Physiology Sheets

Number 2

Doctor Yanal

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Correction

Introduction

In this sheet, we discuss renal blood flow, renal plasma flow, filtration load and clearance. Application by calculations is also discussed.

Definitions; *Renal blood flow (RBF)*

Renal blood flow is defined as the volume of blood entering both kidneys per unit of time. RBF averages 1.25 L/minute.

Renal plasma flow (RPF), on the other hand, is the volume of plasma entering both kidneys per unit of time. 55% of the blood is plasma, and 45% is hematocrit (RPF will be considered to be 650 ml/min throughout this sheet). Accordingly, by measuring RPF, we can know RBF, as we will see later.

<u>Measuring RPF (next sections are complementary)</u>

To measure RPF, we use a material, which we will call X, which, after entering the kidneys with the plasma, should be completely excreted in urine. This means that 0% of X should return in the renal vein. In other words, plasma that enters the kidneys will be completely cleared from X.

To put in an example, let us assume that we are using X, with concentration of 1 mg/ml in plasma, to measure RPF. 650 ml of plasma enter the kidneys in the minute; and so do 650 mg of X, which are excreted in urine after that (650 mg/min of X is excreted). This means that:

The amount of X excreted in urine equals the amount of X provided for excretion

This is consistent with the concept of mass conservation. To calculate these quantities, remember that:

*Amount excreted (mg/min) = urine output $\dot{V}$ (1 ml/min) * concentration in urine (mg/ml)*

To apply these concepts on our example:

- X concentration in plasma is 1 mg/ml; RPF is 650 ml/min
- Accordingly, amount of X entering the kidneys (provided for excretion) is 650 mg/ml (RPF * concentration of X in plasma)
- Amount excreted = provided for excretion; equals 650 mg/ml; so it works as renal plasma flow marker

We can use that to calculate RPF. Since the amount of X excreted in urine equals the amount of X provided for excretion; then:

$$Provided = excreted$$

$$RPF * concentration\ of\ X\ in\ plasma = \dot{V} * concentration\ of\ X\ in\ urine$$

$$RPF = \dot{V} * \frac{concentration\ of\ X\ in\ urine}{concentration\ of\ X\ in\ plasma}$$

Conforming to example:

$$650\ ml/min * 1\ mg/ml = 1\ ml/min * 650\ mg/ml$$

$$650\ mg/ml = 650\ mg/ml$$

Renal Clearance

Renal clearance is defined as the volume of plasma completely cleared of a substance per unit time. Clearance is volume per unit of time.

To build on our example, 650 ml of plasma enter the kidneys per minute carrying 650 mg of X. X is completely removed, and so these 650 ml of plasma get cleared from X. So, X clearance is 650 ml/min.

00:00 – 10:00

When a material has a concentration of 1 mg/ml in plasma, for example, and a concentration of 0 mg/ml in urine, then its clearance equals 0 ml/min. So, X clearance can act as a measure of RPF if plasma entering the kidney is completely cleared from it. Clearance of partially removed materials, however, does not represent RPF.

Although there is no substance in our body with such properties, a special substance (paraaminohippuric acid or PAH) is almost completely excreted. And since all the blood entering the kidneys will be cleared of PAH, the clearance of PAH is the RPF. PAH can be injected to be used to measure RPF. In our example, since the plasma entering the kidneys will be completely cleared from X, then clearance in the input-output equation can be substituted for RPF, as follows:

$$RPF * \text{concentration of X in plasma} = \dot{V} * \text{concentration of X in urine}$$

$$\text{Clearance} * \text{concentration of X in plasma} = \dot{V} * \text{concentration of X in urine}$$

$$\text{Clearance} = \dot{V} * \frac{\text{concentration of X in urine}}{\text{concentration of X in plasma}}$$

And in our example:

$$\text{Clearance of X} = 1\ ml/min * \frac{650\ mg/ml}{1\ mg/ml} = 650\ ml/min$$

Glomerular Filtration and Peritubular Secretion

Filtration is the first step of urine formation. Large amounts of plasma diffuse passively into Bowman's capsule, driven by pressure gradient. Consequently, the composition of the filtrate is essentially similar to that of the plasma; the concentrations of small molecules (having small molecular weight; like ions and glucose; not proteins) is the same as their concentrations in the plasma. However, glomerular capillaries, like most other capillaries are not permeable to proteins. Also, calcium and fatty acids are not freely filtered since they are partially bound to plasma proteins. (Ultra-filtrate = plasma – proteins.)

Glomerular Filtration Rate (GFR)

GFR is the volume of plasma filtered from the glomerular capillaries to Bowman's capsules per unit time. The glomerular filtration rate is 125 ml/min (one fifth of RPF; filtration fraction is 1/5). Generally, substances with molecular weight higher than 70,000 kDa are not filtered.

Filterability of materials ranges from 1 to 0:

- Freely-filtered: concentration in Bowman's capsule = concentration in plasma.
- Partially-filtered: concentration in Bowman's capsule < concentration in plasma.
- Not filtered: concentration in Bowman's capsule = 0; concentration in plasma is more than 0.

  Remember that there is no material whose concentration in Bowman's capsule is more than its concentration in plasma (no filterability more than 1); because filtration is a passive process.

Water Filtration and Reabsorption

Of the 650 ml reaching Bowman's capsule per minute, 125 ml get filtered, and 525 ml proceed to the efferent arteriole. In the peritubular capillaries, 124 ml of water get reabsorbed. According to that, 649 ml of water reach the renal vein. Water extraction is 1/650, which will make up the urine (urine output is 1 ml/min). This 1 ml/min contains waste products, foreign chemicals and metabolites (like creatinine).

Glomerular Filtration Rate and Filtered Load

As we said, glomerular filtration rate (GFR) is the volume of plasma filtered from the glomerular capillaries to Bowman's capsules per unit time. The glomerular filtration rate is 125 ml/min.

If a substance is freely filtered in the kidneys (i.e., its filterability is 1), then the filtration rate of that substance is referred to as the filtered load. In our example, it is the amount of X that is being filtered per minute, and equals 125 mg/ml. and is calculated as follow:

Filtered load (amount per unit time (mg/min)) = GFR x plasma concentration

Peritubular Secretion

Secretion is an active process, in which materials are moved against their chemical gradient. In keeping with that, secretion needs carriers, which are limited by their T_{max}.

Continuing on our example, 525 mg/min of X reach the peritubular capillaries. Here, secretion happens to eliminate 525 mg/min; since X is completely excreted.

By now, we can say:

- 650 mg/min of X is eliminated in urine; with urine concentration of 650 mg/ml (650-fold the concentration in plasma); *X is completely removed*
- 125mg of these are eliminated by filtration and are not reabsorbed (passively); *X is freely filtered*
- 525 mg of these are eliminated by secretion from the peritubular capillaries (actively); *X is completely secreted*

These properties of X make it suitable to be used to measure RPF.

10:00 – 20:00

To sum up:

- To measure RPF, use a substance which is 100% excreted. By that, clearance of such substance can estimate RPF.
- Conservation of mass; everything in urine comes from plasma; so:

*RPF * concentration of X in plasma = $\dot{V}$ * concentration of X in urine*

1. RPF is what we are looking for;
2. Concentration in plasma is obtained from any tissue, since all capillaries have the same concentration;

3. Renal outflow and concentration in urine are easily investigated by collecting urine and analyzing its composition

- Secretion is limited by T_{max}; T_{max} should be known for the used material; more than T_{max} in peritubular capillaries decreases clearance (T_{max} of PAH transporters is 8 mg/min. Therefore, to measure the RPF accurately, PAH reaching the peritubular tubules per minute must not exceed 8 mg; (the doctor said it is 8 , while in the summary it is 80!))

<u>Measuring GFR</u>

Remember that GFR is the volume of plasma filtered from the glomerular capillaries to Bowman's capsules per unit time.

Inulin is a small exogenous substance (5,000 kDa; less than 70,000 KDa) that is freely filtered (i.e., its filterability is 1).

What special about this substance, making it suitable for measuring GFR, is that it is neither absorbed nor secreted. In other words, Inulin that is filtered is that excreted. Thus, the clearance of inulin is, in fact, the GFR.

GFR x concentration in plasma or in Bowman's capsule (same concentration) = $\dot{V}$ x concentration in urine

If the concentration of inulin in plasma is 1 mg/ml, and GFR is 125 ml/min, then excretion of inulin is 125 mg/ml, and its concentration in urine is 125 mg/ml (125-fold its concentration in plasma.)

Note that PAH used to measure RPF is completely excreted as it passes through the kidneys. However, most of the excreted amount is secreted and not filtered. Thus, the clearance of PAH is the RPF rather than the GFR.

Inulin, like PAH, is an exogenous substance. This makes it only suitable to measure GFR for research, and not routine clinical, purposes. So, creatinine is used instead.

20:00 – 30:00

Charts*; applications* (charts in appendix; follow the numbers)

1. (Plasma concentration – filtrated) chart of PAH
2. (Plasma concentration – excreted) chart of PAH
3. (Plasma concentration – secreted) chart of PAH
4. (Plasma concentration – clearance) chart of PAH
5. (Plasma concentration – filtrated) chart of inulin
6. (Plasma concentration – clearance) chart of inulin

Discussion

PAH is readily filtered, so at low levels, 20% of it is filtered. Filtration is a passive process. Secretion of PAH is limited to T_{max} of its carriers. So, at lower concentrations, secretion makes 80% of excreted PAH (actually, for any completely excreted substance, 20% of excreted are filtered, and the rest 80% are secreted). At high levels, not all the quantity of PAH is excreted, and some particles return to the vein.

According to that, increased PAH concentration in plasma means increased its levels in the peritubular capillaries, which, after passing the T_{max}, lowers the extraction ratio. PAH clearance starts declining after reaching T_{max}, and ends up near 125 mg/ml, which is the GFR. This results from the fact that at high concentrations, the amount cleared by secretion is so much less than the amount cleared by filtration; so filtration becomes the main contributor on clearance; resembling inulin. So, at concentrations beyond the carriers' capacity, PAH clearance underestimates RPF. (Remember that excretion of PAH is secretion plus filtration.)

For inulin, it is freely filtered, but neither reabsorbed nor secreted. Accordingly, its clearance is GFR whatsoever, and increasing the concentration increases the excreted amount, which is solely dependent on filtration (passive process).

True RPF Vs. Effective RPF

To measure RPF, we said that we need a material that does not make it to the renal vein (concentration in the vein = 0). However, this is not possible, and that is because not all the blood reaching the kidney reaches the functional parts of the kidney (nephron, the afferent and efferent arterioles, the glomerular capillaries and the peritubular capillaries). Actually, 10% of this blood supplies other parts (cortex, renal pelvis,…) in order to nourish them and supply them with nutrients and oxygen. This 10% do not undergo any filtration, secretion or reabsorption.

So, the calculated RPF using PAH, for example, underestimates the true renal flow. Accordingly:

Effective RPF = the calculated via PAH; 90%; functional

True RPF = the total; including the 10% nourishing blood

So, clearance of PAH = eRPF = 585 ml/min

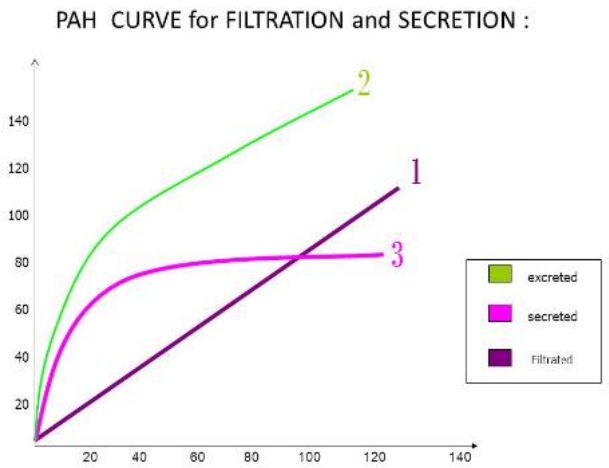
*And tRPF = eRPF * 1/.9 = 650 ml/min*

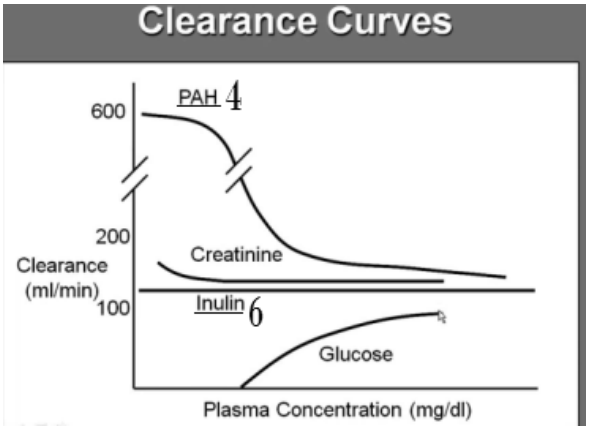
Now, to calculate RBF after measuring RPF:

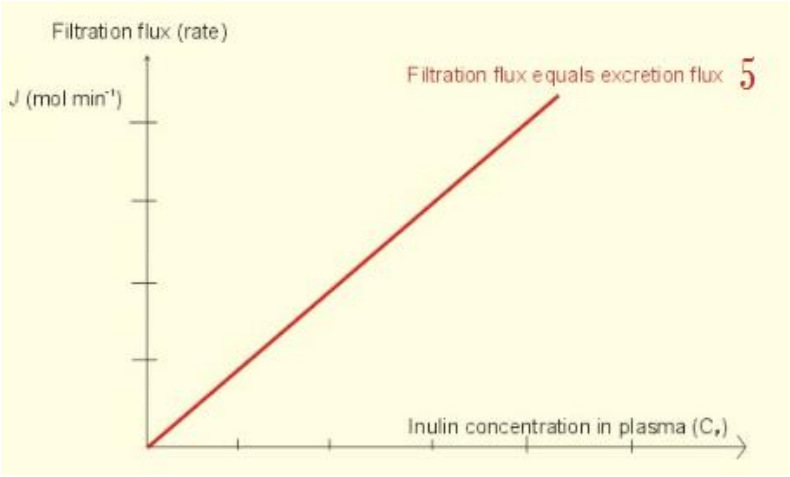
$$\text{RBF} = \text{tRPF} * \frac{1}{1-hematocrit}$$

$$= \quad 1250 \text{ ml/ml}$$

Appendix







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