Kidney International, Vol. 50 (1996), pp. 1321–1326

Early increase in blood pressure and diastolic left ventricular malfunction in patients with glomerulonephritis

ADAM STEFANSKI,[1] KLAUS G. SCHMIDT, RÜDIGER WALDHERR, and EBERHARD RITZ

Departments Internal Medicine, Pediatrics and Pathology, Ruperto Carola University, Heidelberg, Germany

Early increase in blood pressure and diastolic left ventricular malfunction in patients with glomerulonephritis. In patients with diabetic nephropathy blood pressure increases progressively before the conventional threshold of normal blood pressure (140/90 mm Hg) is transgressed. In patients with glomerulonephritis, no information on this point is available. To clarify this issue we sequentially examined 20 untreated patients with biopsy-proven primary chronic glomerulonephritis (GN) who had casual blood pressure below 140/90 mm Hg and normal GFR by inulin clearance. Patients were compared with normotensive healthy controls who were matched for BMI, gender and age. We measured ambulatory 24-hour blood pressure (SpaceLab system), echocardiography (ASE criteria, Acuson 128 XP 10), C_{In} and C_{PAH}, urinary Na excretion, PRA and insulin concentration. In patients with GN, the median 24 hour ($P < 0.0005$), daytime ($P < 0.001$) and nocturnal sleeping time ($P < 0.0001$) MAP values were significantly higher than in matched controls (daytime, mean 97 mm Hg, 85 to 106 GN vs. 89 controls range 82 to 102; nocturnal sleeping time, mean 80.3 mm Hg, 71 to 89.5 GN vs. 73 controls, range 63 to 84). Echocardiographic examination showed significantly greater posterior wall thickness ($P < 0.01$) and ventricular septal thickness ($P < 0.003$). In addition the early diastolic to late diastolic (E/A) ratio of mitral valve peak inflow velocity was significantly ($P < 0.0008$) lower in patients. The data point to left ventricular wall thickening accompanied by LV diastolic malfunction. The study documents elevated ambulatory blood pressure in patients with primary chronic glomerulonephritis despite normal body weight and normal GFR. This is associated with evidence of target organ damage in the heart. The findings suggest that in patients with glomerulonephritis blood pressure increases initially within the normotensive range. This observation in conjunction with evidence of early target organ changes provides an argument for early antihypertensive intervention, but controlled trials to test efficacy and safety of this proposal are necessary.

Several investigators were able to show that patients with type I diabetes who had microalbuminuria, that is, incipient nephropathy, had higher blood pressures than diabetics without microalbuminuria [1, 2]. This was noted even though casual blood pressure still remained within the range of normotension by the WHO definition.

Similar observations in patients with incipient renal damage from diseases other than diabetic nephropathy are sparse. In one study, a reversible increase in blood pressure was noted when children had an episode of nephrotic syndrome secondary to minimal change glomerulonephritis, that is, normal glomeruli by light microscopy [3]. During relapse blood pressure was consistently above the 95th percentile for age and returned towards the normotensive range after remission. Furthermore, some studies documented the presence of arteriolar hyalinosis in normotensive patients with glomerulonephritis, pointing to abnormal intrarenal hemodynamics early on [4].

When a normotensive individual develops glomerulonephritis it is obvious that his or her blood pressure must increase within the range of normotension defined by WHO [5] or Joint National Committee [6] before the blood pressure reaches the frankly hypertensive range. Longitudinal studies to document such a rise in blood pressure would be desirable, but are difficult to perform, because patients are usually not monitored before glomerulonephritis has been diagnosed.

To circumvent this difficulty we chose to perform a case control study. We examined patients with biopsy-confirmed IgA glomerulonephritis as a paradigm of primary chronic glomerulonephritis with a casual blood pressure within the range of normotension by the WHO definition and a normal renal function by inulin clearance. Such patients were compared with controls matched for body mass index (BMI), gender and age. We tested the working hypothesis that circadian blood pressure and cardiac wall thickness are higher in patients with glomerulonephritis than in their matched controls.

Methods

Selection of patients and controls

The 20 patients in this study were recruited consecutively from the renal outpatient clinic of the University of Heidelberg. Inclusion into the study was based on the following criteria: (i) biopsy proven diagnosis of IgA glomerulonephritis; (ii) normotension, that is, <140/90 mm Hg of casual blood pressure in the outpatient clinic using sphygomanometric determination according to the recommendations of the German League against High Blood Pressure; and (iii) no use of an antihypertensive medication. Exclusion criteria were: (i) elevated serum creatinine (>1.1 mg/dl); (ii) age above 45 years; (iii) BMI $\geq$ 28 kg/m^2; (iv) presence of extrarenal disease; (v) proteinuria $\geq$ 3.5 g/24 hr; (vi) hormonal contraception. All consecutive 29 patients biopsied from January 1, 1991 to December 31, 1994 with the diagnosis of IgA glomerulonephritis who met the above criteria were approached; 20 patients agreed to participate in the study after informed consent was obtained. The study protocol had been approved by the ethics committee of the Faculty of Medicine, Heidelberg, Germany.

[1] Current address: Adam Stefanski, Klinika Endokrynologii PAM, u. Arkonska 4, 71455 Szczecin, Poland.

Received for publication February 1, 1996
and in revised form May 2, 1996
Accepted for publication May 2, 1996

Twenty control subjects, matched for BMI, gender and age, were healthy normotensive individuals as confirmed by history and physical examination. They were recruited from the collaborators of the renal unit or were relatives of dialysis patients.

Blood pressure measurements

Casual blood pressure was assessed with a mercury sphygmomanometer before fitting to an ambulatory monitor. Ambulatory blood pressure (BP) was measured during a 24 hour period with a programmable blood pressure monitor (ABD monitor type 90207; SpaceLabs Inc., Redmond, WA, USA). The time interval of measurements was 20 minutes between 6:00 and 22:00 hours, and 30 minutes between 22:00 and 6:00 hours. The daytime period was defined as the interval from 10:00 to 20:00 hours and night time as the interval from midnight to 6:00 hours. Since some studies [7] have shown that in most subjects blood pressure changes rapidly and considerably when subjects fall asleep and wake up, individuals were asked to record their sleeping times. The period selected for night time analysis was well within the period of documented sleep.

Echocardiographic study

After the BP monitoring period, patients and control subjects had an echocardiographic examination by one investigator (K.S.) who was unaware of the renal status. Echocardiographic studies were performed in left lateral supine position using an Acuson 128 X P 10 System (Mountain View, CA, USA) interfaced with 3 or 5 MHz transducers. From real time directed M-mode echocardiography, left ventricular internal diameter (LVID), ventricular septal thickness (VS), and posterior wall thickness (PW) were measured in the parasternal long and short axis cuts at end-diastole (D) and end-systole (S). Aortic diameter (Ao) was measured in the diastole, and left atrial diameter (LA) in the systole. Left ventricular pre-ejection period (PEP), ejection time (ET) and heart rate were measured from opening and closing movements of the aortic valve leaflets and the onset of the R-wave in the ECG. M-mode measurements were made according to the recommendations of the American Society of Echocardiography [8]. They were repeated in three to five consecutive beats and averaged.

From M-mode data we calculated three indices of the LV systolic function, that is: (i) left ventricular fractional shortening (FS) as

$$FS = (LVIDD - LVIDS)/LVIDD$$

and (ii) rate-corrected mean velocity of circumferential fiber shortening (mVcf) as

$$mVcf = (LVIDD - LVIDS)/(LVIDD \times LVETc)$$

Left ventricular ejection time (LVET) was corrected for a heart rate of 60 beats/min by dividing it by the square root of the RR interval.

Finally, (iii) the systolic ratio is PEP/LVET. The left ventricular mass (LVM) was calculated using the formula of Devereux et al [9] as

$$LVM = 0.832 \times \{(VSD + LVIDD + PWD)^3 - LVID^3\} + 0.6$$

LVM was then normalized for body surface area (LVMI).

From the apical window pulsed Doppler interrogation of the aortic and mitral valves was performed just distal to the respective valve ring. Three to five beats were analyzed and averaged. We measured peak velocity (PkV) and mean acceleration (Acc) at the aortic valve and the early diastolic (E) and late diastolic (A) transmitral peak inflow velocities as well as the ratio E/A.

Measurements of renal hemodynamics

Inulin (C_{In}) and PAH (C_{PAH}) clearances were used to determine glomerular filtration rate (GFR) and effective renal plasma flow (RPF), respectively, as described previously [10]. Clearances were measured after an overnight fast at a standardized time (8:00 hours) in the morning. The patients or the control subjects rested in a quiet room in supine position. First, blood was taken for routine chemistry and for plasma renin activity (PRA) and plasma insulin measurements. Subsequently, a bolus of 1500 mg inulin/m^2 of body surface (Inutest, Laevosan-Gesellschaft, Linz, Austria) and 500 mg of paraaminohippurate/m^2 (Nephrotest, Biol. Arbeitsgemeinschaft, Lich, Germany) was administered. This was immediately followed by a continuous infusion of 10 mg/m^2/min of both substances for 270 minutes. Beginning 90 minutes after the bolus injection, blood samples were taken at 10 minute intervals. Blood pressure was measured during the entire period using Dinamap (Criticon Inc., Tampa, FL, USA). Inulin was measured using a two step enzymatic assay [11] and PAH using colorimetry [12].

Ancillary measurements

Plasma insulin was measured using an ELISA/1-Step-Sandwich-Assay (Enzymimmunsystem ES 300; Boehringer Mannheim). PRA was measured according to Haber et al [13], and PTH using the Nichols assay. Urinary protein was measured using the Biuret method. Routine serum and urine parameters were assessed using an autoanalyzer Hitachi 705 (Boehringer Mannheim).

Evaluation of renal biopsies

The presence and severity of intrarenal arterial sclerosis and arteriolar hyalinosis was evaluated on serial biopsy sections using a score system from zero to three. Arterial sclerosis was defined as: 0 = absent; 1+ = mild segmental intimal thickening and fibrosis; 2+ = circumferential intimal thickening and fibrosia; 3+ = severe intimal thickening with pronounced narrowing of the lumen. Arteriolar hyalinosis was defined as: 0 = absent; 1+ = segmental subendothalial hyaline deposits; 2+ = circumferential subendothelial hyaline deposits; 3+ = circumferential subendothelial hyaline deposits with severe narrowing of the lumina.

Statistics

Data are reported as median and range. Comparisons between patients and matched controls were made using Wilcoxon's test for paired samples. Univariate analysis and multivariate analysis were calculated using the Stat-view 4.1. program.

To avoid Bonferroni problems from repetitive testing, only three parameters were preselected for primary hypothesis testing (24 hour MAP, VS, PW) for which a $P < 0.05$ was accepted. Significance testing for the other parameters was considered as a posthoc analysis for the generation of the hypothesis.

Table 1. Baseline data

	Age *years*	Gender *m/f*	BMI *kg/m²*	Serum creatinine *mg/dl*	$UV_{protein}$ *g/24 hr*	UV_{Na} *mmol/day*	PRA *ng Ang I/ml/hr*	Insulin *uU/ml*
Glomerulonephritis	31	10/10	22.1	0.94	1.01[a]	156	0.76	7.55
(N = 20)	(21–45)		(18.7–28.1)	(0.69–1.32)	(0.04–3.40)	(77–278)	(0.15–4.95)	(2.32–14.2)
Matched controls	31	10/10	22.0	0.89	0.05[a]	152	0.65	6.21
(N = 20)	(25–44)		(18.3–31.6)	(0.70–1.15)	(0.04–0.25)	(66–231)	(0.15–1.85)	(2.68–10.1)

Range of values is in the parentheses.

Abbreviations are: BMI, body mass index; $UV_{protein}$, urinary protein excretion; UV_{Na}, urinary sodium excretion; PRA, plasma renin activity; Insulin, fasting insulin.

[a] Significant paired difference

Table 2. Blood pressure (mm Hg)

	Casual blood pressure			24 hr Blood pressure			Daytime blood pressure			Nighttime blood pressure		
	Systolic	Diastolic	MAP	Systolic	Diastolic	MAP	Systolic	Diastolic	MAP	Systolic	Diastolic	MAP
Glomerulonephritis	125	80	95	124.5	76.5	93	129	82	97	111	64.8	80.2
(N = 20)	(110–140)	(70–90)	(83–105)	(107–135)	(69–84)	(82–100)	(107–141)	(73–88)	(85–106)	(96.5–128.5)	(56.5–72)	(71–89.5)
Matched controls	120	72.5	90	114.5	70.5	84.5	119	75	88.5	103	58	73
(N = 20)	(105–130)	(60–85)	(75–100)	(106–135)	(62–79)	(78–96)	(108–144)	(66–87)	(82–102)	(91–117)	(48–70)	(63–84)
P[a]	0.04	0.04	0.02	0.007	0.0006	0.0005	0.012	0.003	0.001	0.003	0.001	0.0001
(GN vs. controls)												

[a] Paired differences

Results

Baseline data

Table 1 illustrates that patients with IgA glomerulonephritis and controls were reasonably matched with respect to BMI, gender and age. By definition all patients had casual systolic blood pressures (and diastolic blood pressures; data not shown) within the range of normotension according to WHO [5], that is, <140/90 mm Hg. Normal blood pressure according to JNC criteria [6], that is, <130/85 mm Hg, was found in 16 of 20 patients. All patients had normal serum creatinine concentration and non-nephrotic proteinuria.

All patients had near normal 1,84 iPTH levels (median 4.9 pmol/liter, range 0.7 to 7.9; normal < 6 pmol/liter).

Evaluation of preglomerular vessels in renal biopsies

The presence of arterial sclerosis and arteriolar hyalinosis in the renal biopsies was evaluated by one examiner (R.W.) who was unaware of the clinical findings. Arteries were not present on serial sections of 5 of 20 biopsies; no sclerosis was found in 8 of 15 and grade 1 arterial sclerosis in 7 of 15 specimens. Arteriolar hyalinosis was absent in 5 of 20 biopsies, grade 1 hyalinosis in 14 of 20 and grade 2 in 1 of 20 of the biopsies.

Blood pressure measurements

Average 24-hour blood pressure was significantly higher in patients compared to their matched controls (Table 2 and Fig. 1). There was no significant difference of heart rates. The elevation was quantitatively similar for the periods when the patients were awake or asleep. This was similarly true for systolic BP and diastolic BP. There was a significant difference of 24 hour MAP between male (95 mm Hg; range 91 to 100 mm Hg) and female patients (88.5 mm Hg; range 82 to 96; $P < 0.005$) as well as male (89 mm Hg; range 81 to 96 mm Hg) and female (83.5 mm Hg; 78 to 89 mm Hg) controls ($P < 0.05$). By multivariate analysis MAP in patients was not related to proteinuria, age or PRA; a modest relation was found to Na excretion ($r = 0.55$; $P < 0.004$), BMI ($r = 0.67$; $P < 0.03$) and fasting insulin level ($r = 0.63$; $P < 0.02$).

Renal hemodynamics

All patients with IgA glomerulonephritis had C_{In} well within the normal range (in our laboratory 121 ± 11 ml/min/1.73 m²). There was no significant difference of baseline C_{In}, C_{PAH} or renovascular resistance (RVR) between patients with glomerulonephritis and healthy controls (Table 3).

Echocardiographic data

Cavity lumina (that is, LVIDD and LA) as well as aortic diameter were not significantly different between patients with IgA glomerulonphritis and their matched controls (Table 4, Table 5 and Fig. 2). In contrast, a significant difference of ventricular septal and posterior wall thickness was noted. LVMI tended to be higher in patients (78.6 g/m²; range 48.4 to 133 g/m²) than in matched controls (70.6 g/m²; range 57.8 to 94.3 g/m²), but the difference did not reach statistical significance. The relative wall thickness, that is, the LVIDD (VS + PW) ratio, was significantly lower in patients compared to matched controls ($P < 0.002$). All indices of systolic LV function were within normal limits and did not show significant differences between patients and matched controls. There was, however, a strikingly significant difference in the E/A ratio indicating a disturbed diastolic LV function. With the exception of one pair there was no overlap of the E/A ratio between matched pairs.

By multivariate analysis, the ventricular septum ($r = 0.56$; $P < 0.03$) and posterior wall thickness ($r = 0.7$; $P < 0.05$) were moderately correlated with BMI in renal patients.

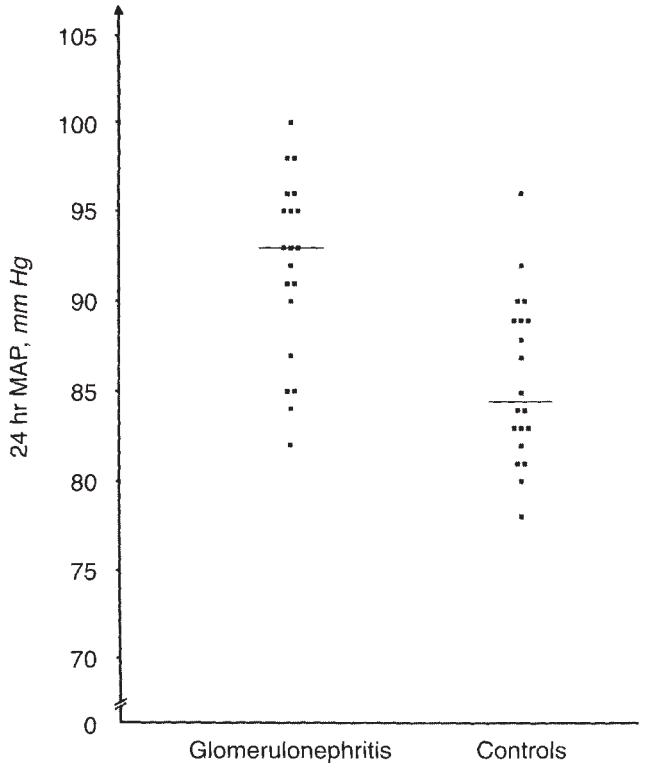

Fig. 1. *Averages of the MAP values (mean arterial blood pressure) of patients with glomerulonephritis and control subjects.* Bar denotes median value.

Discussion

The present study provides controlled quantitative information on the circadian blood pressure profile in patients with biopsy-confirmed IgA glomerulonephritis, normal GFR, non-nephrotic proteinuria and normotension by the WHO definition [5] according to casual blood pressure measurements. Such patients have daytime and night time blood pressure values that are significantly higher than those of controls matched for BMI, gender and age. This finding indicates that early on in the natural history of glomerulonephritis, the circadian blood pressure is clearly inappropriately high, that is, it is shifted to the right with respect to the blood pressure distribution in the normal population. This is the more remarkable since most casual BP values were normal even according to the rigorous Joint National Committee [6] criteria. The argument that such blood pressure values are inappropriate is further reinforced by the observation of early target organ damage: measurements of LV wall thickness showed significantly higher values in patients with IgA glomerulonephritis, although they were still within the normal range [14]. An increase in wall thickness despite no significant change in LV mass index presumably reflects the fact that the relationship between LV internal diameters and volume is changed (so called "ventricular remodeling"). This is suggested by the finding of an increased relative wall thickness in our patients. While systolic LV function was completely normal, striking evidence of abnormal E/A ratios was noted, pointing to early diastolic LV malfunction. Early diastolic malfunction is reminiscent of what has been noted in patients with genetic predisposition to primary hypertension [15]. Whether LV diastolic malfunction in our patients is related to hypertrophy and/or cardiac fibrosis [16, 17] is unknown and only histological studies will resolve this issue in the future. As to the cause of LV wall thickening, several possibilities can be entertained. It may not all be caused by high blood pressure and conceivably volume factors or sympathetic overactivity might play a role, but we assume that high blood pressure is at least a permissive factor. Our data are also in agreement with preliminary observations of cardiac changes in normotensive patients with primary glomerulonephritis [18].

Table 3. Renal hemodynamics

	Baseline		
	C_{in} *ml/min/ 1.73m²*	C_{PAH} *ml/min/ 1.73 m²*	RVR *mm Hg/liter/ min/1.73 m²*
Glomerulonephritis (N = 20)	113 (89.5–140)	639 (472–779)	133 (103–207)
Matched controls (N = 20)	120 (102–177)	661 (451–911)	132 (84.5–202)

Abbreviations are: C_{in}, inulin clearance; C_{PAH}, PAH clearance; RVR, renovascular resistance.

The observed differences are small, but we did not expect otherwise, since we studied normotensive individuals with incipient renal abnormalities. Nevertheless, the strength of our argument is reinforced by the fact that different and independent approaches led to the same conclusion, that is, measurements of blood pressure, of septal and posterior wall thickness, and evaluation of diastolic LV function.

When designing the study we considered several biostatistical artifacts. We recruited all consecutive patients with IgA glomerulonephritis who met the entry criteria to avoid selection bias. Controls were from the same geographical area and reasonably matched for factors known to influence blood pressure, such as body mass index, gender and age. All females were off hormonal contraception. We also monitored several parameters which influence blood pressure, for example, BMI, PRA, fasting insulin concentrations and sodium intake (as assessed from 24-hour urinary sodium excretion).

The data summarized in Table 1 indicate that with respect to BMI, serum creatinine, sodium excretion, PRA and fasting insulin, no significant differences existed between the two study groups. We are aware that circulating PRA is not a good index of the activity of the renal renin system, as recently shown in a study by quantitating glomerular renin mRNA with RT-PCR [19]. Consequently, normal circulating PRA does not imply that high blood pressure is unrelated to the renin system.

All our patients with glomerulonephritis had normal GFR by inulin clearance. We emphasize, however, that a decrease in filtration surface area does not necessarily translate into a decrease in whole kidney GFR because of glomerular adaptive mechanisms [20].

The present study was not designed to examine the mechanisms involved in raising blood pressure. Such mechanisms may include abnormal renal sodium handling [21], inappropriate activity of the intrarenal [22] and extrarenal [23] renin system as well as increased responsiveness to angiotensin II. Inappropriate activity of other pressor or depressor systems, particularly on the renovascular bed, may also play a role, for example, endothelin [24] or

Table 4. Echocardiographic and ancillary data (I)

	LVEDD	LA	AO	VS	PW	LVMI	Relative wall thickness
	mm					g/m^2	
Glomerulonephritis (N = 19)	45 (38–56)	31 (26.5–39)	28 (23–32.5)	9.00 (7–12)	9.00 (6.5–11.5)	78.6 (48.4–133)	2.56 (2.05–3.19)
Matched controls (N = 19)	47.5 (42–55)	31.5 (27.5–37)	29 (25–33)	8.00 (7–9.5)	8.00 (7–10)	70.6 (57.8–94.3)	3.0 (2.21–3.71)
P[a]	0.06	0.68	0.33	0.001	0.004	0.82	0.002

Abbreviations are: LVEDD, left ventricle end-diastolic diameter; LA, left atrial diameter; Ao, aortic root diameter; VS, ventricular septum diameter; PW, posterior wall thickness; LVMI, left ventricular mass index; relative wall thickness (LVEDD/VS + PW) ratio.
[a] Difference is GN vs. matched controls (paired difference; 1 pair could not be evaluated for technical reasons)

Table 5. Echocardiographic and ancillary data (II)

	SF	mVcf *m/s*	PEP/LVET *ms*	PkV(Ao) *m/s*	mAce m/s^2	E/A ratio *m/s*
Glomerulonephritis (N = 19)	0.36 (0.31–0.42)	1.13 (1.03–1.39)	0.31 (0.26–0.34)	1.03 (0.90–1.30)	19.2 (16.9–20.9)	1.77 (1.03–2.42)
Matched controls (N = 19)	0.35 (0.31–0.40)	1.12 (0.97–1.36)	0.30 (0.24–0.34)	1.10 (0.85–1.40)	19.2 (17.5–21.9)	2.29 (1.61–3.19)
P[a]	0.88	0.59	0.59	0.24	0.23	0.0003

Abbreviations are: SF, shortening fraction; mVcf, mean velocity of circumferential shortening; PEP/LVET, ratio pre-ejection period/left ventricle ejection time; mAcc, mean acceleration; E/A ratio, mitral inflow velocity (early diastole/atrial contraction).
[a] Difference is GN versus matched controls (paired difference; 1 pair could not be evaluated for technical reasons)

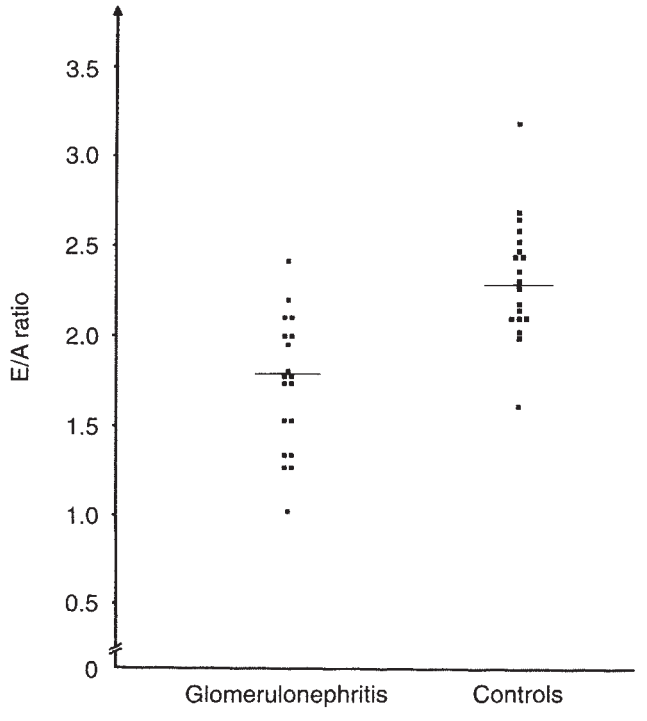

Fig. 2. *Individual values of peak transmitral inflow velocity ratios (E/A = early diastolic/atrial contraction) of patients with glomerulonephritis and control subjects.*

nitric oxide [25]. Recently, sympathetic stimulation by afferent sympathetic signals originating within the diseased kidney [26] has been documented in clinical and experimental studies. Finally, a role for renal blood pressure lowering principles, such as medullipin, has been postulated [27]. Our protocol did not provide measurements addressing these issues, but it is of note that despite normotension, the above patients had marked abnormalities of intrarenal arterioles. This observation is inline with previous reports of Feiner et al [4] and is consistent with abnormal intrarenal pressures.

The finding of increased LV wall thickness is not only interesting as evidence of blood pressure-dependent target organ damage. It may also be relevant for patient survival, since left ventricular mass is related to the risk of cardiac death in patients with essential hypertension [28] as well as in patients with renal failure [29, 30].

Casual blood pressure emerges from the above observations as seriously underestimating the circadian blood pressure load to target organs in patients with glomerulonephritis and normal glomerular filtration. This observation may have practical implications in that it provides a rationale for early antihypertensive intervention. This would be analogous to what is considered state of the art in diabetic patients with microalbuminuria [31, 32]. The finding of intrarenal vascular abnormalities in normotensive patients with IgA glomerulonephritis may provide a further rationale for antihypertensive intervention. The benefit from, and safety of, such early antihypertensive treatment must be documented, however, by controlled trials, before this recommendation can be generally accepted.

Reprint requests to Professor Dr. Dr.h.c. E. Ritz, Department of Internal Medicine, Bergheimer Straße 58, D-691115 Heidelberg, Germany.

References

1. Wiegman TB, Herron KG, Chonko AM, Macdougall MI, Moore WV: Recognition of hypertension and abnormal blood pressure burden with ambulatory blood pressure recordings in type I diabetes mellitus. *Diabetes* 39:1556–1560, 1990

2. HANSEN KW, CHRISTENSEN CK, ANDERSEN PH, PEDERSEN MM, CHRISTIANSEN JS, MOGENSEN CH: Ambulatory blood pressure in microalbuminuric type I diabetic patients. *Kidney Int* 41:847–854, 1992
3. KÜSTER S, MEHLS O, SEIDEL C, RITZ E: Blood pressure in minimal change and other types of nephrotic syndrome. *Am J Nephrol* 10(Suppl 1):76–80, 1990
4. FEINER HD, CABILI S, BALDWIN DS, SCHACHT RG, GALLO RJ: Intrarenal vascular sclerosis in IgA nehropathy. *Clin Nephrol* 18:183–192, 1982
5. Summary of 1993 World Health Organisation-International Society of Hypertension guidelines for the management of mild hypertension. *Brit Med J* 307:1541–1546, 1993
6. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNCV). *Arch Int Med* 153:154–183, 1993
7. PICKERING TG: *Ambulatory Monitoring and Blood Pressure Variability.* London, ICI Pharmaceuticals, Science Press, 1991
8. SAHN DJ, DEMARIA A, KISSLO J, WEYMAN A: Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 58:1072–1083, 1978
9. DEVEREUX RB, ALONSO DR, LUTAS HM, GOTTLIEB GJ, CAMPO E, SACHS Y, REICHEK N: Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am J Cardiol* 57:450–458, 1986
10. SCHMID M, MANN JFE, STEIN G, HERTER M, NUSSBERGER J, KLINGBEIL A, RITZ E: Natriuresis pressure relationship in polycystic kidney disease. *J Hypertens* 8:277–283, 1990
11. KUHNLE HF, VON DAHL K, SCHMIDT PH: Fully enzymatic inulin determination in small volume samples without deproteinization. *Nephron* 62:104–107, 1992
12. BRATTON AC, MARSHALL EK: A new coupling component for sulfanilamide determination. *J Biol Chem* 128:537–550, 1983
13. HABER E, KOERNER T, PAGE LB, KLIMAN B, PURNODE A: Application of radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. *J Clin Endocrinol* 29:1349–1355, 1969
14. HENRY WL, GARDIN JM, WARE JH: Echocardiographic measurements in normal subjects from infancy to old age. *Circulation* 62:1054–1061, 1980
15. WIDGREN BR, PERSSON B, WIKSTRAND J: Reduced left ventricular distensibility in normotensive men with a positive family history of hypertension. *Am J Hypertens* 6:750–757, 1993
16. MALL G, RAMBAUSEK M, NEUMEISTER A, KOLLMAR S, VETTERLEIN F, RITZ E: Myocardial interstitial fibrosis in experimental uremia. Implications for cardiac compliance. *Kidney Int* 33:804–811, 1988
17. MALL G, HUTHER W, SCHNEIDER J, LUNDIN P, RITZ E: Diffuse intermyocardiocytic fibrosis in uremic patients. *Nephrol Dial Transplant* 5:39–44, 1990
18. FABRI A, DEGLI ESPOSTI E, COCCHI R, DI NARDO AM, LUCATELLO A, PRETOLANI M, STURANI A, FUSAROLI M: ABP monitoring in primary glomerulonephritis patients. *J Am Soc Nephrol* 6:640, 1995
19. WAGNER J, DRAB M, GEHLEN M, LANGHEINRICH M, VOLK S, GANTEN D, RITZ E: PCR analysis of human renal biopsies—Renin gene regulation in glomerulonephritis. *Kidney Int* 46:1542–1545, 1994
20. HOSTETTER TH, OLSON JL, RENNKE HG, VENKATACHALAM MA, BRENNER BM: Hyperfiltration in remnant nephrons: A potentially adverse response to renal ablation. *Am J Physiol* 241:185–193, 1981
21. GUYTON AC: Renal function curve: A key to understanding the pathogenesis of hypertension. *Hypertension* 10:1–6, 1987
22. WEIDMANN P, BERETTA-PICCOLI C, STEFEN F, BLUMBERG A, REUBI FC: Hypertension in terminal renal failure. *Kidney Int* 9:294–301, 1976
23. KUCZERA M, HILGERS KI, LISSON C, GANTEN D, HILGENFELDT U, RITZ E, MANN JFE: Local angiotensin formation in hindlimbs of uremic hypertensive and renovascular hypertensive rats. *J Hypertens* 9:41–48, 1991
24. SHICHIRI M, HIARATA Y, ANDO K, EMORI T, OHTA K, KIMOTO S, OGURA M, INOUE T, MARUMO F: Plasma endothelin levels in hypertension and chronic renal failure. *Hypertension* 15:493–496, 1990
25. VALLANCE P, LEONE A, CALVER A, COLLIER J, MONCADA S: Accumulation of an endogenous inhibitor of nitric oxyde synthesis in chronic renal failure. *Lancet* 339:572–575, 1992
26. CONVERSE RL, JACOBSEN TN, TOTO RD, JOST CMT, COSENTINO F, FOUAD-TARAZI F, VICTOR RG: Sympathetic overactivity in patients with CRF. *N Engl J Med* 327:1912–1918, 1992
27. COWLEY AW JR: A tribute to Eric Muirhead. Evolution of the medullolipin concept of blood pressure control. *Nephrol Dial Transplant* 10:1137–1141, 1995
28. MESSERLI FH, KETELHUT R: Left ventricular hypertrophy: A pressure-independent cardiovascular risk factor. *J Cardiovasc Pharmacol* 22(Suppl 1):S7–S13, 1993
29. SILBERBERG JS, RAHAL DP, PATTON DR, SNIDERMAN AD: Role of anemia in the pathogenesis of left ventricular hypertrophy in endstage renal disease. *Am J Cardiol* 64:222–224, 1989
30. PARFREY PS, HARNETT JD, GRIFFITHS SM, TAYLOR R, HAND J, KING A, BARRE PE: The clinical course of left ventricular hypertrophy in dialysis patients. *Nephron* 55:114–120, 1990
31. RITZ E, FLISER D, NOWICKI M: Hypertension and vascular disease as complication of diabetes, in *Hypertension: Pathophysiology, Diagnosis and Management,* (2nd ed), edited by LARAGH JH, BRENNER BM, New York, Raven Press Ltd, 1995
32. MOGENSEN CE, KAENE WF, BENNETT PH, JERUMS G, PARVING HH, PASSA P, STEFFES MW, STRIKER GH, VIBERTI GC: Prevention of diabetic renal disease with special reference to microalbuminuria. *Lancet* 346:1080–1084, 1995