
Positive Mind
Positive Vibes
Positive Life

Regulation of local blood flow

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Overall Objectives

- Know what factors affect tissue blood flow
- Describe the vasodilator and oxygen demand theories
- Know mechanisms of autoregulation
- Describe active & reactive hyperemia
- Describe long term control of blood flow
- Describe angiogenesis ,new vascularization and retrolental fibroplasia

Local Control of Blood Flow

- Each tissue controls its own blood flow in proportion to its needs
- Tissue needs include
  1) Delivery of *oxygen* to tissues
  2) Delivery of *nutrients* such as glucose, amino acids, etc.
  3) Removal of carbon dioxide hydrogen and other *metabolites* from the tissues
  4) Transport various *hormones* and other substances to different tissues
- Flow is closely related to metabolic rate of tissues

Variations in Tissue Blood Flow

	Percent	ml/min	ml/min/ 100 gm
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)	1	5750	4
Bone	5	250	3
Skin (cool weather)	6	300	3
Thyroid gland	1	50	160
Adrenal glands	0	.525	300
Other tissues	3.5	175	1.3
Total	100.0	5000	--

Mechanism of blood flow control

- Local blood flow cam be divide into two phases:

Acute/Rapid control

Long term control

Mechanism of blood flow control

Acute Control

- Rapid change in local vasodilation and vasoconstriction of arterioles, met arterioles and precapillary sphincters.
- Occurring within second to minutes.

Long term Control

- Slow controlled change in flow over a periods of days, weeks and months.
- Change involve increase or decrease in size and no. of actual blood vessels.

Acute control of local blood flow

Factors affecting local control of blood flow

1. **Increased tissue metabolism**

- Increases local blood flow to meet the demands
- Eg: exercising muscles, brain at work

2. **Reduced tissue oxygen availability**

- Increases local blood flow
- Eg: at high altitudes, pneumonia, CO poisoning

Acute Control of Local Blood Flow

- Increases in *tissue metabolism* lead to increases in blood flow
- Decreases in *oxygen availability* to tissues increases tissue blood flow
- Two major theories for local blood flow are:

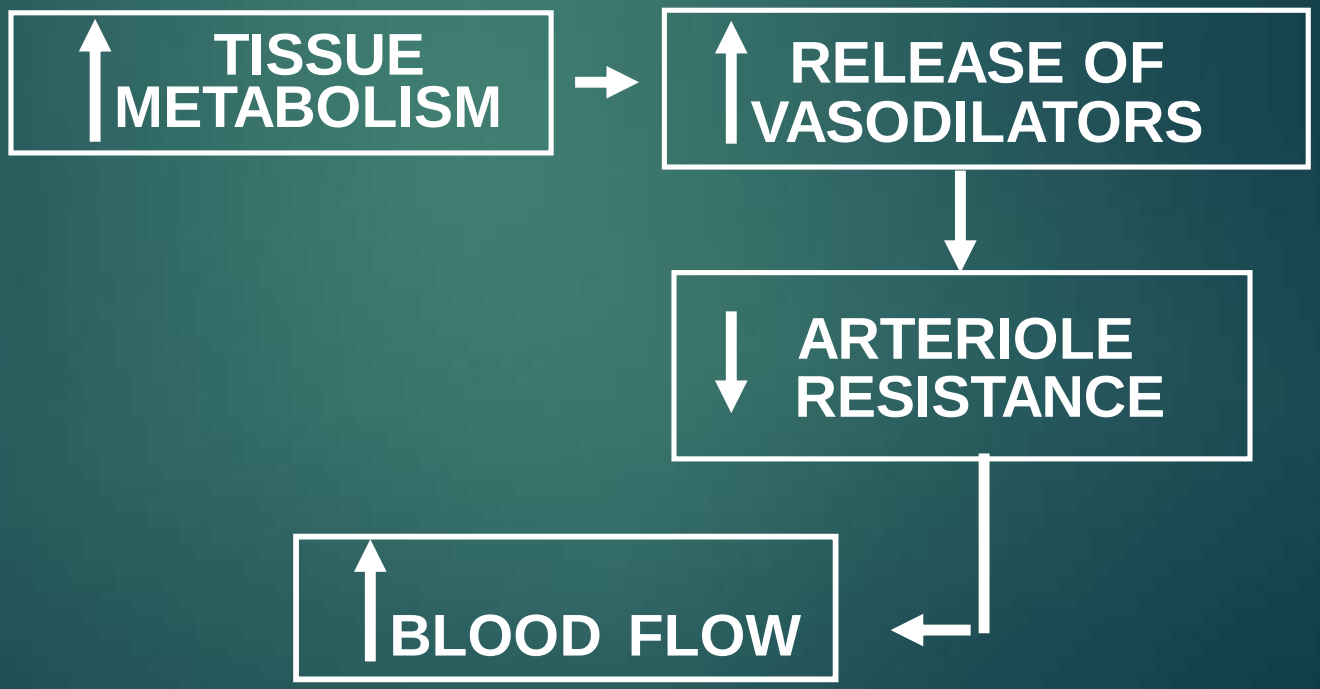
The vasodilator theory

Oxygen demand theory

Vasodilator Theory for Blood Flow Control

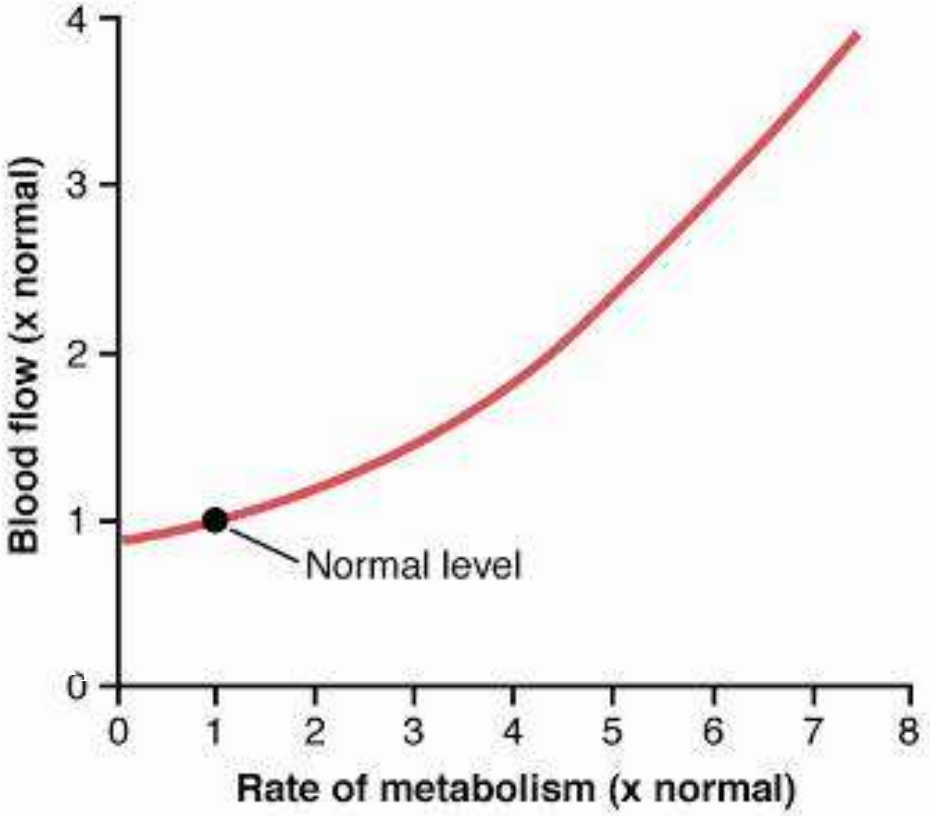
- the greater the rate of metabolism or the less the availability of oxygen or some other nutrients to a tissue, the greater the rate of formation of *vasodilator substances* in the tissue cells.
- The vasodilator substances then are believed to diffuse through the tissues to the precapillary sphincters, metarterioles, and arterioles to cause dilation.

- Vasodilators: Adenosine, CO_2, Lactic acid, ADP compounds, Histamine, K ions, H ions



Effect of Tissue Metabolic Rate on Tissue Blood Flow

↑ Tissue Metabolism → ↑ Blood Flow



Vasodilator Theory for Blood Flow Control

1. • Increase tissue metabolism
2. • Release of Vasodilators
3. • decrease Arteriolar resistance
4. • Increase Blood Flow

Vasodilators

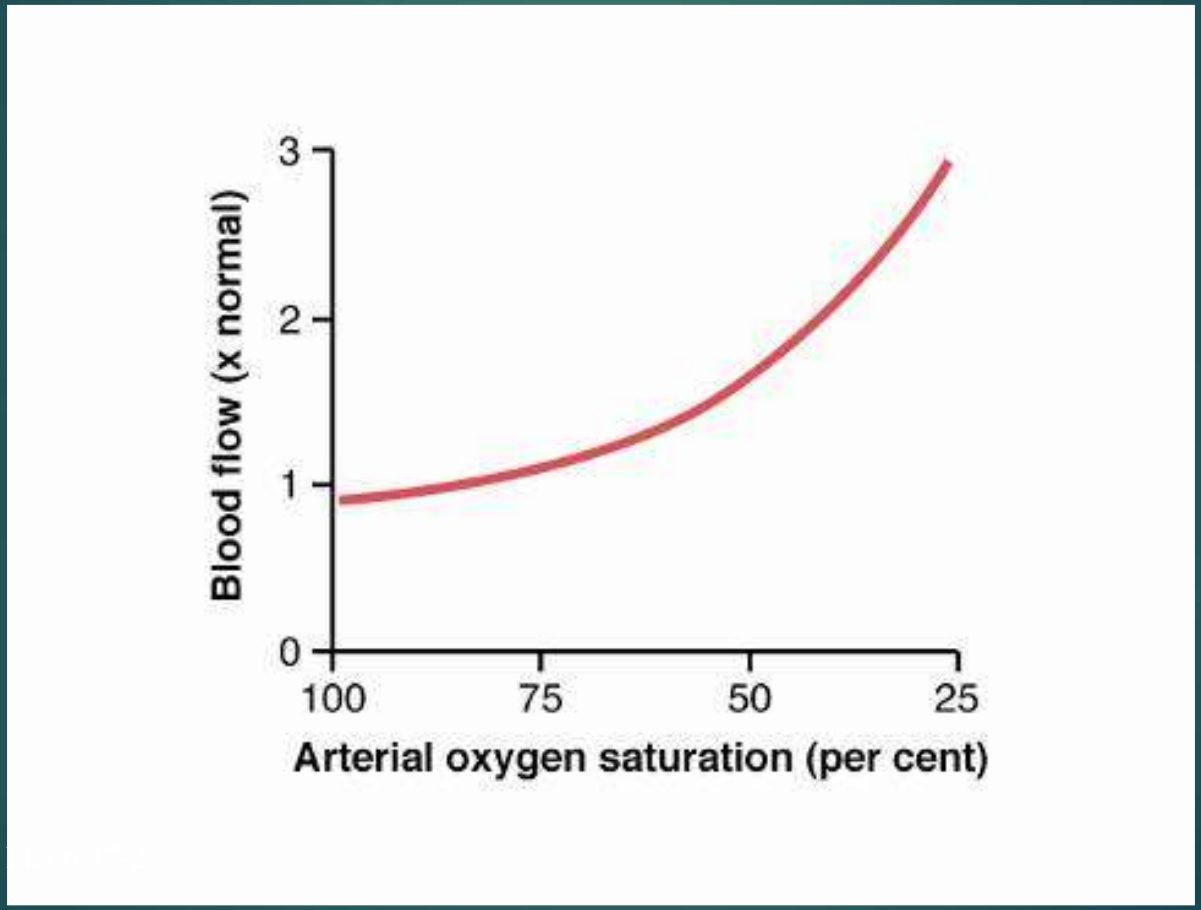
- Adenosine
- CO_2
- Lactic acid
- ADP compounds
- Histamine
- K ions
- H ions

Oxygen Lack Theory for Local Blood Flow Control

- Oxygen (and other nutrients as well) is required as one of the metabolic nutrients to cause vascular muscle contraction.
- in the absence of adequate oxygen the blood vessels simply would relax and therefore naturally dilate.
- increased utilization of oxygen in the tissues as a result of increased metabolism could decrease the availability of oxygen to the smooth muscle fibers in the local blood vessels, and this, too, would cause local vasodilation.

Effect of Tissue Oxygen Concentration on Blood Flow

↑ Tissue Oxygen Concentration → ↑ Blood Flow



Effect of decreasing arterial oxygen saturation on blood flow through an isolated dog leg.

Oxygen Demand Theory for Blood Flow Control

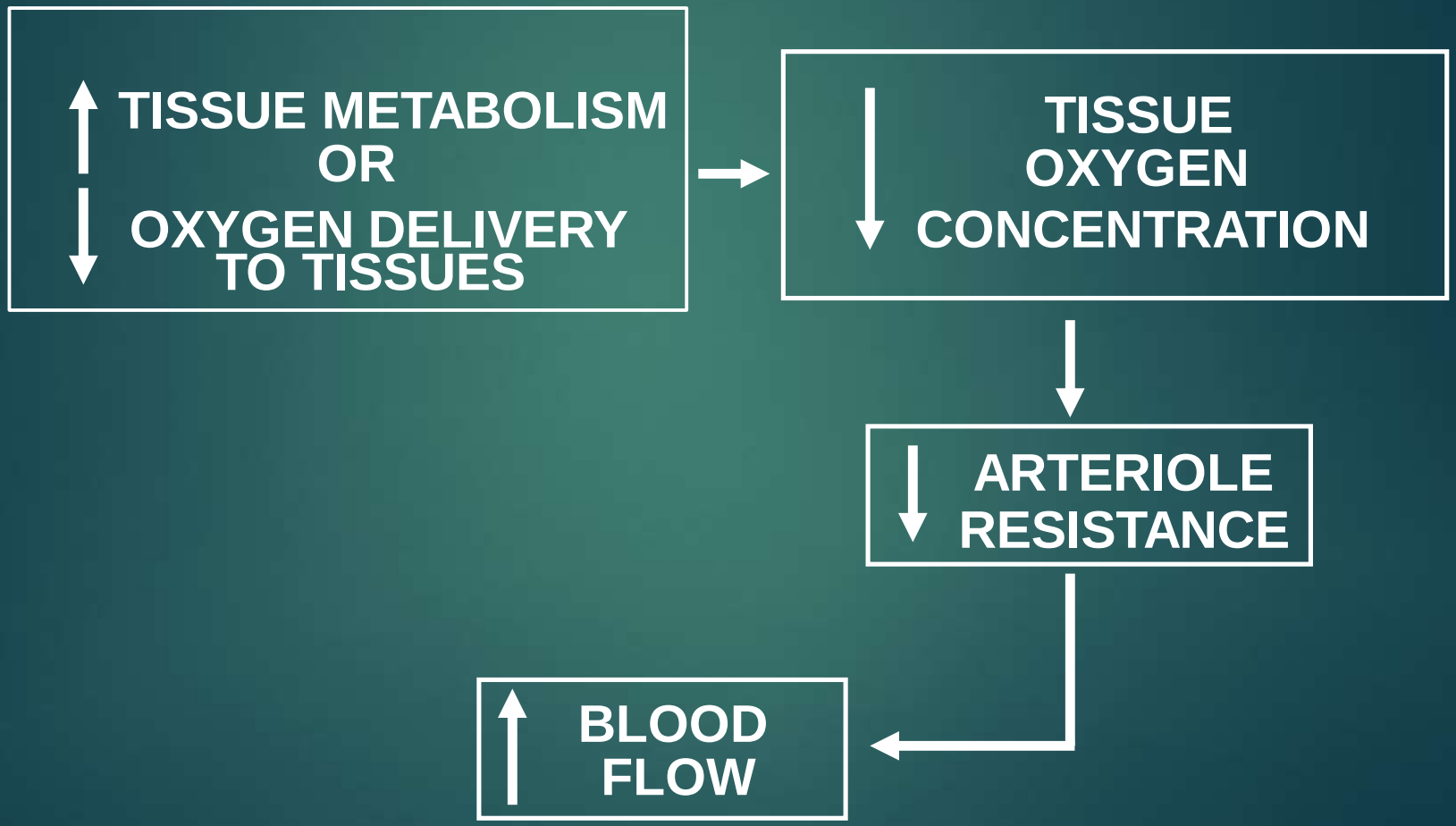
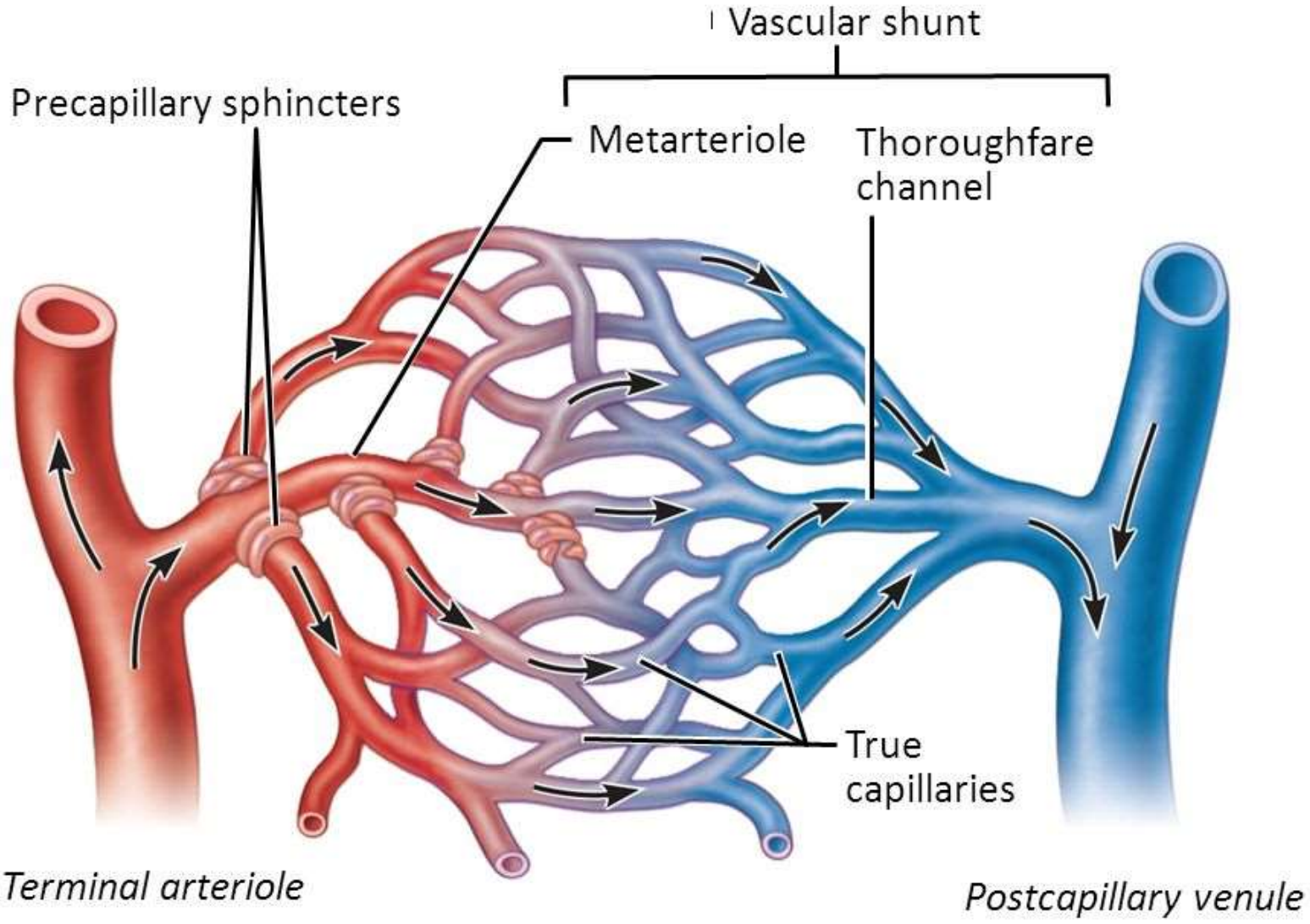


Figure 18.4a Anatomy of a capillary bed.



(a) Sphincters open—blood flows through true capillaries.

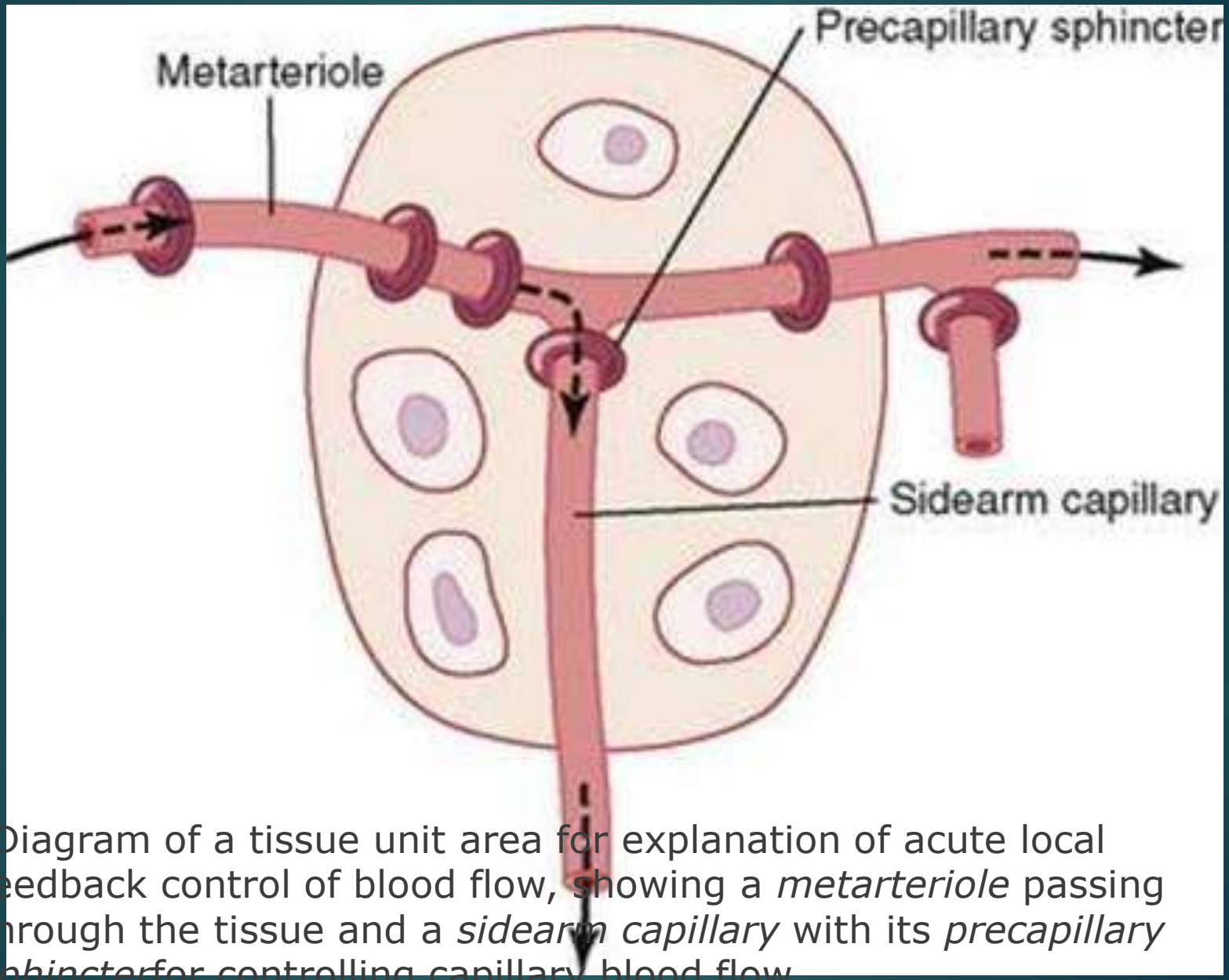
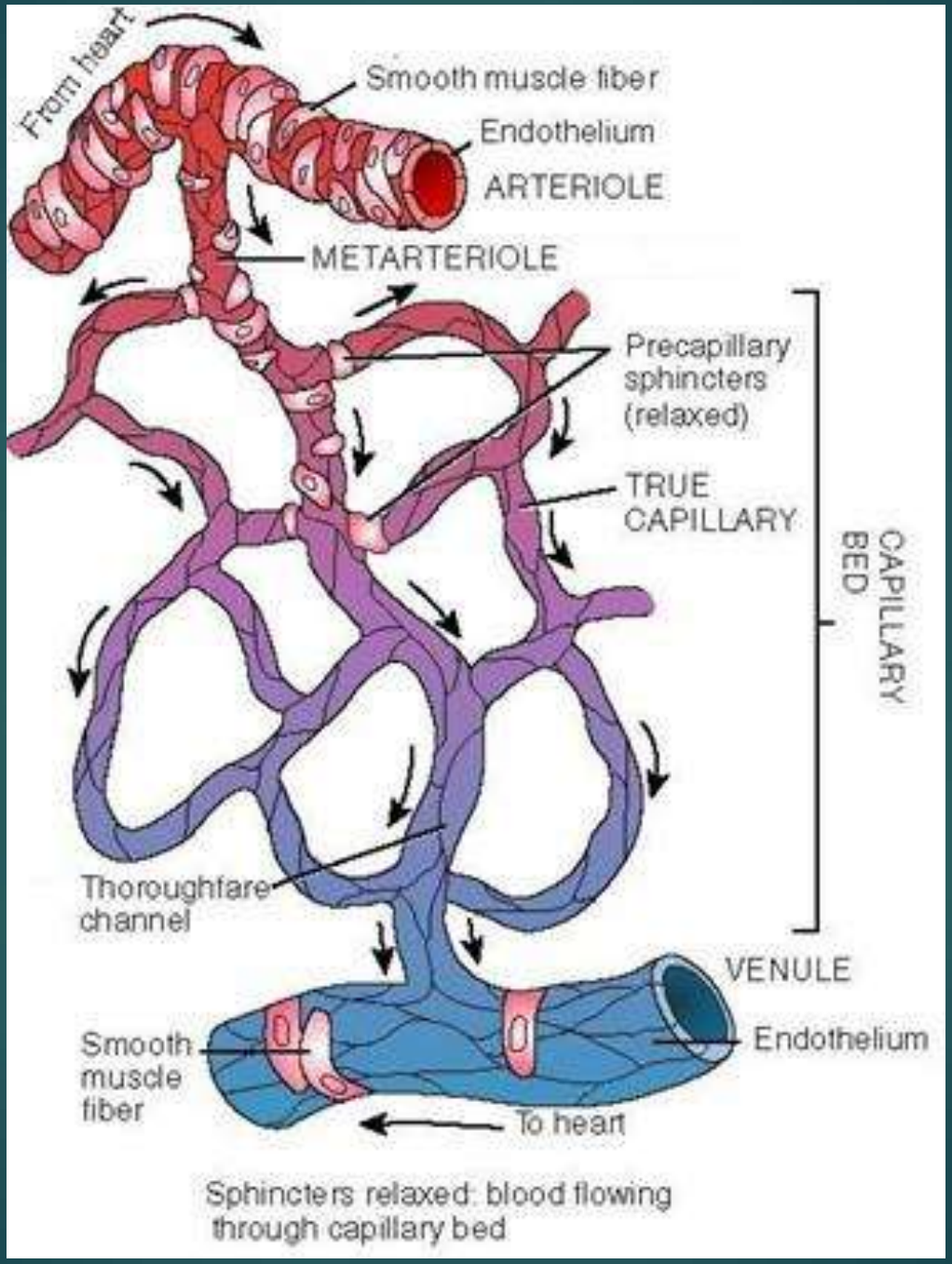


Diagram of a tissue unit area for explanation of acute local feedback control of blood flow, showing a *metarteriole* passing through the tissue and a *sidearm capillary* with its *precapillary sphincter* for controlling capillary blood flow.

- This figure shows a tissue unit, consisting of a metarteriole with a single sidearm capillary and its surrounding tissue.
- At the origin of the capillary is a *precapillary sphincter,* and around the metarteriole are several other smooth muscle fibers.
- The number of precapillary sphincters that are open at any given time is roughly proportional to the requirements of the tissue for nutrition.
- 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.*



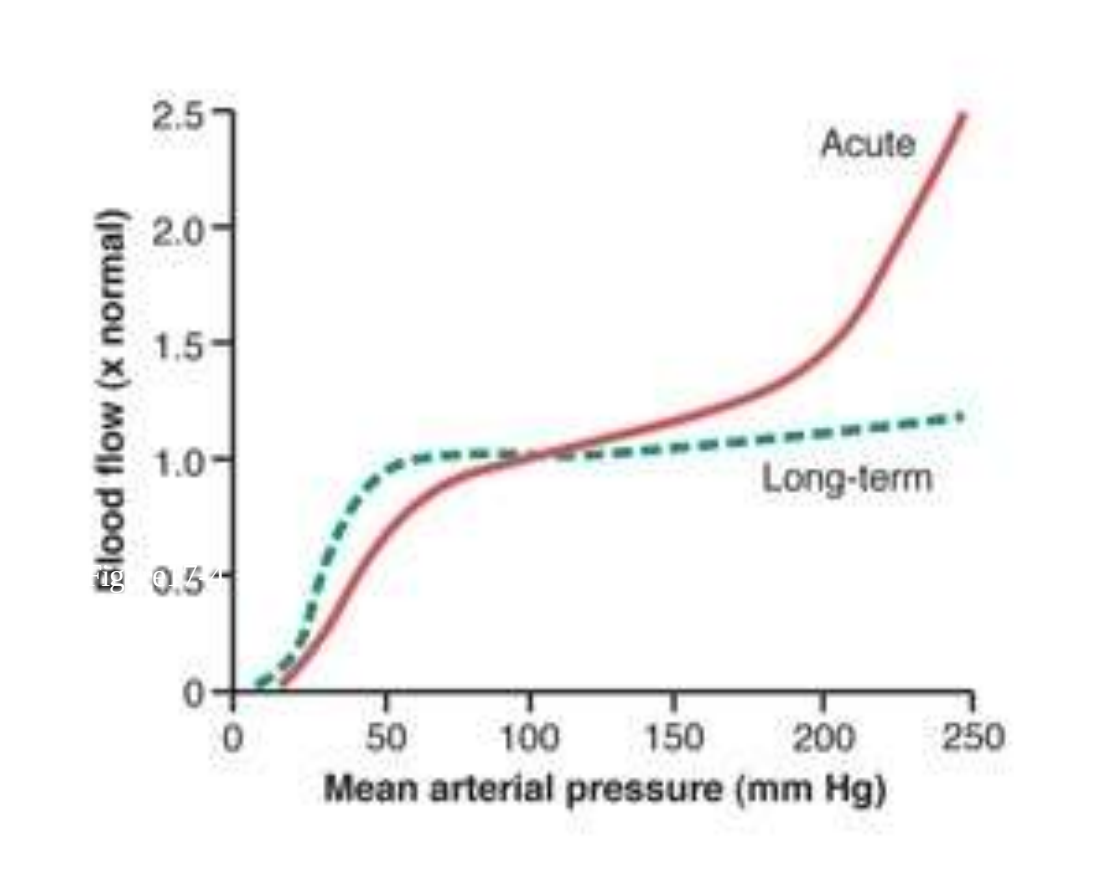
Sphincters relaxed: blood flowing through capillary bed

Possible Role of Other Nutrients Besides Oxygen in Control of Local Blood Flow

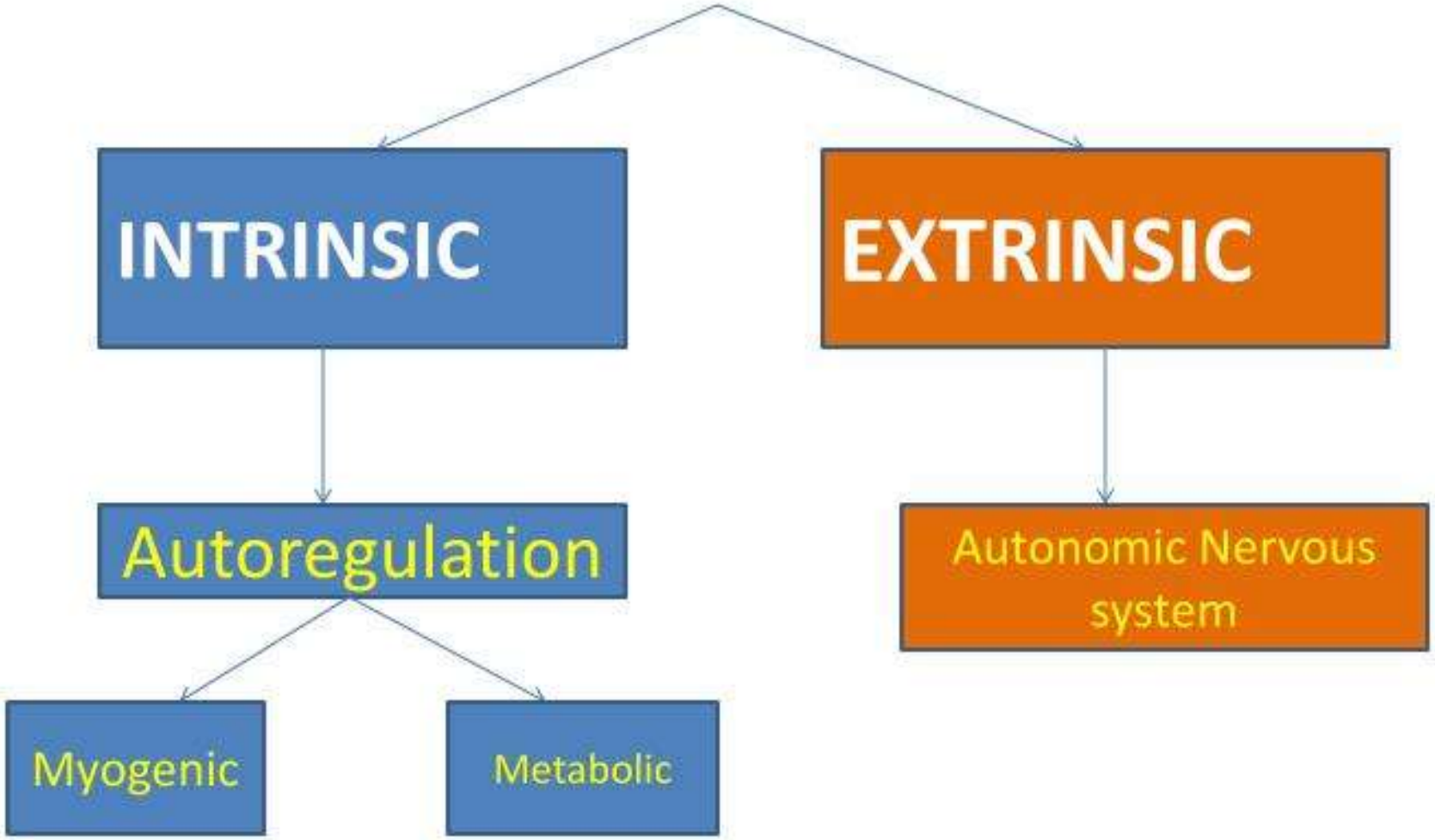
- Under special conditions, it has been shown that lack of glucose in the perfusing blood can cause local tissue vasodilation.
- Also, it is possible that this same effect occurs when other nutrients, such as amino acids or fatty acids, are deficient, although this has not been studied adequately.
- In addition, vasodilation occurs in the vitamin deficiency disease *beriberi,* in which the patient has deficiencies of the vitamin B substances *thiamine, niacin,* and *riboflavin*.

Autoregulation of Blood Flow

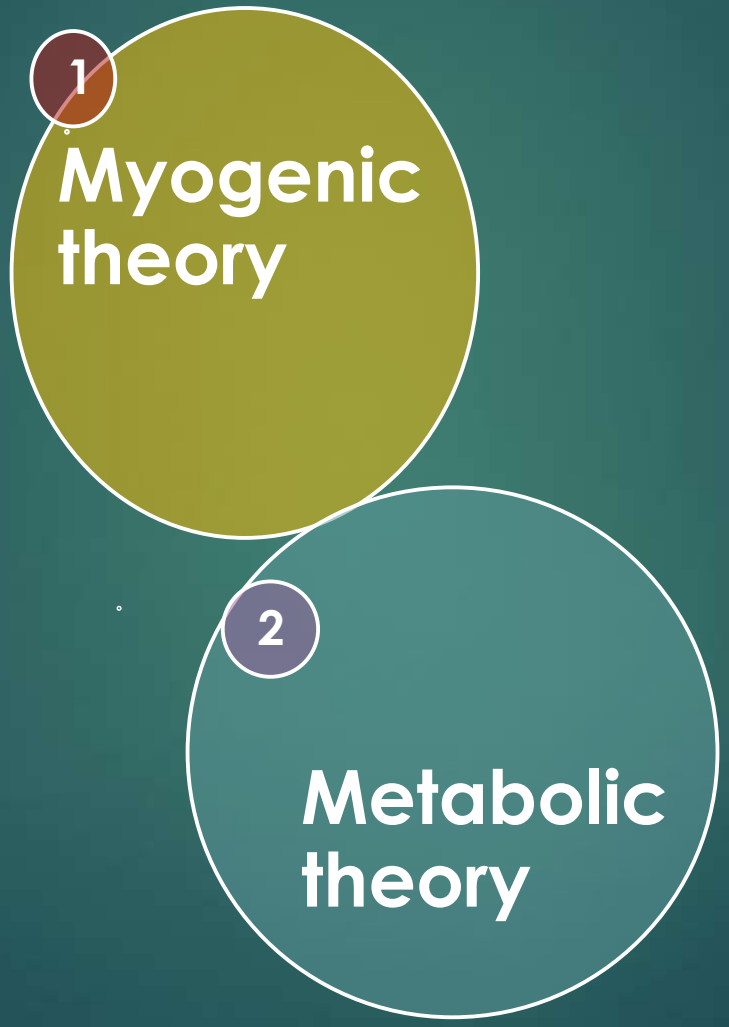
Autoregulation - Ability of a tissue to maintain blood flow relatively constant over a wide range of arterial pressures



MECHANISMS FOR CONTROL OF REGIONAL BLOOD FLOW



Blood Flow Autoregulation Theories



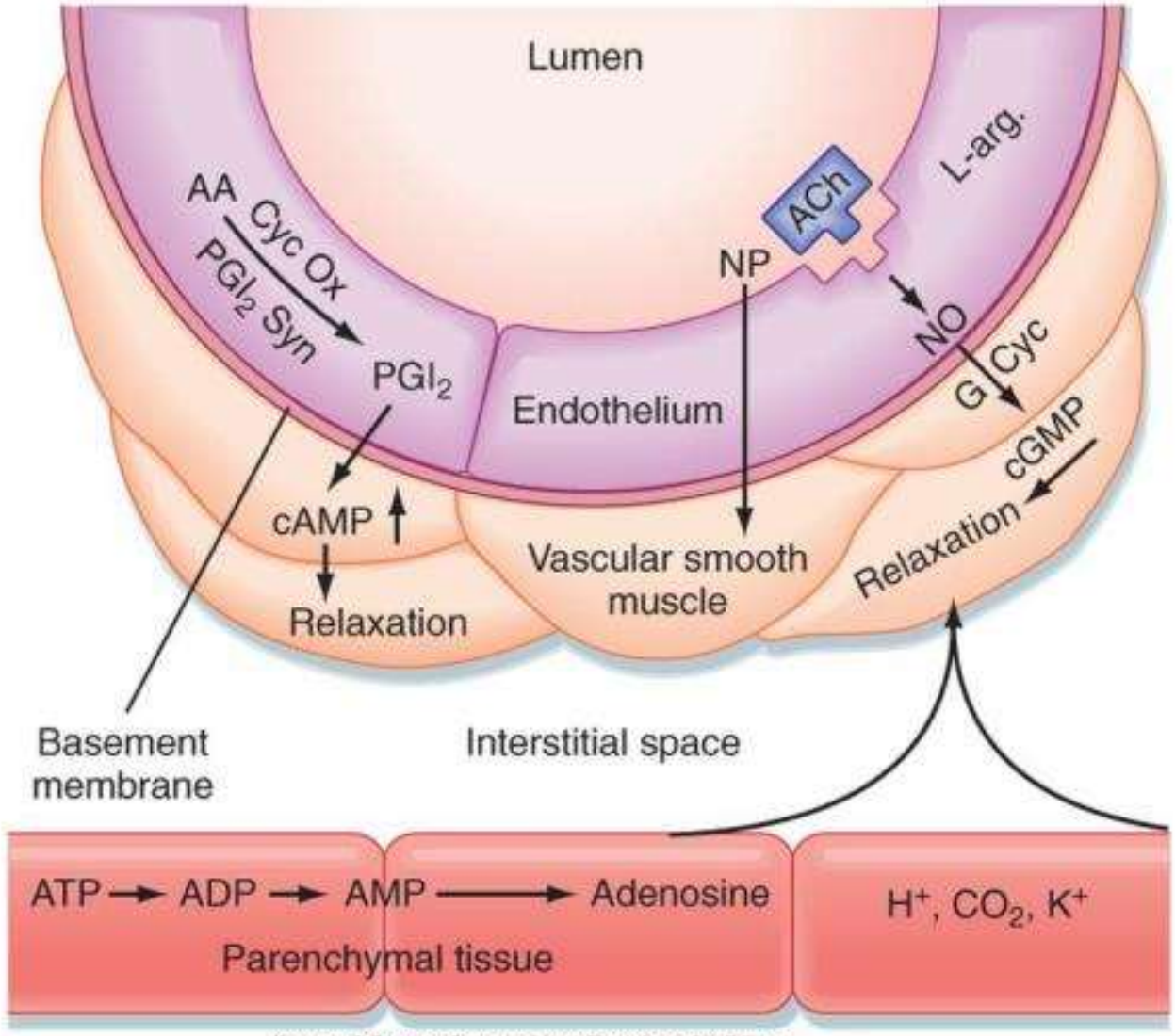
Metabolic theory of Auto regulation

- suggests that as arterial pressure is decreased, oxygen or nutrient delivery is decreased resulting in release of a vasodilator

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 the flow to return nearly to normal despite the increased pressure.

Vasoactive Role of the Capillary Endothelium



Myogenic theory of Autoregulation

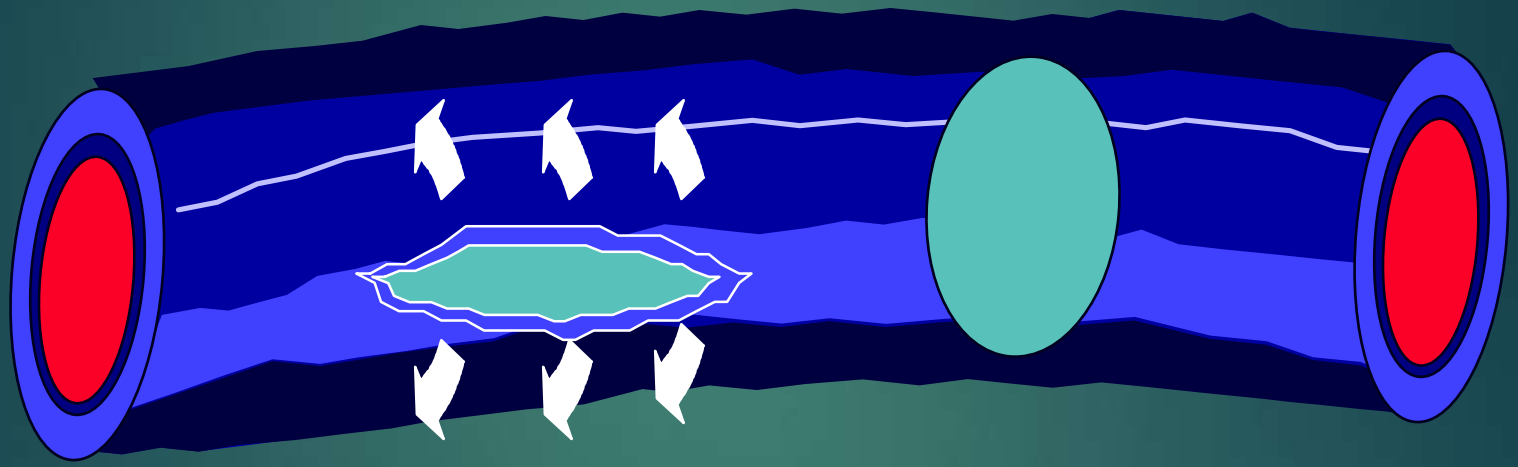
- Proposes that as arterial pressure falls the arterioles have an intrinsic property to dilate in response to decreases in wall tension

Myogenic theory

- sudden stretch of small blood vessels causes the smooth muscle of the vessel wall to contract.
- when high arterial pressure stretches the vessel, this in turn causes reactive vascular constriction that reduces blood flow nearly back to normal.
- Conversely, at low pressures, the degree of stretch of the vessel is less, so that the smooth muscle relaxes, reducing vascular resistance and helping to return flow toward normal.

Laplace's Law: Myogenic mechanism

TENSION = PRESSURE X RADIUS
(dynes/cm) (dynes/cm^2) (cm)



↑ **PRESSURE** → ↑ **TENSION** → ↓ **RADIUS**

↑ (to maintain tension constant)

↓ **PRESSURE** → ↓ **TENSION** → ↑ **RADIUS**

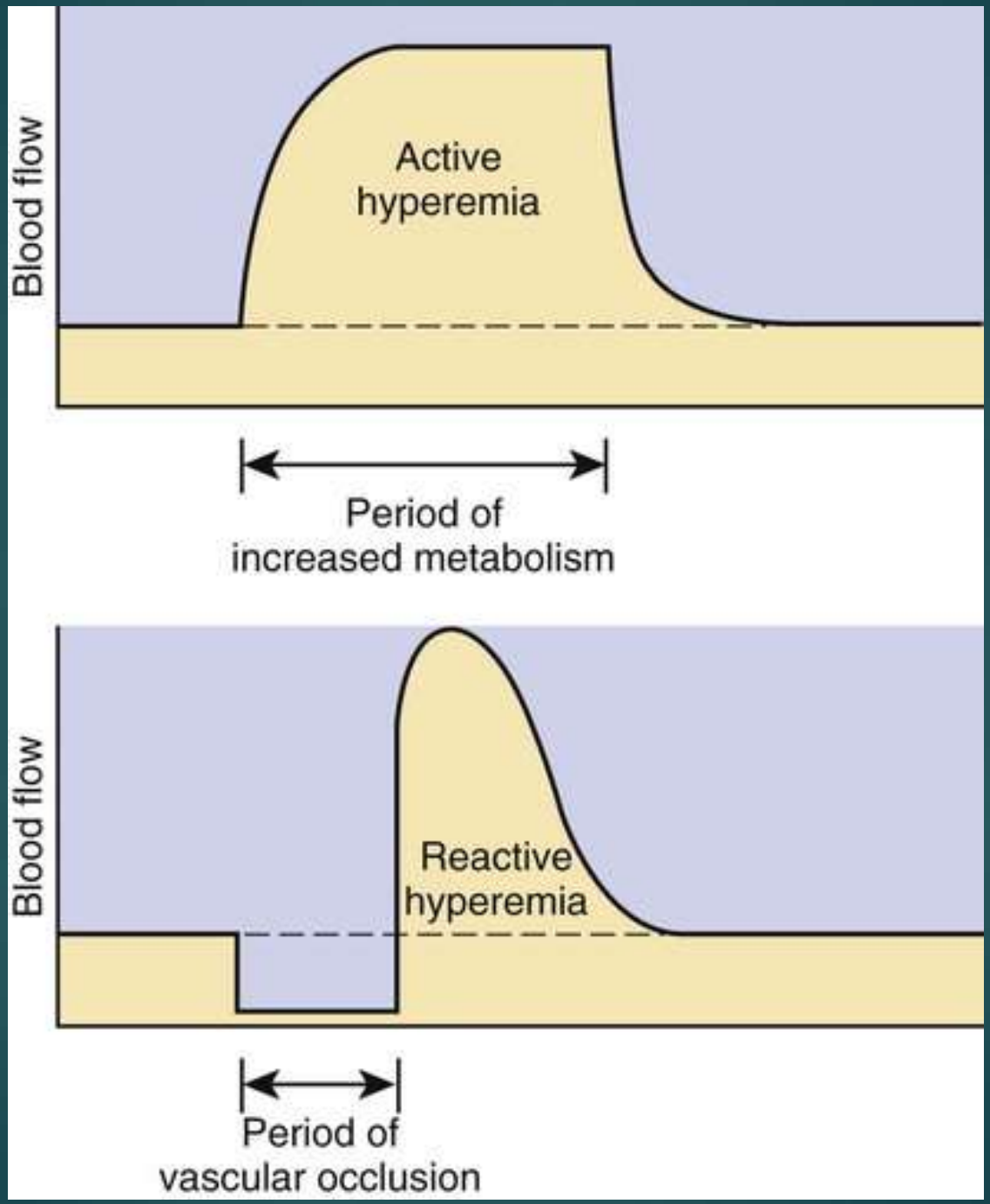
↑ (to maintain tension constant)

- There are several examples of local control of blood flow, including:
- • Autoregulation
- • Active hyperemia
- • Reactive hyperemia
- **Active hyperemia :**
- **Reactive hyperemia :**
- **increase in blood flow in response to** or reacting to a prior period of decreased blood flow (arterial occlusion).

Active Hyperemia

- blood flow to an organ is proportional to its metabolic activity.
- When any tissue becomes highly active e.g
- An exercising muscle,
- A gastrointestinal gland during a hypersecretory period,
- Brain during rapid mental activity,
- the rate of blood flow through the tissue increases.
- active hyperemia in skeletal muscle can increase local muscle blood flow as much as 20-fold during intense exercise.

- When any tissue becomes highly active, such as an exercising muscle, a gastrointestinal gland during a hyper secretory period, or even the brain during rapid mental activity, the rate of blood flow through the tissue increases. Here again, by simply applying the basic principles of local blood flow control, one can easily understand this *active hyperemia*.


Blood flow
Active hyperemia
Period of increased metabolism
Blood flow
Reactive hyperemia
Period of vascular occlusion


TAKE
A
BREAK

Long-term Regulationof Blood Flow

PART 2

Long-term Regulation of Blood Flow

- Long-term regulatory mechanisms which control blood flow are more effective than acute mechanism
- Long-term local blood flow regulation occurs by changing the degree of vascularity of tissues (*size and number of vessels*)
- *Oxygen* is an important stimulus for regulating tissue vascularity

Special Mechanisms for Acute Blood Flow Control in Specific Tissues

. In the *kidneys*

- 1 blood flow control is vested to a great extent in a mechanism called *tubuloglomerular feedback,* in which the composition of the fluid in the early distal tubule is detected by an epithelial structure of the distal tubule itself called the *macula densa*.
- This is located where the distal tubule lies adjacent to the afferent and efferent arterioles at the nephron *juxtaglomerular apparatus*.
- When too much fluid filters from the blood through the glomerulus into the tubular system, feedback signals from the macula densa cause constriction of the afferent arterioles, in this way reducing both renal blood flow and glomerular filtration rate back to or near to normal. The details of this mechanism are discussed in Chapter 26.

Special Mechanisms for Acute Blood Flow Control in Specific Tissues

- **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 dilates the cerebral vessels and allows rapid washout of the excess carbon dioxide or hydrogen ions from the brain tissues.
- This is important because the *level of excitability of the brain itself is highly dependent on exact control of both carbon dioxide concentration and hydrogen ion concentration*.

Blood Flow: Brain

- Blood flow to the brain is constant, as neurons are intolerant of ischemiaMetabolic controls – brain tissue is extremely sensitive to declines in pH, and increased carbon dioxide causes marked vasodilation
- Myogenic controls protect the brain from damaging changes in blood pressure
- Decreases in MAP cause cerebral vessels to dilate to insure adequate perfusion
- Increases in MAP cause cerebral vessels to constrict

- 2 Blood Flow: BrainThe brain can regulate is own blood flow in certain circumstances, such as ischemia caused by a tumorThe brain is vulnerable under extreme systemic pressure changesMAP below 60mm Hg can cause syncope (fainting)MAP above 160 can result in cerebral edema

In the *skin*

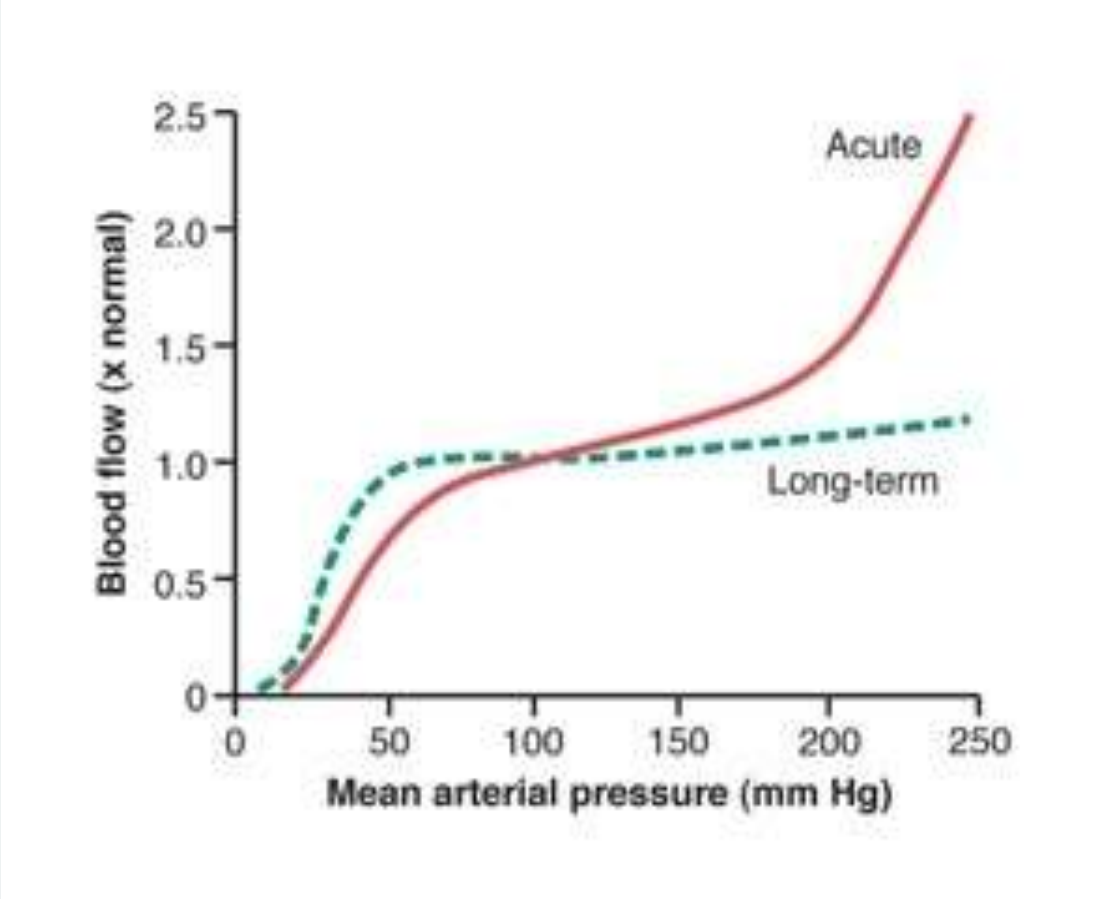
- 3. blood flow control is closely linked to regulation of body temperature.
- Cutaneous and subcutaneous flow regulates heat loss from the body by metering the flow of heat from the core to the surface of the body, where heat is lost to the environment.
- Skin blood flow is controlled largely by the central nervous system through the sympathetic nerves,
- Although skin blood flow is only about 3 ml/min/100 g of tissue in cool weather, large changes from that value can occur as needed.
- When humans are exposed to body heating, skin blood flow may increase manyfold, to as high as *7 to 8 L/min* for the entire body.
- When body temperature is reduced, skin blood flow decreases, falling to barely above zero at very low temperatures. Even with severe vasoconstriction, skin blood flow is usually great enough to meet the basic metabolic demands of the skin.

- **Blood Flow: Skin Blood flow through the skin:** Supplies nutrients to cells in response to oxygen need
- Aids in body temperature regulation and provides a blood reservoir
- Blood flow to venous plexuses below the skin surface:Varies from 50 ml/min to 2500 ml/min, depending upon body temperaturels controlled by sympathetic nervous system reflexes initiated by temperature receptors and the central nervous system

Special Examples of Acute "Metabolic" Control of Local Blood Flow

- **Reactive Hyperemia**
- When the blood supply to a tissue is blocked for a few seconds to as long as an hour or more and then is unblocked, blood flow through the tissue usually increases immediately to four to seven times normal; this increased flow will continue for a few seconds if the block has lasted only a few seconds but sometimes continues for as long as many hours if the blood flow has been stopped for an hour or more. This phenomenon is called *reactive hyperemia*.
- Reactive hyperemia is another manifestation of the local "metabolic" blood flow regulation mechanism; that is, lack of flow sets into motion all of those factors that cause vasodilation. After short periods of vascular occlusion, the extra blood flow during the reactive hyperemia phase lasts long enough to repay almost exactly the tissue oxygen deficit that has accrued during the period of occlusion. This mechanism emphasizes the close connection between local blood flow regulation and delivery of

Long-term Regulation of Blood Flow (cont'd)



Angiogenesis

- *Angiogenesis* is the growth of new blood vessels
- Angiogenesis occurs in response to angiogenic factors released from

  1) Ischemic Tissue

  2) Rapidly growing tissue

  3) Tissue with high metabolic rates

- Most angiogenic factors are small peptides such as Vascular endothelial cell growth factors (VEGF), fibroblast growth factor (FGF), and angiogen

Mechanism of Long-Term Regulation—Change in "Tissue Vascularity"

- The mechanism of long-term local blood flow regulation is principally to change the amount of vascularity of the tissues.
- For instance, 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.
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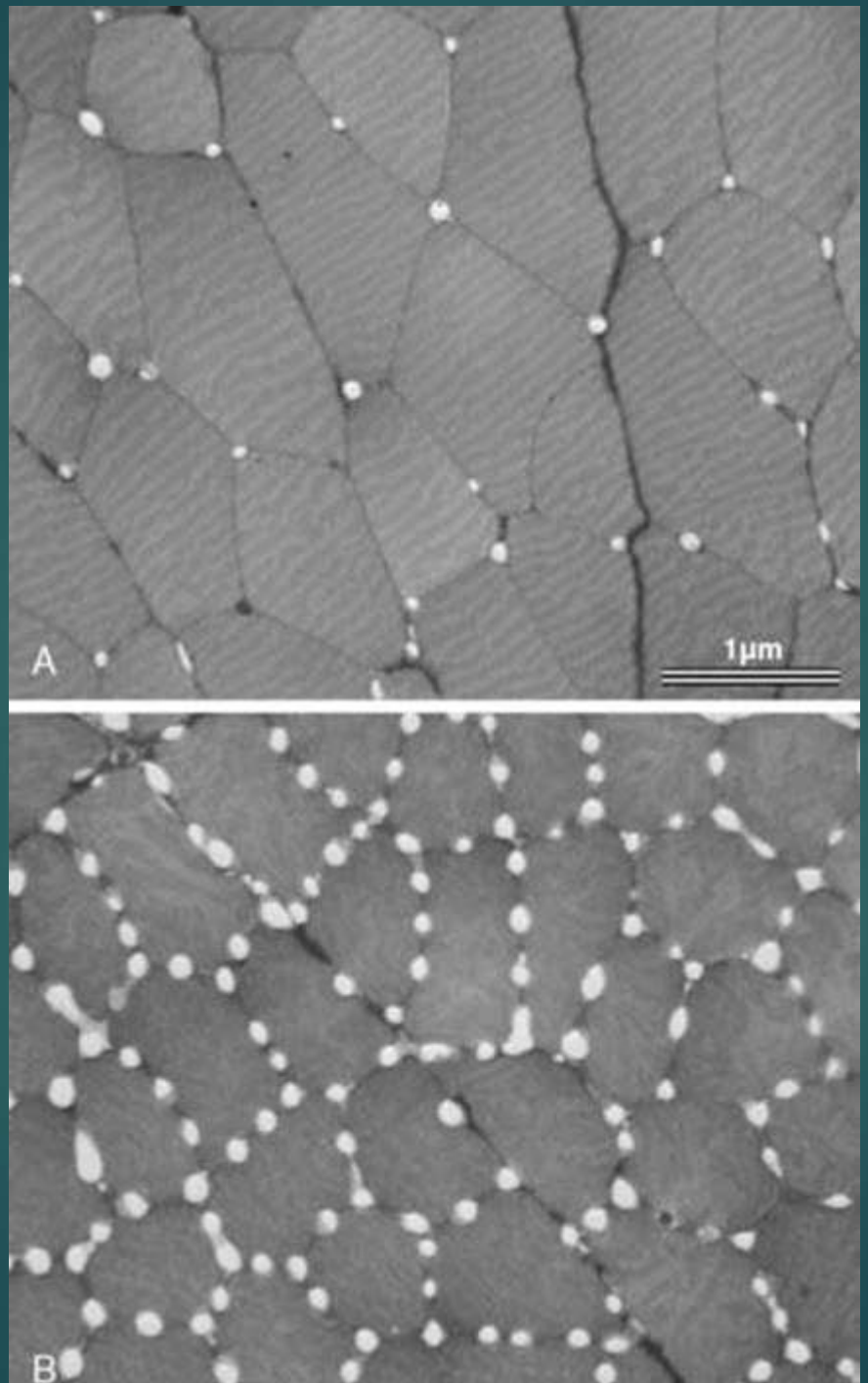
A
1µm
B

- Thus, there is actual physical reconstruction of the tissue vasculature to meet the needs of the tissues.
- This reconstruction occurs rapidly (within days) in young animals.
- It also occurs rapidly in new growth tissue, such as in scar tissue and cancerous tissue; however, it occurs much slower in old, well-established tissues.
- Therefore, 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 the elderly person.
- Furthermore, the final degree of response is much better in younger tissues than in older, so that in the neonate, the vascularity will adjust to match almost exactly the needs of the tissue for blood flow, whereas in older tissues, vascularity frequently lags far behind the needs of the tissues.

Role of Oxygen in Long-Term Regulation

- Oxygen is important not only for acute control of local blood flow but also for long-term control.
- One example of this is increased vascularity in tissues of animals that live at high altitudes, where the atmospheric oxygen is low.
- A second example is that fetal chicks hatched in low oxygen have up to twice as much tissue blood vessel conductivity as is normally true.
- This same effect is also dramatically demonstrated in premature human babies put into oxygen tents for therapeutic purposes. The excess oxygen causes almost immediate cessation of new vascular growth in the retina of the premature baby's eyes and even causes degeneration of some of the small vessels that already have formed. Then when the infant is taken out of the oxygen tent, there is explosive overgrowth of new vessels to make up for the sudden decrease in available oxygen; indeed, there is often so much overgrowth that the retinal vessels grow

- **Importance of Vascular Endothelial Growth Factor in Formation of New Blood Vessels**
- A dozen or more factors that increase growth of new blood vessels have been found, almost all of which are small peptides. Three of those that have been best characterized are *vascular endothelial growth factor (VEGF), fibroblast growth factor,* and *angiogenin,* each of which has been isolated from tissues that have inadequate blood supply. Presumably, it is deficiency of tissue oxygen or other nutrients, or both, that leads to formation of the vascular growth factors (also called "angiogenic factors").

- Essentially all the angiogenic factors promote new vessel growth in the same way. They cause new vessels to sprout from other small vessels. The first step is dissolution of the basement membrane of the endothelial cells at the point of sprouting. This is followed by rapid reproduction of new endothelial cells that stream outward through the vessel wall in extended cords directed toward the source of the angiogenic factor. The cells in each cord continue to divide and rapidly fold over into a tube. Next, the tube connects with another tube budding from another donor vessel (another arteriole or venule) and forms a capillary loop through which blood begins to flow. If the flow is great enough, smooth muscle cells eventually invade the wall, so some of the new vessels eventually grow to be new arterioles or venules or perhaps even larger vessels. Thus, angiogenesis explains the manner in which metabolic factors in local tissues can cause growth of new vessels.

- ertain other substances, such as some steroid hormones, have exactly the opposite effect on small blood vessels, occasionally even causing dissolution of vascular cells and disappearance of vessels. Therefore, blood vessels can also be made to disappear when not needed. Peptides produced in the tissues can also block the growth of new blood vessels. For example, *angiostatin*, a fragment of the protein plasminogen, is a naturally occurring inhibitor of angiogenesis. *Endostatin* is another antiangiogenic peptide that is derived from the breakdown of collagen type XVII. Although the precise physiological functions of these antiangiogenic substances are still unknown, there is great interest in their potential use in arresting blood vessel growth in cancerous tumors and therefore preventing the large increases in blood flow needed to sustain the nutrient supply of rapidly growing tumors.

Development of Collateral Circulation— a Phenomenon of Long-Term Local Blood Flow Regulation

- When an artery or a vein is blocked in virtually any tissue of the body, a new vascular channel usually develops around the blockage and allows at least partial resupply of blood to the affected tissue.
- The first stage in this process is dilation of small vascular loops that already connect the vessel above the blockage to the vessel below.
- This dilation occurs within the first minute or two, indicating that the dilation is likely mediated by metabolic factors that relax the muscle fibers of the small vessels involved.
- After this initial opening of collateral vessels, the blood flow often is still less than one quarter that is needed to supply all the tissue needs.
- However, further opening occurs within the ensuing hours, so within 1 day as much as half the tissue needs may be met, and within a few days the blood flow is usually sufficient to meet the tissue needs.

- The collateral vessels continue to grow for many months thereafter, almost always forming multiple small collateral channels rather than one single large vessel.
- Under resting conditions, the blood flow usually returns very near to normal, but the new channels seldom become large enough to supply the blood flow needed during strenuous tissue activity.
- Thus, the development of collateral vessels follows the usual principles of both acute and long-term local blood flow control, the acute control being rapid metabolic dilation, followed chronically by growth and enlargement of new vessels over a period of weeks and months.

- The most important example of the development of collateral blood vessels occurs after thrombosis of one of the coronary arteries.
- Almost all people by the age of 60 years have had at least one of the smaller branch coronary vessels closed, or at least partially occluded.
- Yet most people do not know that this has happened because collaterals have developed rapidly enough to prevent myocardial damage.
- It is in those other instances in which coronary insufficiency occurs too rapidly or too severely for collaterals to develop that serious heart attacks occur.

Humoral Regulation of Blood Flow

- Vasoconstrictors
  - Norepinephrine and epinephrine
  - Angiotensin
  - Vasopressin
  - Endothelin
- Vasodilator agents
  - Bradykinin
  - Serotonin
  - Histamine
  - Prostaglandins
  - Nitric oxide

YOU SHOULD KNOW…

- ✓ Know what factors affect tissue blood flow
- ✓ Describe the vasodilator and oxygen demand theories
- ✓ Know autoregulation mechanisms
- ✓ Describe how angiogenesis occurs
- ✓ Know how various humoral factors affect blood flow


That's all Folks!