CVS

PHYSIOLOGY

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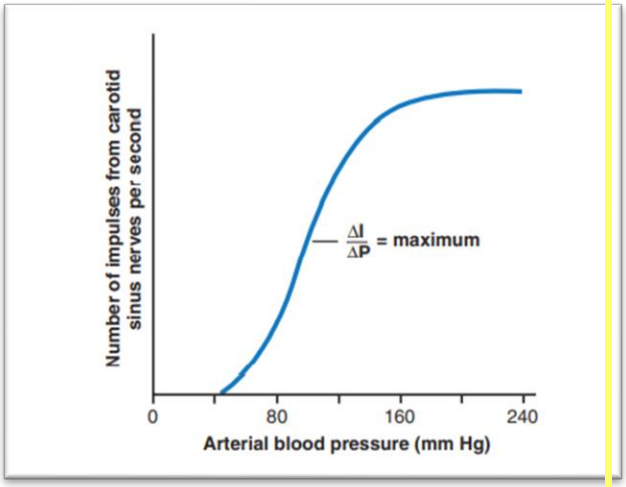
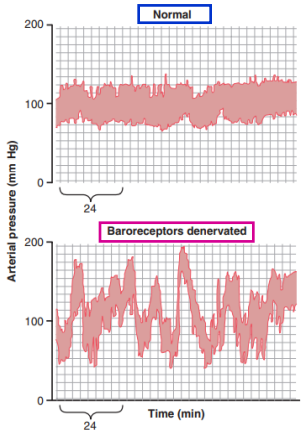
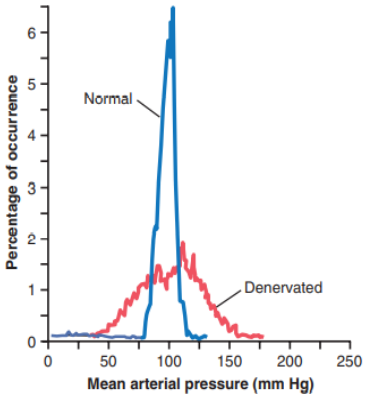
- ΔI is the number of impulses fired by baroreceptors at different levels of arterial pressure. ΔP is the change in arterial blood pressure in mm Hg.
  - Maximal sensitivity (highest slope) occurs near the normal mean arterial pressure which is 100 mmHg; therefore, very small changes in arterial pressure around this "set-point" dramatically alters receptor firing so that autonomic control can be altered in such a way that the arterial pressure remains very near to the set-point. Stated differently, a small increase in BP above 100 mmHg would increase the firing rate of baroreceptors sharply, restoring BP back to normal. Also, a small decrease of BP below 100 mmHg would result in a huge decrease in the firing rate of baroreceptors, raising BP back towards the normal “set-point”. The baroreceptors are called “pressure buffer system” because they resist or oppose any changes in BP above or below the normal value.

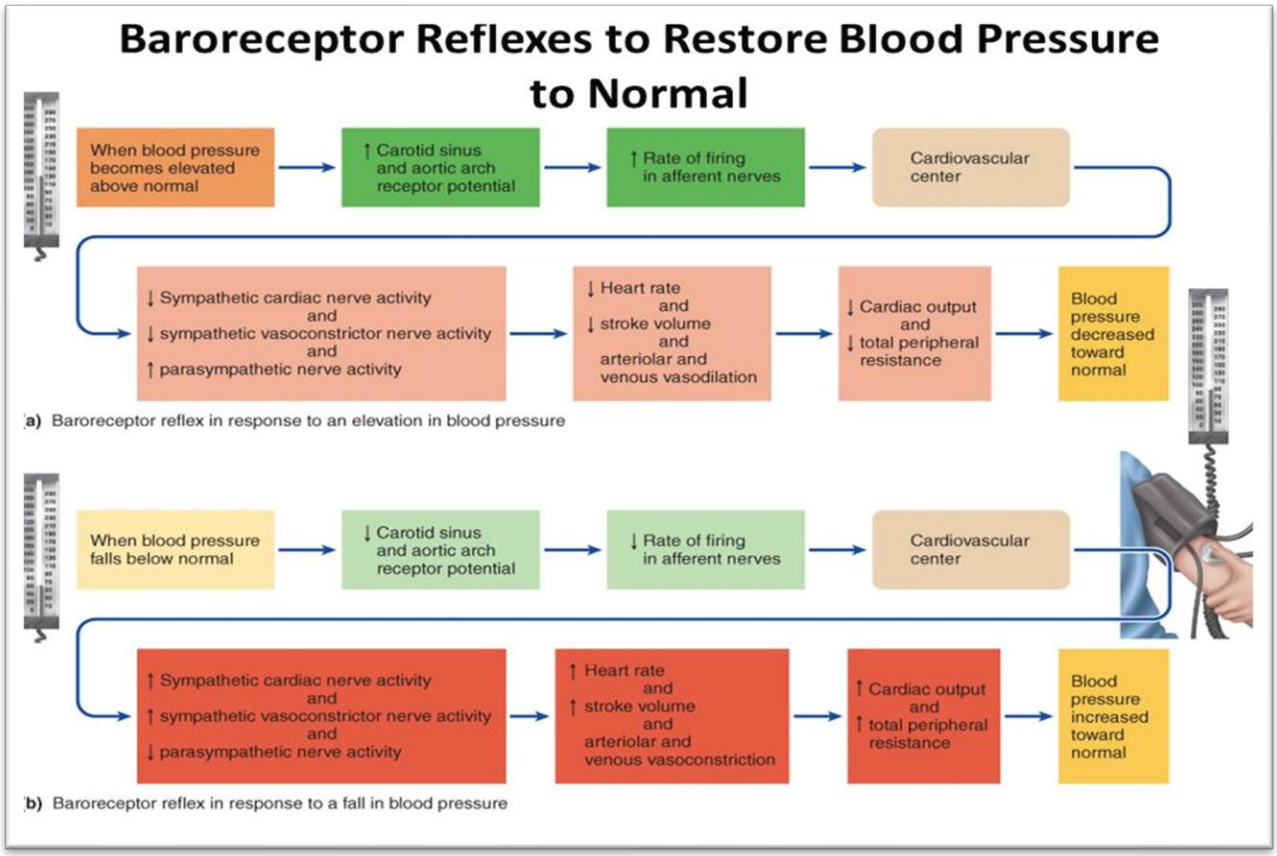


  - Note that the baroreceptors are <u>not</u> stimulated at all by pressures between 0 to 60 mm Hg. And when BP increases to values much higher than the normal MAP, minimal changes in the firing rate are observed.
  - Baroreceptors adapt or 'reset' in response to maintained changes in pressure: It is important to note that baroreceptors adapt to sustained changes in arterial pressure. Therefore, baroreceptors play a crucial role in the short-term control of MAP but no role in the long-term control of blood pressure (the long-term regulation of arterial pressure requires activation of other mechanisms).
- When a person moves from lying down to standing up, especially after prolonged bed rest, pooling of blood in the leg veins due to gravity will take place and it reduces venous return, decreasing SV and thus CO and blood pressure. This fall in blood pressure is normally detected by the baroreceptors, which initiate immediate compensatory responses to restore BP to its proper level. The opposite happens when a standing person rests into a supine position.

- In older people, due to atherosclerotic changes, the arteries become rigid and the baroreceptors are less responsive to stretch. Thus, this reflex is temporarily lost or reduced. The best advice for these people is to stand up slowly in order to give time for the baroreceptors to respond properly.
- The adjacent figures compare the variation in BP in normal innervated baroreceptors and denervated ones (in which baroreceptor nerves from both the carotid sinuses and the aorta are removed).
- When the baroreceptors were functioning normally, the mean arterial pressure remained within a narrow range. Conversely, extreme variability of blood pressure is observed in the absence of innervation.







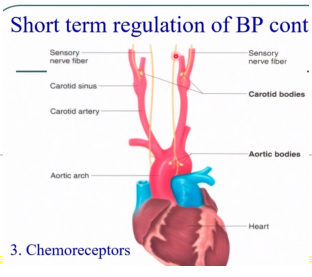
- Low Pressure Baroreceptors: these receptors are located at low pressure areas such as the Rt. Atrium, Rt. Ventricle, as well as the pulmonary artery. They are sensitive to stretch caused by changes in volume.
- An increase in volume → increase in venous return →increase in cardiac output → increase in **MAP** and vice versa.

1. Atrial-Hypothalamic reflex
   - This works through controlling secretion of vasopressin (ADH, also a potent vasoconstrictor)
   a. In cases of high BP → ADH release is inhibited → ↓ECF Volume and TPR → ↓BP (to normal levels).
   b. In cases of low BP → ADH↑ → ↑ ECF volume and ↑TPR (due to vasoconstriction) → increased water retention → Blood pressure is raised to normal levels.

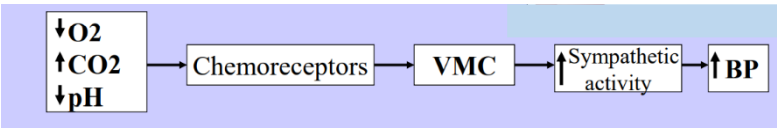
2.Atrio-renal reflex:

- Low pressure baroreceptors work also through affecting the Glomerular Filtration Rate (GFR).
  a. Increased volume → dilation of afferent arterioles → more blood volume reaches the kidneys → ↑GFR → ↑Urine formation.
  b. Decreased volume → constriction of afferent arterioles → ↓GFR → less urine is formed, and volume is conserved.

- Carotid and Aortic Chemoreceptors (carotid and aortic bodies):
  - These receptors are located in the carotid and aortic arteries, thus in close association with but distinct from the baroreceptors (in that they are not stretch receptors). These receptors are sensitive to low O2 or high acid levels [H+] or CO2 on the blood. Activation of chemo-sensitive receptors results in excitation of the vasomotor center.
  - These receptors are highly vascularized to the point that the blood and interstitial fluid content of gases and chemicals is almost the same, this is important to enhance the sensitivity of these receptors towards small changes of gases and chemical concentrations in the interstitial fluid (reflected by blood flow).



- ↓MAP → ↓ blood flow to these receptors → ↓O2, ↑CO2 and ↑[H+] or ↓pH this will activate the VMC to increase sympathetic activity and restore BP back.
- ↑MAP → ↑ Blood flow to these receptors → ↑O2, ↓CO2 and ↓[H+] or ↑pH this will inhibit these receptors.
- The main stimulant for these receptors (carotid and aortic bodies) is decreased O2 levels. The other factors stimulate the receptors to a lesser degree.
- The afferent pathway of these receptors is carried by the same neuronal pathway that carries the baroreceptors impulses (ninth and tenth cranial nerves).
- Chemoreceptors are not stimulated until pressure falls below 80mmHg, thus they are only activated after the baroreceptor reflex whose sole function is blood pressure regulation.



❖ Quiz:

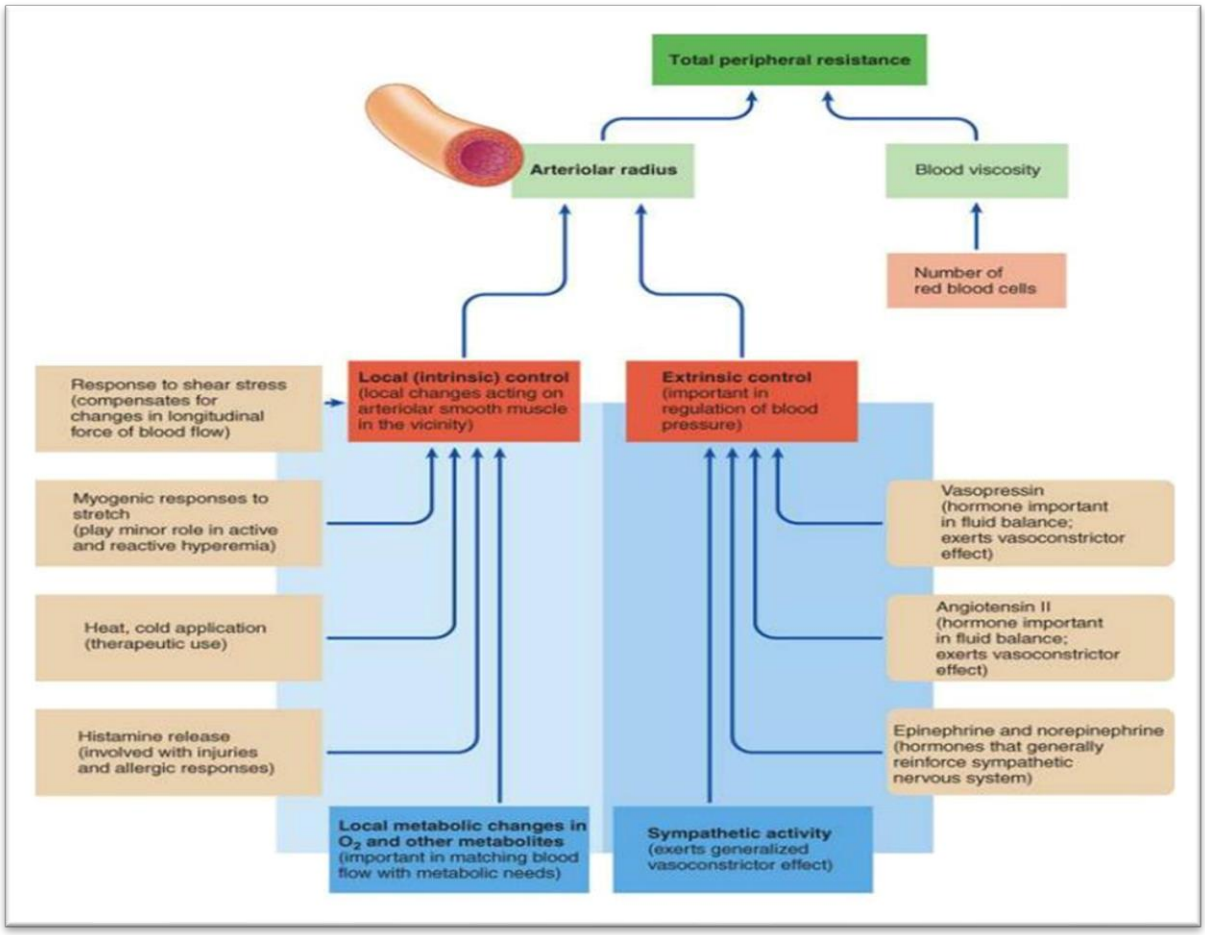
1. An acute decrease in arterial blood pressure elicits which of the following compensatory changes?
   A. Increased parasympathetic outflow to the heart
   B. Decreased firing rate of the carotid sinus nerve
   C. Decreased heart rate
   D. Decreased contractility
   E. Decreased mean systemic pressure
2. A change in blood pressure that decreases the impulses to the cardiovascular center results in increased impulses from which branch of the autonomic nervous system? What would be the effect on blood pressure (BP)?
   A. Parasympathetic; increased BP
   B. Sympathetic; decreased BP
   C. Sympathetic; increased BP
   D. Parasympathetic; decreased BP

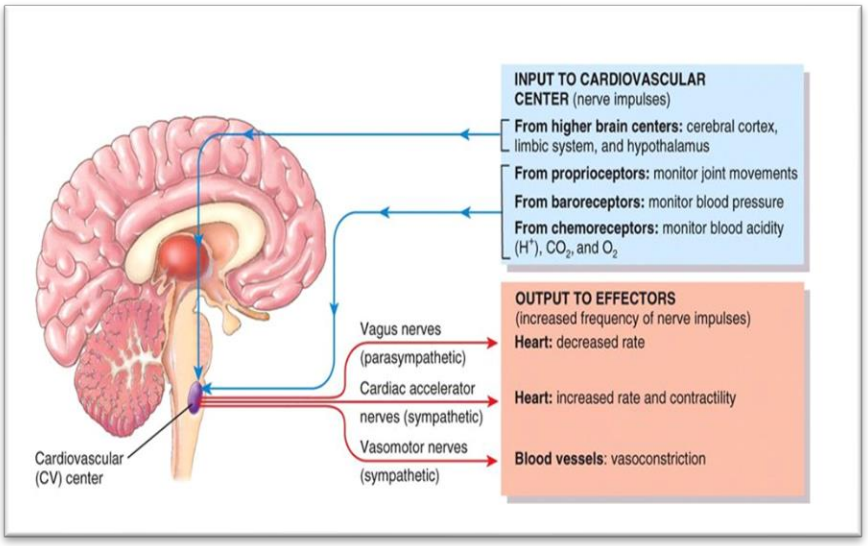
3. If a baroreceptor detects that pressure in an artery is too low, the brain will tell that artery to:
   A. Vasodilate, sending more blood to the target organ
   B. Vasoconstrict, sending more blood to the target organ
   C. Vasodilate, sending less blood to the target organ
   D. Vasoconstrict, sending less blood to the target organ
4. Vasoconstriction in the arterioles of the legs would be expected to:
   A. Increase blood pressure
   B. Decrease blood pressure
   C. Increase blood flow in the legs
   D. Decrease blood flow in the legs
   E. More than one of the above.
5. If right atrial pressure is held constant at 0 mm Hg and arterial blood pressure is increased from 90 mm Hg to 108 mm Hg, and if total peripheral (systemic circulation) resistance is held constant, one could calculate that the cardiac output has done what?
   A. Increased by 80%
   B. Increased by 60%
   C. Increased by 40
   D. Increased by 20%
   E. Decreased by 40%

❖ Answers:

1. B
2. C
3. D
4. E
5. D (From Ohm's Law, we know that $\Delta P = F \times R$. In this case, ΔP has increased by 20% [(108-90)/90], but resistance has not changed. Therefore, the cardiac output (F) must have increased by 20%).

- 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.

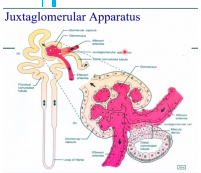
- *What about thirst?* The hypothalamic center regulates ADH secretion (and thus urinary output) and thirst (and thus drinking). ADH and thirst are both stimulated by low H2O levels and suppressed by free water excess.

- 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.

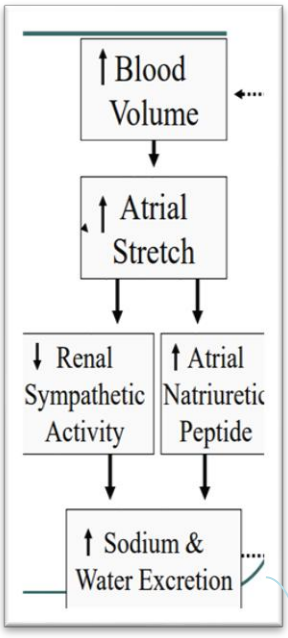
3. Renin-Angiotensin-Aldosterone system: this system requires 1 hour to be effective.



- 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.

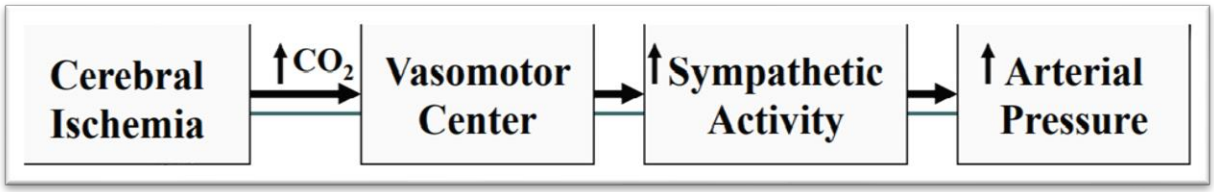
- Until now we have mentioned three mechanisms stimulated by decreased BP → their stimulation raises BP to normal levels.
- Before discussing the fourth mechanism, let's revise the influence of BP over the GFR:
  - ↑ MAP → sympathetic tone is reduced → afferent arterioles of kidney are dilated → more 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.