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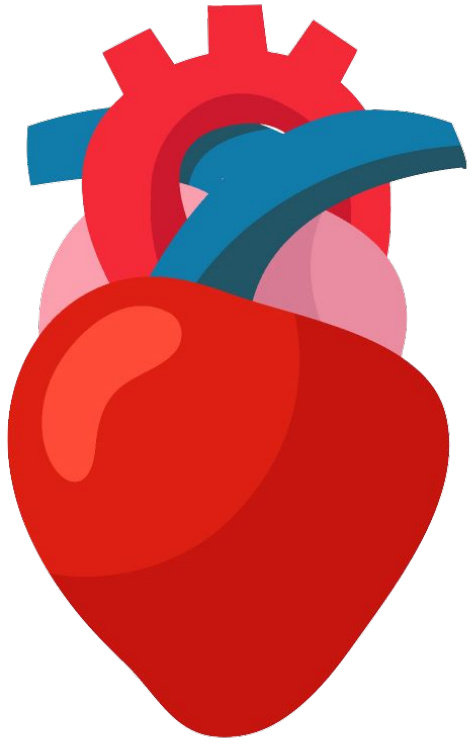

Autoregulation of Cerebral blood flow

PHYSIOLOGY
CNS Block
Team 443

MED 443
King Saud University

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Color Index:

- Main text
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Editing File

Objectives:

At the end of this lecture the student would be able to discuss :

1. Cerebral blood flow(normal rate & autoregulation)
2. Cerebral circulation & Circle of Willis
3. Cerebral blood pressure & Intracranial pressure (ICP)
4. Factors affecting cerebral blood flow
5. Role of carbon dioxide concentration, hydrogen ion concentration, and oxygen concentration in the autoregulation of cerebral circulation (Blood gases & Neural stimuli)
6. CSF formation & absorption & functions.
7. Blood brain barrier (BBB)

Cerebral circulation

Brain receive its blood supply from four main arteries:

the ICA and vertebral arteries are the main arteries that have crucial role in nourishing the whole brain

1-two internal carotid arteries.

2-two vertebral arteries.

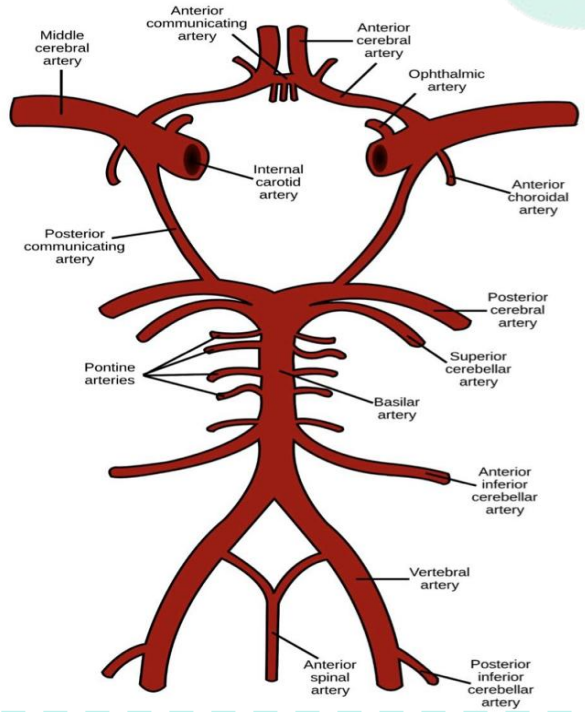
The **vertebral arteries** unite to form Basilar artery

The Basilar artery and the carotids form the **circle of Willis.**

they form the Circle of Willis: A group of arteries near the base of the brain.

The circle of Willis is origin \ consists of six large vessels

- Anterior cerebral artery (left and right)
- Anterior communicating artery
- Internal carotid artery (left and right)
- Posterior cerebral artery (left and right)
- Posterior communicating artery (left and right)
- Basilar artery



Group of arteries near the base of the brain which is called the Arterial Circle of Willis. English physician,Thomas Willis, who discovered it and then published findings in 1664, on Cerebri anatomi

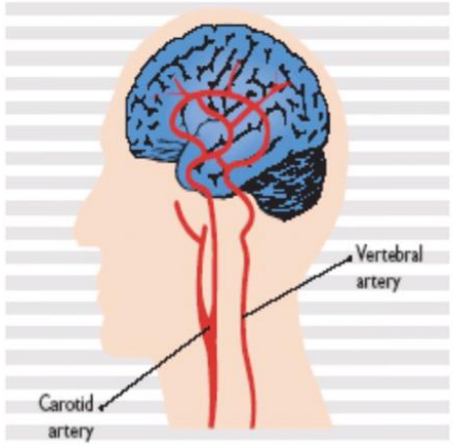
❖ The **Middle Cerebral Arteries** (MCA), supplying the brain, **are not considered part of the circle.**

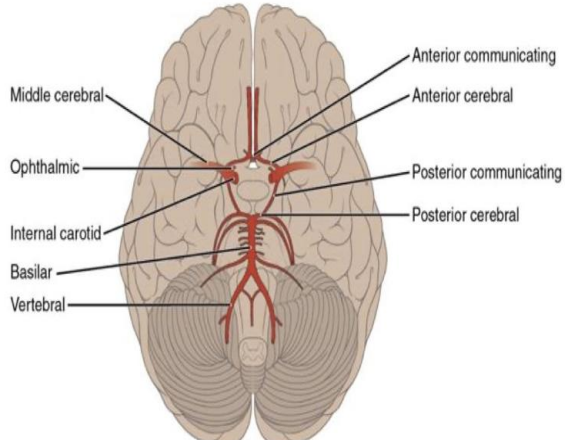
One of the most common types of strokes is due to blockage of the MCA

Cerebral circulation

❖ Substances injected into one carotid artery distributed completely to the cerebral hemisphere on that side. Normally **no crossing over occurs because of equal pressure on both sides.**

❖ The clinical consequences of vascular disease in the cerebral circulation is **depend upon which vessels or combinations of vessels are involved.**





Innervation of cerebral blood flow

Female slides

Three systems of nerves innervate the cerebral blood vessels:

1

Sympathetic

Postganglionic sympathetic neurons have their bodies in the **superior cervical ganglia**. Stimulated during **acute hypertension** it attenuates the increase in CBF.

By causing vasoconstriction of the blood vessels & protect from rupture

2

Parasympathetic

Cholinergic neuron originate in **sphenopalatine ganglion** end on large arteries.

3

Sensory nerves

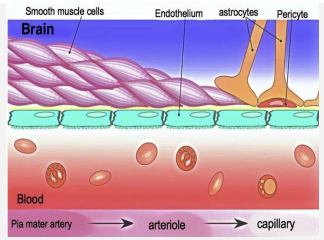
Blood brain barrier

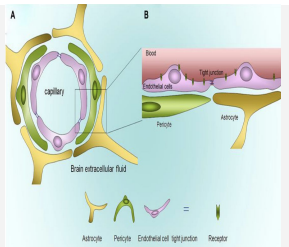
Blood Brain Barrier (BBB)

- ❖ It is between blood & CSF & brain tissue
- ❖ It is formed by the tight junctions between :

1-Choroid plexus epithelial cells (astrocytes & pericytes)

2-At brain capillary membrane (endothelial cells)



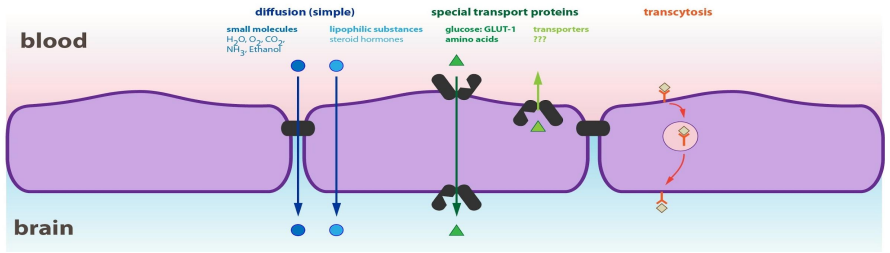


Penetration of substances into the brain

Molecules pass easily	Molecules not pass:	Slight penetration	Glucose
H2O, CO2, O2, lipid-soluble substances (as steroid hormones). Usually they're molecules that are already present in the brain	proteins, antibodies, non- lipid-soluble large molecules. Proteins might have toxic effects on brain. Antibodies cause neural reactions & brain damage .	cl Na K	its passive penetration is slow, but is transported across brain capillaries by GLUTI The brain doesn't need Insulin to transport Glucose inside the brain

Functions of the BBB:

- Maintains the constancy of the environment of the neurons in the CNS.
- Protection of the brain from endogenous and exogenous toxins
- Prevent escape of the neurotransmitters into the general circulation.



An important structural characteristic of the brain capillaries is that most of them are much less "leaky" than the blood capillaries of the body. One reason for this phenomenon is that they are supported on all sides by "glial feet," which are small projections from the surrounding astroglial cells that abut against all surfaces of the capillaries and provide physical support to prevent overstretching of the capillaries in case of high capillary blood pressure. Gyton

Cerebral blood flow

Brain: 1350 gm; 2% of Total Body Weight.

Normal blood flow (rate) through the brain of the adult person averages = ***50 to 65 ml /100 grams of brain tissue / minute.***

For entire brain: **750 to 900 ml/min** = 15 % of the resting cardiac output.

Female slides

CBF is tightly regulated to meet the brain's **metabolic demands.**

It is important to maintain CBF within narrow limits because:-

- ❖ Too much blood can raise intracranial pressure (ICP) which can compress and damage delicate brain tissue.
- ❖ Too little blood flow causes ischemia

Ischemia results if blood flow to the brain is below:- 18 to 20 ml / 100 gm brain tissue / minute

Tissue death (Necrosis) occurs if flow drops below 8 to 10 ml / 100 gm brain tissue / minute.

Cerebral blood flow

Male slides

Factors Effecting Cerebral blood flow:

- **Myogenic / pressure autoregulation**
- **Neurogenic autoregulation**
- **Metabolic autoregulation**

factor	factor
CHEMICAL	MYOGENIC **1. Myogenic / Pressure Autoregulation:**
CMR	Autoregulation / MAP
anesthetics	
temperature	BLOOD VISCOSITY
PaCO2 **3. Metabolic Autoregulation:**	
PaO2	NEUROGENIC **2.Neurogenic Autoregulation:**

Physiological considerations:

- Brain accounts for 2% of body weight yet requires 20% of resting oxygen consumption.
- O2 requirement of brain is 3-3.5 ml/ 100 gm /min.
- And in children it goes higher up to 5ml/100gm/min

Brain has high metabolic rate because:

- Requires more substrate
- Lacks of storage of energy

That's why brain requires higher blood supply

- 55ml/100gm/min is the rate of blood supply.

Cerebral perfusion pressure (CPP)

Cerebral perfusion pressure (CPP)

❖ The net pressure of blood flow to the brain.

❖ CPP can be defined as: **CPP = MAP – ICP**

❖ CPP is normally between **70 - 90 mmHg** in an adult human

❖ The brain maintains proper CPP through the process of autoregulation

CPP is regulated by two balanced, opposing forces:

1 **MAP**

Mean arterial pressure (MAP) is the force that pushes blood into the brain.

2 **ICP**

Intracranial pressure (ICP) is the force that pushes out.

- **normal intracranial pressure 10mmHg**
- pressure > 20 mmHg it's abnormal.

↑ ICP → ↓CBF & ↓cerebral perfusion.

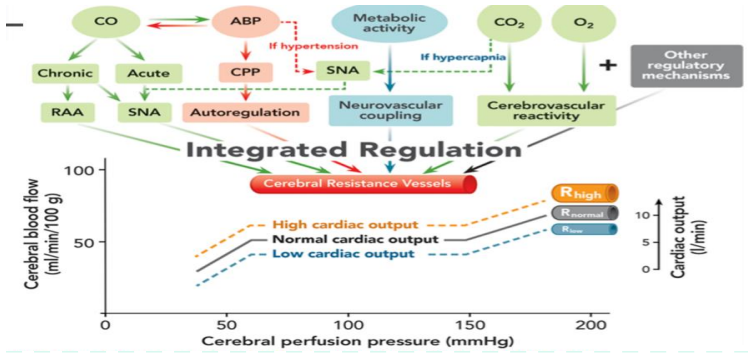
- Effect of ICP changes on systemic blood pressure:

❖ **Cushing reflex** : Normally, the ICP (Intracranial Pressure) ranges from 1 to 15 mm Hg (but other sources give ranges like 8 to 18 mm Hg).

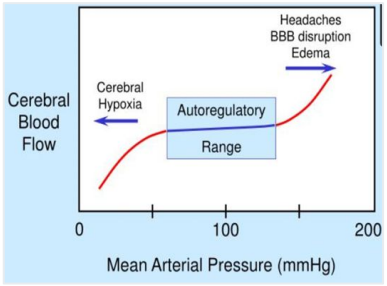
❖ **If ICP > 33 mmHg over a short period of time** → CBF will drop markedly leading to → hypoxia and hypercapnia of vasomotor area causing blood pressure rises.

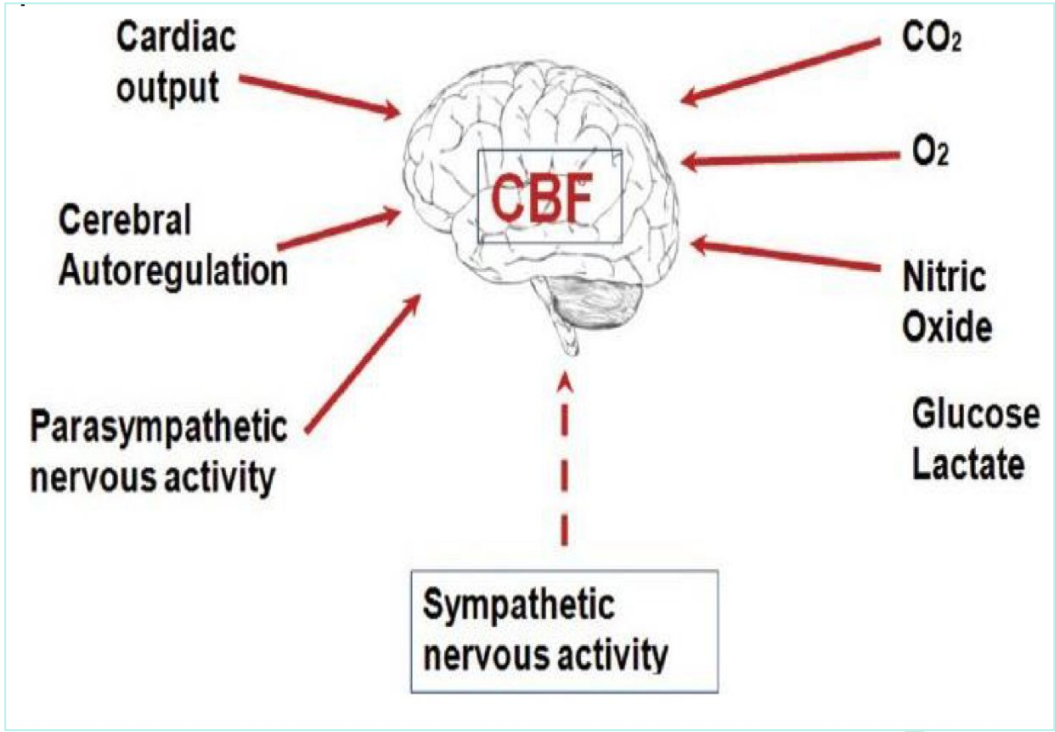
Regulation of Cerebral Blood Flow

Cardiac output (CO); Sympathetic nervous activity (SNA); Renin–angiotensin aldosterone (RAA) system; Arterial blood pressure (ABP); Cerebral perfusion pressure (CPP); Carbon dioxide (CO2) and oxygen (O2); (R) Cerebral resistance vessels at high (R high), normal (R norm), and low (R low)



- When pressures are outside the range of **60 to 150 mmHg** , the blood vessels' ability to autoregulate pressure through dilation and constriction **is lost**, and **cerebral perfusion is determined by blood pressure** alone without autoregulation.
- Thus, **hypotension can result in severe cerebral ischemia** (=If arterial pressure falls below 60 mmHg, cerebral blood flow become severely decreased => ischemia) & **hypertension can result in stroke.**





Regulation of Cerebral Blood Flow

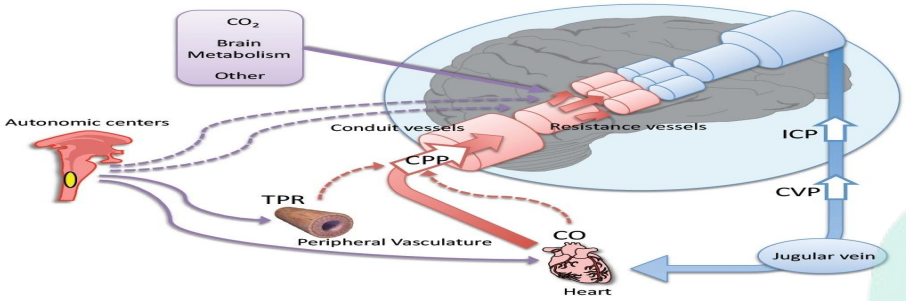
1 Myogenic \ pressure AutoRegulation

- **Arterioles dilate or constrict** in response to changes in **BP** and **ICP** on order to maintain a constant CBF.
- **Myogenic theory:** The **vascular smooth muscles** are **highly responsive to changes in pressure, a process called myogenic activity**, that contributes to auto-regulation of cerebral blood flow.
- **Vascular smooth muscle** within cerebral arterioles **contract to stretch response**, regulating pressure changes. Autoregulation of CBF completely **BP-dependent.**

- The response **to lower pressure is arteriolar dilation** in the brain, while when **blood pressure rises they constrict**.
- At **their most constricted condition**, blood vessels **create a pressure of 150 mmHg**, and at **their most dilated the pressure is about 60 mmHg**. **Thus, changes in the body's overall blood pressure do not normally alter cerebral perfusion pressure (CPP) drastically.**

Team 439 *Guyton: Cerebral Blood Flow Autoregulation Protects the Brain From Fluctuations in Arterial Pressure Changes. During normal daily activities, arterial pressure can fluctuate widely, rising to high levels during states of excitement or strenuous activity and falling to low levels during sleep. However, cerebral blood flow is "autoregulated" extremely well between arterial pressure limits of 60 and 140 mm Hg. That is, mean arterial pressure can be decreased acutely to as low as 60 mm Hg or increased to as high as 140 mm Hg without significant change in cerebral blood flow

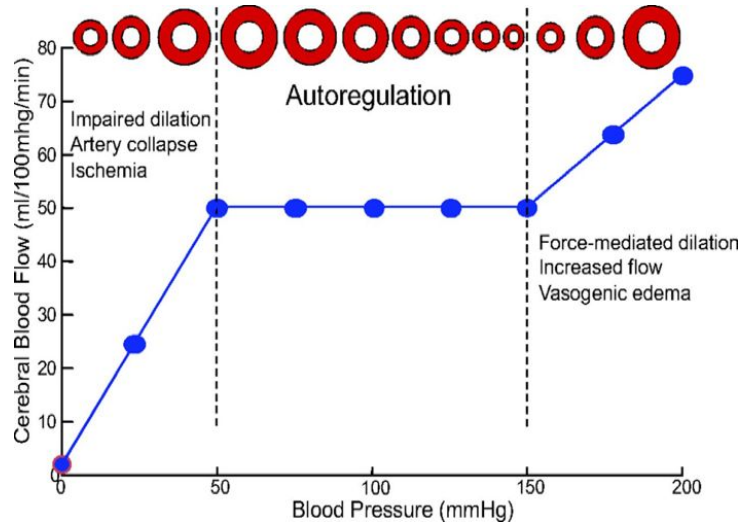
Cardiac output (CO); Cerebral perfusion pressure (CPP); Total peripheral resistance (TPR); Carbon dioxide (CO2); Central venous pressure (CVP); Intracranial pressure (ICP)



Regulation of Cerebral Blood Flow

1 Myogenic \ pressure AutoRegulation

- **Cerebral blood flow is well extremely "auto-regulated"** between arterial pressure limits **of 60 and 140 mmHg.**
- Mean arterial pressure can be decreased acutely to as low as **60 mmHg or increased to as high as 140 mmHg without Significant change in cerebral blood flow.**
- Hypertension, auto-regulation of cerebral blood flow occurs even when the mean arterial pressure rises to As high as **160 to 180 mmHg.**
- **If arterial pressure falls below 60 mmHg, cerebral blood flow become severely decreased.**
- At their **most constricted** condition, blood vessels **create a pressure of 150 mmHg,** and at their **most dilated** the pressure is about **60 mmHg.**



Regulation of Cerebral Blood Flow

2 Metabolic AutoRegulation

-Cerebral blood flow is highly related to metabolism of the tissue.
-Three metabolic factors have potent effects in controlling the Cerebral blood flow:

- **Carbon dioxide (CO2) cons.**
- **Hydrogen ion (H+) cons.**
- **Oxygen (O2) cons.**
- **Neural factors**
- **Other mediators**

Note that: **Nitric oxide & adenosine are autoregulation mediators.**

Increase Cerebral Blood Flow in Response to Excess Carbon Dioxide or Excess Hydrogen Ion Concentration.

Acidity & Carbonic Acid

❖ When activity in a given region of the brain is heightened, the increase in **CO2 and H+ concentrations causes cerebral vasodilatation**, and deliver more blood to the area to meet the increased demand.

❖ Blood vessels dilate in response to low pH (acidity), Arterioles dilate **in response to** potent chemicals that are by-products of metabolism such as **lactic acid, carbon dioxide, pyruvic acid** and H+ .

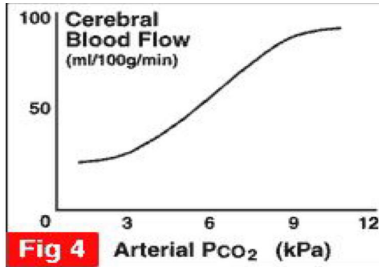
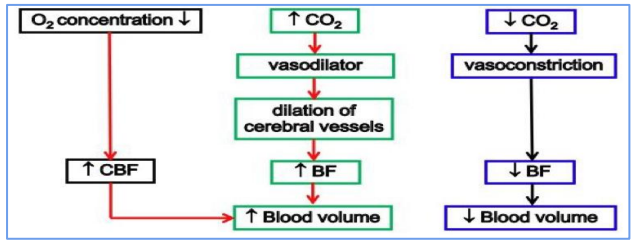
❖ **tissue metabolism → acidic substance** (ex; CO2, H+) **→ increase CBF.**

Acidosis:
❖ Increase in cerebral blood flow, due to vasodilation.
❖ Depress neurotransmitter

Alkalosis:
❖ increase neurotransmitter.
❖ No effect on cerebral blood flow

Regulation of (CBF)-Metabolic Autoregulation cont..

I – CO2 is a potent vasodilator

Increased CO2(Hypercapnia)	❖ Hypercapnia is a condition of abnormally elevated carbon dioxide (CO2) levels in the blood. ❖ Increased arterial pCO2 / decreased BP → Cerebral **Vasodilation**. ❖ As the arterial tension of CO2 (PCO2) rises,**CBV** and **CBF increases**. ❖ Excess carbon dioxide can dilate blood vessels up to 3.5 times their normal size. ❖ 70 % increase in arterial PCO2 approximately doubles the cerebral blood flow.  ❖ **Carbon dioxide increase cerebral blood flow** by combining first with water in the body fluids to form carbonic acid, with subsequent dissociation of this acid to form **hydrogen ions**.(CO2 diffuse through Blood-Brain-Barrier (BBB) into the CSF to form H+ via (Carbonic acid) which then causes the **vasodilation**.)
Decreased CO2 (Hypocapnia)	❖ Decreased CO2 / increased BP → Vasoconstriction. ❖ As the arterial tension of CO2 (PCO2) falls, CBV and CBF **Decreases**, When it is decreased **vasoconstriction is induced.** ❖ **Decreased arterial pCO2 as occurs During hyperventilation →causes cerebral vasoconstriction →decreased blood flow (CBF) → cerebral hypoxia.**
CBF: CO2 and O2	 CO2 dissolves in water making carbonic Acid which then by the help of Carbonic anhydrase breaks into water and bicarbonate, water later on dissociate into two oxygen molecules and one hydrogen (potent vasodilator). So CO2 has an indirect effect while Hydrogen itself has a direct effect of dilation.

Regulation of (CBF)-Metabolic Autoregulation cont..

2 - Hydrogen ions (H+)	
Vasodilation	❖ The hydrogen ions cause **vasodilation** of the **cerebral vessels**. The dilation **directly proportional to the increase in hydrogen ion concentration** up to a blood flow limit of about twice normal. ❖ Increases Hydrogen ion concentration, increase CBF ❖ substances that increase the acidity of brain tissue (such as / include lactic acid, pyruvic acid, and any other acidic material formed during the course of tissue metabolism) & increase hydrogen ion concentration, will increase cerebral blood flow
Neuronal Activity	❖ Increased hydrogen ion concentration greatly **depresses neuronal activity.** ❖ It is fortunate that an increase in hydrogen ion concentration **also causes an increase in blood flow, which in turn carries** hydrogen ions, carbon dioxide, and other **acid forming substances away from the brain tissues.** ❖ Loss of carbon dioxide removes carbonic acid and other acid forming substances away from the brain tissues;, along with removal of other acids, this reduces the hydrogen ion concentration back toward normal. ❖ Thus, this mechanism **helps maintain** a constant hydrogen ion concentration in the cerebral fluids and thereby **helps to maintain a normal, constant level of neuronal activity.**

Regulation of (CBF)-Metabolic Autoregulation cont..

3 - Oxygen (O2)

- The Rate of utilization of O2 by the brain tissue remains within narrow limits—almost exactly **3.5 (± 0.2) ml of oxygen / 100 g of brain tissue/min.**
- Normal value of (PO2) is: **35 - 40 mmHg.**

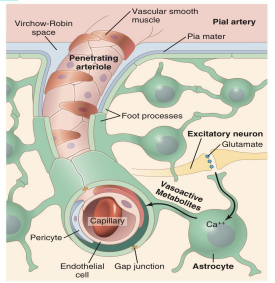
Oxygen Deficiency as a Regulator of CBF

Deficiency mechanism	❖ **If blood flow to the brain insufficient** to supply this needed amount of oxygen, the oxygen deficiency mechanism causing **vasodilation**, returning the brain blood flow and transport of oxygen to the cerebral tissues to normal. ❖ **Decrease** in cerebral tissue **PO2 below** about **30 mm Hg (normal value is 35-40 mmHg) immediately begins to increase cerebral blood flow.** ❖ Brain function becomes unbalanced (**deranged**) at lower values of PO2, especially at PO2 levels below 20 mm Hg. ❖ Oxygen deficiency is a regulator of cerebral blood flow except during periods of **intense** Brain activity (at this time CO2 & H+ are more important). ❖ Hypoxia, or inadequate oxygen, also **dilates** blood vessels and increases blood flow, While high levels of oxygen constrict cerebral B.V. ❖ **Oxygen mechanism for local regulation of cerebral blood flow is important protective response against diminished cerebral neural activity and therefore, against derangement of mental capability.**

Regulation of (CBF)-Metabolic Autoregulation cont..

Extra

Substances Released from Astrocytes Regulate Cerebral Blood Flow.
We should emphasize on the importance of astrocytes in controlling blood flow, electrical stimulation of glutamate releasing neurons can open calcium channels within astrocytes, astrocytes, as we mentioned, have their foot processes on the capillaries, thereby participating in formation of BBB, these astrocytes can be stimulated to release variety of vasodilators that also help maintain blood flow.

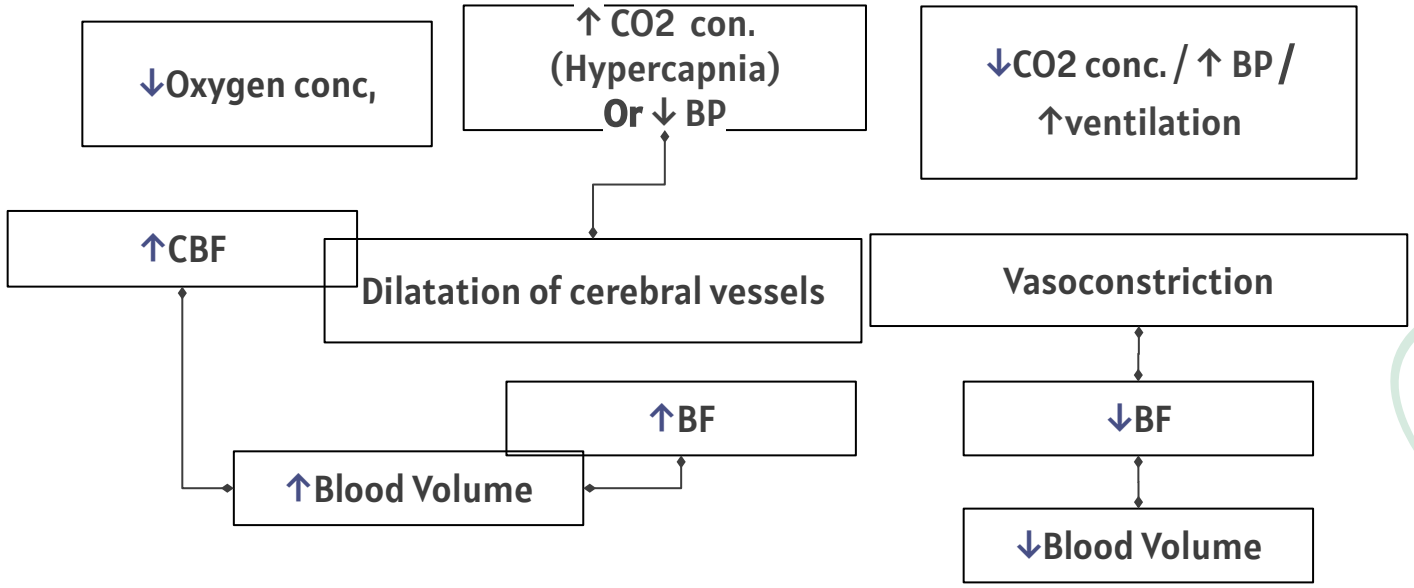


Architecture of cerebral blood vessels and potential mechanism for blood flow regulation by astrocytes. The pial arteries lie on the glia limitans, and the penetrating arteries are surrounded by astrocyte foot processes. Note that the astrocytes also have fine processes that are closely associated with synapses.

438 team

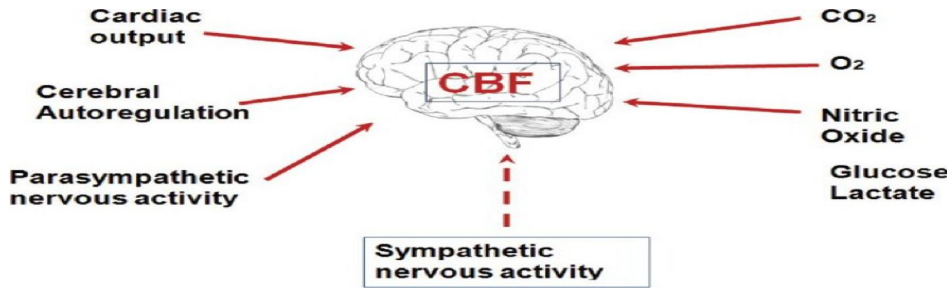
Alkalosis (↓CO2) causes cerebral epileptic seizures. Over breathing in person with epilepsy blows of carbon dioxide and therefore elevates the pH of the blood momentarily leading to a seizure(Increased excitability of cerebral neurons).

While a pH of around 7 (leaning towards acidosis) usually causes come. For example in severe diabetics.



Regulation of (CBF)- Neurogenic regulation

3 Neurogenic AutoRegulation (neural stimuli)



- The cerebral circulatory system has strong sympathetic innervation that passes Upward from the **superior cervical sympathetic ganglia** in the neck and then into the brain along with the cerebral arteries.
- ANS and Neurochemical control has minor role.
- **Pressure** (Myogenic) **and Metabolic** Autoregulation are most important.
- Under **normal** conditions sympathetic has little effect, because the blood flow auto-regulation mechanism can override the nervous effects.
- During Acute hypertension, sympathetic **attenuates** increase in CBF
- The sympathetic nervous system normally **constricts the large and intermediate-sized brain arteries enough to prevent the high pressure from reaching the smaller brain blood vessels. This is important in preventing vascular hemorrhages into the brain for preventing the occurrence of "cerebral stroke."**

Factors disturb Autoregulation

Male slides

• Noxious (Neural) Stimuli

Such as:	Due to
Hypoxia	occlusive cerebro-vascular disease..
Trauma	Head injury.
Brain Compression	Tumors, Hematoma, Cerebral edema.
These factors results in the loss of normal cerebral blood flow (CBF) autoregulation.	

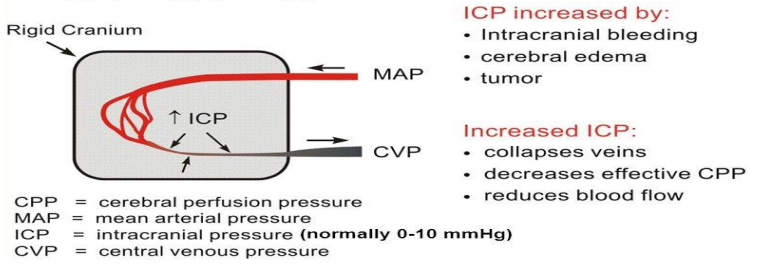
• Cerebral perfusion pressure

ICP increased by:

- ❖ Intracranial bleeding
- ❖ Cerebral edema
- ❖ Tumor

Increased ICP will:

- ❖ Collapsed veins
- ❖ Decreases effective CPP
- ❖ Reduces blood flow



Any lesion that occupies area of the brain will cause increase of ICP which lead to decrease in CBF

• Fainting and Dementia

Fainting	Temporary loss of consciousness, weakness of muscles, and inability to stand up, caused by **sudden loss of blood flow to the brain, changes in blood pressure.**
Dementia	Result from repeated episodes of small strokes **produce progressive damage** to the brain over a period of time. The main clinical feature of dementia is **a gradual loss of memory and intellectual capacity**. Loss of motor function in the limbs and incontinence can also occur

Factors disturb the Autoregulation

- **Stroke**

- Stroke occurs when the blood supply to a part of the brain is blocked resulting in the death of an area.
- **If a large vessel is blocked the outcome may be rapidly fatal or may lead to very severe disability.** The most common types of disability are the loss of functions of one side of the body and speech problems.

Female slides

If the middle cerebral artery is blocked on the left side of the. brain, the person is likely to become:

- Totally demented because of lost function in Wernicke's speech comprehension area in the left cerebral hemisphere
- Unable to speak words because of loss of Broca's motor area for word formation.
- In addition, loss of function of neural motor control areas of the left hemisphere can create spastic paralysis of most muscles on the opposite side of the body

if the posterior cerebral artery is blocked: will cause infarction of the occipital pole on the same side, which causes loss of vision as (hemianopsia)

Factors disturb the Autoregulation- stroke

Principle types of Stroke

Thrombotic
(Common)

Stroke due to the blockage of an artery leading to or in the brain by a blood clot.

Haemorrhagic
(Common)

- Stroke due to bleeding from a ruptured blood vessel, usually a consequence of hypertension.
  - Ruptured aneurysm.
  - Vascular weakening due to chronic hypertension

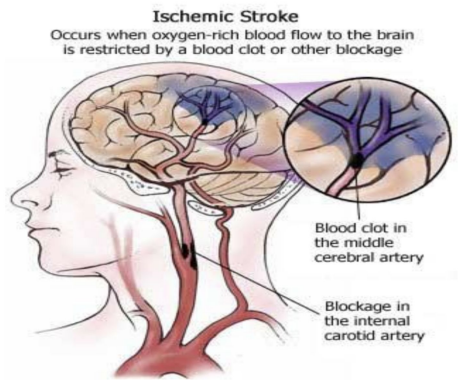
Female slides

Embolic

Stroke due to the formation of a blood clot in a vessel away from the brain. The clot is carried in the bloodstream until it lodges in an artery leading to or in the brain.

Ischemic stroke :

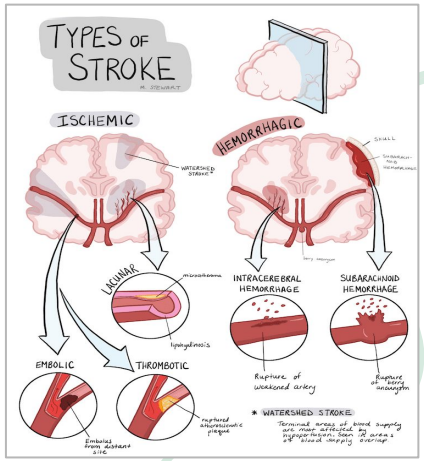
- Thrombus formation or embolism.
- Vasospasm (ET-I?) associated with subarachnoid hemorrhage



Clinical relevance

Endothelin-I receptor antagonists (Bosentan) are used in the treatment of pulmonary hypertension. Inhibition of these receptors prevents pulmonary vasculature constriction and thus decreases pulmonary vascular resistance.

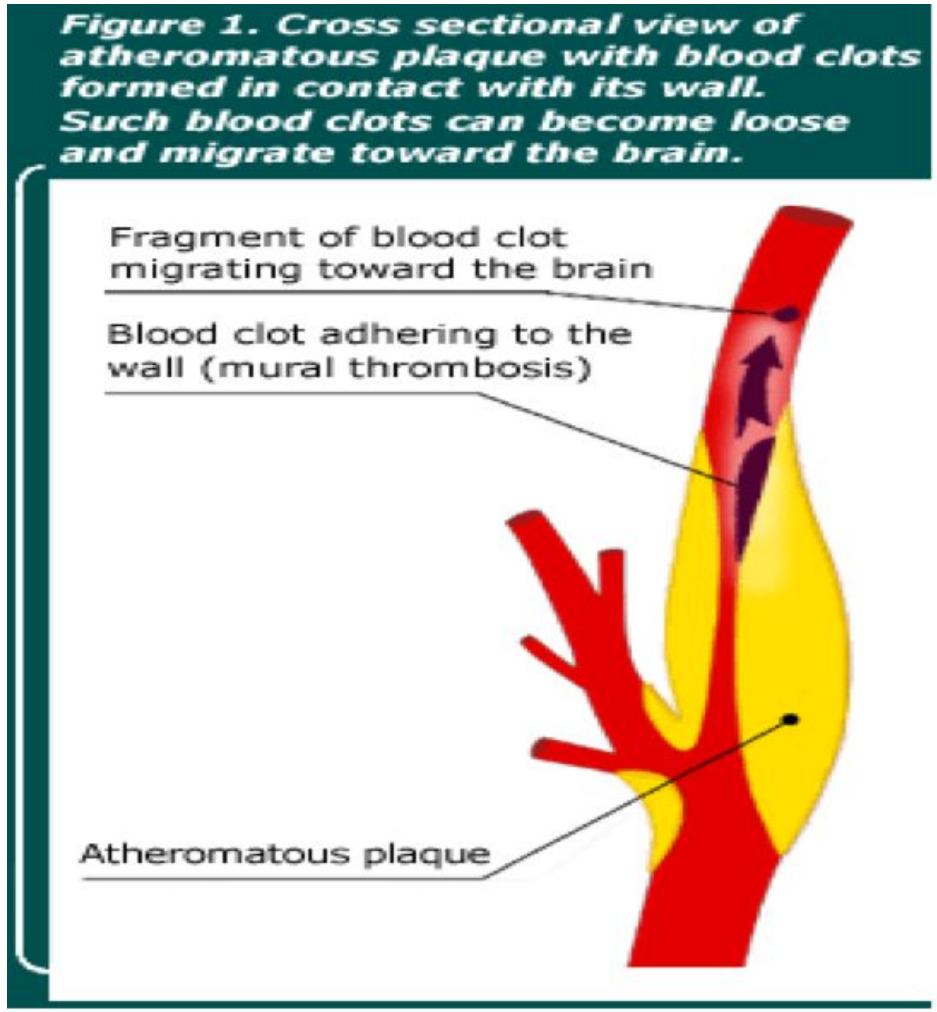
1. "contrecoup phenomenon" When a blow to the head is extremely severe, it is likely to damage the opposite side. And that's due to the fluid shifting to the opposite side creating a vacuum of space in the cranial cavity (as the brain lags). And then as the acceleration stops, it collapses leaving the brain to *strike* the inner surface of the skull causing a bruises or an injury.
2. Endothelin I (ET-I) is a potent vasoconstrictor that is produced by vascular endothelial cells.

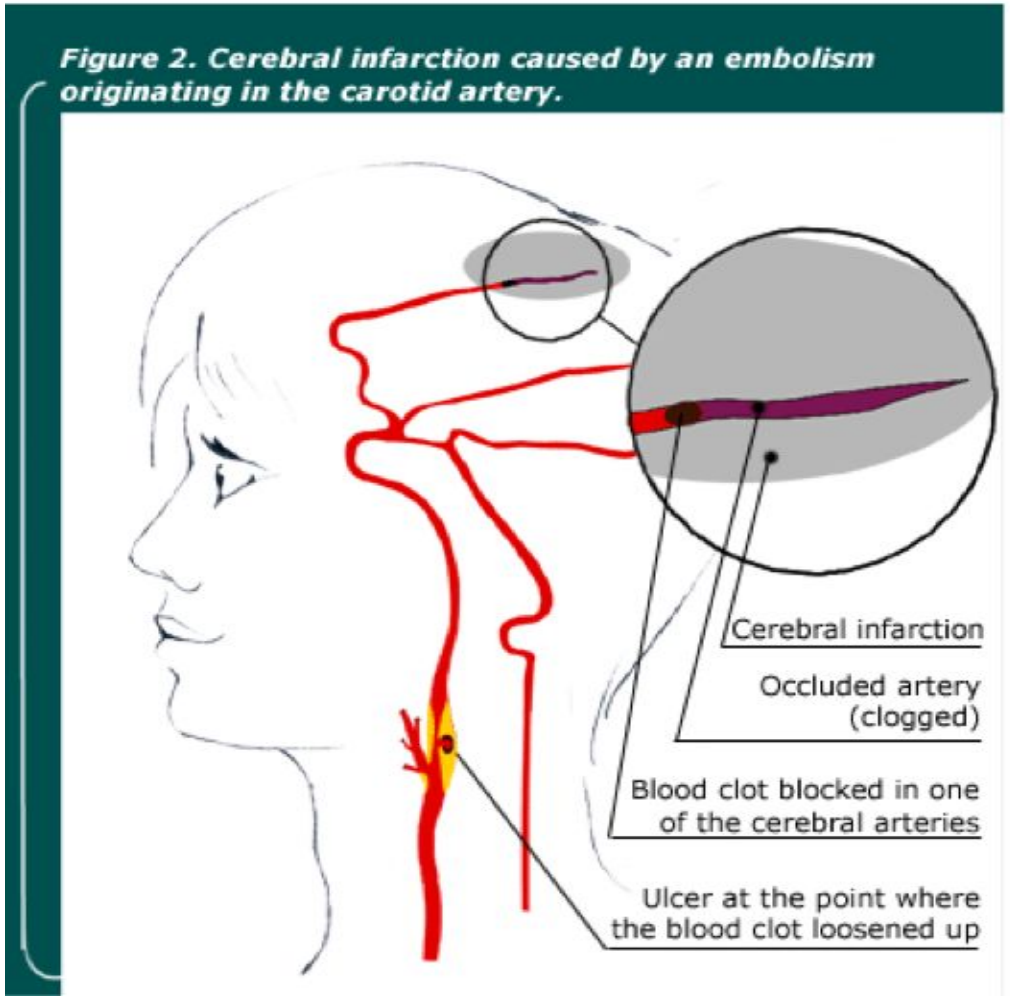


Factors disturb Autoregulation

Male slides

- Infarction



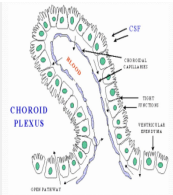


Female slides

Cerebrospinal fluid (CSF)

Cerebrospinal fluid (CSF)

This fluid is present in the ventricles of the brain, cisterna around brain and in the subarachnoid space around both the brain and the spinal cord. All these chambers are connected with one another, and the pressure of the fluid is maintained at a constant level.



- Volume = 150 ml
- Rate of production = 500 ml/day
- Lumbar CSF pressure = 70-180 mm hg
- Absorption of CSF is proportionate to CSF pressure.
- At pressure of 112 mm (normal average): filtration and absorption are equal.
- Below pressure of 68 mm CSF,absorption stops.

Composition of the CSF		
Substance	CSF	Plasma
Na+	147	150
K+	2.9	4.6
HCO3-	25	24.8
PCO2	50	39.5
PH	7.33	7.4
Osmolality	289	289
Glucose	64	100

Functions of the CSF:

- Protective function(cushioning): In air brain weight =1400 gm, but in its water bath of CSF , brain weight = 50 gm, making it suspended and floated effectively.
- Facilitation of pulsatile cerebral blood flow
- Distribution of peptides, hormones, neuroendocrine factors and other nutrients and essential substances to cells of the body(the doctor said cells of the brain)
- Wash away waste products.

- The composition of CSF is nearly the same as brain ECF.
- osmotic pressure, approximately **equal** to that of plasma.
- sodium ion concentration is approximately **equal** to that of plasma.
- **chloride** ion, about **15 percent greater** than in plasma.
- **potassium** ion, approximately **40 percent less.**
- **glucose** about **30 percent less.**

Summary

- The circle of Willis is a group of arteries at the base of the brain , brain receives its blood supply by **two internal carotid arteries and two vertebral arteries.**
- Normal blood flow through the brain of the adult person averages 50 to 65 milliliters / 100 grams of brain tissue per minute.
- The main systems regulate CBF;
  1)Myogenic / pressure Autoregulation.
  2) metabolic Autoregulation.
  3)Neurogenic Autoregulation.
- **Carbon dioxide, Hydrogen and Oxygen concentration have potent effect in the regulation CBF.**
- **Noxious stimuli** such as hypoxia, trauma / head injury or brain compression from tumors, hematomas or cerebral edema, results in the loss of normal cerebral blood flow/ autoregulation.

TEST YOURSELF !

1- Cerebral blood flow is autoregulated when BP is ?

A) 30-60

B) 60-140

C) 100-160

D) 120-180

2- Which of the following plays a role in cerebral blood flow?

A) K+

B) Na+

C) O2

D) Mg+2

3- Which of the following regulates cerebral blood flow?

A) Arterial neurotransmitter level

B) Atrial natriuretic peptide

C) Cerebral metabolic rate.

D) Potassium ions.

4- Which of the following can't cross the blood brain barrier?

A) Protein

B) Glucose

C) Oxygen

D) CO2

Answers : B, C, C, A.

SAQ

Mention three factors that disturb the Autoregulation :

-Stroke, fainting , dementia.

Mention the main systems that involved in the regulation of the CBF :

- Myogenic / pressure Autoregulation.
- Metabolic Autoregulation.
- Neurogenic Autoregulation.

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