

## Partial Ureteral Obstruction: A New Experimental Model In Rats†

Kwang Myung Kim, Dae Kyung Kim and Hwang Choi

Department of Urology, Seoul National University College of Medicine and Children's Hospital  
Seoul 110-744, Korea

= Abstract = **Partial ureteral obstruction in rats has been usually created by implanting the mid ureter into the psoas muscle. However, this method does not allow us to choose the obstruction site or the degree of obstruction. On the other hand, the extrinsic stent insertion method needs highly sophisticated operation skill. Hence, we tried to make a new experimental model using a bisected segment of 8 F feeding tube. We made various sizes of central holes with needles in that piece and then placed the left ureter into the hole through a J-shaped incised route. The occurrence of partial ureteral obstruction was checked by excretory urogram, direct injection of indigocarmine into the upper dilated ureter and histopathological examination. Actually, partial ureteral obstruction occurred in 67% of rats in the 23G group (n=6) and in 57% in the 21G group (n=7) in a week. Complete obstruction occurred in 33% in the 23G group and in 29% in the 21G group. The control group (n=6) in which an 18G needle (greater than ureter diameter) was used showed 33% of partial obstruction but there was no case of complete obstruction. These data show that our new experimental model inducing partial ureter obstruction in rats has reliability, variability and simplicity.**

Key Words: *Partial ureteral obstruction, Experimental model, Rat*

### INTRODUCTION

There are many experimental animal models to study urinary tract obstruction. Among them the rat has been frequently used for the study of ureteral obstruction because of low cost and

despite the small diameter of the ureter. For creating partial ureteral obstruction in rats, Ulm and Miller's classical method (Ulm and Miller 1962) in which the ureter was implanted into the psoas muscle has been popularly used. However, this method yields a high rate of complete or minimal ureteral obstruction (Josephson *et al.* 1980; Huland *et al.* 1988). In addition, a partial ureteral obstruction model is needed for the study of fetal hydronephrosis because the results of most published studies for fetal ureteral obstruction came from the investigation of the pathophysiology of complete

---

Received January 1993, and in final form March 1993.

† This study was supported by Grant No. 02-89-104 from the Seoul National University Hospital Research Fund

서울대학교 의과대학 및 어린이병원 비뇨기과: 김광명, 김대경, 최황

ureteral obstruction in the fetus (Adzick *et al.* 1985; McVary and Maizels 1989). Indeed, the method for creating partial ureteral obstruction in the fetus requires several characteristics such as simplicity, fastness and reproducibility. In the present study, we designed a new method that is fit for the above criteria to create partial ureteral obstruction in small animals, like the rat.

## MATERIALS AND METHODS

We used 12-week-old Wistar rats of either sex, weighing 130 to 180 grams. Under general anesthesia with ketamine hydrochloride, given intraperitoneally at 1 ml/kg, we created a partial ureteral obstruction. Before the operation we made an obstruction inducing segment. First, we filed the tip of an injection needle to make it blunt. Then the outside margin of the tip was sharpened to make it able to penetrate the piece of 8 F feeding tube which had been bisected (5 mm in length). We incised one side of that piece as a J-shaped form to allow the ureter to be placed within the hole. Grasping each side of the incised margin with forceps, we could place the left sided mid ureter, which was already isolated from surrounding tissues under microscopy, into the hole exactly, and then released the margins (Fig. 1). Actually we did not use any suture materials for creating partial ureteral obstruction during surgery except wound closure. Twenty-one and twenty-three gauge needles were used to make the partial ureteral obstruction and an eighteen gauge needle was used for controls. Indeed, the diameter of the twenty-one gauge needle was found to be slightly smaller than that of the ureter under microscopy. The diameter of the eighteen gauge needle is larger than that of the ureter. The number of rats in each group was ten initially. After one week, under the same anesthesia, we opened the previous wound site and examined the dilation of the ipsilateral ureter compared to the contralateral ureter. Indigocarmine (0.1 ml) was injected into the upper dilated ureter or pelvis in the obstructed

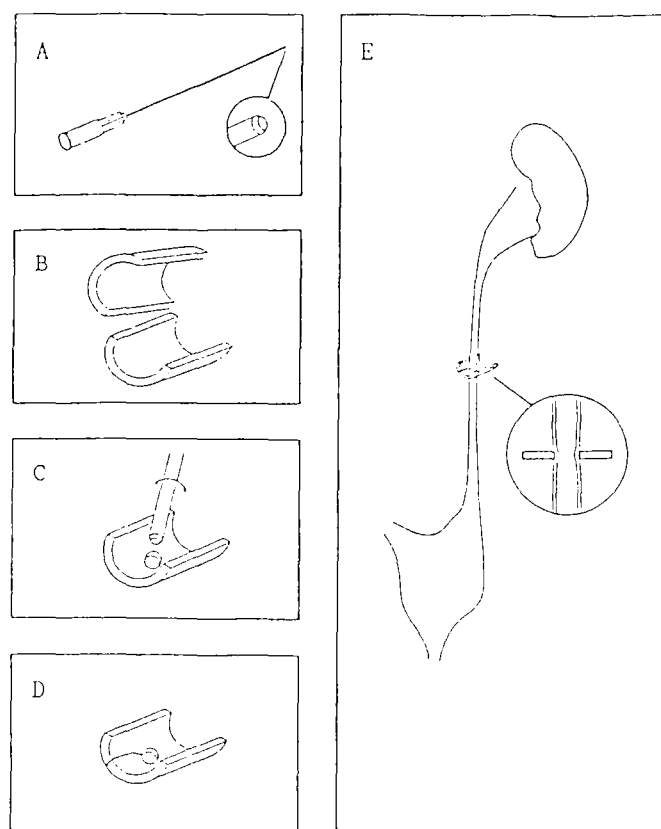


Fig. 1. After filing, the tip of the needle is sharpened to be able to penetrate the bisected 8 F feeding tube segment (A,B). A central hole is made by punching with the prepared needle (C). And then, a J-shaped incision is made to the central hole (D). The segment applied to the ureter is seen schematically (E).

cases. Usually blue colored indigocarmine drained caudally over the obstruction site by peristaltic waves in case of partial ureteral obstruction in a few minutes. Complete obstruction was defined if there was no dye passing through the obstruction site within 30 minutes. And then both kidneys were removed and the wet weight of each kidney was checked. The kidney specimen was fixed and embedded for pathological examination (H-E stain).

We checked excretory urograms in two randomized rats of each group just before the second operation. Iodinated water soluble dye (Rayvist 300, Schering, Germany) was injected into the rat tail dorsal vein (2 ml/kg). If ureteral obstruction was suspected in the early film (10 or 30 min), 1 hour delayed film was obtained.

## RESULTS

Within 2 days after the first operation, eight rats died for diverse reasons. Additionally, in one case in the 23G group the obstructing segment had slipped off the ureter and in one case in the 21G group the incised margin of the segment was separated because an I-shaped route had been made, which was found on the second operation. Neither of these cases had hydroureteronephrosis. In another 21G case with complete obstruction, peritonitis and severe intestinal adhesion around the obstructed site were found. And in one case we simply isolated the ureter without insertion of the obstructing segment. This case showed a normal urinary tract. Hence, we compared the results consisting of 6 cases in 23G group, 7 cases in 21G group and 6 cases in 18G group except above the 11 cases. Actually, partial ureteral obstruction occurred in 67% of rats in the 23G group and in 57% in the 21G group in a week. Complete obstruction occurred in 33% in the 23G group and in 43% in the 21G group. The control group with the 18G needle showed 33% partial obstruction but there was no case of complete obstruction. In contrast, the 18G group only showed normal urinary tracts in 4 cases. (Table 1). We compared the wet weight ratio of ipsilateral to contralateral kidney between partial obstruction, complete obstruction and normal urinary tract cases. When we compared the ratios of ipsilateral kidney weight to the

Table 1. Obstruction status after one week of circumureteric obstructing segment application in the 23G, 21G and 18G groups

Obstruction status	23G No.(%)	21G No.(%)	18G No.(%)
Complete obstruction	2(33)	2(29)	0(0)
Partial obstruction	4(67)	4(57)	2(33)
Normal	0(0)	1(14)	4(67)
Total	6(100)	7(100)	6(100)

contralateral kidney weight between partial obstruction, complete obstruction and normal urinary tract groups, the complete obstruction group showed the highest ratio. The partial obstructed group showed the middle range between that of complete obstruction and control group. Statistically there was a significant difference in the wet weight ratio between the normal and the partial obstruction group and between the normal and the complete obstruction group. However, there is no statistically significant difference between the partial and the complete group (Table 2).

Excretory urograms showed a lesser degree of hydronephrosis in the rats with partial ureter obstruction compared with the completely obstructed rats. (Fig. 2). Generally, there was minimal reactive fibrous change at the obstruction site and we could not find any kinking or deviation of the ureter. Pathological specimens showed moderately dilated renal tubules and nonspecific inflammatory cells aggregation in the kidney with partial ureteral obstruction. These changes were found mainly in renal medulla (Fig. 3). Besides these findings, interstitial hemorrhage was found in the completely obstructed kidney.

## DISCUSSION

Renal impairment due to hydronephrosis depends upon the obstruction degree, site and duration. With the development of high resolution ultrasonography, hydronephrosis is detected earlier than before. Intrauterine and postnatal follow up of congenital hydronephrosis is becoming one of the major fields in pediatric urology. Hence, we need a partial ureteral obstruction model that is fit for the study of fetal and neonatal hydronephrosis. Josephson(1991) said that if experimental studies are planned to investigate congenital hydronephrosis, the created obstructions must correspond to human obstructions. That is, be partial and permanent, be produced in fetal or newborn animals, preferably be moderate in degree, the diameter

Table 2. The wet weight ratio grouped by obstruction status of ipsilateral left kidney and hole size †

Obstruction status	Hole size (gauge)	Lt kid. wt. (gm)	Rt kid. wt. (gm)	Wet wt.ratio (Lt/Rt)
Partial obstruction	23	1.469	0.795	1.85
	23	1.030	0.809	1.27
	23	1.204	1.102	1.09
	23	1.164	1.077	1.08
	21	1.702	1.119	1.52
	21	0.777	0.615	1.26
	21	0.997	0.789	1.26
	21	0.702	0.625	1.12
	18	1.124	0.904	1.24
	18	0.749	0.623	1.20
Complete obstruction	23	1.328	0.992	1.34
	23	1.472	1.255	1.17
	21	1.163	0.883	1.32
	21	0.984	0.808	1.22
Normal	21	0.848	0.822	1.03
	18	1.233	1.098	1.12
	18	0.915	0.877	1.04
	18	0.856	0.853	1.00
	18	0.803	0.819	0.98

†The weight ratios of the partial obstruction group and complete obstruction group are greater than those of the normal group ( $p < 0.01$ ). But no statistically significant difference is found between the partial and complete obstruction group. There are no significant differences among subgroups (23G, 21G, 18G) in the partial obstruction group. (statistical analyses with Wilcoxon's rank sum test)

should grow in pace with the growing ureter, and should be followed for a long period.

We selected adult rats because this animal has a small diameter of ureter and is less expensive than other animals. Actually, we hoped that the results of this experiment could be applied to the fetal sheep experiment. As fetal sheep has similar renal developments to that of the human fetus (Peters and Mandell 1990), many fetal experiments have been performed with sheep. Although the diameter of the fetal sheep ureter is greater than that of adult rats we tried to make a partial ureteral obstruction model which is simple, easy, fast and can be done in the fetus.

There were many methods to create partial ureteral obstruction. Beta irradiation of the ureter (Guze and O'Shea 1958), rapid freezing of the ureter (McDonald *et al.* 1960), aluminum and

cellophane bars (DeLuca *et al.* 1961), S-shaped kinking of the ureter (Weaver 1960), retroperitoneal implantation of the ureter into the psoas muscle (Ulm and Miller 1962), partial ligation with sutures (Boyarsky and Martinez 1964) and insertion of a ureteral stent (Ryan and Fitzpatrick 1987) have been reported as models for partial ureteral obstruction in various animals. In rats, the ureter was usually implanted into the psoas muscle to create partial ureteral obstruction (Josephson *et al.* 1980; Huland *et al.* 1988). But this method needs several sutures and the duration before recognizing partial obstruction is too long for the fetal experiment. One of the experiments with this method (Huland *et al.* 1988) yielded about 30% failure rates for the following reasons; complete obstruction and minimal obstruction. Partial obstruction occurred after a week in only 12 of a total of 52 animals



Fig. 2. Excretory urograms obtained 30 minutes after injection of contrast media in rats applying complete obstruction (A), and partial obstruction (B) of the left ureter. (A) Note much enlarged faintly opacified left kidney due to severe hydronephrosis (arrow). (B) There are hydronephrosis and proximal hydroureter in left side. The degree of hydronephrosis and the size of the left kidney is smaller than that of (A). Note feeding tube segment applied to the ureter appearing as a radioopaque line (arrow). The ureter distal to the obstruction is not dilated (arrowheads).

with partial obstruction and in seven animals of these, it occurred after 12 weeks. Although our experimental period was not long enough to evaluate chronic consequences, we think that our 57 to 67% success rates in a week are more acceptable for the study of partial obstruction.

Our materials for making the obstruction are easily available and the procedure is simple and easy. One of the recent experiments with neonatal guinea pigs used polyethylene tube for creating partial ureteral obstruction (Chevalier *et al.* 1984). The authors did not report the true success rate for creating partial ureteral

obstruction, so we could not compare our data with that method. Truly in our experimental model, total operation time was very short and there was no severe reactive change around the obstructed area by the obstructed piece, which is supported by the finding that there was 33% partial obstruction and 67% normal upper tract in the 18G group but there was no normal upper tract in the 23G and 21G groups. In addition, with this method obstruction site and degree can be selected as the investigator desires.

Radiological and pathological examinations definitely revealed the occurrence of partial

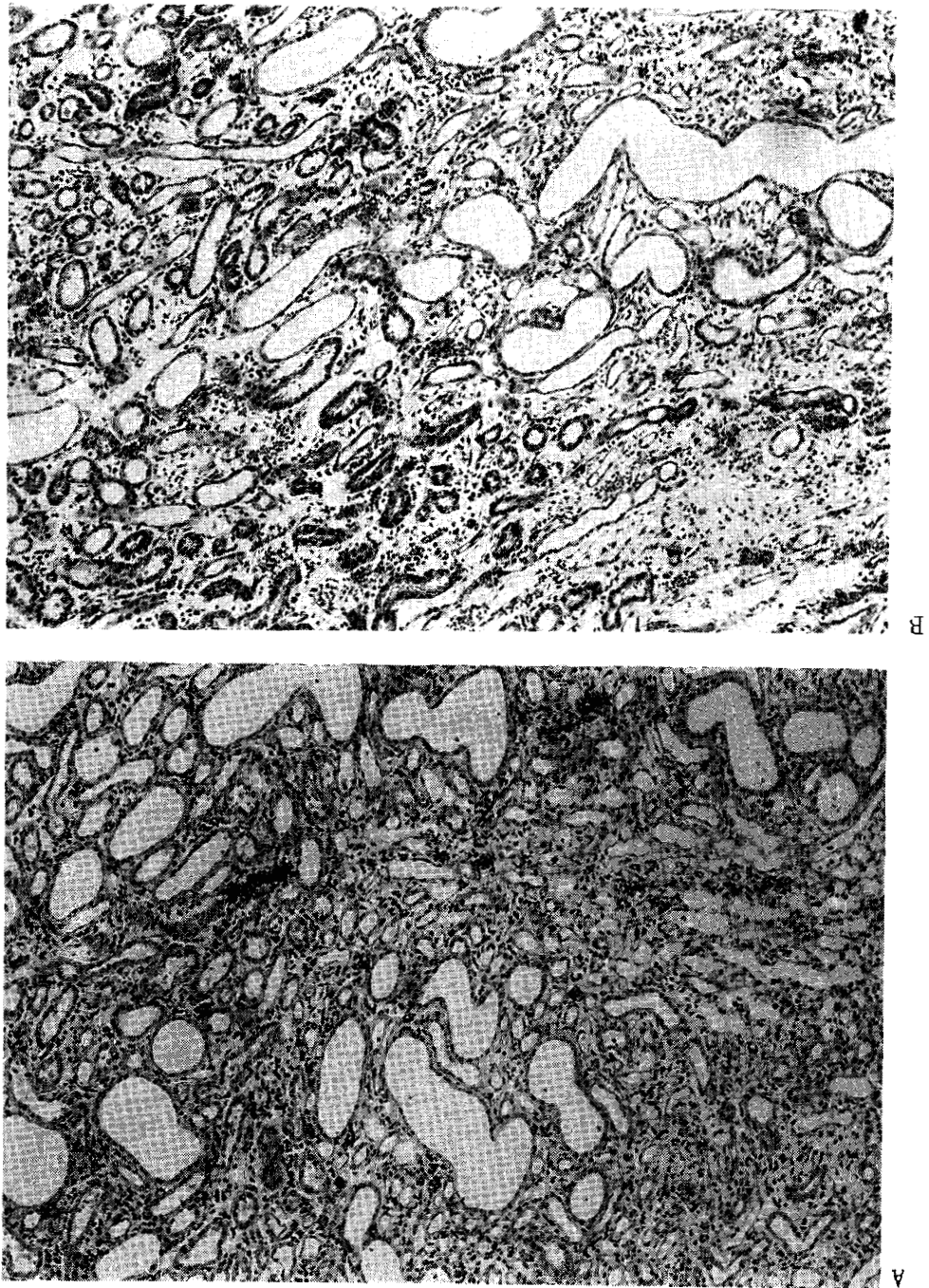


Fig. 3. Dilated renal tubules and nonspecific inflammatory cells aggregation are seen in the renal medulla of the completely (A) and partially (B) obstructed kidney. These findings are more prominent in the completely obstructed specimen. (H&E staining,  $\times 100$ )

obstruction in this study. Indigocarmine dye test was an invaluable confirming procedure. If there is a ureteral obstruction, the wet weight is increased in the ipsilateral kidney during the first few weeks due to renal parenchymal edema. And then the weight is decreased after 4 to 8 weeks because the atrophy of the tissue is greater than the intrarenal edema (Gillenwater

1992). In this study, the wet weight of the ipsilateral kidney compared to the contralateral kidney was also correlated with obstruction degrees although there was no significant difference between the partial and the complete obstruction group.

However, our experimental model seems to have some problems to be confessed. First, there is no clear-cut difference in hydronephrotic changes between individual cases in the partial obstruction group despite different sized needles. In the beginning, we tried to make various partial obstruction degrees but the result was not satisfactory. We think that much attention should be given to make an exact sized hole to get a better result. And when the ureter is going down to be placed into the hole, we had to be very careful to prevent any unexpected damage. And during the operation all procedures should be performed meticulously and aseptically.

We do believe that a new experimental model for partial ureteral obstruction in rats was created. This model has a simple, easy and fast procedure. And reproducibility is highly acceptable. We think that this method can be applied to study for congenital hydronephrosis in the fetus and neonates. At present, chronic durability and reversibility of this method is planned to be evaluated with a longer experimental period in our laboratory.

## REFERENCES

- Boyarsky S, Martinez J. Pathophysiology of the ureter: partial ligation of the ureter in dogs. *Invest Urol* 1964; 2:173-80
- Chevalier RL, Kaiser DL. Chronic partial ureteral obstruction in the neonatal guinea pig. I: Influence of uninephrectomy on growth and hemodynamics. *Ped Res* 1984; 18:1266-71
- DeLuca FG, Swenson O, Smyth B. The effects of chronic mechanical obstruction on ureteral peristalsis. *J Urol* 1961; 85:497-501
- Gillenwater JY. The pathophysiology of urinary obstruction. In Walsh PC, Gittes RF, Perlmutter AD, Stamy TA (Ed) *Campbell's urology*, Vol. 1, Philadelphia, W.B. Saunders Co. 1986: pp.542-578
- Guze LB, O'Shea W. Experimental hydronephrosis produced by irradiation of the ureter. *J Urol* 1958; 79: 801-6
- Huland H, Gonnermann D, Werner B, Possin U. A new test to predict reversibility of hydronephrotic atrophy after stable partial unilateral ureteral obstruction. *J Urol* 1988; 140:1591-94
- Josephson S, Robertson B, Claesson G, Wikstad I. Experimental obstructive hydronephrosis in newborn rats. I. Surgical technique and longterm morphologic effects. *Invest Urol* 1980; 17:478-83
- Josephson S. Suspected pyelo-ureteral junction obstruction in the fetus: when to do what? II. Experimental viewpoints. *Eur Urol* 1991; 19:132-8
- McDonald JH, Calams JA. Experimental ureteral stricture: ureteral regrowth following ureterostomy with and without intubation. *J Urol* 1960; 84:52-9
- McVary KT, Maizels M. Urinary obstruction reduces glomerulogenesis in developing kidney: model in rabbit. *J Urol* 1989; 142:646-51
- Peters CA, Mandell J. Experimental congenital obstructive uropathy. *Urol Clin North Am* 1990; 17: 437-47
- Ryan PC, Fitzpatrick JM. Partial ureteric obstruction: a new variable canine experimental model. *J Urol* 1987; 137:1034-8
- Ulm AH, Miller F. An operation to produce experimental reversible hydronephrosis in dogs. *J Urol* 1962; 88: 337-41
- Weaver RG, Hol R. Hydronephrosis: an experimental production and a study of methods. *J Urol* 1960; 83: 345-50