Regulation of GFR

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Renal Disease

- Acute vs Chronic

- Chronic renal disease is rising in the U.S. and in other parts of the world.

- In the year 2000, in which we have the most reliable available estimates, nearly 400,000 people had to be dialyzed or transplanted due to chronic renal disease.

- That same year, approximately 20 million adults in the U.S. had chronic renal disease that was not yet diagnosed (11.7% of the population).

- The most common risk factors for developing chronic renal disease are diabetes, chronic hypertension, cardiovascular disease, family history of chronic renal disease, and age greater than 60.
Why the Interest in GFR?

- The GFR is the sum of the filtration rates of all the nephrons total.

- The GFR is the best measure of overall renal function.

- Estimating the GFR (along with other tests, such as measuring protein in the urine) can find chronic renal disease in its earliest stages when it is more amenable to therapies.
Chronic renal insufficiency (CRI) is the preferred term for patients with mild-to-moderate renal impairment, whose GFR falls in the range of 30-60 ml/min.

Chronic renal failure (CRF) is usually reserved to describe patients whose GFR is between 15 and 30 ml/min.

End-stage renal disease (ESRD), usually associated with signs and symptoms of uremia, is the term reserved for patients whose GFR has declined to levels of less than 10 to 15 ml/min.
Nephrons

- Two major nephron types are superficial and juxtamedullary.

- Note the common structures they share, as well as the differences.
Renal Corpuscle

- The afferent arteriole brings arterial blood into Bowman’s capsule and is the beginning of the formation of the glomerular capillaries.

- The glomerular capillaries exit Bowman’s capsule as the efferent arteriole.
Peritubular Capillaries and Vasa Recta

- In both superficial and juxtamedullary nephrons, the efferent arterioles form the peritubular capillaries upon exiting Bowman’s capsule.

- In juxtamedullary nephrons only, the peritubular capillary network forms vascular loops called vasa recta that extend down into the inner medulla along with the ascending loop of Henle.
Reabsorption and secretion refer to the direction of transport of substances. Different substances are transported in different ways.
As you will see, formation of urine begins by ultrafiltration by the glomerular capillaries.

The ultrafiltrate is handled in various ways by the different segments of the nephron.

The fluid that eventually reaches the major calyces and enters the ureters to be transported to the bladder for voiding as urine reflects how the plasma was changed by the nephrons.
The glomerular capillary membrane consists of:

1. Fenestrated endothelium
2. Gomerular basement membrane
3. Interdigitated foot processes (podocytes)
4. Slit diaphragms span the podocytes
Ultrafiltration

- Top electron micrograph is the view from Bowman’s space

- The bottom view is from the inside of a glomerular capillary (note fenestrations, which are approximately 30 nM in diameter)
Size / Charge Restrictions To Filtration

- Molecules with a molecular radius of < 18 angstroms generally freely filtered.

- Molecules with a molecular radius between 18 and 36 angstroms filtered to varying degrees, depending on net charge.

- Molecules with a molecular radius of > 36 angstroms generally not filtered to any great extent.
Normal Protein Excretion

- Normal subjects excrete approximately 40 to 80 mg of total protein a day into the urine (upper range of normal being about 150 mg total in 24 h).

- Albumin usually accounts for less than 20 mg of the total daily urinary excretion of protein, while Tamm-Horsfall protein amounts to about 30 to 50 mg day.

- The gold standard for assessing daily protein excretion in the urine is by measuring protein in a 24 h urine collection.
As some of you may know, early detection of small amounts of albumin in the urine is important in identifying diabetic and hypertensive patients who are at high risk for progressing to end stage renal disease (ESRD).

The dipstick is relatively insensitive to detecting early increases in glomerular filtration of albumin (not positive until 24 h excretion > 300 to 500 mg). Advanced glomerular disease can already be present when albumin excretion is this high.

Direct, sensitive measurement of urinary albumin should be done in diabetic / hypertensive patients on a consistent basis (using specialized assays), to detect these early small increases in albumin excretion into the urine (persistent albumin excretion between 30 and 300 mg/day is microalbuminuria, and is indicative of onset of diabetic nephropathy).
The structure of the slit diaphragm has become a major area of interest in terms of the proteinuria seen in many chronic renal diseases.

The slit diaphragm proteins composed of the nephrin and podocin families are now known to be adversely affected in people with Type II diabetes, and may be responsible for the proteinuria seen in those patients that marks the onset of renal disease.
Important Concepts

- Typical GFR in healthy young males (< 30 yrs) is about 115 - 125 ml/min per 1.73 m², and around 90 - 110 ml/min per 1.73 m² for healthy young females.

- (BSA (m²) = 0.20247 x Height(m)0.725 x Weight(kg)0.425

- If a male is filtering 125 ml of plasma per minute, this amounts to a total filtration of 180 L / day (1440 min in a day, times 125 ml/min, equals 180 L in 24 h).

- We produce an average of only 1.5 L of urine each day. Therefore, the vast majority of filtered plasma is being reabsorbed downstream in the nephron, long before it reaches the collecting system to shunt it off to the bladder.
Filtration Fraction

- Remember, the amount of plasma actually FILTERED through the capillaries and into Bowman’s space each minute is around 100 - 125 ml in healthy adults.

- Therefore, it is important to realize the only about 15 to 20 percent of all plasma passing through the glomerular capillaries is filtered.

- This is termed the filtration fraction (Filtration fraction = GFR (ml/min) / Total renal plasma flow (ml/min))
When we talk about the GFR in medicine, we are referring to the TOTAL amount of plasma being filtered across the glomerular capillaries by ALL the nephrons in both kidneys (if you have two), each minute.

Another concept we will discuss later is the “single nephron glomerular filtration rate” (SNGFR). This concept will arise when we talk about disease and loss of functional nephrons.
Dynamics of Ultrafiltration

- Starling’s forces apply to glomerular capillaries, just as they do to other capillaries.

- There are two forces opposing filtration, and two forces promoting filtration,

- Subtracting the pressure exerted by the opposing forces from the pressures promoting filtration gives you the NET ultrafiltration pressure.
Some Observations about Ultrafiltration

- The net ultrafiltration pressure ($P_{UF}$) is about twice as high in glomerular capillaries as other capillaries.

- In addition, the rate of capillary filtration is around 100 x greater in glomerular capillaries than non-glomerular capillaries (180 L/day vs 2-3 L/day).

- This is because the intrinsic permeability and capillary surface area ($K_f$) of glomerular capillaries is much higher than it is in non-glomerular capillaries.
Altering the GFR by changing $P_{UF}$

- How does CONSTRICTING the AFFERENT arteriole affect GFR and RBF?

- How does CONSTRICTING the EFFERENT arteriole affect GFR and RBF?

- How does DILATING the EFFERENT arteriole affect GFR and RBF?

- How does DILATING the AFFERENT arteriole affect GFR and RBF?
Endogenous Factors Regulating GFR via Changes in $P_{UF}$

- Increases in sympathetic outflow from CNS constricts afferent arterioles - effect on $P_{UF}$ and therefore GFR?

- Decreases in sympathetic tone from CNS dilates afferent arterioles - effect on $P_{UF}$ and therefore GFR?
Other Factors Affecting Afferent and Efferent Arteriole Status

- Increases in Angiotensin II during hypovolemic states results in a net increase efferent arteriole constriction - effect on $P_{UF}$ and therefore GFR?

- Intracellular prostaglandins, nitric oxide, and bradykin dilate the afferent arterioles - effect on $P_{UF}$ and therefore GFR if cell levels rise?
Autoregulation of GFR

- Normally, GFR does not change dramatically from minute to minute in healthy individuals, due to autoregulation.

- This is important. Otherwise, normal or abnormal increases or decreases in arterial pressure would result in abnormal increases or decreases in glomerular capillary $P_{uf}$, and subsequently an abnormal change in the GFR.
Myogenic Mechanism

- An inherent property of smooth muscle is to contract in response to a stimulus that forces it to expand (a homeostatic mechanism).

- Therefore, when increases in arterial pressure force the afferent arterioles to expand, they will subsequently contract to some extent after this forced expansion, returning the $P_{uf}$ - and subsequently the GFR - back towards normal (although not COMPLETELY back).
Tubuloglomerular Feedback

- The ascending loop of Henle of a given nephron loops back up between its own afferent and efferent arteriole (the vascular pole).

- Specialized macula densa cells line the ascending loop of Henle as it passes through the vascular pole, putting these cells into close proximity with the smooth muscle cells of the afferent arteriole.
One theory of TGF is that the macula densa cells sense changes in the delivery and reabsorption of NaCl to the Na⁺/K⁺/2Cl⁻ transporters on the macula densa cells of the thick ascending limb.

If a reduction in renal perfusion decreases the net $P_{uf}$ and therefore the GFR, less NaCl will be delivered to these cells.

A signal will then be sent from the macula densa cells to the smooth muscle cells of the afferent arterioles, causing them to dilate in this case.
The Juxtaglomerular Apparatus Also Initiates Renin Release

- A decrease in NaCl delivery to macula densa cells in the thick ascending limb will also provoke a signal to the granular cells (also called juxtaglomerular cells) to stimulate renin release. This renin will then activate the renin-angiotensin-aldosterone cascade.

- As you will see later when we discuss renal sodium handling, increased sympathetic input to the afferent arterioles and decreased perfusion pressure that causes vasoconstriction of afferent arterioles (both of which occur when arterial pressure declines) will directly enhance renin release from granular cells that are present in the afferent arterioles.
Studies performed in animals and humans on tubuloglomerular feedback suggest that it is a major player in terms of maintaining the normal GFR.

However, another very important reason for maintaining a normal GFR is to maintain distal flow in the nephron at a relatively constant rate.

The reason for this (as you will see later) is that reabsorption of Na\(^+\) and other compounds at distal sites in the nephron could be overwhelmed if tubular flow rates were significantly elevated.
Clearance

- You can measure the clearance of substances through the kidneys, liver or other organs, for various reasons. Measuring the clearance incorporates the dimensions of time and volume.

- Measuring the clearance of a substance through the kidneys represents the volume of plasma from which all the substance of interest has been removed and excreted in the urine per unit time.
Example of Clearance

If a substance is present in urine at a concentration of 1 mg/ml, and urine flow rate is 1 ml/minute, then the excretion rate of this substance is:

\[ U_x \times V = 1 \text{ mg/ml} \times 1\text{ml/minute} = 1 \text{ mg/minute} \]

Where \( U_x \) is the concentration of substance X in the urine (usually measured in mg/ml) and \( V \) is the urine flow rate (usually measured in ml/min).
If the amount of this substance X is also measured in plasma and found to be present at a concentration of **1 mg/dl**, then the plasma clearance can be calculated:

\[ C_x = \frac{U_x \times V}{P_x} = \frac{1 \text{ mg/minute}}{1 \text{ mg/dl} (.01 \text{ mg/ml})} = 100 \text{ ml/min} \]

**What does a renal ‘clearance’ of 100 ml/min mean??**
Ideal Characteristics of a Clearance Compound Used to Estimate GFR

- Substance only enters the nephron via glomerular filtration (NO secretion of the substance occurs).
- Once filtered in, the substance is NOT reabsorbed anywhere in the nephron.
- If the above two requirements are met, it means the amount filtered in each day is equal to the amount excreted into the urine each day.
Renal Clearance of Inulin

- Inulin is freely filtered through glomerular capillaries (concentration in ultrafiltrate will be same as concentration in plasma).

- Inulin is not secreted, and not reabsorbed after filtration.

- Therefore, the amount filtered each minute \((P_i \times GFR)\) will be equal to the amount excreted each minute.
Measuring Clearance of Other Compounds to get GFR

- $^{51}$CrEDTA
- $^{125}$I-iothalamate
- $^{99}$Tc-DTPA
24 h Creatinine Clearance to Measure GFR

- Creatinine is produced by metabolism of creatine in muscle, and is present in the plasma in relatively constant amounts.

- Creatinine is freely filtered at the glomerulus, but unfortunately around 15% of the creatinine appearing in the urine was SECRETED into the nephron.

- Creatinine is not reabsorbed once it enters the nephron.
Drawbacks to Creatinine Clearance

- In normal individuals, around 15% of creatinine appearing in the urine was secreted, thus overestimating true GFR. This is offset, however, by an overestimation of plasma creatinine when assayed by the alkalaine picrate colorimetric assay.

- In patients who already have significant renal impairment (true GFR is less than 60 ml/min), amount of creatinine being secreted is much greater (up to 35% of the urinary creatinine was secreted, resulting in a significant OVERestimation of the true GFR.

- 24 h urine collections are often incomplete (non-compliance by patients), which results in an UNDERestimation of the true GFR.

- Role of cimetidine?
Short Urine Collection using Cimetidine

- A loading dose of 1200 to 2000 mg cimetidine is given (with doses adjusted for renal insufficiency) is given on day 1.

- This is followed by 400 mg/day for 3 to 4 days.

- A 1.5-hour urine collection is then obtained. This has been shown to be about as accurate as a 24-hour collection.
The Cockcroft-Gault equation estimates the creatinine clearance:

**Cockcroft-Gault equation (1976)**

\[
\frac{(140 - \text{age}) \times \text{LBW} \times F}{72 \times S_{cr}}
\]

- F = 1 for male; F = 0.85 for female
- LBW = Lean weight (kg)
- \(S_{cr}\) = serum creatinine
Estimating GFR with Equations

- Levey and colleagues (2000) Simplified 4-variable MDRD study formula for estimating GFR (mL/min/1.73 m²):

\[
GFR = 186.3 \times (S_{cr})^{-1.154} \times (\text{age, yr})^{-0.203} \times 1.212 \\
(\text{if patient is black}) \times 0.742 \ (\text{if patient is female})
\]

\(S_{cr} = \text{serum creatinine}\)
Limitations of Prediction
Equations

- MDRD equation has been consistently shown to underestimate the true GFR when estimating GFR in patients who in fact do NOT have kidney disease (Rule et al., 2004, Annals of Internal Medicine, 141(12):929-938).

- MDRD studies have not been validated in children, the elderly, pregnant women, so these equations may not measure GFR as accurately in these groups.

- Perhaps biggest problem of using these equations is standardizing the test for measuring serum creatinine. Read the PDF file on blackboard regarding the position statement from the National Kidney Foundation for testing for chronic kidney disease.
Plasma Creatinine and GFR

- Plasma creatinines and GFR are inversely related.

- If GFR falls by 50% for some reason, filtered load of creatinine (and therefore, urinary excretion) will initially be reduced.

- The decline in filtered load will cause plasma levels to increase. Eventually, filtered load and urinary excretion of creatinine will return to normal when plasma creatinine levels rise enough:

  Initially: \(0.01 \text{ mg/ml} \times 100 \text{ ml/min} = 1.0 \text{ mg/min}\)

  After GFR decline: \(0.01 \text{ mg/ml} \times 50 \text{ ml/min} = 0.5 \text{ mg/min}\)

  After new equilibrium: \(0.02 \text{ mg/ml} \times 50 \text{ ml/min} = 1.0 \text{ mg/min}\)
Creatinine Secretion

- Early DECLINES in GFR (up to 40% to 50% of initial GFR) do NOT cause large INCREASES in plasma creatinine.

- Excessive creatinine secretion by surviving nephrons enables the patient to keep increases in plasma creatinine minimal until disease is advanced.
Notice that the GFR can fall up to 50% before the plasma creatinine \((P_{CR})\) starts to rise into the ‘red flag’ area.

After this, the rise in plasma creatinine for any given drop in GFR is more linear.

Because the rise in \(P_{CR}\) is fairly linear to a given decline in GFR in people with known, advanced renal disease \((GFR < 30 \text{ ml/min})\), \(P_{CR}\) can be used to assess therapeutic effectiveness in these patients.
Cystatin C

- Cystatin C is a glycosylated protein produced at a constant rate by all nucleated body cells.

- Measuring the clearance of cystatin C is now being evaluated as an improved method of measuring GFR in children.