Physiology Team 439

MED439
KING SAUD UNIVERSITY

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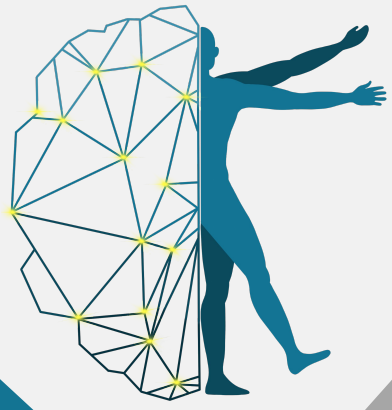


Autoregulation of Cerebral blood flow

Objectives:

- **Cerebral circulation & circle of willis.**
- **Cerebral blood flow (CBF):**

  Normal rate, Factors affecting regulation and Autoregulation of CBF
- (*Metabolic*) Role of **CO2**, **H_+** and **O2** cons.' in the autoregulation of CBF.
- Cerebral blood (perfusion) pressure (CPP).
- Intracranial pressure (ICP).
- Cerebrospinal fluid (CSF) formation, absorption and function.
- Blood brain barrier (BBB).

A Message from the Organizer

Color index:

- Important.
- Girls slide only.
- Boys slide only.
- Dr's note.
- Extra information.

Editing File

1 Cerebral Circulation

Brain receive its blood supply from four main arteries:

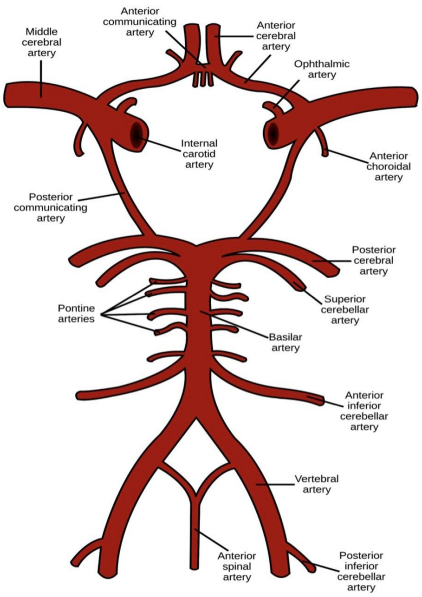
1-two internal carotid arteries.

2-two vertebral arteries. → The **vertebral arteries** unite to form Basilar artery

↓

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

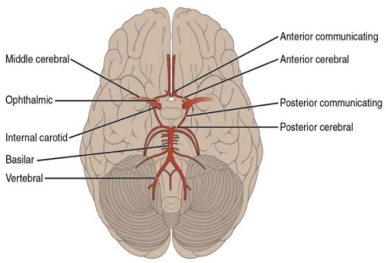
1 and 2 form the **Circle of Willis**: A group of arteries near the base of the brain. → The circle of Willis consists of six large vessels

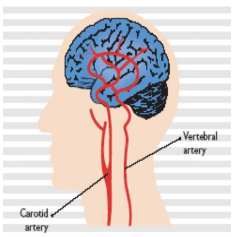


Female slides only

1. Anterior cerebral artery (left and right)
2. Anterior communicating artery
3. Internal carotid artery (left and right)
4. Posterior cerebral artery (left and right)
5. Posterior communicating artery (left and right)
6. Basilar artery

- The Middle Cerebral Arteries (MCA), supplying the brain, are not considered part of the circle.
- The MCA is by far the largest cerebral artery and is the vessel most commonly affected by cerebrovascular accident.
- The clinical consequences of vascular disease in the cerebral circulation is depend upon which vessels or combinations of vessels are involved.
- 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.





2 Cerebral Blood Flow

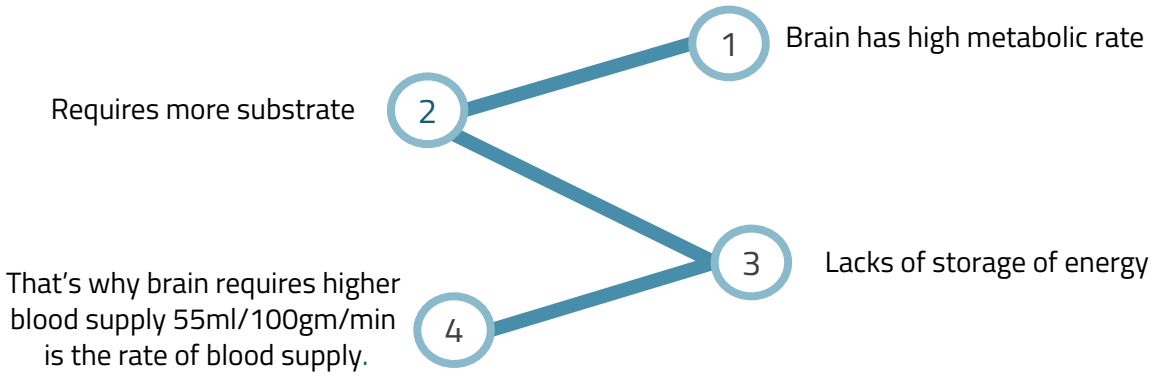
- CBF is tightly regulated to meet the brain's metabolic demands*
- Brain: **1350 gm**; **2%** of Total Body Weight*
- Normal blood flow through the brain of the adult person averages = ***50 to 65 ml /100 grams of brain tissue / minute.***
- For entire brain: **750 to 900 ml/min** = 15 % of the resting cardiac output.
- 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.*

*Values are **important**

Physiological considerations:

*Male slides only

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.



factor	factor
CHEMICAL	MYOGENIC
CMR	Autoregulation / MAP
anesthetics	
temperature	BLOOD VISCOSITY
PaCO2	
PaO2	NEUROGENIC

Factors Affecting Regulation of CBF

- A Myogenic
- B Neurogenic
- C Metabolic

Note that: Nitric oxide & adenosine are autoregulation mediators.

*Male slides only
*Female slides only

3 Regulation of CBF

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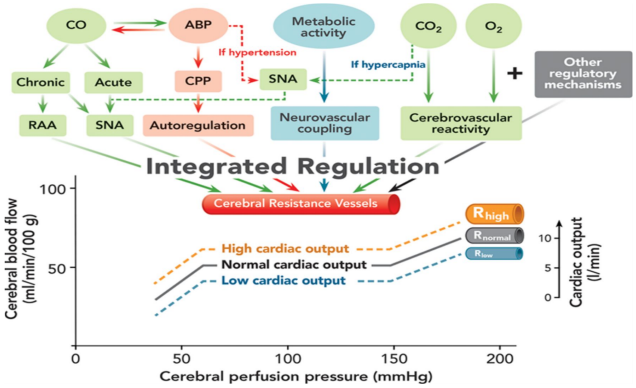
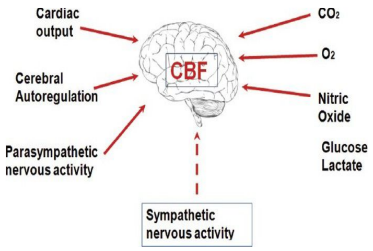




*Cardiac output (CO); Sympathetic nervous activity (SNA); Renin–angiotensin–aldosterone (RAA) system; Arterial blood pressure (ABP); **Cerebral perfusion pressure (CPP)**; Carbon dioxide (CO2) and oxygen (O2); (R) Cerebral resistance vessels at high (R high), normal (R norm), and low (R low)*

A Myogenic AutoRegulation

-Arterioles dilate or constrict in response to changes in BP and ICP to maintain a constant CBF.*
-Vascular smooth muscle within cerebral arterioles **contract to stretch response**, regulating pressure changes. Autoregulation of CBF completely **BP-dependent.***

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.*

Cerebral blood flow (CBF) is well extremely "auto-regulated" between arterial pressure limits *of 60 and 140 mm Hg.*

The brain maintains proper **Cerebral Perfusion Pressure** (CPP) through the process of autoregulation.*

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.***

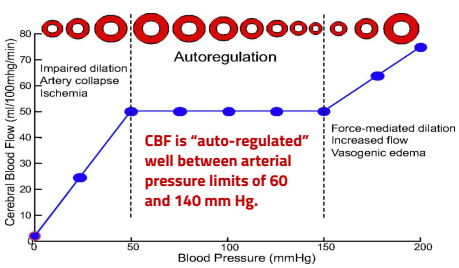
- The response to **lower pressure is arteriolar dilation** in the brain, while when blood **pressure rises they constrict.***

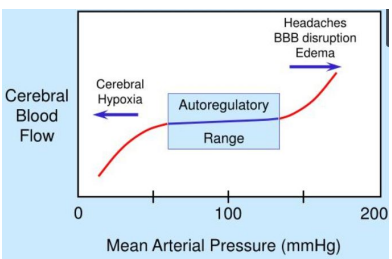
- At their most constricted condition, blood vessels create a pressure of 150 mmHg, and at their most dilated the pressure is about 60 mmHg.*
Thus, changes in the body's overall blood pressure do not **normally** alter cerebral perfusion pressure (CPP) drastically.*

When pressures are outside the range of **60 to 150 mmHg (to 180 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.**

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.





B Neurogenic AutoRegulation

- 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.

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.

*Three systems of nerves innervate the cerebral blood vessels:

- 1 Sympathetic:
Postganglionic sympathetic neurons have their bodies in the superior cervical ganglia. During acute hypertension it attenuates the increase in CBF.

- 2 Parasympathetic:
Cholinergic neuron originate in sphenopalatine ganglia end on large arteries.

*Female slides only

- 3 Sensory nerves.

* 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, preventing the occurrence of "cerebral stroke."

*Male slides only

Noxious (Neural) Stimuli

Such as:	Due
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.	

C Metabolic AutoRegulation Most important one*

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.

Metabolic AutoRegulation cont..

1 - Carbon dioxide (CO2) & 2 - Hydrogen ions (H+)

Acidity & Carbonic Acid

- **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**.)
- 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.

1 - CO2 is a potent vasodilator

Increased CO2 (Hypercapnia)

- **Hypercapnia** is a condition of abnormally elevated carbon dioxide (CO_2) levels in the blood.
- Increased CO2 / decreased BP → **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.*

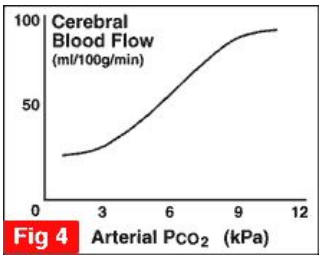
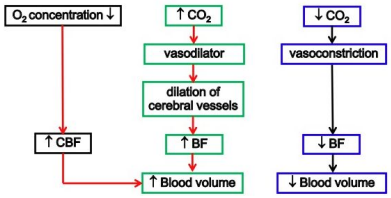


Fig 4

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.*
- **During hyperventilation → decreased CBF → cerebral hypoxia.**

CBF: CO2 and O2



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**.
Neuronal Activity	❖ Increased hydrogen ion **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 from the tissues; this, along with removal of other acids, 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.**

3 - Oxygen (O2)

❖ Rate of utilization of O2 by the brain tissue is: **3.5 (± 0.2) ml of oxygen / 100 g of brain tissue/min.**

❖ Normal value of (PO2) is: **35 - 40 mmHg.**

❖ **high levels of oxygen constrict cerebral B.V.**

❖ Oxygen deficiency is a regulator of cerebral blood flow except during periods of **intense** Brain activity (at this time CO2 & H+ are more important).

❖ Oxygen mechanism for local regulation of cerebral blood flow is important protective response against diminished cerebral neuronal activity and therefore, against derangement of mental capability.

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 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.

4 Factors disturb Autoregulation

A - Cerebral perfusion pressure (CPP)

- The net pressure of blood flow to the brain.
- CPP can be defined as: CPP = MAP – ICP
- is normally between 70 - 90 mmHg in an adult human

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.
(Normally 0-10 mmHg). If pressure > 20 mmHg it's abnormal.
↑ ICP → ↓CBF & ↓cerebral perfusion.

MAP has to be greater than ICP. So, as ICP increases, MAP also increases to compensate

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 hypercapnea of vasomotor area causing blood pressure rises.*

ICP increased by:

- Intracranial bleeding
- Cerebral edema
- Tumor

Cerebral perfusion pressure*

Increased ICP: will:

- Collapses veins
- Decreases effective CPP
- Reduces blood flow

CPP= cerebral perfusion pressure
MAP= mean arterial pressure
ICP= intracranial pressure

*Male slides only
*Female slides only

4 Factors disturb Autoregulation

B - 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.

1 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

2 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)

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 chronic hypertension. Ruptured aneurism.
- **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-1?) associated with subarachnoid hemorrhage

*Male slides only
*Female slides only

4 Factors disturb Autoregulation cont..

C - 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.*

5 CSF & BBB

Female slides only

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

- 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

CSF & BBB cont..

Functions of the CSF:

1	**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.
2	Facilitation of pulsatile cerebral blood flow
3	Distribution of peptides, hormones, neuroendocrine factors and other nutrients and essential substances to cells of the body
4	Wash away waste products.

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).	proteins, antibodies, non- lipid- soluble large molecules.	cl Na K	its passive penetration is slow, but is transported across brain capillaries by **GLUT1**

The brain doesn't need Insulin to transport Glucose inside the brain

Functions of the BBB:

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

MCQ & SAQ:

Q1: the Circle of Willis consists the following arteries except:

A. Internal carotid artery (left and right)
B. Vertebral artery
C. Basilar artery
D. Posterior cerebral artery

Q2: Normal blood flow through the brain of the adult person average:

A. 8 to 10 ml/100 grams of brain tissue /minute
B. 18 to 20 ml/100 grams of brain tissue /minute
C. 35 to 50 ml/100 grams of brain tissue /minute
D. 50 to 65 ml/100 grams of brain tissue /minute

Q3: which type of stroke is usually consequence of chronic hypertension?

A. Thrombotic stroke
B. Hemorrhagic stroke
C. Embolic stroke

Q4: Vasoconstriction is induced when:

A. PCO2 tension constant, CBV dropped, CBF dropped
B. PCO2 tension increases. CBV increases, CBF increases
C. PCO2 tension decreases, CBV dropped, CBF dropped
D. PCO2 tension decreases, CBV dropped, CBF rises

Q5: Decrease in cerebral tissue PO2 below about 30 mm Hg cause:

A. Immediately increase CBF
B. Deranged mental capability
C. PCO2 increases ph levels
D. ischemia to brain tissue

Q6: Activity that Contributes to auto-regulation of CBF via vascular smooth muscles ability to be highly responsive to changes in pressure:

A. O2 deficiency mechanism
B. neuronal stimulus regulation
C. acidity of H+ during less intense periods
D. Myogenic theory processes

answer key:
1: B
2: D
3: B
4: C
5: A
6: D

1- what are the main arteries that supply the brain?

2- what are the functions of Blood Brain Barrier?

3- How the differences between Acidosis & Alkalosis affects CBF Regulation?

4- Describe the Oxygen deficiency mechanism?

A1: 2 internal carotid arteries , 2 vertebral arteries

A2: 1-Maintains the constancy of the environment of the neurons in the CNS 2-Protection of the brain from endogenous and exogenous toxins 3-Prevent escape of the neurotransmitters into the general circulation.

A3: Slide (8)

A4: 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.

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