Obstructive nephropathy: an update of the experimental research

Abstract  Ureteral obstruction (UO) is one of the most common problems confronting the urologist. Although large amounts of animal and clinical research have been done, the pathophysiologic mechanisms accompanying UO are not fully elucidated. Most of our knowledge on UO has been derived from experimental studies in a variety of animal models. Both antenatal and postnatal UO models have been developed mainly by ligation of the ureter or by burying the ureter into the psoas muscle. Most experimental studies have focused on short-term complete ureteral obstruction. The long-term effects of partial ureteral obstruction have been less intensively studied. It is now clear that obstructive nephropathy is not a simple result of mechanical impairment to urine flow but a complex syndrome resulting in alterations of both glomerular hemodynamics and tubular function caused by the interaction of a variety of vasoactive factors and cytokines that are activated in response to UO. Leukocyte infiltration appears to play an important role in obstructive nephropathy suggesting that UO also has an immunological component. Growth factors such as platelet-derived growth factor, transforming growth factor-beta, epidermal growth factor and insulin-like growth factor I may all play a role in the development and progression of fibrotic and sclerotic changes in the obstructed kidney. At present, the selection of patients with congenital hydronephrosis for operative treatment is controversial. Studies in animals and patients have shown that partial unilateral UO does not always cause a loss of renal function or progression in urinary tract dilation during long-term follow-up. The implications of UO continue to raise many questions and further work is necessary to achieve a better understanding of the pathogenesis in obstructive nephropathy.

Key words  Ureteral obstruction · Obstructive nephropathy · Animal model · Hemodynamics · Renal function · Growth factors

Introduction  Ureteral obstruction (UO) is one of the most common problems confronting the urologist. Modern methods of measuring renal function and imaging modalities have challenged the older concepts of ureteral obstruction and its surgical management, creating a dilemma for the urologist. Many patients with apparent ureter–pelvic junction obstruction suffer neither progressive loss of renal function nor progressive urinary tract dilatation during long-term nonoperative follow-up [69]. Similar findings have been observed from animal experiments. Burying the ureter into the psoas muscle produces an initial hydronephrosis, but thereafter not all kidneys deteriorate [61]. Although many animal experiments and clinical studies have been done the pathogenesis of obstructive nephropathy is not fully elucidated. This article reviews the work to date on experimental obstructive nephropathy.

Animal models  Models with complete unilateral ureteral obstruction

Antenatal models  Several animal species have been used in experimental congenital obstructive nephropathy studies, including the rabbit, lamb, ovine, opossum, and chick embryo (for
in vitro experiments) [5, 6, 73, 89, 96, 101]. Most congenital obstructions were induced at the ureteral level. McVary et al. [73] and Thomasson et al. [96] produced hydronephrosis in rabbits by ligation of one ureter during the third trimester. Beck [5] and Glick et al. [37] created complete unilateral ureteral obstruction (CUUO) in fetal lambs at the beginning of the second trimester or in the second trimester by clipping a silastic ring to the ureter. Recently, Steinhardt et al. [89] developed a CUUO model in the opossum during the early metanephric stage of kidney development by ligation of the ureter, which produced a significant hydronephrosis.

**Adult models**

In 1926, Hinman and Morion [48] created a CUUO model by ligating the ureter. Up to now CUUO is mainly produced by surgical methods.

**Changes in renal morphology**

The changes in renal morphology in response to CUUO depend on time of onset, duration, and degree of obstruction. In fetal models, Beck [5] and Glick et al. [37] found that early midtrimester CUUO caused renal dysplasia. In adult models, the gradual destruction or atrophy of the renal parenchyma was associated with an increase in the size of hydronephrosis [47]. Interstitial fibrosis and progression in radial scarring developed in the kidney in response to increasing periods of obstruction. Hydronephrotic atrophy may be associated with destruction of all the renal parenchymal tissue, and a thin-walled sac of watery fluid remains. The time course for this is unknown in humans, but in rats it takes about 4 months, in rabbits 10 months and in dogs 18 months or more after onset of obstruction [27]. However, the acutely obstructed kidney may increase its weight within hours after onset of obstruction due to renal parenchymal edema [76].

**Changes in renal function**

In fetal models, obstruction causes a significant decrease in glomerular filtration rate (GFR) and abnormal tubular function with marked sodium loss [1]. To obviate the effects of surgery and anesthesia on renal function Ward et al. [101] developed a chronically catheterized ovine model where renal function in nonobstructed kidneys was compared with that in obstructed kidneys. The obstructed kidneys had lower creatinine clearance, higher fractional sodium excretion and higher urine sodium/creatinine ratio [101]. In adult animal models, pelvic pressure increased immediately in response to CUUO and GFR decreased when the pelvic pressure exceeded 20 mmHg [52]. The changes in renal function occurred during the first 24 hours of CUUO. In rats with CUUO, GFR was reduced to 52% of baseline value at 4 hours, 23% at 12 hours, and 4% at 24 hours [11, 42]. After 24 hours of CUUO the continued decrease in GFR of the obstructed kidney was associated with a compensatory GFR increase in the contralateral nonobstructed kidney [42, 106]. Redistribution of GFR from the surface nephrons to the deep nephrons was found during CUUO [17], corresponding with blood flow redistribution from the outer cortex to the inner cortex and outer medulla [87]. Postobstructive phosphate excretion by the kidney was markedly decreased after relief of a 24-hour CUUO, despite an increase in the fractional excretion of sodium [82]. There was no absolute increase in sodium and water excretion after relief of CUUO [82].

However, there are controversial reports on the ipsilateral GFR changes. Using electromagnetic blood flow measurement and renal extraction of inulin in dogs, Navar and Baer [78] elegantly showed a dramatic temporary increase in GFR following CUUO. In contrast, studies in rats and pigs uniformly showed an immediate reduction in ipsilateral GFR after onset of acute obstruction [42, 52, 81], indicating that there are major variations in the reactive mechanisms among species.

**Changes in renal blood flow**

The immediate hemodynamic response to short-term CUUO is variable. Complete obstruction of the ureter results ultimately in a progressive reduction in ipsilateral renal blood flow (RBF). In anesthetized dogs, a decrease in RBF to about 40% of controls was found 12 to 24 hours after onset of obstruction [75, 108]. In conscious dogs, RBF was found to be 50% of controls 24 hours after onset of obstruction. RBF was reduced to 30% after 6 days, 20% after 2 weeks, and 12% after 8 weeks of obstruction [99]. In the rat, RBF decreased to 33% of controls 6 days after CUUO, as calculated per g kidney weight [17]. In the rabbit, RBF was reduced to about 40% on the obstructed kidney 1 to 17 weeks after onset of CUUO [55]. By estimating total microsphere uptake and local 125I-antipyrine uptake, Clausen and Hope [17] found that RBF was equally reduced in the outer and the inner cortex, and that the fractional flow to the outer medulla was doubled as compared with controls.

Numerous studies in animals with unipapillary kidneys have shown that the flow reduction is preceded by a transient increase in RBF. In anesthetized dogs, ipsilateral RBF rose from 128 to a maximum of 165 ml/min 15 minutes after CUUO [75, 108]. In contrast, we have recently shown that 15 hours of CUUO in the pig is associated with a consistent and immediate reduction in ipsilateral RBF without a prior significant increase in RBF [29, 52]. The reason for this difference between species is still unclear. Studies in dogs have shown that an immediate increase in ipsilateral RBF is due to a predominant preglomerular vasodilatation [76, 78, 93]. An increased production of prostaglandin E2 (PGE2) from the renal