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Nephron Number in Patients with Primary Hypertension

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ABSTRACT

BACKGROUND

A diminished number of nephrons has been proposed as one of the factors contributing to the development of primary hypertension.

METHODS

To test this hypothesis, we used a three-dimensional stereologic method to compare the number and volume of glomeruli in 10 middle-aged white patients (age range, 35 to 59 years) with a history of primary hypertension or left ventricular hypertrophy (or both) and renal arteriolar lesions with the number and volume in 10 normotensive subjects matched for sex, age, height, and weight. All 20 subjects had died in accidents.

RESULTS

Patients with hypertension had significantly fewer glomeruli per kidney than matched normotensive controls (median, 702,379 vs. 1,429,200). Patients with hypertension also had a significantly greater glomerular volume than did the controls (median, 6.50×10^{-3} mm³ vs. 2.79×10^{-3} mm³; $P<0.001$) but very few obsolescent glomeruli.

CONCLUSIONS

The data support the hypothesis that the number of nephrons is reduced in white patients with primary hypertension.

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Primary hypertension is very common, but its pathogenesis remains elusive. The cause is presumably heterogeneous, though several observations point to the kidney as involved in the genesis of primary hypertension. Cross-transplantation experiments[1-3] suggest that hypertension "travels with the kidney," in that hypertension will develop in the normotensive recipient of a kidney genetically programmed for hypertension. Patients with renal failure who receive renal allografts from donors who have a history of cerebral hemorrhage and thus, most likely, hypertension tend to have higher blood-pressure values than recipients of transplants from normotensive donors.[4] Curtis et al.[5] reported that patients who had dialysis-dependent renal failure as a result of hypertension despite the absence of primary renal disease became normotensive after receiving allografts from normotensive donors, provided the new kidneys functioned well.

It has been proposed that a low number of nephrons increases the risk of both hypertension and progressive renal disease.[6] This hypothesis was based on observations that rat strains with a high complement of nephrons were less susceptible to progressive renal disease.[7] Conversely, in animals and humans, a reduction in the number of nephrons is associated with hypertension and an increased risk of progressive renal disease.[8] The predisposition of some racial and ethnic groups to hypertension and progressive renal disease has been ascribed to renal problems. Indeed, enlarged glomeruli as surrogate markers for reduced numbers of nephrons were found in some members of these groups.[9,10] We designed the present study to test the hypothesis proposed by Brenner et al.[11] that a reduced number of nephrons contributes to essential hypertension in the general population. To this end, we used a three-dimensional stereologic technique to compare the number and volume of glomeruli in 10 middle-aged patients with documented hypertension who had died in accidents with the number and volume in 10 matched subjects without evidence of hypertension who had also died in accidents.

METHODS

STUDY SUBJECTS

One kidney was obtained from each of 10 middle-aged white subjects (age range, 35 to 59 years) who had died in accidents, who met the inclusion criteria, and who underwent autopsy at the Institute of Pathology of Darmstadt in Darmstadt, Germany, and the Institute of Pathology and Forensic Medicine, University of Heidelberg, Heidelberg, Germany. Inclusion criteria comprised death before the age of 60 years; concentric left ventricular hypertrophy, a medical history of primary hypertension, or both; and the characteristic arteriolar lesions of the kidney found in patients with hypertension. Exclusion criteria were evidence of secondary hypertension, diabetes, a history of alcohol or drug abuse, or evidence of renal disease on histologic examination of the kidney. Control subjects had also died accidentally, had no evidence of hypertension, and were closely matched to the patients with respect to sex, age, height, and weight. Written or oral informed consent was obtained from next of kin, the local authorities, and local ethics committees.

TISSUE SAMPLING AND STEREOLOGIC METHODS

The number and volume of glomeruli were estimated with use of a three-dimensional approach that represented a modification of the "fractionator" method.[12,13] The number and area of glomeruli were counted in randomly selected portions of the right kidney. All subjects had two kidneys; in three subjects the left kidney was obtained because the right kidney had been severely damaged during the accident. Major autolysis was not present.

The kidney was carefully removed and weighed. After immersion and fixation in formaldehyde, the whole kidney was cut into 2-mm slices in a cranial-to-caudal direction, and the medulla was removed from the cortical rim. The cortical rim was weighed, and the cortical density was quantitated with use of the volume-replacement method. All kidney slices were placed onto paper marked with a coordinate system. Fifteen tissue blocks (measuring 5 by 5 by 2 mm) were randomly selected with the use of random numbers, according to the area weighted-sampling principle. The blocks were dehydrated and embedded in methacrylate, and the degree of shrinkage was determined in fixed kidney blocks. Assuming isotropic conditions, shrinkage did not exceed 4 percent of the volume. The blocks were serially sectioned (3 μm) and stained with methylene blue. Every first and eighth section was selected for stereologic analysis, which involved the use of two microscopes (microscope A, model BH2, Olympus Optical; microscope B, model B202, Olympus Optical), a video-camera module (model XZ711P, Sony), and a computer screen (Nokia). For each pair of samples, the first section was the reference section and was examined with microscope A; the re-

sulting image was projected onto the computer screen with use of the video camera. A system of coordinates divided the computer screen into 204 squares. Each square represented an area of 6.4×10^{-3} mm² of the examined cortical area. The eighth section was examined with microscope B. To rule out the possibility that differences in results between the two microscopes were due to the microscopes themselves, the comparison and reference sections were exchanged in random samples and examined with microscope A and microscope B, respectively. The maximal mean difference in qualifying glomeruli was 5.23 percent. Several blocks from the remaining kidney tissue were then embedded in paraffin, sectioned (4 μm), and stained with hematoxylin and eosin, periodic acid–Schiff, or silver stains.

To estimate the number of glomeruli and the average glomerular volume per kidney, we determined the number of points on the grid that touched the cortical area, including the glomerular area; the number of points on the grid that touched the glomerular area; and the number of glomeruli found in the reference section. Cortical areas with obvious technical artifacts were excluded. The sampling volume was calculated by multiplying total tissue area (the number of points on the grid that touched the cortical area × the grid area) by the thickness of the section (e.g., 3 μm × 8 sections = 24 μm). A correction for tissue shrinkage (×1.04) was made, and the resulting volume, multiplied by the specific weight of the fixed kidney, yielded the mass of the portion of the cortex being examined ($m_{exam\ cor}$). The weight of the kidney under examination was divided by the weight of the total kidney cortex, yielding a ratio ($m_{exam\ cor}$:$m_{total\ cor}$). The number of glomeruli was then determined with the following equation: number = $1 \div (m_{exam\ cor}:m_{total\ cor}) \times \Sigma Q-$, where Q– is the number of glomeruli found in the reference section but not in the comparison section.

The mean glomerular volume was estimated by calculating the ratio between the portion of the cortical area represented by glomerular area and the numerical density of glomeruli in the cortex. The total glomerular volume per kidney was estimated by multiplying the number of glomeruli by the mean glomerular volume.

VALIDATION OF THE METHOD

In order to validate the method, two kidneys were examined by one of the investigators as well as by a second person familiar with the three-dimensional stereologic method. Both observers were unaware of the subject's disease status. Intraobserver and interobserver error were 0.99 percent and 2.04 percent, respectively.

HISTOLOGIC EXAMINATION OF THE KIDNEY

In addition to the stereologic analysis, all kidneys were examined by light microscopy. In all patients with hypertension, the characteristic findings of medial and intimal thickening with intimal fibrosis of preglomerular arterioles and hyalinosis of afferent arterioles were detected. Such vascular lesions were uniformly absent in the kidneys of normotensive controls. The changes associated with arteriolar lesions and thickening of Bowman's capsule were judged on a four-point scale as absent (a score of 0), minor (a score of 1), moderate (a score of 2), or severe, with the entire Bowman's capsule thickened (a score of 3).

To exclude the possibility that the number of glomeruli in the kidneys of patients with hypertension was spuriously low because glomeruli had vanished, paraffin-embedded sections stained with periodic acid–Schiff and silver stains were carefully examined for potential residues of glomeruli and the number of heavily sclerosed or obliterated glomeruli per 100 glomeruli in the cortical rim was counted. Obsolescent or obliterated glomeruli were defined as structures with heavily sclerosed or no discernible capillary tuft but thickening or visible remnants of Bowman's capsule. The number of such glomeruli was quantitated on sections stained with hematoxylin and eosin, but additional sections were screened with the use of silver and periodic acid–Schiff stains. As an index of periglomerular inflammation, we quantitated the proportion of the area surrounding the glomerulus (as a percentage of the visual field) that was infiltrated by mononuclear cells.

STATISTICAL ANALYSIS

Results are expressed as medians and interquartile ranges. The Mann–Whitney test for paired differences was used.

RESULTS

CHARACTERISTICS OF THE SUBJECTS

Patients with hypertension and control subjects were similar with respect to mean age, height, body weight, and kidney weight (Table 1). The rel-

Table 1. Characteristics of the Subjects.

Variable	Patients with Hypertension							
	Age	Sex	Height	Body Weight	Heart Weight: Body Weight	Absolute Kidney Weight*	Relative Kidney Weight†	Weight of Renal Cortex*
	yr		*cm*	*kg*	*g/kg*	*g*	*g/kg*	*g*
Pair no.								
1	35	M	172	77	7.79	180	2.34	122
2	41	M	177	79	5.69	160	2.03	105
3	43	M	178	59	7.12	120	2.03	91
4	43	F	169	77	4.68	165	2.14	129
5	44	M	187	100	6.95	260	2.60	152
6	47	M	182	92	5.27	155	1.68	99
7	49	M	179	142	4.01	250	1.76	122
8	51	M	179	89	6.46	240	2.70	117
9	58	M	174	110	7.27	185	1.68	104
10	59	M	178	96	5.10	200	2.08	144
Median	45.5	—	178	90.5	6.08‡	184	2.06	120
25th–75th percentiles	43.0–50.5	—	174–179	77.5–99.0	5.14–7.08	161–230	1.83–2.29	104–128
Variable	**Matched Controls**							
	Age	Sex	Height	Body Weight	Heart Weight: Body Weight	Absolute Kidney Weight*	Relative Kidney Weight†	Weight of Renal Cortex*
	yr		*cm*	*kg*	*g/kg*	*g*	*g/kg*	*g*
Pair no.								
1	35	M	201	86	5.12	210	2.44	111
2	39	M	167	79	5.25	190	2.41	107
3	39	M	168	80	4.06	130	1.62	80
4	45	F	163	81	3.95	135	1.67	76
5	41	M	170	83	4.94	170	2.05	135
6	48	M	181	86	4.36	130	1.51	79
7	51	M	179	82	5.49	150	1.83	94
8	50	M	178	92	4.89	175	1.90	97
9	52	M	181	92	5.38	205	2.23	110
10	54	M	175	93	4.19	190	2.04	137
Median	46.5	—	177	84.5	4.92	173	1.86	102
25th–75th percentiles	39.5–50.8	—	168–181	81.4–90.5	4.23–5.22	138–190	1.64–2.19	83.5–111

* The weight of fixed tissue is given.
† The relative kidney weight is the absolute kidney weight divided by the body weight.
‡ P<0.001 for the comparison with the controls.

ative weight of the heart — the ratio of the weight of the heart to the body weight — was significantly higher in patients with hypertension than in controls (P<0.001).

MEAN NUMBER AND VOLUME OF GLOMERULI

The mean number of intact glomeruli was significantly lower — by 46.6 percent — in the kidneys of the patients with hypertension than in the kidneys of control subjects (Fig. 1A). There was no trend toward a difference in results between the sexes (Table 2). The mean glomerular volume was significantly higher — by 133 percent — in the kidneys of patients with hypertension than in the kidneys of matched controls (Fig. 1B). This higher mean glomerular volume resulted in a slightly higher total glomerular volume per kidney in the patients with hypertension than in the matched controls (median, 4.56×10^3 mm^3 vs. 3.98×10^3 mm^3), but the difference was not statistically significant.

OBLITERATED GLOMERULI

There were occasional obliterated glomeruli in a juxtamedullar location. The percentage of obliterated glomeruli was significantly higher in the patients with hypertension than in the matched con-

trols (median, 5.5 percent vs. 0.0 percent; P<0.001). This finding prompted us to validate the reliability of the method of detecting obliterated glomeruli. To this end we examined the kidneys of two elderly women (ages, 89 and 90 years) who had had severe hypertensive heart disease and nephrosclerosis with renal scarring and who were not study subjects. The total number of histologically detectable glomeruli (i.e., intact plus sclerosed glomeruli) was slightly below the range described for patients with hypertension (468,301 and 606,150, respectively), although 25 percent and 30 percent of the glomeruli, respectively, were completely sclerosed. The mean glomerular volume in these two patients was 2.58×10^{-3} mm³ and 2.83×10^{-3} mm³, respectively.

MORPHOLOGIC INVESTIGATION OF THE KIDNEY

Arteriolosclerosis of afferent arterioles was consistently found in all the patients with hypertension (Table 3 and Fig. 2B) but was absent or marginal in the control group (Fig. 2A). In addition, the score for the thickening of Bowman's capsule was significantly higher in the patients with hypertension than in the control group. The percentage of periglomerular interstitium that was infiltrated by mononuclear cells was also significantly higher in patients with hypertension than in normotensive controls. Periglomerular infiltration was seen in all the patients with hypertension (and affected up to 19 percent of the periglomerular area) but was virtually absent in the controls.

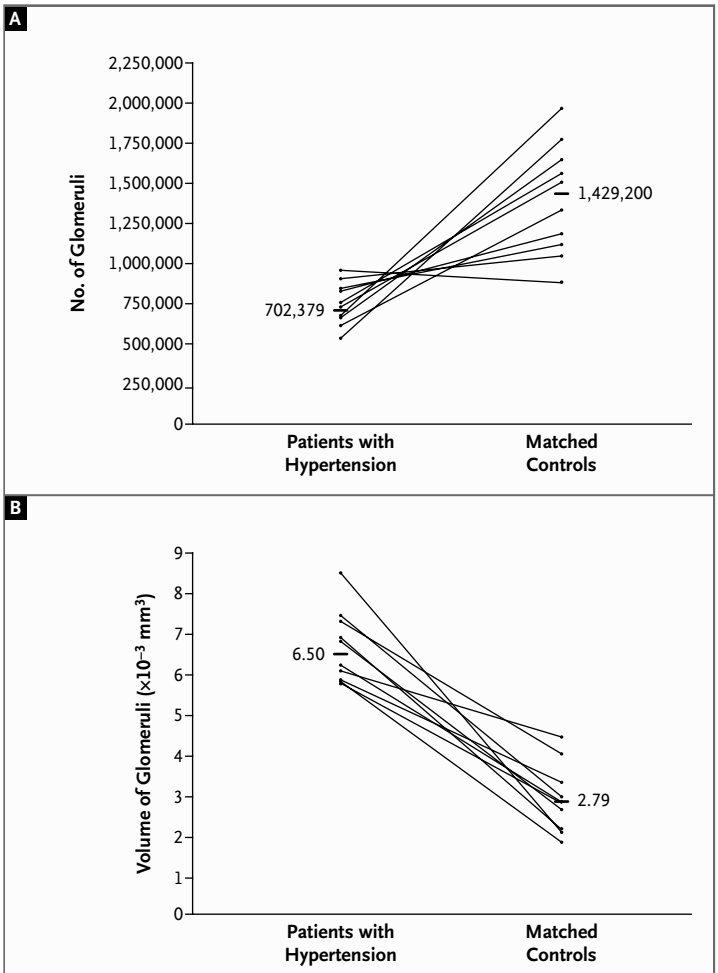

Figure 1. Number of Glomeruli per Kidney (Panel A) and Mean Glomerular Volume (Panel B) in 10 Patients with Hypertension and 10 Matched Normotensive Controls.

The median value is shown for each group.

DISCUSSION

Our findings, obtained in a consecutive series of subjects who died in accidents, suggest that the number of glomeruli is lower in the kidneys of patients with hypertension than in the kidneys of matched normotensive controls. Nyengaard and Bendtsen[14] observed that the number of glomeruli decreases with age owing to the accelerated loss of glomeruli after the age of 60 years. Consequently, we excluded all subjects who were 60 or older. Variable numbers of glomeruli have been reported in the general population, ranging from 331,000 to 2 million glomeruli per kidney, with no difference between the sexes.[15-17] In our opinion these differences are largely explained by differences in the counting methods used. The number of glomeruli in our control subjects was similar to the numbers obtained with the acid-maceration method (580,000 to 2 million),[16,18] which assesses the entire organ and takes into account the differences in the density of glomeruli in the various zones of the renal cortex.[19]

Recently, Bertram et al. reported preliminary findings on the number and volume of glomeruli in forensic-autopsy samples obtained from subjects without kidney disease.[20] They found a considerable variation in the number of glomeruli, ranging from 210,332 to 1,825,380. Using the fractionator technique, Gundersen et al. found lower numbers of glomeruli (331,000 to 1,424,000).[13] The difference in numbers is unexplained, but we did not use the original fractionator method. Differences in findings may in part be explained by tissue shrink-

Table 2. Number and Mean Volume of Glomeruli.

Variable	Patients with Hypertension		Matched Controls	
	No. of Glomeruli	Mean Glomerular Volume	No. of Glomeruli	Mean Glomerular Volume
		$\times 10^{-3}$ mm³		$\times 10^{-3}$ mm³
Pair no.				
1	680,450	8.49	1,959,914	1.99
2	614,596	5.74	1,339,622	2.79
3	901,995	5.84	1,043,416	3.28
4	827,527	6.79	1,183,679	2.62
5	843,290	7.29	1,112,479	3.96
6	724,307	5.82	1,518,778	1.78
7	662,177	6.92	1,649,525	2.11
8	724,307	6.20	1,559,938	2.78
9	531,140	7.44	1,771,787	2.94
10	954,893	6.09	884,458	4.42
Median	702,379*	6.50*	1,429,200	2.79
25th–75th percentiles	626,491–801,722	5.90–7.20	1,130,279–1,627,128	2.24–3.20

* P<0.001 for the comparison with the controls.

age, which interferes with absolute counts in the method we adopted. In the original fractionator method, a correction factor was used to account for the proportion of the sample fraction in which the counting of glomeruli was not performed. This correction was not necessary in our modification, since the fraction of the cortical rim examined was calculated directly from the volume of the sample examined and the density of the cortical rim, but this approach introduced the potential problem of tissue shrinkage, as noted. With our modified three-dimensional stereologic method, intraobserver and interobserver errors did not exceed 0.99 percent and 2.04 percent, respectively.

Irrespective of the ongoing discussion concerning the optimal method of counting glomeruli, we would emphasize that in the present controlled study, the difference between the patients with hypertension and the control subjects was so large and consistent that it is highly unlikely that the result was due to a methodologic artifact.

Of more concern is another potential problem — the loss of glomeruli in the kidneys of patients with hypertension. Using periodic acid–Schiff and silver stains to detect residual material from Bowman's capsules, we observed only a small proportion of obsolescent glomeruli. As a further control, we specifically examined the kidneys of two elderly women with severe hypertension, which we expected to have a high proportion of obliterated glomeruli. We were satisfied that the number of intact plus

Table 3. Ancillary Measurements.

Variable	Patients with Hypertension				Matched Controls			
	Arteriolosclerosis Score*	Thickening of Bowman's Capsule Score†	Periglomerular-Cell Infiltrates	Obliterated Glomeruli	Arteriolosclerosis Score*	Thickening of Bowman's Capsule Score†	Periglomerular-Cell Infiltrates	Obliterated Glomeruli
			percent				*percent*	
Pair no.								
1	1.89	1.04	7	4	0.36	0.38	0	0
2	1.79	1.48	6	9	0.21	0.33	0	0
3	1.92	0.66	19	8	0.28	0.13	0	0
4	1.95	1.11	4	3	0.32	0.20	0	0
5	1.67	1.46	5	6	0.22	0.06	0	0
6	1.77	1.37	13	8	0.17	0.11	0	0
7	1.49	1.24	2	5	0.32	0.23	0	2
8	1.76	1.23	6	12	0.41	0.02	1	1
9	1.82	1.37	8	5	0.60	0.23	0	0
10	1.96	1.52	1	4	0.32	0.26	0	1
Median	1.81‡	1.31‡	6.00‡	5.50‡	0.32	0.22	0.00	0.00
25th–75th percentiles	1.76–1.91	1.14–1.44	4.25–7.75	4.25–8.00	0.24–0.35	0.12–0.25	0.00–0.00	0.00–0.75

* Scores can range from 0 to 3; higher scores indicate more severe abnormalities.
† Scores can range from 0 to 3; higher scores indicate more severe abnormalities.
‡ P<0.001 for the comparison with the controls.

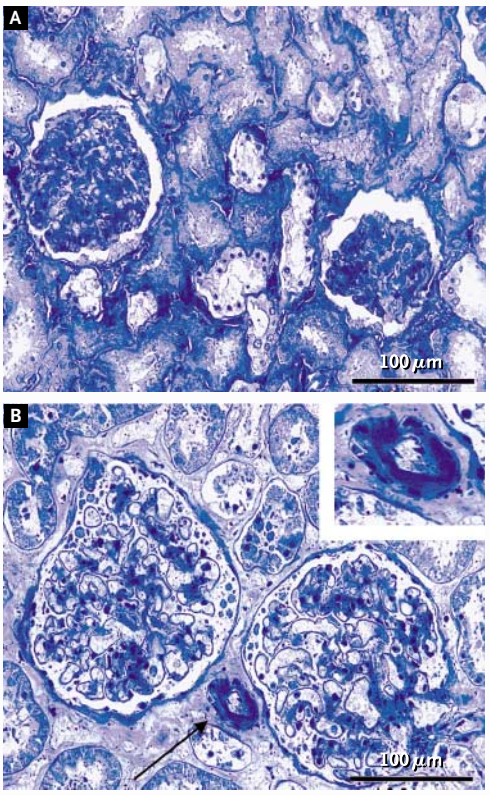

Figure 2. Representative Light Micrographs of Renal Cortex from a Normotensive Control (Panel A) and a Patient with Hypertension (Panel B).

The patient with hypertension has larger glomeruli and typical arteriolar changes with hyalinosis (arrow and inset).

obliterated glomeruli was only slightly below the range expected for patients with hypertension. This observation suggests that even severe hypertension-induced renal damage does not cause the complete disappearance of glomeruli. It may be argued that shrunken glomeruli may not have been detected with our sampling technique and that we may thus have underestimated the number of glomeruli. The smallest glomerular diameter in the kidneys of the patients with hypertension was 97.5 μm, and the distance between two sampling planes with our technique was 24 μm, thus increasing the likelihood that all glomeruli were detected. Although we cannot rule out the possibility that some glomerular loss may have gone undetected, we found no relation between the number of glomeruli and age in our subjects.

The hypothesis that a reduced number of nephrons leads to primary hypertension is given further support by observations that the glomerular volume serves as a surrogate for the number of glomeruli and is very high in members of racial and ethnic groups with a predilection for renal failure over time.[9,10] In this context, it is of note that the numbers of glomeruli are also significantly lower in spontaneously hypertensive rats than in normotensive controls.[21] Furthermore, Fassi et al. showed that the progressive renal damage in the Milan Wistar rat is associated with an inborn deficit of nephrons.[7]

Whether the reduced number of nephrons is caused by genetic or environmental factors is unclear. Several studies suggested that changes in the intrauterine environment lead to retarded renal growth before birth, low birth weight, and hypertension during adult life.[22-24] A correlation between reduced birth weight and decreased formation of nephrons was recently found in experiments in rats.[25] In humans, an association has been found between low birth weight and reduced renal volume, possibly indicating a reduced number of nephrons.[26] All these data are consistent with the concept that the number of nephrons, which is determined during fetal development, is an important determinant of cardiovascular abnormalities during adult life. The present data, obtained at autopsy from white patients with primary hypertension, provide further evidence in support of this concept.

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