LONG-TERM REGULATION OF BLOOD PRESSURE

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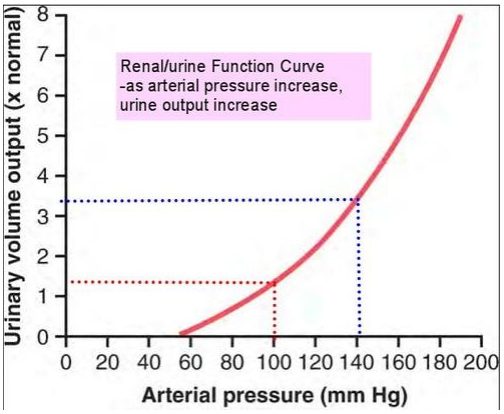
(this lecture draws heavily from A.C. Guyton's excellent book "Textbook of Medical Physiology" [8 edition], W.B. Saunders, Philadelphia, 1991).

Questions and comments by email.

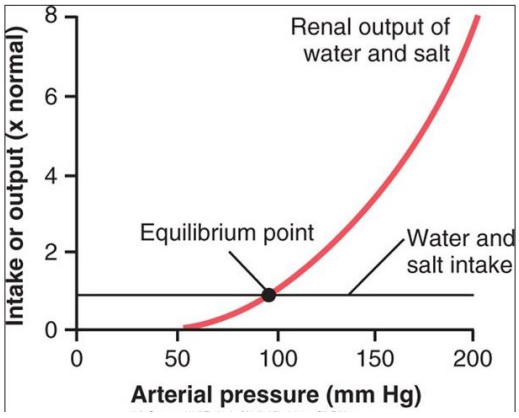
- Pressure diuresis - even a small increase in arterial pressure significantly increases renal water output (why?); it is described by the so-called renal function curve (an example is in this picture).
- The dependence of sodium output on arterial pressure (pressure natriuresis) looks similar.



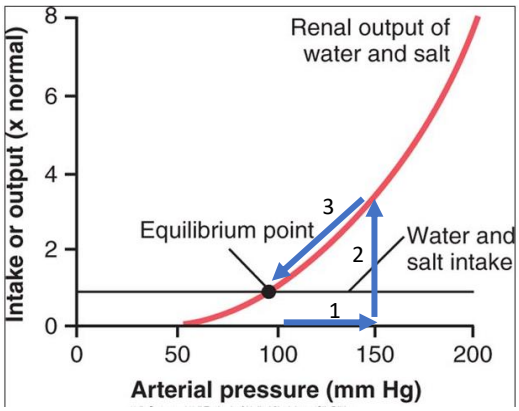
Why does an increase in arterial pressure increase natriuresis/diuresis?

- We would expect that a higher arterial pressure would increase the filtration pressure and thus lead to more filtration.
- But this increases the flow through the proximal tubule to the macula densa segment, which causes preglomerular vasoconstriction (so-called tubule-glomelular feedback) and thus a decrease in filtration pressure towards normal.
- Nitric oxide (NO), released from the endothelium of arterioles as a result of increased mechanical stress on the endothelium at increased pressure, is therefore used rather. NO freely diffuses into the kidney and reduces sodium reabsorption in the tubules.

- The intake of water and salts does not depend on the arterial pressure (therefore it has the form of a straight line parallel to the pressure axis on this graph).
- In the long term, water and salt intake must be equal to their output
- The only place on this graph where intake is equal to output is the intersection of the output curve and the intake line, i.e. the so-called equilibrium point



- The renal function curve shows that if the arterial pressure increases (arrow 1 in the figure on the right), this leads (if the kidney function does not change) to an increase in the output of water and salt by the kidneys (arrow 2)
- The output of water and salts therefore exceeds their intake, the organism therefore loses water, blood volume decreases, cardiac output decreases and arterial pressure decreases
- This negative fluid balance lasts until the arterial pressure drops to the extent that fluid output is again equal to fluid intake, i.e. to the equilibrium point (arrow 3)



A reduction in cardiac output reduces arterial pressure by two mechanisms:

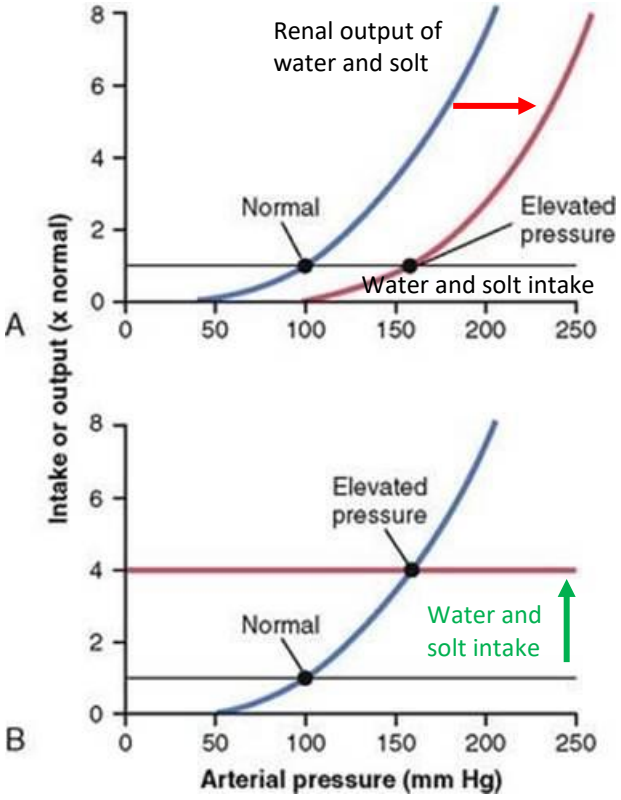
1. Directly - Pressure is directly proportional to flow, a reduction in flow reduces pressure.
2. Through local autoregulation of flow - tissues respond to a decrease in flow by autoregulatory "effort" to increase it locally by locally reducing vascular resistance. Blood pressure is directly proportional to resistance, so reducing resistance reduces pressure.

- When the pressure drops, these events take place in the opposite direction than when the pressure increases.
- **In the long run, the arterial pressure must always have a value corresponding to the equilibrium point.**

There are only 2 ways to change the value to which the arterial pressure is set for a long time:

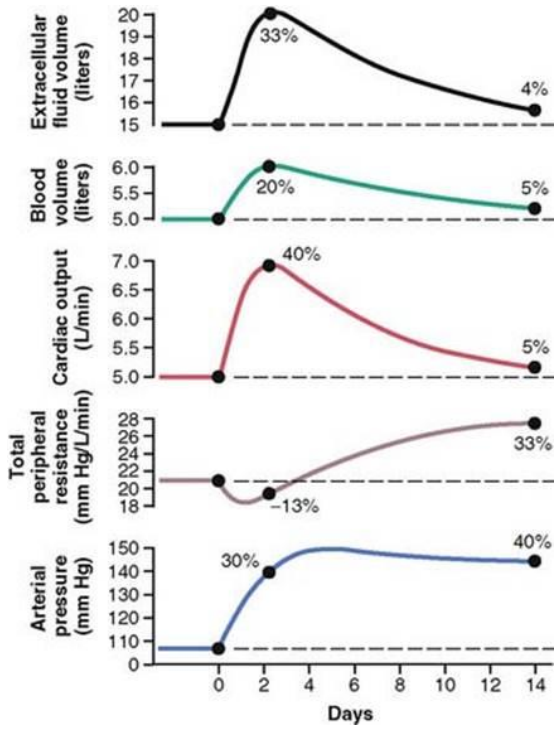
1. Change the output of water and salts (shift the renal function curve), or
2. Change water and salt intake.

In both cases, the equilibrium point shifts.



- Therefore, peripheral vasoconstriction does cause an acute increase in arterial pressure, but (if kidney function remains unchanged), the pressure normalizes within a few hours at the cost of a decrease in cardiac output.
- In many cases of peripheral vasoconstriction, however, renal vasoconstriction also occurs, which can shift the renal function curve and thereby cause hypertension.
- In such a case, however, the main cause is an increase in renal vascular resistance, not an increase in total peripheral vascular resistance.
- Water is relatively easily excreted, more easily than salt, therefore an increase in salt will more easily cause hypertension.
- More salt - higher osmolarity - stimulation of the thirst center (more drinking) and release of ADH (reabsorption of water in the renal tubules).
- Hypertension is usually considered to be arterial pressure higher than about 135/90 mmHg (median 110 mmHg).
- Hypertension affects more than 20% of adults.
- Damages the endothelium, leading to smooth muscle proliferation, atherosclerosis, heart attack, stroke, chronic heart and renal failure.
- Volumetric hypertension (e.g. salt drinking in dogs with reduced kidney tissue, i.e. in order for water excretion to continue as with normal kidneys, a higher pressure is needed, i.e. the renal function curve shifts to the right, in addition, salt and water intake is also increased):

- First, an increase in blood volume and therefore cardiac output and arterial pressure.
- Peripheral resistance decreases due to baroreceptors.
- However, they reset after a few days and resistance starts to increase and cardiac output decreases due to autoregulation.
- Finally, blood volume and cardiac output are nearly normal and peripheral resistance is increased, but this is secondary (blood volume decreased due to increased filtration due to increased pressure).



- It is the same with primary aldosteronism (adrenergic tumor) - increased reabsorption of sodium and water.
- Similarly with repeated dialysis.

Renin - angiotensin

- Enzyme **renin** released by juxtaglomerular cells in the walls of afferent renal arterioles; its release increases:

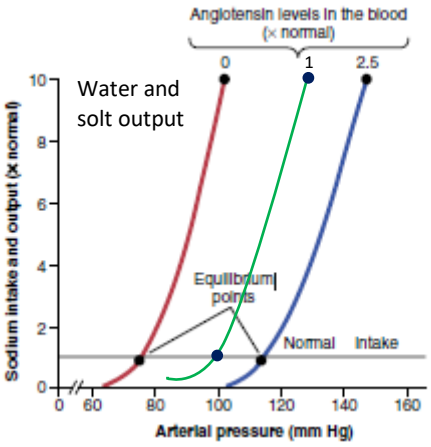
1. Decreased reabsorption of Na in the area of the macula densa (result of reduced filtration - due to reduced blood pressure - or increased reabsorption of Na in the more proximal parts of the nephron). ATTENTION – it is used to be thought that it was the other way around, i.e. that the increased supply of Na to the cells of the macula densa increases the production of renin - this can be found in some older textbooks, but today it is certainly known that this is not true.
2. Reduction of intravascular pressure in the juxtaglomerular apparatus (the so-called intrarenal baroreceptor mechanism).
3. Decreased sympathetic activity (beta1 receptors) - significant hl. during exertion, postural changes and bleeding.
4. Decreased level of circulating angiotensin II (negative feedback).

- It cleaves **angiotensin I** (10 amino acids) from angiotensinogen in the plasma
- This is converted to **angiotensin II** by the endothelial **angiotensin-converting enzyme** (ACE) (ACE also inactivates bradykinin)

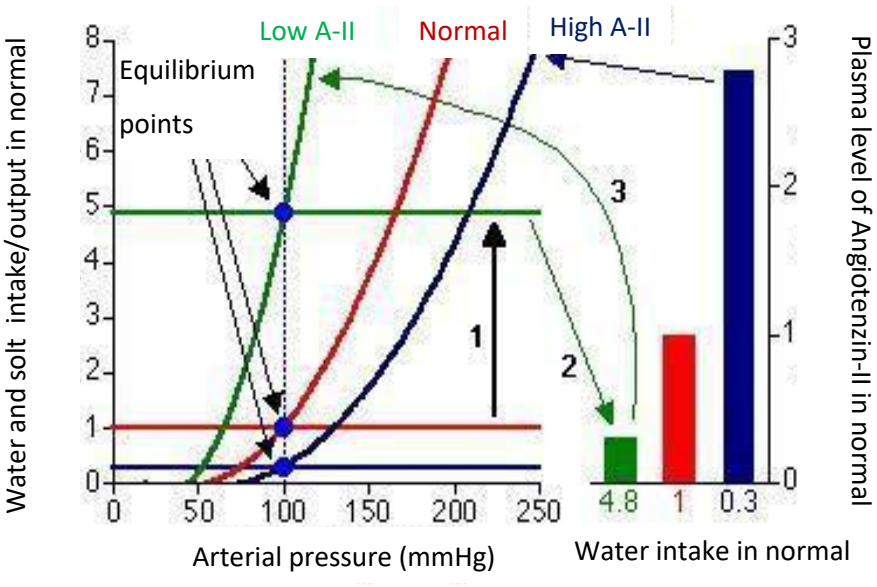
In somatic tissues, ACE is a glycoprotein of 140 kDa and has 2 homologous domains (the amino, or N-terminal, and carboxy, or C-terminal, sites) that are both catalytically active and that both require the presence of Zn^{2+} for activity. The full-length ACE protein is anchored in the plasma membrane via a hydrophobic region near its C-terminus. ACE may be released from the cell membrane by a carboxypeptidase that cleaves the protein between Arg-663 and Ser-664 to generate the soluble or circulating form of somatic ACE. Mice genetically engineered to express only the N-terminal domain of ACE have no tissue-bound ACE and are hypotensive; this finding supports the concept that tissue-bound ACE is more important than circulating ACE in the metabolism of angiotensin I and bradykinin.

- Angiotensin II increases pressure by peripheral vasoconstriction and retention of water and sodium (shift of the renal function curve), this is a consequence of renal vasoconstriction and stimulation of aldosterone secretion

  Angiotensin II also increases the sensitivity of tubuloglomerular feedback

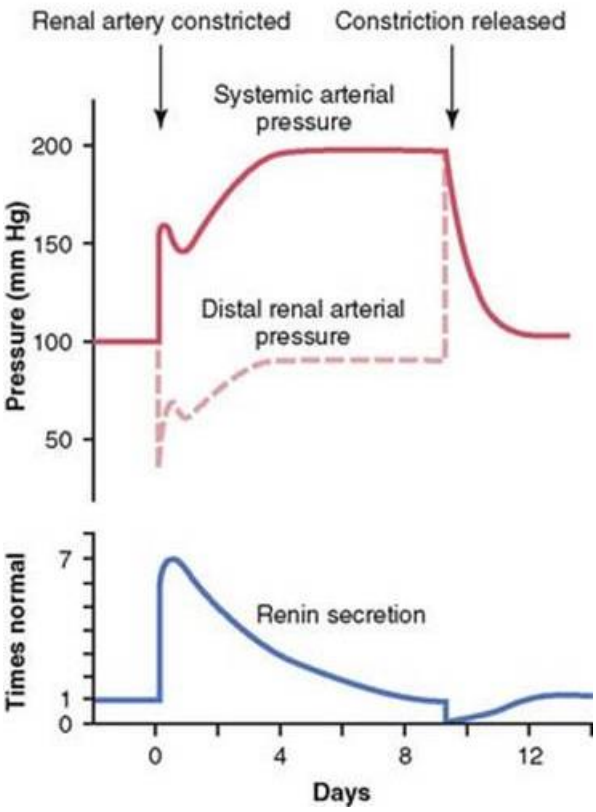


- Renin - angiotensin system allows us to drink a lot of water and salt without our blood pressure has changed a lot:



- An increase in water intake (1) causes a decrease in renin formation and thus a decrease in the plasma concentration of angiotensin II (2) compared to normal. This shifts the renal function curve to the left (3) from normal so that its intersection with the new (increased) value of fluid intake corresponds to an approximately similar pressure value as under normal conditions. When fluid intake is reduced, these events take place in the opposite direction. The plasma concentration of angiotensin II increases and this shifts the renal function curve to the right so that its intersection with the new (reduced) value of fluid intake corresponds to a pressure value approximately similar to that under normal conditions.

- **Coarctation of the aorta**: the kidney "sees" low pressure, therefore it creates renin, generalized vasoconstriction will raise the pressure everywhere (much above the coarctation) until its own pressure normalizes. In the meantime, however, water retention occurred (thanks to activated renin - angiotensin) and the first phase of volume hypertension, and the second occurs - normalized blood volume and cardiac output and secondarily increased peripheral resistance



Summary of blood pressure regulation mechanisms

Rapid and short-term (seconds - minutes):

- Baroreceptor feedback
- CNS ischemic mechanism
- Chemoreceptors

Medium-term (minutes - hours):

- Renin-angiotensin vasoconstriction
- Fluid shifts between vessels and interstitium

Long-term (hours - days)

- Kidneys