Pathophysiology of Upper Urinary Tract Obstruction

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- Summary

Pathology

Macroscopically

- **Renal Pelvis Dilates**. No studies in humans but hydronephrosis in rabbits occurs after 24 hours. Generally assumed to occur in the first few days after ureteral obstruction. Extrarenal pelvis dilatation>>intrarenal dilatation. Increased intrarenal pelvic pressure results in papillary compression and thinning, with eventual septation and production of a 'rim' of functioning cortex.
- **Initial Increase in Mean Kidney Weight**. Oedema > atrophy in first three months. Animal studies in rabbits have shown a decrease in mean kidney weight after 90 days.
- **Pigmentation, Focal Ischaemia and Necrosis**. Focal necrosis and haemorrhage of papilla and fornix in particular.

Microscopically

Tubular damage and interstitial fibrosis

- **Tubular Apoptosis**. Delicate tubules bear brunt. Initial dilatation and thinning of epithelium. Apoptosis within 30 mins in animal models . Dysregulation of proliferation and apoptosis, evidenced by increased p53 and p21 levels. Disappearance of recognisable tubular subunits within 21 days.
- **Glomerular Sparing**. Slight thickening of GBM with loss of filtration slits. Hyalinisation reported but not until ~ 6-9 months following obstruction, and then only in a relatively small number of glomeruli.
- **Inflammatory Infiltrate**. Influx of predominantly macrophages but a few T-cells after 3-4 hours. Associated conversion of fibroblasts to

myofibroblasts. Production of mediators (TXA2, PAF and TGFB), leading to tubuloinsterstitial fibrosis (TGF beta major is determinant)

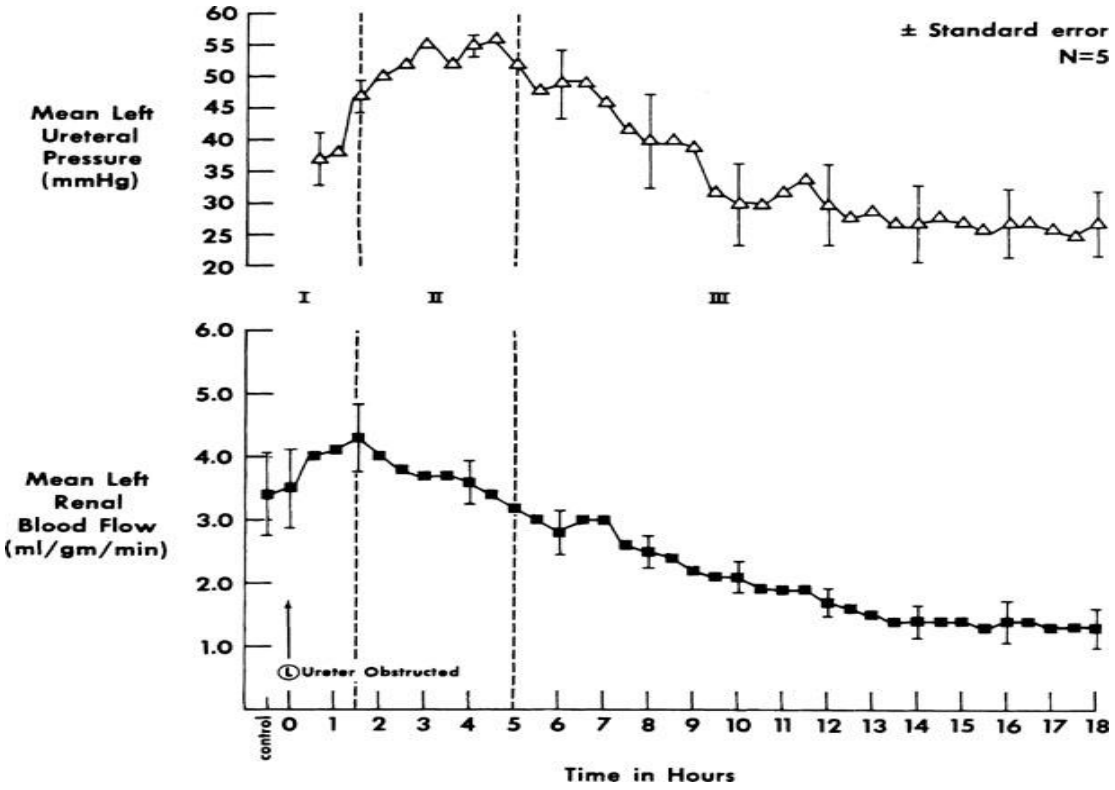
- **Tubulointerstitial fibrosis**. Thought to be major determinant of deranged renal function and failed recovery following release of obstruction

Physiology

Unlilateral Ureteric Obstruction (UUO)

A. Renal Blood Flow, Glomerular Filtration Rate, and Ureteral Pressure

- Characterisation by Moody and Gillenwater (Investig Urol 1975;13:246–251). Acute UUO in five awake dogs.
- Desribed a triphasic response of RBF in relation to ureteral pressure



- Phase I (0-90 mins).

  Pre-glomerular vasodilatation

  Increased RBF in response to increased ureteral pressure. Due to **pre-glomerular vasodilatation**, a compensatory response intended to increase capillary hydrostatic pressure and thus GFR. Vascular mediators thought to play major role:

- **Eicosanoids.** Implicated for years. Pre-treatment with indomethacin abolishes RBF response in dogs (Allen, 1978). **PGE2** probably responsible (Frokiaer, 1995). PGE2 excretion from contralateral kidney markedly increased in UUO, and inhibition with indomethacin significantly attenuates response.
- **Nitric Oxide.** Nitric oxide synthase inhibition attenuates RBF increase in acute UUO (Lanzone 1995). Furthermore L-arginine infusion reverses indomethacin-mediated abolition of RBF increase. (Schulsinger 1997). Micropuncture studies show an increase in glomerular capillary hydrostatic pressure after UUO - ? release of NO in response to endothelial stretching.

<u>WARNING</u>: Most of the studies in dogs or rats, which have unicalyceal kidneys. Studies in pigs, baboons and lambs (which have multicalyceal kidneys) fail to demonstrate an increase in RBF with acute UUO.

- <u>Phases II and III</u>

  Post-glomerular vasoconstriction, then pre- and post-glomerular vasoconstriction

  <u>Phase II (90 mins – 4/5 hours)</u> characterised by a **fall in RBF** with a continued **rise in ureteral pressure**. Due to **post-glomerular vasoconstriction.** Further attempt by kidney to maintain GFR.

  <u>Phase III (5 hours+)</u> associated with concomitant falls in **RBF and ureteral pressure.** Further fall in RBF due to **pre-glomerular vasoconstriction**. By 24 hours tubular pressure and ureteral pressure fall to 30% and 50% of control values respectively.

  Vaso-constrictive mediators in Phase II and III:

  - **Eicosanoids.** Potent vasoconstrictors **TXA2 and TXB2 implicated** in decline of RBF (and ureteral pressure) following UUO. Thromboxanes thought to be derived from inflammatory infiltrate, and specifically **released by platelet activating factor**. Irradiation of the obstructed kidney, significantly reducing the cellular infiltrate, markedly reduces urinary TXB2 and improves RBF and GFR (Schreiner 1988). However treatment with TXA2 synthesis inhibitors/ receptor blockers leads to improved RBF and GFR in some animal studies but not in others.
  - **Renin/ Angiotensin II.** Elevated renin and AII levels in obstructed dogs and rats. Intrarenal generation of AII in obstructed pigs. ACE inhibitors and AT blockers shown to improved RBF and GFR in

some studies (dog and rat), but results not confirmed in other studies (including those in pigs).

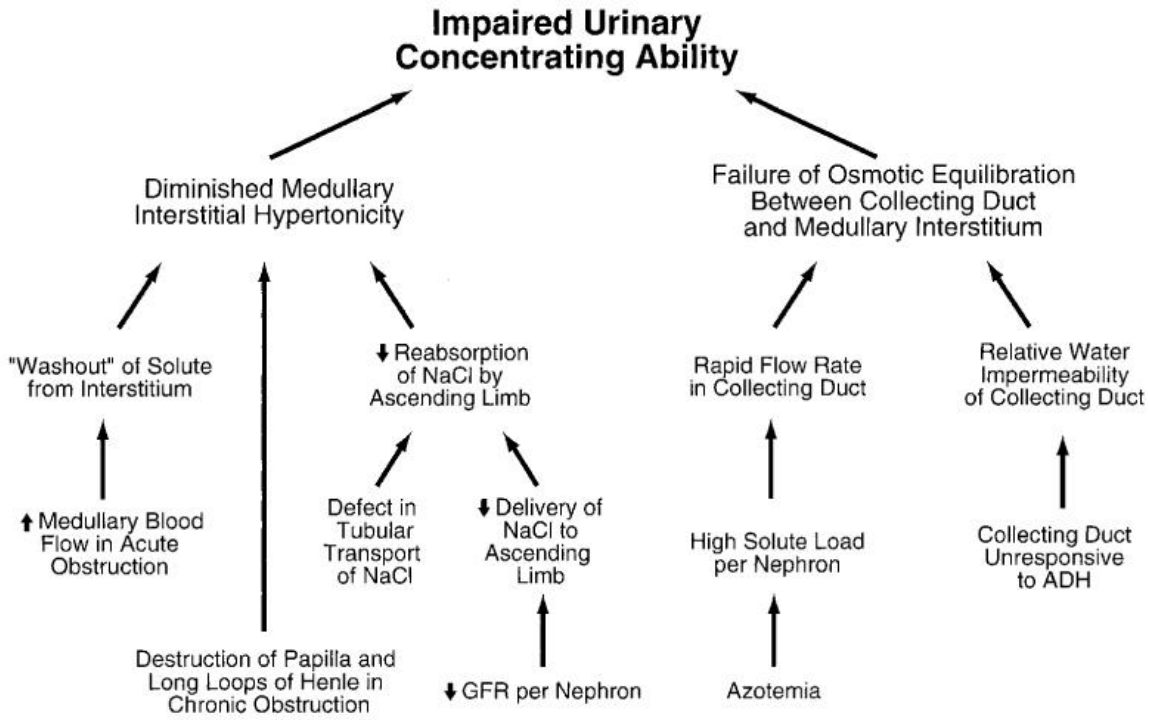
- **Endothelin.** Vascular derived mediator. Released in response to endothelial stretch. Causes marked vasoconstriction by allowing calcium influx into smooth muscle cells. Elevated endothelin levels documented in obstructed dogs (Kahn 1995). Same group significantly improved RBF and GFR in post-obstructed kidney by verapamil infusion.

Decreased GFR due to (i) reduced single-nephron renal blood flow and (ii) shunting of blood from outer to inner cortex, decreasing the total number of perfused glomeruli. ? Mechanism of shunting. Increased production of renin witnessed in outer vs. inner cortex.

Fall in ureteral pressure due to;

- Reduced GFR
- Pelvicalyceal dilatation
- Pyelolymphatic and pyelovenous backflow

B. Tubular Function in Unilateral Ureteric Obstruction



- GFR markedly reduced following release of obstruction, but total excretion from post-obstructed kidney normal/ slightly elevated, due to ineffective

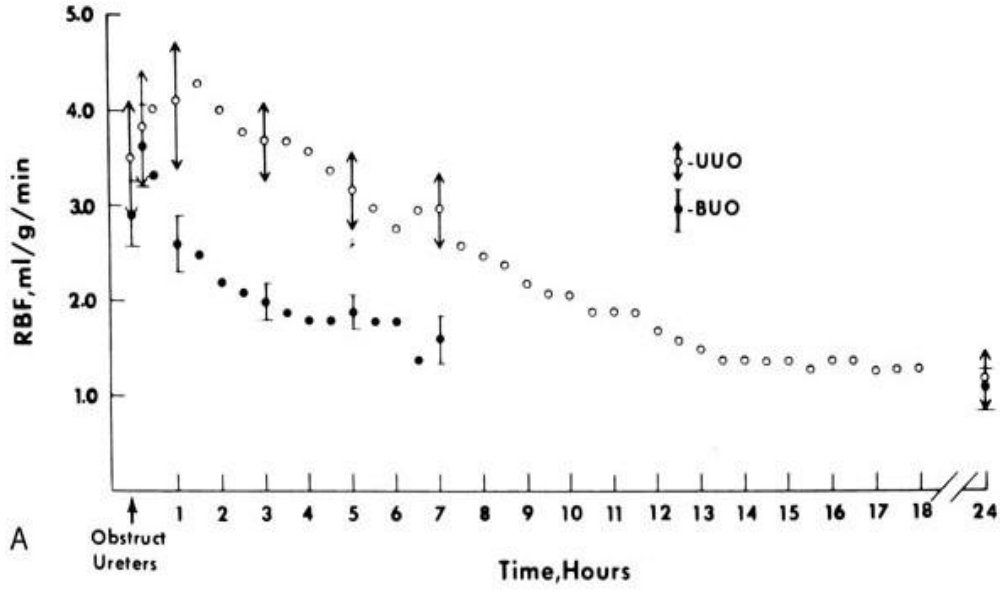
Na reabsorption and water retention in the tubules, leading to impaired concentrating ability

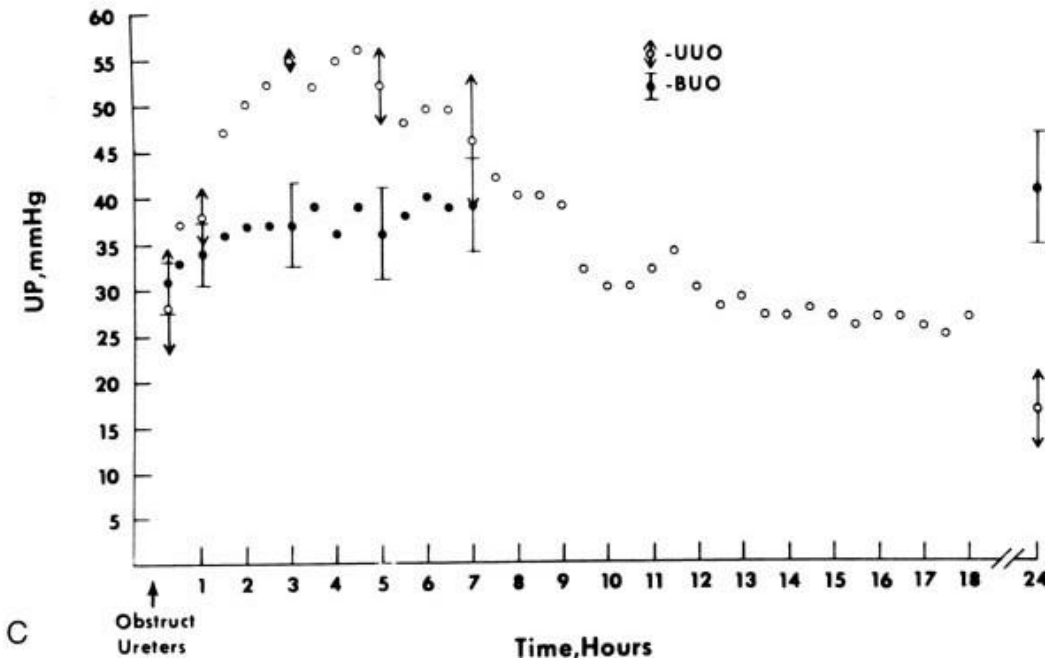
- Active transport markedly impaired. Selective down-regulation of both transporter activity and transporter protein synthesis after 24 hours of obstruction [NB. PGE2 known to inhibit Na/K ATPase and aquaporins]
- Proximal tubule relatively spared, but marked failure of active transport mechanisms from loop of Henle to collecting duct. Reduced reabsorption of sodium in ascending limb, leads to a reduction in interstitial hypertonicity. Combined with insensitivity to ADH in collecting duct, results in impaired concentrating ability.
- Potassium excretion falls proportionate to fall in GFR, due to defective distal tubular secretion. Failed active transport also leads to an inability to acidify urine.
- Urine
    - Normal/ mildly elevated excretion of filtered load
    - Low osmolality
    - Normal/ high pH
    - High sodium content (increased filtered fraction)
    - Low potassium content
    - Low phosphate content

Bilateral Ureteric Obstruction (Obstructed Solitary Kidney)

A. <u>Changes in RBF, GFR and Ureteric Pressure</u>

Moody and Gillenwater (Investig Urol 1975;13:246–251).





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- No triphasic pattern
- Biphasic pattern
    - Initial short-lived rise in RBF as in UUO, due to pre-glomerular vasodilatation
    - Marked fall in RBF, associated with a persistently elevated ureteric pressure > 24 hours. Associated with post-glomerular vasoconstriction.
    - **NO pre-glomerular vasoconstriction seen in late-stage BUO**. ? accumulation of a 'substance' which prevents pre-glomerular vasoconstriction. Confirmed by Harris (1975): GFR preservation, diuresis and natriuresis in UUO with contralateral nephrectomy, and with contralateral urine perfusion of obstructed kidney, but not in UUO with normal contrateral kidney. Substance believed to be **Atrial Natriuretic Peptide**

<u>Atrial Natriuretic Peptide</u>

- Characterised by Cogan (Annu Rev Physiol 1990;52:699–708)
- Released by cardiac atrium in response to increased intravascular volume
- Effects designed to maximise diuresis and natriuresis
    - Increased GFR thro' pre-glomerular vasodilatation and post-glomerular vasoconstriction
    - Increased glomerular capillary ultrafiltration co-efficient (leakier membrane)
    - Direct inhibition of tubuloglomerular feedback mechanism (renin/ AII)

    - Specific inhibition of NaCl co-transport in ascending limb of loop of Henle
    - Blocks vasopressin-mediated osmotic water permeability
- Elevated in BUO but not in UUO in rats (Fried 1987)

B. Tubular Function in Bilateral Ureteric Obstruction

- Similar tubular defects as seen in UUO, but exacerbated due to activity of ANP
- Marked post-obstructive diuresis and natriuresis may be seen. Multiple investigators in animal and human studies have shown that degree and duration of diuresis proportional to intravascular volume status as reflected by circulating ANP levels. NB. Diuresis not thought to be related to circulating urea as an osmotic load. (Jaenike 1972) as a urea infusion fails to produce a diuresis in UUO.
- A marked increase in Na delivery to the distal nephron, combined with elevated serum potassium, results in an increased filtration fraction of potassium
- Urine
    - Significantly increased total excretion of filtered load
    - Low osmolality (lower cf. UUO)
    - Normal/ High pH
    - High sodium content
    - High potassium content

Renal Function after Release of Ureteric Obstruction

A. Unilateral Ureteric Obstruction

- Seminal work by Vaughan and Gillenwater (Investigative Urology 1971a; 9:109-118). Subsequently confimed by Fink 1980.
    - 15 dogs: different durations of acute UUO
    - If reversed within 2 weeks = full recovery of function
    - After 14 days ~ up to 70% return of function
    - No functional recovery after 6 weeks
    - Continued improvement up to 6 months following obstruction
- Very few other studies of functional return
- Situation appears to be different in humans
    - Anecdotal reports of total return to function after as long as 6 months (Better 1973;Shapiro 1976; Dhabuwala 1982; Okubo 1998;)
    - ? due to multi-calyceal kidney or pyelolymphatic ‘escape’.

B. Bilateral Ureteric Obstruction

- No clear relationship between the duration of obstruction and recoverability of function. Furthermore no pre-release chemistry which can predict recoverability.
- Best human study by Jones et al. Examined 21 patients prospectively and following release of 3 months obstruction. Described 2 phases of recovery of function: An initial 'tubular' phase associated with improvements in creatinine clearance and fractional excretion of sodium; a further 'glomerular' phase associated with a gradual improvement in GFR over approximately 3 months

Post-obstructive diuresis

After release of bilateral urinary obstruction or obstructed solitary kidney
Typically normal physiological response to accumulated fluid and electrolytes.
Once free water and solute excess resolves, diuresis resolves
Most patients only require access to oral fluid and regular monitoring (vital signs, hourly urine output, daily weight and daily U+E and Mg)
~10% of patients demonstrate pathological diuresis due to impaired concentrating ability (downregulation of sodium and aquaporin channels)
Diuresis may be isotonic or hypotonic. In general sodium chloride should be given initially, but hypotonic fluid may be given if serum osmolality high and/or urine osmolality low.Studies from North West have shown that a UO > 20mml/h for >= 6 hours increases the likelihood of a pathological diuresis.IV fluids should be administered if there are signs of hypotension or impaired cognition

General rule of thumb

If UO >= 200 ml/h for more than 6 hrs institute IV fluid replacement at input = output - 50ml/h [Allowing for insensible losses (~800ml) removes 2L/day if patient NBM; 1L oral fluid restriction therefore leads to losses of 1L/day]