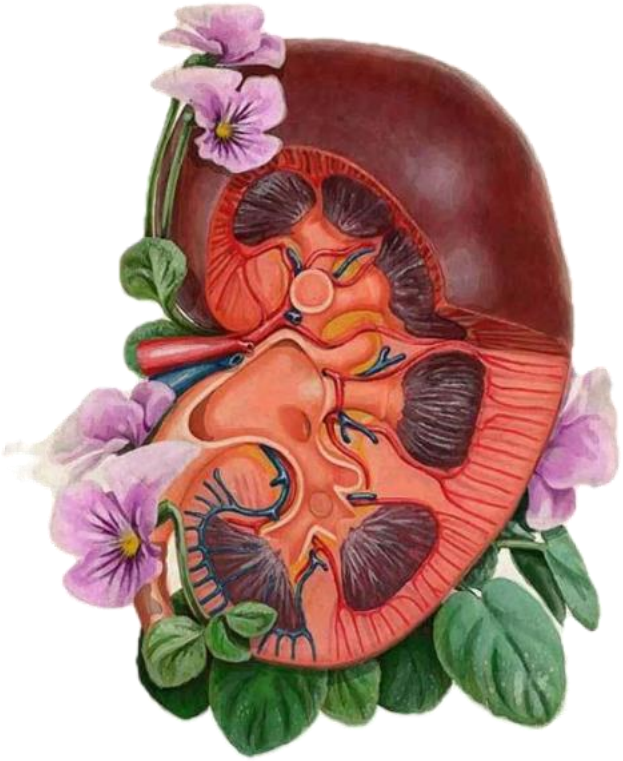
UGS Physiology Sheet 4 - V1



Doctor: Yanal A Shafagoj. MD, PhD

Written by: Sara Alzoubi and Mas Nafoukh

Note: In this lecture, the doctor went over the slides and figures covering topics from Sheets 1–3, so some overlap may be noticed; however, previously discussed topics were referenced to their relevant sheet number, and newly discussed topics were noted where relevant. Best of luck, and don't worry about the number of pages.

Autoregulation of GFR

We do not prefer an increased GFR because it may lead to the loss of important substances such as amino acids and glucose.

On the other hand, a decreased GFR is also harmful, as the kidneys will not be able to adequately excrete toxic substances such as urea and creatinine.

The hydrostatic pressure in the glomerular capillaries is about 60 mmHg, and it originates from the pressure generated by the left ventricle through the aorta.

If the aortic pressure is around 100 mmHg, the glomerular capillary pressure is maintained at approximately 60 mmHg.

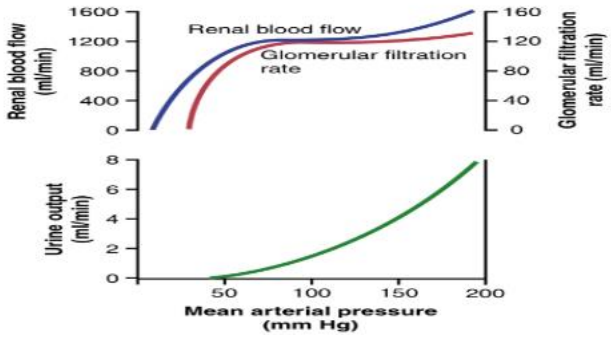
If the aortic pressure drops to about 80 mmHg, the glomerular capillary pressure may fall significantly (e.g., toward 40 mmHg).

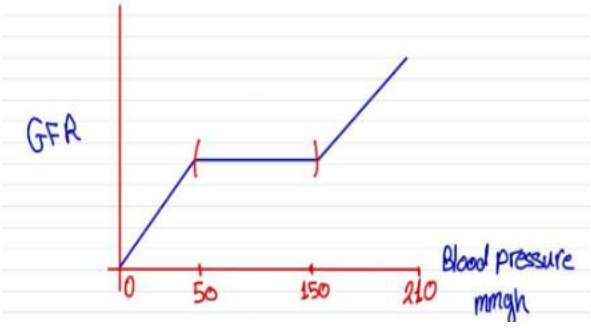
When the glomerular hydrostatic pressure decreases to around 40–50 mmHg, the GFR approaches zero, because the filtration pressure is no longer sufficient to overcome the opposing forces (oncotic pressure and Bowman's capsule pressure).

So, this does not happen. During the day, arterial blood pressure normally fluctuates between 120 and 80 mmHg, but this fluctuation does not significantly affect the GFR, which remains relatively constant.The GFR is maintained steady over a range of arterial blood pressure between 50 and 150 mmHg.

This indicates that there is a separation (uncoupling) between arterial blood pressure (ABP) and GFR, meaning there is no direct linear relationship between them.

This phenomenon is called **autoregulation** of GFR, and it is mediated by angiotensin II, which increases or decreases in response to changes in arterial blood pressure to maintain a normal GFR. *(further on this topic at the end of the lecture)*





Hypoxia and Erythropoiesis

When there is hypoxia (decreased oxygen delivery), such as at high altitude, the kidneys sense the low oxygen level and increase the secretion of erythropoietin (EPO).

EPO stimulates the bone marrow to increase erythrocyte (RBC) production.

As a result:

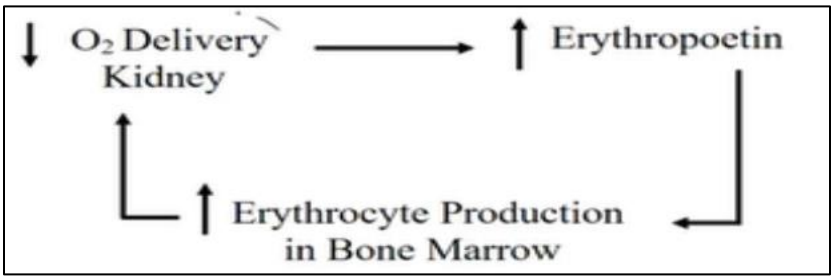
- Hematocrit (Hct) may increase to > 60%
- Blood volume may increase to > 6 L
- RBC count may reach around 6 million/μL

This becomes a problem because it increases blood viscosity, leading to increased total peripheral resistance (TPR).

According to the equation:

$$P_a = Q \times TPR$$

An increase in TPR leads to an increase in arterial pressure (Pa).



Afferent vs Efferent arteriolar effects on GFR *(sheet 3, page 3)*

Afferent arteriolar constriction (e.g., NSAIDs that inhibit prostaglandins which normally cause vasodilation) lead to decreased blood flow entering the glomerular capillaries, resulting in a decrease in GFR.

In contrast, efferent arteriolar constriction increases resistance to outflow from the glomerular capillaries, which increases the glomerular hydrostatic pressure, and therefore leads to an increase in GFR.

Remember from the respiratory system: Kidneys are reconditioning organs i.e. Receive too much blood. RBF=(20-25% of Q) → This makes the A-V oxygen difference small (1.4 ml/dl).

Renal blood flow = 1200 ml/min, Renal Plasma Flow = ~650 cc / min total ,Renal Cortex = ~500 cc / min , Outer Medulla = ~125 cc / min , Inner Medulla = ~25 cc / min

(cc stands for cubic centimeter (cm^3) = mL)

Renal plasma flow is approximately 650 mL/min. Most of it (500) goes to the renal cortex, which contains the glomeruli, proximal and distal tubules, and cortical collecting ducts. Therefore, the cortex appears red in color due to its rich blood supply. Because of this high blood flow, solutes in the cortical interstitium are continuously "washed out," so the osmolarity of both interstitial fluid and capillaries remains nearly constant at around 300 mOsm, without significant concentration changes.

In contrast, the renal medulla receives a much lower blood supply via the vasa recta (~25 mL/min). Due to this low blood flow, solutes such as Na^+ and Cl^- are not washed out effectively, allowing accumulation and the formation of a hyperconcentrated medulla. However, a hyperconcentrated cortex does not occur because high blood flow prevents solute accumulation.

Clearance of different substances

Clearances of Different Substances

Substance	Clearance (ml/min)
inulin	125
PAH	585
glucose	0
sodium	0.9
urea	70

Clearance of inulin (C_{in}) = GFR

if Cx < Cin : indicates reabsorption of x

if Cx > Cin : indicates secretion of x

Clearance creatinine (C_{creat}) ~ 140 (used to estimate GFR)

Clearance of PAH (C_{PAH}) ~ effective renal plasma flow

Clearance of Na^+:

Clearance of Na = $\frac{[UNa]}{[PNa]} \times V\,urine$ $\qquad\qquad$ $\frac{[UNa]}{[PNa]} = \frac{100}{140} < 1$

In this case, the clearance of Na^+ is about 0.9, which is less than 1. This indicates that sodium is mostly reabsorbed by the kidneys.

Clearance of urea:

Urea clearance is about 70 mL/min, while the expected value would be around 125 mL/min (≈ GFR) because it is considered a waste product.

Since it is lower than GFR, this indicates that urea is partially reabsorbed.

Very important notes

From clearance, we can determine the renal handling of a substance.

For example, inulin clearance is about 125 mL/min, which is equal to the GFR.

This means that inulin is freely filtered at the glomerulus and is neither reabsorbed nor secreted by the renal tubules. *Can you explain renal handling of PAH (585ml/min)???*

Chronic renal failure and clearance:

In **end-stage renal failure (ESRF)**, the GFR is very low, usually < 5 mL/min.

In this condition, creatinine clearance becomes unreliable for accurately estimating GFR. This is because creatinine is not only filtered, but also secreted by the renal tubules, and this tubular secretion becomes relatively more significant when GFR is very low. As a result, creatinine clearance tends to overestimate the true GFR. (most creatinine in urine comes from *secretion* and not filtration in ESRF)

Therefore, in advanced renal failure, many of the standard clearance equations cannot accurately reflect kidney function.

This is why no single method works in all situations ("not one size fits all"), and different markers or approaches are used depending on the clinical condition.

Renal Handling of Water and Solutes *(sheet 2)*

Filtration load Na = concentration of Na in plasma × GFR

= 142 ×180 L /day = 25,560 mmol/day

25,410 will be reabsorption SO just 150 mmol/day excreted

Filtration load of Glucose = concentration of Glucose in plasma × GFR

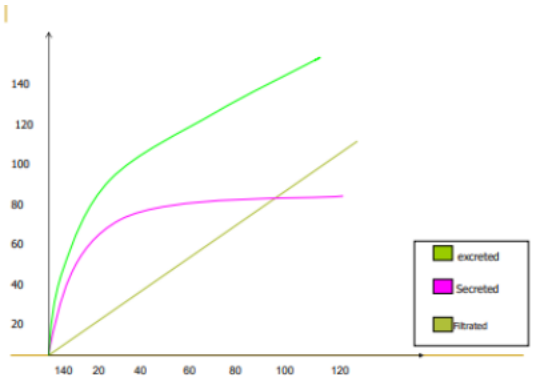
= 1g/L ×180 L/day =180g/day

All of glucose (180) will be reabsorbed, so NO excretion (0).

Renal Handling of Water and Solutes

	Filtration	Reabsorption	Excretion
Water (liters/day)	180	178.5	1.5
Sodium (mmol/day)	25,560	25,410	150
Glucose (gm/day)	180	180	0
Creatinine (gm/day)	1.8	0	1.8

PHA CURVE for Filtration and Secretion *(sheet 2 , page 10)*



PHA is used to measure RPF because it is almost completely cleared from the plasma by filtration and tubular secretion.

1. **Filtration of PAH** is freely filtered at the glomerulus. Filtration is a passive process, as plasma PAH concentration increases, filtered PAH increases linearly. There is no transport maximum (Tm) for filtration. About 20% of PAH entering the kidney is removed by filtration**.**
2. **Secretion of PAH** is actively secreted in the proximal tubule. Secretion increases with plasma PAH concentration until the transporters become saturated. Maximum secretory rate (Tm) for PAH ≈ 80 mg/min. After reaching Tm: Secretion plateaus, No further increase despite rising plasma PAH concentration
3. **PAH excretion** = PAH filtration + PAH secretion

Before secretory Tm, excretion increases rapidly; after Tm, secretion is constant and excretion increases only due to filtration.

Glomerular Filtration Rate *(sheet 3, page 2)*

GFR = 125 ml/min = 180 liters/day

- Plasma volume is filtered 60 times per day.
- Glomerular filtrate composition is about the same as plasma, except for large proteins
- Filtration fraction (GFR / Renal Plasma Flow) = 0.2 (i.e. 20% of plasma is filtered)

The entire plasma volume is only about 3 liters, whereas the GFR is about 180 L/ day. Thus, the entire plasma can be filtered and processed about **60** times each day.

Determinants of Glomerular Filtration Rate *(sheet 3, page 5)*

Recall that:

$$GFR = DF \times K_f = 10*12.5 = 125ml/min$$

Normal Values:

- GFR = 125 ml/min
- Net Filt. Pressure = 10 mmHg (DF)
- K_f= 12.5 ml/min per mmHg (for both kidneys), or 4.2 ml/min per mmHg/ **100gm** (per 1 kidney, assuming their total weight is 250gm)
- **K_f** = hydraulic conductivity x surface area.
  - Cannot be measured directly
  - Normally, it is not highly variable.

Filtration through the systemic capillaries (whole-body) is about 20 L/day. (Remember 20L filtered out, 17 L reabsorbed back and the remaining 3L are removed through the lymphatic system. In contrast, the kidneys alone filter about 180 L/day. This is due to both a high net filtration pressure (driving force) and the exceptionally high permeability of the glomerular capillaries (which is 400 times greater than in many other tissues).

Diseases that can reduce K_f and consequently GFR

Chronic hypertension, obesity, diabetes mellitus (which causes microangiopathy in the renal vasculature, increasing the thickness of the basement membrane. This in turn alters glomerular filtration), glomerulonephritis (mostly autoimmune).

Effect of reducing GFR by 50 % on serum creatinine concentration and creatinine excretion rate *(NEW TOPIC)*

Normally, muscles produce creatinine that moves to the blood and then to the kidney for excretion in urine (recall that creatinine is freely filtered and is not reabsorbed or secreted, so its excretion rate equals its filtration rate).

If 2 mg is produced by muscles per day (or about 1.5 mg/day in women), The same amount is transferred to the kidney by blood and then excreted by the kidney. This relationship can be expressed as: $GFR \times [Pcr] = \dot{V} \times [Ucr]$, meaning that how much is excreted is equal to how much is provided for excretion, which is the filtered load.

When the GFR is reduced by 50% in the case of donating one kidney for example, now we have only 1M nephron instead of 2M. However, muscles will continue to produce 2 mg/day, so we need to excrete this amount despite the reduced GFR.

Therefore, the kidneys will transiently filter and excrete only half as much creatinine, causing the accumulation of creatinine in the body fluids and raising plasma concentration. The plasma concentration of creatinine will continue to rise until the filtered load of creatinine and creatinine excretion returns to normal, and a balance between creatinine production and creatinine excretion is reestablished. This response will occur when the plasma creatinine level increases to approximately **twice** normal.

$$GFR \times [P_{cr}] = \dot{V} \times [U_{cr}]$$

$$\frac{GFR}{2} \quad 2\,[P_{cr}] = \dot{V} \times [U_{cr}]$$

$[P_{cr}]$ = creatinine plasma concentration, $[U_{cr}]$ = creatinine urine concentartion, $\dot{V}$ = urine output

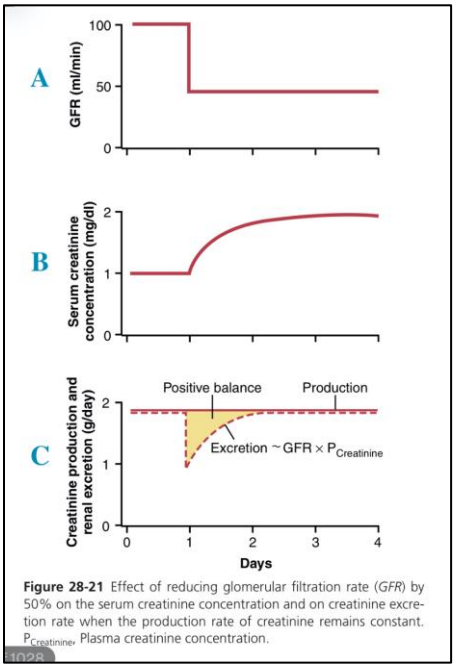


Figure 28-21 Effect of reducing glomerular filtration rate (*GFR*) by 50% on the serum creatinine concentration and on creatinine excretion rate when the production rate of creatinine remains constant. $P_{Creatinine}$, Plasma creatinine concentration.

Figure A: reduced GFR by 50%.

Figure B: increased creatinine in plasma twice normal.

Figure C: creatinine excretion initially decreases due to reduced GFR but then it gradually increases as the plasma creatinine increases and goes back to normal.

In-lecture MCQ: If GFR suddenly decreases by 50%, WHICH OF THE FOLLOWING IS FALSE?

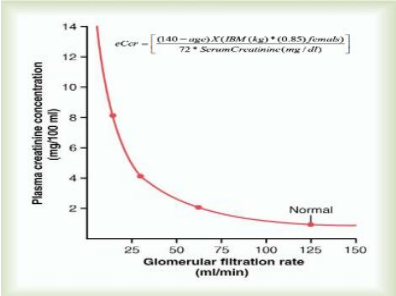
A) Creatinine execration per day remains the same
B) Creatinine production by muscle per day remains the same
C) Filter load of creatinine remains the same
D) Plasma concentration of creatinine remains the same.

Plasma creatinine can be used to estimate changes in GFR.

Decreasing GFR by 50% will increase plasma creatinine level to **twice** normal if creatinine production by the body remains constant. The relation becomes *most evident* when GFR is reduced by 50%, at which point plasma creatinine begins to increase *steeply*.

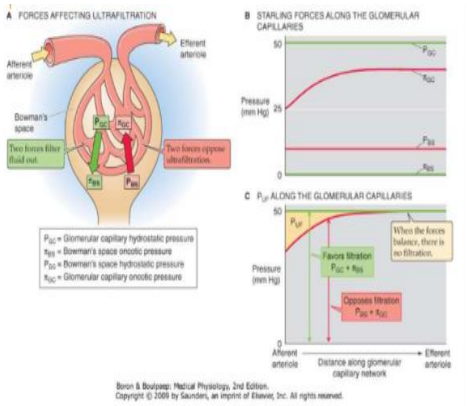
Thus, when GFR decreases from 125 to 100 ml/min, plasma creatinine does not rise significantly; however, when GFR is reduced by half, plasma creatinine increases sharply.

This indicates that the relationship between GFR and plasma creatinine is not linear (i.e., not a straight-line relationship).



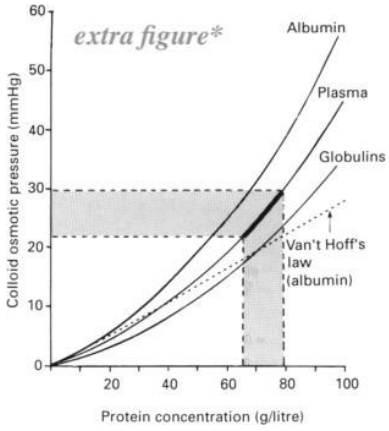
Starling forces along glomerular capillary *(sheet 3, page2)*

In the **systemic circulation**, the colloid osmotic pressure (π) remains relatively constant along the capillary and is approximately the same at both the arterial and venous ends. However, in the **glomerular capillaries**, this is not the case. As plasma is filtered, protein concentration in the blood increases along the length of the capillary, so the colloid osmotic pressure (π) is higher at the efferent end compared to the afferent arteriole. (about 20% increase).



Albumin concentration and colloid osmotic pressure (π)

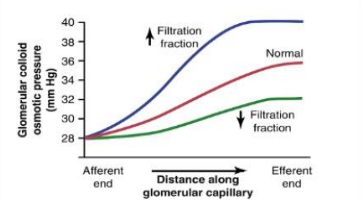
The relationship between albumin concentration and colloid osmotic pressure is *non-linear* and exhibits a shift to the left (more than expected). An increase in albumin concentration produces a greater rise in colloid osmotic pressure compared to an equivalent increase in globulin. This shift is attributable to underlying phenomena.



	[plasma]	MW	π
Albumin	4.5 mg (x1.5 globulin)	70,000	22 (4x higher than globulin)
Globulin	3mg	140,000 (2x albumin)	6

Albumin is more concentrated and has a lower molecular weight than globulin, so it forms more particles in plasma. Because colloid osmotic pressure depends on particle number, albumin generates a much higher oncotic pressure (~22 mmHg vs ~6 mmHg), making its effect about four times greater.

Effect of Filtration Fraction on Glomerular Colloid Osmotic Pressure (πGC)



Normally, πGC at the afferent end is about 28 mmHg and increases to about 36 mmHg at the efferent end due to filtration of water, which concentrates plasma proteins along the capillary.

If the filtration fraction **increases above normal** (>20%), more fluid is filtered out of the plasma, leading to a greater rise in protein concentration in the remaining blood. As a result, πGC at the efferent end increases further, reaching approximately 40 mmHg.

Conversely, if the **filtration fraction is reduced**, less fluid is filtered and protein concentration rises less along the capillary. Therefore, πGC at the efferent end increases less than normal and may remain closer to the afferent value (around 28 mmHg), reflecting lower protein concentration in the plasma.

Pressure and Vascular Resistances in the Circulation of Normal Kidney (sheet 3, page 10)

Afferent arteriole:

- Pressure at the beginning ≈ 85 mmHg (similar to interlobular artery pressure)
- Pressure at the end ≈ 60 mmHg
- ΔP = 85 − 60 = 25 mmHg
  → Afferent resistance ≈ 25% of total renal vascular resistance

	Pressure mmHg		% Total Vascular R
	Beginning	End	
Renal Artery	100	100	≈ 0
Interlobar, arcuate and interlolbular arteries	100	85	15
Afferent	85	60	25
Glomerular capillaries	60	59	1 only 1mmHg which means little resistance
Efferent	59	18	43 resistance mainly resides her
Peritubular Capillaries	18	8	10
Interlobar, arcuate and interlolbular veins	8	4	4
Renal vein	4	≈4	0

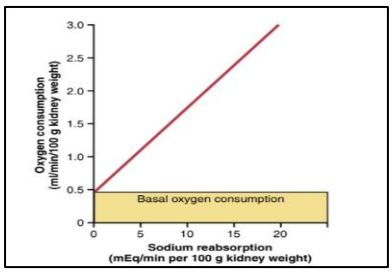
Efferent arteriole:

- Pressure at the beginning ≈ 59 mmHg (similar to pressure at the end of interlobular arteries)
- Pressure at the end ≈ 18 mmHg
- ΔP = 59 − 18 ≈ 41 mmHg
  → Efferent resistance ≈ 40–45% of total renal vascular resistance

Together, afferent and efferent arterioles account for roughly 65–70% of total intrarenal vascular resistance, with the efferent arteriole contributing to the larger portion.

Renal oxygen Consumption and sodium reabsorption

Sodium reabsorption is directly related to the oxygen consumption in the kidney; higher [Na+] leads to higher O2 consumption. Recall that about 90% of O2 consumption by the kidney is to reabsorb sodium. Accordingly, people with kidney failure should receive a lowered sodium diet.



Autoregulation – clinical senario

During surgery, blood pressure is often deliberately lowered to improve surgical field visibility and reduce bleeding. As a result, renal perfusion pressure decreases, which leads to a reduction in GFR.

To monitor kidney function in this setting, a Foley catheter is used to measure urine output continuously. This allows real-time assessment of renal perfusion and function.

Normally, urine output is expected to be about 60 mL/hour; if it drops below approximately 20 mL/hour, this raises concern for acute kidney injury.

Conceptually, flow is determined by the pressure gradient (Flow = ΔP / R). However, in physiological conditions, renal blood flow is often maintained relatively constant over a range of blood pressures due to autoregulation.

Therefore, when blood pressure changes, the kidney adjusts vascular resistance (mainly at the afferent arteriole) to stabilize blood flow. This means that instead of flow changing proportionally with pressure, resistance changes in response to blood pressure to maintain relatively stable perfusion.

Importance of Autoregulation

Arterial Pressure	GFR	Reabsorption	Urine Volume
1- Poor Autoregulation + no change in tubular reabsorption			
100	125	124	1.0
120	150	124	26.0 = 37.4 L/day!
2- Good Autoregulation + no change in tubular reabsorption			
120	130	124	6.0
3 Good Autoregulation+adaptive increase in tubular reabsorption			
120	130	128.8	1.2

Case 1: Poor autoregulation

If arterial pressure increases to about 120 mmHg, GFR rises to approximately 150 mL\min. However, tubular reabsorption does not change.

This results in a urine output of about 26 mL/min (≈ 37 L/day), which is potentially lethal within a short time due to severe water loss and dehydration.

Case 2: Good autoregulation
With intact autoregulation, when arterial pressure increases, the kidney maintains GFR relatively constant (as shown in figure; page 2). However, urine output still increases.

This phenomenon is called ***pressure diuresis*** or ***pressure natriuresis*.**

For example:

At normal arterial pressure: ~1 mL out of 125 mL filtered → ~1.5 L/day urine

At higher arterial pressure: ~2.5 mL out of 125 mL filtered → ~4 L/day urine

If blood pressure is high, the kidney responds by increasing urine output to help lower blood pressure through ***pressure diuresis*** or ***pressure natriuresis***. This means that with increased arterial pressure, more sodium is excreted along with water and other fluids, reducing blood volume and thereby contributing to a reduction in blood pressure.

CORRECTIONS:

Page 11: 150 ***L/day*** -> 150 ***mL\min***