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Renal injury in complete ureteric obstruction

A functional and morphological study

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Summary. This preliminary study examined reno-vascular injury sustained by the multipapillary porcine kidney in acute and chronic complete ureteric obstruction. In combination with measurement of upper tract pressure, regional function was assessed by [^{99m}Tc]-dimercaptosuccinic acid (DMSA) uptake and qualitative renal perfusion, by resin casting of the arterial tree prior to scanning electron microscopy (SEM). In acute obstruction, segmental defects were noted in the renal poles on both [^{99m}Tc]-DMSA scanning and casting. On SEM there was a polar afferent arteriolar vasodilatation after 30 min of obstruction and, subsequently, a segmental reduction in cortical perfusion. In kidneys that had been obstructed for 20 days, we observed a marked reduction in outer cortical perfusion coincident with afferent arteriolar vasoconstriction. The pathogenesis and significance of segmental injury to the multipapillary kidney in obstructive uropathy is discussed.

Key words: Obstructive uropathy – Multipapillary kidney – Segmental renovascualar injury

The association between obstructive nephropathy and abnormalities in the renal circulation is well established. Techniques such as direct collection of renal vein blood, indirect clearance of para-amino hippuran (PAH), electromagnetic flow probes and radiodensimetry have all indicated that unrelieved ureteric obstruction induces an initial short-lived increase in global renal blood flow, followed by a sustained reduction [4, 7, 9, 11, 12]. This is associated with an increase in renal vascular resistance, a lengthening of the renal circulation time, and a reduction in the calibre of the renal artery on angiography [1, 3, 5]. In the completely obstructed rat kidney there is an overall reduction in blood flow to both cortex and medulla, with blood flow within the cortex being heterogeneously distributed and large areas of renal tissue remaining relatively underperfused [13]. The mechanism of the reduction in cortical perfusion is thought to be a preglomerular arteriolar vascoconstriction that is initially reversible but becomes irreversible after a given period of persistent and prolonged ureteric obstruction [2].

The pathophysiology of the vascular injury in hydronephrosis has been investigated to date in unipapillary animal models such as the rat and the dog [9, 10, 12]. Man has a multipapillary kidney. The same is true for the miniature pig, and the distribution of simple and compound papillae in the Göttingen strain is mast similar to that in the human (M. L. Godley, personal communication).

Following the clinical impression that the parenchymal damage in obstructive uropathy is segmental and, like reflux nephropathy, is related to papillary morphology, this preliminary work wa performed to examine progressive renal injury resulting from confirmed complete ureteric obstruction by combining intrapelvic pressure measurement, regional function as assessed by [^{99m}Tc]-dimercaptosuccinic acid (DMSA) scanning, and postmorten scanning electron microscopy (SEM) of the renal microvasculature.

Materials and methods

A total of 9 kidneys in 14 miniature pigs were obstructed for periods of 0.5 h ($n=2$), 24 h ($n=2$), 96 h ($n=1$), 240 h ($n=2$) and 480 h ($n=3$). The 240-h and 480-h kidneys were studied 2 weeks after ureteric reimplantation had been performed to relieve upper tract obstruction; four normal kidneys served as controls. In acute obstruction (<5 days), upper tract pressure was recorded just prior to nephrectomy via a needle nephrostomy, but in chronic obstruction, it was monitored throughout using a subcutaneous nephrostomy.

Live, anaesthetised animals received an intravenous bolus of [^{99m}Tc]-DMSA (7 MBq/kg) at 10 min prior to nephrectomy. All kidneys underwent insitu cannulation of the renal artery, irrigation with 0.9% heparinised saline and perfusion fixation with buffered glutaraldehyde at mean arterial pressure for 15 min. Once resected, the organs were imaged on a gamma camera, following which they underwent plastic casting of the arterial tree with Batson's #17 anatomical corrosion compound (Polysciences Inc., USA). After a

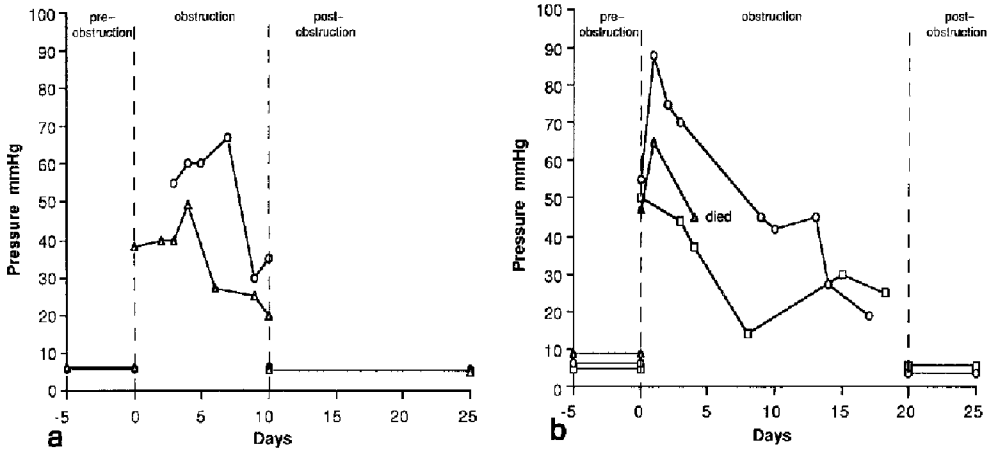


Fig. 1 a, b. Upper tract pressure before, during and after **a** 10- and **b** 20-day chronic obstructions followed by relief

Table 1. Upper tract pressure in acute obstruction

Length of obstructed period	Upper tract pressure (mean) at end of obstructed period
30 min	35 mmHg
24 h	74 mmHg
96 h	65 mmHg

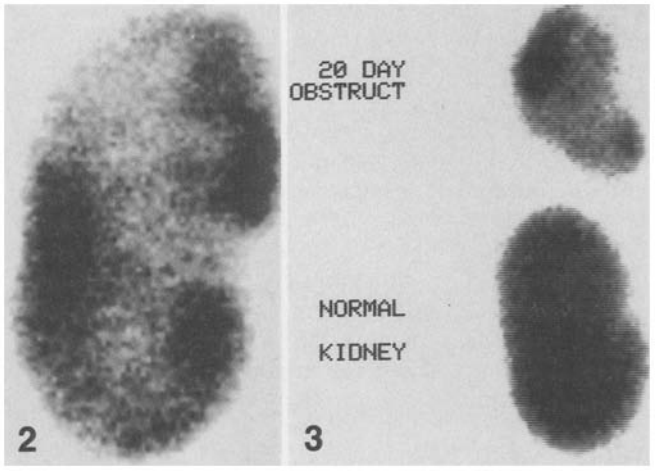


Fig. 2. Reduction in the uptake of [^{99m}Tc]-DTPA in the poles of a kidney following 5 days of obstruction

Fig. 3. The patchy uptake of [^{99m}Tc]-DTPA in a small kidney after 20 days of obstruction followed by relief, as compared with uptake in a control kidney

further 24 h, the kidneys were cut on the coronal axis and all renal tissue was dissolved with 36% HCl.

At least three sections from each cast (one from each pole and one from the middle of the kidney) were then cut and dried, glued to metal sample stubs and sputter-coated with gold. The casts were examined using an ISI DS 130 electron microscope at an accelerating voltage of 10 kV at both low power (magnification, ×15–20) and high power (×300–400). Particular attention was paid to the gross appearance of the cast at low power, to the number of glomeruli per low-power field, and to the appearance of both the afferent arteriole and the glomerulus at high power.

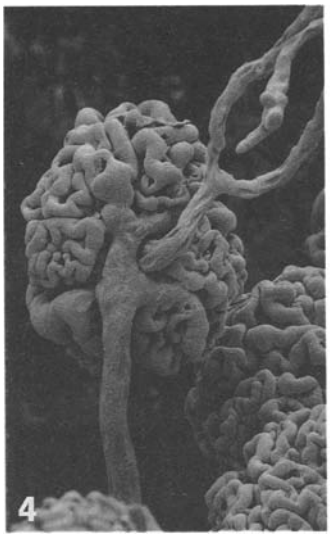
Results

The relationship of upper tract pressure with time in both the acute and chronic obstructive state is demonstrated in Table 1 and Fig. 1. There was a prompt rise in upper tract pressure to 60–90 mmHg at 24 h, followed by a sustained and steady fall. In neither the 240- or 480-h period of obstruction did the pressure fall the pre-obstruction levels. Following relief of obstruction, upper tract pressure fell to normal levels in all cases.

[^{99m}Tc]-DMSA scans were normal for up to 24 h. At 96 h there was a marked focal reduction in radiolabel uptake in both poles. Scans obtained following 10 days of obstruction and subsequent relief were not grossly abnormal, but after 20 days of obstruction followed by relief, kidneys were small and the uptake was patchy (Figs. 2 and 3). On SEM, normal kidneys revealed no apparent vascular abnormality (Figs. 4 and 5). SEM of kidneys that had been obstructed for 0.5 h revealed a normal gross appearance but a marked vasodilatation of the afferent arteriole in both polar regions (Fig. 6). Kidneys that had undergone 24 h of obstruction exhibited areas of marked underfilling in the poles in which the casts were grossly abnormal, but they appeared normal elsewhere. At 96 h of unrelieved obstruction, the polar areas were not filled at all and the perfused cast demonstrated a narrowing of the afferent arteriole at high power. The casts of kidneys that had been obstructed for 20 days and then relieved showed a non-uniform filling that was consistent with the defects seen on [^{99m}Tc]-DMSA scanning. There was also a consistent reduction in cortical perfusion at both 10 and 20 days, as well as narrowing of the afferent arteriole that was more extensive in the 20-day specimens (Figs. 7 and 8).

Discussion

The haemodynamic response to a complete unilateral ureteral occlusion is thought to be triphasic [12]. Immediately following ligation, there is an initial increase in renal blood flow and ureteric pressure. After 1 h of complete obstruction, blood flow begins to fall as ureteric pressure continues to rise, and after 5 h both parameters decline together [6].



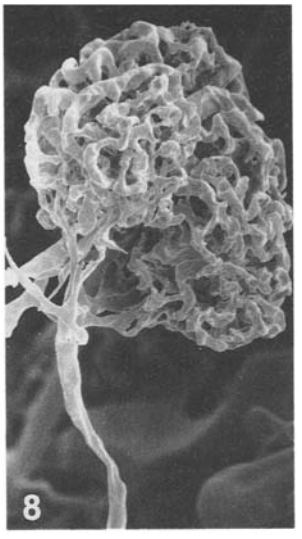


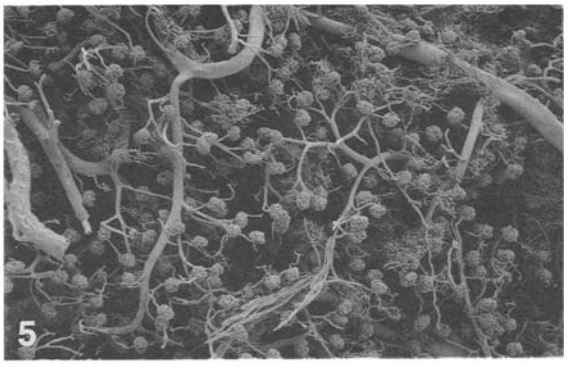
Fig. 4. SEM of a normal afferent arteriole and glomerulus and efferent arteriole

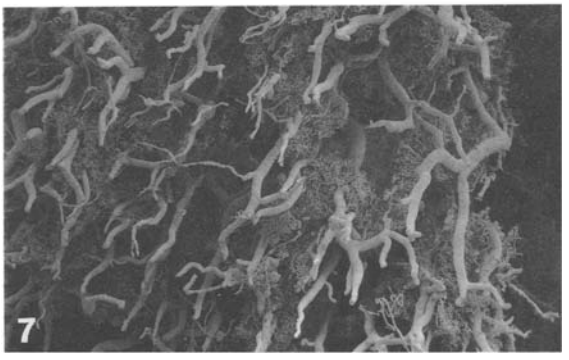
Fig. 5. Low-power SEM of a control kidney

Fig. 6. SEM of an afferent arteriole and glomerulus following 30 min of obstruction showing marked arteriolar dilatation

Fig. 7. Low-power SEM of renal cortex after 20 days of obstruction

Fig. 8. Marked reduction in the calibre of as afferent arteriole in a kidney following 20 days of obstruction





Following 30 min of obstruction, resting upper tract pressure had reached 30–40 mmHg, and at 24 h it was 70–90 mmHg, although levels may already have been falling by that point. Beginning at 24 h, pressure fell gradually but never reached pre-obstruction levels until ureteric reimplantation and relief had occurred. This observation conflicts with previous work in the unipapillary model [11] in which upper tract pressure had approximated pre-obstruction levels after only 24–48 h of complete ureteric obstruction.

Although they are not quantitative, both [^{99m}Tc]-DMSA scanning and casting of the renal microvasculature are qualitative indicators of renal perfusion. Following 30 min of obstruction, DMSA scans were normal but SEM revealed an arteriolar vasodilatation in the renal poles. At 24 h there was focal underperfusion and arteriolar vasoconstriction in the poles on SEM, with corresponding focal lesions being visible on the [^{99m}Tc]-DMSA scans. At 96 h we obseved gross polar defects on the [^{99m}Tc]-DMSA image in areas in which no filling occurred on casting. Of even greater interest is that at the time at which this perfused, fixed kidney was bivalved, these areas of underperfusion were drained by compound type III papillae.

Although the number of animals examined in the present study were small and our conclusions were therefore tentative, the changes seen on SEM mirror those observed on [^{99m}Tc]-DMSA scanning, with the exception that the latter changes occur later than those seen on SEM. A suitable explanation for this would be that the focal reduction in the polar areas is the result of a relative ischaemia, which is associated early with relatively normal tubular function that subsequently deteriorates.

In reflux nephropathy, scarring is segmental and is thought to be related to papillary morphology [8], with areas of the kidney that are drained by simple papillae being spared as compared with those containing compound papillae. The pathogenesis of these scars is unknown, buth they do appear as photon-deficient areas on [^{99m}Tc]-DMSA scanning. Also, the magnitude of pyelotubular backflow, a pressure-related phenomenon seen in areas drained by compound papillae, is enhanced under conditions of relative ischaemia [10].

In conclusion, this work suggests that (1) following a given period of obstruction, the uptake of [^{99m}Tc]-DMSA by the renal cortex may be abnormally segmental in nature; (2) complete upper tract obstruction is associated with marked changes in perfusion of the renal microvasculature that are at first polar but later become generalised; and (3) these areas of relative cortical underperfusion may be related to the configuration of papillary morphology.

Accordingly, these segmental changes are seen only in the multipapillary kidney and may be explained by the locally high intratubular pressure occurring in areas that are drained by compound papillae, resulting in the exertion of a negative vasoconstrictive feedback on the

afferent arteriole that is at first reversible but becomes irreversible with continuing obstruction. Subsequent permanent parenchymal damage is then inevitable. Ultimately, if the obstruction remains unrelieved, these effects are seen throughout the kidney and hydronephrotic atrophy becomes generalised.

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