Local and humoral control of tissue blood flow-4

• Most tissues have the ability to control their own local blood flow in proportion to their specific metabolic needs.

• Organs have special requirements, such as skin and kidney.

Table 17-1 Blood Flow to Different Organs and Tissues Under Basal Conditions

	Percentage of Cardiac Output	ml/min	ml/min/100 g of Tissue Weight
Brain	14	700	50
Heart	4	200	70
Bronchi	2	100	25
Kidneys	22	1100	360
Liver	27	1350	95
• Portal	(21)	(1050)	
• Arterial	(6)	(300)	
Muscle (inactive state)	15	750	4
Bone	5	250	3
Skin (cool weather)	6	300	3
Thyroid gland	1	50	160
Adrenal glands	0.5	25	300
Other tissues	3.5	175	1.3
Total	100.0	5000	

BF inc X 20 during exercise

Why to control blood flow by local tissues?

- Why not continuously provide a very large blood flow through every tissue of the body that would always be enough to supply the tissue's needs, regardless of whether the activity of the tissue is small or large?
- The answer is:
- such a mechanism would require many times more blood flow than the heart can pump.
- Experiments have shown that the blood flow to each tissue usually is regulated **at the minimal level** that will supply the tissue's requirements—**no more, no less**, and the workload on the heart is kept at a minimum.

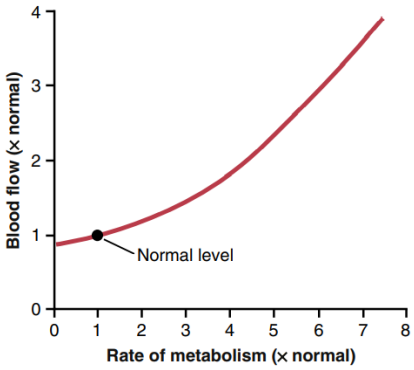
Phases of local blood flow control

• Local blood flow control can be divided into two phases:

• **acute control, (rapid).**
• **long-term control.**
• **Acute control :** is achieved by **rapid** changes in local **vasodilation** or **vasoconstriction** of the arterioles, metarterioles, and precapillary sphincters that occur within seconds to minutes to provide rapid maintenance of appropriate local tissue blood flow.
• **Long-term control ,(structural changes in vessels) :** means **slow**, controlled changes in flow over a period of days, weeks, or even months.

- In general, these long-term changes provide even **better control** of the flow in proportion to the needs of the tissues.
- These changes come about as a result of an increase or decrease in the physical sizes and numbers of blood vessels supplying the tissues.

Acute control
• **Increases in Tissue Metabolism Increase Tissue Blood Flow**:



- **Reduced Oxygen Availability Increases Tissue Blood Flow**:
- (1) at a high altitude at the top of a high mountain.
- (2) in pneumonia.
- (3) in carbon monoxide poisoning (which poisons the ability of hemoglobin to transport oxygen).

- (4) in cyanide poisoning (which poisons the ability of the tissues to use oxygen).
- The blood flow through the tissues increases markedly.

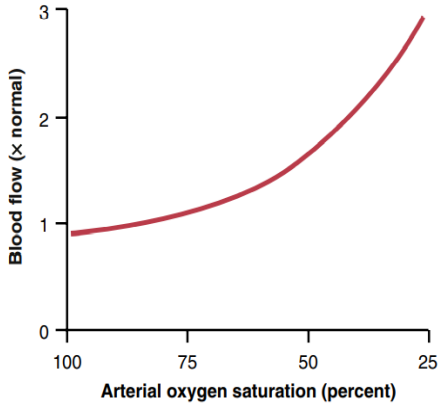
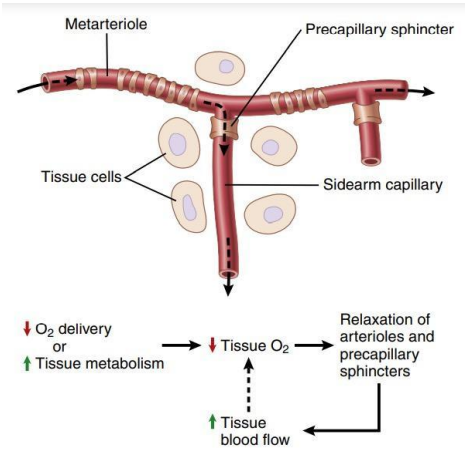


Figure 17-2. Effect of decreasing arterial oxygen saturation on blood flow through an isolated dog leg.



Vasodilator theor

Mechanism? • two main theories have been proposed:

• the oxygen demand theory	**• the vasodilator theory.**
• the precapillary sphincters are normally completely open or completely closed. • The number of precapillary sphincters that are open at any given time is roughly proportional to the requirements of the tissue for nutrition.	• Low O2 and nutrients---ಆincrease formation of vasodilator substances in the tissues --ಆdiffuse to vasculature and cause vasodilation.

	● adenosine, carbon dioxide, adenosine phosphate compounds, and hydrogen ions.

Vasomotion

- The precapillary sphincters and metarterioles open and close cyclically several times per minute, with the duration of the open phases being proportional to the metabolic needs of the tissues for oxygen.
- The cyclical opening and closing is called **vasomotion**.
- the strength of contraction of the sphincters would increase with an increase in oxygen concentration

Role of nutrients

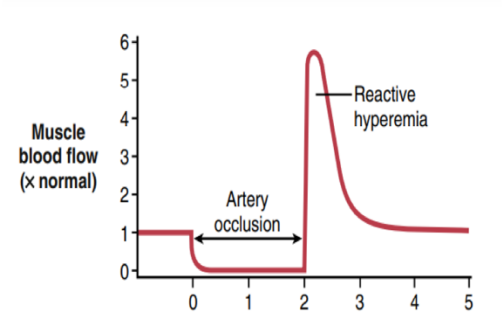
- lack of **glucose** in the perfusing blood can cause local tissue vasodilation.
- Vasodilation can also occur in **vitamin** deficiency such as vitamin B substances thiamine, niacin, and riboflavin.
- Because all these vitamins are necessary for oxygen-induced phosphorylation, which is required to produce ATP in the tissue cells,
- lead to diminished smooth muscle contractile ability and therefore local vasodilation as well.

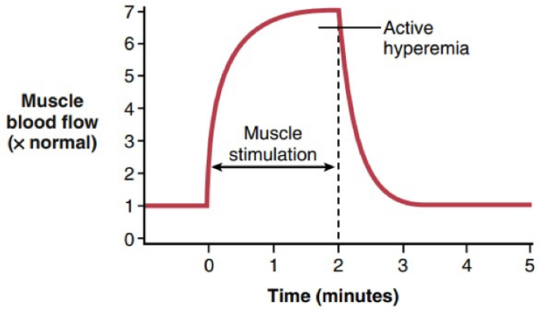
Reactive hyperemia

• When the blood supply to a tissue is blocked for a few seconds to hours then is unblocked, blood flow through the tissue usually increases immediately.

Active hyperemia

- When a tissue becomes highly active, such as an exercising muscle or the brain during increased mental activity, the rate of blood flow through the tissue increases.
- The release large quantities of vasodilator substances result is dilation of local blood vessels and increased local blood flow.
- In this way, the active tissue receives the additional nutrients required to sustain its new level of function.





Autoregulation of Blood Flow During Changes in Arterial Pressure

• In any tissue of the body, a rapid increase in arterial pressure causes an immediate rise in blood flow. However, within less than 1

minute, the blood flow in most tissues returns almost to the normal level, even though the arterial pressure is kept elevated.

Metabolic theory

• when the arterial pressure becomes too great, the excess flow provides **too much oxygen** and too many other **nutrients** to the tissues and **washes out the vasodilators** released by the tissues.

• These nutrients (especially oxygen) and decreased tissue levels of vasodilators then cause the blood vessels to **constrict** and return flow to nearly normal, despite the increased pressure.

Myogenic theory

• **Sudden stretch of** small blood **vessels causes** the **smooth muscle** of the vessel wall **to contract**. Therefore, when high arterial pressure stretches the vessel, reactive vascular constriction results, which **reduces blood flow** nearly back to normal.

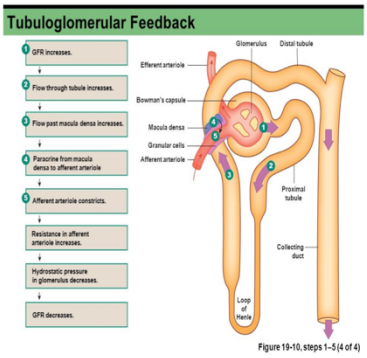
- Conversely, at low pressures, the degree of stretch of the vessel is less, so the smooth muscle relaxes, reducing vascular resistance and helping to return flow toward normal.
- It is most pronounced in arterioles but can also be observed in arteries, venules, veins, and even lymphatic vessels.
- The **myogenic response is inherent to vascular smooth muscle** and can occur in the absence of **neural** or **hormonal** influences.
- Myogenic contraction is initiated by **stretch-induced vascular depolarization,** which then rapidly increases calcium ion influx into the cells, causing them to contract.
- Changes in vascular pressure may also open or close other ion channels that influence vascular contraction.

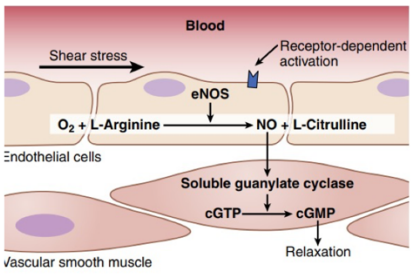
- • The **myogenic mechanism** appears to be important in **preventing excessive stretching of blood vessels** when blood pressure is increased.
- • **Metabolic factors appear to override the myogenic mechanism** in circumstances in which the metabolic demands of the tissues are significantly increased, such as during vigorous muscle exercise, which causes dramatic increases in skeletal muscle blood flow.

Special mechanisms

• In **the brain**, in addition to control of blood flow by tissue oxygen concentration, the concentrations of **carbon dioxide and hydrogen ions play prominent roles.**

- An increase of either or both of these substances **dilates the cerebral vessels.**
- This mechanism is important because the level of **excitability** of the brain is highly dependent on exact control of both carbon dioxide concentration and hydrogen ion concentration.





Endothelium derived constricting or relaxing factors

• Nitric oxide: vasodilator

- The most important of the endothelium derived relaxing factor.
- Endothelial derived nitric oxide synthase (eNOS) enzymes synthesize NO.
- Activates soluble guanylate cyclases in vascular smooth muscle cells, resulting in relaxation the blood vessels.

NO

• The flow of blood through the arteries and arterioles causes **shear stress** on the endothelial cells which **causes significant increase in NO release.**

• NO synthesis and release also stimulated by some **vasoconstrictors, such as angiotensin II**, which bind to specific receptors on endothelial cells. The increased NO release protects against excessive vasoconstriction.

• **When endothelial cells are damaged** by chronic hypertension or atherosclerosis, impaired NO synthesis may contribute to **excessive vasoconstriction** and worsening of the hypertension and endothelial damage.

NO- Clinical applications

• **Angina pectoris**:

• Nitrate derivatives release NO and cause dilation of blood vessels throughout the body, including the coronary blood vessels.

• **Erectile dysfunction**:

• Sildenafil inhibits cGMP-specific phosphodiesterase-5 (PDE-5), which prolongs the actions of NO to cause vasodilation.

Endothelium – derived constricting or relaxing factors

• **Endothelin: vasoconstrictor**

• The usual stimulus for release is damage to the endothelium, like in **trauma** and **hypertension**.

Long term blood flow regulation

• Over a period of hours, days, and weeks, a long-term type of local blood flow regulation develops in addition to the acute control.
• Gives far more complete control of blood flow and extreme effectiveness.
• A key mechanism for long-term local blood flow regulation is to **change the amount of vascularity of the tissues**.
• if the **metabolism** in a tissue is increased for a prolonged period, vascularity increases, a process generally called **angiogenesis**; if the metabolism is decreased, vascularity decreases.

- The actual physical reconstruction of the tissue vasculature occurs to meet the needs of the tissues.
- occurs **rapidly (within days) in young** subjects. It also occurs rapidly in **new growth tissue**, such as in cancerous tissue, but occurs much more slowly in old,

  well-established tissues**.**

• The time required for long-term regulation to take place may be only a few days in the **neonate** or as long as months in older adults.
• Furthermore, the final degree of response is much better in **younger** than in **older** tissues;

<u>Role of oxygen in long term regulation</u>

• **In premature babies** who are put into **oxygen tents** for therapeutic purposes, the excess oxygen causes cessation of new vascular growth in the **retina** and degeneration of some of the small vessels that already have formed.
• When the infant is **taken out of the oxygen tent**, explosive **overgrowth of new vessels** then occurs to make up for the sudden

decrease in available oxygen. Often, so much overgrowth occurs that the retinal vessels grow out from the retina into the eye's vitreous humor, eventually causing **blindness**, a condition called

retrolental fibroplasia.

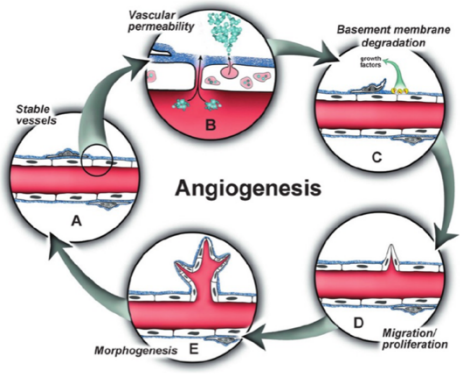
<u>Vascular growth factors:</u> (you don't have to know exact names and mechanisms).

• Many factors increase the growth of new blood vessels, such as **VEGF), PDGF, FGF** and angiogenin.

• **Angiogenesis** begins with new vessels **<u>sprouting</u>** from other small vessels.

• other substances, such as some **steroid hormones**, have the **opposite effect** on small blood vessels, occasionally even causing dissolution of vascular cells and disappearance of vessels.

• **Antiangiogenic peptides** produced in the tissues can block the growth of new blood vessels. For example, **angiostatin**, and **endostatin**.



Long-term vascular control

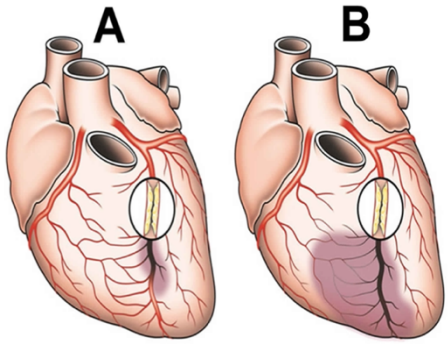
• An especially valuable characteristic of long-term vascular control is that vascularity is **determined mainly by the maximum level of**

blood flow required by the tissue rather than by average need. (like in heavy exercise).

Collateral circulation

- In most tissues of the body, when an artery or a vein is blocked, a new vascular channel usually develops around the blockage and allows at least partial resupply of blood to the affected tissue.
- Development of collateral vessels follows the usual principles of acute and long-term local blood flow control; the acute control is rapid metabolic dilation, followed chronically by growth and enlargement of new vessels over a period of weeks and months.

- An **<u>important example</u>** of the development of collateral blood vessels occurs after thrombosis of one of the coronary arteries.



<u>Vascular remodeling</u>

• Vascular growth and remodeling are critical components of tissue development and growth and occur as an adaptive response to long-term changes in **blood pressure** or **blood flow**.

• **Chronic reductions in blood pressure and blood flow** have effects opposite to those previously described.

- When blood flow is greatly reduced, the diameter of the vascular lumen is also reduced.

- when blood pressure is reduced, the thickness of the vascular wall usually decreases.

Vascular remodeling in Hypertension

• In **small blood vessels** that **constrict** in response to increased blood pressure, the vascular smooth muscle cells and endothelial cells gradually rearrange themselves around the smaller lumen diameter, a process called **inward eutrophic remodeling**, with **no change in the total cross-sectional area of the vascular wall.**

In **larger arteries** that do not constrict in response to the increased pressure, the vessel wall is exposed to increased wall tension that stimulates a **hypertrophic remodeling** response and an **increase in the cross-sectional area** of the vascular wall.

The hypertrophic response increases **the size of vascular smooth muscle cells** and stimulates formation of additional extracellular matrix proteins, such as **collagen** and **fibronectin** that reinforce the strength of the vascular wall to withstand the higher blood pressure, which makes the vessels **stiffer**.

Vascular remodeling in renal dialysis

• In patients with renal failure who undergo **dialysis**, an arteriovenous (A-V) fistula directly from the radial artery to the antecubital vein of the forearm is created to permit vascular access for dialysis.

• The **blood flow** rate in the radial **artery** may increase as much as 10 to 50 times the normal flow rate, depending on the patency of the fistula. As a result of the high flow rate and high shear stress on the vessel wall, the luminal diameter of the radial artery increases progressively (**outward remodeling**), whereas the thickness of the vessel wall may remain unchanged, resulting in an **increase in cross-sectional area** of the vascular wall.

• **Wall thickness, lumen diameter, and cross-sectional area** of the vascular wall on the **venous** side of the fistula increase in response

to increases in pressure and blood flow (**outward hypertrophic remodeling).**

Vascular remodeling in CABG

• the change that occurs when a large vein (often the saphenous vein) is implanted in a patient for a coronary artery bypass graft procedure.

Humoral control of the circulation

• Humoral control of the circulation means control by substances secreted or absorbed into the body fluids, such as **hormones** and **locally produced factors.**

Vasoconstrictors

1. • **Epinephrine and Norepinephrine**:

- Norepinephrine is an especially powerful vasoconstrictor hormone; **epinephrine** is less powerful as a vasoconstrictor.
- When the **sympathetic** nervous system is stimulated, norepinephrine is released, which excites the heart and constricts the veins and arterioles.
- In addition, the sympathetic nerves to the **adrenal medullae** cause these glands to secrete norepinephrine and epinephrine into the blood.

2. • **Angiotensin II**:

   • The effect of angiotensin II is to constrict the small arterioles powerfully.

   • The importance of angiotensin II the regulation of arterial pressure.

3. • **Vasopressin: (ADH)**

   Even more powerful than angiotensin II as a vasoconstrictor. It is formed in nerve cells in the

hypothalamus.
It is **also called antidiuretic hormone**.

Vasodilators

1. • **Bradykinin**:
   • Bradykinin causes both powerful arteriolar dilation and increased capillary permeability **(Edema**).
   • Play special roles in regulating blood in **inflamed tissues.**
2. • **Histamine:**

- Released in almost every tissue of the body if the tissue becomes damaged or inflamed or is the subject of an allergic reaction.
- Most of the histamine is derived from **mast cells in the damaged tissues** and from **basophils in the blood.**
- Histamine has a powerful vasodilator effect on the arterioles and, like bradykinin, has the ability to increase capillary porosity greatly, allowing leakage of fluid and plasma protein into the tissues, inducing edema.

Vascular effects of ions and other chemical factors

• An increase in intracellular **calcium** ion concentration causes **vasoconstriction** because of the general effect of calcium to stimulate smooth muscle contraction.

• An increase in **potassium** ion concentration, within the physiological range, causes **vasodilation**.

• This effect results from the ability of potassium ions to inhibit smooth muscle contraction**.**

• An increase in **magnesium** ion concentration causes powerful **vasodilation** because magnesium ions inhibit smooth muscle contraction.

• An increase in **hydrogen** ion concentration (decrease in pH) causes **dilation of the arterioles.**

• **Anions** that have significant effects on blood vessels are acetate and citrate, both of which cause mild degrees of **vasodilation.**

• An increase in **carbon dioxide** concentration causes moderate **vasodilation** in most tissues **but marked vasodilation in the brain**.

• Also**, carbon dioxide in the blood**, acting on the brain vasomotor center, has an extremely powerful indirect effect, transmitted through the sympathetic nervous vasoconstrictor system, that causes widespread **vasoconstriction throughout the body.**

• Most Vasodilators or Vasoconstrictors Have Little Effect on Long-Term Blood Flow Unless They Alter the Metabolic Rate of the Tissues.

Good luck, Rayyan shtewe ☺.