Kidney Function:
What Can We Learn From Operations?

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Functions of the Kidney

- **Excretion** of waste products of metabolism and drugs
- **Regulation** of homeostasis of body water
  - homeostasis of ions in the body
  - blood volume and pressure
- **Endocrine (Hormonal) Functions**
  - Erythropoietin – stimulated red blood cell formation
  - Renin – controls blood pressure
  - Calcitriol (active form of vitamin D) – bone formation
NEPHRON – the Basic Functional Unit of the Kidney

One million nephrons per kidney in humans
Organization of Nephrons and Blood Vessels

Source: Vander’s Human Physiology. McGraw-Hill Higher Education
Nephron is a High Efficiency Processing Unit
Kidney is a High Efficiency Plant

- In humans both kidneys account for 0.5% of body weight
- But they receive 25% of cardiac output
- Cardiac output in a healthy adult is 4.9 liters/min
- So, 1.23 liters of blood passes through kidneys every minute
  \[(4.9 \times 0.25 = 1.23)\]
- Total volume of blood in a healthy adult is 6.2 liters
- It takes only 5 min for the whole blood in the body to pass through the kidneys (6.2 liters ÷ 1.23 liters/min = 5 min)
- No man-made machine or filter can reach such efficiency with the given size of the filtering unit – the kidney
# Renal Handling of Water, Electrolytes and Solutes

<table>
<thead>
<tr>
<th>Substance</th>
<th>Filtered</th>
<th>Excreted</th>
<th>Reabsorbed</th>
<th>% Filtered load reabs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>180</td>
<td>1.5</td>
<td>178.5</td>
<td>99.2</td>
</tr>
<tr>
<td>Na⁺</td>
<td>25,200</td>
<td>150</td>
<td>25,050</td>
<td>99.4</td>
</tr>
<tr>
<td>K⁺</td>
<td>720</td>
<td>100</td>
<td>620</td>
<td>86.1</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>540</td>
<td>10</td>
<td>530</td>
<td>98.2</td>
</tr>
</tbody>
</table>

L/day; mEq/day; mmol/day; g/day
Water Handling by the Human Kidney

Filtered Water ...................... 180 L/day
Reabsorbed Water .................. 178.5 L/day
Excreted Water ..................... 1.5 L/day
Fractional Reabsorption .......... 99.2%
Fractional Reabsorption of Water vs. Daily Urine Output

- Fractional Reabsorption (%)
- Daily Urine Output (Liters)

Δ 0.6%

99.2%
98.6%
Starling Forces and Glomerular Filtration Rate (GFR)

\[ \text{GFR} = P_{GC} \times K_f \times P_{BS} \]

\( K_f \) = Filtration Coefficient of glomerular bed

<table>
<thead>
<tr>
<th>Forces</th>
<th>mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favoring filtration:</td>
<td></td>
</tr>
<tr>
<td>Glomerular capillary blood pressure ( P_{GC} )</td>
<td>60</td>
</tr>
<tr>
<td>Opposing filtration:</td>
<td></td>
</tr>
<tr>
<td>Fluid pressure in Bowman’s space ( P_{BS} )</td>
<td>15</td>
</tr>
<tr>
<td>Osmotic force due to protein in plasma ( \pi_{GC} )</td>
<td>29</td>
</tr>
<tr>
<td>Net glomerular filtration pressure = ( P_{GC} - P_{BS} - \pi_{GC} )</td>
<td>16</td>
</tr>
</tbody>
</table>
Water Absorption Along the Nephron

Aquaporin-1

Aquaporins-2, 3 & 4

67% (120.6 liters)

15-17% (27 liters, 30.6 liters)
Stations Involved in Water Processing by Nephron

<table>
<thead>
<tr>
<th>Station Name</th>
<th>Type of Machines</th>
<th>Max. Capacity (% of total)</th>
<th>Regulated or not</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomerulus</td>
<td>Filtering units</td>
<td>Filters</td>
<td>Yes</td>
</tr>
<tr>
<td>Proximal Tubules (PT)</td>
<td>Aquaporin-1 (AQP1)</td>
<td>67 (reabsorption)</td>
<td>No</td>
</tr>
<tr>
<td>Descending Thin Limb (ASL)</td>
<td>Aquaporin-1 (AQP1)</td>
<td>15 (reabsorption)</td>
<td>No</td>
</tr>
<tr>
<td>Collecting Duct (CD) (includes all regions of CD)</td>
<td>Aquaporins-2, 3 and 4 (AQP2, AQP3, AQP4)</td>
<td>15 – 17 (reabsorption)</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Design of the Kidney as High Efficiency Plant

• **Unique architecture** and arrangement of nephrons and blood vessels – comparable to the design of a physical plant

• **Overall function** of the kidney is the sum of the functional capacity of each nephron

• **High input** of raw materials and high processing capacity

• **Stations:** Different segments of nephron

• **Machines:** Different aquaporins and ion transporters

• **Supply Chains** for raw materials: Blood vessels - arteries

• **Delivery lines** for the finished product - collecting ducts

• **Recycling mechanisms:** reabsorption through capillaries, which drain into veins
Principles and Metrics of Process Analysis (1/2)

• **Process Boundaries:** Glomerulus (entry point) to the end of the collecting duct (exit point)

• **Process Flow Diagram:** Already shown

• **Capacity of Each Station in the Process:** Already discussed

• **Process Capacity:** Summation of the capacities of individual nephrons (1 million in each kidney) – much higher than what is needed to handle water even at times of increased demand.

• **Capacity Utilization:** Overall capacity utilization under normal conditions is about 0.3
Principles and Metrics of Process Analysis (2/2)

- **Throughout Rate (Flow Rate):**
  
  At glomerulus 125 ml/min (180 liters filtrate per day)
  
  Flow rate decreases dramatically towards the end to about 1 ml/min (1.5 ml urine / 24 hours)

- **Flow Time:** Some what difficult to determine

- **Cycle Time:** For whole blood in the body (6.2 liters) it is about 5 min

- **Process Time:** For 1 liter of blood is 0.8 min (5 ÷ 6.2 = 0.8)

- **Idle Time:** For actively processing nephrons there is no idle time.
  
  For the nephrons at rest (70% under normal conditions) there is idle time
Tubulo-glomerular Feedback Mechanism (TGF)
Insights into Process Flow from Gene Knockout Mice

• Gene knockout technology pioneered by Prof. Mario Capecchi

• Provides extremely useful tools into biological processes and how they operate and how they can be deranged

• Gene coding for a particular protein is suppressed at early embryonic stage

• Technology has advanced to the extent that we can knockout the target gene from specific cells (or stations) in the kidney

• Using this technology specific aquaporins have been knocked out in the kidneys of mice

• When specific aquaporins are deleted, each deletion produced different types of defects at the individual stations, or at the whole animal level.
Knocking of Aquaporin-1, the Machine at Station # 1

Knocking out Aquaporin-1 had significant effect both at station # 1 and at the whole kidney level.
Knocking out Aquaporin-4 had significant effect at station #4 only with modest effect at the whole kidney level.
Future Perspectives

Application of principles of operation will provide:

• Better understanding of normal kidney function

• Newer insights into the disease processes

• Rationalization of drug development

• Help identify effect of drug interactions based on process flow

• Open a new interdisciplinary field to advance knowledge
Look, I finished it in 6 months and the box says 3 to 5 yrs.
Magnitude of Kidney Diseases in the USA

• Chronic Kidney Disease (CKD) – 26 million / 90,000 die each year

• Leading cause of CKD – diabetes mellitus and hypertension (account for 2/3rds of all CKD)

• Number of ESRD (End-Stage Renal Disease) patients in the USA
  500,000 – Medicare cost in 2006 was $23 billion
  By 2020 - ESRD patients 1.2 m, Medicare cost $53.6 billion

• Acute Kidney Failure – an ICU condition – affects 5% of all hospitalized patients with a mortality rate of > 50%

• One million Americans suffer from kidney stones. Most of them are aged between 20 to 40 years

• Anemia associated with kidney failure - $12 billion annual market – pharma giants fighting neck to neck, often in the courts
Central Control of Water Processing by the Kidney

- \( \uparrow \text{Na}^+ \) and H\(_2\)O loss due to diarrhea
  - \( \downarrow \) Plasma volume
  - \( \downarrow \) Venous pressure
  - \( \downarrow \) Venous return
  - \( \downarrow \) Atrial pressure
  - \( \downarrow \) Ventricular end-diastolic volume
  - \( \downarrow \) Stroke volume
  - \( \downarrow \) Cardiac output
  - \( \downarrow \) Arterial blood pressure
  - \( \uparrow \) Activity of renal sympathetic nerves
    - Reflexes mediated by venous, atrial, and arterial baroreceptors

Kidneys
- \( \uparrow \) Constriction of afferent renal arterioles
  - \( \downarrow \) Net glomerular filtration pressure
    - \( \downarrow \) GFR
  - \( \downarrow \) Na\(^+\) and H\(_2\)O excreted

Reflexes mediated by cardiovascular baroreceptors
- Posterior pituitary
  - \( \uparrow \) Vasopressin secretion
  - \( \uparrow \) Plasma vasopressin

Collecting ducts
- \( \uparrow \) Tubular permeability to H\(_2\)O
  - \( \uparrow \) H\(_2\)O reabsorption
  - \( \downarrow \) H\(_2\)O excretion

(see Fig. 14-18)
Sensors Involved in Central Control Mechanisms

- ↓ Plasma volume
- ↑ Plasma osmolarity
- Dry mouth, throat
- Metering of water intake by GI tract
- Baroreceptors
- Osmoreceptors
- ↑ Angiotensin II
- Thirst

Graphs A and B:

- Graph A: Plasma [ADH] vs. Plasma osmolality (mOsm/kg H₂O)
- Graph B: Maximum % Change in blood volume or pressure
Clinical Applications of Process Flow in Nephron

Derangement of process flow in a number of clinical conditions

**Diabetes Insipidus:** (Water Diabetes)

An umbrella group of disorders – excess water loss
Inherited (rare) or acquired (common) forms
Acquired DI is often due to defective functions of one or more stations along the nephron (often station # 4)

**Loop Diuretics:** (e.g., Furosemide of Lasix)

Inhibit the function station # 5
Results in reduced water absorption at station # 4
Loss of water in the urine