

CARDIOVASCULAR PATHOPHYSIOLOGY

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These lecture notes accompany my lectures on pathophysiology in the study module "Heart and Circulation" at Innsbruck Medical University. The English version serves two purposes: as a learning aid for international students and to encourage German-speaking students to familiarize themselves with medical English; the lectures are delivered in German. The translation from the original [German version](#) is my own; I am afraid it will occasionally sound appalling to native English speakers, but it should at least be intelligible.

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1. ADJUSTMENT OF CARDIAC OUTPUT AND TISSUE PERFUSION

To keep all their cells well-supplied, multi-cellular organisms depend on efficient logistics. Some supplies, like energy-providing molecules, may be stored in cells to a limited extent. Others, like oxygen or carbon dioxide, have to be delivered or removed just in time.

Our body's circulation system has to meet requirements that may be compared to those of our electrical power supply. Many takers, disposed in parallel, with strong variations in power consumption have to be supplied at all times. This means, the output of the power plant, our heart, has to be regulated over a broad power spectrum. The "current" produced by our heart may be measured as cardiac output per minute: stroke volume x heart rate.

Scene 1: We're sitting at the breakfast table, still somewhat slowed down from last night's long studying session. Our heart rate is 60 per minute, our stroke volume 70 ml. Ploddingly, we calculate our cardiac output: $60 \times 70 = 4200$ ml, that is 4.2 l/min. *Yawn* Um, what day is it? Wednesday?!! Pathophysiology in first period!! And the bus is arriving in three minutes!!!

Scene 2: We grab our back bag, slam the door and sprint up the hill to the bus station. There's the bus! A final mad dash! The friendly bus driver reopens the door. Gasping for air, we collapse in the next available seat. Our pulse races at 185/min, our stroke volume has shot up to 120 ml. Our cardiac output is $185 \times 120 = 22,200$ ml. At more than 22 liters/min, it is **five times** as much as a few minutes earlier.

So, our cardiovascular system has to adjust pretty fast, at several levels.

In our example, oxygen and energy consumption of muscle tissue goes from very low to max within seconds, multiplying perfusion requirements of skeletal muscle and, of course, the heart itself. At rest, only about 20% of muscle capillaries are perfused. When sprinting, all capillaries are opened, reducing the radius of Krogh's cylinder, the volume of tissue a single capillary supplies with oxygen. Meanwhile, our regulatory system needs to keep an eye on other organs, as well. It would be of little help if we diverted all the blood to our muscles: our brain would be the first to notice, or rather, miss to notice, because it sits on top, with the lowest hydrostatic pressure. If its oxygen supply would go south, we would just lose consciousness and collapse.

Thus, it is not sufficient to regulate cardiac output. Somebody has to look at the requirements of various organs and reign in demands that would endanger the entire system. This somebody has to be pretty smart, because our different organs have very different perfusion requirements. We always have to supply CNS and heart, otherwise we are dead. One step below are kidneys and liver: once we shut them down, we are not immediately dead, but in deep trouble. Other organs, like the gut, will tolerate a certain time on minimal blood supply. For the skin, it depends: by itself, it will do fine, as it can get oxygen from the outside. On the other hand, depending on temperature, we may need its cooling function, which works only with plenty of perfusion. In summary, the smart somebody overseeing all this will have to adjust billions of little precapillary faucets at the same time, to make sure that the requirements of all cells in our body are met.

Let's start with a look at the ground floor of our logistics system, microcirculation.

2. MICROCIRCULATION

Autoregulation

Autoregulation is an entirely local mechanism that keeps perfusion nearly constant over a wide range of pressures. Increased perfusion leads to stretch of vascular smooth muscle cells, in turn triggering a contraction. Also, an increase in P_{O_2} or a decrease in P_{CO_2} or, equivalently, an increase in pH trigger vasoconstriction and *vice versa*. In addition, local concentrations of ATP, ADP, adenosin, lactic acid and K^+ make contributions.

In some vital organs, especially in the central nervous system and the heart, autoregulation cannot be overruled by systemic factors. In most parts of the body, however, perfusion is modified by systemic factors, most importantly the autonomic nervous system.

Capillaries

For an efficient exchange of oxygen, CO_2 and metabolites, diffusion distance needs to be low and flow must be slow. Our tissues are permeated by a dense network of capillaries, which consist of nothing but a single endothelial layer with a basement membrane. While blood in the 4 cm² aorta is speeding along at velocities up to 20 cm per second, it moves only at about one third of a millimeter per second in a capillary. Total cross-sectional area of all capillaries of the systemic circulation has been estimated to be around 3000 cm², with lung capillary area amounting to even 4000 cm². Pressure is low, around 10-20 mm Hg, but depends a lot on position: if we cut our finger, we raise it to help stop the bleeding.

There are different types of capillaries:

- Most organs have continuous capillaries, with tight junctions here and there between cells, but also lots of intercellular clefts, enabling solutes to leak into and out of the vessel. Macromolecules may also pass endothelial cells by transcytosis. Much tighter are the capillaries of the CNS, which have continuous tight junctions plus a second cellular layer consisting of astrocytic endfeet to maintain the blood-brain-barrier. In brain capillaries, all polar molecules, including glucose and amino acids, have to be actively transported across the endothelium.

- If solutes have to be transported at higher rates, endothelial cells are fenestrated. Fenestrated capillaries are found in the gut or in glomeruli.
- Discontinuous or sinusoidal capillaries are wide, with gaps between endothelial cells in addition to large fenestrae. Sinusoids are the typical microvessels of the liver.

Endothelium

Endothelial cells are mesenchymal cells that ultimately have their origin in bone marrow. It was noted, for example, that in patients suffering from chronic myelogenous leukemia some endothelial cells carried the Philadelphia chromosome. Thus, endothelial progenitor cells leave the bone marrow and home to sites of capillary growth or tissue repair. They are guided by factors like VEGF.

The luminal surface of endothelial cells is very modifiable, in the normal state preventing adherence of platelets and leukocytes while in the activated state promoting clotting and leukocyte extravasation.

Resting endothelial cells display a thick glycocalyx of glycoproteins and proteoglycans. Proteoglycans carry long glycosaminoglycan side chains like heparansulfate. For their many polar groups, these bind an enormous amount of water, giving rise to a glide gel layer for cells and platelets chuting along. The total volume of hydrated endothelial glycocalyx in our body has been estimated to amount to 1.7 liters. This gel protects blood cells from mechanical injury, as well as endothelial cells themselves from viscous drag or damage by the shearing effect of blood. In addition, the numerous negative electrical charges present on both the glycocalyx and surface of blood cells help to prevent adherence.

Endothelial cells use cyclooxygenase to produce prostacyclin (prostaglandin I_2), which inhibits platelet aggregation and relaxes vascular smooth muscle cells.

Endothelial activation

Endothelial cells react to mechanical as well as to chemical signals. Although the exact mechanisms are still debated, endothelial cells are able to sense deformation from shear stress, vessel wall tension or muscle activity. They also express receptors for numerous soluble signaling molecules, including, e. g., histamine, VEGF, $TNF\alpha$, and they react to the biggest danger related to their function, hypoxia.

As we have seen when studying inflammation, endothelial activation by $TNF\alpha$ leads to the appearance of selectins at the endothelial surface. Lectins are sugar-binding proteins, and P- and E-selectins both bind sialyl-Lewis^x, that is present on the surface of neutrophils and macrophages. On activation by mechanical stress, cytokines or hypoxia, endothelial cells rapidly externalize granules called Weibel-Palade bodies which contain P-selectin, within minutes transforming the previous leukocyte chute into a velcro rolling pad. Shortly after P-selectin gets to the cell surface, E-selectin is newly synthesized and within two hours becomes the predominant selectin. At the same time, the endothelial cells express ICAM-1 and ICAM-2, which are ligands for integrins on phagocytes. In addition to P-selectin, Weibel-Palade bodies contain von Willebrand factor and CXCL8 (interleukin-8).

To clot or not to clot

Clotting is necessary to prevent the loss of precious blood. Coagulation is also necessary to prevent spreading of invading microorganisms via the bloodstream. On the other hand, clotting is dangerous, because occlusion of vessels may lead to tissue necrosis. One of the most important jobs of the endothelium is to make intelligent decisions regarding this question.

Von Willebrand factor consists of large multimers of a 250 kDa protein. One of several functions of von Willebrand factor is to bind to the platelet receptor glycoprotein Ib (Gp Ib). In conditions of high endothelial shear stress, the von Willebrand multimer uncoils, decelerating platelets and mediating their adherence. Von Willebrand factor is also a carrier protein for clotting factor VIII, protecting it from proteolysis.

Von Willebrand disease is the most common inherited bleeding disorder. Deficiency may be quantitative, qualitative or total. Accordingly, symptoms in many patients are moderate and characteristic of platelet dysfunction, including nose bleeding, skin hematomas and excessive menstrual bleeding. With total deficiency, factor VIII levels are diminished, too, resulting in symptoms more characteristic of hemophilia.

A breach of the endothelium exposes platelets to extracellular matrix containing collagen, fibronectin and laminin. In addition, plasma-exposed extracellular matrix binds von Willebrand factor. All of the above activate platelets via receptors of the integrin type and Gp Ib.

Platelet aggregation

Activated platelets secrete the contents of their granules: Serotonin, Ca^{2+} , ATP and ADP from dense-core granules, von Willebrand factor, factor V and fibrinogen from α granules (fibrinogen originates in the liver, but is taken up by endocytosis). They also synthesize thromboxane A_2 via cyclooxygenase. Serotonin, ADP and thromboxane A_2 together activate additional platelets, leading to platelet aggregation. The large von Willebrand factor then forms bridges between adjacent platelets. Via an increase in cytosolic Ca^{2+} concentration, platelet activation induces conformational change in another platelet receptor, Gp IIb/IIIa, allowing it to bind not only von Willebrand factor, but also fibrinogen, which contributes to bridge building.

Immune thrombocytopenic purpura (ITP), a bleeding disorder, is frequently caused by autoantibodies against Gp IIb/IIIa. Gp IIb/IIIa inhibitors use this concept for therapy.

Pharmacology cross reference: Platelet inhibition

1. Low doses of **acetylsalicylic acid** are being used to reduce the risk for thromboembolic events, especially in coronary heart disease. Although both pro-coagulation thromboxane and anti-coagulation prostacyclin should be affected at the same time, the net effect at these doses is a reduction in clotting probability. This works via inhibition of COX1 and, thereby, thromboxane synthesis, in platelets. In contrast to other NSAIDs, which function as reversible competitive inhibitors, acetylsalicylic acid inactivates the reactive center of COX enzymes irreversibly by acetylation. Thrombocytes, which lack a nucleus, cannot

compensate by expressing new COX1. Endothelial cells, in contrast, continuously reexpress COX1, resulting in prostacyclin synthesis and a combined overall effect of reduced clotting. (Reduced inhibition of thrombocytic COX1 by COX2 inhibitors may account for the increase in thromboembolic events seen in direct comparisons with conventional COX inhibitors.) A second effect contributes to tipping the scale towards anti-coagulation: acetylsalicylic acid is ingested and reaches its highest concentrations in portal blood, where platelets are regularly washed through. Due to a first pass effect in the liver, concentrations in the rest of the body, where endothelial cells are fixated, are lower.

2. **Clopidogrel** inhibits P_{2Y12} receptor activation by ADP.

As both drugs use different mechanisms, they may be combined to strong, "double" platelet inhibition.

3. **Glycoprotein IIb/IIIa inhibitors** are administered intravenously in short-term interventions, e. g. the treatment of NSTEMI (non ST elevation myocardial infarction) or during angioplasty:

- Abciximab, a monoclonal antibody
- Tirofiban
- Eptifibatid, a cyclical peptide developed from the venom of the Florida ground rattlesnake

Forming a fibrin net

Aggregating platelets form a primary hemostatic plug at the site of injury, but this plug has to be mechanically stabilized and tied down with a fibrin net. Thrombin (factor IIa) is required to cleave fibrinogen to fibrin monomers. Fibrin monomers polymerize spontaneously and are subsequently covalently linked by factor XIIIa.

Active thrombin may be generated from prothrombin via two pathways.

1. We already mentioned one of the two when thinking about innate immune mechanisms: the intrinsic pathway or contact activation. This process is activated when Hageman-factor (clotting factor XII), high molecular weight-kininogen (HMWK) and prekallikrein meet on negatively charged surfaces. Via activation of factors XI, IX and VIII, the pathway leads to formation of a complex on the surface of platelets consisting of plasma membrane phospholipids, Ca²⁺ released by platelets, VIIIa and IXa which activates factor X.
2. In the context of heart disease and problems concerning tissue perfusion, the extrinsic system is of higher importance. It starts with tissue factor (TF), a transmembrane glycoprotein expressed by most cells, but not by endothelial cells. In case of vascular injury, tissue factor is exposed to blood plasma containing all of its clotting factors. Tissue factor recruits and activates factor VII and recruits factor X. The process leads to formation of a complex very similar to the one of the intrinsic pathway, consisting of plasma membrane phospholipids, Ca²⁺ from platelets, tissue factor and VIIa, which again activates factor X.

Intrinsic and extrinsic pathways join at the activation of factor X. Factors Xa and Va, together with membrane phospholipids and Ca²⁺ once more form a complex called prothrombinase. Prothrombinase acts on factor II (prothrombin) to form thrombin.

Factors II, VII, IX and X find their respective places in the complexes only by binding to the membrane surface via Ca²⁺. The Ca²⁺-binding ability of these factors depends on the

presence of vitamin K in the liver, which is required to attach a second COO^- group to the second to last-carbon atom of glutamic acid residues. The two adjacent negative charges fit nicely with the two positive charges of Ca^{2+} .

Practical application: One way to prevent blood drawn from a patient from clotting is to remove soluble Ca^{2+} via EDTA or citrate.

Pharmacology cross reference:

- **Vitamin K antagonists** like acenocoumarol prevent the carboxylation reactions required to equip factors II, VII, IX, and X with Ca^{2+} -binding "feet". Without them, they may be present in the plasma, yet they are unable to form the complexes required to activate the clotting system. Correct dosing requires careful monitoring, and the lipophilic substances have long biological half-lives, meaning the inhibition of clotting cannot be reversed quickly.
- Direct **factor Xa inhibitors** like rivaroxaban or apixaban (Xa-bans) are much more expensive. Due to their shorter half-lives, they allow a faster return to normal clotting times in case of emergencies and they do not require frequent monitoring.
- Another oral anticoagulant, dabigatran, is a direct **thrombin inhibitor**. It does not require frequent monitoring and may be rapidly inactivated by an antagonist derived from a monoclonal antibody (Idarucizumab).

Direct Xa and thrombin inhibitors are referred to as DOACs (direct oral anticoagulants). They are very expensive.

- **Low-molecular-weight heparin** is inexpensive and its effect is quickly reversible, yet it needs to be injected subcutaneously. It forms a complex with plasma protein antithrombin III (AT-III), which again inhibits Xa and thrombin.

Thrombin is a serine protease that activates not only fibrinogen, but also upstream factors VIII and V, resulting in positive feedback loops. Also, thrombin activates platelets, endothelial cells and monocytes via protease-activated receptor, a receptor carrying its own ligand that needs to be cut loose to activate the receptor.

Preventing excessive coagulation

Endothelial cells adjacent to the site of injury limit platelet aggregation and clotting to prevent the process from spreading further than necessary.

- From their glycocalyx, endothelial cells shed heparin-like molecules, which combine with antithrombin-III to inhibit thrombin and factors IXa and Xa.
- Thrombomodulin competes with the thrombin receptor to bind thrombin. The thrombomodulin-thrombin complex activates protein C. With the help of protein S, protein C inactivates factors Va and VIIIa.
- Endothelial cells produce NO, prostacyclin and adenosine diphosphatase to inhibit platelet aggregation.
- Endothelial cells produce tissue plasminogen activator (t-PA) to activate fibrinolysis.

Fibrinolysis. Tissue plasminogen activator activates the plasma protein plasminogen to an active protease. Plasmin cleaves fibrin to fibrin degradation products, especially downstream

of the original clotting site. As fibrin is crosslinked via its D domain, the presence of D dimers in blood may be used to ascertain fibrinolysis somewhere in the body. Absence of D dimers practically excludes the presence of thrombosis.

Endothelial products affecting perfusion and blood pressure

Endothelial cells contribute to the regulation of perfusion and blood pressure via several pathways:

- **NO:** In response to the pattern of inputs, endothelial cells react by modulating their ongoing synthesis of NO by eNOS (endothelial NO synthase). For example, bradykinin or mechanical shear stress leads to an increase in NO production. Molecular oxygen binds to the heme group of eNOS, is reduced and transferred to arginine, to form NO and citrullin. The reaction requires tetrahydrobiopterin as a cofactor.

Oxidative stress causes oxidation of tetrahydrobiopterin to dihydrobiopterin. This might be relevant for the observed earlier onset of atherosclerosis in smokers and diabetics: both smoking and diabetes increase oxidative stress in tissues. If tetrahydrobiopterin levels are too low, eNOS becomes "uncoupled" and produces superoxide anion radicals, which are highly reactive and damage the endothelial cell. In addition, these radicals make the problem worse by oxidizing the remaining tetrahydrobiopterin to dihydrobiopterin. Endothelial injury is thought to initiate atherosclerosis.

NO diffuses into neighboring vascular smooth muscle cells, activating soluble guanylyl cyclase to produce cGMP. cGMP-dependent protein kinase (PKG) phosphorylates myosin light-chain kinase (MLCK) and the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA). The phosphorylations inhibit MLCK, reducing the interaction between myosin and actin, but activate SERCA, removing Ca^{2+} from the cytosol. Both mechanisms contribute to vascular smooth muscle cell relaxation.

Pharmacology cross reference: Organic nitrates like nitroglycerin chemically/enzymatically release NO, resulting in instant vasodilation. They are used for relief of attacks of angina pectoris.

- **Angiotensin converting enzyme (ACE)** is an integral membrane protein that is shed from the surface with the help of a metalloprotease. Both integrated and soluble forms are active. It is most prominently expressed by endothelial cells in the lung and in renal glomeruli. We will discuss implications below and in renal pathophysiology.
- **Endothelin-1** is a 21 amino acid polypeptide and the most potent vasoconstrictor known. The endothelin receptor subtype for vasoconstriction is ET_A , which predominates in high-pressure parts of the circulatory system. Three other receptor subtypes exist; ET_{B2} mediates vasodilation. Normally, endothelin vasoconstrictive effects are balanced by vasodilators like NO and prostacyclin.

Pharmacology cross reference: endothelin antagonists like bosentan are used to treat pulmonary arterial hypertension.

Lymphatic vessels

Lymphatic capillaries are histologically inconspicuous, as they are usually collapsed and consist only of endothelial cells. These cells are loosely connected, allowing them to behave like microvalves: fluid can come in if interstitial pressure is higher than inside the vessel, but it cannot come out if it is the other way round. These lymph "flaps" may also be opened by dendritic cells, which squeeze through to reach local lymph nodes. Lymphatics are absent from brain- recall that the CNS is an immunologically privileged site. Further "down the drain", secondary lymph valves direct flow, and even further down, lymph vessels are equipped with some smooth muscle cells. Thus, lymph flow is heavily dependent on interstitial pressure. Each day, the lymphatics return the difference between filtrated and reabsorbed interstitial fluid, about 2 to 4 liters, to the circulation. This volume contains 100-200g of plasma proteins.

3. REGULATION VIA THE AUTONOMIC NERVOUS SYSTEM

Short-term regulation of cardiac output is based on our blood pressure. Blood pressure is continuously monitored by baroreceptors in the carotid sinus and the aortic arch. Neural endings in the vessel wall are equipped with stretch-sensitive ion channels, leading to graded changes in receptor potential in response to changes in blood pressure. Current stretch of the carotid sinus is reported to the medulla oblongata as a frequency of action potentials: increasing blood pressure – greater stretch – higher frequency.

In our breakfast example, the opposite situation would arise: as soon as we dash off, oxygen demand of our largest muscles goes through the roof: the supplying arterioles expand via autoregulation. This would cause an unwelcome dip in blood pressure followed by a secondary correction via the baroreflex, if it were not for our CNS. The CNS is an organ for precalculating the future, it avoids detours by exerting anticipatory control. Before that may happen via the baroreflex, our CNS proactively increases blood pressure and cardiac output by increasing sympathetic tone in a split second.

Is that always good? If we actually start running, yes. But when we get into an emotional stress situation that we would really like to run away from, yet cannot in the real world, things are very different. We end up with a throbbing heart and elevated blood pressure without getting any benefit from it.

Unlike parasympathetic signals, most of which are carried by cranial nerve X (the vagus nerve), sympathetic output from the CNS is carried by fibers leaving the spinal cord at thoracic and lumbar spinal root segments and is switched in para- and prevertebral ganglia. Sympathetic tonus contributes to controlling blood pressure every moment of our life: severing of the spinal cord above T1 causes a dramatic fall in blood pressure. Sympathetic fibers mostly follow arteries to target organs. Most, but not all postganglionic sympathetic neurons release norepinephrine onto visceral targets. One ganglion is specialized: the adrenal medulla consists of postganglionic chromaffine cells that release epinephrine into the bloodstream. That's just to make sure everybody gets the message, even those who might have a cable problem. Both norepinephrine and epinephrine are recognized by G protein-coupled adrenergic receptors.

Control of vascular tonus

In the periphery, an increase in sympathetic tonus causes arterial vasoconstriction via adrenergic α_1 receptors on vascular smooth muscle cells in regions of the body that are momentarily of lesser importance, like skin, gastrointestinal tract and kidney. Venous return is increased by vasoconstriction of veins, also via α_1 receptors.

What about the skeletal muscles themselves? General sympathetic vasoconstrictive action would not be helpful, as skeletal muscles need lots of oxygen and fuel in a fight or flight situation. Autoregulation clearly has an important role. Yet, unrestrained opening of vessels by autoregulation would soon make it impossible to maintain blood pressure. It is still a matter of debate how this problem is solved. It has been proposed that blood vessels in skeletal muscles receive both adrenergic vasoconstrictive and cholinergic vasodilatory sympathetic innervation. The vasoconstrictive component, guided by baroreceptors, would enforce the marginal conditions required to maintain blood pressure. Importantly, the vasodilatory component would not be a reaction to input from baroreceptors, but receive its instructions ultimately from the cerebral cortex, where the "running plan" has its origin. This would allow to divert as much blood flow as possible to those muscles which presently need it most to implement the plan.

As we mentioned before, it would also make absolutely no sense to limit blood flow to CNS or heart. Therefore, blood vessels supplying the CNS and coronary vessels have little sympathetic innervation and are primarily subject to autoregulation.

To sum up, sympathetic activation causes generalized vasoconstriction except in CNS and heart, limits vasodilation in skeletal muscle to maintain blood pressure, yet seems to allow more vasodilation in those muscles that are presently most active.

Control of heart activity

At the same time, pumping capacity of the heart is increased via β_1 receptors. The cardiac conduction system includes the sinoatrial node, AV node, bundle of His, a single right and two left bundle branches and the Purkinje fibers. Components of this system are prone to spontaneous depolarization. The most "nervous" of these tissues is the sinoatrial node with a resting frequency of about 60 per minute. If the sinoatrial node fails, the AV node takes over at a slower pace of 40 per minute. Sympathetic activation increases the frequency of sinoatrial depolarization, but activation of their β_1 receptors motivates all cells of the cardiac conduction system as well as all cardiomyocytes to perform at higher levels. In summary, sympathetic activation of the heart has the following effects:

- positively chronotropic (increasing pacemaker frequency)
- positively inotropic (increasing the strength of contraction)
- positively dromotropic (increasing conduction velocity)
- positively bathmotropic (increasing excitability)
- positively lusitropic (increasing velocity of relaxation)

While sitting at the breakfast table in scene 1, our sympathetic tonus is low. Instead, parasympathetic activity is high, slowing our heart beat via ACh released by postganglionic fibers of the vagus nerve, but having little effect on ventricular action. We will take a more in-depth look at the mechanisms of these regulations when we deal with arrhythmia.

Additional sympathetic actions

We reach the bus panting heavily, because running has dramatically increased our muscles' and heart's consumption of oxygen and production of carbon dioxide and lactate. Sympathetic activation helps to deliver oxygen by widening airways via β_2 receptors. Smooth muscle cells in gut, bladder and uterus relax, too, via β_2 stimulation.

Active muscles need not only oxygen, they need fuel, too.

- The supply of glucose from glycogen in the muscle cell itself is stimulated via β_2 receptors. Replenishment of glucose via the blood is provided by the liver by breakdown of glycogen or by gluconeogenesis. Both processes are stimulated by glucagon as well as by the sympathetic system via β_2 receptors.
- Lipolysis in adipose tissue is increased by activation of adipose triglyceride lipase (ATGL, releases the first fatty acid from the triglyceride) and hormone-sensitive lipase (cuts out the second fatty acid) via β_3 receptors. Here, too, glucagon acts together with the sympathetic system. This helps to supply muscle with the second type of fuel in the form of fatty acids.

Thermogenesis in brown or beige adipocytes is also promoted via β_3 receptors.

Finally, as we will consider in a minute, renin secretion is promoted via β_1 receptors.

4. REGULATION OF CIRCULATORY VOLUME

So, in the very short term, circulation is managed via the regulation of blood vessel cross-sections and cardiac activity by our autonomic nervous system. Yet, considering how things develop over a somewhat longer time frame, it becomes clear that our organism has to manage a second parameter: blood volume. If blood volume decreases too much, we are not able to maintain blood pressure, no matter how far up we crank sympathetic activation. How do we regulate blood volume? In principle, it works like this: first, we gauge pressures in both arterial high and atrial low pressure systems, as well as osmotic pressure in the CNS. We keep osmotic pressure constant in all instances. As we cannot regulate effective circulatory volume directly, we regulate total extracellular volume (which we cannot measure directly) and use colloid osmotic pressure to distribute this extracellular volume between blood vessels and interstitial space. In a nutshell, we constantly adjust volume to keep the measured pressures in the correct range. Several control circuits contribute to this process: ADH, the sensation of thirst, plasma protein synthesis, natriuretic peptides; but paramount for our understanding of pathophysiology and therapy of congestive heart failure is the renin-angiotensin-aldosterone system (RAAS).

Renin-angiotensin-aldosterone system

Several sensors help to detect a decrease in blood volume and contribute to computing renin output at any point in time:

1. The first mechanism is a logical extension of short-term regulation. As we have seen, a decrease in blood pressure leads to sympathetic activation via decreased baroreceptor firing. Adrenergic stimulation increases renin secretion via β_1 receptors. Thus, if a slight

increase in cardiac pumping combined with peripheral vasoconstriction are able to solve the problem: fine! Baroreceptors are back to neutral, and little renin will be released. Yet, if baroreceptors keep reporting blood pressure on the low side, sympathetic activation will go on, and renin release will add up over time.

2. In a functionally parallel mechanism, a decrease in pressure in the glomerular afferent arteriole causes juxtaglomerular cells, specialized smooth muscle cells in the wall of the arteriole, to secrete renin.
3. A decrease in Cl^- delivery at the *macula densa* in the distal tubule promotes renin release. Cl^- acts as a proxy for NaCl. Reduced delivery of NaCl at the distal nephron may indicate a deficit in salt and water.

In response, renin initiates a complex program to minimize further loss of salt and water, to fill up if possible and to stabilize blood pressure.

Renin, a protease, excises the decapeptide angiotensin I from the plasma protein angiotensinogen, which is produced by the liver. Angiotensin I is converted to the octapeptide angiotensin II by angiotensin converting enzyme (ACE) via removal of two amino acids. ACE is expressed by endothelial cells, most prominently in the lung and the renal glomerulus.

The majority of angiotensin II's effects are mediated via the AT1 receptor. Angiotensin II stimulates synthesis of aldosterone in the adrenal cortex. Aldosterone is our salt-saving hormone. This mineralocorticoid hormone increases integration of sodium channels (epithial sodium channel, ENaC) and transporters into the membrane of collecting duct cells, helping to reabsorb sodium and water. Angiotensin II also has effects in the brain: it contributes to generating the sensation of thirst. Thirst entices us to fill up our extracellular volume. Angiotensin II also promotes release of arginine vasopressin/antidiuretic hormone. It increases secretion of catecholamines in the adrenal and elsewhere, helping to sustain sympathetic activity. As its name implies, at higher concentrations angiotensin II increases the tonus of arteriolar walls, directly increasing blood pressure. In addition, angiotensin II acts as a growth factor for myocardial cells; chronically elevated angiotensin II levels contribute to cardiac hypertrophy. We will return to the renin-angiotensin-aldosterone system in more detail later when thinking about renal pathophysiology.

[The direct vasoconstrictive effect of angiotensin II at very high concentrations only comes to pass in emergencies. It curtails blood flow to the splanchnic area and the kidneys, thereby increasing capacity to supply the vital organs. Frequently, this mechanism causes problems in residents of homes for the elderly who drink too little. Reduced circulating volume by dehydration may result in a vicious circle, in which reduced blood supply to the kidney leads to acute renal failure. In German hospital jargon, this condition is referred to by the somewhat surreal-sounding term *prärenales Nierenversagen* (prerenal renal failure).]

Arginine vasopressin/antidiuretic hormone

A situation in which there is sufficient sodium, but limited water is corrected by ADH (anti-diuretic hormone = AVP, arginine vasopressin). ADH, a nonapeptide, is synthesized in the *nucleus supraopticus* and the *nucleus paraventricularis* of the hypothalamus and released in the posterior lobe of the pituitary once plasma osmolality exceeds 280 mOsm. ADH causes insertion of aquaporin-2 water channels into the apical membrane of the collecting duct, resulting in increased water resorption. Only at maximal secretion in acute stress situations

does the molecule actually act as "vasopressin", i. e. lead to contraction of smooth muscle cells in arteriolar walls.

Natriuretic peptides (ANP, BNP)

Our pressure sensors in the high-pressure system (carotid sinus, aortic arch) primarily provide information about whether the heart pumps adequately with regard to demand. From these signals, there is little to be learned about our extracellular volume. Our pressure sensors in the low pressure system (in the atria) are a workable solution to estimate adequacy of our blood volume, which is in balance with our extracellular volume. Atrial natriuretic peptide (ANP) is released mainly by atrial cardiac cells when stretched incrementally by volume loading. It has a plasma half-life of a few minutes. ANP is a 28 amino acid polypeptide that binds to receptors with guanylate cyclase activity, making cGMP its second messenger. B-type natriuretic peptide (BNP, originally brain natriuretic peptide, an unfortunate term) is a very similar peptide of 32 amino acids, which binds to the same receptors but with tenfold lower affinity. Functionally, this makes it less important. BNP is mainly secreted by ventricular cardiomyocytes under stretch conditions. In addition, BNP and its co-secreted cleaved prohormone fragments have a longer half-life than ANP, so they can be used in the diagnosis of heart failure.

ANP has renal effects and general effects:

1. In the kidney, ANP increases the excretion of sodium and water:

-It relaxes smooth muscle cells in the wall of renal arterioles, in the afferent arteriole more than in the efferent one. As a result, it increases renal blood flow in cortex and medulla and tends to wash out the osmotic gradient in the renal medulla.

-In addition, it increases the glomerular filtration rate and the filtration fraction. ANP closes apical Na^+ channels (ENaC) in the collection tube, thereby reducing Na^+ reabsorption.

2. Only at higher concentrations, ANP also dilates vessels in the general circulation, lowering systemic blood pressure. This second effect then limits the first one, since lowering blood pressure tends to reduce GFR and thus also the excretion of Na^+ and water.

The effect of ANP in volume regulation depends on conditions:

- In healthy individuals, ANP is a major player in Na^+ elimination, and thus in the correction of increased extracellular volume. The RAAS is not active in this case.
- However, when both systems are activated simultaneously, ANP is not up to the powerful renin-angiotensin-aldosterone system. Patients with heart failure have high levels of ANP, but at the same time retain Na^+ massively.

Pressure-volume relation

Together, blood volume and blood vessel tonus, regulated by the autonomic nervous system, are responsible for diastolic ventricular filling. Regulatory mechanisms are best illustrated by a pressure-volume diagram of the left ventricle. When higher cardiac output is needed, stroke volume may be increased in two ways: by increased preload (increased filling pressure by blood returning to the heart: Frank-Starling mechanism) or by increased contractility. Higher preload squeezes more blood into the ventricle during diastole. Higher contractility allows the heart to squeeze more blood into the aorta during systole. Under sympathetic stimulation, increased stroke volume multiplied by an increased heart rate allows to increase cardiac output by a factor of four or five.

The increase in stroke volume comes at a cost: cardiac work goes up (increased area within the pressure-volume loop during a heart cycle). This also increases oxygen consumption, but pumping work only accounts for a small fraction of total oxygen requirement. The major variable responsible for oxygen consumption is the wall tension the heart needs to generate. Wall tension is directly proportional to the blood pressure generated and to the radius of the ventricle, but inversely proportional to the double thickness of the ventricular wall (law of Laplace: $T = p \times r / 2d$. T =tension, p = pressure, r = radius of ventricle, d = thickness of ventricular wall. Strictly speaking, the decisive value would be the area under the curve of tension over time, as tension continually changes with the heart cycle, but let's graciously ignore this fact). Arterial hypertension increases oxygen consumption without more blood being pumped. An increase in diastolic filling increases the ventricle's radius, and thereby oxygen consumption.

5. CHRONIC HEART FAILURE

It's fascinating that our heart is able to pump ceaselessly at the required delivery rates for more than 80 years. Yet, the pump's adaptive range decreases with age.

The heart's age-dependent decline is accelerated in case it constantly has to work against high arterial pressure, or if the heart itself is not supplied well, as in coronary heart disease (CHD). From the perspective of the left ventricle, we call high arterial pressure "increased afterload". At the end of systole, increased afterload slams the aortic valve shut earlier, causing the ventricle to eject less volume. In other words, with increasing afterload, stroke volume declines. Thus, cardiac output can only be maintained via an increase in heart rate.

While the heart's pumping capacity deteriorates by aging, alone or in combination with additional diseases like hypertension or CHD, the compensatory mechanisms, sympathetic activation and increasing preload, are able to make up for it for a long time. Only under strain, as in sports or in climbing stairs, reduced capacity manifests itself in the form of dyspnea.

For the myocardium, chronically slaving away under the whip of compensatory mechanisms, like sympathetic activation (with increased afterload) or increased preload, over time results in structural remodeling. Remodeling, in turn, has a negative impact on heart function. Left ventricular hypertrophy and cardiac dilatation are frequent consequences. Myocardial

structural remodeling with impairment of cardiac function is subsumed under the term "cardiomyopathy".

Systolic and diastolic dysfunction

Two components contribute to various extents to any impairment of heart function: systolic and diastolic dysfunction. In a purely systolic dysfunction, the ventricle lacks the power to eject the normal fraction of its end-diastolic volume: ejection fraction sinks below 48% (normal: >55%). As a result, the ventricle continually works in a state of increased volume and tension; the pressure-volume loop is shifted to the right. A purely diastolic dysfunction is characterized by the ventricle's inability to relax properly: in diastolic filling, increased venous pressure struggles to extend a rigid ventricular wall. Diastolic dysfunction is especially sensitive to tachycardia. As there is hardly any filling in the short time window between two contractions, stroke volume goes down dramatically. Systolic and diastolic dysfunction lead to the same end result: increased end-diastolic pressure with the risk of congestion and edema in dependent drainage areas.

Dysfunction is accompanied by action potentials of extended duration and flattened oscillations of intracellular Ca^{2+} . During systole, the spike in cytosolic Ca^{2+} concentration is muted, capping power, while during diastole, it takes too long to pump the Ca^{2+} back into the sarcoplasmic reticulum, interfering with proper relaxation.

Progression

Gradually, the heart's decreased adaptive range manifests itself in more aspects of everyday life. The guidelines of the **American Heart Association (AHA)** describe four stages of this "cardiovascular continuum":

- A. At high risk for heart failure in the absence of structural heart disease or symptoms of heart failure. Risk factors include hypertension, lipid disorders, diabetes mellitus or metabolic syndrome, smoking.
- B. Structural heart disease but without signs of symptoms of heart failure: previous myocardial infarction, left ventricular dysfunction, asymptomatic valvular disease.
- C. Structural heart disease with current symptoms or symptoms that have been successfully treated.
- D. Refractory heart failure.

The **New York Heart Association (NYHA) functional classification** uses clinical criteria to define the severity of heart failure. Therapy guidelines are usually based on this classification.

- NYHA I: Cardiac disease, but no symptoms and no limitation in ordinary physical activity.
- NYHA II: Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
- NYHA III: Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
- NYHA IV: Symptoms even while at rest.

In the initial stages of heart failure, adequate output can only be maintained at increased end-diastolic pressure. Pressure, in turn, is kept up by retention of salt and water via the chronically activated renin-angiotensin-aldosterone system. Once the required ventricular filling pressure surpasses a critical value, venous congestion prevents interstitial water from being reabsorbed into the blood, resulting in edema.

In case it is mainly the left heart which has trouble pumping at the required rate, consequences are seen in the lung. First, the interstitial fluid film between alveoli and lung capillaries thickens. The increase in diffusion distance slows the transport of oxygen and carbon dioxide. Only part of the hemoglobin gets oxygenated, further contributing to shortness of breath under strain. Once lung congestion gets stronger, backed-up fluid starts to fill alveoli, causing life-threatening pulmonary edema.

If the right heart is primarily affected, venous congestion and accumulation of interstitial fluid affect the systemic circulation. Congestion of the liver or the stomach may cause pain in the upper abdomen. Added hydrostatic pressure causes water to accumulate in the lower legs: in the evening, shoes pinch and ankles are swollen. In bed during the night, when the hydrostatic component of venous pressure is suspended, interstitial water is reabsorbed and eliminated via the kidneys: nycturia.

Increased wall tension also leads to secretion of natriuretic peptides by the ventricle (misleadingly termed BNP, brain or B-type natriuretic peptide, and Nt-proBNP, N-terminal pro-BNP). While in principle antagonistic to the RAAS, in this situation, they lack the power to reduce volume efficiently. Yet, their concentration is informative of the severity of heart failure and a valuable prognostic parameter.

So, while well-intended, the two compensatory mechanisms, volume expansion and sympathetic stimulation, eventually become part of the problem. Here, therapy comes in, trying to reign in these mechanisms.

Pharmacology cross reference: therapeutic targets

Angiotensin II is a linchpin of compensatory mechanisms. It mediates salt- and water retention and increases blood pressure via direct and indirect effects. In addition, it contributes to myocardial remodeling. There are two ways to limit its effects: by blocking its generation via ACE-inhibitors or by antagonizing its effects via AT₁-receptor blockers.

ACE inhibitors (e. g., Captopril, Enalapril, Lisinopril) thus lower both preload and afterload. By reducing end-diastolic volume, they allow the heart to work at lower wall tensions. As afterload is reduced at the same time, the ventricle is nonetheless able to maintain or even increase stroke volume. An unwanted side effect of ACE inhibitors results from the fact that ACE, which is produced in the lungs, is also required to inactivate kinins, especially bradykinin. Bradykinin promotes contraction of non-vascular smooth muscle cells. With inhibition of ACE, elevated local concentrations of bradykinin cause spastic coughing bouts in many patients.

AT₁-receptor antagonists (e. g., Losartan, Valsartan) have quite similar effects, but avoid the coughing problem, as they don't have any effect on bradykinin.

Beta-blockers were introduced into congestive heart failure therapy via an unusual route. Logical reasoning first suggested the use of positive inotropic β -sympathomimetic drugs. This was expected to increase the heart's contractive power and thereby, stroke volume. What was actually observed, in contrast, was an increase in mortality under medication. Beta-blockers, on the other hand, had an unexpected therapeutic effect. Stimulation of cardiac activity by sympathetic activation via β -receptors constitutes a crucial compensatory mechanism. Yet, continuous activation via β -receptors has negative effects: it promotes counter-productive remodeling. With continuous stimulation, more and more cardiomyocytes enter apoptosis; the ventricle expands, ejection fraction comes down.

Upon cautious treatment with beta-blockers (e. g., Metoprolol), a marginally compensated ventricle will over time decrease in size and improve its ejection fraction. During the first days of treatment, beta-blockers have the drawback of reducing contractive power. Therefore, they have to be initiated at a very low dose. Yet, a reduction in instances of sudden cardiac death was observed right from the start of treatment, probably by countering ventricular arrhythmia.

[In spite of the aforementioned issues, positive inotropic Dobutamine is still being used, but only via perfusor over short periods in situations of acutely decompensated low output heart failure.]

Aldosterone antagonists (e. g., spironolactone) may complement treatment with ACE inhibitors or AT_1 -receptor antagonists in patients with severe heart failure (NYHA III or IV). In these patients, aldosterone tends to remain elevated even in the presence of anti-angiotensin II medication. Additional treatment with an aldosterone antagonist helps to stop salt and water retention.

Inhibition of ANP degradation: In addition, fluid retention can be counteracted by enhancing ANP action. ANP also inhibits remodeling of the myocardium, resulting in two beneficial effects. Direct application of ANP has not proved successful, but positive effects have been observed with inhibition of ANP degradation. ANP, along with many other peptides, is degraded by the neutral peptidase neprilysin (note: this means, the positive effects observed in the pivotal study might in part also be the result of inhibition of degradation of other peptides). The drug used is a combination of a **neprilysin inhibitor**, sacubitril, with the AT_1 receptor antagonist valsartan.

In stringent studies, the drugs mentioned above have been shown to reduce mortality. This is not the case for the following two classes of drugs, which are used nonetheless, as they alleviate symptoms of congestive heart failure.

Diuretics are used to counter fluid retention and to reduce preload in acute cardiac decompensation. Typical agents are loop diuretics (e. g., furosemide) and thiazides.

Use of **cardiac glycosides** (Digoxin, Digitoxin) is restricted by their narrow therapeutic range. They have positive inotropic effects and enhance the AV node's ability to filter atrial depolarizations, which makes them especially useful in symptomatic heart failure in the presence of atrial fibrillation.

6. CONDUCTION ABNORMALITIES

Cardiac myocytes are much shorter than skeletal muscle cells. They are branched and connected by desmosomes for strength as well as by gap junctions for transmission of excitation. If depolarization by ion currents through gap junction reaches threshold potential, an action potential is generated in the next cell. Pacemaker cells and normal cardiac myocytes receive synaptic input from the autonomic nervous system, but this neural input modulates, rather than initiates, the generation of action potentials.

Normal cardiac myocytes have a static resting potential. They are only excited via depolarizing ion currents coming in through gap junctions from neighboring cells. Their action potential is characterized by ion currents of Na^+ , Ca^{2+} and K^+ , abbreviated I_{Na} , I_{Ca} and I_{K} . The changes of membrane potential during an action cycle encompass five steps:

- Phase 0, the rapid depolarization upstroke, due to I_{Na} and I_{Ca}
- Phase 1, rapid repolarization, a short traceback due to inactivation of most Na^+ and Ca^{2+} channels
- Phase 2, a plateau due to small continuing I_{Ca} and I_{Na} currents
- Phase 3, the main downstroke due to repolarization by I_{K}
- Phase 4, the baseline or electrical diastolic phase.

In the sinoatrial node, AV node and Purkinje fibers, (Fig.21-4 and 21-2), this cycle is modified. Pacemaker cells do not have a static resting potential. In sinoatrial and AV node, classical voltage-activated Na^+ channels remain largely inactive, as the required negative membrane potentials of -80 mV are not reached. Instead, they express HCN (Hyperpolarization-activated Cyclic Nucleotide-gated) channels, non-selective cation channels which, at given extracellular and intracellular concentrations and negative membrane potential conduct mainly Na^+ currents. They have the "funny" property that they do not conduct at positive potentials but are activated by hyperpolarization at the end of phase 3; in addition, they conduct a lot better in the presence of cAMP. Thus, the channel opens slowly at maximum diastolic potential, producing an inward, depolarizing current consisting mainly of Na^+ ions. The current is designated pacemaker current or funny current or, short, I_{f} . Following an action potential, the funny current starts and inexorably drives membrane potential towards the threshold, initiating the next action potential. Depending on the intracellular concentration of cAMP, this happens faster or slower. Thus, the pacemaker current is the basis of pacemaker automaticity.

Putting these elements together, we arrive at the following modified sequence of currents in pacemaker myocytes:

- Phase 0, the upstroke, is slower and generated only by I_{Ca}
There is no phase 1 or phase 2, as the voltage dependent I_{Na} is missing
- Phase 3, repolarization by I_{K} , immediately follows phase 0
- Phase 4 now looks different: The most negative membrane potential, about -60mV, is termed the maximum diastolic potential. Following hyperpolarization, I_{f} produces a slow depolarization towards the threshold. The steepness of this depolarization depends on the concentration of cAMP.

Excitation-contraction coupling

As opposed to contraction in skeletal muscle, cardiac contraction has an absolute requirement for Ca^{2+} influx from extracellular fluid through L-type Ca^{2+} channels. A process known as Ca^{2+} -induced Ca^{2+} release then triggers additional release from the sarcoplasmic reticulum through Ca^{2+} release channels, which remain open longer than the L-type channels. Ca^{2+} allows cross-bridging between myosin heads and actin; cross-bridge cycling persists for as long as Ca^{2+} remains present. Ca^{2+} reuptake into the sarcoplasmic reticulum is mediated by SERCA (sarcoplasmic and endoplasmic reticulum Ca^{2+} -ATPase).

Influence of the autonomic nervous system

To understand the effects of common drugs like β -blockers, we take another look at the impact of parasympathetic and sympathetic activity on the heart. Cardiac function moves elastically between these poles; if we weaken the influence of one side, we automatically strengthen the other one.

Stimulation of the vagus nerve has a negatively chronotrope effect via all three of the sinoatrial ion currents. Acetylcholine activates muscarinic M_2 receptors coupled to G_i proteins, causing a decrease of cAMP but an increase in cGMP.

- I_f is decreased, reducing the steepness of phase 4 depolarization. How does it work? Cyclic AMP binds directly to funny current channels encoded by the HCN4 gene, increasing their open probability. Thus, lower cAMP translates into a decrease of I_f .
- I_K : $\beta\gamma$ -subunits released from the G_i protein bind to and activate GIRK channels (G protein-coupled inwardly-rectifying K^+ channels). The resulting increase in I_K hyperpolarizes the membrane of the sinoatrial cell, slowing the rate at which the membrane potential approaches the threshold for firing action potentials.
- I_{Ca} is decreased via both of the second messengers. Cyclic AMP increases L-type Ca^{2+} channel open probability via phosphorylation by PKA; cGMP reduces L-type Ca^{2+} channel open probability via phosphorylation by PKG. If cAMP goes down and cGMP goes up, the effect is additive. It increases the threshold for action potentials.

In contrast, **sympathetic activation** of β_1 -receptors activates adenylate cyclase via G_s , raises cAMP and increases heart rate by two mechanisms:

- I_f is increased, increasing the steepness of phase 4 depolarization.
- I_{Ca} is facilitated via phosphorylation of L-type Ca^{2+} channels by PKA, increasing their open probability. This lowers the threshold for Ca^{2+} -dependent action potentials.

I_{Ca} is increased in all cardiac myocytes; in atrial and ventricular muscle, this contributes to the positive inotropic and bathmotropic effects. Catecholamines also increase the sensitivity of the sarcoplasmic release channel and enhance SERCA pump activity, over time increasing sarcoplasmic Ca^{2+} stores. Together, all these mechanisms are positively inotropic by making more Ca^{2+} available for cross-bridge cycling. In the AV node, the increase in I_{Ca} increases conduction velocity, a positive dromotropic effect. Finally, only in cardiac muscle, not in skeletal muscle, SERCA is inhibited by the protein phospholamban. This inhibition is abrogated if phospholamban is phosphorylated by PKA. Sympathetic activation thus enhances the rate of cardiac myocyte relaxation: the positive lusitropic effect.

Pharmacology cross reference:

- **Beta blockers** slow heart rate yet have a negative inotropic effect, which is often undesired. Nonselective beta blockers like propranolol inhibit β_1 as well as β_2 adrenergic receptors. The drawback: they also antagonize β_2 -mediated relaxation of smooth muscle cells, leading, e.g., to bronchial constriction. Therefore, they are contraindicated in asthma and COPD. Selective blockers of β_1 receptors like Metoprolol or Bisoprolol attenuate this problem by antagonizing β_1 receptors more than β_2 receptors.
- **I_f blockers** (ivabradine) block only funny current channels without decreasing cardiac contractility. Thus, they may be used to slow heart rate in patients with chronic stable angina pectoris and sinus rhythm who do not tolerate β -blockers.
- **β_2 -Adrenoceptor agonists** are used to treat asthma and COPD. As their β_2 -selectivity is limited, they may cause tachycardia, restlessness, tremor and sweating. Usually, they are administered locally by inhalation to keep systemic effects to a minimum.

Pacemaker backup systems

Cells of the SA node demonstrate the highest rate of spontaneous oscillations, overriding automaticity in lower parts of the conduction system and resulting in heart rates between 60 and 100 beats per minute. If the SA node becomes suppressed, the AV node takes over, with an automaticity of 40-50 beats per minute. Oscillations of the His-Purkinjy system below the AV node occur at only 20-30 per minute and are unreliable.

Conduction blocks

Conduction blocks may result from ischemia, scarring, inflammation or from certain drugs. "Block" sounds more total than it necessarily is. Consider AV block: there are actually three degrees of "block":

1. first-degree AV block is a prolonged conduction, usually a benign, asymptomatic condition
2. second-degree AV block implies that some, but not all impulses entering from the atria are blocked. There are two forms:
 - Wenckebach-periodicity (or Mobitz-type I): the degree of delay increases with each beat, until one impulse is completely blocked by the still refractory AV node
 - Mobitz (or Mobitz II)-type: intermittent nonconduction of atrial impulses, usually with a fixed rate of nonconducted to conducted impulses (e. g., 2:1)
3. third-degree or complete AV block, with slow ventricular escape rhythm and complete disconnect between atrial and ventricular rhythms, requiring permanent artificial pacemaker therapy

Re-entry phenomena

Blocks may be bidirectional or unidirectional. Unidirectional blocks facilitate **re-entry** phenomena. A wave of electric excitation flowing through a branch point may hit an unidirectional block on one of the two conduction pathways. Excitation may reach this region later via a retrograde pathway. Able to pass the block in the retrograde direction, excitation subsequently reaches the original branch point. Further development hinges on the length of the interval the loop took to reach this point the second time. If the time was short, the branch point is still refractory and excitation ends. If the time was long enough, the refractory phase

is over and a self-propagating reentry loop may establish. This may cause, e. g., atrial flutter, atrial fibrillation, ventricular tachycardia or ventricular fibrillation.

Pharmacology cross reference: In principle, there are two strategies to counter re-entry.

1. Re-entry can only occur if excitation, upon closing the circle, encounters tissue that is no longer refractory. One potential countermeasure, therefore, is to keep the tissue refractory for a longer time. This may be achieved by slowing down the K^+ channels (eg, by amiodarone, sotalol) so that repolarization is delayed and the plateau phase (phase 2) of the action potential lasts longer.
2. The second strategy is to further impede stimulus conduction in the unidirectional block, bringing it to a standstill. In principle, this is possible via Na^+ or Ca^{2+} channel blockers.

Looking at these opposing strategies, it becomes clear that, to a certain extent, these are attempts to exorcise the devil with Beelzebub. Despite their comforting name, antiarrhythmics often trigger arrhythmia.

Atrial fibrillation usually develops on a basis of atrial enlargement and is frequently seen in elderly persons. Many of the chaotic 350 to 600 impulses per minute encounter refractory cells at the AV node, resulting in a non-rhythmic ventricular rate between 100 and 160 bpm. With scant time to fill the ventricle, cardiac output is compromised, requiring rate control with digitalis, β -blockers or Ca^{2+} channel blockers. Stasis, particularly in the left atrial appendage, may lead to thromboembolism. Apart from typical strokes, many small, unrecognized thromboembolic events may occur as well, over time leading to cognitive decline. For these reasons, atrial fibrillation is an indication for anticoagulation. In more than 90% of the cases, ectopic depolarizations have their origin in the area where the main pulmonary veins drain into the left atrium, so that it is possible to isolate this area by means of catheter ablation: an isolation strip is burnt or frozen between this area and the rest of the atrial myocardium.

Accessory conduction pathways

Accessory conduction pathways may alter the pattern of excitation. In Wolff-Parkinson-White syndrome, there is an accessory bundle of muscle cells, the bundle of Kent, bypassing the delay in the AV node. Via this route from the atrium to the ventricular septum, some septal muscle is already depolarized before excitation reaches it by the slower AV nodal pathway. This appears as a small shoulder, or delta wave, at the beginning of the QRS complex. The interval between the p wave and this modified QRS complex is shortened. Bundles conducting only in the retrograde direction exist, too; in these cases, there is no delta wave. With two independent pathways between atria and ventricles, the anatomical requirements for a depolarization loop are met. This can lead to attacks of supraventricular tachycardia, with re-entry causing ventricular rates between 150 and 200 beats per minute. WPW syndrome is not uncommon, affecting 1-3 in 1000 people.

Long QT syndrome

Long QT syndrome is a rare, mostly inherited condition which may lead to seizures, syncope or to ventricular fibrillation. In particular, patients are susceptible to early afterdepolarizations, changes of the membrane potential in the positive direction that interrupt normal repolarization. This may happen because the interval of inactivity for Ca^{2+} or Na^+

channels is already over, with the positive membrane potential stimulating a new action potential. The process can be self-perpetuating and lead to a series of depolarizations, *torsades de pointes*, a form of ventricular tachycardia characterized by QRS complexes spirally rotating their axes. Torsades de points may in turn degrade to ventricular fibrillation. Alleles carrying alterations in several ion channels may cause long QT syndrome by interfering with normal repolarization:

- A deletion of three amino acids, Δ KPQ in the region between repetitive domains III and IV of the heart Na^+ channel may result in prolonged channel opening or repetitive reopening, leading to a prolonged plateau of the action potential.
- Repolarization is predominantly a result of K^+ currents, which explains why some families carry mutations in the KCNQ1 or KCNH2 genes, both encoding proteins of the Kv family of voltage-gated K^+ channels. Reduced K^+ currents are believed to delay repolarization.
- Mutations in minK, a membrane protein associating with the KCNQ1-encoded KvLQT1 channel, also cause the syndrome.

Pharmacology cross reference: Antiarrhythmic drugs like amiodarone or sotalol, tricyclic antidepressants or erythromycin may prolong the QT interval. Many of these drugs bind to two aromatic amino acids at the center of the KCNH2-encoded hERG channel, impairing outward K^+ current.

Hypocalcemia increases the risk of complications by QT prolongation, too.

Arrhythmia by deviations of calcium concentration

Hypocalcemia increases the open probability of Na^+ channels at any membrane potential near the resting potential. Hypocalcemia thus reduces the threshold for action potential firing and results in hyperexcitability and spontaneous twitching of skeletal muscles. At the heart, this translates into an increased risk of arrhythmia. Hypocalcemia prolongs the QT interval, increasing the risk for *torsades de pointes*. Intracellularly, less Ca^{2+} is available for cross bridge cycling, resulting in a negative inotropic effect with reduced contractility.

Hypercalcemia, on the other hand, decreases the open probability of Na^+ channels, thereby shortening QT interval and promoting arrhythmia, as well. With increasing concentrations of free Ca^{2+} , threshold potential moves farther and farther away from membrane resting potential until it finally becomes unattainable and no longer allows action potentials: in extreme cases, this may lead to cardiac arrest. In the central nervous system, this leads to fatigue, drowsiness, stupor and coma; at the skeletal muscles, to weakness and sluggish reflexes. By increasing intracellular Ca^{2+} concentration as well, low-grade hypercalcemia has a positive inotropic effect.

7. ARTERIAL HYPERTENSION

Our arterial blood pressure is highly variable and is constantly adjusted to actual physiological needs. To obtain comparable benchmarks, we gauge blood pressure at rest. If measured values are persistently beyond normal limits, we call this arterial hypertension. Hypertension contributes to the risk of stroke, coronary heart disease and renal damage.

Which factors determine our blood pressure? Let's start with a detour via electricity. Recall Ohm's law: voltage = current x resistance ($U = I \times R$). This law describing electrical currents may be applied to fluid currents as well. In terms of human hemodynamics, we obtain: blood pressure = cardiac output x peripheral resistance. All factors that increase either cardiac output or peripheral resistance increase blood pressure as well.

We have already identified such factors at the outset. Sympathetic activation increases both cardiac output and peripheral resistance. This raises our blood pressure if we are frightened or under stress. Adjustment of blood volume is another factor, with the renin-angiotensin-aldosterone system playing a major role. We have seen how an increase in blood volume raises cardiac volume via improved ventricular filling.

Hypertension is quite prevalent. Only in a small percentage of patients, it is a logical consequence of a disorder in another system. In more than 90% of people with hypertension, there is no identifiable cause; we call this primary or essential hypertension.

Once more, our understanding of the mechanisms underlying essential hypertension is fragmentary at best. Yet, it seems safe to assume that many genetic factors contribute to the condition, as well as a few environmental factors that may be modified by our lifestyle.

Genetic factors

During human evolution, selection probably favored a tendency to slightly increased blood pressure. An individual with low blood pressure feels flabby, drained, worn-out. Fatigue is prone to counterselection. In contrast, an individual with increased blood pressure remains fit for many years. Negative consequences manifest themselves only later in life, following the stages of reproduction and raising children, and do not cause negative selection.

When analyzing the many polymorphic alleles contributing to high or low blood pressure, genes involved in handling our body's Na^+ stand out. Two groups of alleles have been identified:

1. Alleles with a strong effect on blood pressure that are passed on in families as monogenetic causes of disease. Two examples:

- **GRA:** The allele causing this disease is a fusion gene consisting of two parts. In this fusion allele, the gene encoding aldosterone synthase, which catalyzes the last step in aldosterone synthesis, is under control of the promoter of an entirely different gene in an unequal crossing over-event. The "erroneous" promoter stems from the adjacent 11β hydroxylase gene which directs a step in cortisol synthesis and is expressed under control of ACTH. In consequence, these patients produce large amounts of aldosterone, retain salt and fluid volume and develop marked hypertension. However, symptoms may be suppressed by administration of glucocorticoids, because glucocorticoids inhibit release of ACTH and with that, the activity of the "erroneous" promoter. This phenomenon gave the disease its name: glucocorticoid-remediable aldosteronism (GRA).
- *Gitelman's* syndrome is characterized by opposite features. Patients have two defective alleles of SLC12A3 (synonym: NCCT, Na-Cl-Co-Transporter). This solute carrier is the target of thiazide diuretics: patients suffering from *Gitelman's* syndrome show symptoms

similar to thiazide overdosing. The defect causes reduced reabsorption of salt in the distal convoluted tube. This is corrected in the collecting duct, where increased aldosterone drives reabsorption of Na^+ in exchange against K^+ and H^+ . Loss of K^+ and H^+ results in hypokalemia and metabolic alkalosis. Despite this corrective action via aldosterone, blood pressure in these patients is frequently low. In line with this mechanism, heterozygous carriers of such an allele are protected from hypertension.

2. Alleles with small individual effects on blood pressure, identified in genome-wide association studies (GWAS):

- The gene CYP17A1 codes for the enzyme 17 α -hydroxylase. This enzyme is the "switch" where glucocorticoid synthesis branches away from the pathway leading to aldosterone. Polymorphisms that slightly reduce the efficiency of this enzyme enhance aldosterone synthesis and reinforce its salt retaining effect.
- Polymorphisms in the genes encoding natriuretic peptides ANP (atrial natriuretic peptide) and BNP (B-type natriuretic peptide) correlate with divergence in blood pressure.
- Polymorphisms in NPR3, a receptor for natriuretic peptides, correlate with variation in blood pressure as well.

From these observations, the way our organism handles Na^+ seems to have marked effects on our blood pressure. - Why? In the extracellular fluid compartment of our body, which accounts for about 40% of total body water, we carry a lot of Na^+ with us. Life on our planet originated in the sea, and in our extracellular volume, we carry a diluted form (from 3.5% to 0.9% salinity, or from about 480 mmol/L to 140 mmol/L Na^+) of "inner" sea with us, which we need to maintain carefully. This was all the more essential as, until a few thousand years ago, Na^+ was quite scarce in human nutrition. Thus, our organism is optimized for salt conservation. For many ten-thousands of years, the human organism confronted the following problem: Our "inner sea" consists mainly of water and salt; while water was readily available to fill up, salt was not. The human body needed to get rid of a lot of water-soluble substances (like urea), yet retain the salt.

This problem is solved by our kidneys. Every single day, we filtrate about 180 liters of "inner sea" containing (180x140 mmol) 25 mol salt. This is about 1.5 kg of salt, while our daily intake contains only a few grams! There is only one option: we need to retrieve 99.5% of all filtrated salt. This is achieved in steps: 67% of filtrated sodium is reabsorbed in the proximal tubule, mainly in exchange for H^+ . Twenty-five percent is reabsorbed in the thick ascending limb of loop of Henle by co-transport of Na-K-2Cl. In the distal convoluted tube, a further 5% are absorbed by Na-Cl-co-transport. Actual Na^+ -excretion is regulated by the renin-angiotensin-aldosterone system, which controls reabsorption of the last 0-3% in the collecting duct via the epithelial Na^+ channel (EnaC).

To sum up, many different polymorphic genes contribute to Na^+ retention and with that, to extracellular volume and blood pressure. In the genetic lottery, each of us has drawn a certain combination of these alleles. In case several Na^+ retention-enhancing alleles coincide, this adds up to a genetic disposition for increased blood pressure. Whether and to what extent this predisposition manifests itself, depends to a large extent on our lifestyle.

Environmental factors/ lifestyle

Salt consumption

By our evolutionary adaptation to the African steppes, we humans are optimized for an environment where salt is scarce. The availability of water was a prerequisite for human habitation, but in addition, to maintain extracellular volume in the warmth of Africa, it was essential to conserve the body's store of salt very stringently. While we have a highly efficient salt retention system in the renin-angiotensin-aldosterone system, our mechanisms to get rid of surplus salt are far less sophisticated, as salt abundance hardly ever occurred during evolution of modern *Homo sapiens*.

Thus, we are equipped with a strong appetite for salt. Supporting this assertion is the fact that during human history, salt was traded as a valuable asset. *Salarium*, the etymological root of "salary", in ancient Rome was a payment to soldiers, sometimes reportedly directly in the form of salt or else as money to buy salt. A lot of money could be made with salt. States and potentates made good use of this appetite, levying taxes by monopolizing the trade in salt.

Today, our built-in salt appetite coincides with an abundant supply of cheap salt. Result: we take in way too much of it. At the margin, more Na⁺ means increased extracellular volume, increased blood volume, increased cardiac output and with that, increased blood pressure. At this point, increased blood pressure actually does enable excretion of more salt via pressure natriuresis. However, the increase in pressure over time results in a shift in target value. The organism starts to regard the increased values as normal and increases peripheral vascular resistance accordingly.

Blood pressure reaction in response to salt intake depends on an individual's genetic background, specifically on her endowment regarding salt saving alleles. For example, certain allelic variants of ACE and angiotensinogen contribute to salt sensitivity. In Europe, almost half of hypertension patients are salt sensitive.

Overweight

Overweight promotes the development of arterial hypertension, although the links between the two are not yet sufficiently clear. Overweight increases both sympathetic tonus and renin-angiotensin-aldosterone system activity. In an animal model where dogs are fed a fat-rich diet until they become overweight, the dogs develop sodium retention and hypertension. Renal denervation prevents both of these outcomes, suggesting that an increase in sympathetic tonus may be the decisive initial factor, activating renin via β_1 -adrenergic receptors. The resulting increase in renin-angiotensin-aldosterone activity is in turn crucial for the elevation in blood pressure.

It seems reasonable that a heavy body requires a higher sympathetic tonus to keep going than a more delicate frame. Among proposed sympathicotonic mechanisms is leptin, a satiety hormone produced by fat cells. People who are overweight are frequently leptin resistant, meaning they still have an (un)healthy appetite in the presence of high levels of leptin. There are indications that this type of resistance may only affect the appetite-regulating neurons in the hypothalamus, but not other target cells, such as those responsible for sympathetic regulation of thermogenesis. In mice, elevated levels of leptin cause hypertension associated

with increased urinary catecholamine elimination. In this model, blocking β -adrenergic receptors prevents leptin-induced hypertension at concentrations that have no effect on blood pressure in animals with normal leptin levels.

Stress and lack of exercise

The stress levels typical of our society tend to increase sympathetic activity, contributing to hypertension. In contrast, regular exercise helps to dampen sympathetic tonus at rest.

Overconsumption of alcohol

Although alcohol itself has a vasodilatory effect, regular consumption of alcohol exceeding a certain threshold increases arterial blood pressure. This threshold is around 20g of pure alcohol per day in women, about 30g in men (500 ml of beer contain 20g of alcohol, 250 ml of wine 24g). It seems probable that here, too, an increase in sympathetic tonus starts the chain of cause and effect.

By how much may changes in life style reduce systolic arterial blood pressure? In the following, a few estimates:

- DASH eating plan (Dietary Approaches to Stop Hypertension- reduced intake of sodium, increased intake of potassium and reduction of saturated fatty acids by an eating plan emphasizing fruit, vegetables and low-fat dairy products): 8-14 mm Hg
- bringing weight to normal levels: 5-10 mm Hg
- physical exercise: 4-9 mm Hg
- stopping alcohol overconsumption: 2-4 mm Hg

Pharmacology cross reference: therapeutic targets

By its pathophysiological role in the development of arterial hypertension, Na^+ retention is an obvious target for drug therapy. Na^+ retention may be inhibited by some diuretic drugs as well as by interfering with the renin-angiotensin-aldosterone system.

- **Thiazide diuretics** inhibit the Na-Cl-co-transporter (NCCT, synonym: SLC12A3) in the distal convoluted tube, directly antagonizing Na^+ retention.
- **ACE inhibitors** antagonize not only Na^+ retention, but also the direct blood pressure-increasing effect of angiotensin II.
- **AT₁-receptor antagonists**, too, inhibit not only aldosterone production, but also the immediate blood pressure-increasing function of angiotensin II.

The blood pressure-increasing effects of sympathetic activation may be mitigated by the following pharmaceuticals:

- **Beta-blockers** have a dual effect: as we have noted above, they reduce cardiac output. Yet in addition, β -blockers inhibit renin secretion and with that, Na^+ retention.

- **Calcium channel blockers** have a vasodilative effect on arterioles and a negative inotropic and chronotropic effect on the heart.

If elevated blood pressure fails to respond to these pharmaceuticals, this can sometimes be explained by other medications the patient takes, e. g., NSAIDs, β -sympathomimetics or glucocorticoids.

8. ATHEROSCLEROSIS

Pipe systems which function as conduits for fluids over many years tend to develop pipe wall erosion; their surfaces may be degraded by precipitations and deposits. Unfortunately, this is also true for our blood vessels. These changes are primarily found in the arterial leg of our systemic circulation; summarily, we call them atherosclerosis. [*Author's note: In this translation of the original German version, the different usage of terms in German and English poses problems. In German, the most commonly used umbrella term is arteriosclerosis, while in English, it's atherosclerosis. Yet, in both languages, people are mainly concerned with the formation of atheromatous plaques, which is the most urgent clinical problem.*]

The term arteriosclerosis encompasses three pathological changes that are defined morphologically:

- atherosclerosis, the development of lipid-rich fibrous plaques in the wall of large arteries
- medial calcific sclerosis (*Mönckeberg's* calcific sclerosis): calcification of the *Tunica media* of midsize arteries
- arteriolosclerosis/hyalinosis: changes in small arteries and arterioles, mostly in conjunction with hypertension and *diabetes mellitus*

While these changes affect virtually everybody and their consequences are among the most frequent causes of death, large gaps remain in our understanding of their causes. Two things are clear: 1. manifestation of atherosclerosis is greatly influenced by our lifestyle, 2. atheromatous wall lesions develop in distinctive stages.

On hearing the word "atherosclerosis", we automatically think of older people. Nothing could be further from the truth. From investigations like the PDAY-Study (Pathobiological Determinants of Atherosclerosis in Youth) we know that intima lesions start during childhood. An intima-protecting lifestyle cannot start early enough.

Risk factors

Since we are all aware of our excellent chances of developing life-threatening disease from atherosclerosis: what can we do to put that off? Many of the known risk factors may be addressed by changes in our lifestyle.

Lifestyle-modifiable risk factors:

Hypercholesterolemia. In our blood, cholesterol and cholesterol esters are mainly found in LDL and HDL lipoprotein particles. The higher LDL-cholesterol, the higher the risk of atherosclerosis: deposits of LDL-cholesterol in the arterial wall are an important feature of the disease. HDL removes cholesterol from the periphery and delivers it to the liver, a mechanism termed reverse cholesterol transport. Therefore, high levels of HDL are indicative of a metabolic status that protects from atherosclerosis.

LDL cholesterol levels are predominantly determined by genetics, to a far lesser extent by life style. A central issue is uptake of LDL particles from blood into cells via the LDL receptor. Specifically, the receptor binds to ApoB100. Allelic variants of either partner interfering with this process may lead to familial hypercholesterolemia. In rare cases, familial hypercholesterolemia can be traced back to a third gene, encoding PCSK9 (if you really demand to know what that stands for: proprotein convertase subtilisin/kexin type 9). PCSK9 is a protease involved in readying proteins in the endoplasmic reticulum by removal of prodomains. Packed in vesicles together with its substrates, it is then transported to the cell membrane and secreted. Surprisingly, secreted PCSK9 has a second function completely independent from the first. It binds to the LDL receptor, inducing its breakdown following internalization. This is in marked contrast to the usual procedure, where the receptor is recycled to the membrane following uptake of a LDL particle. With less LDL receptor on recipient cells, once more mainly hepatocytes, less LDL is cleared from the blood. Thus, the higher PCSK9 activity as a result of specific allelic variants, the more LDL receptors are degraded and the higher remain plasma LDL cholesterol levels.

Foods rich in cholesterol (eggs, butter, red meat; note that plants do not contain cholesterol), and foods containing a lot of trans-unsaturated fatty acids increase LDL-cholesterol levels. Unfortunately, a switch from a high-cholesterol to a low-cholesterol diet is able to bring down LDL-cholesterol by no more than 10%.

Aerobic physical training and moderate consumption of red wine promote a protective metabolic status, characterized by raised HDL. Smoking and obesity negatively affect HDL levels.

Pharmacological cross-reference:

- **Statins (HMG-CoA reductase inhibitors):** LDL-cholesterol levels remaining high in spite of a low-cholesterol diet may be reduced by inhibiting cholesterol synthesis. Statins like Simvastatin, Atorvastatin or Rosuvastatin inhibit HMG-CoA reductase (hydroxymethylglutaryl-CoA reductase), the rate limiting enzyme of cholesterol biosynthesis. Apart from reducing LDL-cholesterol, statins appear to have additional anti-atherosclerosis effects via alternative mechanisms which are not yet sufficiently understood.
- **PCSK9 inhibitors:** Monoclonal antibodies like evolocumab and alirocumab bind to and neutralize PCSK9 and thereby lower LDL-cholesterol. They are very expensive and, of course, need to be injected. They may be used if statins are not tolerated or if LDL-cholesterol remains inadequately controlled by statins. Statins tend to increase PCSK9, limiting their own efficacy; in this case, a combination of the two may further reduce LDL cholesterol levels.

Arterial Hypertension. Elevated blood pressure directly increases fluid shear stress on endothelial cells.

Smoking. One packet of cigarettes per day doubles mortality by coronary heart disease. Ultrasound examination of intima-media-thickness of carotid arteries in 18 year-old Austrian army recruits revealed marked thickening in smokers compared to non-smokers already at this young age (ARMY-Study).

Diabetes and Metabolic Syndrome promote atherosclerosis via several mechanisms: they increase LDL-cholesterol, they promote non-enzymatic glycation of proteins in arterial walls, and they promote generation of pro-inflammatory signaling molecules by adipose tissue. [Eliminating overweight](#) in a timely fashion diminishes the risk of atherosclerosis significantly.

Nephropathy, assessed as albuminuria or a reduction in glomerular filtration rate. Nephropathy, too, may be caused by hypertension, diabetes, metabolic syndrome, but has been shown to independently contribute to atherosclerosis itself. The mechanism remains to be elucidated.

TMAO (trimethylamine-N-oxide) levels correlate with atherosclerotic plaque burden and the risk of cardiovascular events like myocardial infarction and stroke. TMAO is a metabolite formed by interaction between diet, gut microbiota and liver. Carnitine and choline-containing phospholipids, abundant in red meat, are metabolized by specific species of gut microbes to trimethylamine (TMA, three methyl groups attached to nitrogen). TMA is taken up and oxidized by hepatic flavin-containing monooxygenases to TMAO. TMAO activates endothelial cells, promotes scavenger receptor expression and foam cell formation in macrophages, reduces reverse cholesterol transport and facilitates platelet activation. Interestingly, a vegan diet seems to counterselect TMA-producing microbes in the gut.

Risk factors that are independent of lifestyle:

Some risk factors can't be modified. The **older** we are, the more lesions accumulate in our arteries. **Men** develop atherosclerotic lesions earlier than women. **Family histories** illustrate how risk alleles for atherosclerosis from many polymorphic loci are passed on. Classic examples are the different types of familial hypercholesterolemia.

Lipoprotein(a), or short, **Lp(a)**. Lp(a) resembles the LDL particle, but contains apolipoprotein(a) in addition to ApoB100. Its concentration varies over one thousandfold between individuals and depends almost exclusively on genetic factors. Individuals with high Lp(a) concentrations in their blood are at high risk for atherosclerosis. Firstly, Lp(a), like LDL, accumulates in the arterial wall. Secondly, apo(a) mimics plasminogen, displacing it from its binding sites. As plasminogen counters thrombosis, high levels of apo(a) have a pro-thrombotic effect.

Hyperhomocysteinemia. Elevated levels of homocysteine correlate strongly with atherosclerosis. High levels are primarily the result of genetic factors, but nutritional factors may contribute. With the help of folate and vitamin B12, homocysteine is converted to methionine; nutritional deficiency in one of these two factors increases homocysteine levels.

Pathogenesis

Endothelial injury or dysfunction

Obviously, the very first step in the development of an atheromatous lesion is especially hard to analyze, so it's hardly surprising that the nature of this step is unclear and controversial. There is some consensus that the process starts with an activation/injury of the endothelium, which responds with changes in function, especially an increase in permeability (response to injury hypothesis). Below is a list of mechanisms activating/damaging endothelial cells. Which of them are the most relevant is a matter of debate:

- Mechanical damage: endothelium continuously suffers enormous strain by arterial blood pressure. This is especially true for patches of endothelial cells below turbulent flow, e. g., at branch points and bifurcations. The higher blood pressure rises, the more strain it exerts.
- Chemical damage by constituents of cigarette smoke: Serial sonography examinations in army recruits demonstrated that intima-media-thickness of the carotid artery was already increased in 20 year-olds who smoked, compared to non-smoking control subjects. Uncoupled eNOS might be involved.
- According to some reports, elevated LDL-cholesterol may result in production of ROS that directly damage endothelial cells. Yet, the main effect of increased LDL-cholesterol is expected to occur subsequent to endothelial damage.
- Advanced glycation end products due to persistently elevated blood sugar levels. These are recognized by RAGE (receptor for advanced glycation end products), a receptor of the immunoglobulin superfamily expressed, e.g., by monocytes. This receptor also acts as a pattern or danger recognition receptor which recognizes the intracellular DNA-binding protein HMGB1 (high mobility group protein B1) that is released upon cell damage. Activation of RAGE leads to the activation of the transcription factor NF κ B and to the release of the macrophage cytokine cocktail (IL-1 β , TNF α , etc.).
- Damage by infections and immune mechanisms. Several prevalent microbial causes with low pathogenicity have been accused of initiating atheromatous lesions. In aortas heavily affected by atherosclerotic lesions, the intracellular bacterium *Chlamydia pneumoniae* is detected on a regular basis. Cytomegalovirus has been demonstrated, too. Based on these observations, the concept was developed that atheromatous lesions might be initiated by an inflammatory process in the arterial wall. Several studies suggested an increased risk for cardiovascular events in probands who persistently demonstrated slight elevations in CRP (lab parameter: high-sensitivity CRP, hsCRP). One further hypothesis in this direction postulates damage of endothelial cells by a cross-reaction of the immune system against heat shock protein 60 (hsp60). Hsp60 is an antigen of infectious bacteria (e. g., *Chlamydia*). At the same time, a related form of hsp60 is expressed in human cells under strain and is exposed at the cell surface in a form that may be recognized by T lymphocytes.
- Hyperhomocysteinemia causes direct damage of endothelial cells.

Importantly, these mechanisms are not mutually exclusive. It seems reasonable to assume that they contribute to a variable extent to the initial endothelial damage in each individual.

Lipoprotein accumulation in the intima

Following initial injury, impairment of endothelial sealing causes plasma lipoproteins to enter the arterial intima. LDL tends to deposit cholesterol in the intima; HDL is able to take it up and remove it. Therefore, LDL/HDL ratio determines the amount of cholesterol deposits. Subsequently, LDL lipids are oxidized by reactive oxygen species (ROS) or inflammatory 12- and 15-lipoxygenase enzymes. Minimal oxidized LDL (mo-LDL) generated by these mechanisms further modifies functions of adjacent endothelial cells. For example, mo-LDL inhibits endothelial production of NO. Consequently, NO's relaxing effect on smooth muscle cells, as well as its inhibiting effect on platelet adhesion fall by the wayside. In addition, endothelial cells produce chemokines and express cell-cell adhesion molecules, enticing (additional) monocytes and T cells into the intima.

Development of foam cells and fatty streaks

With increased production of ROS, deposited mo-LDL is oxidized further. Highly-oxidized LDL (HO-LDL) tends to aggregate and is taken up by macrophages. This is not mediated by the normal LDL receptor, which is downregulated once intracellular levels have reached a certain threshold, but rather by so-called scavenger receptors, which are not subject to downregulation. Macrophages continue stuffing themselves with HO-LDL until they are filled with lipid droplets, hence the name "foam cells". Macroscopically, endothelium covering a dense patch of foam cells features a lighter, buttery color, a phenomenon we call "fatty streak".

Growing into an atheromatous plaque

Further development is determined by the net flow of lipids into or out of the intima. In principle, foam cells are able to produce ApoE, which helps to remove lipids from the intima and to transport them to the liver. Yet, as long as average LDL or Lp(a) concentrations remain elevated, intimal lipid mass continues to accrue. The extracellular cholesterol-rich lipid mass increases steadily by influx of LDL and apoptosis of foam cells. Macrophages, lymphocytes and endothelial cells produce cytokines promoting immigration of smooth muscle cells. The smooth muscle cells may either proliferate out of the *Tunica media* into the intima, or develop from progenitor cells immigrating from the blood. The smooth muscle cells also produce extracellular matrix. In this way, an atheromatous plaque develops: a thin diaphragm of endothelium and connective tissue with smooth muscle cells covering a growing patch of largely amorphous, necrotic lipid mass. Progressively, the plaque area loses the normal elasticity of the arterial wall, a process further enhanced by calcification.

Unstable plaques and thrombus formation

The thickness of the fibrous cap results from the dynamics of synthesis and breakdown of extracellular matrix. Critical for further development is whether continuous endothelial lining of the artery can be maintained. Pulsating arterial pressure tugs at the border between elastic

arterial wall and inelastic plaque. Plaques with a robust cap are stable. Plaques with thin diaphragms are vulnerable: the thin membrane tends to tear at the shoulder of the plaque. Once that happens, a thrombus forms immediately on the exposed surface. That way, a coronary artery or an artery in the CNS may quickly become completely occluded.

Inflammatory processes may promote plaque instability. In a trial (CANTOS) in patients who had suffered myocardial infarction and who had elevated levels of high-sensitivity CRP, the anti IL-1 β monoclonal antibody Canakinumab reduced successive cardiovascular events, although at the expense of more infections.

Arterial wall rupture, formation of aneurysms

Pronounced plaques may weaken the underlying media. This may lead to local widening in the form of an aneurysm, to rupture of the arterial wall with hemorrhaging into the surrounding tissues, or to wall dissection.

9. SHOCK

Circulatory shock is a life-threatening condition, representing an acute breakdown of blood circulation leading to inadequate supply of oxygen to many vital organs. In the face of maximum sympathetic stimulation and heart rate, blood pressure falls below normal limits. The two parameters may be combined to yield the shock index (heart rate divided by systolic blood pressure), which allows a rough estimate of the severity of circulatory failure: Values >1 are indicative of shock; a person suffering a manifest shock frequently demonstrates values around 1.5 (e.g., heart rate 105/min with systolic blood pressure of 70 mm Hg).

The organism first attempts to minimize damage by activating compensatory mechanisms. Yet, if the underlying problem cannot be solved, these same compensatory mechanisms actually aggravate the situation: a vicious circle develops.

Shock may be caused by

1. insufficient cardiac output (cardiogenic shock)
2. blood volume falling below critical limits (hypovolemic shock)
3. wall tension of blood vessels being inadequate (distributive shock)
4. an obstruction of blood flow outside of the heart (obstructive shock)

Cardiogenic shock

Cardiogenic shock may be caused by any condition which strongly impairs cardiac output. Examples are myocardial infarction, ischemia, arrhythmia, acidosis, heart valve malfunction, papillary muscle rupture or ventricular septal rupture.

Our organism tries to survive by putting first things first. Organs which are absolutely vital are supplied as effectively as possible under the given circumstances. These are only CNS and

heart. Everything else gets shut down temporarily: skin, gastrointestinal tract, skeletal muscle, kidneys. This phenomenon is termed centralization.

How is that achieved? First and foremost by sympathetic activation via baroreceptors. In this case, there is no graded response as in chronic heart failure: sympathetic activation goes all-out. Heart frequency and contractility are increased via β_1 -receptors. By activating α_1 -receptors, epinephrine and norepinephrine mediate contraction of arterioles in peripheral organs, virtually shutting down their blood supply. In the heart itself and in the CNS, this reaction is overruled by local autoregulation. The tonus of capacitance vessels is increased via α_1 -receptors, enhancing venous return to the heart.

Stimulation via β_2 -receptors widens airways by smooth muscle relaxation; gastrointestinal tract motility is stopped by the same mechanism.

Energy is mobilized via β_3 -receptors: hormone-sensitive lipase drives lipolysis, shivering produces thermal energy.

In addition, sympathetic activation causes profuse sweating. The typical appearance of a person in shock is ashen-faced and sweaty ("cold sweat").

Massive reduction in renal blood supply, combined with strong sympathetic stimulation of the juxtaglomerular apparatus cause strong renin secretion and with that, maximal activation of angiotensin II. At these concentrations, angiotensin II becomes true to its name and reinforces vasoconstriction. At least, these compensatory mechanisms buy time, enabling medical intervention to remove the underlying cause of pump failure, if possible (e. g., reopening a coronary artery, draining a pericardial tamponade).

Once the state of shock extends for too long, peripheral organs suffer damage from inadequate perfusion. Stasis engenders secondary problems in microcirculation. Erythrocytes agglutinate, platelets aggregate and activate blood coagulation. Hypoxia forces cells to switch to anaerobic glycolysis, resulting in metabolic acidosis. Activation of endothelial cells via hypoxia and acidosis causes capillary leakage as well as neutrophil adherence and activation. The neutrophils' NADPH oxidase churns out reactive oxygen species, further damaging endothelial cells. In fact, all these events are aspects of an inflammatory reaction. As they proceed in multiple organs of the body at the same time, we speak of a systemic inflammatory response syndrome. (SIRS). It is characterized by the presence of at least two of the following: body temperature >38 or $<36^\circ\text{C}$, leukocyte count $>12,000$ or $<4,000/\mu\text{l}$, heart rate above 90/min, breathing rate exceeding 20/min.

Even in case perfusion is restored, e.g., by percutaneous coronary intervention, this may lead to additional damage, termed reperfusion injury. Simply put, after consuming most of the oxygen, enzymes like NADPH oxidase had stopped doing much harm. With oxygen levels back up, the enzymes resume cranking out reactive oxygen species. End result is persistent microvascular obstruction. Beyond a certain point, tissue damage is irreversible, even if circulation can be temporarily restored. The end point is multi-organ failure.

Cardiogenic shock in the wake of myocardial infarction is among the most frequent causes of death.

Hypovolemic shock

Losses of more than 30% of blood volume by external or internal injuries cause hypovolemic shock. Other causes include extreme dehydration (by, e. g., persistent vomiting and diarrhea, diuretics overdose or osmotic diuresis in diabetes mellitus) and fluid loss due to massive burns.

Apart from actual shock, hypovolemia can produce less pronounced dips in blood pressure accompanied by sympathetic activation. One particular example is known as (early) dumping syndrome, seen in people who have lost pyloric function due to gastric surgery. Approximately 15 minutes after ingesting a meal rich in carbohydrates, these patients develop tachycardia, sweating, nausea and abdominal cramps. In this case, transitory hypovolemia is the result of a massive shift of fluid volume from the vascular system into the intestinal lumen due to the osmotic effect of high sugar concentrations.

In hypovolemic shock, compensatory mechanisms are essentially the same as in cardiogenic shock: centralization. In a specific response to an acute loss of blood, a considerable volume of interstitial fluid may be recruited into the vascular system. First, pressure comes down in all parts of the system. Reduced capillary pressure then results in net resorption of water and electrolytes from the interstitial space, compensating for part of the loss in blood volume. Over time, this fluid shift reduces colloid osmotic pressure in the vascular system, while increasing it in the interstitial space. The shift in fluid ends when a new equilibrium is reached. The drawback, of course, is dilution with respect to plasma proteins and cellular elements. Within a few days, the protein deficit can be made up for by the enormous capacity of the liver to synthesize plasma proteins. Natural replacement of lost blood cells, especially of erythrocytes, takes much longer.

In hypovolemic shock, prognosis is favorable in case the lost volume is balanced quickly, e. g., by infusion of colloid volume replacement solutions like hydroxyethyl starch (HES). In many cases, preferred solutions are hyperosmotic or hyperoncotic "volume expanders", supporting the shift of fluid from interstitial space into the vascular system. If necessary, hematocrit may be raised by infusion of erythrocyte concentrates at a later time point.

Distributive shock

Distributive shock is characterized by plummeting vessel tonus. There is too much "vessel space" in relation to present blood volume, so blood pressure takes a nosedive. By definition, there is no centralization under these circumstances, the patient's skin feels warm. According to the underlying cause, we distinguish anaphylactic, septic and neurogenic shock.

-Anaphylactic shock

An anaphylactic shock is the extreme form of a Type I hypersensitivity reaction. It is caused by generalized release of histamine in large parts of the body. In principle, the job of the IgE-mast cell- eosinophil granulocyte-system is to fight parasites (protozoa and worms). Therefore, IgE-loaded mast cells lie in wait for parasites in the loose connective tissue below external (skin) and internal (mucosal) surfaces that parasites need to penetrate to invade our body. Unfortunately, we sometimes produce IgE against innocuous "threat mock-ups" like

food components or penicillin. The moment these spread in the body, they cause vasodilation, increase in permeability and edema in all those regions at the same time. In the skin, we call that *urticaria*, swelling and edema in the soft tissues of face and throat, *angioedema* or *Quincke's edema* (where edema of the epiglottis may lead to airway obstruction and suffocation). Asthma attacks may result from swelling of airway epithelia. In the gastrointestinal tract, analogous mechanisms cause nausea, vomiting and abdominal cramps. Once vessels in all of these regions dilate at the same time, accompanied by loss of fluid into the interstitial space, blood volume is insufficient to maintain blood pressure.

In the first place, therapy needs to match blood volume to the now-increased vessel space by infusions. In addition, it is important to stop antigen exposure as soon as possible and to curtail further damage by administration of epinephrine (vasoconstriction via α -receptors, bronchodilation via β_2 -receptors), highly-dosed glucocorticoids and histamine antagonists.

-Septic shock

In septic shock, too, we find generalized vasodilation and abnormal permeability. An additional aggravating factor is disseminated intravascular coagulation, due to simultaneous activation of clotting and fibrinolysis systems. All of this is caused by macrophage activation.

Normally, an infected wound, e. g., a small injury of our hand, does not cause much harm. Our inborn immune system is designed to prevent the infection from spreading. In the infected area, monocytes and macrophages recognize invading bacteria via their Toll-like receptors and phagocytize them. At the same time, they release a cocktail of cytokines including TNF α and IL-1 β , which mediate vasodilation and activate endothelial cells, raising permeability. Other leukocytes adhere to the activated endothelium and enter the inflamed tissue. In draining venules, the clotting system is activated, preventing bacteria from spreading all over the organism via the blood. This helps to detour incoming plasma, which is forced into the interstitial space; our finger swells up and "throbs". Via lymphatic vessels, bacteria, macrophages and interstitial fluid are pushed into the local lymph node. The lymph node filters pathogens and cells from the fluid, swelling painfully in the process.

On the very rare occasion that inflammation fails to confine the pathogens, this useful mechanism changes to the dangerous opposite. Once bacteria manage to escape via the blood, all of the above-mentioned mechanisms run simultaneously all over the body: activation of macrophages, vasodilation, endothelial activation with massive increase in permeability, leukocyte adherence and clotting. A large part of blood volume gets lost into interstitial space. Coincident activation of clotting and fibrinolysis systems all over the body is called disseminated intravascular coagulation (DIC). The process ends up consuming all clotting factors and platelets, leaving the body unable to stem diffuse internal bleeding. The mortality rate from septic shock is about 50%.

Treatment of septic shock is especially difficult, as many problems have to be handled at the same time. Controlled volume management, antibiotic therapy with pathogen identification and stabilization of the clotting system pose extreme challenges for intensive care teams.

Pharmacology cross reference: In the case of bleeding in the context of disseminated intravascular coagulation, it is necessary to replenish the consumed fibrinogen. Yet, replenishment does not make sense as long as hyperfibrinolysis continues. Hyperfibrinolysis can be rapidly measured by rotational thrombelastometry (ROTEM), using the resistance

curve of a rotating stamper in whole blood. The therapeutic strategy is therefore to first slow down fibrinolysis by administering **tranexamic acid**. Tranexamic acid is somewhat similar to the amino acid lysine and binds to plasminogen at several sites that would otherwise be bound by the lysines of fibrin. Subsequently, purified **fibrinogen** is administered, which entails a lower risk of infection than fresh frozen plasma.

-Neurogenic shock

The tonus of our blood vessels is continually controlled by our autonomous nerve system. A trauma may cause the ANS to malfunction, resulting in loss of vasotonus and shock. By definition, sympathetic compensation does not occur as shock is precisely the result of its failure.

Obstructive shock

Massive pulmonary embolism may obstruct such a large part of the arterial cross sectional area that the left ventricle fails to fill sufficiently to build up normal pressure. Tension pneumothorax and pericardial tamponade are categorized here, too, as they lead to the same consequences.

Hemodynamic and laboratory parameters

Typically, under conditions of shock, blood pressure and cardiac output cannot be kept within normal limits despite an increased heart rate. Yet, there are exceptions: septic shock, e. g., may start in a hyperdynamic form in which output is actually increased.

Further informative parameters may be measured with the help of appropriate catheters. Central venous pressure (CVP) is reduced in hypovolemic shock; in other forms of shock, it tends to be somewhat increased. It is strongly increased in obstructive shock. Pulmonary capillary wedge pressure (PCWP) is increased in cardiogenic shock due to blood backing up from the left heart. In most of the other shock types, it tends to be decreased due to a relative shortage in volume.

Determination of lactate levels helps to estimate the extent of oxygen deficiency: lactate is the end product of anaerobic glycolysis. Coagulation assays, including platelet numbers, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen and fibrin degradation products (D-dimer) help to recognize incipient disseminated intravascular coagulation.

10. CARDIOMYOPATHY

The term cardiomyopathy is not entirely satisfactory, as it represents a mixed bag of conditions with little in common. What these conditions actually do have in common is this: cardiomyopathies are diseases of the myocardium that lead to impairment in function. The term does not imply any specific cause. Causes may be "unknown" (idiopathic

cardiomyopathy), genetic factors, other diseases (specific cardiomyopathy: coronary heart disease, hypertension, valve defects, inflammation, alcohol etc. etc.) or chronic overload. Categorized by formal criteria, there are four types:

- Hypertrophic cardiomyopathy: the wall of the left ventricle is thicker than normal, but the ventricle's volume is not increased.
- Dilated cardiomyopathy: the left and/or right ventricle's volume is markedly increased.
- Restrictive cardiomyopathy: scarred or infiltrated tissue impairs dilation during diastole, impairing ventricle filling.
- Arrhythmogenic right ventricular cardiomyopathy: this inherited condition usually affects the right ventricle. Myocardial tissue is progressively replaced by fat, resulting in right heart failure and arrhythmia.

Genetic causes

Genetic causes may be found in almost all cases of hypertrophic and in 20-50% of dilated cardiomyopathy. In hypertrophic cardiomyopathy, disease alleles encode mainly sarcomere proteins like actin, myosin heavy and light chains, myosin-binding protein C, troponin, tropomyosin or titin. Dilated cardiomyopathy is primarily associated with abnormalities of cytoskeletal proteins, like sarcoglycan, dystrophin or desmin, but also with mitochondrial proteins or nuclear membrane proteins lamin A and C. Yet, considerable overlap exists: for several of these genes, specific alleles are associated with either of these cardiomyopathies.

Dilated cardiomyopathy

Ventricle volume is increased, the myocardium is overextended. Normally, two systems counter extension: the collagen fibers embedded into the extracellular matrix and the contractive force of cardiomyocytes. Weakening of either component increases the chances of dilation. Therefore, non-genetic causes of dilated cardiomyopathy are:

- Inflammatory: Damage to cardiomyocytes may be caused by the infectious agent itself or by an inflammatory infiltrate. In addition, macrophages release matrix-metalloproteases like collagenase and stromelysin that digest fibers of the extracellular matrix. Damage to the tough collagen network increases the strain on myocytes. Examples are viral myocarditis (adenoviruses, Coxsackie B, Parvovirus B19), sarcoidosis or Chagas disease due to *Trypanosoma cruzi*.
- Toxic: anthracycline antitumor antibiotics sometimes cause dilated cardiomyopathy, as does trastuzumab (anti-HER2, with HER2 strongly expressed by cardiomyocytes), so the two cannot be combined. Chronic alcohol ingestion is another typical cause.
- Metabolic: chronic hypocalcemia sometimes causes the condition, maybe by constantly reducing contractionary myofibrillar force. Hypothyroidism is another cause.

Dilated cardiomyopathy is characterized by systolic dysfunction: damage to cardiomyocytes compromises contractive force. Stroke volume is reduced, causing congestion upstream of the ventricle. The increase in preload pushes and extends the ventricle's volume. Ejection fraction

(stroke volume by end-diastolic volume) comes down. All of this makes the heart operate under unfavorable conditions, because higher wall tension commands higher oxygen consumption. In addition, the increase in wall tension stands in the way of myocardial blood supply. Over time, ischemic areas develop which further reduce contractility and which may become the origin of arrhythmia. Dilation may extend to the ring anchoring the mitral valve, leading to mitral insufficiency. Mitral regurgitation reduces ejection volume by an equal amount and adds to pulmonary congestion and to the risk of pulmonary edema.

Hypertrophic cardiomyopathy

Based on slight genetic modifications of sarcomere proteins, pumping strain over time leads to thickening of individual cardiac muscle cells, resulting in hypertrophy of the ventricular wall. Instead of the normal 15 μm , the diameter of cardiomyocytes may reach up to 40 μm ; increased diffusion distances have a negative effect on oxygen supply. In addition, blood supply via the coronary arteries cannot grow in proportion with the myocardial mass. Strands of cardiomyocytes are in a pattern of disarray, oriented in chaotic directions, with whirls and loops. Chaotic texture may lead to irregular propagation of excitation, with re-entry resulting in spontaneous ventricular fibrillation.

Hypertrophy and irregular texture are accompanied by interstitial fibrosis, i.e. an increase in extracellular fibers. Together, these changes impair ventricular relaxation, resulting in diastolic dysfunction: diastolic filling pushes against a stiff ventricular wall, causing a marked increase in end-diastolic pressure. Ventricular filling is especially compromised at a fast heartbeat, meaning cardiac output cannot keep up with increases in physical strain.

In about a third of cases, the thickened septum protrudes into the outflow area of the left ventricle. During contraction, the narrowing between septum and mitral cusp constrains the outflow, resulting in a strong drop of pressure between ventricle and aorta. Thus, even higher ventricular pressure is needed to maintain aortic pressure, further augmenting oxygen requirement.

Restrictive cardiomyopathy

Normal myocardial relaxation may be restricted by any of the following causes:

- Deposition of amyloid: Amyloid is an interstitial protein precipitate. Some proteins are more prone to form aggregates than others; they precipitate if produced in large quantities. Two examples are acute phase protein serum amyloid A in chronic infection or immunoglobulin light chains in plasma cell disorders.
- Sarcoidosis: typical granulomatous infiltrates may also affect the myocardium
- Systemic sclerosis
- Hemochromatosis
- Glycogen storage diseases
- Radiation therapy

The result is mainly diastolic dysfunction. Impaired diastolic filling reduces cardiac output and causes congestion upstream of the ventricle.

Arrhythmogenic right ventricular cardiomyopathy

Any one out of a dozen genetic conditions, usually autosomal dominant with variable penetrance, may lead to slow degeneration of myocardial tissue, which is eventually replaced by fat. It is not clear why mainly the right ventricle is affected. Among the involved proteins are desmosome components as well as intermediate filaments, cytoskeleton components force-fitted to desmosomes.

The disease is found all over the world, with local clustering in the northern Italian Veneto region at 1:2000 to 1:5000.

Young people suddenly dropping dead while engaged in sportive activities frequently demonstrate either hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy on autopsy.

Takotsubo (stress) cardiomyopathy

Situations of overwhelming emotions, usually negative but also positive, sometimes cause an inability of the left ventricular apex to contract. In X-ray analysis, the contour of the heart with bulging out of the apex is reminiscent of a Japanese octopus trap (takotsubo). Causative mechanisms remain controversial; vasospasms in response to massive catecholamine release have been proposed. Symptoms may mimic acute myocardial infarction. Systolic dysfunction entails a marked reduction in ejection fraction. Long term prognosis is good.

11. ARTERIAL CIRCULATORY DISORDERS

Stenosis and occlusion

While large arteries branch out like a tree, this analogy does not apply to smaller vessels. Small arterial vessels form anastomoses, which enable collateral circulation in case of stenosis or blockage.

Stenoses of pelvic or leg arteries are readily diagnosed by duplex sonography. Stenoses up to 20% cause turbulent flow, stenoses between 20 and 50% show increases in systolic flow velocity. Only stenoses of more than 50% reduce flow velocity beyond the obstruction and lead to negative consequences in the supply zone.

Beyond a stenosis, arteries tend to dilate and may even form aneurysms. This way, turbulence tends to aggravate stenosis over time.

Pressure drop caused by an obstruction engenders collateral circulation via tenuous anastomoses. Arterioles forming the distal leg of these anastomoses widen by autoregulation, facilitating flow reversal. Flow velocity in anastomoses is high due to the large pressure gradient. Increased shear stress leads to structural modification of the small vessels:

reinforced by added connective tissue and smooth muscle cells, they grow in diameter as well as in length and end up as tortuous collateral vessels reminiscent of corkscrews.

Fontaine classification of peripheral artery occlusive disease:

- I verified partial arterial obstruction in the absence of subjective symptoms
- II claudication (intermittent limping): after walking a certain distance, ischemic muscle pain forces the patient to pause
- III rest pain
- IV ischemic necrosis

Steal syndromes

In vessels connected in parallel, flow rates are inversely proportional to individual resistance. If the resistance in an artery becomes too large, the flow rate in bypass circuits with reverse flow will increase and may lead to steal phenomena.

Subclavian steal syndrome is typically caused by a stenosis at the branch point of the left subclavian artery. Exercising the left arm's muscles makes them require more oxygen and thus more blood. In this case, the path of least resistance is the left vertebral artery, which now supplies the arm by flow reversal. This blood is taken from the "ring line" of the Circle of Willis and in fact "stolen" from the brain: subclavian steal syndrome may thus cause vertigo, ataxia, syncope or impaired vision.

A second example is coronary-subclavian steal syndrome in patients who have received a coronary bypass using the *A. mammaria interna*. If a stenosis develops in the subclavian artery at the same spot as discussed before, exercising the left arm's muscles may induce them to steal blood from the coronary artery (robbing Peter to pay Paul? In this case, it's stealing from the heart to feed the biceps). Work done by the left arm may cause myocardial ischemia and *angina pectoris*.

Aneurysms

A weakening of the arterial wall, e.g., by atherosclerotic lesions, may lead to a local widening of the artery, an aneurysm. In an *aneurysma verum*, the dilation involves all of the vascular wall layers; in an *aneurysma spurium*, a tear of the intima and media causes bleeding, but the bleeding remains contained by adventitia and surrounding tissue. An *aneurysma verum* leads to turbulent as opposed to laminar flow in the blood, which often results in thrombosis.

Aortic dissection

A tear in the intima allows blood to burrow between intima and media, giving rise to a second lumen. The false lumen either ends blind, or finds a way back into the lumen proper by a secondary tear, or it completely perforates media and adventitia at some location and causes bleeding into pericardium (with cardiac tamponade), pleural cavity or retroperitoneum. In

addition, symptoms may be caused by narrowing of the branch points of the large arteries in the aortic arch, or by compromising the function of the aortic valve.

Typically, aortic dissections start in two locations:

- in the ascending aorta not far from the aortic valve
- in the descending aorta directly following the branching off of the left subclavian artery

In younger patients, dissection may be facilitated by weakness of connective tissue due to genetic factors, as in Ehlers-Danlos or Marfan syndromes. Older patients typically combine atherosclerosis with pronounced hypertension.

Vascular spasms: Raynaud's phenomenon

Primary Raynaud's phenomenon is quite common in young women. When exposed to the cold, fingers and the back of the hands turn white / livid and painful. The phenomenon is an exaggeration of the normal sympathetic response to cold or emotional stress, with extreme vasoconstriction resulting in tissue hypoxia. Usually, the spasms end before causing structural damage.

Secondary Raynaud's phenomenon occurs as a corollary of another disease, e. g., systemic sclerosis or systemic lupus erythematosus. Patients who newly develop Raynaud's phenomenon should therefore be evaluated for these diseases.

Fistulas

Solitary arteriovenous fistulas may be the result of trauma or may be constructed intentionally to provide access for hemodialysis. Multiple small-scale arteriovenous fistulas may be found as a genetic condition.

Arteriovenous fistulas result in changes nearby as well as on a systemic scale. The steep pressure gradient near the fistula causes development of collateral vessels similar to those seen with stenosis. Part of the diverted blood supplies the periphery, another part further contributes to fistula volume by retrograde flow. Both vessels, the feeding artery as well as the draining vein, extend in diameter. With a stethoscope, a machine-like bruit generated by turbulent flow may be heard. Venous pressure behind the fistula is increased and may lead to problems with venous drainage in the affected extremity, including ulcers due to venous insufficiency.

Systemically, the fistula flow rate strongly decreases peripheral resistance while increasing cardiac volume. Additional demand placed on the heart becomes critical above a shunt volume of 1000-1500 ml per minute.

12. VENOUS CIRCULATORY DISORDERS

Blood pressure in venules, postcapillary resistance vessels, is about 20 mm Hg, while pressure in the right atrium, central venous pressure, is below 6 mm Hg. These low pressure levels mean veins are seldom filled completely. Usually, they are in a partly collapsed state. With slight increases in pressure, a lot of volume can be accommodated until veins are filled. From then on, additional volume extends the veins in diameter, and pressure rise is steeper.

At any given time, the venous part of systemic circulation contains 50-60% of our total blood volume, the arterial leg only about 15%. In other words, the venous system provides the space to "park" blood while it's not needed elsewhere. "Parking" does not mean actual standstill, of course, but rather a slower flow back due to increased vessel diameters at more relaxed tonus levels. While tissue autoregulation contributes a lot to the tonus of arteries, venous tonus is almost exclusively adjusted centrally via the sympathetic system. If we jump up to run to the bus, our sympathetic nervous system increases not only our heart's pumping rate, but also the tonus of our venous volume stores, returning more blood to the heart. Also, considerable blood loss may be compensated for by increase in venous tonus via neuronal sympathetic activity and release of catecholamines. There is no dramatic fall in blood pressure until the volume of blood lost exceeds this reserve capacity.

When standing up from lying down, the partly collapsed veins of the lower part of our body fill instantly, causing a sudden quasi-loss of volume between 600 and 700 ml. Normally, this is compensated for within seconds by an increase in tonus. In an upright position, considerable hydrostatic pressure adds to the otherwise low venous pressure. To enable the return of venous blood to the heart, two mechanisms cooperate: venous valves and muscular pump. If groups of muscles locked into fascia-surrounded compartments contract, they squeeze veins included in the compartment. The valves determine pumping direction. When we walk, run or bike, this muscular pump greatly contributes to total circulation. By contrast, standing still for a long time increases the risk of syncope.

Deep vein thrombosis

Venous occlusion is usually caused by thrombosis, only rarely by external compression due to tumors, hematomas, aneurysms etc. In most cases, thrombotic events are triggered by a concurrence of hypercoagulability and venous stasis.

The following factors may promote clotting:

- Pregnancy
- oral contraceptives
- genetic disorders of hemostasis, like factor V Leiden, (5% of Europeans), prothrombin G20210A (3% of Europeans), antithrombin III deficiency, protein C deficiency, plasminogen deficiency
- some tumors

Factor V Leiden: It is important that coagulation, once started, does not spread everywhere. To this end, intact endothelial cells adjacent to the coagulation site use integral membrane protein thrombomodulin to bind active thrombin (factor IIa), with the complex activating protein C. Protein C, in turn, helped by protein S, breaks down active factors Va and VIIIa.

Factor V Leiden, however, resists being broken down by protein C. Therefore, already in heterozygotes with factor V Leiden, coagulation, once started, spreads more easily.

Prothrombin G20210A: This single nucleotide polymorphism (SNP) does not alter the amino acid sequence. It affects the last nucleotide in the 3' untranslated region of the mRNA; More efficient 3'-end processing of mRNA increases mRNA and protein levels. The moderately elevated prothrombin level promotes coagulation.

Venous stasis is promoted by work in standing, a bedridden state or by prolonged immobilization, as in bus or air travel.

Occlusion of a deep vein causes venous pressure on the far side of the obstruction to rise. Blood is diverted via congested collaterals, part of which are superficial. Depending on intensity, this may result in cyanotic discoloration, edema and pain. Diagnosis may be confirmed by color duplex sonography in the presence and absence of compression.

Phlegmasia coerulea dolens is an extreme form of venous occlusion. Venous pressure rises to a point where endothelial cells of upstream capillaries are damaged, leading to increased permeability. Extravasation of fluid and proteins causes tissue pressure to rise dramatically. Blood volume lost to edema in a single leg may exceed several liters, which may result in circulation problems up to hypovolemic shock. Decline in systemic pressure in combination with a local increase in tissue pressure may cause capillaries to collapse with the risk of microvascular insufficiency and gangrene.

Parts of a thrombus may break off and cause pulmonary embolism.

While symptoms of acute thrombosis usually abate with time, thrombosis may have lingering after-effects called post-thrombotic syndrome. In most cases, venous valves in the thrombotic region are damaged irreversibly. Even in case of successful recanalization, the resulting rigid tube replacing the former elastic and tonus-adjustable vein forms a functional stenosis.

Chronic venous insufficiency

Chronic impairment of venous drainage may affect deep as well as superficial veins, usually of the lower extremities. Obstruction of deep veins is mostly a result of thrombotic events, while in superficial veins, it is frequently a consequence of varicosis. Varicosis may be promoted by genetic factors, e. g. collagen polymorphisms, and thus tends to run in families. An increase in vessel diameter leads to insufficiency of venous valves.

Mechanical obstruction of drainage, incompetent valves and insufficiency of the musculovenous pump contribute to venous insufficiency and are mutually reinforcing.

Potential symptoms include intermittent claudication, increased capillary permeability with trophic changes of the skin (induration, hyperkeratosis, hyperpigmentation) and ultimately, ulcers.
