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1. **REGULATION OF MEAN ARTERIAL PRESSURE**:

In each cardiac cycle arterial blood pressure fluctuates between diastolic and systolic pressure. However, the body behaves from day to day as if it regulated the mean arterial blood pressure, which is the average between diastolic and systolic pressures. Such regulation is achieved by interdependent adjustments of only 3 parameters: Heart rate (HR), ventricular stroke volume (SV) and total peripheral vascular resistance (TPVR). These are related as follows: HR - SV = Cardiac Output (CO); CO - TPVR = Mean Arterial Blood Pressure. The regulatory system includes stretch-sensitive sensors, central nervous integrators/evaluators and neuro-humoral effector mechanisms. Central nervous integration and evaluation of incoming signals occurs mostly in the pons/medulla regions of the midbrain. The most important effector mechanisms are the parasympathetic and sympathetic divisions of the autonomic nervous system, the renin-angiotensin system and vasopressin. Short-term regulation of arterial blood pressure is dominated by the baroreceptor mechanism, whereby pressure is sensed by both cardio-pulmonary nerve endings and stretch-sensitive cells in renal afferent arterioles. Long-term regulation involves mainly the regulation of extracellular fluid volume by pressure natriuresis mechanisms residing in the kidney and by widespread actions of angiotensin. Studies in hypertensives have suggested that the long-term-controlled variable is not arterial blood pressure, but the balance between intake and output of fluid and electrolytes. If the kidney requires a higher perfusion pressure to achieve that balance then daily blood pressure regulation occurs around an appropriately higher setpoint.

Long-term regulation of arterial pressure is linked closely to volume homeostasis through the renal body fluid feedback mechanisms. A key feature of the renal body fluid feedback control system is pressure natriuresis or the ability of the kidneys to respond to changes in arterial pressure by altering the renal excretion of salt and water. Importantly, neurally induced changes in peripheral resistance and cardiac output, which are essential for rapid regulation of arterial pressure, do alter arterial pressure chronically, unless they are also associated with sustained changes in renal excretory

function. The sensitivity of the pressure natriuresis mechanism can be modified by a number of extrarenal neurohormonal regulatory systems. For example, one hormonal system that is particularly important to arterial pressure homeostasis is the renin-angiotensin system. This is because the renin-angiotensin system is a nonadapting hormonal mechanism that chronically alters the sensitivity of pressure natriuresis. As arterial pressure or sodium intake increases, the renin-angiotensin system is suppressed, which enhances the ability of the kidneys to excrete salt and water. Conversely, when either arterial pressure or sodium intake is reduced, high endogenous levels of angiotensin (Ang) II decrease renal excretory function, which promotes sodium retention. In the absence of appropriate changes in the renin-angiotensin system, there is an abnormal shift in the pressure natriuresis relationship, resulting in sustained alterations in arterial pressure. Although the importance of the renin-angiotensin system in long-term regulation of arterial pressure is firmly established, it is unclear whether the sympathetic nervous system also plays a similar role in body fluid volume and arterial pressure homeostasis. One way in which the sympathetic nervous system could alter pressure natriuresis and contribute to long-term regulation of arterial pressure is through changes in renal sympathetic nerve activity. Indeed, there is considerable evidence from acute studies that baroreflex-mediated changes in renal sympathetic nerve activity influence pressure natriuresis and contribute to short-term regulation of body fluid volumes. However, it is not clear whether compensatory changes in renal sympathetic nerve activity are sustained chronically and alter pressure natriuresis during long-term perturbations in body fluid volumes and arterial pressure. This uncertainty is a result of technical limitations that prevent determination of both the long-term changes in renal sympathetic nerve activity and the sodium excretory responses to chronic alterations in renal adrenergic activity. Finally, although arterial and cardiac baroreflexes mediate changes in renal sympathetic nerve activity during acute perturbations in body fluid volumes and arterial pressure, it is also recognized that baroreceptors reset to the prevailing level of blood pressure. Consequently, if baroreflexes completely reset, then they could not possibly play a role in the long-term regulation of arterial pressure. Therefore, it is not clear what afferent mechanisms might detect chronic disturbances in body fluid volumes and arterial pressure and subsequently evoke sustained compensatory changes in renal sympathetic nerve activity.

Renin-Angiotensin-Aldosterone System (RAAS)

Renin is a peptide hormone released by the granular cells of the juxtaglomerular apparatus in the kidney. It is released in response to:

.Sympathetic stimulation

.Reduced sodium-chloride delivery to the distal convoluted tubule

.Decreased blood flow to the kidney

Renin facilitates the conversion of angiotensinogen to angiotensin I which is then converted to angiotensin II using angiotensin-converting enzyme (ACE).

Angiotensin II is a potent vasoconstrictor. It acts directly on the kidney to increase sodium reabsorption in the proximal convoluted tubule. Sodium is reabsorbed via the sodium-hydrogen exchanger. Angiotensin II also promotes release of aldosterone. ACE also breaks down a substance called bradykinin which is a potent vasodilator. Therefore, the breakdown of bradykinin potentiates the overall constricting effect. Aldosterone promotes salt and water retention by acting at the distal convoluted tubule to increase expression of epithelial sodium channels. Furthermore, aldosterone increases the activity of the basolateral sodium-potassium ATP-ase, thus increasing the electrochemical gradient for movement of sodium ions. More sodium collects in the kidney tissue and water then follows by osmosis. This results in decreased water excretion and therefore increased blood volume and thus blood pressure.

Anti-Diuretic Hormone (ADH)

The second mechanism by which blood pressure is regulated is release of Anti Diuretic Hormone (ADH) from the OVLT of the hypothalamus in response to thirst or an increased plasma osmolarity.

ADH acts to increase the permeability of the collecting duct to water by inserting aquaporin channels (AQP2) into the apical membrane.

It also stimulates sodium reabsorption from the thick ascending limb of the loop of Henle. This increases water reabsorption thus increasing plasma volume and decreasing osmolarity.

Further Control of Blood Pressure

Other factors that can affect long-term regulation of blood pressure are natriuretic peptides. These include:

Atrial natriuretic peptide (ANP) is synthesised and stored in cardiac myocytes. It is released when the atria are stretched, indicating of high blood pressure. ANP acts to promote sodium excretion. It dilates the afferent arteriole of the glomerulus, increasing blood flow (GFR). Moreover, ANP inhibits sodium reabsorption along the nephron. Conversely, ANP secretion is low when blood pressure is low.

Prostaglandins act as local vasodilators to increase GFR and reduce sodium reabsorption. They also act to prevent excessive vasoconstriction triggered by the sympathetic nervous and renin-angiotensin-aldosterone systems.

2.

A. **PULMONARY CIRCULATION:**

Deoxygenated blood leaves the heart, goes to the lungs, and then re-enters the heart; Deoxygenated blood leaves through the right ventricle through the pulmonary artery. From the right atrium, the blood is pumped through the tricuspid valve (or right atrioventricular valve), into the right ventricle. Blood is then pumped from the right ventricle through the pulmonary valve and into the main pulmonary artery.

Lungs

The pulmonary arteries carry deoxygenated blood to the lungs, where carbon dioxide is released and oxygen is picked up during respiration. Arteries are further divided into very fine capillaries which are extremely thin-walled. The pulmonary vein returns oxygenated blood to the left atrium of the heart.

Veins

Main structure: Pulmonary vein

The oxygenated blood then leaves the lungs through pulmonary veins, which return it to the left part of the heart, completing the pulmonary cycle. This blood then enters the left atrium, which pumps it through the mitral valve into the left ventricle. From the left ventricle, the blood passes through the aortic valve to the aorta. The blood is then distributed to the body through the systemic circulation before returning again to the pulmonary circulation.

Arteries

Main structure: Pulmonary artery

From the right ventricle, blood is pumped through the semilunar pulmonary valve into the left and right main pulmonary arteries (one for each lung), which branch into smaller pulmonary arteries that spread throughout the lungs.

Development

The pulmonary circulation loop is virtually bypassed in fetal circulation. The fetal lungs are collapsed, and blood passes from the right atrium directly into the left atrium through the foramen ovale: an open conduit between the paired atria, or through the ductus arteriosus: a shunt between the pulmonary artery and the aorta. When the lungs expand at birth, the pulmonary pressure drops and blood is drawn from the right atrium into the right ventricle and through the pulmonary circuit. Over the course of several months, the foramen ovale closes, leaving a shallow depression known as the fossa ovalis.

Clinical significance

A number of medical conditions can affect the pulmonary circulation.

.Pulmonary hypertension describes an increase in resistance in the pulmonary arteries

.Pulmonary embolus is a blood clot, usually from a deep vein thrombosis that has lodged in the pulmonary vasculature. It can cause difficulty breathing or chest pain, is usually diagnosed through a CT pulmonary angiography or V/Q scan, and is often treated with anticoagulants such as heparin and warfarin.

.Cardiac shunt is an unnatural connection between parts of the heart that leads to blood flow that bypasses the lungs

.Vascular resistance

.Pulmonary shunt

B. **CIRCLE OF WILLIS**:

The Circle of Willis is the joining area of several arteries at the bottom (inferior) side of the brain. At the Circle of Willis, the internal carotid arteries branch into smaller arteries that supply oxygenated blood to over 80% of the cerebrum. The circle of Willis (also called Willis' circle, loop of Willis, cerebral arterial circle, and Willis polygon) is a circulatory anastomosis that supplies blood to the brain and surrounding structures. It is named after Thomas Willis (1621—1675), an English physician.

Structure

The circle of Willis is a part of the cerebral circulation and is composed of the following arteries:

.Anterior cerebral artery (left and right)

.Anterior communicating artery

.Internal carotid artery (left and right)

.Posterior cerebral artery (left and right)

.Posterior communicating artery (left and right)

The middle cerebral arteries, supplying the brain, are not considered part of the circle of Willis.

Origin of arteries

The left and right internal carotid arteries arise from the left and right common carotid arteries.

The posterior communicating artery is given off as a branch of the internal carotid artery just before it divides into its terminal branches - the anterior and middle cerebral arteries. The anterior cerebral artery forms the anterolateral portion of the circle of Willis, while the middle cerebral artery does not contribute to the circle.

The right and left posterior cerebral arteries arise from the basilar artery, which is formed by the left and right vertebral arteries. The vertebral arteries arise from the subclavian arteries.

The anterior communicating artery connects the two anterior cerebral arteries and could be said to arise from either the left or right side.

All arteries involved give off cortical and central branches. The central branches supply the interior of the circle of Willis, more specifically, the Interpeduncular fossa. The cortical branches are named for the area they supply. Since they do not directly affect the circle of Willis, they are not dealt with here.

Variation

Considerable anatomic variation exists in the circle of Willis. Based on a study of 1413 brains, the classic anatomy of the circle is only seen in 34.5% of cases. In one common variation the proximal part of the posterior cerebral artery is narrow and its ipsilateral posterior communicating artery is large, so the internal carotid artery supplies the posterior cerebrum; this is known as a fetal posterior communicating cerebral artery. In another variation the anterior communicating artery is a large vessel, such that a single internal carotid supplies both anterior cerebral arteries; this is known as an azygos anterior cerebral artery.

Function

The arrangement of the brain's arteries into the circle of Willis creates redundancy (analogous to engineered redundancy) for collateral circulation in the cerebral circulation. If one part of the circle becomes blocked or narrowed (stenosed) or one of the arteries supplying the circle is blocked or narrowed, blood flow from the other blood vessels can often preserve the cerebral perfusion well enough to avoid the symptoms of ischemia.

Clinical significance

.Aneurysms

.Subclavian steal syndrome **:** The redundancies that the circle of Willis introduce can also lead to reduced cerebral perfusion. In subclavian steal syndrome, blood is "stolen"

from the circle of Willis to preserve blood flow to the upper limb. Subclavian steal syndrome results from a proximal stenosis (narrowing) of the subclavian artery, an artery supplied by the aorta, which is also the same blood vessel that eventually feeds the circle of Willis via the vertebral and internal carotid arteries.

C. **Splanchnic Circulation:**

The splanchnic circulation comprises the gastric, small intestinal, colonic, pancreatic, hepatic, and splenic circulations. They are arranged in parallel and fed by the celiac artery and the superior and inferior mesenteric arteries.

The resistance arterioles are the primary determinant of vascular resistance in the splanchnic circulation. Neuronal control of the mesenteric circulation is almost entirely sympathetic in origin. The parasympathetic fibers from the vagi have little effect on blood flow. Overall splanchnic blood flow requires about 25% of cardiac output. The splanchnic venous capacitance reservoir contains about one-third of the body's total blood volume. The sympathetic postganglionic fibers cause arteriolar vasoconstriction and decrease splanchnic perfusion. Sympathetic stimulation also contracts the smooth muscle of the capacitance veins in the splanchnic circulation, and may expel a large volume of pooled blood from the splanchnic into the systemic circulation. Autoregulation in the splanchnic circulation is less marked than in the cerebral, cardiac, or renal circulations. The response is present, however, and serves to restore blood follow to areas suffering hypoperfusion because of an acute reduction in perfusion pressure. The splanchnic circulation also responds to reduced perfusion pressure by the redistribution of blood flow within individual organs. For example, in hypovolemic shock perfusion usually favors the mucosa of the gut at the expense of the muscularis mucosa.

The liver is unique in that it has both an arterial and a venous afferent blood supply. In the resting adult the liver receives approximately 500 mL min of blood via the hepatic artery and a further 1300 mL min from the portal circulation.

The splanchnic circulation powerfully influences systemic arterial pressure via two distinct mechanisms. Widespread contraction of arteries in the splanchnic bed reduces blood flow to the region. The low oxygen consumption of splanchnic organs allows for a very large reduction in blood flow without producing ischemia. Arterial constriction causes dramatic increases in systemic arterial pressure and total peripheral resistance. Cardiac output also may increase due to passive discharge of stored blood from downstream veins into the central circulation. Active constriction of veins in the splanchnic organs reduces regional blood volume. This has relatively little effect on total peripheral resistance but raises cardiac output and arterial pressure by increasing central blood volume and thus cardiac preload. Generalized arterial and venous constriction in the splanchnic circulation occur mainly in response to extrinsic neural and hormonal inputs. Catecholamines, angiotensin II and vasopressin are among the

most powerful hormonal vasoconstrictors. They serve this function particularly in response to major challenges to overall circulatory homeostasis, for example acute hypovolemia caused by hemorrhage. Extrinsic neural regulation is achieved almost exclusively through the sympathetic branch of the autonomic nervous system.

The splanchnic circulation consists of the blood supply to the gastrointestinal tract, liver, spleen, and pancreas. It consists of two large capillary beds partially in series. The small splanchnic arterial branches supply the capillary beds, and then the efferent venous blood flows into the PV. The PV and hepatic artery supply blood flow to the liver.

The splanchnic circulation is composed of gastric, small intestinal, colonic, pancreatic, hepatic, and splenic circulations, arranged in parallel with one another. The three major arteries that supply the splanchnic organs, cellac and superior and inferior mesenteric, give rise to smaller arteries that anastomose extensively. The circulation of some splanchnic organs is complicated by the existence of an intramural circulation. Redistribution of total blood flow between intramural vascular circuits may be as important as total blood flow. Numerous extrinsic and intrinsic factors influence the splanchnic circulation. Extrinsic factors include general hemodynamic conditions of the cardiovascular system, autonomic nervous system, and circulating neurohumoral agents. Intrinsic mechanisms include special properties of the vasculature, local metabolites, intrinsic nerves, paracrine substances, and local hormones. The existence of a multiplicity of regulatory mechanisms provides overlapping controls and restricts radical changes in tissue perfusion.

D. CORONARY CIRCULATION:

Coronary circulation is the circulation of blood in the blood vessels that supply the heart muscle (myocardium). Coronary arteries supply oxygenated blood to the heart muscle, and cardiac veins drain away the blood once it has been deoxygenated. Because the rest of the body, and most especially the brain, needs a steady supply of oxygenated blood that is free of all but the slightest interruptions, the heart is required to function continuously. Therefore its circulation is of major importance not only to its own tissues but to the entire body and even the level of consciousness of the brain from moment to moment. Interruptions of coronary circulation quickly cause heart attacks (myocardial infarctions), in which the heart muscle is damaged by oxygen starvation. Such interruptions are usually caused by ischemic heart disease (coronary artery disease) and sometimes by embolism from other causes like obstruction in blood flow through vessels.

Coronary arteries supply blood to the myocardium and other components of the heart. Two coronary arteries originate from the left side of the heart at the beginning (root) of the aorta, just after the aorta exits the left ventricle. There are three aortic sinuses (dilations) in the wall of the aorta just superior to the aortic semilunar valve. Two of

these, the left posterior aortic sinus and anterior aortic sinus, give rise to the left and right coronary arteries, respectively. The third sinus, the right posterior aortic sinus, typically does not give rise to a vessel. Coronary vessel branches that remain on the surface of the heart and follow the sulci of the heart are called epicardial coronary arteries.

The left coronary artery distributes blood to the left side of the heart, the left atrium and ventricle, and the interventricular septum. The circumflex artery arises from the left coronary artery and follows the coronary sulcus to the left. Eventually, it will fuse with the small branches of the right coronary artery. The larger anterior interventricular artery, also known as the left anterior descending artery (LAD), is the second major branch arising from the left coronary artery. It follows the anterior interventricular sulcus around the pulmonary trunk. Along the way it gives rise to numerous smaller branches that interconnect with the branches of the posterior interventricular artery, forming anastomoses. An anastomosis is an area where vessels unite to form interconnections that normally allow blood to circulate to a region even if there may be partial blockage in another branch. The anastomoses in the heart are very small. Therefore, this ability is somewhat restricted in the heart so a coronary artery blockage often results in myocardial infarction causing death of the cells supplied by the particular vessel.

The right coronary artery proceeds along the coronary sulcus and distributes blood to the right atrium, portions of both ventricles, and the heart conduction system. Normally, one or more marginal arteries arise from the right coronary artery inferior to the right atrium. The marginal arteries supply blood to the superficial portions of the right ventricle. On the posterior surface of the heart, the right coronary artery gives rise to the posterior interventricular artery, also known as the posterior descending artery. It runs along the posterior portion of the interventricular sulcus toward the apex of the heart, giving rise to branches that supply the interventricular septum and portions of both ventricles.

Anastomoses

Cast of coronary arteries (right = yellow, left = red)

There are some anastomoses between branches of the two coronary arteries. However the coronary arteries are functionally end arteries and so these meetings are referred to as potential anastomoses, which lack function, as opposed to true anastomoses like that in the palm of the hand. This is because blockage of one coronary artery generally results in death of the heart tissue due to lack of sufficient blood supply from the other branch. When two arteries or their branches join, the area of the myocardium receives dual blood supply. These junctions are called anastomoses. If one coronary artery is obstructed by an atheroma, the second artery is still able to supply oxygenated blood to the myocardium. However, this can only occur if the atheroma progresses slowly, giving the anastomoses a chance to proliferate.

Under the most common configuration of coronary arteries, there are three areas of anastomoses. Small branches of the LAD (left anterior descending/anterior interventricular) branch of the left coronary join with branches of the posterior interventricular branch of the right coronary in the interventricular sulcus (groove). More superiorly, there is an anastomosis between the circumflex artery (a branch of the left coronary artery) and the right coronary artery in the atrioventricular groove. There is also an anastomosis between the septal branches of the two coronary arteries in the interventricular septum. The photograph shows area of heart supplied by the right and the left coronary arteries.

Variation

The left and right coronary arteries occasionally arise by a common trunk, or their number may be increased to three; the additional branch being the posterior coronary artery (which is smaller in size). In rare cases, a person will have the third coronary artery run around the root of the aorta.

Occasionally, a coronary artery will exist as a double structure (i.e. there are two arteries, parallel to each other, where ordinarily there would be one).

Coronary artery dominance

The artery that supplies the posterior third of the interventricular septum — the posterior descending artery (PDA) determines the coronary dominance.

If the posterior descending artery is supplied by the right coronary artery (RCA), then the coronary circulation can be classified as "right-dominant".

If the posterior descending artery is supplied by the circumflex artery (CX), a branch of the left artery, then the coronary circulation can be classified as "left-dominant".

If the posterior descending artery is supplied by both the right coronary artery and the circumflex artery, then the coronary circulation can be classified as "co-dominant".

Approximately 70% of the general population are right-dominant, 20% are co-dominant, and 10% are left-dominant. A precise anatomic definition of dominance would be the artery which gives off supply to the AV node i.e. the AV nodal artery. Most of the time this is the right coronary artery.

Function

Supply to papillary muscles

The papillary muscles attach the mitral valve (the valve between the left atrium and the left ventricle) and the tricuspid valve (the valve between the right atrium and the right ventricle) to the wall of the heart. If the papillary muscles are not functioning properly,

the mitral valve may leak during contraction of the left ventricle. This causes some of the blood to travel "in reverse", from the left ventricle to the left atrium, instead of forward to the aorta and the rest of the body. This leaking of blood to the left atrium is known as mitral regurgitation. Similarly, the leaking of blood from the right ventricle through the tricuspid valve and into the right atrium can also occur, and this is described as tricuspid insufficiency or tricuspid regurgitation.

The anterolateral papillary muscle more frequently receives two blood supplies: left anterior descending (LAD) artery and the left circumflex artery (LCX).[4] It is therefore more frequently resistant to coronary ischemia (insufficiency of oxygen-rich blood). On the other hand, the posteromedial papillary muscle is usually supplied only by the PDA.[4] This makes the posteromedial papillary muscle significantly more susceptible to ischemia. The clinical significance of this is that a myocardial infarction involving the PDA is more likely to cause mitral regurgitation.

Changes in diastole

During contraction of the ventricular myocardium (systole), the subendocardial coronary vessels (the vessels that enter the myocardium) are compressed due to the high ventricular pressures. This compression results in momentary retrograde blood flow (i.e., blood flows backward toward the aorta) which further inhibits perfusion of myocardium during systole. However, the epicardial coronary vessels (the vessels that run along the outer surface of the heart) remain open. Because of this, blood flow in the subendocardium stops during ventricular contraction. As a result, most myocardial perfusion occurs during heart relaxation (diastole) when the subendocardial coronary vessels are open and under lower pressure. Flow never comes to zero in the right coronary artery, since the right ventricular pressure is less than the diastolic blood pressure.

Changes in oxygen demand

The heart regulates the amount of vasodilation or vasoconstriction of the coronary arteries based upon the oxygen requirements of the heart. This contributes to the filling difficulties of the coronary arteries. Compression remains the same. Failure of oxygen delivery caused by a decrease in blood flow in front of increased oxygen demand of the heart results in tissue ischemia, a condition of oxygen deficiency. Brief ischemia is associated with intense chest pain, known as angina. Severe ischemia can cause the heart muscle to die from hypoxia, such as during a myocardial infarction. Chronic moderate ischemia causes contraction of the heart to weaken, known as myocardial hibernation.

In addition to metabolism, the coronary circulation possesses unique pharmacologic characteristics. Prominent among these is its reactivity to adrenergic stimulation.

Branches

The following are the named branches of the coronary circulation in a right-dominant heart:

.Aorta

.Left coronary artery / Left main coronary artery (LMCA)

.Left circumflex artery (LCX)

.Obtuse marginal artery #1 (OM1)

.Obtuse marginal artery #2 (OM2)

.Left anterior descending artery (LAD)

.Diagonal artery #1

.Diagonal artery #2

.Right coronary artery (RCA)

.Atrioventricular nodal branch

.Right marginal artery

.Posterior descending artery (PDA)

.Posteriolateral artery #1 (PL#1)

.Posteriolateral artery #2 (PL#2)

Coronary anatomy

Cardiac veins

The vessels that remove the deoxygenated blood from the heart muscle are known as cardiac veins. These include the great cardiac vein, the middle cardiac vein, the small cardiac vein, the smallest cardiac veins, and the anterior cardiac veins. Cardiac veins carry blood with a poor level of oxygen, from the myocardium to the right atrium. Most of the blood of the coronary veins returns through the coronary sinus. The anatomy of the veins of the heart is very variable, but generally it is formed by the following veins: heart veins that go into the coronary sinus: the great cardiac vein, the middle cardiac vein, the small cardiac vein, the posterior vein of the left ventricle, and the vein of Marshall. Heart veins that go directly to the right atrium: the anterior cardiac veins, the smallest cardiac veins (Thebesian veins).

Coronary arteries

The vessels that deliver oxygen-rich blood to the myocardium are the coronary arteries. When the arteries are healthy, they are capable of autoregulating themselves to maintain the coronary blood flow at levels appropriate to the needs of the heart muscle. These relatively narrow vessels are commonly affected by atherosclerosis and can become blocked, causing angina or a heart attack. The coronary arteries that run deep within the myocardium are referred to as subendocardial. The coronary arteries are classified as "end circulation", since they represent the only source of blood supply to the myocardium; there is very little redundant blood supply, that is why blockage of these vessels can be so critical.

E. CUTANEOUS CIRCULATION:

The cutaneous circulation is the circulation and blood supply of the skin. The skin is not a very metabolically active tissue and has relatively small energy requirements, so its blood supply is different to that of other tissues.

Some of the circulating blood volume in the skin will flow through will flow through arteriovenous anastomoses (AVAs) instead of capillaries. AVAs serve a role in temperature regulation. In this article we shall consider the different adaptations of the cutaneous circulation, and its role in body temperature control.

Arteriovenous Anastomoses

AVAs are low-resistance connections between the small arteries and small veins that supply and drain the skin. These allow the shunt of blood directly into the venous plexus of the skin, without it passing through capillaries. Since AVAs contain no capillary section, they are not involved in transport of nutrients to/from the tissues, but instead play a major role in temperature regulation.

Temperature Regulation

The skin is the bodys main heat dissipating surface: the amount of blood flow to the skin determines the degree of heat loss and therefore the core body temperature. The blood flow through AVAs is heavily influenced by the sympathetic nervous system. At rest, the sympathetic nervous system dominates and acts to constrict AVAs.

Any changes in core temperature are detected by the thermoregulatory centre in the hypothalamus. It regulates temperature by altering the level of sympathetic outflow to the cutaneous vessels, to return temperature to its normal range:

In high core temperatures:

Sympathetic innervation is decreased, reducing the vasomotor tone in the AVAs.

More blood flows through the AVAs and reaches the venous plexus (close to the surface

of the skin), increasing heat loss to reduce core temperature.

In low core temperatures:

Sympathetic innervation is increased, increasing the vasomotor tone in the AVAs.

Less blood flows to the apical skin (of nose, lips, ears, hands and feet), reducing heat loss to increase the core temperature.

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3.

During exercise, increases in cardiac stroke volume and heart rate raise cardiac output, which coupled with a transient increase in systemic vascular resistance, elevate mean arterial blood pressure. However, long-term exercise can promote a net reduction in blood pressure at rest. A meta-analysis of randomized controlled interventional studies found that regular moderate to intense exercise performed 3—5 times per week lowers blood pressure by an average of 3.4/2.4 mmHg. While this change may appear small, recent work shows that even a 1 mmHg reduction in systolic BP is associated with 20.3 fewer (blacks) or 13.3 fewer (whites) heart failure events per 100,000 person-years. Thus, reductions in blood pressure observed when exercise is included as a behavioral intervention along with dietary modification and weight loss could have a significant impact on CVD incidence.

Lower ambulatory blood pressure, associated with chronic aerobic and resistance exercise, is thought to be driven largely by a chronic reduction in systemic vascular resistance. Contributing to this effect, shear forces, as well as released metabolites from active skeletal muscle during exercise, signal the production and release of nitric oxide (NO) and prostacyclin from the vascular endothelium, which promotes enhanced vasodilation via relaxation of vascular smooth muscle cells. This effect is especially significant because a reduction in eNOS activity that occurs with aging or due to NOS3 polymorphism, has been reported to contribute to hypertension. Long-term exercise training increases eNOS expression as well as NO production in hypertensive individuals, consistent with the blood pressure lowering effect of physical activity. An important role of NO in mediating the vascular effects of exercise is further supported by results showing that rats with hypertension induced by chronic NOS inhibition undergoing a swimming exercise regimen for 6 weeks have significantly elevated eNOS protein expression and improved acetylcholine-induced vasodilation. Thus, improvements in NO production and bioavailability appear to represent significant factors that contribute to improved endothelium-dependent vasodilation following exercise training, which can reduce resting vascular resistance and lower blood pressure. However, in addition to NO-mediated reductions in resistance vascular tone, adaptive reductions in sympathetic nerve activity, prevention or reversal of arterial stiffening, and suppression of inflammation are also likely contributors to the blood pressure lowering effects of exercise, although the impact of exercise on these outcomes may be population specific

(e.g., at-risk versus healthy adults). As with changes in blood lipid profile, it remains unclear to what extent the blood pressure lowering effects of exercise can account for the beneficial effects of exercise on CVD risk and mortality.

Cardiac adaptations

During exercise, the heart is subjected to intermittent hemodynamic stresses of pressure overload, volume overload, or both. To normalize such stress and to meet the systemic demand for an increased blood supply, the heart undergoes morphological adaptation to recurrent exercise by increasing its mass, primarily through an increase in ventricular chamber wall thickness. This augmentation of heart size is primarily the result of an increase in the size of individual terminally differentiated cardiac myocytes. Adaptive remodeling of the heart in response to exercise typically occurs with preservation or enhancement of contractile function. This contrasts with pathologic remodeling due to chronic sustained pressure overload (e.g., during hypertension or aortic stenosis), which can proceed to a loss of contractile function and heart failure.

Recent work in experimental animal exercise models has identified several cellular and molecular alterations involved in the physiologic growth program of the heart that accompanies exercise conditioning. Whereas pathologic remodeling of the heart is associated with a reduction in oxidative energy production via fatty acid oxidation and more reliance on glucose utilization, mitochondrial biogenesis and capacity for fatty acid oxidation are enhanced following exercise. A recent study suggests that changes in myocardial glycolytic activity during acute exercise and the subsequent recovery period can also play an important role in regulating the expression of metabolic genes and cardiac remodeling. Possibly upstream of these metabolic changes, studies have also revealed a dominant role for IGF-1 and insulin receptor signaling, via the PI3K/Akt1 pathway leading to the activation of transcriptional pathways associated with protein synthesis and hypertrophy. Untargeted approaches have identified other major determinants of transcriptional programs that drive the exercise-induced hypertrophic response. For instance, it has been reported that exercise-induced reduction in the expression of CCAAT-enhancer binding protein β (C/EBPβ) relieves its negative regulation by CBP/p300-interactive transactivator with ED-rich carboxy-terminal domain-4 (Cited 4). Activation of Cited4 has been found to be necessary for exercise-induced cardiac hypertrophy, and cardiac-specific overexpression of the gene is sufficient to increase heart mass and protect against ischemia/reperfusion injury. Other transcriptional pathways known to be activated by pathologic stimuli and cardiac hypertrophy, such as NFATc2, are decreased in exercise models, suggesting that some signaling pathways activated during exercise-induced growth program may directly antagonize specific factors that promote pathological remodeling.

In addition to metabolic and molecular remodeling, exercise can also promote functional adaptation of the heart, which may ultimately increase cardiac output and reduce the risk of arrhythmia. Clinical studies have shown that exercise-trained individuals have improved systolic and diastolic function, while results of studies using animal models of

exercise show that endurance exercise promotes enhanced cardiomyocyte contraction-relaxation velocities and force generation. This effect of exercise on cardiomyocyte contractile function may be related to alterations in the rise and decay rates of intracellular Ca2+ transients, possibly due to enhanced coupling efficiency between L-type Ca2+ channel-mediated Ca2+ entry and activation of subsarcolemmal ryanodine receptors (RyR; i.e., calcium-induced calcium release), and increased expression and activity of the sarcoendoplasmic reticulum Ca2+ ATPase (SERCA2a) and sodium-calcium exchanger (NCX). In addition, the sensitivity of the cardiomyocyte contractile apparatus may also become more sensitive to Ca2+, thus producing a greater force of contraction at a given [Ca2+]i, following exercise. These changes may at least partially depend on upregulation of the Na+/H+ antiporter and altered regulation of intracellular pH.

During pathologic remodeling of the heart, electrical instability can result from a lack of upregulation of key cardiac ion channel subunits associated with action potential repolarization relative to an increase in myocyte size. In contrast, increased myocyte size in physiological hypertrophy is associated with the upregulation of depolarizing and repolarizing currents, which may be protective against abnormal electrical signaling in the adapted heart. For example, cardiac myocytes isolated from mice after 4 weeks of swim training were found to have elevated outward K+ current densities (i.e., Ito,f, IK,slow, Iss, and IK1) and increased expression of underlying molecular component Kv and Kir subunits in parallel with increases in total protein levels. Interestingly, a follow up study found that while increases in K+ channel subunit expression following exercise training requires PI3K, these changes occur independently of Akt1 and hypertrophy.

Blood and vasculature

The oxygen carrying capacity of blood, determined by the number of circulating erythrocytes and their associated intracellular hemoglobin concentration, is an important determinant of exercise performance and resistance to fatigue. High endurance athletes commonly have athlete's anemia, possibly due to loss of erythrocytes, or low hematocrit secondary to an expansion of plasma volume. Yet, overall total erythrocyte mass is increased in athletes, especially those who train at high altitude. This is in part due to a dose-dependent effect of O2 on hypoxia-inducible factor (HIF)-mediated erythropoietin production as well as upregulation of erythropoietin receptors, iron transporters, and transferrins. Multiple studies have shown that hematopoiesis is enhanced immediately following exercise. Intense exercise is associated with the release of a variety of stress and inflammatory factors that are active on the bone marrow such as cortisol, IL-6, TNF-α, PMN elastase, and granulocyte colony stimulating factor. Although HPCs appear to modestly decline in the period immediately following an exercise session in conditioned runners, one study found that circulating CD34+ hematopoietic progenitor cell counts were 3- to 4-fold higher in runners vs. non-runners at baseline, which may represent an adaptive response that facilitates tissue repair. A subsequent study found that a bout of intense exercise was associated with a release of CD34+/KDR+

endothelial progenitor cells from the bone marrow and that this effect was enhanced in individuals with elevated LDL/HDL and LDL/TC profiles. Likewise, a significant increase in the number of circulating EPCs, associated with increased levels of VEGF, HIF-1α, and EPO was found within hours after varying intensities of resistance training in women. Nonetheless, the physiological significance of these responses remains unclear, as the effects of exercise on angiogenesis and the wound healing response have not been systematically studied.

The resistance arterial vascular network also undergoes functional and structural adaptation to exercise. During acute exercise, small arteries and pre-capillary arterioles that supply blood to the skeletal muscles must dilate to increase blood flow through the release of vasodilatory signals (e.g., adenosine, lactate, K+, H+, CO2) from active surrounding muscle. Repeated exercise leads to an adaptive response in skeletal muscle arterioles that includes increased vascular density coupled with greater vasodilatory capacity, such that enhanced perfusion can occur after conditioning. This may be partly due to adaptation of the endothelium to the complex interplay of recurrent variations in hemodynamic stresses and vasodilatory stimuli of exercise. Endothelial synthesis of NO is greatly increased at rest and during exercise in conditioned individuals/animals. A similar adaptive response to exercise has also been noted in the coronary vasculature, which must dilate to meet the increased metabolic demands of the myocardium . Exercise-trained humans and animals demonstrate reduced myocardial blood flow at rest, which may reflect a reduction in cardiac oxygen consumption primarily as a result of lower resting heart rate. However, a large body of evidence suggests that multiple mechanisms converge to enhance the ability of the coronary circulation to deliver a greater supply of oxygen to the conditioned myocardium during exercise. This includes structural adaptations consisting of an expansion in the density of intramyocardial arterioles and capillaries as well as enhanced microvascular collateral formation . Additionally, like skeletal muscle arterioles, coronary arterial network enhances its responsiveness to vasoactive stimuli via a number of distinct mechanisms including, but not limited to, augmentation of endothelial NO production, altered responsiveness to adrenergic stimuli, or changes in the metabolic regulation of vascular tone . In addition, some studies implicate hydrogen peroxide (H2O2)-mediated vasodilation in opposing exertion-induced arterial dysfunction in overweight obese adults after a period of exercise training, suggesting enhanced contribution of NO-independent mechanisms to improved microvascular endothelial function with exercise. Collectively, these adaptations may act to support enhanced myocardial function and increased cardiac output during repeated exercise, and increased total body oxygen demand following exercise conditioning. Further advancement of our understanding of how blood flow is improved in response to exercise could lead to novel therapeutic strategies to prevent or reverse organ failure in patients resulting from inadequate blood flow.