mmHg (95% CI 0.5–6.5) ($P < 0.05$). Clonidine did not reduce MABP below 80 mmHg during any of the treatment periods.

The mean difference in changes of GFR induced by clonidine between placebo and isradipine treatment was −4.6 ml · min^{-1} · 1.73 m^{-2} (95% CI −10.0 to 0.6) ($P = 0.08$; Table 3). Six (patients 2, 3, 8, 10, 11, and 16; Table 2) of 16 patients had impaired/abolished autoregulation of GFR during isradipine treatment, whereas all patients had normal GFR autoregulation during placebo ($P < 0.05$). Clonidine induced a comparable reduction in MABP during isradipine treatment in patients with ($n = 6$) or without ($n = 10$) impaired autoregulation (12 ± 2.6 vs. 11 ± 1.9 mmHg, respectively). The six patients with impaired autoregulation of GFR had an increase in baseline GFR of 10.6 ml · min^{-1} · 1.73 m^{-2} (95% CI −1.1 to 22.4) ($P = 0.07$) during isradipine treatment, whereas baseline GFR remained unchanged (mean difference 0.0 ml · min^{-1} · 1.73 m^{-2} [95% CI −9.4 to 9.4]) in the ten remaining patients during isradipine treatment ($P = 0.07$ between the groups).

Isradipine induced a similar reduction in MABP in patients with ($n = 6$) and without ($n = 10$) impaired autoregulation (8.9 ± 2.5 vs. 6.5 ± 2.2 mmHg, respectively). Furthermore, the patients with ($n = 6$) and without ($n = 10$) impaired autoregulation had nearly the same MABP level during treatment with isradipine (103 ± 5.8 vs. 99 ± 7.1 mmHg, respectively). No statistically significant differences in age, BMI, known diabetes duration, insulin treatment, HbA_{1c}, baseline BP, baseline GFR, and baseline UAER were revealed between patients with and without impaired autoregulation.

We found no significant correlation between the absolute changes in MABP (mmHg) and the absolute changes in GFR (ml · min^{-1} · 1.73 m^{-2}) during either of the two treatments. Furthermore, no significant correlation was found between the relative changes in MABP (%) and the relative changes in GFR (%) during either of the two treatments.

Blood glucose was not changed by intravenous injection of clonidine (Table 3). Neither a period effect (placebo/isradipine vs. isradipine/placebo; average difference 3.5 ± 12.9 vs. −1.0 ± 8.8, $P = 0.43$) nor a treatment–period interaction (placebo/isradipine vs. isradipine/placebo; average levels 7.4 ± 7 vs. 4.6 ± 8, $P = 0.43$) was found in relation to GFR.

The patients had no serious adverse events. Two patients experienced edema, one headache, one blushing, and one dizziness during isradipine treatment, whereas only one patient experienced an adverse reaction (dizziness) during the placebo treatment. Apart from dry mouth and sleepiness, no side effects were observed after clonidine injection.

CONCLUSIONS — Our double-blind randomized crossover study in hypertensive type 2 diabetic patients without overt nephropathy showed preserved autoregulation of GFR during treatment with pla-

Table 2—*Arterial BP, GFR, and UAER in 16 hypertensive type 2 diabetic patients without overt nephropathy*

	BP		GFR		UAER	
	Before clonidine (mmHg)	After clonidine (mmHg)	Before clonidine ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	After clonidine ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	Before clonidine ($\mu g/min$)	After clinidine ($\mu g/min$)
Placebo subject						
1	154/92 ± 2/1	132/84 ± 2/2	131	120	6	6
2	134/89 ± 2/2	112/78 ± 2/1	113	104	14	5
3	167/85 ± 2/1	141/81 ± 3/1	96	94	3	8
4	139/92 ± 1/1	125/86 ± 1/1	104	103	3	3
5	130/84 ± 2/3	123/63 ± 2/2	121	114	2	5
6	132/90 ± 2/1	108/73 ± 2/2	103	102	6	2
7	155/100 ± 2/3	131/86 ± 1/1	109	111	21	15
8	143/83 ± 2/2	131/73 ± 3/3	104	96	1	4
9	183/87 ± 1/1	176/80 ± 1/1	91	92	111	45
10	153/89 ± 1/1	130/79 ± 2/1	66	67	7	2
11	161/88 ± 2/1	114/65 ± 3/1	93	84	5	2
12	146/75 ± 1/1	133/67 ± 1/1	93	87	7	6
13	150/80 ± 3/1	132/67 ± 1/1	121	117	273	218
14	159/96 ± 1/1	136/86 ± 1/1	94	97	11	12
15	161/83 ± 3/2	138/70 ± 2/1	107	106	164	30
16	152/78 ± 2/1	124/69 ± 3/2	90	83	6	2
Mean	151/87 ± 3/2	130/75 ± 4/2	102 ± 4	99 ± 4	10 ± 1*	7 ± 1*
P	<0.001		<0.01		NS	
Isradipine subject						
1	146/84 ± 1/1	127/84 ± 2/2	129	126	5	5
2†	127/75 ± 1/1	107/70 ± 2/1	121	93	6	3
3†	163/80 ± 2/1	138/79 ± 2/1	128	104	3	4
4	138/92 ± 1/2	117/69 ± 2/2	118	106	2	5
5	133/78 ± 2/2	121/67 ± 4/2	123	123	3	2
6	139/92 ± 2/1	110/76 ± 3/2	103	103	8	3
7	146/89 ± 1/1	128/79 ± 1/2	104	103	21	15
8†	151/80 ± 2/1	125/72 ± 3/2	112	92	10	4
9	155/73 ± 1/1	136/73 ± 2/1	76	80	7	6
10†	126/77 ± 2/2	113/76 ± 2/1	78	67	3	2
11†	146/81 ± 1/1	113/64 ± 1/2	96	72	9	3
12	129/70 ± 2/2	126/69 ± 1/1	86	83	1	1
13	156/81 ± 3/1	131/76 ± 2/1	147	142	214	105
14	149/82 ± 2/1	130/75 ± 1/2	101	96	11	9
15	143/81 ± 1/2	128/77 ± 2/1	88	98	93	97
16†	132/71 ± 2/1	121/63 ± 2/1	91	79	4	3
Mean	143/80 ± 3/2	123/73 ± 2/1	106 ± 5	98 ± 5	8 ± 1*	6 ± 1*
P	<0.001		<0.01		<0.05	

Data are means ± SE or *geometric mean ± antilog SE. †Patients with blunted autoregulation during isradipine therapy.

cebo, whereas isradipine therapy induced a variable response ranging from no impact to impaired or abolished GFR autoregulation. Even though intravenous injection of clonidine reduced MABP more during placebo treatment compared with isradipine therapy, none of the placebo-treated patients experienced a reduction in GFR >13% (the limit of normal GFR autoregulation in healthy humans [15]), whereas 38% of the isradipine-treated patients showed complete pressure-passive vasculature ($\Delta MABP\% \leq \Delta GFR\%$).

A reduced autoregulation capacity during isradipine treatment is also supported by the clonidine-induced pressure-dependent reduction in UAER. A limited power, due to a large variation in the response to clonidine injection during the isradipine therapy, is a likely explanation for the borderline significant difference between the mean differences in GFR.

The validity of applied methods to evaluate GFR autoregulation has previously been described in detail (16,17). We used the maximal initial dose of isradipine (5 mg o.d.) recommended in Denmark.

Table 3—*Changes in GFR, systolic and diastolic BP, MABP, UAER, and blood glucose induced by intravenous injection of 75 μg clonidine in 16 hypertensive type 2 diabetic patients without overt nephropathy treatment with placebo or 5 mg isradipine retard*

	Before clonidine	After clonidine	Mean difference (95% CI)	*P*
GFR (ml · min^{-1} · 1.73 m^{-2})				
Placebo	102	99	3.7 (1.3 to 6.1)	<0.01
5 mg isradipine retard	106	98	8.3 (2.5 to 14.2)	<0.01
Systolic BP (mmHg)				
Placebo	151	130	21 (16 to 26)	<0.001
5 mg isradipine retard	143	123	19 (15 to 24)	<0.001
Diastolic BP (mmHg)				
Placebo	87	75	12 (9 to 14)	<0.001
5 mg isradipine retard	80	73	7 (4 to 11)	<0.001
MABP (mmHg)				
Placebo	108	94	15 (12 to 18)	<0.001
5 mg isradipine retard	101	90	11 (8 to 15)	<0.001
Log (UAER) (μg/min)				
Placebo	1.01	0.87	0.15 (−0.06 to 0.35)	NS
5 mg isradipine retard	0.89	0.75	0.13 (0.02 to 0.25)	<0.05
Blood glucose (mmol/l)				
Placebo	9.1	9.5	−0.4 (−2.0 to 1.2)	NS
5 mg isradipine retard	9.3	9.9	−0.6 (−1.7 to 0.5)	NS

Because markers of the immune destruction of the β-cell, such as autoantibodies to GAD, were not measured in our study, we cannot exclude that a fraction of the patients might have type 1 latent-autoimmune diabetes in adults, e.g., patient 11.

Experimental studies suggest that autoregulation in GFR is due to autoregulation in two of the main GFR determinants, i.e., renal plasma flow and glomerular capillary hydraulic pressure (18). The afferent arteriole plays a pivotal role in regulating glomerular capillary pressure, renal plasma flow, and consequently GFR (19). The myogenic control of renal autoregulation is primarily regulated by afferent arteriolar smooth muscle permeability to Ca^{2+} (20), whereas the efferent arteriolar seems to be less responsive to alterations in membrane Ca^{2+} permeability (20). Data have revealed that the major vasoconstrictive effect of raised extracellular ionized Ca^{2+} is a pressure-dependent alteration in membrane Ca^{2+} permeability (4). Because calcium-channel blockers interfere with the influx of Ca^{2+}, they may affect normal renal autoregulation. In agreement with our study, studies in dogs (5), isolated perfused rat kidneys (4), normal rat kidneys (21), rat remnant kidney models (22), models of spontaneously hypertensive rats (23), and rat models of diabetes (24) have all demonstrated that calcium-channel blockers may impair renal autoregulation. However, even though most studies show that both dihydropyridine and nondihydropyridine calcium-channel blockers impair autoregulation, some studies indicate that there might be differences in the vascular responses within and between the different classes of the drugs (25–27). The different actions of the various calcium-channel blockers on renal function, structure, and autoregulation may be related to differences in tissue selectivity and binding sites (28). Griffin et al. (29,30) recently demonstrated that dihydropyridine and selective T- and L-type calcium-channel blockers, but not nondihydropyridine calcium-channel blockers, cause additional impairment of the already impaired renal autoregulation in rat remnant kidney models. Furthermore, at any given BP elevation, greater glomerulosclerosis was seen in the rats with additional impairment (abolished) of renal autoregulation compared with untreated rats. Because 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 BP can lead to enhanced transmission of the systemic pressure into the glomerular capillary network, inducing glomerular hypertension (31,32). This hemodynamic alteration is associated with an increase in albuminuria and acceleration of the glomerular damage (33). Consequently, it is of major pathophysiological importance that the GFR autoregulation is intact. In this context, it is also important to select an antihypertensive treatment that does not interfere with GFR autoregulation. Our study revealed that patients with impaired autoregulation of GFR had an increase in GFR during isradipine treatment. The enhanced GFR in these patients probably reflects a more pronounced vasodilatation of the afferent arteriole during isradipine treatment as compared with patients without this response. This vasodilatation enhances the transmission of the systemic BP into the glomerular capillary network, resulting in exaggerated GFR variation.

Recently, we demonstrated that an angiotensin II receptor antagonist reduced BP from 153/89 to 141/85 mmHg without altering the preserved ability to autoregulate GFR in hypertensive type 2 diabetic patients without nephropathy (17). The demographic, clinical, and laboratory data in these patients (17) and the present patients are very similar. Furthermore, the BP levels in the aforementioned and present study during the placebo treatment period were also almost the same. This comparison suggests that the

impaired autoregulation demonstrated in the present study is not due to the BP-lowering effect of isradipine but is due to impairment of the GFR autoregulation. This interpretation is also supported by the comparison between the six patients with abolished autoregulation compared with the ten with preserved autoregulation. The two groups had identical reduction in BP after clonidine injection. Finally, we did not find any correlation between the relative changes in BP and in GFR or with the absolute changes in BP or GFR. From a kidney point-of-view, angiotensin II receptor blockers, ACE inhibitors, and β-blockers may therefore be superior to, e.g., calcium-channel blockers.

Several studies in streptozotocin-induced diabetic rats and dogs have suggested that hyperglycemia induces impaired autoregulation of renal blood flow and GFR (34). In the present study, there was no difference in glycemic control during the examinations. Furthermore, we have evaluated the impact of acute changes in blood glucose in type 2 diabetic patients without nephropathy and found that autoregulation was not affected by blood glucose levels >15 mmol/l (16).

The potential importance of insulin resistance in relation to renal autoregulation remains to be clarified.

In conclusion, isradipine impairs the autoregulation of GFR in a sizeable proportion of hypertensive type 2 diabetic patients.

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