RENAL MICROVASCULATURE IN CHRONIC RENAL FAILURE

BY

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Abstract

The renal microvasculature was examined stereoscopically after intraarterial injection of silicone rubber. Specimens studied were: 29 cases of normal kidney, 4 cases of sclerotic kidney, 10 cases of acute renal failure, and 10 cases of chronic renal failure from the final stage of chronic glomerulonephritis, malignant nephrosclerosis, diabetic nephropathy, and cortical necrosis. The followings were common evidences for chronic renal failure: much reduction and wide deficiencies of filling in the cortex, increased filling of vasa recta, narrowing and spiralling of interlobular arteries and cortical afferent arterioles, appearance of giant glomeruli, rarefaction of the peritubular capillary plexus, and relative preservation of glomeruli in the juxtamedullary zone and vasa recta in the medulla may be the major pathway, after the interlobular arteries and afferent arterioles in the subcapsular cortex are destroyed, and these vascular architectural changes may be intimately related to the pathophysiology of chronic renal failure.

Introduction

The kidney plays an important role in the regulation of general circulation by controlling of water and electrolytes excretion, and the renal circulation is the major determinant of nephron activity. The relationship between structure and function has been an interesting theme since the pioneering publication of Malpighi in 1666[1]. It has been the most fundamental work to elucidate the finer microvasculature in the normal and diseased kidney.

The remodelling approach, both by standard histological techniques and various injection methods, has provided a more detailed information concerning the tubular pattern and the vascular architecture of the kidney. The previous injection materials, such as dyes or plastic materials, could not reveal much detail, of either the pattern of the capillaries or of the three-dimensional fine vasculature. By the use of low-viscosity silicone rubber solutions for injection[2], more precise details and stereoscopic figures of vasculature could be readily obtained.

Little work has been carried out on the intrarenal vascular architecture of diseased kidney. Classically, Gaensslen[3] investigated 11 cases of chronic nephritis and secondary contracted kidney by injection of dyes and examination of celloidin-embedded and thick-sliced preparations. He observed extreme poorness of dye-injected glomeruli, giant glomeruli, corkscrew-like running of interlobular arteries, and a chaotic change from the regular meshwork of the peritubular capillary plexus. Recently, Takazakura et al.[4] examined the intrarenal vascular changes in 33 normal and 30 diseased kidneys by microangiographic and histological techniques, and reported that the cortical

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arterial tree was destroyed by obliteration of the cortical arteriole-glomerular (A-G) units whereas the medullary A-G units became continuous and were relatively well preserved, thus maintaining the medullary circulation.

Changes in the intrarenal vascular architecture in chronic renal failure were investigated by the silicone rubber injection method and histological techniques, and findings of the previous studies[3-7] have been conformed and extended in this report.

MATERIALS AND METHODS

Materials: The kidneys were obtained postmortem or by nephrectomy from 10 patients, aged from 31 to 77 years. The ten cases of chronic renal failure were composed of 3 cases of chronic glomerulonephritis in final stage, 2 cases of malignant nephrosclerosis, 3 cases of diabetic nephropathy, and 2 cases of cortical nerosis. The clinical data were summarized in Tables 1 and 2. All except Cases 6 and 8 had undergone peritoneal dialysis and/or hemodialysis. The patients with chronic glomerulonephritis had been suffering from renal func-

tional disturbane for 5–13 years, although they had been treated by dialysis for 1–2 years. The direct cause of death was ascribed to uremic pneumonitis (Case 1) and sepsis (Case 2). In the diabetic nephropathy group, diabetes mellitus had been controlled for 10–20 years. The patient of Case 10 had a episode of acute glomerulonephritis 3 years before death, and died of cortical necrosis after labor.

Twenty-nine kidneys were obtained from autopsy cases without kidney disease, aged from 0 to 82 years, were used for normal controls. Four cases of sclerotic kidneys and 10 cases of acute renal failure were used for comparison.

Methods: The kidneys were removed with the full length of renal artery and vein. Silicone rubber (MV-112, Canton Biomedical Inc.) was injected into the renal artery under a pressure of between 120 and 150 mmHg, after perfusion of saline with added heparin. Injection was stopped at optimal filling of the subcapsular cortex. After vulcanization for 7 hr at room temperature, the kidneys were hardened and dehydrated in graded alcohol

Table 1. Materials

Case No.	Origin	Age (yrs.)	Sex	Clinical diagnosis	Pathological diagnosis	Weight of kidney (g)
1	SN–4658[1]	31	F	Uremia and heart failure	Chronic glomerulonephritis	85/70
2	SN–4774	46	M	Chronic renal failure	Chronic glomerulonephritis	60/50
3	Nephrectomy	37	M	Chronic renal failure	Chronic glomerulonephritis	55/50
4	Nephrectomy	47	M	Malignant nephrosclerosis	Malignant nephrosclerosis and pyelonephritis	130/120
5	TLAH–323[2]	62	M	Malignant nephrosclerosis	Malignant nephrosclerosis	80/45
6	SN–4663	77	F	Diabetic nephropathy and encephalomalacia	Diabetic glomerulosclerosis	140/145
7	NSN–816[3]	73	M	Diabetic nephropathy	Diabetic glomerulosclerosis	80/80
8	SN–4811	65	M	Diabetes mellitus and pulmonary tuberculosis	Diabetic glomerulosclerosis	150/140
9	No. 6397[4]	67	M	Esophageal carcinoma and renal failure	Cortical necrosis	130/140
10	SN–4786	26	F	Renal failure and hypofibrinogenemia	Cortical necrosis	139/100

1): Autopsy number of Tokyo Medical and Dental University, 2): Tokyo Labor Affair Hospital, 3): Nakano Sōgō Hospital, and 4): Tokyo Women's Medical College.

Table 2. Summary of clinical data

Case No.	Total duration of renal failure	Peritoneal dialysis (times)	Hemodialysis (times)	BUN (mg/dl)	Creatinine (mg/dl)
1	2 years	5	0	135	13.4
2	1.5 years	0	31	180	23.5
3	9 months	14	24	63	12.5
4	6 months	0	19	—a)	—a)
5	2 years and 8 months	0	279	94	12.4
6	1 month	0	0	176	7.6
7	4 months	32	0	117.3	10.3
8	2 months	0	0	132	5.7
9	1 month	14	9	90.1	6.0
10	3.5 months	11	36	87	10.2

a): Not known

and cleared in methyl salicylate. The injection cast was observed with a micro-stereoscope. Slices measuring 1–3 mm in thickness were photographed with the aid of a profile projector V-16A (Nikon). For histological examination, 2 or 4 blocks were taken from the right kidneys, and stained with Hematoxylin-Eosin, Masson's trichrome, PAS, Yajima's PAM, and Watanabe's silver impregnation methods.

RESULTS

Macroscopic and microscopic findings: In chronic glomerulonephritis in the final stage, the kidneys were markedly contracted, and had a fine granular and partly smooth surface. The cortex was narrowed, usually measuring less than 3 mm in width. In microscopic pictures, almost all the glomeruli showed hyalinization and complete solidification, associated with tubular atrophy, although a few glomeruli remained intact in the juxtamedullary zone (Fig. 1). Cellular and mucoid thickening of the intima and medial hypertrophy of the interlobular and arcuate arteries (Fig. 5) were distinctly observed in cases treated by dialysis over extended periods.

In the malignant nephrosclerosis, the kidney from Case 4 was not reduced in size and weight, but the kidney from Case 5 treated 279 times by hemodialysis was markedly contracted and had a smooth surface speckled by large granules. Microscopically, the Case 4 kidney showed massive fibrinoid necrosis of the arterioles and focal glomerular tufts, together with marked narrowing of the interlobular arteries (Fig. 6). However, the majority of glomeruli showed no striking changes (Fig. 2). The Case 5 kidney showed completely solidified and hyalinized glomeruli, and reduction of lumens of interlobular and arcuate arteries by forming of fine mucinous rings of intima. Prominent reduplication of elastic fibers of arcuate arteries was observed.

In the diabetic nephropathy group, the kidneys were not reduced in size and weight, and had a fine granular surface. The glomeruli showed various lesions, i.e., nodular lesion, exudative fibrin cap formation, and intercapillary hyalinization (Fig. 7). Arterio- and arteriolosclerosis were prominent in Case 7 (Fig. 3) and 8.

In the cortical necrosis group, it was difficult to strip off the capsule. The section showed thin, yelowish, and band-like necrosis of the whole cortex of 2–3 mm in width. In Case 9, numerous fibrin thrombi were observed in the interlobular arteries, afferent arterioles and glomerular tufts

(Fig. 4). A small number of glomeruli were free from necrosis in the juxtamedullary zone. In Case 10, complete necrosis of glomeruli and tubules in the whole cortex occured, followed by fibrosis and calcification (Fig. 8).

Findings on injection figures: Observation was mainly focused on the branches of the intrarenal arteries, from the arcuate artery down to the capillary level. The veins were not distinctly visualized in any of the cases.

In normal cases, microvasculature revealed by the silicone rubber cast was characterized by smooth and straight running of interlobular arteries and afferent arterioles, and compact filling of the peritubular capillary plexus in the cortex (Fig. 10). The peritubular capillary plexus was formed of dense "reticular" mesh near the glomerulus and loose "fascicular" mesh away from it. In the juxtamedullary zone, the afferent arterioles branched from the arcuate arteries and the proximal part of the interlobular arteries, and had a larger caliber than those in the cortex. The efferent arterioles in this region mostly ran down to the medulla with or without formation of the peritubular capillary plexus. Several efferent arterioles ran parallel to the arcuate artery and down to the papilla. The aglomerular arteries branched from the arcuate artery and ran straight down to the medulla, not through the glomerular tuft. In the medulla, the vascular architecture of the vasa recta was made up from bundles of efferent arterioles and aglomerular arteries. About 2–4 efferent arterioles and 10–15 aglomerular arteries constituted one bundle of vasa recta and this proportion seemed to decrease in the aged kidneys. In the infant kidneys, efferent arterioles were large and capillaries from the peritubular capillary plexus in the jux-

tamedullary zone frequently anastomosed with vasa recta (Fig. 9).

In the chronic glomerulonephritis in the final stage, Cases 1 and 3 showed wide deficiencies in filling in the cortex and increased filling in the medulla. Tortuous running of interlobular arteries and marked rarefaction of the peritubular capillary plexus were also observed (Fig. 12). In Case 2, enlargement of a few remaining glomeruli and peritubular capillary plexi, which were condensedly filled with injected materials, were distinctly observed (Fig. 11). Anastomoses between afferent and efferent arterioles were apparent in this group.

In the malignant nephrosclerosis group, further prominent defects in filling of the cortex and increased filling of the vasa recta were observed. Almost all the interlobular arteries had blind ends and afferent arterioles anastomosed with efferent arterioles in Case 4 (Fig. 13). Case 5 showed much rarefaction and irregular distribution of capillaries in the cortex, together with anastomoses between vasa recta in the outer zone of the medulla.

In the diabetic nephropathy group, vascular filling in the cortex was better visualized than in the other groups. Slightly distorted and rarefied peritubular capillary plexus was observed, in contrast with compact filling of the capillary plexus in the juxtamedullary cortex (Fig. 14).

In cortical necrosis, complete and band-like deficiency in filling of the cortex was in direct contrast to increased filling of the medulla. Some penetrating arteries remained in the cortex. These were regularly distributed and anastomosed with stellate veins (Fig. 15). A small number of hypertrophied glomeruli survived in the juxtamedullary cortex, giving off efferent arterioles of large caliber. Extremely compact

filling of vasa recta, which were composed of aglomerular arteries, was characteristic. Fine and close anastomoses developed between vasa recta (Fig. 16).

DISCUSSION

There is a troublesome technical deficiency of the injection method that complete filling of the renal arteries may not always be achieved. In every case of normal subjects, the almost complete filling was usually obtained. These events are due to partly pathological conditions of kidney examined and partly our technical errors. Histological preparations revealed that the silicone rubber solutions were completely injected into the arterioles and 80–90% to the capillary levels.

The next problem is whether the all injected figures may be the functioning blood vessels or not. Goemoeri et al.[8] have suggested that the figures of vascular injection are determined in large measure by the physiological state of the animal before death. It is desirable that the vascular injection pattern of extirpated kidney should be compared with angiography while the patient is alive, as Bager and Herd[9] using the animal model.

Ljungqvist et al.[6] observed four types of departure from the basic pattern during ageing; spiralling of the afferent arterioles, cortical aglomerular arterioles, increased vasa recta and altered juxtamedullary glomeruli. Our results are mostly consistent with their findings. In addition, we observed, parallel with ageing, the tendency to more irregular and distorted distribution of the peritubular capillary plexus in the cortex, and several enlarged glomeruli and increase in aglomerular arteries in the juxtamedullary zone.

It is not easy to differentiate between the aged and sclerotic kidneys. The difference may be quantitative rather than qualitative.

In regard to the dialysis effect, Cases 2, 5 and 10 had undergone hemodialysis over a long time, and changes in their vascular figures were more severe than those of others. Anastomoses between vasa recta in the outer zone of the medulla, which were observed in Cases 5 and 10, may be ascribed to long-term hemodialysis. However, the effect of the progress of disease can not be excluded.

Our results on vascular injection figures in chronic renal failure are similar to those which we previously reported in acute renal failure (Takemura and Matsubara[10]), in that they show definite reduction in filling of the subcapsular cortex and a relative increase in filling of the medulla. These observations support Trueta's suggestion[11] that hemodynamic control of cortex and medulla is separately conditioned.

There are some characteristic findings for each group, depending on the site of obliteration; the cortical arteriole-glomerular unit for the chronic glomerulonephritis group, cortical afferent arteriole and the distal part of the interlobular artery for the malignant nephrosclerosis group. The diabetic nephropathy group showed better filling in the cortex than other groups.

The common findings among the four groups are: apparent reduction and wide deficiency in filling of the cortex, the appearance of giant glomeruli and relative preservation of juxtamedullary glomeruli and vasa recta. The arteriole-glomerular units in the juxtamedullary zone and vasa recta in the medulla may be the major intrarenal circulatory pathway in chronic renal failure. Maintenances of the juxtamedullary and medullary circulation may be possively enhance the washing out of

the osmotic gradient, as Takeuchi *et al.*[12,13] suggested, and affect the tubular functions of concentration and dilution.

The elegant microdissection studies of Addis and Oliver[14] have shown that hypertrophy and hyperplasia in nephrons from human chronic renal disease occur chiefly in the glomerulus and proximal tubules. We also observed the extreme condensation and hypertrophy of injection figures of the survived glomerulus and peritubular capillary plexus around the proximal tubule in the kidneys of chronic renal failure, except in the kidneys treated by hemodialysis over a long period. These findings suggest that the functioning remnant vasculature is hypertrophic and may be working at an increased rate, whereas most of the renal arteries and capillaries are destroyed. These aspects are consistent with Bricker's "intact nephron theory"[15,16], in terms of the adaptation of the vascular architecture to the condition of chronic renal failure.

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Explanation of Figures

Plate 1

Photomicrographs (Hematoxylin-Eosin stain). Original magnification: ×10.

Fig. 1. Solidification of glomeruli and numerous hyaline casts in the tubules in Case 2.

Fig. 2. Lamellar thickening of intima and medial hypertrophy of arcuate and interlobular arteries in Case 4.

Fig. 3. Arterio-arteriolosclerosis, hyalinization of glomeruli and interstitial fibrosis in Case 7.

Fig. 4. Diffuse cortical necrosis with numerous fibrin thrombi in interlobular arteries, afferent arterioles and glomerular tufts in Case 9.

Plate 2

Photomicrographs (Hematoxylin-Eosin stain). Original magnification: ×120.

Fig. 5. Intimal thickening and muscular hypertrophy of the interlobular arteries, hyalinization of afferent arterioles, solidification of glomeruli, and atrophy of tubules in Case 3.

Fig. 6. Lamellar thickening of all layers of interlobular artery and afferent arteriole and atrophic tubules in Case 4.

Fig. 7. Sclerosis of interlobular artery, hyaline thickening of afferent arteriole, nodular sclerosis of glomerulus, and marked atrophy of tubules in Case 7.

Fig. 8. Complete obliteration of interlobular artery and abundant calcium deposits on the devastated glomeruli and tubules in Case 10.

Plate 3

Microvasculature of silicone rubber cast of normal infantile and adult kidneys. Original magnification: ×20.

Fig. 9. Straight running of interlobular artery and regular peritubular capillary plexus in 3-old boy.

Fig. 10. Regular distribution of compact "reticular" and "fascicular" peritubular capillary plexus and slight increase in number of aglome-

rular arterioles in the outer medulla in 31-year-old female.

Plate 4

Microvasculature in chronic glomerulonephritis. Original magnification: ×20.

Fig. 11. Markedly tortuous running of interlobular artery, giant glomeruli, and marked rarefaction of peritubular capillary plexus in the cortex, in contrast with increased filling of vasa recta in outer medulla in Case 2.

Fig. 12. Markedly tortuous running of arcuate and interlobular artery and devastation of peritubular capillary plexus. Increased filling of vasa recta and aglomerular artery in the medulla in Case 3.

Plate 5

Microvasculature in malignant nephrosclerosis and diabetic nephropathy. Original magnification: ×20.

Fig. 13. Prominent deficiency in filling of the cortex and increased filling of the vasa recta and aglomerular artery. Numerous blind ends of interlobular artery in Case 4.

Fig. 14. Ill-defined contour of glomerulus and peritubular capillary plexus in Case 7. Considerable preservation of filling of the cortex in other cases.

Plate 6

Microvasculature in cortical necrosis. Original magnification: ×20.

Fig. 15. Massive deficiency of filling of the cortex with a small number of surviving glomeruli in the juxtamedullary zone. Penetrating artery and stellate vein are seen in Case 9.

Fig. 16. Severe deficiency of filling of the cortex, in contrast with the marked filling of vasa recta in Case 10. Extensive anastomosis of vasa recta is seen.