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A Urologist's View of Renal Pathophysiology Part II

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Lesson 26

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A Urologist's View of Renal Pathophysiology Part II

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In Part I we discussed renal blood flow, glomerular filtration rate, and the heterogeneity of nephron function: three pathophysiologic processes that alter renal function. Part II continues with three additional factors of importance to urologists: 1) impaired *tubular* function, 2) acute tubular necrosis (ATN), and 3) obstruction to urine flow.

Impaired Tubular Functions

Whether congenital or acquired, defects in tubular functions result in characteristic findings. Several of these are of particular importance in urology:

1) defective tubular hydrogen ion secretion,
2) defective tubular reabsorption of amino acids,
3) defective tubular reabsorption of calcium and phosphate,
4) defective tubular sodium reabsorption, and
5) defective tubular concentrating ability.

Defective Tubular Hydrogen Ion Secretion

Defects in renal tubular hydrogen ion secretion also termed renal tubular acidosis (RTA) may occur either in the proximal tubule (RTA type 2) or in the distal tubule (RTA type 1).

Proximal RTA (Type 2)

Three major processes occur in the nephron to rid the body of excess acid: sodium bicarbonate reabsorption, ammonia trapping, and titratable acid formation. Unlike the distal tubule, in the proximal tubule the formation of titratable acid and NH_4^+ is negligible; its major function is the reabsorption of bicarbonate. One bicarbonate ion is reabsorbed for each hydrogen ion secreted. The proximal tubule has a high capacity bicarbonate transport system, it reabsorbs approximately 80 percent of filtered bicarbonate. In proximal RTA the reabsorptive threshold (Tm) for bicarbonate is thought to be lowered (Figure 1). This results in large amounts of sodium bicarbonate delivered distally. The distal tubule has a relatively low capacity for bicarbonate reabsorption (however, it is a "high gradient system" being able to secrete hydrogen ions across a large gradient). Thus the hydrogen ions secreted distally primarily go towards absorption of the unreabsorbed bicarbonate with little NH_4^+ and titratable acid secretion. This results in an alkaline, bicarbonate rich urine. Extracellular volume contraction occurs secondarily to this massive anion (HCO_3^-) loss. In an attempt to compensate for this extracellular volume contraction chloride reabsorption is increased resulting in a hyperchloremic metabolic acidosis. As systemic acidosis progresses, the filtered load of sodium bicarbonate diminishes allowing only small amounts of bicarbonate to be delivered distally. Thus, below this lowered bicarbonate reabsorptive threshold (Tm), distal acidification processes can compensate for defective proximal acidification. This results in more complete bicarbonate reabsorption distally with titratable acid and NH_4^+ production and urine ph of 5.0 or less. However, the amount of bicarbonate required to maintain a normal serum level is massive, since it must equal the amount of bicarbonate excretion. In proximal RTA, potassium and calcium excretion are increased. However, since citrate excretion is relatively normal, nephrocalcinosis and renal calculi formation are rare. Clinically, the effects on children include: osteomalacia, rickets, abnormal gut calcium absorption, decreased phosphorus, and vitamin D metabolism.

Distal RTA (Type 1)

In distal RTA the distal tubule is unable to secrete hydrogen ions against a large gradient and thus unable to produce a urine ph less than 5.4 even when challenged. Minimal urine ph in distal RTA ranges from 5.4 to 6.5 depending on the severity of the transport defect. The distal tubule normally accounts for at most 15 percent of total bicarbonate reabsorption. Since proximal reabsorption is not affected in distal RTA, the urinary bicarbonate concentration is only 5 mEq/l even at a urine ph of 6.5. Thus daily excretion of bicarbonate is not usually greater than 10 to 15 mEq/day in distal RTA.

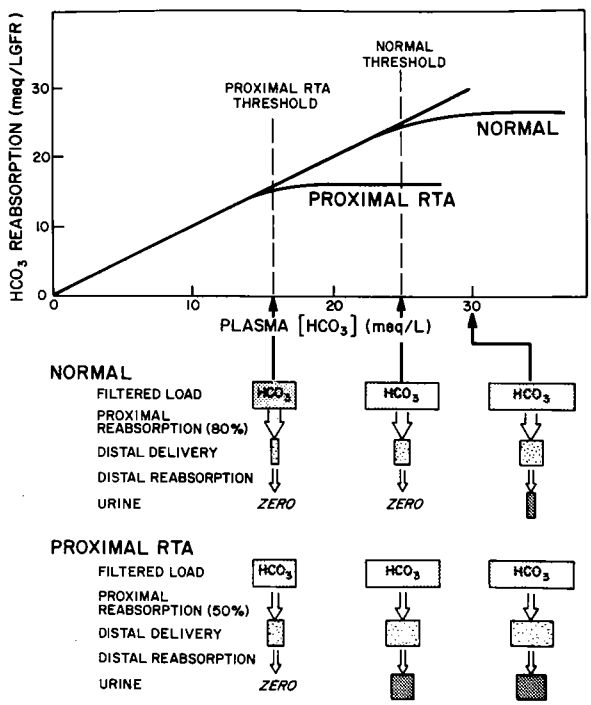

Figure 1

*Schematic representation of the single-nephron correlates of the whole kidney bicarbonate titration curves (top portion of figure) in normal subjects and in patients with proximal renal tubular acidosis (RTA). In each case reabsorption is complete at the plasma bicarbonate concentration threshold when distal hydrogen ion secretory processes are capable of reabsorbing bicarbonate delivered out of the proximal nephron. The fractional proximal bicarbonate reabsorptive capacity is suggested to be reduced in patients with proximal RTA (i.e., 50 percent versus the normal 80 percent) so that acid-base homeostasis can be achieved only at the expense of systemic metabolic acidosis. (from Cogan MG, Rector FC, Seldin DW: Acid-base disorders, in Brenner BM and Rector FC (eds): **The Kidney,** Philadelphia, WB Saunders, 1983, p 868.*

Therefore, in distal RTA, acidosis is more easily controlled as compared to the acidosis of proximal RTA. However, unlike the situation in proximal RTA in which systemic pH can be normal, the patient is *always* slightly acidotic in distal RTA. Systemic acidosis results in increased bone reabsorption and in turn increased urinary calcium. In addition, the urine is mildly alkaline (unlike proximal RTA where an almost normal urine ph is found) and nephrocalcinosis is common in distal RTA secondary to the low solubility of this excess calcium in a mildly alkaline urine.

The acidosis of RTA is a *non-anion gap* acidosis (anion gap being defined as the difference between the major intravascular cations, sodium and potassium minus the sum of the major anions, chloride and bicarbonate; normally between 12 and 16) associated with *hyperchloremia* and *hypokalemia* in contradistinction to the acidosis associated with ATN or reduced GFR (a hypochloremic and hyperkalemic acidosis). The hyperchloremia results from increased NaCl reabsorption stimulated by volume contraction secondary to sodium bicarbonate loss in the urine. The hypokalemia results from stimulation of the renin-angiotensin-aldosterone (secondary to volume contraction) axis as well as increased distal Na-K exchange occurring with the increased distal delivery of $NaHCO_3$.

Defective Tubular Reabsorption of Amino Acids

Cystinuria is the most common familial aminoaciduria. The defect in transport occurs both in the proximal tubule as well as in the jejunum. The excretion of this dibasic amino acid greatly exceeds the 40 to 80 mg/day of cystine found in normal subjects. Renal function otherwise is not compromised. The formation of cystine stones occurs secondary to the low urine ph (pk cystine = 8.0). Although cystine stones usually lack calcium, they are faintly radiopaque due to their sulfur content. Chemolysis of these stones is successful if urinary ph approaches 8.

Defective Tubular Reabsorption of Calcium and Phosphate

Approximately 60 percent of serum calcium is not bound to plasma albumin. It is this fraction which is freely filtered at the glomerulus. In the proximal tubule calcium reabsorption parallels sodium reabsorption, in fact, a portion of calcium reabsorption is sodium-dependent. More distally, calcium reabsorption is dependent upon parathyroid hormone (PTH). **Unlike the proximal tubule where calcium reabsorption is inhibited by PTH, in the distal tubule calcium reabsorption is stimulated by PTH. This distal reabsorption accounts for the hypocalciuric effects of PTH.** In the loop of Henle calcium reabsorption is inhibited by furosemide, which is why it is used in the emergency treatment of hypercalcemia. In the distal tubule calcium reabsorption is *directly* and *indirectly* stimulated by thiazides. The direct effect is by an active process enhanced by PTH. It should be noted that like sodium a whole kidney Tm does not appear to exist for calcium. The indirect effect occurs secondary to volume contraction and a consequent increase in calcium reabsorption in both the proximal and distal tubule.

Inorganic phosphate balance is maintained primarily by renal excretion and is handled by the kidney like glucose. In fact they probably share some transport systems. Unlike glucose, the Tm (transport maximum) for phosphate (approximately 2 m/dl) is usually always exceeded with phosphate ending up in the urine unless filtered load is reduced. Parathyroid hormone *increases* phosphate *excretion* by reducing tubular reabsorption of phosphate and by reducing the Tm. In acute renal failure phosphate is retained by the poorly functioning kidney raising the serum concentration. Since PTH secretion increases in chronic renal failure, increased amounts of inorganic phosphate are excreted in the urine as well as with primary hyperparathyroidism. Since the secondary hyperparathyroidism occurring with renal failure increases serum and urine calcium levels, the calcium: phosphate product increases resulting in urolithiasis as well as possible "metastatic calcification."

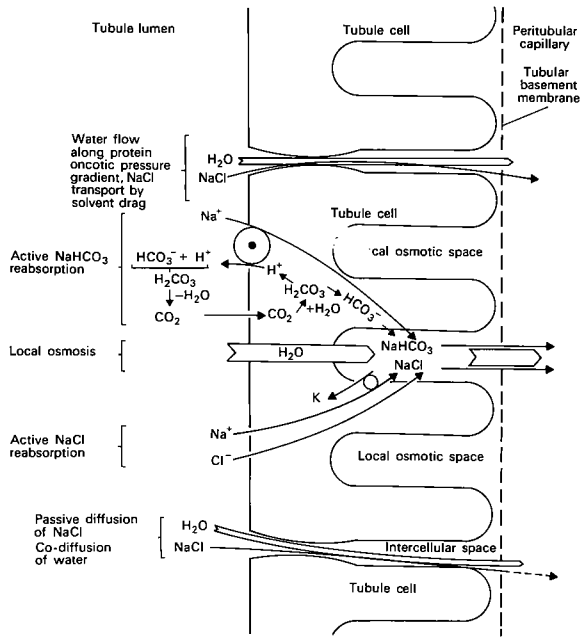

Figure 2

Mechanism of NaCl, $NaHCO_3$ and water reabsorption in the proximal tubule.[1]

Defective Tubular Sodium Reabsorption

Salt and water homeostasis is a process with multiple physiological mechanisms. In the proximal tubule (Figure 2) active transport of NaCl and Na HCO_3 results in a solvent drag of water through the intercellular spaces. A small amount of transcellular movement (local osmosis) also occurs. As discussed previously, diffusion of NaCl with co-diffusion of water through the intercellular space might account for an appreciable degree of sodium reabsorption. This would likely result from an increased filtration fraction and therefore a greater colloid osmotic pressure of the fluid leaving the efferent arteriole generating a greater transcellular gradient for fluid movement.

In the distal nephron (Figure 3)[1] the intercellular pathway does not contribute very much to salt and water transport due to "tight junctions." In this part of the nephron large concentration and electrical gradients are developed secondary to active transport processes. Furthermore, in the most distal segments (i.e., the distal convoluted tubule and collecting duct) the permeability of the membrane itself can be altered by antidiuretic hormone (ADH).

Multiple sensory and effector mechanisms are present to precisely control salt and water homeostasis. The *volume sensors*

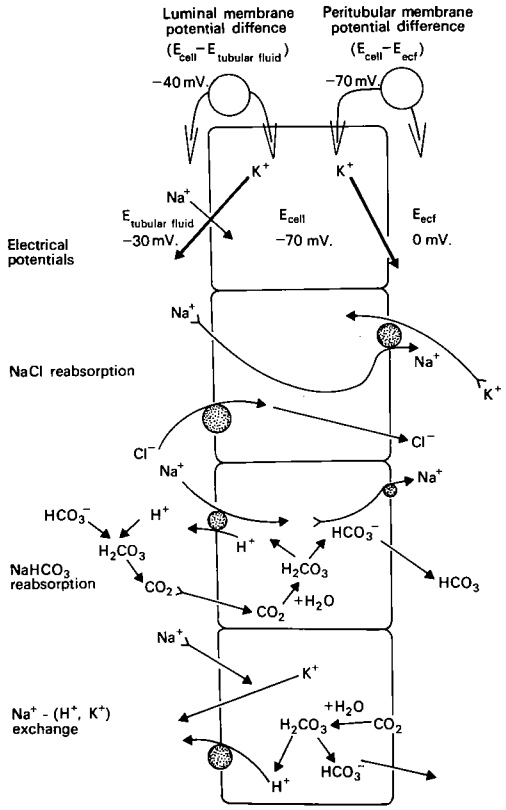

Figure 3

Mechanism of sodium chloride and bicarbonate reabsorption in the distal nephron.[1]

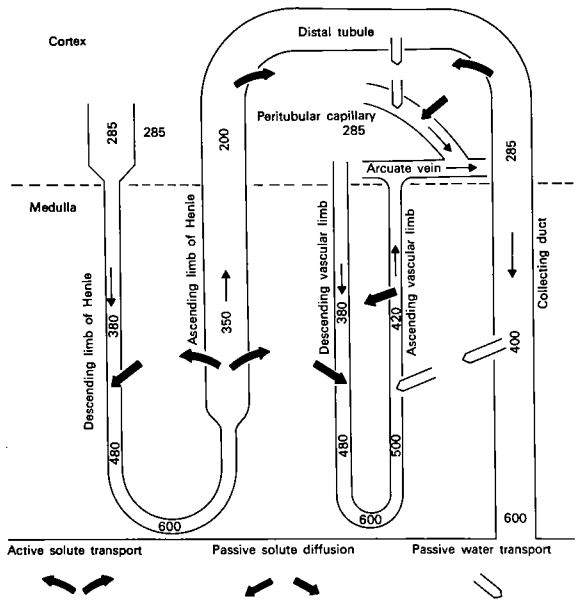

Figure 4

Solute and water transport during antidiuresis (free-water reabsorption). The numbers indicate osmolar concentration of tubular, vascular, and interstitial fluids. In this example a urine of 600 mOsm/l is being produced.[1]

are located in the heart, kidney, CNS, liver, and arterial tree. The *effectors* include GFR, Starling forces (both glomerular and peritubular mechanisms as described above), intrarenal blood flow alterations secondary to neural and hormonal influence, aldosterone, and atrial naturetic hormone.

Chronic renal failure, whether due to prerenal (decreased renal perfusion), renal (glomerulonephritis, acute interstitial nephritis, acute tubular necrosis, acute renal vascular disorder) or post renal (obstructive) factors produces a similar end stage kidney. **Acute renal failure, however, is the situation in which diagnostic tests are useful in order to define the precise mechanism and hence the appropriate treatment (Table I).** Many analytical equations have been described to differentiate between prerenal azotemia and acute oliguric renal failure. Spot urines are obtained to evaluate the sodium concentration. Although most patients with prerenal causes have a low urinary sodium concentration (< 20 mEq/L) overlap does occur. One of the better ways of differentiating the two is by fractional sodium excretion. This is a more direct measurement of tubular function. When a kidney is functioning properly >99 percent of filtered sodium should be reabsorbed and less than one percent of filtered sodium should appear in the urine. Since the fractional excretion of sodium (FEna) is simply the excreted load of sodium (Ena) divided by the filtered load of sodium (Fna) multiplied x 100 we have:

Fna = GFR*Pna = Ccr*Pna = [(Ucr*V)/Pcr] *Pna

and

Ena = Una*V

where: GFR = glomerular filtration rate (ml/min)
Pna = plasma sodium concentration (mg/ml)
Una = urine sodium concentration (mg/ml)
Ccr = creatinine clearance (ml/min)
Pcr = plasma creatinine concentration (mg/ml)
Ucr = urine creatinine concentration (mg/ml)
V = urine flow (ml/min)

therefore

FEna (%) = (Ena/Fna)* 100 = (Una*V) / ([(Ucr*V)/Pcr] *Pna)

or

FEna (%) = [(Una/Pna) / (Ucr/Pcr)] *100)

rearranging

$$\text{FEna (\%)} = \frac{[U/P]na \times 100}{[U/P]cr}$$

Example:

A 70-year-old male after a TURP has serum creatinine of 2.5 mg/dl. His Una = 20mEq/l,Pna = 130mEq/l and Ucr = 50mg/dl; are his kidneys functioning properly?

FEna (%) = ([Una/Pna] / [Ucr/Pcr]) * 100
= ([20/130] / [50/2.5]) * 100
= 0.77%

Since less than one percent of the filtered sodium appears in the urine, we can at least say that the kidneys appear to be handling sodium properly.

Defective Concentrating Mechanism

Under normal circumstances, urinary concentration is determined by processes occuring in the distal nephron. In the proximal tubule isosmotic reabsorption of salt and water occurs. It is in the loop of Henle that the separation of salt and

Differential Diagnosis of Prerenal, Intrarenal, and Postrenal Failure

MEASUREMENT	NORMAL	PRERENAL	INTRARENAL	POSTRENAL
Blood				
CVP, cm H_2O	5–8	Low to normal	Normal to elevated	Normal to elevated
BUN/creatinine ratio	10:1	>10:1	10:1	10:1+
Urine				
Sodium, mEq/L	15–40	<15	>40	>40
Potassium, mEq/L	15–40	Variable	Variable	Variable
Osmolality, mOsm/L	400–600	>450	<300	<300
Volume, ml	800–1200	Low	Variable	Variable; initially low
Urine/blood ratio				
Urea	20:1	>20:1	<10:1	<5:1
Osmolality	1.5–2.0	>1.5:1	<1.2:1	<1.0:1
Creatinine	20:1	>40:1	<20:1	<20:1
Fractional sodium excretion, %	Variable	<1.0	>1.0	>1.0
Urine—microscopic analysis	0–1 RBC 0–1 WBC Occasional hyaline cast No cellular casts	Occasional hyaline cast	Tubule epithelial casts RBCs, free heme or myoglobin	RBCs and WBCs Malignant cells Crystals

TABLE I

(from McDougal WS: Kidney and ureter, in Gillenwater JY, Grayhack JT, Howards SS, Duckett JW (eds): *Adult and Pediatric Urology*. Chicago, Yearbook Medical Publishers, 1987, chap 15, p 487.)

water transport allow for the formation of a medullary concentration gradient (Figure 4). In the water impermeable ascending portion of the loop, the active transport of chloride results in a hypertonic medullary interstitium. Since the descending portion of the loop is water permeable, the tonicity of fluid in the descending loop of Henle approximates that of the medullary interstitium. This results in an increase in the tonicity of fluid traversing the ascending segment of the loop. Again chloride reabsorption occurs against a concentration gradient this time adding to the already hypertonic medullary interstitium. Also, since the epithelia of the ascending portion of the loop is water impermeable, the term tonicity and osmolarity can be used interchangeably. **This process of continually being able to increase the osmolality (mosm/kg) of the medullary interstitium by selective segmental transport has been termed the counter current multiplier effect.** Urinary concentration is then determined by the permeability characteristics of the collecting duct epithelia. This is controlled by antidiuretic hormone (ADH) which is peptide hormone released by the supraoptic nucleus of the hypothalmus in response to serum osmolarity. An increase in serum osmolarity results in an increased release of ADH.

Urea follows water out of the loop in the descending limb. Since its permeability is controlled in the distal tubule also by ADH, it adds to the tonicity of the medullary interstitium and thereby increases the medullary concentration gradient.

The osmolar clearance can be determined by employing the generalized formula for clearance developed earlier:

$$Cosm = \frac{(Uosm \times V)}{Posm}$$

where:

Cosm = osmolar clearance (ml/min)
Uosm = urine osmolality (mosm/kg)
Posm = plasma osmolality (mosm/kg)
V = urine volume flow (ml/min)

Water excretion then can be either greater or less than that needed to maintain an isosmotic fluid. Water excretion greater than required to maintain a urine osmolality equal to that of plasma is termed free water clearance. This can be determined as follows:

$$Cwater = V - Cosm$$
$$= V - \frac{(Uosm \times V)}{Posm}$$

or,

$$Cwater = V\,[1 - (Uosm/Posm)]$$
$$= (ml/min)$$

The term Cwater is termed *free water clearance.* A negative free water clearance is denoted by $Tc(H_2O)$.

Acute Renal Failure (ARF)

There are three major types of injury that result in acute renal failure:

1) **Ischemic tubular injury**
   major trauma, septic shock, transfusion reactions, postoperative hypotension
2) **Nephrotoxic tubular injury**
   antibiotics: aminoglycosides, penicillin, tetracyclines, amphotericin
   x-ray contrast agents
   interstitial nephritis
3) **Vascular injury**
   arterial (thrombosis), embolism, stenosis
   venous (renal vein thrombosis)
   injury to the glomeruli and small blood vessels.

Overview

Characteristically both GFR and tubular transport functions are affected. The patient is anuric or oliguric with a daily urine

output no greater than 200 to 400 ml. Urine composition is variable but generally resembles glomerular filtrate with a relatively high sodium concentration (30 to 40 mEq/L). Potassium concentration in the urine is low with minimal acid excretion. Therefore the patient is *acidotic* with *hyperkalemia*. In the anuric/oliguric state the patient rapidly becomes *fluid overloaded*. In certain circumstances the reduction in GFR and tubular functions yields a normal or increased urine volume (> 400 ml/24 hours). This state is termed non-oliguric acute renal failure and can lead to salt and water depletion since the urine composition would essentially resemble an ultrafiltrate of plasma. Patients with non-oliguric renal failure however have a more benign course than oliguric renal failure. They have a decreased incidence of gastrointestinal bleeding, decreased need for dialysis and reduced mortality. **The mean duration of non-oliguric renal failure is seven days whereas the duration of oliguric renal failure averages approximately two weeks.**[2]

Molitoris and Schrier[2] have clearly differentiated *acute renal failure* from prerenal and postrenal *azotemia*. Acute renal failure is characterized by rapid deterioration over a period of *days*. It is furthermore associated with the accumulation of nitrogenous waste products (azotemia) *not* due to extrarenal factors. They defined prerenal azotemia as a diminished GFR resulting from inadequate perfusion of the kidneys, usually reversible within four *hours*. Postrenal azotemia results from mechanical or functional obstruction of the urinary tract and is at least partially reversible if the obstruction is removed.

Classically, acute renal failure results in a decreased GFR and RBF. However, the histologic changes are variable as is the potential for complete recovery. The mechanism of ARF is not precisely delineated. There are at least four mechanisms proposed to explain the observed changes: 1) tubular obstruction from cell debris, 2) alteration in renal vascular dynamics, 3) glomerular permeability barrier alterations, 4) back-leak of reabsorbed tubular fluid through defective epithelium. No single mechanism appears to completely explain acute renal failure.

A blood urea nitrogen (BUN) to serum creatinine ratio of greater than 10:1 suggests a prerenal cause of the ARF. This laboratory finding together with the clinical findings of decreased urine output, decreased systemic blood pressure, decreased right and left heart filling pressures and tachycardia make the diagnosis of a prerenal cause clear. Also, fully ten percent of all causes of ARF are due to bladder outlet obstruction. This postrenal azotemia is usually easily assessed by history, physical exam, and catheter passage. Table I reviews the differential parameters in prerenal and postrenal azotemia as well as acute renal failure.

Once prerenal and postrenal azotemia have been eliminated, the cause of ARF can be assessed. Urinalysis is the single most important test in the evaluation of acute renal failure. It is particularly useful in delineating the medical renal cause of ARF (e.g., nephrotoxic damage, interstitial nephritis, or glomerulonephritis). Glomerulonephritis is associated with red blood cell casts (white blood cell and granular casts are usually also present). Nephrotic range proteinuria (> 3 gm/24 hours) is also seen. Interstitial nephritis is usually associated with eosinophils in the urine (seen with a Wright stain of the urine). Red cell, white cell, and granular cell casts may also be present along with a mild proteinuria. Ischemic disorders as well as nephrotoxic disorders are associated with renal tubular cell casts, pigmented brown tubular casts and occasionally mild proteinuria.

As mentioned earlier, fractional excretion of filtered sodium is the best way to differentiate between prerenal azotemia and acute oliguric renal failure.

Treatment

Once ARF occurs, treatment is directed at minimizing or eliminating the complications of renal failure. The major complications that one might anticipate are metabolic, hematologic, neurologic, or infectious. The primary organic systems affected by these complications are cardiovascular and gastrointestinal.

Metabolic complications involve the retention of water, potassium, phosphorus, and magnesium. This can result in fluid overload with congestive heart failure and/or hypertension. Therapy is therefore restriction of fluid intake, elimination of potassium, magnesium, and phosphorus from enteral and/or parenteral fluids, as well as close monitoring of serum electrolytes.

Hematologic disorders include a normochromic normocytic anemia, thrombocytopenia, decreased platelet function, and a poorly characterized coagulopathy. Neurologic disorders usually manifest themselves as a decreased sensorium.

The two most common problems resulting in death from acute renal failure are gastrointestinal hemorrhage and infection. Platelet dysfunction as well as a generalized coagulopathy occurring during ARF are probably responsible for the 20 to 30 percent incidence of gastrointestinal bleeding. Clinically significant infections, found in up to 70 percent of cases of ARF, are probably related to altered immunologic factors. **Prophylactic antibiotics are not advocated.** Rather, treatment with organism specific antibiotics should be instituted when systemic infection occurs.

Dialysis is required in approximately 50 percent of patients with ARF. **Absolute indications for dialysis include: 1) volume overload, 2) refractory hyperkalemia, 3) pericarditis, 4) gastrointestinal hemorrhage, 5) central nervous system disorders and 6) serum creatinine > 10 to 15 mg/dl. Early and frequent (every 48 to 72 hours) dialysis is often key in maintaining homeostasis.**

Obstruction to Urine Flow

Obstruction to urine flow can occur at any point along the urinary tract. The pathophysiologic consequences are dependent upon whether the obstruction is unilateral or bilateral, partial or complete, intermittent or constant.

Complete bilateral ureteral obstruction or obstruction of a solitary kidney results in anuric renal failure. With complete ureteral occlusion there is progressive impairment of the more distal mechanisms of urinary concentration and acidification, followed by changes in glomerular filtration rate resulting from the persistant obstruction. Although not as well documented, partial obstruction yields similar alterations in renal function. However, the time course is longer and the change from baseline less marked.

Unilateral Ureteral Obstruction

Complete unilateral ureteral obstruction (UUO) results in a well described alteration of ureteral pressure, renal blood flow (RBF), glomerular filtration rate (GFR), and tubular fluid (salt and waste) reabsorption.[3]

Ureteral pressure proximal to the point of obstruction is a function of urine flow and compliance of the pelvo-ureteral conduit. It is limited by the decompressive effect of pelvocalyceal extravasation. Normal renal pelvic pressure has been measured as 11 mmHg thru a ureteral catheter[4,5] and 6.5 mmHg

with percutaneous puncture.[5] Ureteral pressures have been measured at 50 to 70 mmHg within minutes of UUO and can be raised to 100 mmHg by saline or mannitol diuresis. These pressures decrease to 50 percent of maximal levels within 24 hours after UUO and then gradually decline to near baseline pressure within eight weeks.[6]

Glomerular filtration rate precipitously decreases with UUO: 50 percent in four hours, 75 percent in 12 hours and by 95 percent within 24 hours. Maintenance of a modicum of GFR (approximately two percent at 48 hours) occurs secondary to continuing tubular transport processes as well as fluid backflow across the epithelium which occurs in the face of complete UUO.

A triphasic relationship exists between ipsilateral renal blood flow and ureteral pressure (Figure 5). During *Phase I*, which occurs in the first couple of hours after UUO, renal blood flow increases. Since ureteral pressure is increasing at this time, this suggests that the hydrostatic pressure at the glomerular capillary proximal to the efferent arteriole is increasing. This would occur with a *decrease in preglomerular* (afferent arteriolar) *resistance* which is the proposed mechanism based upon micropuncture pressure measurements.[7] This phase is blocked by pretreatment with indomethicin suggesting a dependence upon prostaglandins.

Phase II, begins approximately 1.5 to 2 hours after UUO. Renal blood flow is now decreasing while ureteral pressure continues to rise. This suggests an *increase in postglomerular* (efferent arteriolar) *resistance*. In *Phase III* (also termed the chronic phase, measured from 5 to 18 hours) both renal blood flow and ureteral pressure are decreasing suggesting an *increase in preglomerular* (afferent arteriolar) *resistance*. This is suggested by experimental work on obstruction of a single nephron.[8] A progressive decrease in renal blood flow occurs with time; 70 percent of control at 24 hours, 50 percent at 72 hours, 20 percent at two weeks and 12 percent at eight weeks.[3,6,9] The nephrons of the inner cortex and outer medulla appear to be less affected than those of the outer cortex.

Complete and partial UUO (acutely) produce marked alterations in tubular function. Urinary volume decreases, osmolality increases, and urinary sodium concentration is reduced. These effects are a direct result of a more complete reabsorption in the distal nephron. Additionally, both the proximal and distal tubule become permeable to low molecular weight solutes such as creatinine, mannitol, sucrose when ureteral pressure is increased.[10] After release of acute UUO a concentration defect is noted for several hours, probably related to medullary solute washout occurring during UUO.

Bilateral Ureteral Obstruction

Complete bilateral ureteral obstruction (BUO) results in anuria. It is only after release of the obstruction or with incomplete obstruction, that physiologic derangements have been measured.

It appears that the ability of the kidney to concentrate urine is affected first by BUO. After the release of obstruction, concentrating ability returns to a variable degree. All types of mechanisms of urinary acidification are affected by BUO (bicarbonate reabsorption, ammonia excretion, and titratable acidity). If BUO persists, tubular function, in particular proximal tubular transport processes, are next affected. Glomerular filtration is the last to be damaged by BUO. All patients studied with chronic BUO have decreased renal blood flow with increased filtration fractions. This suggests that RBF decreases to a greater extent than GFR.

A marked difference between UUO and BUO occurs with release of obstruction. In BUO, after release of obstruction a three to tenfold increase in urine flow is noted, even in states of hydropenia.[11] Normally, this diuresis is "physiologic" in that water and endogenous salts retained during the obstruction are excreted. To this extent the diuresis is self limited. Occasionally a "pathologic" diuresis ensues in which salt and water in excess of that retained during the obstruction is excreted. Proposed mechanisms for this "pathologic" diuresis have included 1) impaired sodium reabsorption, 2) impaired urine concentration ability, 3) solute diuresis due to retained endogenous (e.g., urea) or exogenous (e.g., glucose) substances and 4) presence of a naturetic factor.

Postobstructive diuresis does not appear to occur often after release of UUO. One recent report[12] found a pathologic diuresis to ensue in two patients after release of unilateral ureteral obstruction. The proposed mechanism was thought to be due to preservation of glomerular filtration of the obstructed kidney with distal tubular damage.

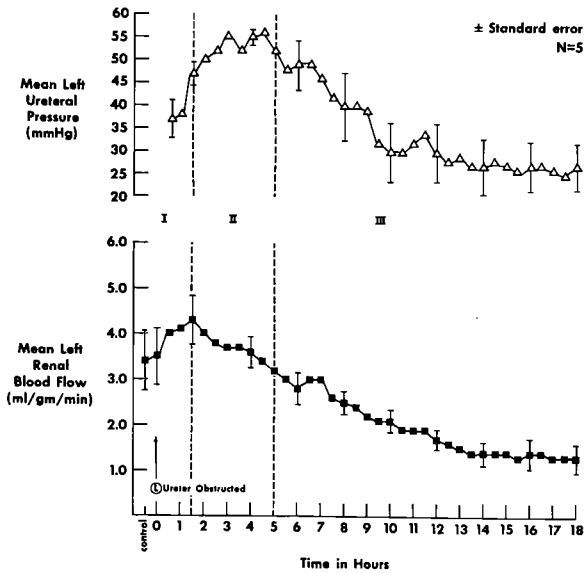

Figure 5

The triphasic relationship between ipsilateral renal blood flow and left ureteral pressure during 18 hours of left ureteral occlusion. The three phases are designated by Roman numerals and are divided by vertical dashed lines. In Phase I, the left renal blood flow and ureteral pressure increase together. In Phase II, the left renal blood flow begins to decline while the ureteral pressure remains elevated and, in fact, continues to rise. Phase III shows the left renal blood flow and ureteral pressure declining together.[3]

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Study Questions Volume VII Lesson 26

1. The major difference in hydrogen ion handling by the distal tubule as compared to the proximal tubule is that the distal tubule can:
   a) produce a greater quantity of titratable acid.
   b) secrete hydrogen ions across a large gradient.
   c) reabsorb large quantities of bicarbonate.
   d) produce a urine pH < 5.4 in distal RTA (Type 1).
   e) exchange Ca++ for H+.

2. All of the following are involved in salt and water homeostasis except:
   a) glomerular filtration rate.
   b) atrial naturetic factor.
   c) aldosterone.
   d) parathyroid hormone.
   e) antidiuretic hormone.

3. For a substance which is filtered but neither secreted or reabsorbed:
   a) GFR remains constant.
   b) filtered load equals excreted load.
   c) its glomerular clearance is equal to renal blood flow.
   d) its clearance cannot be determined.
   e) would be useful in measurement of renal plasma flow.

4. There is evidence that Angiotensin II causes an increase in efferent arteriolar resistance. Administration of an angiotensin converting enzyme inhibitor would:
   a) reduce proximal sodium absorption.
   b) increase GFR.
   c) reduce GFR.
   d) increase urinary volume.
   e) reduce medullary tonicity.

5. Significant unilateral renal artery stenosis leads to which changes when compared to the other side?
   a) reduced urinary volume, reduced sodium, higher osmolality
   b) reduced urinary volume, reduced sodium, lower osmolality
   c) reduced urinary volume, higher sodium, higher osmolality
   d) equal volume, lower sodium, higher osmolality
   e) equal volume, higher sodium, lower osmolality

6. A 70-year-old male exhibits a postobstructive phenomenon following catheterization for urinary retention. His urinary volume/24 hours is 5760 ml, his serum osmolality 300 mOsm, and urinary osmolality 150 mOsm. His osmolar clearance is:
   a) 1 ml/min.
   b) 2 ml/min.
   c) 3 ml/min.
   d) 4 ml/min.
   e) 1.5 ml/min.

7. Continuing with this patient, the calculated free water clearance would suggest that the underlying defect is:
   a) physiologic sodium diuresis.
   b) pathologic sodium diuresis.
   c) solute diuresis.
   d) inappropriate ADH syndrome.
   e) an abnormal renal concentrating mechanism.

8. To tell if this type of postobstructive diuresis is physiologic or pathologic you could administer:
   a) aldosterone.
   b) ADH.
   c) ACTH.
   d) a sodium load.
   e) ANF.

9. A patient postradical nephrectomy is oliguric with two consecutive urine outputs of < 30cc/hour. The urine values show a sodium of < 10 mEQ/liter, urinary osmolality of 650 mOsm/L a blood BUN/Cr ratio > 10:1. The most likely problem is:
   a) urinary obstruction.
   b) toxic renal injury.
   c) renal vein thrombosis.
   d) ATN.
   e) prerenal azotemia.

10. The best initial next step in this previous patient is:
    a) dialysis.
    b) vasopressors.
    c) a bolus infusion of crystalloid over 30 minutes.
    d) lasix 160 mg i.v.
    e) arteriogram.

Fill in answers on answer sheets provided.