Doctor.021
no. 2

CVS
PHYSIOLOGY

Dr. Fatima's handout for the 2nd interactive book

Learning objectives:

1. Understand the physiology of vascular smooth muscle contraction and the importance of vascular tone.
2. Relate the structure of the arteriole to its function.
3. Recognize the importance of arterioles to determine vascular resistance.
4. Know the local chemical factors controlling blood flow to the tissues and the mechanism of action.
5. Know the local physical factors controlling blood flow to the tissues and the mechanism of action.
6. Understand the concept of vascular autoregulation.
7. Differentiate between acute and long-term control mechanisms of blood flow to the tissues.
8. Recognize the different mechanisms of long-term control of local blood flow.
9. Understand the remodeling changes in the vessels to control local blood flow.
10. Link the remodeling mechanisms to clinical situations that led to such remodeling.
11. Apply the basic knowledge acquired in this book in related clinical scenarios.

Arterioles

Function:

When an artery reaches the organ it is supplying, it branches into numerous arterioles within the organ.

Arterioles are the main resistance vessels in the vascular tree because their radius is small enough to offer considerable resistance to flow.

In contrast to the low resistance of the arteries, the high degree of arteriolar resistance causes a marked drop in mean pressure as blood flows through these small vessels. This helps establish the pressure gradient that encourages the flow of blood from the heart to the organs downstream.

Arteriolar resistance also converts the pulsatile systolic-to-diastolic pressure swings in the arteries into the nonfluctuating pressure present in the capillaries.

Vascular tone:

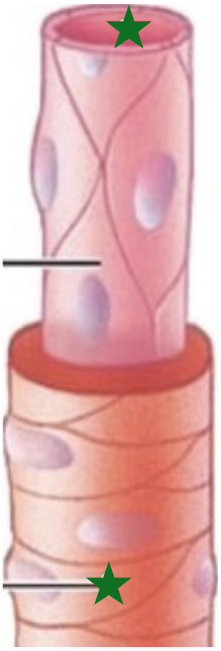
The extent of contraction of arteriolar smooth muscle depends on the cytosolic Ca++ concentration.
Arteriolar smooth muscle normally displays a state of partial constriction known as **vascular tone**, which establishes a baseline of arteriolar resistance.

Two factors are responsible for vascular tone.

1. Arteriolar smooth muscle is tonic smooth muscle that has sufficient surface-membrane voltage-gated Ca++ channels open to trigger partial contraction. This myogenic activity is independent of any neural or hormonal influences, leading to self-induced contractile activity.
2. The sympathetic fibers supplying most arterioles continually release norepinephrine, which further enhances vascular tone.

This ongoing tone makes it possible to either increase or decrease contractile activity to accomplish vasoconstriction or vasodilation, respectively.
Vascular smooth muscle can undergo graded changes in force in response to chemical, physical, and neural factors without undergoing action potentials. These agents largely act via second-messenger pathways.

★ Arterioles are arteries with a diameter <0.1 mm.
The internal diameters of the arterioles range from as little as 4 micrometers to as much as 25 micrometers. However, their strong vascular walls allow the internal diameters to change tremendously, often as much as fourfold.



★ The tunica media of arterioles consists of 1-3 layers of smooth muscle cells.
Smooth muscles are richly innervated by sympathetic nerve fibers, and sensitive to many local chemical changes, to a few circulating hormones, and to mechanical factors such as stretch.

The smooth muscle layer runs circularly around the arteriole;so when the smooth muscle layer contracts, the vessel's circumference becomes smaller, increasing resistance and decreasing flow through that vessel.
The terminal arterioles that supply blood to capillary beds are called metarterioles. The smooth muscle layer of meta-arterioles is not continuous; rather, individual muscle cells are spaced apart, and each encircles the endothelium of a capillary arising from the meta-arteriole, allowing them to act as a sphincter upon contraction, controlling blood flow into the capillary bed.

Vascular resistance

In the systemic circulation, about two thirds of the total systemic resistance to blood flow is resistance in the arterioles.
Blood pumped by the heart flows from the high-pressure part of the systemic circulation to the low-pressure side through blood vessels arranged in series and in parallel.
The arteries, arterioles, capillaries, venules, and veins are collectively arranged in series. When blood vessels are arranged in **series**, flow through each blood vessel is the same, and the total resistance to blood flow is equal to the sum of the resistances of each vessel:
R(total) = R1 + R2 + R3
The total peripheral vascular resistance is therefore equal to the sum of resistances of the arteries, arterioles, capillaries, venules, and veins.
Blood vessels branch extensively to form parallel circuits that supply blood to the many organs and tissues of the body. This parallel arrangement permits each tissue to regulate its own blood flow, to a great extent, independently of flow to other tissues.
For blood vessels arranged in **parallel**, the total resistance to blood flow is expressed as follows: **1/R(total) = 1/R1 + 1/R2 + 1/R3**
It is obvious that for a given pressure gradient, far greater amounts of blood will flow through this parallel system than through any of the individual blood vessels. Therefore, the total resistance is far less than the resistance of any single blood vessel.

Flow through each of the parallel vessels is determined by the pressure gradient and its own resistance, not the resistance of the other parallel blood vessels. However, increasing the resistance of any of the blood vessels increases the total vascular resistance. It may seem paradoxical that adding more blood vessels to a circuit reduces the total vascular resistance. Many parallel blood vessels, however, make it easier for blood to flow through the circuit because each parallel vessel provides another pathway, or conductance, for blood flow.

The total conductance (the reciprocal of resistance) for blood flow is the sum of the conductance of each parallel pathway: For example, brain, kidney, muscle, gastrointestinal, skin, and coronary circulations are arranged in parallel, and each tissue contributes to the overall conductance of the systemic circulation. Blood flow through each tissue is a fraction of the total blood flow (cardiac output) and is determined by the resistance for blood flow in the tissue, as well as the pressure gradient. Therefore, amputation of a limb or surgical removal of a kidney also removes a parallel circuit and reduces the total vascular conductance and total blood flow while increasing the total peripheral vascular resistance.

https://youtu.be/QrqktwsfkTs
(For this lesson, you can skip and start watching from minute 4:29 which starts to discuss parallel vs series resistance.)

Q: If you removed a kidney for a patient, what will be the effect on total resistance?
A- Total resistance will increase.
B- Total resistance will decrease.
C- Total resistance will not change.

Acute control of blood flow

Local control of blood flow:

It is not possible simply to increase blood flow everywhere in the body when a particular tissue demands increased flow.
Instead, the microvessels of each tissue, especially the arterioles, continuously monitor tissue needs. Then dilate or constrict to control local blood flow at the level required for the tissue activity. Also, nervous control of the circulation from the central nervous system and hormones provides additional help in controlling tissue blood flow.
Arterioles change blood flow based on 2 control systems:

1. Intrinsic (local) control.
2. Extrinsic control.

Local controls are changes within an organ that adjust blood flow through the organ by affecting the smooth muscle of the organ's arterioles to alter their caliber and resistance.

Local influences may be either chemical or physical.

Local chemical influences on arteriolar radius include:

1. local metabolic changes.
2. histamine release.

Local physical influences include:

1. how much the vessel is stretched.
2. the extent of shear stress.
3. local application of heat or cold.

These local chemical changes act on arteriolar endothelial cells. Arteriolar endothelial cells release vasoactive substances which act on the underlying smooth muscle to alter its state of contraction, thus locally regulating arteriolar caliber.

NO is an important vasodilator, whereas endothelin is a potent vasoconstrictor.

Histamine is another local chemical mediator that influences arteriolar smooth muscle, but it is not released in response to local metabolic changes and is not derived from endothelial cells.

When organs are injured or during allergic reactions, histamine is released and acts as a paracrine in the damaged region. By promoting relaxation of arteriolar smooth muscle, histamine is the major cause of vasodilation in an injured area. The resultant increase in blood flow into the area produces the redness and contributes to the swelling seen with inflammatory responses.

Local blood flow control can be divided into two phases:

1. Acute control
2. 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:
Slow, controlled changes in flow over a period of days to months. In general, these long-term changes provide 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.

According to the vasodilator theory:
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 are then believed to diffuse through the tissues to the precapillary sphincters, metarterioles, and arterioles to cause dilation.

Some of the different vasodilator substances are:
Adenosine, carbon dioxide, adenosine phosphate compounds, histamine, potassium ions, and hydrogen ions.

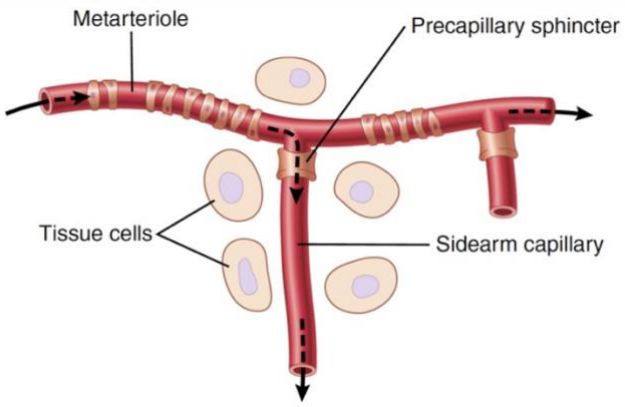
Q: High Oxygen level is also a vasodilator?

- True.
- False.

The number of precapillary sphincters that are open at any given time is roughly proportional to the requirements of the tissue for nutrition.

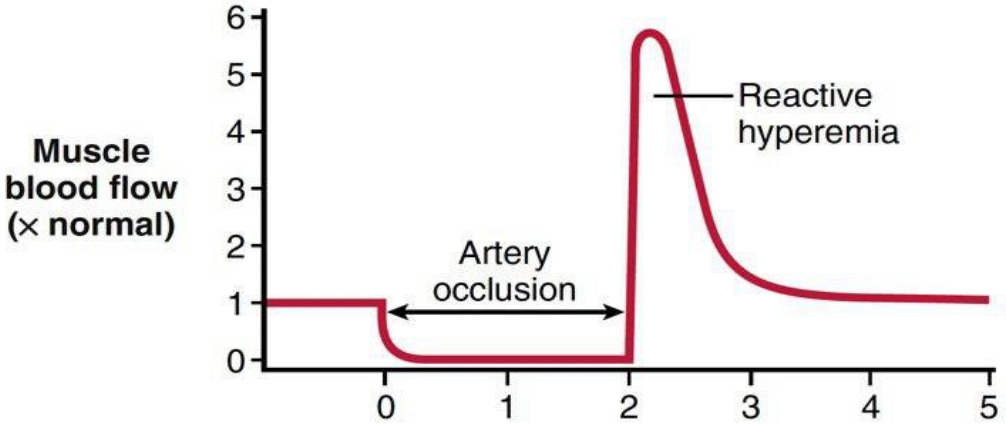
The precapillary sphincters and metarterioles open and close cyclically several times per minute, with the duration of the open phases being proportional to the metabolic needs of the tissues for oxygen.

The cyclical opening and closing is called **vasomotion**.

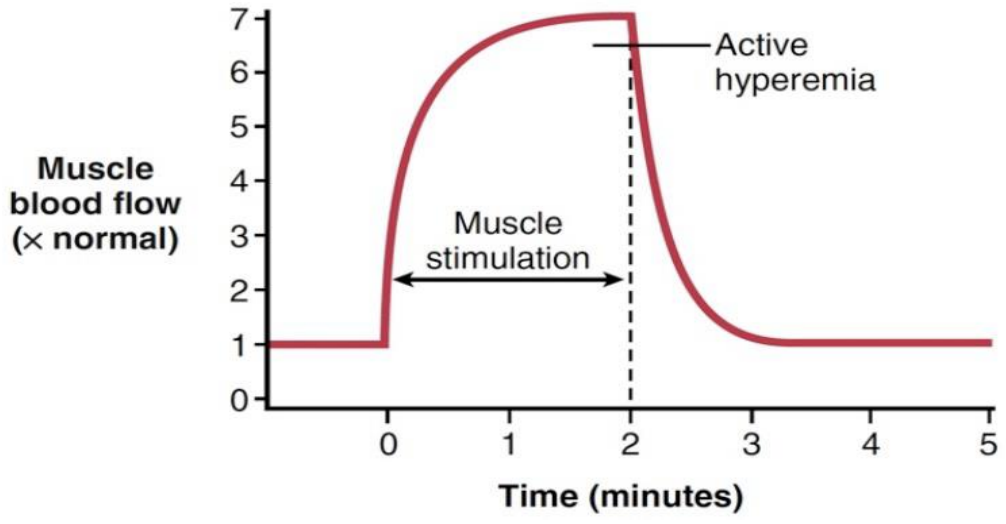


Another theory is called **the oxygen demand theory or the nutrient demand theory**. Oxygen is one of the metabolic nutrients required to cause vascular muscle contraction, with other nutrients required as well. Therefore, in the absence of adequate oxygen, it is reasonable to believe that the blood vessels would relax and therefore dilate. Also, increased utilization of oxygen in the tissues as a result of increased metabolism theoretically could decrease the availability of oxygen to the smooth muscle fibers in the local blood vessels, causing local vasodilation.

When the blood supply to a tissue is blocked for a few seconds to as long as 1 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**.



The increase in local metabolism causes the cells to consume tissue fluid nutrients rapidly and release large quantities of vasodilator substances. The 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. **Active hyperemia** in skeletal muscle can increase local muscle blood flow as much as 20-fold during intense exercise.



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Q: True or false? Elevated blood pressure will induce vasoconstriction.

- True.
- False.

Autoregulation

The effect of arterial pressure on blood flow in many tissues is usually far less than one might expect.
This is because an increase in arterial pressure not only increases the force that pushes blood through the vessels, but also initiates compensatory increases in vascular resistance within a few seconds through activation of the local control mechanism.

Conversely, with reductions in arterial pressure, vascular resistance is promptly reduced in most tissues, and blood flow is maintained at a relatively constant rate.

The ability of each tissue to adjust its vascular resistance and to maintain normal blood flow during changes in arterial pressure between approximately 70 and 175 mm Hg is called **blood flow autoregulation.**

Blood flow changes rarely last for more than a few hours in most tissues, even when increases in arterial pressure or increased levels of vasoconstrictors are sustained. The reason for the relative constancy of blood flow is that each tissue's local autoregulatory mechanisms eventually override most of the effects of vasoconstrictors to provide a blood flow that is appropriate for the needs of the tissue.

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.

The myogenic theory, however, suggests that another mechanism not related to tissue metabolism explains the phenomenon of autoregulation.
This theory is based on the observation that a sudden stretch of small blood vessels causes the smooth muscle of the vessel wall to contract.
Therefore, it has been proposed that 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.

The myogenic response is inherent to vascular smooth muscle and can occur in the absence of neural or hormonal influences.
It is most pronounced in arterioles but can also be observed in arteries, venules, veins, and even lymphatic vessels.

Myogenic contraction is initiated by stretch-induced vascular depolarization, which then rapidly increases calcium ion entry from the extracellular fluid 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.

Norepinephrine and Epinephrine

Norepinephrine is an especially powerful vasoconstrictor hormone; epinephrine is less powerful as a vasoconstrictor and, in some tissues, even causes mild vasodilation.

When the sympathetic nervous system is stimulated in most parts of the body during stress or exercise, the sympathetic nerve endings in the individual tissues release norepinephrine, 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.

Angiotensin II

The effect of angiotensin II is to constrict the small arterioles powerfully.
The real importance of angiotensin Il is that it normally acts on many arterioles of the body at the same time to increase the total peripheral resistance and decrease sodium and water excretion by the kidneys, thereby increasing the arterial pressure.
Thus, this hormone plays an integral role in the regulation of arterial pressure.

Vasopressin

Vasopressin, also called antidiuretic hormone, is even more powerful than angiotensin Il as a vasoconstrictor, thus making it one of the body's most potent vascular constrictor substances.
It is formed in nerve cells in the hypothalamus of the brain but is then transported downward by nerve axons to the posterior pituitary gland, where it is finally secreted into the blood.
It is clear that vasopressin could have enormous effects on circulatory function. Yet, because only minute amounts of vasopressin are secreted in most physiological conditions, most physiologists have thought that vasopressin plays little role in vascular control. However, experiments have shown that the concentration of circulating blood vasopressin after severe hemorrhage can increase enough to attenuate reductions in arterial pressure markedly. In some cases, this action can, by itself, bring the arterial pressure almost back up to normal.

Vasopressin has the major function of greatly increasing water reabsorption from the renal tubules back into the blood and therefore helps control body fluid volume.

Ca++

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

H+

An increase in hydrogen ion concentration (decrease in pH) causes dilation of the arterioles. Conversely, a slight decrease in hydrogen ion concentration causes arteriolar constriction.

Bradykinin

Several substances called kinins cause powerful vasodilation when formed in the blood and tissue fluids of some organs.
Bradykinin causes both powerful arteriolar dilation and increased capillary permeability.
Kinins appear to play special roles in regulating blood flow and capillary leakage of fluids in inflamed tissues.
It is also believed that bradykinin plays a normal role to help regulate blood flow in the skin, as well as in the salivary and gastrointestinal glands.

Histamine

Histamine is 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.

In many pathological conditions, the intense arteriolar dilation and increased capillary porosity produced by histamine cause large quantities of fluid to leak out of the circulation into the tissues, inducing edema.

K+

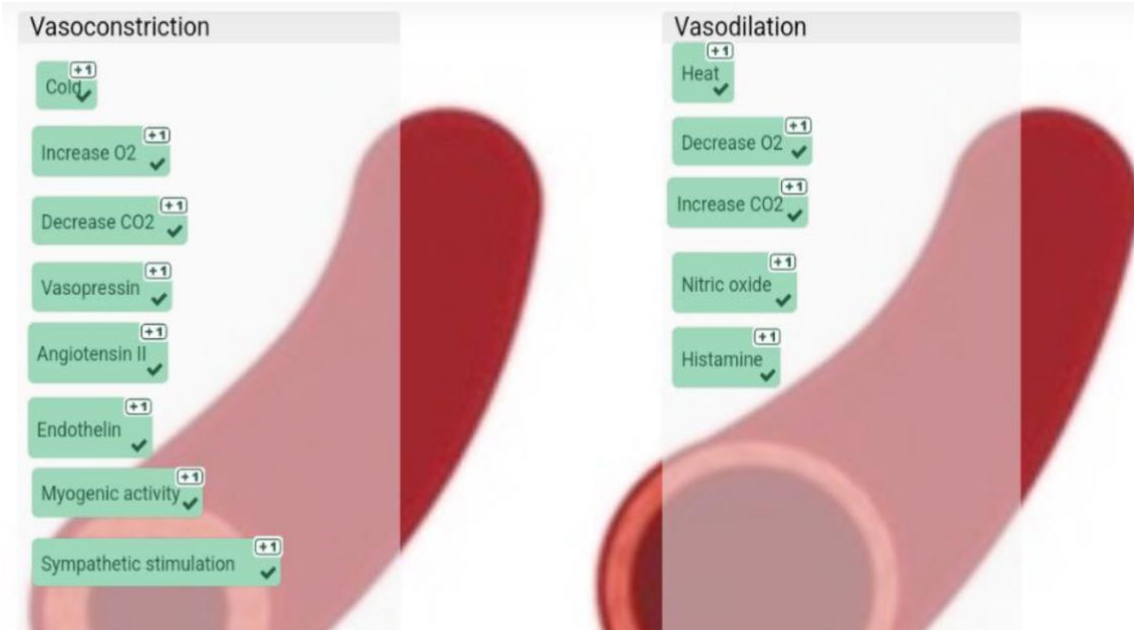
An increase in potassium ion concentration, within the physiological range, causes vasodilation. This effect results from the ability of potassium ions to inhibit smooth muscle contraction.

Mg++

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

CO2

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.



Long-term control of blood flow

Long-term regulation of blood flow is especially important when the metabolic demands of a tissue change. Thus, if a tissue becomes chronically overactive and requires increased quantities of oxygen and other nutrients, the arterioles and capillary vessels usually increase both in number and size within a few weeks to match the needs of the tissue, unless the circulatory system has become pathological or too old to respond.

A key mechanism for long-term local blood flow regulation is to change the amount of vascularity of the tissues. For example, 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.
Thus, actual physical reconstruction of the tissue vasculature occurs to meet the needs of the tissues. This reconstruction occurs rapidly 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.

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 older adults.
Furthermore, the final degree of response is much better in younger than in older tissues; thus, 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.

Oxygen is important not only for acute control of local blood flow but also for long-term control.

Some of the factors involved are: Vascular endothelial growth factor (VEGF), fibroblast growth factor, platelet-derived growth factor (PDGF), angiogenin, hypoxia inducible factors (HIFS).

Angiogenesis begins with new vessels sprouting from other small vessels. The first step is dissolution of the basement membrane of the endothelial cells at the point of sprouting. This step is followed by rapid reproduction of new endothelial cells, which 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 how metabolic factors in local tissues can cause growth of new vessels.

Certain 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. Therefore, blood vessels can also be made to disappear when they are not needed. Peptides produced in the tissues can also block the growth of new blood vessels. Such as angiostatin and Endostatin.
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.
However, after extra vascularity does develop, the extra blood vessels normally remain mainly vasoconstricted, opening to allow extra flow only when appropriate local stimuli such as a lack of oxygen, nerve vasodilatory stimuli, or other stimuli call forth the required extra flow.

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.

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.
After this initial opening of collateral vessels, the blood flow often is still less than 25% of that required to supply all the tissue needs. However, further opening occurs within the ensuing hours, so that 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, usually forming multiple small collateral channels rather than one single large vessel.
Under resting conditions, the blood flow may return to nearly normal, but the new channels seldom become large enough to supply the blood flow needed during strenuous tissue activity.
Thus, 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.

Type of vascular remodeling:

1. Outward hypertrophic remodeling.
Vascular remodeling in the **venous** side of arteriovenous (A-V) fistula in patients on renal dialysis.

2- Outward remodeling.
Vascular remodeling in the **arterial** side of arteriovenous (A-V) fistula in patients on renal dialysis.

3- Hypertrophic remodeling.
Vascular remodeling in the Saphenous vein in patient for coronary artery bypass graft procedure.

4- Inward eutrophic remodeling.
Vascular remodeling in the arterioles in patient with chronic hypertension.

Remodeling in Hypertension

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 pressures. However, this hypertrophic response also makes the large blood vessels stiffer, which is a hallmark of chronic hypertension.

Remodeling in CABG

CABG procedure:
When a large vein (often the saphenous vein) is implanted in a patient for a coronary artery bypass graft procedure. Veins are normally exposed to much lower pressures than arteries and have much thinner walls, but when a vein is sewn onto the aorta and connected to a coronary artery, it is exposed to increases in intraluminal pressure and wall tension. The increased wall tension initiates hypertrophy of vascular smooth muscle cells and increased extracellular matrix formation, which thicken and strengthen the wall of the vein; as a result, several months after implantation into the arterial system, the vein will typically have a wall thickness similar to that of an artery.

Remodeling in A-V fistula

A-V fistula in Renal failure patients

The creation of a fistula connecting a large artery and large vein, thereby completely bypassing high-resistance small vessels and capillaries, provides an especially interesting example of remodeling in the affected artery and vein. In patients with renal failure who undergo dialysis, anarteriovenous (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 increases. 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.

In contrast, 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).

Summary

This pattern of remodeling is consistent with the idea that long-term increases in vascular wall tension cause hypertrophy and increased wall thickness in large blood vessels, whereas increased blood flow rate and shear stress cause outward remodeling and increased luminal diameter to accommodate the increased 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 and, when blood pressure is reduced, the thickness of the vascular wall usually decreases.

Thus, vascular remodeling is an important adaptive response of the blood vessels to tissue growth and development, as well as to physiological and pathological changes in blood pressure and blood flow to the tissues.