Kidney International, Vol. 56 (1999), pp. 1517–1523

Impaired autoregulation of the glomerular filtration rate in patients with nondiabetic nephropathies

Per K. Christensen, Eva E. Hommel, Peter Clausen, Bo Feldt-Rasmussen, and Hans-Henrik Parving

Steno Diabetes Center, Gentofte, and Department of Nephrology, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark

Impaired autoregulation of the glomerular filtration rate in patients with nondiabetic nephropathies.

Background. 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. Defective autoregulation of GFR has been demonstrated in diabetic nephropathy. Whether this is also the case in patients with nondiabetic nephropathies is not known.

Methods. We investigated the effect of acute lowering of blood pressure (BP) on GFR in 16 (8 males and 8 females) albuminuric subjects suffering from different nondiabetic nephropathies and in 14 (7 males and 7 females) controls matched with respect to sex, age, BP, and baseline GFR. The subjects received in random order an intravenous injection of either clonidine (150 to 225 μg) or saline (0.154 mmol/liter) within two weeks. We measured GFR ([^{51}Cr]-EDTA), albuminuria (enzyme-linked immunosorbent assay; ELISA), and BP (Takeda TM-2420).

Results. Clonidine induced similar reductions in mean arterial BP 17 (2) versus 19 (2) mm Hg [mean (SE)] in patients with nephropathy and in controls, respectively. GFR diminished in average from 89 (6) to 82 (5) ml/min/1.73 m^2 ($P < 0.05$), and albuminuria declined from a geometric mean of 1218 (antilog SE 1.3) μg/min to 925 (1.3) in the patients with nondiabetic nephropathies ($P < 0.05$), whereas these variables remained unchanged in the control group. The mean difference between changes in GFR (95% confidence interval) between the nondiabetic macroalbuminuric and control subjects was 6.1 (−0.03 to 12.21) ml/min/1.73 m^2 ($P = 0.051$).

Conclusion. Our study suggests that albuminuric patients with nondiabetic nephropathies frequently suffer from impaired autoregulation of GFR.

The ability of the kidney to maintain constancy of glomerular filtration rate (GFR) over a wide range of renal perfusion pressures is termed autoregulation [1]. We have previously demonstrated that autoregulation of GFR is defective in type 1 and type 2 diabetic patients with diabetic nephropathy [2, 3]. Furthermore, it has been shown that an initiation of antihypertensive treatment induces a faster initial and slower subsequent decline in GFR in hypertensive type 1 and type 2 diabetic patients with incipient or overt diabetic nephropathy [4–6], which may be due to a functional (hemodynamic) effect of antihypertensive treatment and/or changes in autoregulation mechanisms in patients with diabetic nephropathy [7, 8]. The same biphasic phenomenon has also been shown in patients with nondiabetic nephropathies, but the autoregulation of GFR has not been evaluated [9, 10].

Elevated blood pressure (BP) is common in patients with nephropathy and may accelerate the injuries of the glomerular capillaries because the protection against increased hydrostatic pressure and/or increased flow is diminished because of impaired autoregulation.

Therefore, the aim of our case-control study was to investigate the effect of acute BP reduction on GFR in albuminuric patients with nondiabetic nephropathies.

METHODS

We selected 16 nondiabetic subjects with albuminuria (>300 mg/24 hr). A kidney biopsy had been performed in 15 of the 16 patients, showing different types of glomerulonephritis ($N = 12$), minimal change ($N = 1$), focal glomerulosclerosis ($N = 1$), and near normal structure ($N = 1$) (Table 1). Fourteen nondiabetic normoalbuminuric subjects who matched the patients with nephropathy in respect to sex, age, and arterial BP level were studied as a control group (Tables 1 and 2).

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

Three of the patients with albuminuria received anti-

Key words: albuminuria, renal perfusion pressure, glomerular filtration rate, blood pressure, autoregulation.

Received for publication January 11, 1999
and in revised form April 13, 1999
Accepted for publication May 18, 1999

Table 1. Clinical data of nondiabetic subjects with and without nephropathy

Subjects	Sex	Age *years*	Time between kidney biopsy and examination *years*	Diagnosis	Duration of disease[a] *years*
Patients with macroalbuminuria *N* (M/F) = 8/8					
1	M	33	0.5	GN, epimembranous	0.5
2	M	34	6	GN, unclassified	27
3	F	21	1	GN, proliferative	1.5
4	F	23	0.5	GN, proliferative	12
5	M	33	0.5	GN, unclassified	4
6	M	49	0.5	GN, epimembranous	0.5
7	F	59	1.5	Minimal change	3
8	M	50	0.5	Glomerulosclerosis	0.5
9	M	15	0.5	GN, proliferative	0.5
10	F	42	7	GN, proliferative	7
11	F	38		Not done	2
12	F	29	1	GN, proliferative	1
13	M	31	9	GN, proliferative	9
14	F	49	2	GN, proliferative	30
15	F	44	17	GN, proliferative	18
16	M	51	7	Near normal structure	9
Mean (SD)		38 (12)			
Control subjects *N* (M/F) = 7/7					
1	F	35			
2	M	35			
3	M	32			
4	M	32			
5	F	36			
6	F	25			
7	F	33			
8	M	50			
9	M	30			
10	M	45			
11	F	66			
12	F	32			
13	F	60			
14	M	35			
Mean (SD)		39 (12)			

Abbreviation GN is glomerulonephritis.
[a]Time between onset of albuminuria and examination.

hypertensive treatment before the study. One was treated with β-blocker, one with bendroflumethiazid, and one with spironlacton and nifedipine. None of the controls received antihypertensive treatment.

Patients treated with antihypertensive drugs stopped the antihypertensive treatment four weeks before the first examination.

We performed a randomized single-blind case-control study. The study was performed twice within two weeks, with the subjects receiving a slow intravenous injection (10 min) of either clonidine (150 to 225 μg; Boehringer, Ingelheim, Germany) or saline (0.154 mmol/liter) in random order.

The patients had their usual breakfast.

The GFR was measured in a four-hour period (9 a.m. to 1 p.m.) after a single intravenous injection of 3.7 MBq of Na ^{51}Cr-labeled eidetic acid ([^{51}Cr]-EDTA) by determining the radioactivity in venous blood samples taken at 180, 200, 220, and 240 minutes after the injection [11, 12]. The small underestimation (10%) of ^{51}Cr-EDTA clearance versus clearance of inulin was corrected for by multiplying EDTA clearance by 1.10 [11]. 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 from day to day was 4%.

To correct for baseline/residual radioactivity, a venous blood sample was taken at each GFR determination before the injection of ^{51}Cr-EDTA.

Patients rested supine during the entire investigation and drank approximately 200 ml of tap water per hour. BP and heart rate was measured with the Takeda TM2420 device (A&D, Tokyo, Japan) using the 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 of rest in the supine position and every 10 minutes during the GFR measurements. The mean arterial BP (MABP) was calculated as the diastolic BP plus one third of the pulse amplitude.

Urinary albumin excretion (UAE) during the four-hour period was determined by using an enzyme-linked

Table 2. Arterial blood pressure (BP), glomerular filtration rate (GFR) and urinary albumin excretion (UAE) in nondiabetic subjects with and without nephropathy

	BP[a] *mm Hg*		GFR[a] *ml/min/1.73 m²*		UAE[b] *μg/min*	
Subjects	Before clonidine	After clonidine	Before clonidine	After clonidine	Before clonidine	After clonidine
Patients with nephropathy						
1	130/83 (6/3)	108/68 (4/6)	99	97	2961	1942
2	129/76 (5/5)	109/69 (8/5)	121	102	726	477
3	121/68 (4/6)	95/53 (3/3)	107	73	964	255
4	115/70 (5/4)	95/59 (7/4)	100	87	804	1052
5	108/70 (5/3)	100/69 (3/3)	82	79	1527	2004
6	140/87 (8/5)	121/78 (7/4)	75	71	1417	1595
7	121/78 (5/3)	88/59 (5/3)	74	79	203	152
8	156/95 (5/8)	129/84 (6/5)	69	62	9297	6749
9	122/77 (4/6)	108/68 (3/3)	137	132	4825	6976
10	155/96 (1/13)	118/84 (15/14)	40	48	888	758
11	127/85 (8/5)	104/71 (14/7)	115	99	693	756
12	118/78 (8/5)	94/66 (11/8)	88	92	1977	1064
13	171/109 (8/6)	127/89 (5/4)	95	79	322	250
14	110/74 (5/6)	96/63 (4/4)	85	78	682	374
15	133/93 (6/4)	104/79 (5/4)	66	68	681	351
16	164/108 (9/4)	118/87 (8/5)	69	58	3932	2537
	133/84 (19/13)	107/72 (12/11)	89 (24)	81 (20)	1218 (1.3)	925 (1.3)
	$P < 0.01$		$P < 0.05$		$P < 0.05$	
Control subjects						
1	118/82 (3/4)	99/71 (8/8)	101	105	7	7
2	139/88 (5/8)	103/65 (7/5)	93	90	10	5
3	112/67 (2/3)	101/64 (4/3)	98	97	7	7
4	109/75 (2/1)	78/52 (6/7)	98	98	6	7
5	133/89 (5/4)	104/76 (3/6)	92	89	5	6
6	147/108 (3/6)	130/93 (4/5)	113	105	28	17
7	129/88 (5/11)	110/75 (4/3)	88	92	3	4
8	181/114 (4/4)	146/97 (6/3)	79	75	6	7
9	152/99 (7/5)	127/83 (6/3)	99	99	7	5
10	178/109 (8/4)	146/99 (6/3)	76	73		
11	149/87 (7/5)	108/73 (12/7)	70	61	2	2
12	123/76 (5/7)	94/58 (8/5)	119	115	4	4
13	145/91 (7/4)	115/78 (10/4)	87	88	8	3
14	160/85 (6/6)	117/71 (4/4)	111	119	4	3
	141/89 (22/14)	113/75 (19/14)	95 (14)	93 (16)	6 (1.2)	5 (1.2)
	$P < 0.01$		NS		NS	

Results are expressed as [a]mean (SD) and [b]geometric mean (antilog SE)

immunoadsorbent assay (ELISA), intra-assay variation 2.1%, and interassay variation 8.3% [13]. Residual urine was determined by an ultrasonic diagnosis apparatus (Toshiba Sonolayergraph SAL-20A; Tokyo Shibaura Electric Co., Tokyo, Japan). Morning urine was tested for bladder infection by a stix (Nephur-Test, Boehringer Mannheim, Germany).

Statistical analysis

Normally distributed data are expressed as mean and standard deviation (SD) or standard error of the mean (SE). Values for albuminuria 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. Fisher's exact test was used to evaluate proportions or dichothomans variables. All BP 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 were transformed into relative changes, and linear regression analysis was used to analyze for correlations. 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 causes of albuminuria in the nondiabetic patients are shown in Table 1. The two groups were well matched regarding age, sex, BP, and GFR (Tables 1 and 2).

Five (31%) patients with albuminuria and seven

(50%) of the controls had a baseline BP > 140/90 mm Hg (P = NS). In the group of patients with nondiabetic nephropathies, three had previously received antihypertensive treatment. No one in the control group had previous been treated with antihypertensive drugs. Intravenous clonidine injection induced an equal and significant reduction in MABP of 17 mm Hg and 19 mm Hg in patients with nephropathy and control subjects, respectively ($P < 0.05$; Table 2). MABP was reduced below 80 mm Hg in six (38%) of the patients with nephropathy versus four (29%) in the controls (P = NS). The arterial BP reduction for each patient is shown in Table 2.

Twelve out of 16 patients with nephropathy had a reduction in GFR (mean difference 7.4 ml/min per 1.73 m^2, $P < 0.05$) versus the control group, in which only 8 out of 14 patients had a reduction (mean difference of 1.3 ml/min per 1.73 m^2, P = NS) after clonidine injection. Seven of the patients with nephropathy had an abnormal autoregulation of GFR, that is, a more than 10% reduction in relative GFR compared with only one in the control group. The mean difference between changes in GFR (95% confidence interval) between the nephropathic and control subjects was 6.1 (÷ 0.03 to 12.2) ml/min/1.73 m^2 ($P = 0.051$).

The reduction in GFR in the control group between subjects with and without hypertension was alike. The mean difference between changes in GFR was 1.7 (÷ 3.7 to 7.2) ml/min/1.73 m^2 (P = NS).

We found no significant correlation between the relative change in mean arterial blood pressure (MABP; %) and the relative change in GFR (%) in the patients with albuminuria (Fig. 1). Three patients with nephropathy had a nearly equal relative change in MABP and GFR (Fig. 1), whereas none in the control group had a complete pressure-passive vasculature. A significant correlation between the relative reduction in MABP (%) and the relative change in albuminuria (%) was demonstrated in patients with nondiabetic nephropathies (r = 0.55, $P < 0.03$).

A significant correlation between the relative change in GFR (%) and baseline GFR was revealed in the group of patients with nephropathy (r = 0.55, $P < 0.03$).

No correlation was found between the autoregulation index [relative change in GFR (%)/relative change in MABP (%)] and the duration of kidney disease (r = 0.09, P = 0.74) nor baseline albuminuria (r = 0.41, P = 0.17) in the albuminuric patients.

Eleven out of 16 patients with nondiabetic nephropathy had a reduction in albuminuria ($P < 0.05$), and seven of these patients also had a reduction in GFR.

The relative change in GFR (%) did not correlate with the relative change in albuminuria (%). Apart from a dry mouth and sleepiness, no side-effects were observed after clonidine injection.

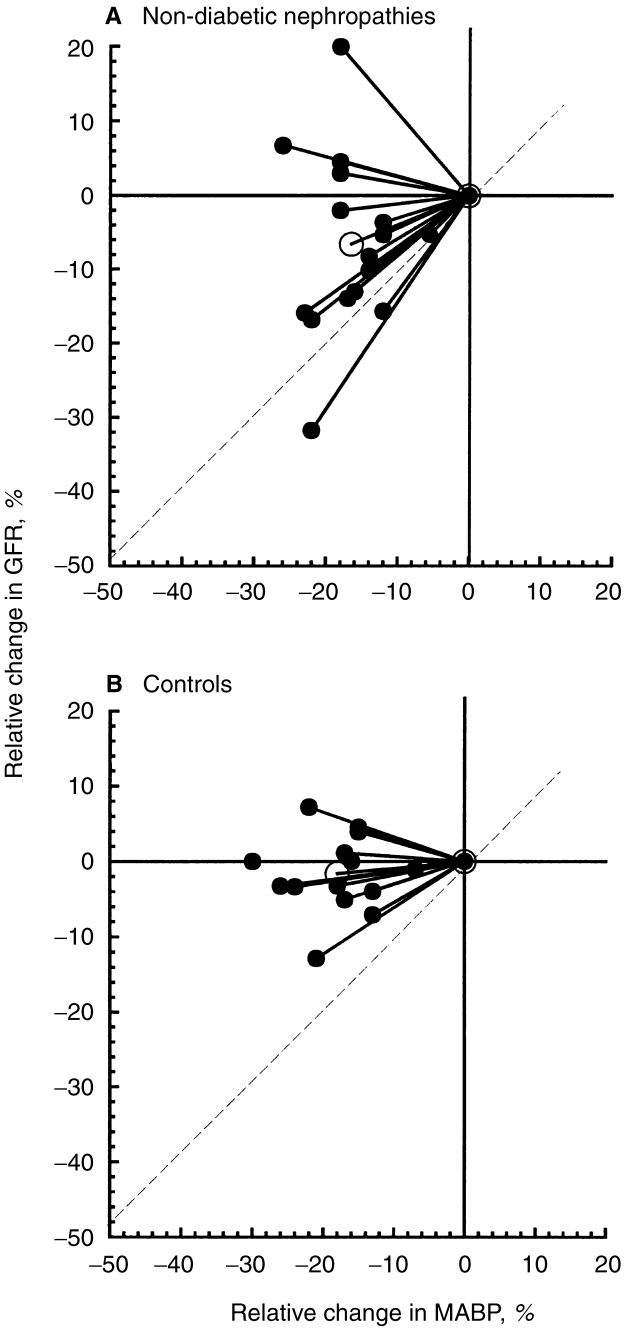

Fig. 1. Relative change in glomerular filtration rate (GFR; percentage change of control GFR) and relative change in mean arterial blood pressure (MABP; percentage change of control MABP) induced by intravenous injection of clonidine. (*A*) Sixteen patients with nondiabetic nephropathies (●) and their mean response (○). (*B*) Fourteen controls (●) and their mean response (○).

DISCUSSION

Our randomized, single-blinded case-control study shows that acute lowering of BP following an intravenous injection of clonidine reduces GFR and albuminuria in patients with different nondiabetic nephropathies. The

changes in GFR induced by acute lowering of BP revealed a wide variation in autoregulation capability ranging from normal to severely impaired. A complete pressure-passive vasculature was found in 3 out of 16 albuminuric patients [Δ MABP (%) = Δ GFR (%)], whereas none of the control subjects revealed this phenomenon. Our results suggest that the lower normal limit of the autoregulation of the kidney in normoalbuminuric nondiabetic human beings may be below the lower normal limit of autoregulation, that is, 80 mm Hg found in animal studies [1, 14–17].

We used clonidine as a BP-lowering drug because clonidine has no direct pharmacological effects on the renal vessels [18–20] and no peripheral sympathetic inhibition. Intravenous injection of clonidine in normotensive and hypertensive subjects induces a slight but insignificant reduction in peripheral and renal vein renin concentration [18, 20]. The decrease in the BP is due to diminished cardiac output, not to effects on total peripheral resistance [19, 20]. An intravenous injection of clonidine (150 to 300 μg) to normotensive and hypertensive nondiabetic subjects induces no significant change in renal plasma flow and GFR [2, 18, 20]. The average reduction in MABP ranges from 17 to 27 mm Hg in the three studies mentioned earlier in this article. Because the relative reduction in GFR did not exceed 10% of the baseline value in any of these studies, this level was used as a cutoff for normal GFR autoregulation.

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 the classic renal clearance procedures [11, 12]. Furthermore, subjects receiving intravenous clonidine cannot stand up and void within four to five hours after the injection because of the orthostatic BP drop.

Originally, we reported defective GFR autoregulation in type 1 diabetic patients with diabetic nephropathy and in hypertensive type 2 diabetic patients with or without diabetic nephropathy also applying clonidine as a BP-lowering drug [2, 3]. In our prior studies of diabetic patients with and without nephropathy and in this study, an intravenous injection of (150 to 225 μg) clonidine induced nearly the same reduction in average MABP in all groups, ranging from 14 to 21 mm Hg (Fig. 2). This reduction in MABP reduced significant GFR with 7 to 9 ml/min in patients with nephropathy, whereas no significant reduction in GFR was demonstrated in the normoalbuminuric groups (Fig. 2). These results suggest that autoregulation is impaired in albuminuric patients independent of the cause of albuminuria. The lack of correlation between relative change in MABP (%) and that in GFR and between the relative change in GFR (%) and that in albuminuria and between the autoregulation index and baseline albuminuria is not entirely unexpected taking into account the heterogenous causes of proteinuria, its only partial dependence on glomerular capillary hydraulic pressure (P_{GC}), the rise in P_{GC} when systemic arterial BP drops below the autoregulatory range [21], and the rather small number of patients investigated. Furthermore, the variation in the relative change in MABP (%) between patients was rather narrow.

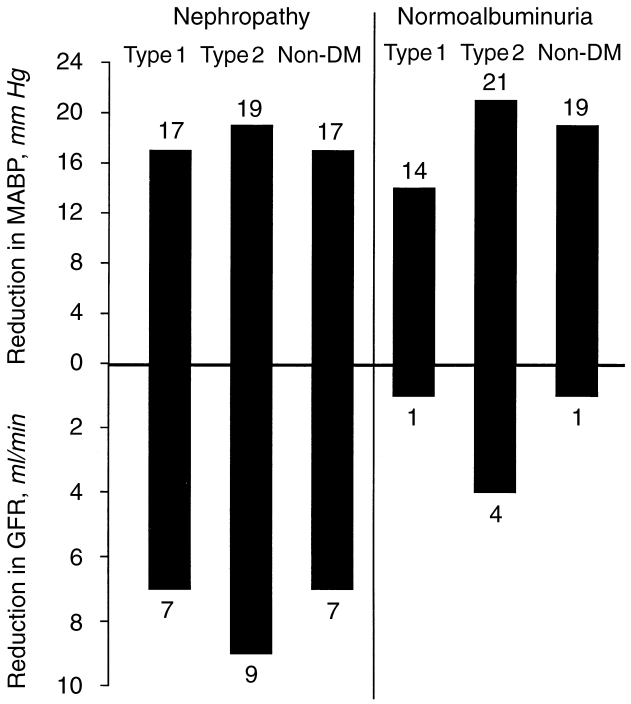

Fig. 2. Reduction in mean arterial blood pressure (MABP) and glomerular filtration rate (GFR) induced by intravenous injection of clonidine in type 1 and type 2 diabetic patients with or without nephropathy and in nondiabetic (non-DM) subjects with or without nephropathy.

Experimental data indicate that when BP drops below the autoregulatory range, the efferent arteriole will constrict, thereby decreasing renal plasma flow and increasing glomerular capillary hydraulic pressure in order to maintain GFR [21]. This compensatory phenomena may have contributed to the lack of correlation, as six of the albuminuric patients (38%) had a reduction in MABP to below 80 mm Hg.

The positive correlation between the relative change in GFR (%) and baseline GFR was unexpected, but strongly depended on one patient, number 10, who had a 20% increase in GFR despite an 18% lowering of MABP ($r = 0.34$, $P = 0.22$). This correlation disappeared if patient number 10 (this patient had an increase of 20% in GFR) was excluded.

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 [22, 23]. Experimental studies suggest that autoregulation of GFR

is due to autoregulation of two of the main GFR determinants, that is, renal plasma flow and glomerular capillary pressure [1, 24]. The afferent arteriole plays a pivotal role in regulating glomerular capillary pressure, renal plasma flow, and, consequently, GFR [1, 25–29]. 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, a 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, and glomerular hypertension [30–32]. This hemodynamic alteration is associated with an increase in proteinuria and an acceleration of glomerulosclerosis [24].

In our nephropathic patients, only one patient had arteriolar lesions, but lesions could have developed in some of the other patients because our study was performed 0.5 to 17 years after the kidney biopsies were performed. However, impaired autoregulation can be observed in some animal models in the absence of arteriolar hyalinosis [33–35]. Prostaglandins and the renin-angiotensin system may contribute [22, 23, 33, 36, 37], but information is as yet inconclusive [29, 37–39].

Albuminuria is the best single predictor of renal disease progression independent of the nature of the underlying disease [40]. Conversely, it is important to evaluate the effect and possible mechanisms of antihypertensive drugs on albuminuria in patients with nephropathy. We found a decrease in albuminuria induced by acute BP reduction and a significant correlation between the relative reduction in MABP (%) and the relative change in albuminuria (%), suggesting that albuminuria, to some extent, is pressure dependent, probably because of diminished glomerular capillary hydrostatic pressure, associated with the decrease in systemic arterial BP. Furthermore, some studies have shown that antihypertensive drugs, which are capable of reducing albuminuria in patients with nondiabetic nephropathies, are more renoprotective compared with antihypertensive drugs without this effect [41–45]. Studies in the 5/6 renal ablation model have revealed that glomerular transmission of hypertension plays a predominant role in the pathogenesis of progressive glomerular injury and proteinuria [46]. Furthermore, these studies stress the critical importance of an autoregulatory mechanism in such a transmission and suggest that antihypertensive agents, such as short-acting nifedipine, which adversely affects autoregulatory ability and thereby enhances pressure transmission, may not provide renoprotection despite significantly reducing systemic arterial BP.

Initiation of antihypertensive treatment induces a faster initial and a slower sustained decline in GFR in diabetic and nondiabetic patients [5, 8, 10, 47]. An acutely steep initial decline in GFR may predict a more stable decline in GFR later [10]. These findings may in part explain the initial decline in GFR and the long-term beneficial effect of aggressive antihypertensive treatment on albuminuria and the progression of diabetic and nondiabetic nephropathies.

In conclusion, this study demonstrates that nondiabetic patients with albuminuria often suffer from defective autoregulation of GFR, making the kidney unprotected against changes in systemic BP.

Reprint requests to Per K. Christensen, M.D., Steno Diabetes Center, Niels Steensens Vej 2, DK-2820 Gentofte, Denmark.

REFERENCES

1. Maddox DA, Brenner BM: Glomerular ultrafiltration, in *The Kidney*, edited by Brenner BM, Philadelphia, Saunders, 1996, p 286
2. Parving H-H, Kastrup J, Smidt UM, Andersen AR, Feldt-Rasmussen B, Christiansen JS: Impaired autoregulation of glomerular filtration rate in type 1 (insulin-dependent) diabetic patients with nephropathy. *Diabetologia* 27:547–552, 1984
3. Christensen PK, Hansen HP, Parving H-H: Impaired autoregulation of GFR in hypertensive non-insulin dependent diabetic patients. *Kidney Int* 52:1369–1374, 1997
4. Björck S, Mulec H, Johnsen SA, Nordén G, Aurell M: Renal protective effect of enalapril in diabetic nephropathy. *BMJ* 304:339–343, 1992
5. Parving H-H, Andersen AR, Smidt UM, Hommel E, Mathiesen ER, Svendsen PA: Effect of antihypertensive treatment on kidney function in diabetic nephropathy. *BMJ* 294:1443–1447, 1987
6. Lebovitz HE, Wiegmann TB, Cnaan A, Shahinfar S, Sica D, Broadstone V, Schwartz SL, Mengel MC, Segal R, Versaggi JA, Bolten WK: Renal protective effects of enalapril in hypertensive NIDDM: Role of baseline albuminuria. *Kidney Int* 45(Suppl 45):S150–S155, 1994
7. Hansen HP, Rossing P, Tarnow L, Nielsen FS, Jensen BR, Parving H-H: Increased glomerular filtration rate after withdrawal of long-term antihypertensive treatment in diabetic nephropathy. *Kidney Int* 47:1726–1731, 1995
8. Hansen HP, Nielsen FS, Rossing P, Jacobsen P, Jensen BR, Parving H-H: Kidney function after withdrawal of long-term antihypertensive treatment in diabetic nephropathy. *Kidney Int* 52(Suppl):S49–S53, 1997
9. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G, for the Modification of Diet in Renal Disease Study Group: The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med* 330:877–884, 1994
10. Apperloo AJ, De Zeeuw D, De Jong PE: A short-term antihypertensive treatment-induced fall in glomerular filtration rate predicts long-term stability of renal function. *Kidney Int* 51:793–797, 1997
11. Bröchner-Mortensen J, Rödbro P: Selection of routine method for determination of glomerular filtration rate in adult patients. *Scand J Clin Lab Invest* 36:35–45, 1976
12. Bröchner-Mortensen J: A simple method for the determination of glomerular filtration rate. *Scand J Clin Lab Invest* 30:271–274, 1972
13. Feldt-Rasmussen B, Dinesen B, Deckert M: Enzyme immunoassay: An improved determination of urinary albumin in diabetics with incipient nephropathy. *Scand J Clin Lab Invest* 45:539–544, 1985
14. Thurau K: Renal hemodynamics. *Am J Med* 36:698–719, 1964
15. Selkurt EE, Hall PW, Spencer MP: Influence of graded arterial pressure decrement on renal clearance of creatinine, p-aminohippurate and sodium. *Am J Physiol* 159:369–378, 1949
16. Forster RP, Maes JP: Effect of experimental neurogenic hypertension on renal blood flow and glomerular filtration rate in intact denervated kidneys of unanesthetized rabbits with adrenal glands demedulated. *Am J Physiol* 150:534–540, 1947
17. Shipley RE, Study RS: Changes in renal blood flow, extraction

of insulin, glomerular filtration rate, tissue pressure and urine flow with acute alteration of renal artery blood pressure. *Am J Physiol* 167:676–688, 1951
18. Brod J, Horbach L, Just H, Rosenthal J, Nicolescu R: Acute effects of clonidine on central and peripheral haemodynamics and plasma renin activity. *Eur J Clin Pharmacol* 4:107–114, 1972
19. Onesti G, Bock KD, Heimsoth V, Kim KE, Merguet P: Clonidine: A new antihypertensive agent. *Am J Cardiol* 28:74–83, 1971
20. Onesti G, Schwartz AB, Kim KE, Paz-Martinez V, Swartz C: Antihypertensive effect of clonidine. *Circ Res* 28:53–69, 1971
21. Robertson CR, Deen WM, Troy JL, Brenner BM: Dynamics of glomerular ultrafiltration in the rat. III. Hemodynamics and autoregulation. *Am J Physiol* 223:1191–1200, 1972
22. Dustin P: Arteriolar hyalinosis. *Int Rev Exp Pathol* 1:73–138, 1962
23. Østerby R, Gall M-A, Schmitz A, Nielsen FS, Nyberg G, Parving H-H: Glomerular structure and function in proteinuric type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 36:1064–1070, 1993
24. Anderson S: Relevance of single nephron studies to human glomerular function. *Kidney Int* 45:384–389, 1994
25. Aukland K, Oeien AH: Renal autoregulation: Models combining tubuloglomerular feedback and myogenic response. *Am J Physiol* 252:F768–F783, 1987
26. Hayashi K, Epstein M, Loutzenhiser R: Determinants of the renal actions of atrial natriuretic peptide (ANP): Lack of effect of ANP on pressure-induced vasoconstriction. *Circ Res* 67:1–10, 1990
27. Hayashi K, Epstein M, Loutzenhiser R: Pressure-induced vasoconstriction of renal microvessels in normotensive and hypertensive rats: Studies in the isolated perfused hydronephrotic kidney. *Circ Res* 65:1475–1484, 1989
28. Hayashi K, Epstein M, Loutzenhiser R, Forster H: Impaired myogenic responsiveness of the afferent arteriole in streptozotocin-induced diabetic rats: Role of eicosanoid derangements. *J Am Soc Nephrol* 2:1578–1586, 1992
29. Iversen BM, Kvam FI, Matre K, Ofstad J: Resetting of renal blood autoregulation during acute blood pressure reduction in hypertensive rats. *Am J Physiol* 44:R343–R349, 1998
30. Hill GS, Heptinstall RH: Steroid-induced hypertension in the rat. *Am J Pathol* 52:1–39, 1968
31. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM: Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 77:1925–1930, 1986
32. Iversen BM, Ofstad J: Loss of renal blood flow autoregulation in chronic glomerulonephritic rats. *Am J Physiol* 254:F284–F290, 1988
33. Pelayo JC, Westcott JY: Impaired autoregulation of glomerular capillary hydrostatic pressure in the rat remnant nephron. *J Clin Invest* 88:101–105, 1991
34. Griffin KA, Picken MM, Bidani AK: Method of renal mass reduction is a critical modulator of subsequent hypertension and glomerular injury. *J Am Soc Nephrol* 4:2023–2031, 1994
35. Bidani AK, Schwartz M, Lewis E: Renal autoregulation and vulnerability to hypertensive injury in remnant kidney. *Am J Physiol* 252:F1003–F1010, 1987
36. Wang X, Aukland K, Iversen BM: Acute effects of angiotensin II receptor antagonist on autoregulation of zonal glomerular filtration rate in renovascular hypertensive rats. *Kidney Blood Press Res* 20:225–232, 1997
37. Iversen BM, Kvam FI, Mrkrid L, Sekse I, Ofstad J: Effect of cyclooxygenase inhibition on renal blood flow autoregulation in SHR. *Am J Physiol* 32:F534–F539, 1992
38. Beeuwkes IR, Ichikawa I, Brenner BM: The renal circulation, in *The Kidney*, edited by Brenner BM, Rector FC, Philadelphia, W.B. Saunders, 1981, p 249
39. Brenner BM, Ichikawa I, Deen WM: Glomerular filtration, in *The Kidney*, edited by Brenner BM, Rector FC, Philadelphia, W.B. Saunders, 1981, p 289
40. Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G: Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. *Kidney Int* 53:1209–1216, 1998
41. Janssen JJWM, Gans ROB, Van Der Meulen J, Pijpers R, Ter Wee PM: Comparison between the effects of amlodipine and lisinopril on proteinuria in nondiabetic renal failure: A double-blind, randomized prospective study. *Am J Hypertens* 11:1074–1079, 1998
42. Ruggenenti P, Perna A, Benini R, Remuzzi G: Effects of dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibition, and blood pressure control on chronic, nondiabetic nephropathies. *J Am Soc Nephrol* 9:2096–2101, 1998
43. Tarif N, Bakris GL: Preservation of renal function: The spectrum of effects by calcium-channel blockers. *Nephrol Dial Transplant* 12:2244–2250, 1997
44. GISEN Group: Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 349:1857–1863, 1997
45. Holdaas H, Hartmann A, Berg KJ, Lund K, Fauchald P: Renal effects of losartan and amlodipine in hypertensive patients with non-diabetic nephropathy. *Nephrol Dial Transplant* 13:3096–3102, 1998
46. Griffin KA, Picken MM, Bidani AK: Deleterious effects of calcium channel blockade on pressure transmission and glomerular injury in rat remnant kidneys. *J Clin Invest* 96:793–800, 1995
47. Klahr S: The modification of diet in renal disease study. *N Engl J Med* 320:864–866, 1989