Renal Physiology

Basics
2 kidneys
10-11 cm long
150g each
1 million nephrons/kidney
25% of cardiac output: RBF ~ 625ml/min/kidney
20% filtered: GFR ~ 125 ml/min (range 80-140ml/min)
Functions:

1. Excretion
   a. Metabolic endproducts
      Acid (organic or inorganic)
      Nitrogenous waste (urea)
      Nucleic acid turnover (uric acid/xanthine)
   b. Drugs/Toxins
      Filtration or secretion
      Often same disposal as acids

2. Maintenance of fluid volume
   Sodium and water regulation via RAA and in response to ADH

3. Maintenance of body fluid composition
   Na+, K+, Cl-, pH, Mg+, Ca+, phosphate, water

4. Hormonal regulation
   Renin
   Erythropoetin
   1,25 dihydrocholecalciferol

Glomerular filtration
Passive ultrafiltration of plasma across semipermeable glomerular membrane
Determinants of GFR:
   Glomerular permeability (Lp)
   Glomerular surface area (S)
   Pushing pressure (difference in hydrostatic pressure)
   Pulling pressure (difference in oncotic pressure)

   \[ \text{GFR} = \text{LpS} \times (\Delta \text{hydrostatic pressure} - \Delta \text{oncotic pressure}) \]

(i) Glomerular permeability
   Fenestrated negatively-charged (anionic) capillary endothelial cell layer with microvilli
   Size and charge selective
   Free filtration of water and neutral molecules less than 26 Angstroms
   Some filtration of neutral/positively-charged molecules up to 60A
   No filtration of highly-negative molecules (albumin) or >60A

(ii) Transglomerular hydraulic pressure
   Autoregulation of afferent and efferent arterioles acts to maintain glomerular blood pressure at a constant 50-60mmHg
   Proximal tubular hydrostatic pressure effectively zero, except when downstream obstruction
(iii) Oncotic pressure
   Constant at ~25mmHg
   In normal conditions plasma proteins not filtered so Bowman’s space
   oncotic pressure zero

**Autoregulation of glomerular filtration**
GFR preserved across wide range of blood pressure (80 – 180mmHg) due to
2 complimentary mechanisms:
   (i) Afferent arteriolar myogenic stretch
      Laplace’s law governs that a rise in pressure/increase in radius
      (volume) increases wall tension
      Myogenic tone of afferent arteriole ‘pushes’ back; conversely
      relaxes when pressure/radius, thereby regulating flow into
      glomerulus
   (ii) Tubuloglomerular feedback (juxtaglomerular apparatus)
      Macula densa cells in distal tubule monitor flow
      Increased pressure – increased GFP – increased tubular flow
      Leads to production of substances (endothelin, TXA2, AT2) from
      granular cells of juxtaglomerular apparatus, leading to
      constriction of afferent arteriole

NB. Granular cells of JGA secrete renin in predominantly in response to low
   tubular chloride rather than sodium. Sodium follows chloride, leading to a rise
   in ECF volume and blood pressure (see appendix)

**Assessment of glomerular filtration**
GFR cannot be measured directly – needs to be estimated. Methods comprise
Plasma creatinine and other markers, mathematical formulae, and plasma
 clearance
(i) **Plasma markers**
   Creatinine
      Constant production in individual
      10% secreted – therefore typically overestimates GFR
      Patient to patient variation based on age, sex, muscle mass and
      race. Low production (little old ladies) overestimates GFR; high
      intake (bodybuilders) underestimates GFR
      Mathematical formula used to ‘normalise values’:
      (i) Cockcroft & Gault (individuals with normal function)
      \[
      \text{CrCl} = \frac{[(140-\text{age}) \times (\text{IBW in kg})]}{[\text{PCR}(\text{mg/dL}) \times 72]} \times 0.85(\text{women})
      \]
            Does not describe a linear relationship – see graph
      overleaf. Also calculates creatinine clearance, not
      glomerular filtration rate
      (ii) MDRD (individuals with impaired renal function)
      Modification of diet in renal disease (1999). Derived as
      a screening tool to identify patients with renal disease
Renal physiology

\[
GFR = 186 \times (PCr)^{-1.154} \times (age)^{-0.203} \\
\times (0.742 \text{ if female}) \times (1.210 \text{ if African American})
\]

Calculates GFR not creatinine clearance. Underestimates eGFR at high values. Therefore a number of hospitals give eGFR of > 60ml/min rather than a figure for high filtration rates. Requires fudge factor for blacks – not calculated automatically. New formula CKD EPI set to supercede MDRD as better predictor across range of GFRs.

Steady reciprocal relationship between GFR (or creatinine clearance) and serum creatinine (see below).

NB. Increased production (rhabdomyolysis, supplements) underestimates GFR. Reduced production (cirrhosis, reduced muscle mass, elderly) overestimates GFR.

Urea
Freely filtered but up to 50% reabsorption by tubule

Cystatin C
Nucleic acid breakdown molecule. Constant production, unaffected by diet, not secreted, expensive.

\[(ii) \text{ Clearance}\]
Best way of estimating GFR is by measuring clearance of a substance from plasma.
Clearance = the amount of plasma that is completely cleared of a substance per unit time.
\[
Cl = \frac{[U] \times V}{[P]}
\]

To be accurate the substance must:
Achieve steady state in plasma
Excreted solely by kidney
Freely filtered
Not secreted, reabsorbed or metabolised by tubule.
Good example inulin, but impractical. Typically creatinine clearance, but secreted by proximal tubule, thus overestimates GFR by 10-20% at normal levels. Overestimation greater as renal function deteriorates – more creatinine secreted. Radiolabelled EDTA most accurate (DTPA can be used but slightly secreted). Typically single injection of $^{51}$Cr-EDTA, then measure blood levels at specified intervals 2-5 hours after injection to demonstrate decay curve.

<table>
<thead>
<tr>
<th>Tubular function</th>
<th>Major site of electrolyte and glucose reabsorption</th>
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</thead>
<tbody>
<tr>
<td>Proximal tubule</td>
<td>Secretion of organic acids/drugs and toxins</td>
</tr>
<tr>
<td>Loop of Henle</td>
<td>Generation of osmotic gradient for variable water reabsorption (countercurrent mechanism)</td>
</tr>
<tr>
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<td>Additional NaCl reabsorption</td>
</tr>
<tr>
<td>Distal tubule/</td>
<td>Hormone sensitive fine tuning</td>
</tr>
<tr>
<td>collecting duct</td>
<td>Aldosterone NaCl reabsorption K+ excretion</td>
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<td>ADH Water reabsorption H+ excretion dependent on acid base status</td>
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Proximal Tubule
Divided into three segments: S1/S2 concerned with reabsorption, S3 predominantly concerned with secretion

Reabsorption
- 15% Mg ++
- 65% Na+, K+, Ca++
- 80% Water, phosphate, HCO$_3^-$
- 100% Glucose **, amino acids
  * Na+ is the only solute actively reabsorbed via basolateral Na+/K+ pump. Remainder passively reabsorbed down concentration, osmotic (water) or electrochemical gradients
  ** Glucose absorption threshold 200mg/dL
Glutamine converted to ammonia throughout PCT

Secretion
Drugs and toxins via active organic ion (cation or anion) pumps
Liver often converts uncharged molecules to charged ones for excretion

Loop of Henle
Two purposes of LoH
Reabsorption of 25-30% Na+
Generation of vertical osmotic gradient
(i) Thin descending limb
Highly water permeable (aquaporin 1 channels)
Negligible solute transport
(ii) Thin ascending limb
Minimal water permeability
Passive NaCl and urea diffusion down concentration gradient
(iii) Medullary thick ascending limb
Water impermeable
25-30% Na+ reabsorption
Passive transport into cell (Na+K+Cl2 co transporter*)
Active transport out (basolateral Na-K ATPase)
*Targeted by loop diuretics
15% Ca++; 60% Mg++ reabsorption
Passive paracellular, driven by electrochemical gradient.
Dissipation of gradient by loop diuretics inhibits Ca++ and Mg++ absorption
10-20% HCO3- reabsorption
Minimal K+ reabsorption
Recycling of K+ in TALH crucial to generate electrochemical gradient
Countercurrent mechanism (300-1200 mosm/l)
NaCl and urea (50% from loop; 50% from collecting duct) make interstitium hypertonic. Water osmotically absorbed from TDLH = more concentrated urine at hairpin = more diffusion of solute = more diffusion of water, etc. Under ADH, urea and water diffuse into interstitium. Water rapidly reabsorbed by vasa recta (also aquaporins in cortical collecting duct) thereby preserving concentration gradient
Production of Tamm-Horsfall mucoprotein

Distal tubule
Divided into DCT and connecting tubule
Principle cells – aldosterone dependent secretion of K+/absorption of Na+
Intercalated cells – hormone-independent absorption of K+
Distal convoluted tubule:
5-10% Na+ absorption
Passive Na+K+Cl2CL2 co-transport, driven by basolateral Na+/K+ ATPase
Co-transporter inhibited by thiazide diuretics
Na+ absorption dependent on luminal [Na+]. – frusemide increases Na+ absorption by DCT (net Na+ loss however)
10-15% Ca+ reabsorption
Passive, independent of Na+ absorption
Driven by basolateral Na+/Ca+ pump (Ca+ out).
Reduced intracellular Na+ 2’ thiazides postulated as a reason for hypocalciuric effect but exact mechanism unknown
Connecting tubule:
Sodium absorption and potassium loss under influence of aldosterone
K+ secretion rate influenced by sodium delivery, and urine flow rate.
Tubular damage impairs potassium secretion (interstitial nephritis etc.)

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<thead>
<tr>
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<th>Proximal nephron</th>
<th>LOH</th>
<th>Distal nephron</th>
</tr>
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<tbody>
<tr>
<td>Na+ reabsorption*</td>
<td>67%</td>
<td>25%</td>
<td>8%</td>
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<tr>
<td>Water reabsorption*</td>
<td>65%</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Ca++ reabsorption</td>
<td>65%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Mg++ reabsorption</td>
<td>15%</td>
<td>60%</td>
<td>10%</td>
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<tr>
<td>* maximum values</td>
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Diuretics

**Loop diuretics**
inhibit Na+K+CL-CL- pump in TALH
Organic acids requiring secretion into PCT for effect. In renal failure more competition for secretion from accumulating toxins. Explains usage of large doses (250mg-1g) for effect in renal failure
Up to 25% increased sodium excretion
Loss of NaCL, water, K, Mg and Ca

**Thiazide diuretics**
inhibit NaCL co-transport in DCT
5-10% increased sodium excretion
Loss of NaCl, water. Loss of K by increasing sodium load to DCT.

**Potassium-sparing**
Spironolactone, amiloride, triamterine
5% increased sodium excretion
Spironolactone competes with aldosterone for intracellular mineralocorticoid receptor – inhibits Na-K ATPase
Amiloride/triamterine directly blocks sodium channels

**Acid-base balance**
pH 7.35 – 7.45
Tightly controlled by buffers
HCO3/CO2 principal buffer system
Lungs excrete CO2 rapidly

Kidney
Reclamation of all filtered HCO3
Excretion of H+ with generation of HCO3
Mechanisms:
glutamine into NH4 and HCO3 in PCT
H-ATPase in DCT excretes H+ and generates HCO3 (H+ buffered by PO4 or as free acid)

**Determining appropriateness of compensation**
**Renal physiology**

**Boston Rules**

**pH, pCO₂ & HCO₃**

*Metabolic Acidosis*
- Expected CO₂ = 1.5*HCO₃ + 8 (±/- 2) mmHg (divide by 7.6 for kPa)
- 0.2*HCO₃ + 1 kpa

*Respiratory Acidosis*
- Acute: 1mmol rise HCO₃ for every 10 mmHg increase in CO2
- Chronic: 4 for 10

*Respiratory Alkalosis*
- Acute: 2mmol fall in HCO₃ for every 10mmHg fall in CO2
- Chronic 5 for 10 (+/- 2) (max fall HCO₃ to 12-15)

*Metabolic Alkalosis*
- Expected CO₂ = 0.7 * HCO₃ + 20 (+/- 5)
- Expected CO₂ = 0.6 * BE + 40

**In mmHg**

(divide by 7.6 for kPa)

**Anion gap and Metabolic acidosis**

Na + K – Cl – HCO₃

Normal < 15-20*

High > 15-20*

* Depends on lab measurement. Newer ion-specific techniques more accurate. New classification HIGH = 12 or above

Blood electrochemically neutral. ‘Positive’ anion gap because more unmeasured anions than cations. Unmeasured cations magnesium, calcium and gamma globulins. Unmeasured anions sulphates, albumin and phosphate. Where a pure loss of bicarbonate occurs, chloride released to ‘bridge the gap’. In situations where new acids are produced electrochemical neutrality is maintained (salicylate plus H+), thus chloride remains unchanged

**High anion gap**
- Lactic acidosis
- Ketoacidosis
- Salicylate poisoning

**Normal anion gap**
- Gut losses (Vomiting, fistula, diarrhoea)
- Renal losses (RTA)
- Chloride ingestion/administration

**NB**
- Renal tubular acidosis (RTA)
  - Family of diseases characterized by failure of tubular H+ secretion and urinary acidification:
**Renal physiology**

Type 1  
distal failure of H+ secretion  
Diagnostic triad
  - Hyperchloraemic metabolic acidosis  
  - High urinary pH (>5.5)  
  - Low serum HCO3  
Associated low sodium, hyperaldosteronism, with low potassium (and low citrate)  
**Calcium phosphate stone disease** – Rx with sodium bicarbonate

Type 2  
Proximal failure of bicarbonate reabsorption  
Same triad as above, with low sodium and potassium  
Citrate normal - no stone disease  
Usually children - growth retardation and osteomalacia (Tiny Tim)

Type 3  
Actually type 1

Type 4  
Impaired distal H+ and K+ secretion. As above but with hyperkalaemia

**Metabolic alkalosis**  
Ingested alkali normally rapidly excreted by kidney. Persistent alkalosis usually due to impairment of HCO3 excretion from kidney, typically due to chloride deficiency. Replacement of Cl usually reverses alkalosis.  
Chloride responsive = Gut losses and diuretics (90% - often with paradoxical aciduria due to aldosterone action) - low urinary Cl  
Chloride unresponsive = mineralocorticoid excess leading to acid and potassium loss from tubule. Normal urinary Cl (>15 MEq/l)
Homeostasis and renin-angiotensin axis

NB. Control of renin release is rate-limiting step in RAA axis

Vasoconstrictors
- Angiotensin 2
- Vasopressin
- Noradrenaline
- Endothelin
- Platelet activating factor

Vasodilators
- Nitric oxide
- Carbon monoxide
- PGE2/PGI2
- Acetylcholine
- Serotonin
### ANP

**Angiotensin 2**
- Mediates effects via AT1 receptor – efferent constriction>> afferent vasoconstriction

**Endothelin**
- Highly potent vasoconstrictor released from endothelial cell membrane

**ANP**
- Atrial natriuretic peptide (Cogan 1990)
- Released in response to increased intravascular volume
- Effects:
  - Increased GFR (dilatation AE and constricts EA)
  - Inhibits juxtaglomerular apparatus (decreased renin, AT2 and aldosterone) = natriuresis
  - Inhibits vasopressin release and effects = diuresis
  - Prevents phase 3 (shutdown) in bilateral UO vs. unilateral UO by maintaining AE dilatation

### Glucocorticoids

**Nitric oxide**
- Synthesised by endothelial NOS (eNOS) and released from endothelium

**Carbon monoxide**
- Produced as a byproduct of heme metabolism by Heme oxygenase (HO). Exerts renoprotective effect vs ischaemia, especially in renal medulla

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### Calcium homeostasis

- Major source of cholecalciferol is dermal synthesis from cholesterol
- Other source from diet
- Initial 25a-hydroxylation in liver
- Second 1α-hydroxylation in kidney to form 1,25 dihydroxy-cholecalciferol (calcitriol)
- Acts on gut to increase calcium and phosphate reabsorption. Acts on bone to increased calcium resorption
- PTH – acts on kidney to stimulate calcium reabsorption and phosphate excretion
- Calcium in plasma bound to albumin (46%), complexed with citrate/phosphate (7%) or ionized/free (47%). Acidosis displaces Ca from albumin increasing free ionized calcium. Reverse in alkalosis. May not be identified as serum calcium estimation measures total calcium, not ionized forms.
Erythropoiesis
EPO produced by interstitial cells of kidney in response to low oxygen tension. HIF-1a and HIF-2a stabilised in hypoxic conditions to assemble apparatus for promoting transcription of EPO. Anaemia in renal failure simple secondary to loss of functioning interstitial cells.