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Renal haemodynamics and prostaglandin synthesis in partial unilateral ureteric obstruction

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Abstract Haemodynamic changes in partial unilateral ureteric obstruction (PUUO) may be related to altered prostaglandin synthesis. In 12 dogs the left ureter was partially obstructed for 5 weeks. In six dogs the ureter was reimplanted into the bladder and to investigate the effect of this procedure on the contralateral side the other six animals underwent ipsilateral nephroureterectomy. Renal blood flow (RBF) was measured by the distribution of radiolabelled microspheres. Changes in urinary prostaglandin (PG) concentrations were validated by renin activity using angiotensin I. Reduced left RBF during obstruction was associated with increased thromboxane A_2 synthesis ($P<0.01$). Increased RBF to the non-obstructed side was associated with elevated PGE_2 formation ($P<0.05$). Elevated angiotensin I levels ($P<0.01$) corresponded to maximal increases in PG synthesis. Reimplantation of the obstructed kidney did not exert a direct effect on contralateral RBF or PG concentration. Haemodynamic changes in PUUO in vivo are associated with alterations in renal PGs.

Key words Partial ureteric obstruction · Blood flow
Prostaglandins

The haemodynamic response of the kidney in reducing blood flow in ureteric obstruction is well documented [3, 12, 15, 21]. The apparent vasoconstrictor and vasodilatory aspects of this response have given rise to many hypotheses to explain their mediation. Post-obstructive renal failure may result from a vascular injury [9] and experimental evidence strongly suggests a role for prostaglandins and thromboxanes [4, 5, 12]. How this response is initiated is unclear but may involve the renin-angiotensin system [22, 25], platelet-activating factor [20, 23] or possibly an autonomic neuronal pathway.

Return of renal function following relief of obstruction is dependent on many factors including the nature of the occlusion, complete or partial, and the duration of the obstruction. The relationship between the ability of the kidney to recover function is poorly understood [6]. Complete ureteric obstruction has been widely investigated and there is an abundance of pathophysiological data available. In the clinical practice, however, the problem of partial obstruction is considerably more common. Many studies have been performed in acute or ex vivo isolated perfused models. The short half-life of many of the proposed humoral mediators is such that their investigation in vivo is difficult [16]. There are also many problems in differences in laboratory assay techniques and validation.

Ryan and Fitzpatrick have developed a reproducible model of partial obstruction [17] which has been subsequently used to study changes in total and regional blood flow which occur as a response [7]. In this paper, the model is adapted to study prostaglandin synthesis in partial unilateral ureteric obstruction and investigates the relationship between changes in urinary prostaglandins and the altered haemodynamics of this condition.

Materials and methods

This study was performed using 12 adult female mongrel dogs. The animals weighed 21.2 ± 5.7 kg (mean $\pm$ SD) and were maintained on a standard dog chow diet (Purina Laboratories, USA) for the duration of the study. Animals were not fed for 24 h prior to surgery but were allowed water ad libitum. At surgery, each animal was given Augmentin 600 mg i.v. (Beecham Research Laboratories, UK) and anaesthesia was induced with thiopentone sodium 30 mg/kg body weight i.v. The dogs were intubated and ventilated using a Manly Pulmovent ventilator. Anaesthesia was maintained using 40% oxygen, 60% nitrogen and 1% halothane. Intraoperatively the animals were given an i.v. infusion of 0.9% saline at 30 ml/kg per hour.

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Postoperative analgesia was provided by morphine sulphate 2 mg and antibiotics were continued for 48 h. Normal diet was resumed 24 h after surgery.

Initially bilateral nephrostomies were inserted. Both kidneys were exposed through flank incisions, and following mobilisation a small incision was made in the renal capsule. Through this incision a 14F Nutricath "S" catheter (Vignon, France) was passed over its guidewire through the kidney substance and situated in the renal pelvis. The free end of the catheter was tunnelled away from the wound to lie subcutaneously on the animal's back.

Four weeks later, a grade 3 partial obstruction was developed in the left ureter in all animals as previously described [17, 18]. Using a transabdominal approach, a 2-cm length of semirigid plastic stent (internal diameter 0.3 mm) was inserted into the lower left ureter via transverse ureterotomy (Fig. 1).

After 5 weeks of partial obstruction, the stent was excised and the ureter was reimplanted into the bladder in six of the animals. In the remaining six animals a left nephroureterectomy was performed to investigate the effect of reimplanting the previously obstructed kidney on the contralateral side. The study was continued for a further 5 weeks when all animals were put to death using pentobarbitone sodium 500 mg and the remaining kidneys were harvested. Throughout the study, the animals remained healthy and, despite multiple urinary tract procedures repeated during sampling, there were no septic complications.

To confirm the development of partial ureteric obstruction after stent insertion and its subsequent relief, provoked intrapelvic pressures were recorded [24]. An 18-gauge needle was inserted into the subcutaneous nephrostomies and the system was perfused with 0.9% saline via a three-way tap connected to a perfusion pump (Perfusor Secura E, B Braun, FRG). Intrapelvic pressure was monitored via a Bentley Transtec Model 800 pressure transducer and recorded on a Devices four-channel recorder. Provoked intrapelvic pressure was measured during incremental perfusions of saline from 1 ml/min to 10 ml/min.

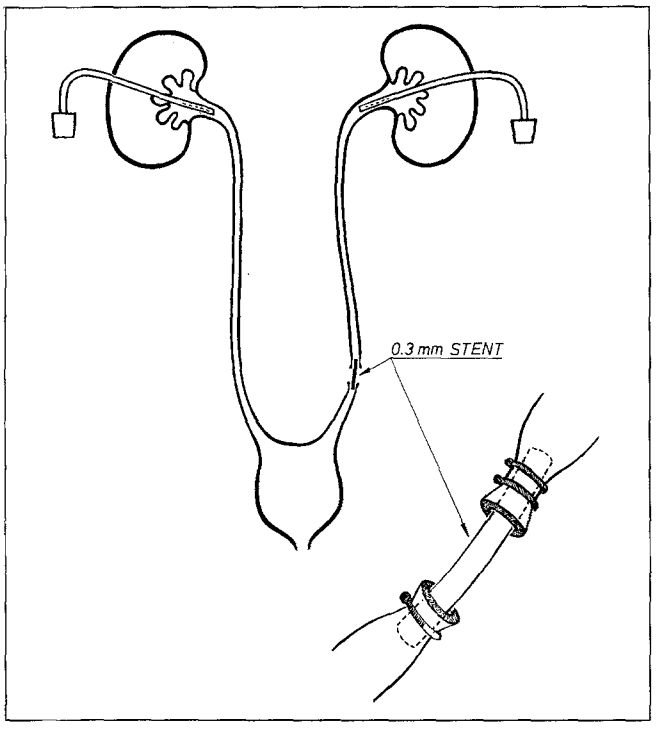

Fig. 1 Schematic representation of operative procedures

Blood flow measurement

Total and regional blood flow was measured by determining the distribution of radiolabelled microspheres (NEN-Trac, Dupont, USA) at three points during the study: immediately prior to left ureteric obstruction, 5 weeks after development of obstruction and 5 weeks following its relief. The isotopes used were cobalt-57, tin-113 and strontium-85 and the radioactive labelled microspheres (15 μm diameter) were suspended in 0.9% saline and 0.01% Tween 80 surfactant.

A double-lumen Cordyn-Katheter catheter (B Braun, FRG) was placed by the transfemoral route into the aortic bulb and the catheter tip position confirmed radiographically. Approximately 1 million microspheres were injected through the catheter and flushed with 20 ml normal saline. Simultaneously, blood was withdrawn through the proximal port of the catheter, sited at the level of the renal arteries, at a rate of 20 ml/min. This provided a reference value for determining renal blood flow (RBF).

On completion of the study, the kidneys were fixed in 10% formalin solution and were divided into three coronal sections. The middle section, which was 1 cm thick, was divided into approximately six radial sections. These sectors were dissected into their anatomical components, the outer and inner cortex and the renal medulla. The remaining anterior and posterior coronal sections were divided into small pieces weighing an average of 6.3 ± 1.8 g. The reference blood samples and all kidney sections were weighed and underwent scintillation counting in a gamma well counter (ST7 Gamma Counter, NE Technology, UK).

Each isotope produces a distinctive photopeak and therefore the distribution and activity of the three types of radiolabelled microspheres were determined. Using the reference sample method [2], blood flow in millilitres per minute per gram was measured in the inner and outer cortex, the renal medulla and for the whole kidney at the times indicated above. Due to the study design, there was a necessary time lapse of 10 weeks between the injection of the ^{57}Co-labelled microspheres and scintillation counting and similarly a 5-week delay for the ^{113}Sn isotope. This, however, would not have had any effect on the accuracy of measurement of blood flow as the reference blood sample for each isotope also underwent the same degree of radioactivity decay. Furthermore, activity counts were performed within one half-life of each of the isotopes ($t_{1/2}$: ^{85}Sr 65 days, ^{57}Co 200 days, ^{113}Sn 115 days).

Prostaglandin assay

Renal prostaglandin synthesis was determined by measuring urinary PGE_2 and thromboxane A_2 (TXA_2). An 18-gauge needle was passed aseptically through the skin into both nephrostomies and the time taken to withdraw approximately 1 ml urine was recorded. PGE_2 and TXA_2 were both measured by radioimmunoassay of their stable metabolites 13,14-dihydro-15-keto PGE_2 and thromboxane B_2 (TXB_2) respectively, using commercially available assay systems (Amersham, UK). Urine was obtained prior to each operation and was also taken for three consecutive days subsequently. These samples were collected into plain tubes and were frozen immediately for batch analysis. Prostaglandin levels are expressed as nanograms per millilitre per minute.

Renin activity

Independent validation of changes in renal function was provided by plasma renin activity. This was measured in peripheral venous blood by angiotensin I assay (Compagnie Oris Industrie SA, France). Blood samples were taken concurrently with the urine samples described above. Sampling conditions and preparation were carefully standardised and 5 ml blood was collected into pre-chilled sodium ethylenediaminetetra-acetic acid (EDTA). Serum was retrieved by cold centrifugation at 2000 *g* for 15 min and then

frozen for batch assay. Angiotensin I levels are presented as nanogram per millilitre per hour. Assay or both the prostaglandins and renin activity was performed blindly.

Statistical analysis

All data are presented as mean and standard error. All statistical analysis was performed by Student's paired *t*-test and a *P* value of less than 0.05 was considered significant.

Results

During the period of partial ureteric obstruction, stent patency was confirmed by nephrostograms. Whitaker tests confirmed the development and subsequent relief of obstruction in all animals. The mean provoked left pelvic pressure increased from 5 ± 2 mmHg to 51 ± 8 mmHg ($P<0.01$) following partial ureteric obstruction (Fig. 2). Relief of obstruction in the reimplantation group resulted in a fall of pelvic pressure to 11 ± 4 mmHg ($P<0.01$).

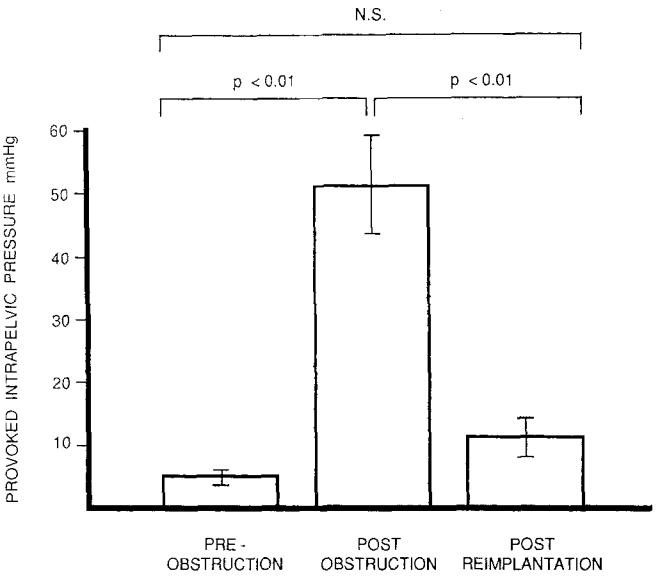

Fig. 2 Provoked left intrapelvic pressure at 10 ml/min

Blood flow

Changes in RBF in the reimplantation group are shown in Table 1. Following partial obstruction, total flow in the left kidney decreased from 142 ± 51 ml/min to 97 ± 37 ml/min ($P<0.01$). After reversal of obstruction there was no significant change in this flow, 89 ± 18 ml/min ($P<0.34$). In the non-obstructed right side a compensatory increase in flow occurred after left-sided obstruction from 155 ± 48 ml/min to 218 ± 71 ml/min ($P<0.04$). After release of the obstruction right RBF fell to 187 ± 60 ml/min, which was not significantly different from the pre-obstruction value.

On both sides, outer cortical flow was significantly reduced following stent insertion: right 6.4 ± 1.9 ml/min per gram to 4.2 ± 1.5 ml/min per gram ($P<0.02$), left 7.2 ± 2.7 ml/min per gram to 4.4 ± 2.4 ml/min per gram ($P<0.05$). While this flow change was reversed on the right side after relief of obstruction, 4.2 ± 1.5 ml/min per gram to 6.7 ± 1.7 ml/min per gram ($P<0.01$), there was no significant change in outer cortical flow on the left side.

Regional blood flow changes in the inner cortex on both sides demonstrated a compensatory increase in flow in the post-obstruction period: right 3.8 ± 1.6 ml/min per gram to 7.0 ± 2.0 ml/min ($P<0.005$), left 4.4 ± 1.3 ml/min per gram to 6.0 ± 2.1 ml/min per gram ($P<0.02$). Again, this altered flow in the right kidney returned to normal after left ureteric reimplantation (7.0 ± 2.0 ml/min per gram to 3.6 ± 1.2 ml/min per gram, $P<0.01$). In contrast, left inner cortical flow remained unchanged. There were no significant changes in medullary flow in either side for the duration of the study.

In the nephroureterectomy group, there was a marked similarity in total and regional flow in the right kidney to that of the reimplant group. In the outer cortex there was a significant fall in flow from 7.4 ± 1.4 ml/min gram to 4.1 ± 1.6 ml/min per gram ($P<0.005$) following obstruction, which returned to normal following left nephroureterectomy (Table 2). An increase in blood flow from 4.5 ± 2.1 ml/min per gram to 6.8 ± 2.2 ml/min per gram ($P<0.04$) was seen in the inner cortex during the obstructive period which also returned to normal (4.1 ± 1.5 ml/min per gram) following its relief ($P<0.03$). Total right

Table 1 Total and regional renal blood flow

	Pre-obstruction	*P*	Post-obstruction	*P*	Post-reimplant
Left kidney reimplant group					
Outer cortex (ml/min/g)	7.2 ± 2.7	0.05	4.4 ± 2.4	0.31	5.3 ± 2.1
Inner cortex (ml/min/g)	4.4 ± 1.3	0.02	6.0 ± 2.1	0.38	5.6 ± 2.0
Medulla (ml/min/g)	0.8 ± 0.4	0.4	0.5 ± 0.4	0.3	0.5 ± 0.4
Total flow (ml/min)	142 ± 51	0.02	97 ± 37	0.34	89 ± 18
Right kidney reimplant group					
Outer cortex (ml/min/g)	6.4 ± 1.9	0.02	4.2 ± 1.5	0.01	6.7 ± 1.7
Inner cortex (ml/min/g)	3.8 ± 1.6	0.005	7.0 ± 2.0	0.01	3.6 ± 1.2
Medulla (ml/min/g)	0.4 ± 0.4	0.5	0.4 ± 0.2	0.3	0.5 ± 0.3
Total flow (ml/min)	155 ± 48	0.04	218 ± 71	0.15	187 ± 60

Table 2 Total and regional renal blood flow

	Pre-obstruction	*P*	Post-obstruction	*P*	Post-nephrectomy
Left kidney nephrectomy group					
Outer cortex (ml/min/g)	6.5±2.9	0.03	3.2±1.5	–	–
Inner cortex (ml/min/g)	4.5±1.8	0.01	6.9±0.9	–	–
Medulla (ml/min/g)	0.7±0.3	0.5	0.6±0.4	–	–
Total flow (ml/min)	162±61	0.01	80±33	–	–
Right kidney nephrectomy group					
Outer cortex (ml/min/g)	7.4±1.4	0.005	4.1±1.6	0.05	6.8±1.9
Inner cortex (ml/min/g)	4.5±2.1	0.04	6.8±2.2	0.03	4.1±1.5
Medulla (ml/min/g)	0.9±1.0	0.4	0.5±0.4	0.4	0.4±0.3
Total flow (ml/min)	123±29	0.005	191±46	0.007	246±38

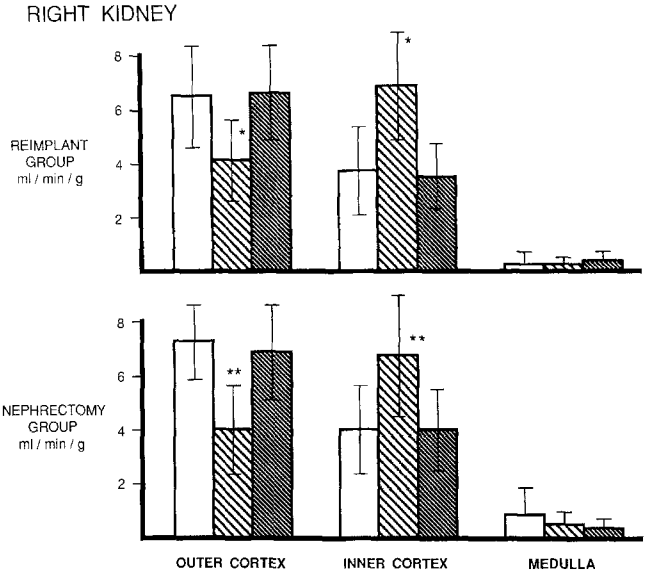

Fig. 3 Comparison of intra-renal flow in right kidney between reimplanted and nephrectomised animals. * $P<0.01$ compared with pre- and post-relief of obstruction, ** $P<0.04$ compared with pre- and post-relief of obstruction. ☐ Pre obstruction; ▨ post obstruction; ▩ post relief

RBF rose from 123±29 ml/min to 191±46 ml/min ($P<0.005$). The changes in left total and regional blood flow in this group were also very similar to those seen in the reimplant group. Outer cortical flow fell from 6.5±2.9 ml/min per gram to 3.2±1.5 ml/min per gram ($P<0.03$) while, as seen in all other kidneys, there was a compensatory increase in inner cortical flow from 4.5±1.8 ml/min per gram to 6.9±0.9 ml/min per gram ($P<0.01$). Total left RBF also decreased from 162±61 ml/min to 80±33 ml/min following insertion of the stent ($P<0.01$). There were no significant differences between the reimplant and nephroureterectomy groups in terms of changes in intra-renal blood flow in the right kidney (Fig. 3).

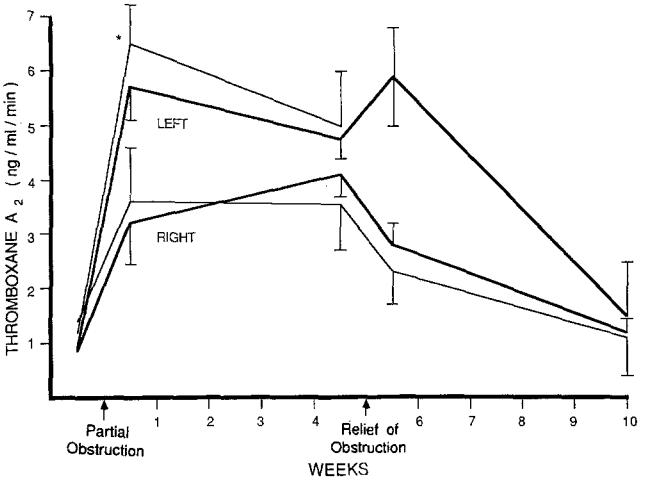

Fig. 4 Thromboxane A_2 synthesis. * $P<0.01$; *light line*, nephrectomy group; *bold line*, reimplant group

Prostaglandin synthesis

Thromboxane A_2

In both kidneys in the two groups, TXA_2 synthesis, as measured by thromboxane B_2, increased following the onset of obstruction (Fig. 4). In the left kidneys these levels (reimplant 5.8±0.6 ng/ml per minute, nephroureterectomy 6.5±0.8 ng/ml per minute) were significantly greater than the baseline values ($P<0.01$ for both groups). The increase in the right kidneys was not significant. Thromboxane A_2 levels remained elevated in all kidneys for the whole obstruction period and then slowly returned to normal after relief of obstruction.

Prostaglandin E_2

There was a steady increase in the synthesis of the stable metabolite of PGE_2, 13,14-dihydro-15-keto-PGE_2, in all kidneys during left ureteric obstruction (Fig. 5). This rise was not significant in the left kidneys in either group. In contrast, statistical significance at the 1% level was found in the increase in the right kidneys (reimplant 5.8±1.1 ng/ml per minute, nephroureterectomy 5.6±0.6 ng/ml per minute).

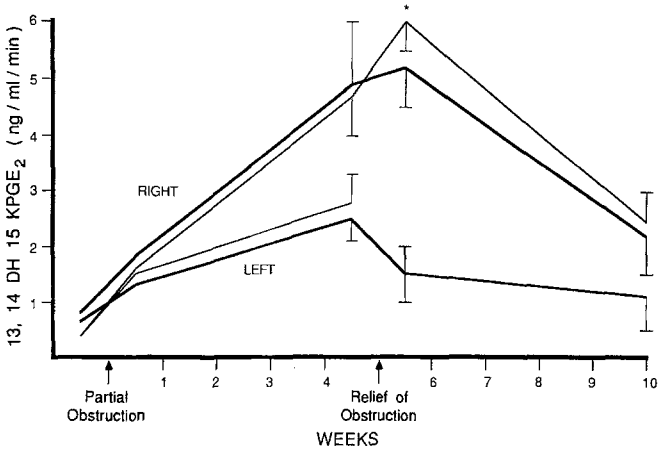

Fig. 5 Prostaglandin E_2 synthesis. * $P<0.01$; *light line*, nephrectomy group; *bold line*, reimplant group

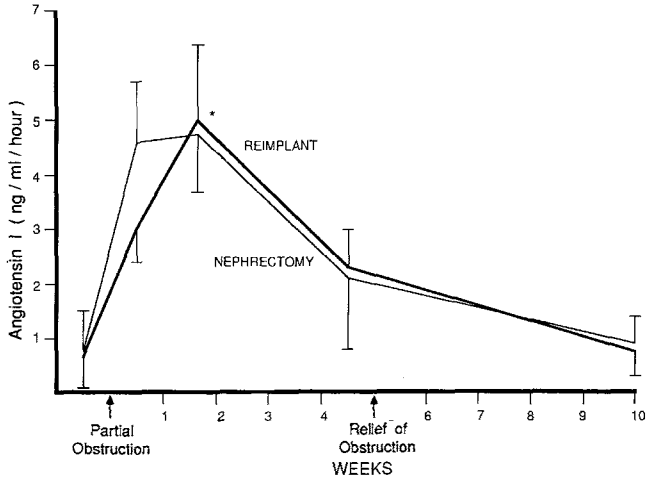

Fig. 6 Peripheral plasma renin activity. * $P<0.01$; *light line*, nephrectomy group; *bold line*, reimplant group

Renin activity

Angiotensin I levels rose immediately following obstruction in the two groups, reaching maximal synthesis at day 10 (Fig. 6). The values in both groups were: reimplant 5.0 ± 1.4 ng/ml per hour, nephroureterectomy 4.8 ± 1.0 ng/ml per hour ($P<0.01$ for both groups).

Discussion

The pathophysiology of renal failure in complete ureteric obstruction has been shown to have a dual mechanism. The initial upward transmission of increased renal tract pressure through the renal pelvis is transient and returns to normal within 12 h [12]. If obstruction continues, a phase of increased RBF is followed by secondary hypoperfusion [21]. This reduction in blood flow persists if obstruction continues for more than 24–36 h and thus limits recovery of renal function. It appears, therefore, that surgical decompression of the upper tract must be performed before the onset of the secondary vascular injury if permanent damage is to be avoided.

The development of impaired renal function in partial obstruction follows the same mechanism though, as would be expected, at a slower rate [17, 18]. Ipsilateral renal hypoperfusion and regional redistribution of blood flow have also been demonstrated in this condition [7, 18].

This animal model of partial obstruction has been well validated and results have been reproduced [7, 17, 18]. It differs from other models of partial obstruction in that a precise degree of obstruction can be introduced rather than studies employing external compression. In this respect, the Whitaker test as used in this study has reliably been shown to be able to detect both the presence of ureteric obstruction and the degree of partial obstruction [19]. It permits investigation of chronic obstruction rather than the acute experiments which are widely used. In vivo study of prostaglandin synthesis can be notoriously difficult but in this study assays were performed on urine samples obtained through the nephrostomies which did not contribute to the degree of obstruction. It is also important that female animals be used if there is any risk of contamination by seminal fluid in the lower tract.

In this study both groups of animals were identical up to where obstruction was relieved by either ureteric reimplantation or nephroureterectomy. The results show that changes in blood flow were as have been previously documented [7] but were repeated to study the correlation with alterations in prostaglandin synthesis. After the onset of partial obstruction, blood flow was diverted from the obstructed left side to the non-obstructed right kidney. Measurement of regional flow during ureteric obstruction demonstrated redistribution of blood from the outer to the inner cortex in all kidneys. Following relief of left ureteric obstruction, intra-renal blood flow in the non-obstructed right kidney returned to normal. In contrast, changes in regional flow in the previously obstructed left kidney in the reimplanted group were irreversible.

Eicosanoid synthesis increased in all kidneys after left ureteric obstruction. Formation of the potent vasoconstrictor thromboxane A_2 was elevated in both right and left kidneys during the obstructive period but this was only significant in the obstructed kidneys. In both kidneys, prostaglandin E_2 production was also increased during the same period. However, the levels of this vasodilator were only significantly increased on the right side.

Many studies have proposed humoral mediators for the RBF changes. While this may occur within the kidney itself they do not appear to have any influence on the contralateral kidney. This is supported by the finding that there was no difference in right intra-renal blood flow whether the left ureteric obstruction was relieved by reimplantation or by nephroureterectomy. The presence

of a previously obstructed kidney does not appear to exert a direct effect on the contralateral side. Nor did it influence right renal prostaglandin synthesis following release of the obstruction.

It is not the purpose of this paper to discuss changes in total and regional blood flow in detail as this has been adequately covered in previous publications. The mediators which initiate these changes have not as yet been identified. Several factors have been postulated as having a potential role but the majority of such studies have been on complete obstruction and there are few available data on their activity in partial unilateral ureteric obstruction.

The association between ureteric obstruction and increased urinary TXA_2 production was initially shown in the isolated perfused hydronephrotic kidney [13]. Inhibition of TXA_2 synthesis might therefore reverse the secondary renal hypoperfusion. However, an intact arachidonic acid cascade is required for the development of renal vasodilatation in response in ureteric obstruction, outruling the use of cyclo-oxygenase inhibitors such as indomethacin [1]. Klotman et al. have shown that direct suppression of TXA_2 by thromboxane synthetase inhibitors may improve both renal function and blood flow [8]. It is unlikely that TXA_2 is responsible for the rise in renal resistance and therefore doubt has been cast on its role [4, 10, 11].

This study demonstrated increases in TXA_2 bilaterally, which were significant only on the obstructed side. This is in agreement with the results of Morrison and Thornton, who showed increased urinary excretion of TXA_2 from the obstructed side compared with the normal kidney in humans [14]. There was not the sharp increase in ipsilateral TXA_2 formation following release of the obstruction as previously observed [11].

The ability of PGE_2 to cause renal vasodilatation is well documented [1, 5, 6] and its inhibition prevents this haemodynamic response in ureteric obstruction. While prostaglandin and thromboxane inhibition may give further insight to the haemodynamic changes, it may not be therapeutically useful as the vascular response may in fact be protective. In contrast to the immediate rise in TXA_2 seen in this study, PGE_2 increased at a steady rate during the period of obstruction, which may be a function of the nature of the obstruction.

Partial ureteric obstruction not only resulted in the expected increases in urinary PGE_2 and TXA_2 but also had a similar effect on the non-obstructed contralateral side. While the results indicate that there may not be a direct effect on the contralateral kidney following release of obstruction, there must be some form of control during the obstructive phase. Though the role of angiotensin II is ambiguous, it is a potent stimulator of prostaglandin and thromboxane synthesis [12]. In this experiment, peripheral renin activity increased following partial obstruction, a finding which has been demonstrated previously [22]. It may be possible that the renin-angiotensin system stimulates prostaglandin activity in the contralateral kidney.

The primary aim of this study was to investigate the association between partial unilateral ureteric obstruction, its resulting altered haemodynamics and prostaglandin synthesis. While we have not shown a causal relationship, we have confirmed that changes observed in complete obstruction also develop in this model of in vivo chronic partial ureteric obstruction.

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