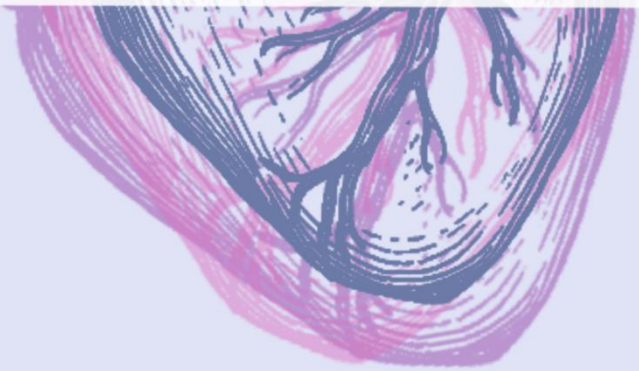
Cardio-Vascular System

16

Physiology



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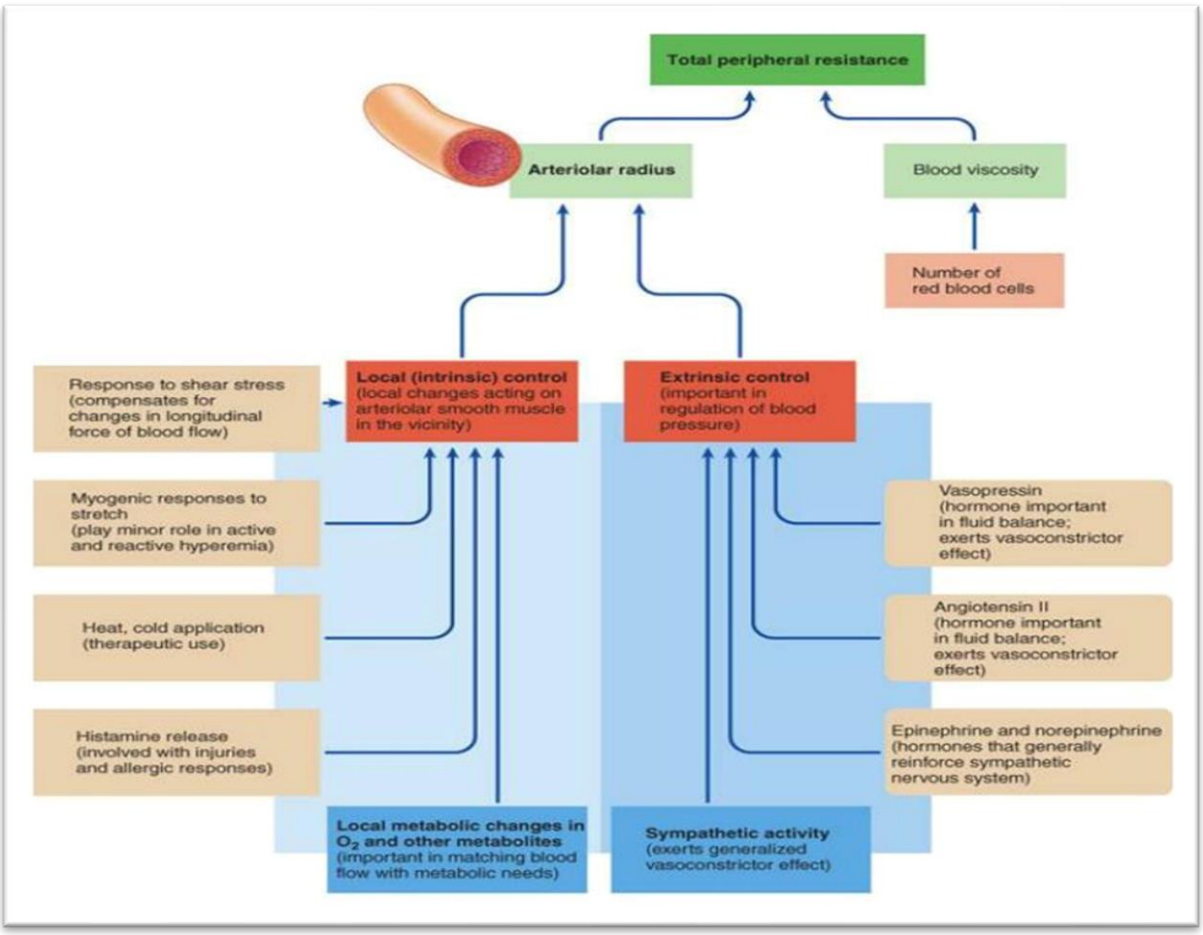
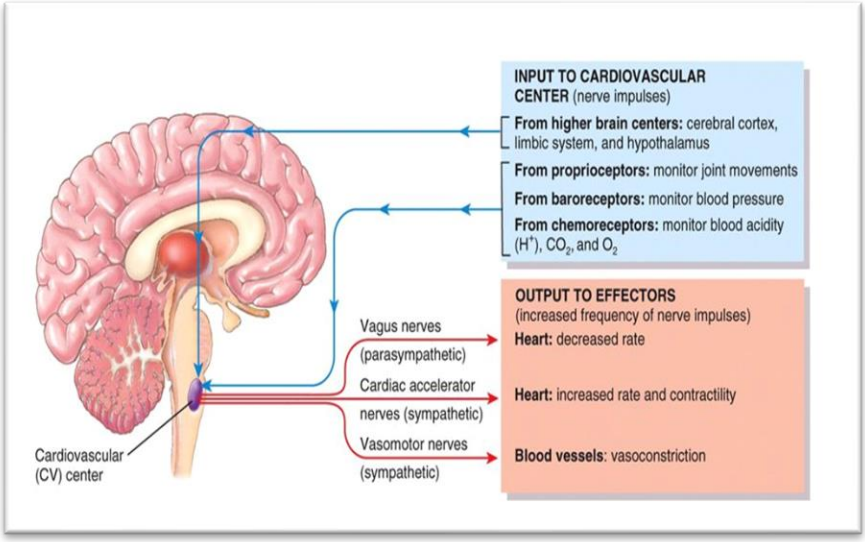
- In the previous sheet we went over the short-term regulators of BP, in this lecture we will continue talking about BP regulation but over a "long-period" of time.
- Factors affecting TPR:
  - The main determinant of TPR is the adjustable arteriolar radius. Two major categories influence arteriolar radius:
    a) Local (intrinsic) control: "selfish adjustments to increase blood flow" this control is important in matching blood flow with the tissue's metabolic needs. Decreased O2, increased CO2 or acid [H+] produce arteriolar relaxation (to increase blood flow during increased metabolic activity).
    b) Extrinsic control of arteriolar radius: recall that a certain level of ongoing sympathetic activity contributes to vascular tone. Increased sympathetic activity produces generalized arteriolar vasoconstriction (↑TPR), whereas decreased sympathetic activity leads to generalized arteriolar vasodilation (↓TPR). Every single aspect of the sympathetic actions over the TPR and the consequent BP will be covered in this sheet as we proceed.
  - TPR is also directly proportional to the blood viscosity which is primarily controlled by the number of RBCs and plasma proteins. (relatively stable variable except in some pathological conditions like severe anemia).



- The adjacent figure summarizes the nervous control over the heart.
- Afferent fibers reach the cardiovascular center of the brain which respond by increasing or decreasing the tone of the efferent (sympathetic or parasympathetic) neurons to adjust the TPR, CO and consequently the MAP. (The details of this process are explained in the previous sheet).



- Intermediate / Long term Regulation of BP:
  1. Epinephrine – Adrenal medulla system:
     Sympathetic stimulation of the adrenal medulla causes this gland to release epinephrine (80 %) and nor-epinephrine (20%) into the blood, to produce generalized vasoconstriction → ↑TPR → ↑MAP. This mechanism works as an intermediate term of BP regulation because it is activated after 10 minutes of blood pressure dropping.
     Extra: please remember that this generalized vasoconstriction is achieved by the activation of α1 receptors found in almost all arterioles. Arterioles of the heart and skeletal muscles are equipped with β2 receptors that result in vasodilation once activated by the same hormones, but through different signaling pathways.
  2. ADH (vasopressin) system: (This system requires 30 minutes to start working). Vasopressin is involved in maintaining water balance by regulating the amount of water the kidneys retain for the body during urine formation. To maintain water balance on the intake side, thirst influences the amount of fluid ingested, and on the output side, the kidneys can adjust the amount of urine formed under the influence of many regulators including ADH.
     Now, what's the ultimate goal of ADH? Before we answer this question, we should clarify when and why ADH is secreted in the first place?
     - Do you remember the story of low-pressure receptors (found mainly in the Rt. Atrium)? These receptors are sensitive to changes in volume (ECF volume), in other words these receptors monitor the "fullness" of the vascular system. *How much volume is passing through the vessels?*
     - If these receptors sense that the ECF volume is reduced (decreased MAP), reflexes are immediately initiated to restore BP.

- One of these reflexes is the atrial-hypothalamic reflex which induces the release of ADH to stimulate the kidneys to absorb more water and form less urine, this retained volume would increase the ECF volume.

- *What about thirst?* The hypothalamic center regulates ADH secretion (and thus urinary output) and thirst (and thus drinking). ADH and thirst are both stimulated by low H2O levels and suppressed by free water excess.

- ADH is alternatively know as vasopressin, because it is a potent vasoconstrictor and thus it increases the TPR.

  - ↓ ECF volume → increase the release of ADH directly or indirectly through activation of the atrial hypothalamic reflex + ↑thirst → ↑H2O retention → ↓ urine formation → ↑ECF volume → ↑MSFP → ↑Venous return → ↑ CO (according to Fra…)

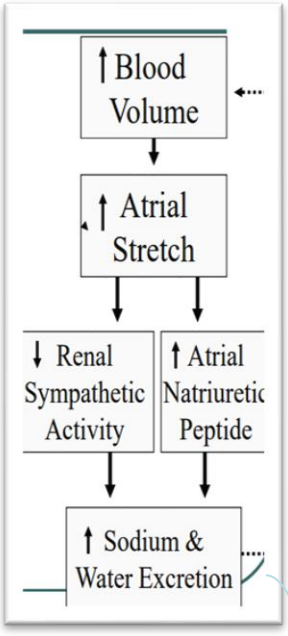
    Also, vasopressin increases TPR. Since both TPR and CO are elevated, MAP pressure is raised.

3. Renin-Angiotensin-Aldosterone system: this system requires 1 hour to be effective.

- RAAS is activated in response to: ↓Na+, ↓ECF volume, and ↓BP. The cells of the afferent arteriole secrete Renin (an enzymatic hormone) into the blood in response to decreased blood pressure. Also, the macula densa cells of the juxtaglomerular apparatus work as sensors for Na+. In response to fall in NaCl, the macula densa cells stimulate the afferent arteriolar cells to secrete renin. Once secreted into the blood, renin acts as an enzyme to activate angiotensinogen (α2-globulin, 14 a.a peptide) into angiotensin I (10 a.a peptide). Angiotensinogen is synthesized by the liver and present in the plasma. Angiotensin I is converted into angiotensin II by angiotensin converting enzyme ACE, which is abundant in the pulmonary capillary endothelial cells.
- *Angiotensin II is the most potent vasoconstrictor*, and the main stimulus for secretion of the hormone aldosterone from Zona glomerulosa layer of the adrenal cortex. Aldosterone increases Na+ reabsorption. RAAS thus promotes salt retention and a resulting water retention → ↑ECFV → ↑MSFP → ↑ venous return→ ↑ CO + ↑ TPR→ ↑MAP
- Angiotensinogen II is also a positive inotropic agent (increases SV by increased contractility).
- The opposite situation exists when the Na+ load, ECF volume, and arterial blood pressure are above normal. Under these circumstances, renin secretion is inhibited. Therefore, angiotensinogen is not converted to angiotensin I and II, and aldosterone secretion is also not stimulated.

- ↓Na+ → ↓H2O (lost in urine) → ↓ECFV → ↓ venous return → ↓CO → ↓MAP (similar to how diuretics work?)
- Extra: angiotensin II also stimulates thirst and vasopressin.

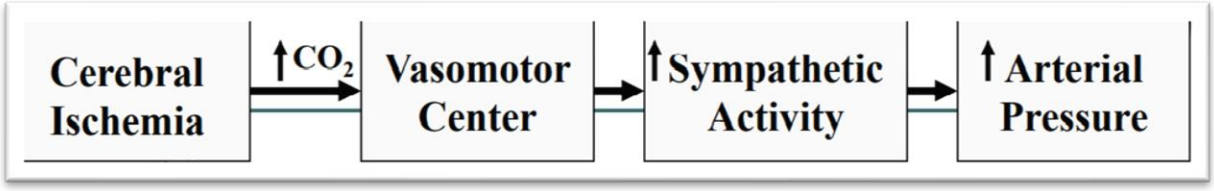
- Until now we have mentioned three mechanisms stimulated by decreased BP → their stimulation raises BP to normal levels.
- Before discussing the fourth mechanism, let's revise the influence of BP over the GFR:
  - ↑ MAP → sympathetic tone is reduced → afferent arterioles of kidney are dilated → more blood enters the glomeruli → ↑GFR → more urine is formed → ↓ECFV (normal again) → MAP is reduced
  - ↓MAP → ↑ sympathetic stimulation → vasoconstriction of afferent arterioles → less blood enters the glomeruli → ↓ GFR → less urine is formed →water retention → ↑ ECFV → MAP is raised
  - The GFR is influenced by many factors that adjust BP, including the atrio-renal reflex.
- Atrial Natriuretic peptide (ANP):
  - A blood pressure-lowering system that involves the hormone ANP, this hormone is produced mainly by the right atrium, although both atria can secrete it. The main action of ANP is to inhibit Na+ reabsorption and consequently promotes its excretion, water will osmotically follow Na+.



  - ↑ECFV and ↑ MAP → the additional volume stretches the heart muscles → release of ANP → ↑ Na+ and water excretion → more urine is formed → ↓ ECFV and MAP
  - ANP causes vasodilation in the afferent arterioles → ↑GFR → more urine is formed → Na+ and water are lost → ↓ECFV and MAP
  - The opposite happens when MAP is reduced (ANP is inhibited).
- Increase in blood volume activates low-pressure receptors which in turn lower arterial pressure.
  - Activation of low-pressure receptors enhances Na+ and water excretion by:
    a) Decreasing rate of antidiuretic hormone (atrial-hypothalamic reflex).
    b) Increasing glomerular filtration rate (atrio-renal reflex).
    c) Decreasing Na+ reabsorption.

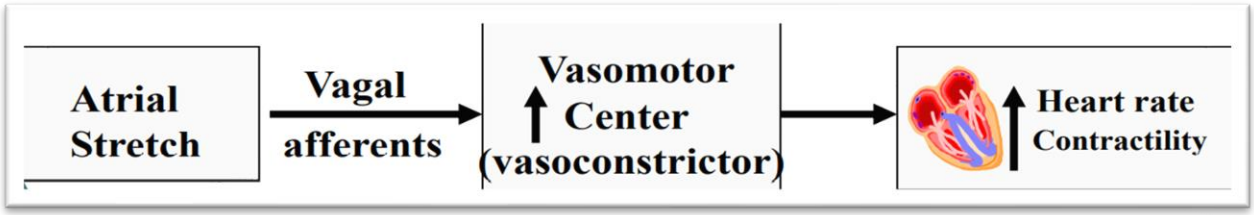
CNS Ischemic Response:

- when blood flow to the vasomotor center is decreased severely enough to cause cerebral ischemia, the vasoconstrictor and cardioaccelerator neurons in the vasomotor center respond directly and become strongly excited. This effect is believed to be caused by failure of blood to carry carbon dioxide away from the brain stem vasomotor center.
- the CNS ischemic response is one of the most powerful activators of the sympathetic vasoconstrictor system (extensive stimulation). It is sometimes called the "last-ditch stand" (last-chance) pressure control mechanism.
- This response occurs to prevent multiple end-organ failure and death in severely hypotensive patients.
- CNS Ischemic response is not activated until pressure falls below 60mmHg; greatest activation occurs at pressures of 15-20mmHg.
- Cushing reaction (brain edema) is a special type of CNS ischemic response.
- Prolonged CNS ischemia has a depressant effect on the vasomotor center.

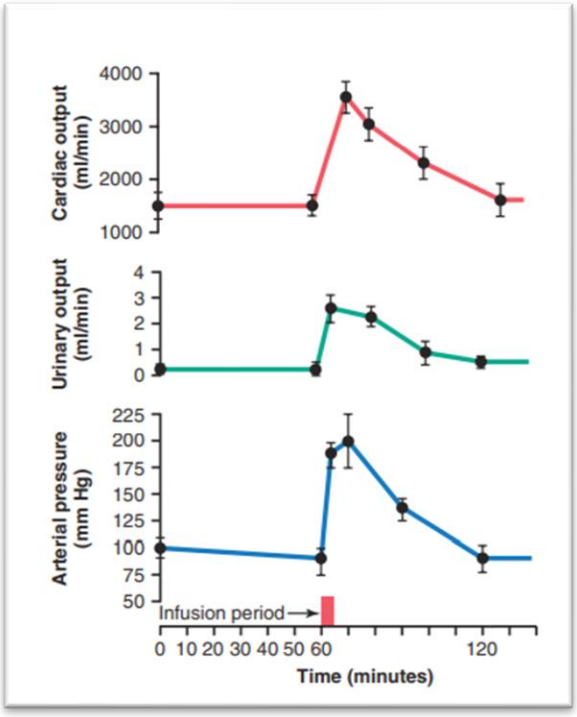


Bainbridge Reflex:

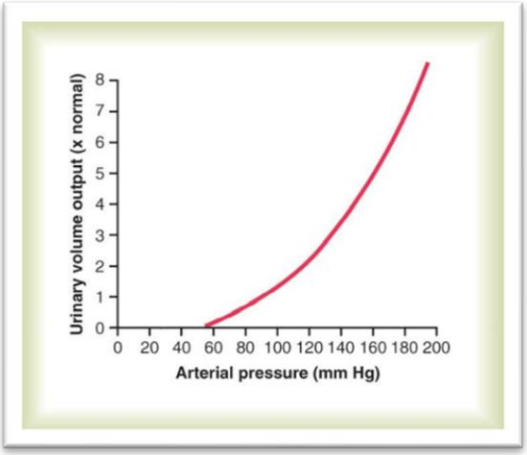
- When right atrial pressure increases, the resultant volume stretches the SA node and thus increases its discharge → HR↑
- Also, the stretch of atria sends afferent signals (through the vagus) to the brain to activate the vasomotor (vasoconstrictor + cardio-acceleratory) to further increase the HR and contractility (to a lesser degree) of the heart.
- This reflex Prevents damming of blood in veins atria and pulmonary circulation.

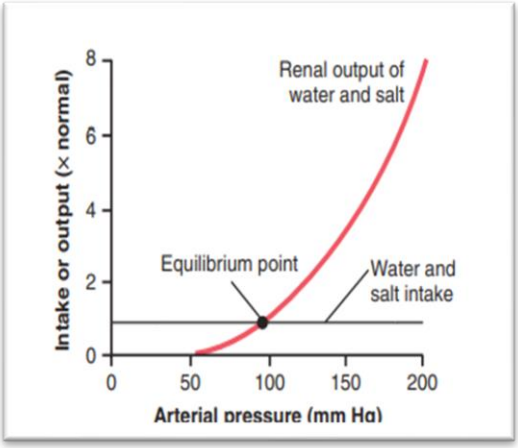


- Renal Body Fluid System for Long-Term Arterial Pressure Control:
  - A volume of blood is infused intravenously and thus the ECFV is increased.
  - The extra volume will raise the MSFP. Consequently, the venous return and CO are increased.
  - The resultant increase in CO will raise the MAP.
  - the middle curve is the effect of this increased arterial pressure on urine output, which increases to multiple folds. Along with this tremendous loss of fluid in the urine, both the cardiac output and the arterial pressure returned to normal.
  - Kidneys have extreme capability to eliminate excess fluid volume from the body in response to high arterial pressure, to return the arterial pressure back to normal.

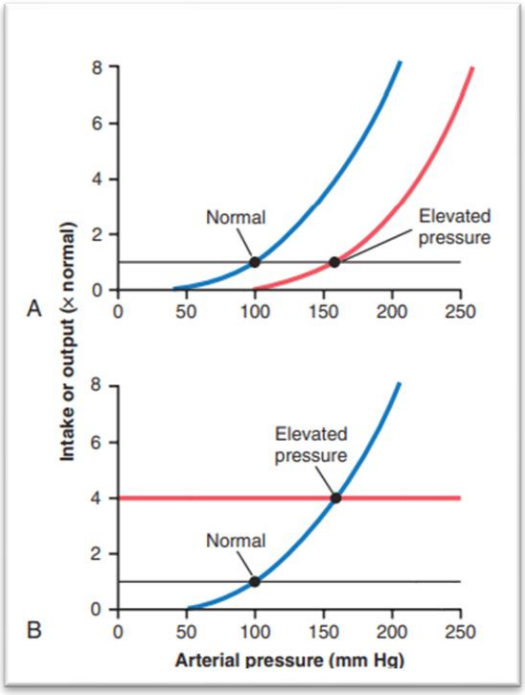


- The adjacent figure represents the renal output curve for water and salt in response to rising arterial pressure.
  - The effect of pressure to increase water excretion → diuresis.
  - The effect of pressure to increase Na excretion → natriuresis.
- To maintain a constant BP, sodium and water intake must equal their output (urinary volume).
  - The horizontal line represents the net water and salt intake, and the red curve is the same renal output curve.
  - The only place on the graph at which output equals intake is where the two curves intersect, called the **equilibrium point**.





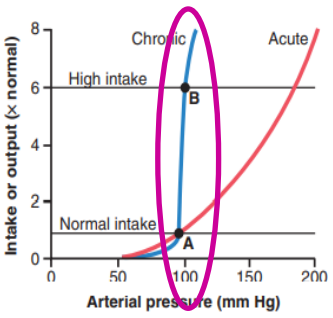
- The two primary determinants of the long-term arterial pressure level are:
  1. The degree of pressure shift of the renal output curve for the same water and salt intake.
  2. The level of the water and salt intake.



a) In this case, the normal curve is shifted to the right. The intake is not altered. But the kidneys are functioning abnormally (for example angiotensin II levels are elevated). Shifting the renal curve to a higher value will increase the arterial pressure (the equilibrium point is also shifted to the right).

b) Changing the level of salt and water intake also can change the arterial pressure (equilibrium point is also shifted to a higher value). Conversely, a decrease in the intake level would reduce the arterial pressure.

c) Luckily, with normal functioning kidneys, increased salt intake causes only small changes in arterial pressure. Over a long period of chronic intake of salt, the renal curve becomes much steeper to maintain normal BP. (I've added this figure to clarify the meaning of steepness).

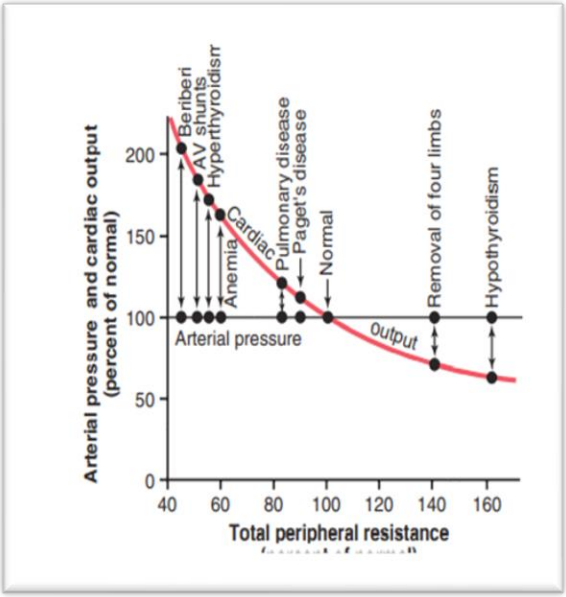


- Renal body fluid feedback system has an infinite gain:
  - One of the causes that baroreceptors do not play a role in long-term regulation of BP (other than being adaptable) is because their gain is small. In contrast, the renal system has almost infinite gain.
  - Now, what does gain mean? It is a measure of effectiveness of a particular control system to resist changes in homeostasis.

    Gain = Correction / error
  - The higher the gain the higher the effectiveness of a control system. For example, if blood pressure is elevated from 100 mmHg to 150 mmHg, the baroreceptor reflex can decrease the pressure to almost 120 mmHg. What is the gain in this situation?

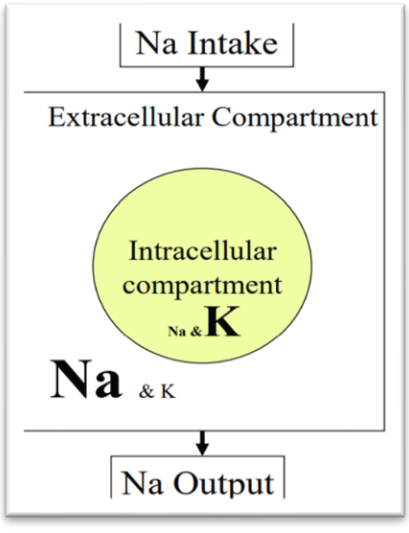
- Gain = (120-150)/20 = - 1.5, the negative sign indicates a negative feedback mechanism. You can notice that the gain is so small because the short-term compensatory measures have limited ability to minimize a change in blood pressure.
- On the other hand, the renal system returns the blood pressure exactly to the original value (100 mmHg). Because the error is almost zero, the gain is infinite.

Failure of Total Peripheral Resistance to Elevate Long-term Arterial Pressure:



- Changing the TPR has no effect on arterial pressure on the long term, because when the kidneys are normally functioning, blood pressure will be adjusted by increasing or decreasing the cardiac output.
- If TPR is decreased (after the ingestion of vasodilators for example), the kidneys respond and retain more fluids to increase the CO and maintain a constant arterial pressure. That's why diuretics are prescribed with vasodilators (to counteract the compensatory measures →decrease CO and consequently decrease arterial pressure).
- Conversely, if TPR is increased, the kidneys respond and excrete more Na+ and water in the urine to decrease the ECFV and consequently the CO.
- One must alter the renal function curve in order to have long-term changes in arterial pressure. Changing renal vascular resistance does lead to long-term changes in arterial pressure not the TPR.

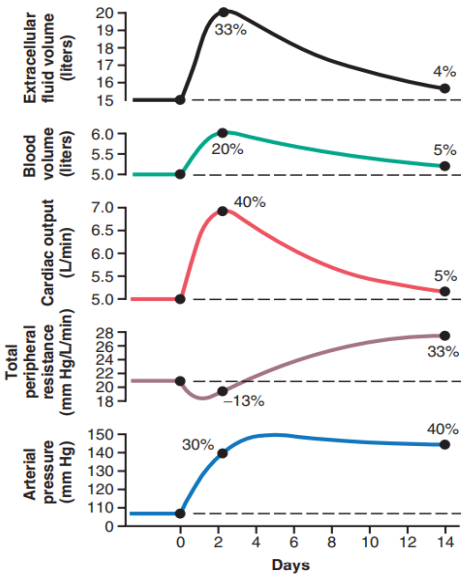
Sodium is a Major Determinant of ECFV:



- Why sodium? Because it is the major cation in the ECF. Changing Na+ concentration will change the ECFV because water follows sodium osmotically.
- As Na+ intake is increased; Na+ stimulates drinking, increased Na+ concentration stimulates thirst and ADH secretion.
- Changes in Na+ intake leads to changes in extracellular fluid volume (ECFV).
- ECFV is determined by the balance of Na+ intake and output.

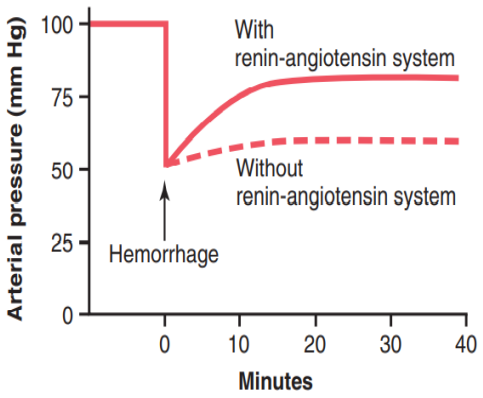
Volume Loading Hypertension:

a) Increasing the ECFV.
b) Increased ECFV increases blood volume.
c) The increased volume increases venous return and thus CO.
d) Increasing the CO decreases the TPR a little bit through receptive relaxation of the vessels (according to Dr.Faisal), [actually this decrease was caused by the baroreceptor mechanism because the arterial pressure was suddenly increased, after a few days the receptors adapt and the TPR increases back to normal levels] .
e) This will increase the arterial pressure, but if the kidneys are normal, the BP will be adjusted.

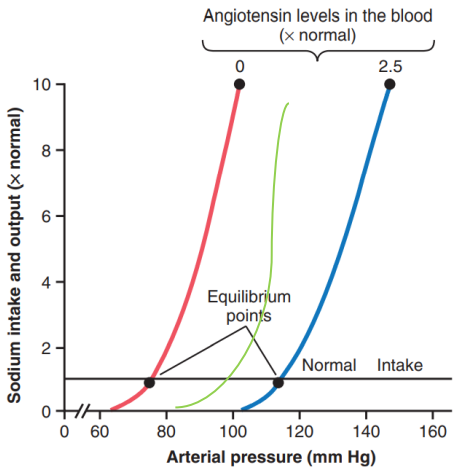


Actions of the Renin Angiotensin System:

- the effect of hemorrhage on the arterial pressure under two separate conditions:
  1. with the renin-angiotensin system is functioning, the arterial pressure rose back to a higher value.
  2. without the system functioning, more time is spent to elevate BP, and the maximum value is far less than the normal value.

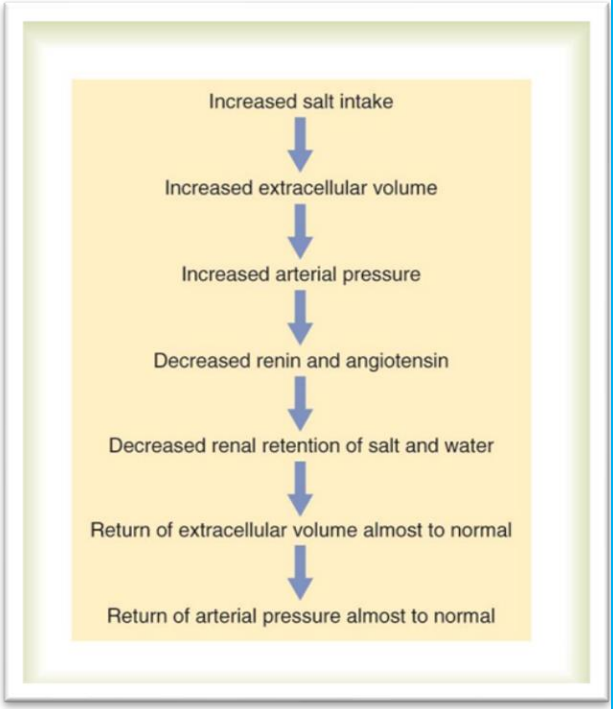


- The renin-angiotensin system is powerful in returning the arterial pressure back to almost normal values after severe hemorrhage. Therefore, sometimes it can be lifesaving, especially in circulatory shock.
- The figure shows different levels of Angiotensin II in the blood. The normal level is something in between the blue and red curves (the additional green curve).
- When the angiotensin system is blocked and no Angiotensin II is formed, the renal curve is shifted to the left (equilibrium point is shifted to the left → lower BP at the same salt intake level).

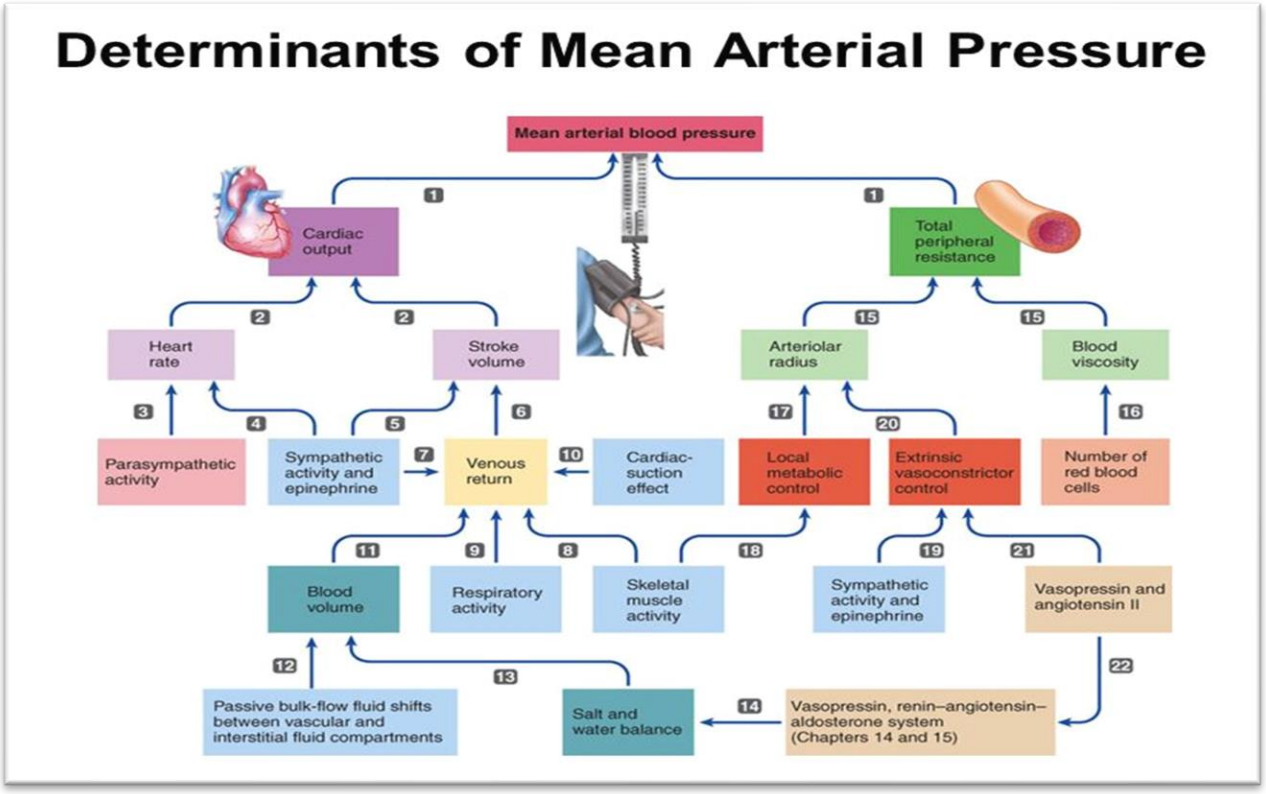


- When angiotensin II level is above the normal level (like in hypertension), the curve is shifted to the right (equilibrium point is also shifted to the right → higher BP at the same salt intake level).

- Angiotensin II Causes vasoconstriction and Na+ retention by direct and indirect acts (through aldosterone) on the kidney → Causes shift in renal function curve to right
- ACE inhibitors (captopril) and angiotensin receptor blockers are used to treat hypertension, because they shift the renal curve to the left (towards normal levels).



- RAS is important in maintaining a normal AP during changes in Na+ intake.
  - As Na+ intake is increased renin levels fall to near 0.
  - As Na+ intake is decreased renin levels increase significantly.
- Factors Which Decrease Renal Excretory Function and Increase Blood Pressure:
  1. Angiotensin II
  2. Aldosterone
  3. Sympathetic nervous activity
  4. Endothelin (vasoconstrictor released by endothelial cells).
- Factors Which Increase Renal Excretory Function and Reduce Blood Pressure:
  1. Atrial natriuretic peptide
  2. Nitric oxide (local vasodilator)
  3. Dopamine (vasodilator)



- Everything in the previous figure has been explained in details. Just go over it quickly to revise the main concepts of BP regulation.
- Consequences and Compensations of Hemorrhage:
    1. Following severe blood loss, the reduced volume leads to a decrease in venous return and a fall in CO and arterial blood pressure.
    2. The baroreceptor reflex increases the sympathetic and decrease parasympathetic activity to the heart.
    3. The heart rate is increased to compensate for the decreased SV.
    4. Increased sympathetic activity to the veins produce generalized veno-constriction, increasing the venous return.
    5. Sympathetic stimulation increases the contractility of the heart, to beat more forcefully and eject more blood → increased SV.
    6. The increased HR and SV collectively increase CO.
    7. Sympathetically induced generalized arteriolar vasoconstriction leads to an increase in TPR.
    8. Together, the increase in CO and TPR increase the arterial pressure.
    9. Urinary output is reduced, thereby conserving water that normally would have been lost from the body. This additional volume helps expand the reduced plasma volume.
    - Reduction in urinary output results from decreased renal blood flow (afferent arteriole vasoconstriction → ↓GFR).

10. The reduced plasma volume triggers the secretion of ADH and activates the renin-angiotensin-aldosterone hormonal pathway, which further reduces urinary output and elevate BP.
11. Thirst is also stimulated; the resultant fluid intake helps restore plasma volume.

- I've only mentioned the points that are related to our lecture.
- Some figures are not added to this sheet, please refer to the slides and check them.