Urol Res (1999) 27:29–39

REVIEW ARTICLE

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Obstructive nephropathy: an update of the experimental research

Received: 12 January 1998 / Accepted: 18 June 1998

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

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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 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 ^{125}I-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 E_2 (PGE_2) from the renal

medulla has been suggested as the responsible mechanism. It has been demonstrated that the renal medulla is a rich site of PGE_2 production [2]. Furthermore, the increase in RBF subsequent to ureteral pressure increase can be blocked by administration of cyclooxygenase inhibitors [30]. This supports the view that vasodilatory prostaglandins are important for the initial hemodynamic response to CUUO, as well as for maintaining RBF during obstruction. It has also been suggested that a myogenic reflex caused by a reduction in the transmural pressure due to increased interstitial pressure may result in an RBF increase [100]. Finally, a tubuloglomerular feedback mechanism has been suggested to be responsible for the hemodynamic changes [21].

Similar to the results from studies in pigs with CUUO, studies in rats with acute CUUO did not demonstrate vasodilatation of the afferent arteriole in response to ureteral obstruction [7]. Several methodological differences have been suggested to explain this phenomenon. If the vasodilatation is prostaglandin mediated, it has been suggested that an artifact caused by the recent abdominal surgery would depress a sufficient response of the prostaglandin system. However, most acute experiments in dogs under general anesthesia have shown an increase in ipsilateral RBF [76, 93]. In addition, the degree of consciousness has been suggested to be important for the hemodynamic response, since an increase in RBF has been the consistent finding in the anesthetized dogs [108]. In conscious dogs, total RBF remains stable for 1–3 hours after CUUO [75, 108]. Others have suggested that the hydration prior to and during obstruction is important [63, 78]. Taken together, major differences exist among the numerous animal models and the methods used to study renal hemodynamics in response to CUUO.

The reduction in RBF during acute CUUO is primarily thought to be caused by an intrarenal vasoactive mechanism. Several studies have provided evidence that angiotensin II (ANG II) participates in the regulation of renal hemodynamics by increasing ipsilateral renal vascular resistance during CUUO. In pigs, CUUO of the kidney results in a net renal secretion of ANG II from the obstructed kidney [29, 30]. In the early stages of CUUO, the concentration of renin in the renal vein was increased both in vivo and in vitro [25, 29, 30]. Renin cleaves angiotensinogen to form the decapeptide angiotensin I, which is later converted to the active form, ANG II, by angiotensin-I-converting enzyme. Infusion of the angiotensin-I-converting enzyme inhibitor, captopril, improved RBF in response to a release of 24-hour CUUO [108]. In addition, numerous studies suggested that reduction in RBF during CUUO is caused, in part, by the vasoconstricting agent thromboxane A_2 [100, 109]. Furthermore, both angiotensin II and thromboxane A_2 have been shown to contract mesangial cells in culture and, therefore, they potentially may reduce the glomerular capillary area available for filtration [74]. It has been demonstrated that administration of thromboxane synthethase inhibitors significantly increases GFR after relief of obstruction [109]. However, GFR and renal plasma flow did not return to preobstruction levels, implying influence of other factors.

The reasons for the persistent RBF reduction in response to chronic CUUO have not been fully established. The ureteral pressure is not significantly elevated in chronic CUUO. Thus, passive compression of the renal vessels cannot explain the reduction in RBF. The increased renal pelvis volume has also been considered to cause some passive compression of the arteries and veins. This is supported by the transient increase in RBF immediately after release of the ureteral occlusion [25]. However, the lack of evidence for a passive mechanism to cause the decrease in RBF may suggest that active humoral, neural or reflex phenomena are responsible. In one study, El-Dahr [26] found that kidneys subjected to chronic CUUO expressed elevated renin mRNA levels in the juxtaglomerular apparatus (JGA), increased numbers of JGAs, which contain immunoreactive renin, and an expanded distribution pattern of renin within the renal vasculature. This increase in renin secretion may contribute to the increased renal vascular resistance and deceased GFR resulting from CUUO. One explanation for the recruitment of renal cortical cells secreting renin following CUUO is a reduced sensitivity to inhibitory stimuli controlling secretion. Also, systemic catecholamine depletion with alpha-adrenergic blockades by phenoxybenzamine in dogs ameliorated the expected rise in renal vascular resistance during chronic CUUO, suggesting that catecholamines are partly responsible for the decreased RBF [35].

Models with partial unilateral ureteral obstruction

A variety of methods has been used to produce partial unilateral ureteral obstruction (PUUO) in several animal species including rat, opossum, rabbit, pig, dog, sheep, and monkey [61, 72, 88, 95, 97, 105]. The majority of these models was surgically induced after birth. Few animal models with hereditary congenital hydronephrosis have been described [28, 86].

Antenatal models

Tanagho et al. [95] developed a PUUO model in the fetal lamb at 70 to 75 days gestation by wrapping a silastic tube around the ureter. A similar model was described by Hawtrey et al. [46]. Later, Steinhardt et al. [88] developed a fetal PUUO model by surgical intervention in the opossum.

Inbred unilateral congenital hydronephrosis in the rat was established in 1960 [86]. In 1979, Friedman et al. [28] reported that the pelvic pressure is higher in the inbred congenital hydronephrotic rat than in the normal rat, suggesting that the congenital hydronephrotic rat manifests an obstruction that is at the level of the ureteral – pelvic junction. However, Sellers et al. [86] found that

the obstruction was located at the junction between the upper and the middle third of the ureter in the male rat, and slightly higher in the female rat, where the ureter is located between the ileolumbar vessels dorsally and the internal spermatic vessels ventrally.

Newborn models

In 1983 the newborn PUUO model was developed [94]. By encompassing the ureter through a plastic tube, Taki et al. [94] and Chevalier et al. [94] created PUUO models in newborn guinea pigs, whose nephron differentiation is complete at birth. Although slit, the internal diameter of the plastic tube was fixed and long-term effects on the kidney were difficult to interpret. Josephson et al. [61] produced a PUUO model in newborn rats by embedding a small segment of the ureter into the psoas muscle similar to Ulm and Miller's technique [97]. The glomeruli in the outer quarter of the renal cortex in newborn rats are still in the S-stage [70], which corresponds to the second or third trimester in the human fetus. In this PUUO model, the observed dilation appeared early and did not progress despite the continued presence of a long-term permanent obstruction [61]. This model seems to mimic the mild congenital hydronephrosis in infants and children. Recently, we established two different degrees of PUUO (mild and severe) [103, 104] in newborn rats by embedding different segments of the ureter into the psoas muscle. In the severely obstructed kidney the hydronephrosis progressed significantly with time compared with the mildly obstructed kidney [103, 104].

Adult models

In 1962 Ulm and Miller [97] described a simple and reliable technique to create PUUO in dogs by embedding the ureter into a psoas muscle tunnel. Later, Djurhuus et al. [24] established PUUO in the pig using the same method. Boyarsky and Martinez [9] used another method to create PUUO in dogs by placing a 3-F ureteral catheter along the ureter. Subsequently a silk ligature was tied around the ureter and the catheter was withdrawn. Later, a similar method was used successfully to develop PUUO in the monkey [106]. Recently, Masui et al. [72] induced PUUO in the dog using a specially designed polypropylene obturator.

Changes in renal morphology

The effect of PUUO on renal morphological changes has been the subject of debate over the past decade. Several studies have shown that the presence of a pronounced hydronephrosis was associated with very few changes in renal morphology [18, 19, 54, 61]. In newborn rats, Claesson et al. [19] found a substantial papillary distortion and a moderate dilatation of the collecting ducts/distal tubules within 1 week of onset of PUUO. After 6–9 weeks, wet and dry kidney weight (KW) was 16% lower than that of the contralateral nonobstructed kidney. The obstructed kidneys were small but without any signs of atrophy. In other studies PUUO was associated with a decreased glomerular volume and an increased glomerular crowding together with tubular dilation and progressive glomerular sclerosis, tubular atrophy and interstitial fibrosis [15]. In contrast, PUUO in newborn guinea pigs induced a progressive glomerular sclerosis, tubular atrophy, and interstitial fibrosis [15]. The KW was reduced by 30%–40% after 8 weeks of obstruction [15]. Due to the inability to quantify the degree of obstruction it is difficult to compare the effect of PUUO on renal morphological changes in newborn rats with those in newborn guinea pigs.

Changes in renal function

Compared with CUUO, the renal function deterioration in PUUO is relatively mild. As a result of PUUO, GFR may increase, remain unchanged, or decrease, depending on the duration, the severity of obstruction and the diuretic state [32, 39, 78, 93]. In antenatal PUUO models, GFR and RBF were significantly decreased and the ability of the obstructed kidney to conserve water and concentrate urine was markedly impaired [88]. However, the degree of obstruction was not quantified or correlated with the anatomical and functional results. In postnatal animal PUUO models, it has been reported that total GFR was preserved with a normal single nephron GFR after 4 weeks of obstruction [54]. In other studies with PUUO for 4 days to 4 weeks using dogs or rats, GFR was variably reduced to 20%–70% of normal levels [77, 80, 91]. The results after 5–9 weeks of obstruction are conflicting. In rats, Josephson et al. [57, 58] found that GFR was 16% lower on the obstructed side compared with the contralateral nonobstructed kidney. However, Chevalier et al. [15, 16] and Taki et al. [94] found that GFR in guinea pigs was decreased by about 95%. This difference may partly be explained by a marked variation in methods and models.

Micropuncture studies in a rat model with PUUO demonstrated that surface nephron GFR was reduced, but less than whole kidney GFR, and that proximal tubular reabsorption was normal or enhanced [106]. Intracortical GFR was not redistributed in PUUO rats although there were significant indications of a reduction in the absolute glomerular numbers and GFR on the hydronephrotic side [59]. The decrease in cortical blood flow previously observed was too small to explain the reduction in filtration [57]. Glomerular plasma flow, at least in superficial glomeruli, was not affected [54]. But the filtering surface may be affected by the reduction in the glomerular numbers that has previously been observed [58].

The literature on electrolyte and water excretion during PUUO are also conflicting. Generally, during

acute PUUO there is a significant decrease in sodium, potassium, and solute excretion, with a decrease in urine sodium concentration and increase in urine osmolality. However, during chronic PUUO, sodium excretion is increased [80], or unchanged [91, 94, 106]. Potassium excretion is slightly increased [80] or decreased [58, 95] and osmotic excretion is unaffected [58, 106] or decreased [80, 91]. This discrepancy is difficult to explain. It may be due to species differences (dogs, rats), different degrees of hydration with different types of fluids and/or differences in diets, the latter of special importance for potassium balance.

Micropuncture studies in obstructed rat kidneys have shown that sodium reabsorption is enhanced in the proximal tubule but decreased in the distal parts of the nephrons [41]. It might be postulated that in the severely hydronephrotic kidney the effect of reduced distal sodium reabsorption will balance the effect of reduced filtration and enhanced proximal tubular reabsorption of sodium. The impaired reabsorption in the distal tubule, deeper nephrons, or in the collecting ducts was largely responsible for the decreased concentrating ability and enhanced fractional excretion of sodium [41]. Since the loop of Henle and the collecting duct are mainly responsible for the concentration of urine, reduced concentration capacity may represent an index of medullary and inner cortical dysfunction. In addition, a reduction in urinary acidification following release of obstruction was found both in patients and experimental animals [53, 66]. The acidifying defect could be due either to a decreased hydrogen ion secretion in the distal tubule of surface nephrons and the collecting ducts or to marked alterations in the reabsorption of bicarbonate in the juxtamedullary nephrons [66].

The progress of renal damage in chronic PUUO has been the subject of debate in recent years. In newborn guinea pigs, Chevalier et al. [15, 16] reported that renal damage at 8 weeks after onset of obstruction was more severe compared with the damage 3 weeks after onset of obstruction. In young rats, Stenberg et al. [92] found that 12 weeks of PUUO results in minor morphological changes in the kidney and a slightly decreased kidney function. After 1 year, the GFR measured in this group of animals was reduced in the obstructed kidney by about 60% compared with the contralateral kidney [92]. This indicates that hydronephrosis during a short period of time is not harmful to kidney function, but if sustained for an extended period of time kidney function will deteriorate. In contrast, Josephson et al. [60] reported that in newborn rats sequential studies from day 1 to 1 year showed that the moderate changes in GFR described above were established within 1–3 weeks of induction of PUUO. Subsequently, and despite the proven persistence of obstruction-to-flow, no significant progressive deterioration was observed, although the microstructural damage tended to be more severe. An explanation for the absence in further deterioration of renal function could be that during the acute phase of the obstruction even small increases in urine flow are capable of producing sudden, sharp increases in intrapelvic pressure, which causes renal damage. However, once the pelvis is distended and lax such bouts of pressure increase occur much more seldom and slowly [68].

The effects of PUUO on the obstructed kidney have not been fully established. Standardization of the PUUO model is necessary for further investigations of the morphological and functional changes.

Changes in renal blood flow

The data on hemodynamic responses to PUUO are limited. In dogs chronic PUUO has been reported to decrease RBF to 25% of normal [91] and the outer cortical blood flow was found to decrease whereas deep cortical blood flow increased relatively [108]. Recently, MR imaging has successfully been used to follow the changes in renal vein blood flow (RVBF) [83] from 10-day-old rats with PUUO induced at birth [103]. RVBF decreased with time in response to both mild and severe PUUO. In mild PUUO, a significant decrease in RVBF occurred after 18 weeks of obstruction. In severe PUUO, a significant decrease in RVBF occurred after 10 weeks of obstruction. RVBF decreased to 57% of controls 24 weeks after onset of obstruction. These results indicate that the RBF reduction in PUUO is mild compared with CUUO and is related to the duration and severity of obstruction and that RBF can remain stable for a relatively long time after the initial decrease following induction of the obstruction.

The mechanisms underlying the hemodynamic response to PUUO are still not fully elucidated. However, similar to CUUO, activation of the renin–angiotensin system may play a significant role in the production and maintenance of renal vasoconstriction during PUUO [13, 14].

Renal functional changes in response to bilateral ureteral obstruction

Bilateral ureteral obstruction (BUO) is different from unilateral ureteral obstruction (UUO) in many aspects. The major differences in characteristics and outcomes of UUO and BUO are shown in Table 1. The ureteral pressure was significantly higher in BUO than UUO within 24 hours of onset of obstruction in rats [50]. After 24 hours, the intratubular pressure remained above normal levels, while RBF was significantly decreased to a level similar to that in UUO. The RBF of the BUO rats before release of a 24-hour obstruction was approximately 69% of controls with no redistribution of intrarenal blood flow [50]. Siegel et al. [87] found that the outer cortical perfusion decreased by 20% in rats in response to 24 hours BUO. One hour after release of BUO, there was normalization of the cortical blood flow and a modest return of GFR and an almost complete normalization in RBF. This manifestation is

Table 1 Major differences in renal function before and after release of unilateral ureteral obstruction (UUO) and bilateral ureteral obstruction (BUO)

	UUO	BUO
During obstruction [65]		
Renal hemodynamics	GFR decline due to a decrease in intraglomerular capillary pressure	GFR decline due to both a decrease in intraglomerular capillary pressure and a persistent elevation of the intratubular pressure
Intratubular pressure	Increased (↑) within 1 h. Decline after 5–6 h and back to baseline after 24 h	Increased (↑↑) within one h. Decline after 5–6 h but not back to baseline after 24 h
In circulation [46]		
Increase of atrial natriuretic peptide	(–)	(+ + +)
Increase of prostacyclin	(–)	(+ +)
Thromboxane A_2 production	(↑↑)	(↑)
After release of obstruction		
Renal function	More impairment	Less impairment
Tubular abnormalities [63]		
Ability to concentrate the urine	Decreased (↓) and seldom > 400 mOsm/kg H_2O	Decreased (↓↓) and < 400 mOsm/kg H_2O
Postobstructive diuresis and natriuresis	(±)	(+ + +)
Fractional sodium and water excretion	Increased (↑) compared with contralateral kidney	Increased (↑↑↑)
Absolute potassium excretion	Decreased (↑↑↑)	Decreased (↓)
Fractional potassium excretion	Decreased (↓↓↓)	Increased (↑↑)

GFR glomerular filtration rate

different from that of UUO in which the outer cortical perfusion remained decreased by 21% and both GFR and RBF remained markedly depressed [87]. Thus, rats with BUO show less renal functional impairment than rats with UUO. Recent data suggests that atrial natriuretic peptide (ANP) may be important in maintaining these differences [47]. ANP and prostacyclin (6-ketoprostaglandin $F_{1\alpha}$) are increased in BUO and may help to diminish the vasoconstrictor effects of BUO [47].

Tubular dysfunctions in BUO are similar to that seen in UUO. However, impairment of concentrating ability, particularly in the proximal tubules, is one of the earliest pathologic changes in chronic BUO. The most striking difference between UUO and BUO is the dramatic postobstructive diuresis (POD) and natriuresis that follow the release of BUO. Salt and water restriction during the obstruction period does not prevent the POD and natriuresis [107]. Although numerous reports concerning the pathophysiological aspects of POD have been published, the molecular mechanisms involved in the decreased ability to concentrate urine are incompletely understood. Recently, we found a marked reduction in the expression of aquaporin-2 (AQP-2) coinciding with the development and maintenance of postobstructive polyuria in the BUO rat [31]. Importantly rats with reduced levels of AQP-2 in collecting duct-principal cells showed a reduced urinary concentrating capacity, suggesting that downregulation of AQP-2 may play an important role in POD [31].

Several vasoconstrictors, including angiotensin II, thromboxane and vasopressin have been proposed to mediate the reduction of RBF during BUO [109]. The decreased RBF during obstruction and high ureteral pressure may be the reason for more severe tubular damage in BUO than in UUO.

Prediction of renal recovery potential

Selecting the appropriate management for obstructive nephropathy depends on our ability to accurately assess the severity of existing renal damage and to predict the potential for recovery of renal function if the obstruction is relieved. At present the natural history of congenital hydronephrosis is incompletely described and no clinical examinations are currently able to predict the functional outcome in congenital hydronephrosis. However, a number of factors known to play an important role in these pathophysiological changes are delineated below.

Duration of obstruction

The severity of renal damage has been recognized as related to the duration of obstruction. A progressive loss of functional recovery has been reported with increasing periods of obstruction. In dogs, a near complete return of function follows correction after 4 days of obstruction [27]. After 14 days of obstruction, GFR and tubular

function returned to 46% of the control levels by 4 months after relief of obstruction, and no changes were seen thereafter [98]. However, Bander et al. [4] found long-term loss of nephrons in rats subjected to 24 hours of total obstruction in which 15% of the superficial and juxtamedullary nephrons of the obstructed kidney were lost, and this loss was present for as long as 60 days. Recovery of tubular function is also related to the duration of obstruction. Complete recovery of concentrating ability occurs if the obstruction time is limited to 1 week. With 4 weeks of obstruction, permanent damage of urinary concentrating ability occurs [11].

Acidification ability, lysosomal enzymes and creatinine

Ability to acidify the urine to pH < 6.0 preoperatively has been reported to be a good predictor of the recovery potential of an obstructed kidney [11, 53]. Urine concentrations of lysosomal enzymes such as *N*-acetylglucosaminidase (NAG) may also be useful [12, 51]. NAG is a proximal tubular lysosomal enzyme that is a sensitive marker for tubular damage [51]. In the "destructive phase", the period when most of the functional nephron damage occurs, high levels of NAG can be identified in the urine [51]. After this period, the concentration of NAG stabilizes, indicating the end of the destructive phase. However, the use of short-term nephrostomy tube drainage with measurement of creatinine clearances has been reported to be the best predictor of recovery of renal function after release of obstruction [36].

Interstitial fibrosis

The pathologic marker of irreversible renal injury is interstitial fibrosis. The degree of interstitial fibrosis is the most useful measure of the degree of renal injury, and it correlates with impairment of renal function [8]. The amount of collagen present in the interstitium and tubular basement membranes is partially associated with the degree of irreversible kidney damage [40].

Compensatory growth in the contralateral normal kidney

The contralateral normal kidney has been reported to have an important effect on functional recovery of the obstructed kidney after release of obstruction. In rats the destruction of a hydronephrotic kidney occurs faster if the contralateral kidney is present [3]. Hinman [49] has shown in dogs and rats that no repair will take place in a severely damaged hydronephrotic kidney after release of obstruction provided that the contralateral kidney has a normal function. Furthermore, the function of the hydronephrotic kidney shows a dramatic improvement when the contralateral kidney is removed [27]. Recently, in a longitudinal experimental study we confirmed a compensatory growth in the normal kidney contralateral to severe PUUO created in rats at birth using MR imaging. However, significant renal compensatory growth occurred later than the significant deterioration of the contralateral obstructed kidney suggesting the renal compensatory growth may not be useful for predicting the early deterioration of the obstructed kidney, as suggested by Brandell et al. [11].

Although many parameters have been suggested, at least in part, to predict renal recovery potential, a reliable predictor has not yet been found in PUUO. Further investigations are therefore necessary.

Mechanisms and mediators involved in renal functional changes during obstructive nephropathy

It is well recognized that obstructive nephropathy is not the result of a simple mechanical impairment to urine flow but a complex syndrome resulting in both glomerular hemodynamics and tubular functional alterations.

Intrapelvic and intrarenal hydrostatic pressure

The pathophysiologic process of nephron destruction in obstructive nephropathy is initially believed to be the result of a combination of pressure increases and ischemic atrophy. The elevated intrapelvic pressure is transmitted to the renal tubules, the glomerulus, the preglomerular arteries, and the interstitial space as verified by micropuncture studies [38]. The elevated pressure in the calices may also directly affect the degree of atrophy seen, as evidenced by flattening and atrophy of the renal papillae. However, the intrapelvic pressure return to near-normal levels after 24 hours of obstruction [56], where renal vascular resistance remains increased [100] suggesting that the vasoconstriction and decreased RBF are the most important determinants.

Leukocyte infiltration and fibrosis

Recent studies have demonstrated that progressive renal injury is associated with monocytic infiltration of the glomerular and tubulointerstitial compartments [45, 85]. Both in acquired and congenital obstructive nephropathy there is an influx of leukocytes, consisting predominantly of macrophages, into the renal cortex and medulla within the first 24 hours of obstruction [85]. The second major leukocyte population consists of T lymphocytes of the cytotoxic, suppressor cell subclass [45]. There are experimental data supporting the role of the infiltrating renal macrophage as a mediator of interstitial fibrosis in unilateral obstruction. In addition, macrophages are capable of releasing a variety of other products that potentially could injure the glomerulus, including proteolytic enzymes (collagenase, elastase),

reactive oxygen products, cyclooxygenase and lipoxygenase products, platelet-derived growth factor, coagulation factors and platelet-activating factors [79]. Elimination of leukocyte infiltration in rats with ureteral obstruction resulted in a higher postobstructive GFR and renal plasma flow compared with controls [43] indicating that leukocyte infiltrate may play an important role in obstructive nephropathy [45], possibly via the production of vasoactive prostanoids and other yet undefined products. However, elimination of leukocyte infiltration from the renal parenchyma does not restore the renal function to normal in the postobstructed kidney. This suggests that factors other than leukocyte infiltration play an important role in the development of vasoconstriction and subsequent fibrosis during obstructive nephropathy.

Renin–angiotensin system and thromboxane A_2

The renin–angiotensin system and the eicosanoid thromboxane A_2 have been suggested to play an important role in the progressive development of interstitial fibrosis in the obstructed kidney. Studies using an angiotensin–converting enzyme inhibitor or an angiotensin-II receptor antagonist demonstrated that the increased production of extracellular matrix protein in the tubulointerstitium of the obstructed kidney was ameliorated [65]. Thromboxane A_2 has been shown to stimulate extracellular matrix protein synthesis related to renal interstitial fibrosis [62]. The expression of both the renin–angiotensin system and thromboxane A_2 are enhanced in obstructed kidneys and the role of these systems has been reviewed previously [44]. Two distinct sites of thromboxane production have been recognized: one from the infiltrating macrophages and the other as an intrarenal site located to the glomeruli [44].

Growth factors

Recently, growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), epidermal growth factor (EGF) and insulin-like growth factor-I (IGF-I) have been reported to play a role in the development and progression of fibrotic and sclerotic changes in the obstructed kidney. Importantly, administration of PDGF to rats was associated with enhanced development of fibrotic changes in the chronically obstructed kidney [79]. In vitro experiments, using renal interstitial fibroblasts, showed that PDGF induces fibroblast proliferation [67]. In an opossum model of CUUO, it has been reported that PDGF-A mRNA correlates with the morphologic features of tubulointerstitial damage indicating that PDGF–A may participate in this form of fetal kidney damage [71]. TGF-β1 is a cytokine, which stimulates extracellular matrix synthesis and inhibits its degradation [84]. Expression of TGF-β mRNA is increased in the obstructed kidney [102]. Recent evidence also suggests that the infiltrating macrophage may play a role in propagating initial glomerular injury to the development of glomerulosclerosis via TGF-β stimulating matrix accumulation [22]. Diamond et al. [23] proposed that the markedly increased expression of TGF-β1 following UO induced a profibrogenic state and initiated a cascade of dysregulatory events, including the upregulation of tissue inhibitors such as metalloproteinase. In addition, TGF-β1 may serve as a potent stimulus for the modulation of quiescent interstitial fibroblasts into myofibroblasts [23]. The decrease of EGF expression has been associated with the development of obstructive nephropathy [102]. In addition, the injection of EGF in 1-day-old rat pups reduces the fraction of apoptotic renal cells by 50% in less than 2 hours [20] indicating that the reduced EGF in the obstructed kidney would contribute to increased apoptosis. Furthermore, EGF has been shown to have antiproliferative effects in the developing kidney [34]. In the obstructed kidney IGF-I ameliorated the development of fibrosis, tubular cystic change and caliceal dilatation suggesting that this mediator also plays an important role in obstructive nephropathy [90].

Conclusion

Most of our knowledge on UO is derived from the studies in experimental animal models. There are some degrees of confusion from the conflicting results from the animal experimental models of UO and the lack of standardized animal models may account for these incongruities. Moreover, the majority of reports only deal with the findings after release of obstruction and may thus very well reflect the response to release of obstruction rather than functional characteristics of the obstructed kidney. In general, UO results in decreased RBF and GFR in the ipsilateral kidney and increased RBF to the intact opposite kidney. However, the effects of UO on RBF and GFR depend on the duration, severity of obstruction, and the diuretic state. A number of circulating hormones and paracrine factors are implicated in the renal vasoconstriction, including thromboxane and angiotensin. The increased vasoconstrictor activity appears to be balanced by a parallel increase in opposing vasodilators, such as prostaglandin. However, the decrease in RBF resulting from UO is a central factor leading to obstructive nephropathy. The effects of an altered expression of growth factors, tubular atrophy, and interstitial fibrosis are considered to be secondary to the functional changes. Although progress has been made, our knowledge of obstructive nephropathy is still limited. The effects of long-term urinary tract obstruction or partial urinary tract obstruction have been less well studied. At the moment the postnatal management, and operative or nonoperative follow-up of antenatally detected hydronephrosis is much debated. A simple analytical test, which can be used in the clinic to precisely predict the renal function, has not yet been developed.

Since PUUO occurs frequently in humans with a broad spectrum in the degree of obstruction, experimental studies that correspond to different degrees of PUUO should be performed. In order to compare the effects of obstruction on kidney function the quantitation of the obstruction as a baseline for further analysis seems necessary in future studies.

Acknowledgement Dr. Jain Guo Wen was supported by a grant from the Aarhus University – Novo Nordic Research Center.

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