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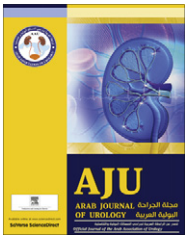

ONCOLOGY/RECONSTRUCTION

ORIGINAL ARTICLE

Does the afferent tubular segment in an orthotopic bladder substitution compromise ureteric antireflux properties? An experimental study in dogs

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KEYWORDS

Orthotopic bladder;
Antireflux;
Ureter;
Renal compromise

ABBREVIATIONS

AC, ascending cystography; BUN, blood urea nitrogen

Abstract ***Objective:*** To study the effects of a short ureter on renal function and histology in an orthotopic bladder substitution model using a long afferent limb, in a canine model.

Materials and methods: The study included nine adult mongrel dogs. A 40-cm segment of ileum was isolated, the distal half detubularized, configured into a U-shape and sutured to form a flat plate; this was then used to augment the bladder. The proximal half of the isolated ileum remained in continuity with the enterocystoplasty to form an isoperistaltic ileal 'chimney'. The left ureter was divided at its lumbar part and anastomosed to the chimney using a refluxing end-to-side Nesbit technique. The contralateral ureter was divided at its lower end and then anastomosed directly to the augmented segment of the bladder in a similarly refluxing manner to act as a control. The assessment after surgery included biochemical studies, ascending cystography, intravenous urography (IVU) and radioisotope renography at 6 weeks. The last two methods were repeated at intervals of 3 and 6 months after surgery. Urine culture was obtained and both kidneys were examined histopathologically at 6 months.

Results: The biochemical values assessed in all dogs were comparable to those before surgery. The urine culture obtained from the augmented bladders showed significant bacterial growth in all dogs. IVU at all follow-up sample times showed a

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normal configuration of both kidneys. Ascending cystography showed reflux in four of nine dogs on the right and six on the left side. There was a progressive decrease in the mean selective renographic clearance values of each of the right and left kidneys at intervals of 6 weeks, 3 and 6 months. The mean percentage reduction of renographic clearance was significantly higher in the left kidneys at 6 weeks and 3 months. Histopathological examination showed evidence of interstitial nephritis in all nine dogs and pyelonephritis in four of the left kidneys, while none of the right kidneys showed evidence of inflammation.

Conclusion: Adequate peristalsis in a healthy long ureter is superior to the ileal segment substitution for protecting the kidney tissue against inflammation in the absence of an anatomical antireflux mechanism.

Introduction

The preservation of renal function is a primary aim in orthotopic bladder substitution procedures. Individual components of bladder substitution include the construction of a large-volume low-pressure reservoir, a continent outlet and an antireflux mechanism to prevent ureteric reflux. Currently there is controversy about the critical need for an antireflux mechanism, with proponents of the isoperistaltic afferent tubular segment stating the safety of the afferent ileal loop alone for preserving renal function, on the basis of the presence of a low-pressure reservoir. The detrimental effects of VUR have been well recognised for over three decades, particularly in the presence of infection [1–3], and while it is true that a low-pressure reservoir is critical in maintaining a 'safe' system, it is recognised that reservoir pressures increase during voiding, or during 'hypercontinent' states and during outlet obstruction.

Evidence for the safety of the afferent isoperistaltic ileal segment, as described by Studer et al. [4] has so far been less than optimal. One study [5] reported a 4–5% renal deterioration rate after a median follow-up of 84 months, but used relatively insensitive tools in the evaluation of their cases, such as renal parenchymal thickness, renal size and upper tract dilatation on IVU, and serum creatinine in the presence of normally functioning dual renal units. Consequently, in the absence of objective data such as those from nuclear renography or urodynamics involving intrapelvic pressure studies, this debate remains open.

We hypothesise that the ureter, by virtue of its natural length and peristaltic activity, has intrinsic antireflux properties, and that creation of an afferent tubular segment, which results in the loss of ureteric length, compromises the ability of the ureters to resist reflux.

The current study aimed to assess the effects of the long afferent limb, with a short ureter, on renal function and histology in a canine model, providing objective data on renal function, morphology and biochemical changes.

Materials and methods

Experimental animals

Nine adult mongrel dogs (five females and four males; 18–25 kg) were used in the study. All procedures were conducted with the dogs under general anaesthesia, with endotracheal intubation and using thiopental sodium for induction of anaesthesia and maintenance.

Preoperative assessment

Before surgery all dogs were assessed using ascending cystography (AC), IVU and ^{99m}Tc-MAG3 renography. Serum creatinine, sodium, potassium, blood urea nitrogen (BUN) levels were measured, and urine cultured, before starting the experiments. Dogs that had primary VUR or an abnormality in the configuration or function of one or both kidneys were excluded from the study.

Experimental model

Through a midline transabdominal incision, a 40-cm segment of ileum was isolated with its mesentery, and bowel continuity was restored using an interrupted 4/0 polyglactin suture. The distal 20 cm of the mobilised segment of ileum was detubularised, configured into a U-shape and sutured in-between to form a flat bowel plate. The urinary bladder was opened transversely between stay sutures and the intestinal plate sutured onto it, to augment the bladder and create a large-volume low-pressure reservoir, using continuous 4/0 polyglactin absorbable sutures. The afferent loop of the mobilised ileal segment remained in continuity with the enterocystoplasty to form an isoperistaltic ileal chimney. The left ureter was severed at its lumbar part to ensure a straight pathway to the interposed ileal segment. The spatulated end of the left ureter was anastomosed to the chimney using a refluxing end-to-side Nesbit technique in all dogs. Thus an isoperistaltic

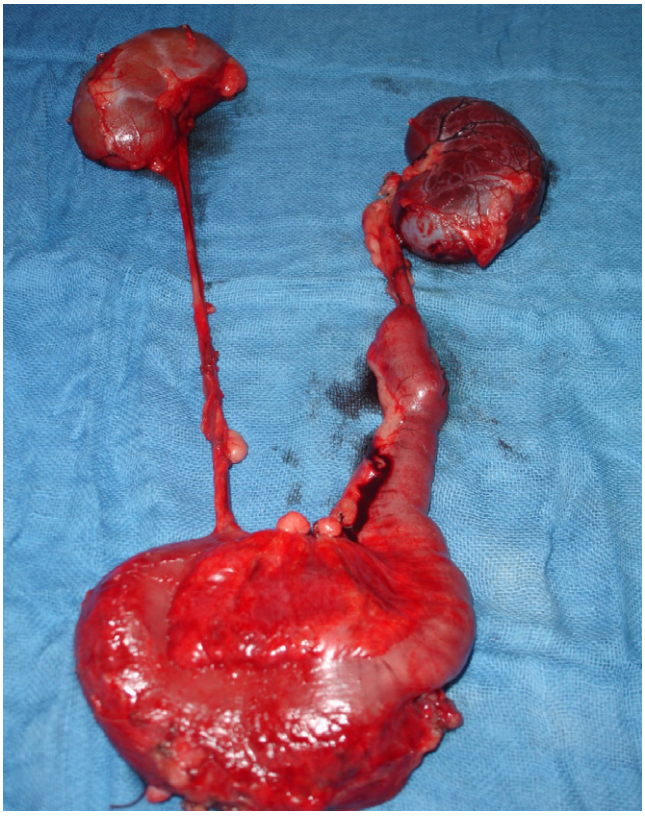

Figure 1 A necropsy specimen showing the technique of left ureteric replacement by an ileal chimney and direct uretero-ileal anastomosis of the right ureter into an augmented ileal bladder.

conduction of urine from the ureter to the reservoir was ensured. The anastomosis was made using interrupted 5/0 polyglactin sutures, ensuring precise mucosal coaptation. The contralateral right ureter was divided at its lower end and then anastomosed directly to the augmented segment of the bladder in a similarly refluxing manner, to act as control (Fig. 1).

Both uretero-ileal anastomoses were stented using 4-F ureteric stents; these were removed 1 week after surgery. The augmented bladder was drained by a urethral catheter for 2 weeks after surgery. The abdomen was closed in layers, and after surgery the dogs were allowed to recover on a light oral fluid diet as tolerated for 5 days, followed by standard animal food.

Postoperative assessment

After surgery, weekly blood samples were tested for serum creatinine, sodium, potassium and BUN levels. At 6 weeks after the procedure, and ascending gravity cystogram, ^{99m}Tc-MAG3 renal scan and IVU were carried out in all dogs. Radioisotope renography and IVU were then also repeated at intervals of 3 and 6 months.

The follow-up was for 6 months and then urine samples from the augmented bladder were obtained before the dogs were killed humanely. Both kidneys, ureters and the chimney, together with the augmented bladder, were then examined (Fig. 1). Sections from the renal parenchyma of both sides were obtained and assessed for histopathology by an expert pathologist unaware of the surgical technique used in the left and right renal units.

Statistical analysis

Student's paired sample *t*-test, one-way ANOVA and chi-square tests were applied as appropriate, with $P < 0.05$ taken to indicate statistical significance.

Ethical considerations

The study was approved by the local ethics committee, and the dogs were treated according to the guidelines of declaration of Helsinki.

Results

All dogs tolerated the surgery, with no deaths during the procedures. The dogs were observed for 6 weeks to 6 months. One dog died at 6 weeks from sepsis, one completed the 3-month follow-up and died from unknown causes, and the remaining eight completed the study and were killed at 6 months, the end-point of the experimental design.

The biochemical profile of all the dogs, including serum creatinine, sodium, potassium and BUN levels, were comparable to those before surgery, with no statistically significant differences. BUN showed an initial increase after surgery which declined 2–3 weeks afterwards; this

Table 1 The results of the biochemical studies.

	Mean (SD)			
Sample	Serum creatinine (mg/dL)	BUN (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)
Basal	0.9 (0.10)	11 (3.9)	142 (2.6)	3.9 (0.4)
1 week	1.1 (0.28)	22 (12)	146 (4.9)	4.5 (0.7)
1 month	1.0 (0.20)	19 (15.4)	143 (3.4)	4.0 (0.5)
3 months	1.2 (0.20)	18 (12)	143 (3.0)	4.1 (0.6)
6 months	0.9 (0.20)	14 (10)	146 (3.3)	4.5 (0.5)
P	0.86	0.91	0.19	0.64

(a)

(b)

Figure 2 (a) A postoperative IVU image showing the left chimney and right long ureter with normal upper tracts. (b) a voiding cystogram showing the reflux on the left side.

could be explained as an initial response to the surgical stress (Table 1). The urine culture obtained from the augmented bladders showed significant bacterial growth in all surviving dogs, with *Escherichia coli* found in six and *Klebsiella* in two.

All surviving dogs assessed with IVU at all sample times of the follow-up showed a normal configuration of both kidneys. The radiological pelvicalyceal anatomy was comparable to that before surgery in the control right kidney, and in the left (Fig. 2a).

AC using contrast medium showed evidence of reflux in four of nine renal units on the right (control) and six of nine on the left (chimney) (Fig. 2b). For the control side, the degree of reflux was grade I in two and grade II in two. For the left (study) side the degree of reflux was grade I in one, grade II in one and grade III in four.

There was a progressive decrease in the mean selective renographic clearance values of each of the right and left kidneys at the three sample times of the follow-up. The reduction of renal function was significant when compared with the mean values for both the right ($P < 0.01$, Fig. 3a) and left ($P < 0.01$, Fig. 3b) sides before surgery. Nevertheless, the mean percentage reduction in renographic clearance (compared with the mean before surgery) was significantly higher in the left kidneys at 6 weeks ($P = 0.05$) and 3 months ($P = 0.02$) of follow-up. The difference was no longer significant at 6 months, presumably because of the marked reduction in sample size (two dogs died before 6 months; Table 2).

The results of the histopathological examination of the renal parenchyma showed clear evidence of interstitial nephritis in the left kidneys in all dogs. Furthermore, there was frank evidence of pyelonephritis in four of nine left renal units (Fig. 4). Sections from the right kidneys showed no signs of inflammation in any unit.

Discussion

Continent urinary diversion is frequently required when a bladder substitution is indicated. An orthotopic intestinal reservoir is the first choice of diversion technique when the patient, tumour, renal and bowel indices permit. A low-pressure high-capacity reservoir, reliable continence mechanism and safe uretero-intestinal anastomotic technique are the prerequisites for an optimal procedure. The preservation of renal function is of critical importance. Intact healthy kidneys have a wide range of reserve to tolerate some stress factors, like reflux with or without infection, provided that there is no obstruction. The necessity of an anti-reflux ureterobowel anastomosis is still a matter for debate.

A short-term approximate evaluation of renal status using IVU, ultrasonography or even serum creatinine levels might encourage the use of a non-refluxing ureteric anastomosis to the low-pressure reservoirs. However, there are many reports which confirmed the absence of a low-pressure system in many kinds of orthotopic reservoirs [5–7]. These systems might be at

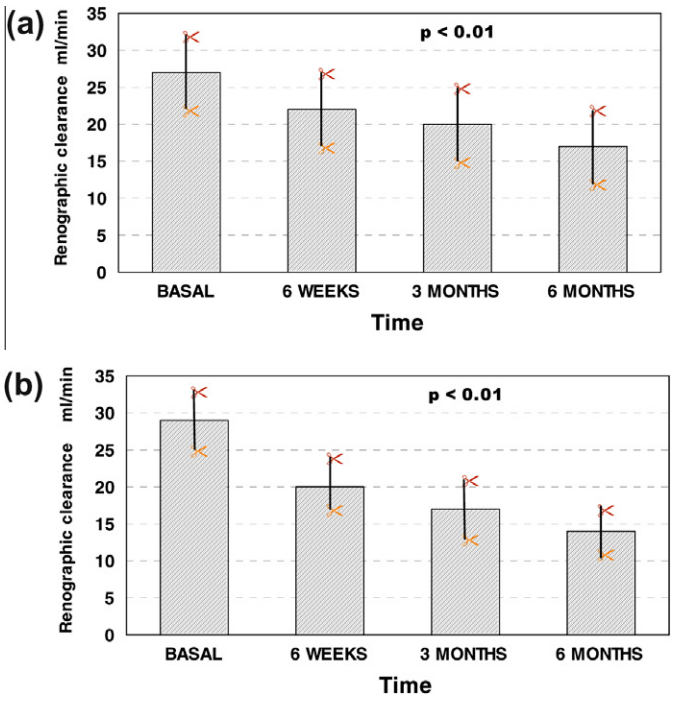

Figure 3 The renographic clearance on (a) the right, and (b) the left side.

low-pressure during the filling phase but not during a Valsalva manoeuvre. The pressure spikes and the high intra-abdominal pressures have at least a theoretical risk of causing reflux of the infected urine to the kidneys [8–12]. Intestinal reservoirs are frequently infected, and although many of them are asymptomatic, cultures of urine provide evidence of significant growth in these systems. Reflux of these pathogens to the kidney in the long-term might carry a risk of renal deterioration. It has been reported that 20–25% of the kidneys show deterioration during a longitudinal follow-up [13–17].

In a recent report, Jin et al. [18] followed up their patients for longer, and ≈20% of them developed some form of renal impairment with no evidence of ureteric obstruction. The possible explanation for this is that the recurrent episodes of subclinical renal infections were secondary to the reflux of infected urine to the upper tracts, possibly as a consequence of a shortened ureter. One aim of the present study was to show that for a normal ureter, a length of ≈27 cm is important, and that this ureteric length should be maintained.

Furthermore, the normal ureter has propulsive, conductive, caudally directed peristalsis which permits unidirectional flow of urine in addition to the antireflux effect of the vesico-ureteric junction. These facts induced us to study the critical importance of a long ureter as a protective mechanism for the kidneys. This is because in some orthotopic reservoirs, such as that produced by the Studer technique, it is necessary to truncate the ureters near to the kidney to ensure a straight, kink-free chimney. As noted above, excluding a long section of healthy ureter might deprive the kidney of a natural protective mechanism, i.e. an adequate length of ureter.

Table 2 The percentage decrease in the mean renographic clearance of the study and control kidneys.

Time of study	Percentage decrease		P
	Control (right)	Study (left)	
6 weeks	19	31	0.05
3 months	26	41	0.02
6 months	37	48	0.11

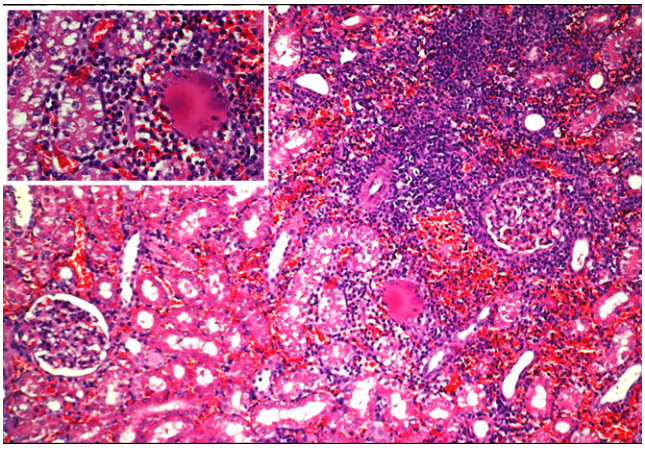

Figure 4 Histopathology image (haematoxylin and eosin stain) showing marked interstitial inflammation with tubular effects. The inset shows a higher magnification in one of the left kidneys.

AC cannot be used to provide radiological evidence of visible reflux in all renal units when using conventional contrast media. There was clear evidence of significant renal infection and inflammatory cell infiltrate in the renal units with short ureters when compared with the contralateral renal units. Importantly, the augmented ileo-cystoplasty showed urine infected with *E. coli* or *Klebsiella* in all dogs.

In the present study the progressive decrease of renal function of both the study and control kidneys could be explained by the absence of an effective antireflux uretero-ileal anastomosis, and the presence of UTI. The reduction of renal function was more evident on the left side, presumably because of the short ureter.

We assume that the triad of reflux, infection and a short ureter was responsible for the marked inflammation apparent on histopathological examination of the left kidneys. However, it seems that the presence of a normal length of the ureter on the right side protected the kidney tissue from inflammation, as shown by the histopathology specimens.

It might be expected that the long-term effect of this inflammation would be renal scarring. Silent renal scarring is a progressive disorder and can cause renal failure. A similar mechanism of reflux nephropathy has been reported in neglected patients with VUR, which can result in renal impairment. The 6-month follow-up in the present canine model is roughly equivalent to 7that for a normal ureter, a length years of human age [19].

The present study could be criticised for having no urodynamic studies to provide evidence of a low-pressure system. Moreover, there were few dogs and a third of them died before reaching the final follow-up. In addition, the collection of urine from the renal pelvis might provide evidence of renal infection with the same organism as in the augmented bladder. However, this was reported in another experimental study carried out in the same institution [20].

In conclusion, the present study provided evidence of the critical importance of keeping the maximum length of a healthy ureter as a protective mechanism to the kidney in orthotopic bladder substitution. Adequate peristalsis in a healthy long ureter is superior to the substituted ileal segment in protecting the kidney tissue against inflammation in the absence of an anatomical antireflux mechanism.

Conflict of interest

No conflict of interest to declare.

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