2. PATHOPHYSIOLOGY OF THE CARDIOVASCULAR SYSTEM

CIRCULATORY FAILURE:

The role of circulation is to provide the tissues with oxygen and nutrients according to their actual needs, and also to carry away CO_2 and other waste-products. Circulation is not sufficient if it cannot perform this role despite normal arterial gas-composition (O_2, CO_2 contents) and in the microcirculation O_2-deficiency and waste-product accumulation develops.

A *local circulatory failure* affects only a hypoperfusion and ischemia of certain tissues or organs. In *generalized circulatory failure* hypoperfusion affects the whole body, naturally with uneven severity at different locations. The cause of local circulatory abnormality/failure necessarily prevails in the periphery. Generalized circulatory failure may also originate at the periphery (filling and tone of vessels, etc.); such peripheral circulatory failure may develop with unaffected heart functions, but may also develop as a result of severe uncompensated deficiency of the pumping function of the heart.

Depending on its severity, lasting circumscribed tissue hypoperfusion (local circulatory failure) causes local ischemic tissue damage (local degeneration, necrosis, gangrene, etc.), eventually with dangerous generalized consequences (e.g. important general consequences of localized myocardial/brain ischemia). In contrast, lasting severe generalized circulatory failure leads to functional failure of several organs or to acute life-threatening (peripheral or cardiogenic) circulatory shock.

Defense against tissue hypoperfusion is based on modification of microcirculation of the affected organ/tissue – in generalized cases this is adjoined by altered distribution of cardiac output between various organs. The way of compensation – depending on the origin of circulatory failure – may be different. Disturbance of cardiac function, for example, may be compensated for a long time, thus heart failure (although it may occasionally be coupled with pronounced transient symptoms and transient hypoperfusion of certain tissues) results in serious generalized circulatory failure only in the most severe cases.

Table 2.1.

Local vs. generalized dirculatory disturbances

	LOCAL CIRCULATORY DISRDER	GENERALIZED CIRCULATORY DISORDER			
		VASCULAR (peripheral)			CARDIAL
Occurrence	obstruction of big arteria/vein	decreasing venous return (orthostasis)	volume loss, distrib. abnorm		pump function + compensation
Consequence	local ischemia, necrosis	collapse	shock	acute, or end-stage	decompensation
Possible outcome	depends on localization	usually transient			death or chronic heart failure

2.1. HEART FAILURE

Heart failure basically means a deficiency of pump function: the result of pumping function does not correspond to the actual needs, i.e. the cardiac output (CO) is relatively (in end-stage chronic heart failure or in acute failure) lower than normal even at rest and its distribution is abnormal. At earlier stages maintenance or even slight elevation of cardiac output (or its maintenance at elevated level in high output cardiac failure) can be secured only by the help of compensatory mechanisms. In fact, not so much the absolute level of cardiac output characterizes the heart failure, rather the way of functioning of the heart pump, the ever narrowing ability to increase cardiac output, and the maldistribution of cardiac output between various organs.

Cardiac capacity could be precisely described by the maximal cardiac output: this amount would secure the maximal blood perfusion of tissues. Maximal cardiac output is, however, not determined routinely, rather the ways and possibilities of increasing cardiac output (or maintaining it at a high level) (ch. 2.1.2. or 2.1.10.) must be known since this describes the differences between healthy and failing heart functions.

HEART FUNCTION IN HEALTHY YOUNG ADULTS

During physical exercise the resting cardiac output of about 5 liters/min may increase above 20-25 (in athletes even up to 35-40) liters/min. The mechanisms of this increase:

1) *Increased contractile force of the myocardium:* Elevated ejection fraction (EF) leads to better systolic emptying of the ventricles and to about 10% increase of the stroke volume (Fig. 2.8.). At rest about 70 ml is ejected from the 110 ml end-diastolic volume (i.e. the EF is about 65-70%), while the systolic residual volume is 40 ml. With enhanced contractile force the EF is 75-80% and the stroke volume rises to 80 ml and the systolic residual volume decreases (in case of unchanged diastolic filling).

2) *Elevation of heart rate:* In young athletes the maximal heart rate is about 200 bpm (this decreases with age). Mainly an enhanced sympathetic tone and the positive chronotropic activity of circulating catecholamines are responsible for the tachycardia. With unchanged stroke volume this could increase the cardiac output by about 3-times. Maximal heart rate can be maintained for short time only, since in tachycardia the diastolic time is relatively shortened, negatively affecting the coronary circulation (coronary blood flow depends on diastolic time and pressure), while in tachycardia the oxygen need of the myocardium is high. With less severe tachycardia an increase in stroke volume secures the elevation of cardiac output. Thus, independent of the previous steps, in tachycardia an increase of stroke volume is unavailable. Elevation is made possible only by enhanced diastolic filling and increased diastolic ventricular volume.

3) *Increase of stroke volume:* The normal resting 70 ml stroke volume may easily increase to 100-140 ml or even above this. At the beginning the increase is due to higher EF, but this is limited (total systolic emptying is not possible). Later a higher diastolic filling (end-diastolic volume = EDV; cf. Frank-Starling rule) coupled with the high EF significantly increases the stroke volume. In athletes the good diastolic compliance of the ventricle allows an increase of EDV without pronounced increase in end-diastolic pressure (EDp). Although an enhanced venous return is absolutely necessary for the increased ventricular filling, during moderate exercise of athletes this still does not necessarily need extreme elevation of filling pressure (it is coupled with hardly any venous congestion).

Factors influencing stroke volume:

a) *preload:* this secures the enhancement of ventricular filling, and it is determined basically by the *venous return*. This return depends on the blood distribution in the body, on the relationship between fluid spaces in the plasma and the interstitium, on body position, on the intrathoracic and intrapericardial pressure and on eventual shunts. Physiologically the most important regulators which determine the filling pressure are the venous tone and the capacity to alter stores of blood (catecholamines increase the venous tone and decrease the blood stores) and also the pumping function of peripheral muscles (m. triceps surae, etc.) in the venous system (Fig. 2.1.).

The active ventricular dilation that had been demonstrated for the early phase of diastole makes the atrial contraction unimportant: the atria play a role only in special cases. In contrast, the ventricular distensibility (ventricular compliance) helps filling

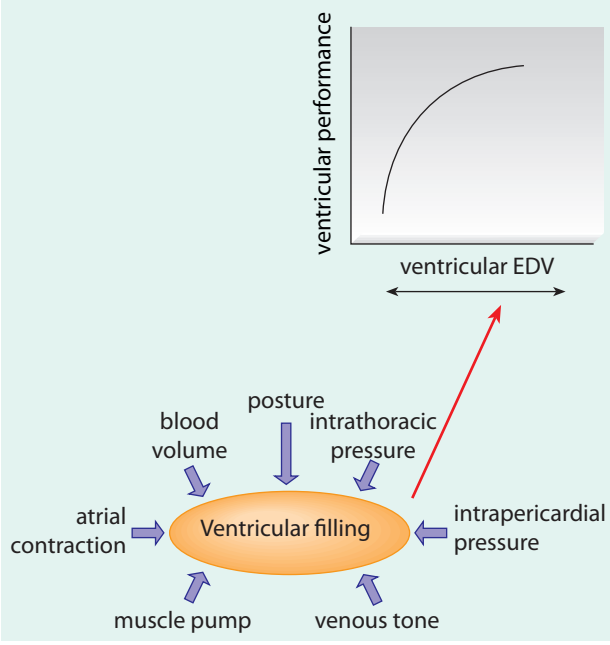

Fig. 2.1.: Factors influencing ventricular filling and performance.

and allows accepting more returning blood, thereby causing greater EDV with normal or hardly increasing EDp.

The normal systemic filling pressure is about 7-8 mmHg, i.e. there is influx from the central vein and normal filling even if the diastolic ventricular pressure is at this level. In extreme cases of strongly increased venous tone and muscle pump function, the filling pressure may be 4-times higher.

Greater venous return is possible without significant rise of the filling pressure, e.g. in case of an a-v shunt (see high output cardiac failure): the venous tone and the muscle pump effect do not contribute, neither does the venous/atrial or the diastolic ventricular pressure – as long as the ventricular compliance is normal, the contractility can be increased and the afterload is normal. In case of unaltered venous return an isolated rise of the filling pressure could have only a moderate effect on the performance of the heart (such theoretical possibility should be considered in cases of compensation of abnormal inhibition of ventricular filling, e.g. in atrio-ventricular stenoses). In contrast, the cardiac performance significantly increases in those (more frequent) cases when the venous return and the filling pressure are enhanced simultaneously. Such synchronous changes provide an important possibility for enhancing the diastolic filling in cases when a decreased ventricular contractility needs to be compensated.

Although in different extent, in these cases the atrial pressure increases in order to secure the required cardiac output. However, no increase in atrial pressure is needed if – besides the high venous return – an increase in ventricular contractility or decrease in afterload (by more complete systolic emptying) or early diastolic filling helps the enhancement of cardiac performance.

b) *myocardium contractility:* for this mainly the norepinephrine, that is released at local nerve endings to excite the β-adrenergic receptors, may be responsible. Positive (although moderate) inotropic effects have the circulating catecholamines, and digitalis-like drugs, calcium. In contrast, narcotics, hypoxia, hypercapnia, acidosis, dysfunction of the myocardium (inflammation, degeneration, infarction, etc.), or mechanical damage have negative inotropic effects (Fig. 2.2.). During physical activity of healthy persons first the contractility increases. The contractility can be well characterized by the stroke volume rendered to the EDV: with similar EDV a high stroke volume (= high EF) suggests increased contractility.

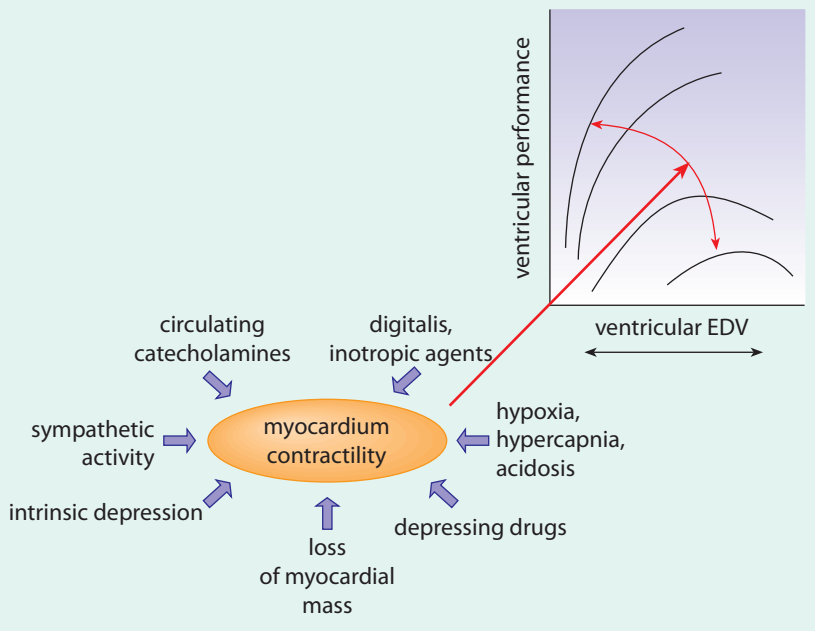

Fig. 2.2.: Factors influencing myocardial contractility.

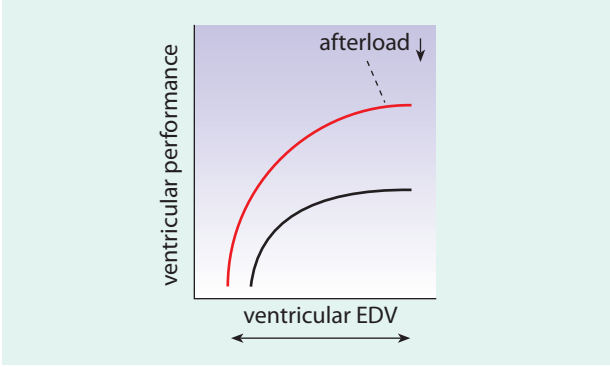

Fig. 2.3.: Decrease of afterload increases performance at unchanged contractility.

c) *afterload*: low intraaortic resistance or low TPR (i.e. decreased impedance) make easier ejection from the ventricle, may increase the stroke volume without altering the strength of contraction (as if it would save the force of ventricular contraction) (Fig. 2.3.). During physical exercise of healthy young persons, the TPR decreases partly because the dilation of vessels of muscles, partly due to redistribution of the cardiac output. Exogenous or endogenous vasodilator substances decrease the afterload. In contrast, an elevation of circulating catecholamines (e.g. in stress or any form of heart failure), or other vasoconstrictor substances increase the afterload.

In Fig. 2.4. a loop representing the ventricular volume- and pressure-changes in the course of a ventricular revolution is demonstrated: in this case the EDV is 110 ml, the stroke volume 75 ml, the EF is ca. 68% (Fig. 2.6.). The subsequent revolution exhibits slight shifts of the loop due to moderate changes in filling time/pressure and EDV, e.g. due respiratory changes of intrathoracic pressure (Fig. 2.5.). Connecting the lower points of the loops (passive stretch) a curve is given characterizing the ventricular diastolic compliance, while the curve from systolic peaks (provided the afterloads are standard) represents an active stretch (pressure) curve which refers to the strength of contractions (Fig. 2.5.).

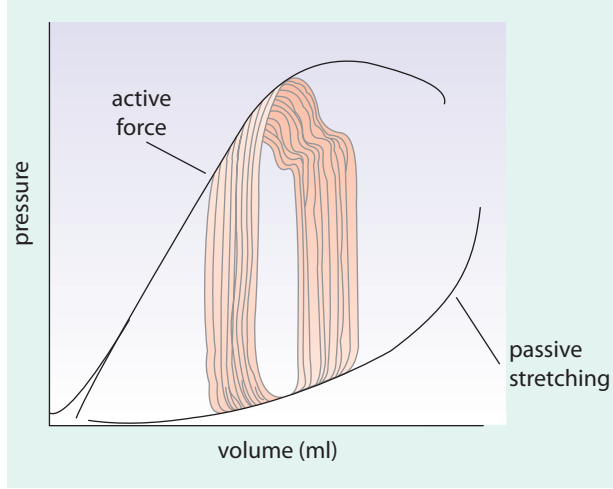

Fig. 2.5.: Active stretching associated with contractility, compared with passive stretching i.e. diastolic compliance.

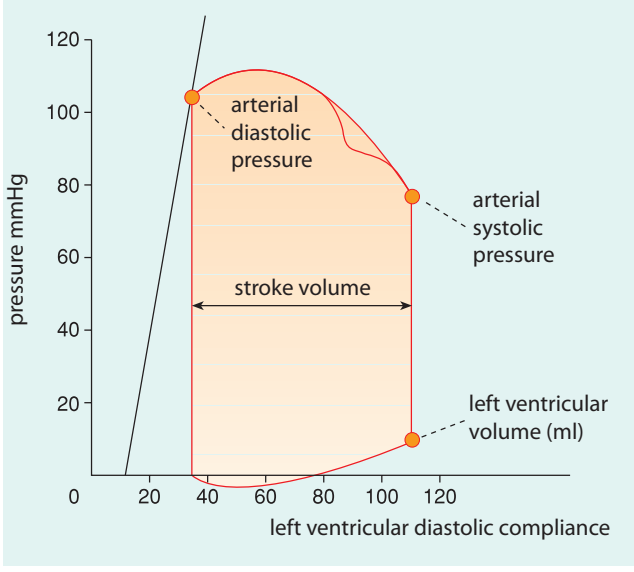

Fig. 2.4.: Ventricular pressure-volume curve: at the beginning of diastolic filling the pressure transiently decreases (a "sucking" effect) some increase in pressure is seen only at the end of the diastole.

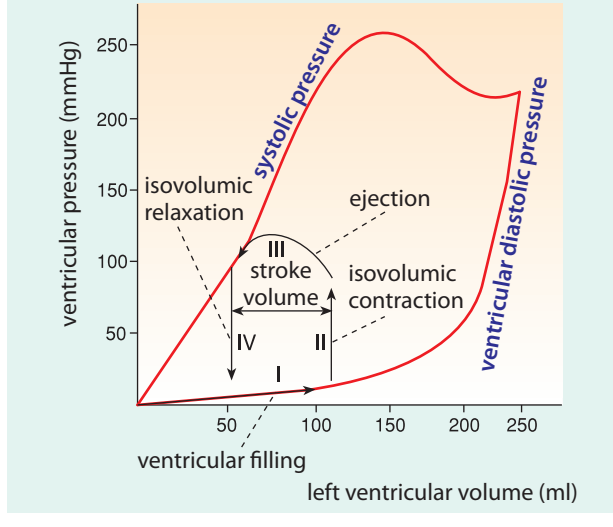

Fig. 2.6.: Systolic ventricular pressure/tension and diastolic pressure/volume relations referring to contractile force and diastolic compliance, respectively. Inside left ventricular pressure-volume associations during a cardiac cycle, and deriving from these the diastolic tension curve and systolic pressure curve reflecting to contractile forces under normal circumstances (cf. Fig. 2.5.).

Table 2.2.

Distribution of cardiac output (CO) at rest and during moderate exercise.

at rest	1300 ml	GI tract, liver	600 ml	exercise
	1100 ml	kidneys	550 ml	(moderate)
	400 ml	skin	1700 ml	
	700 ml	brain	700 ml	
	200 ml	coronaries	550 ml	
	750 ml	skeletal muscle	8000 ml	
	550 ml	bone, other	450 ml	
	5000 ml	total	12500 ml	

The latter curve also describes the ventricular performance (size of stroke volume, see Fig. 2.2.). The performance may also be enhanced by decreased afterload (Fig. 2.3.). During physical exercise the position of the loops characterizing the ventricular contraction is altered, but pathologically (Fig. 2.10.) the position and shape of the loop also changes (Fig. 2.6.) to show the ventricular performance, according to the actual compliance and contractility (Fig. 2.10/1-4).

The mechanisms of elevating cardiac output during physical exercise: higher preload (increased venous return and filling pressure). high sympathetic activity (it increases ventricular contractility and heart rate), vasodilation in working muscles that decreases the peripheral resistance and afterload. The systolic (but not diastolic) pressure increases, indicating ventricular stretch during contraction. The unchanged diastolic pressure refers to the low afterload. Apart from the increased of cardiac output during physical exercise the *distribution* of cardiac output also changes (Table 2.2.). In increased cardiac output of other (e.g. heat) origin the distribution changes partly differently (in hot environment the skin gets more, the muscle gets less of the high cardiac output). It is important that the brain perfusion remains stable in most cases.

Changes of cardiac output distribution is secured by relatively independent resistance elements of the individual vascular territories within the regulatory systems (Fig. 2.7.). Such changes are important not only in physiological but also in pathological changes in the distribution of cardiac output.

FAILING (AGING) HEART AND COMPENSATION

The level of maximal cardiac output of the failing heart is smaller than normally, although the resting level may be normal and the patient may still be able for some increase of it during activity (there is still some reserve capacity). However, the ability of an early enhancement of the EF is missing, thus tachycardia is the first step to increase cardiac output. This is not ideal (it decreases coronary blood flow), therefore the EDV must be elevated at an early stage – this may secure the normal (or even slightly elevated) stroke volume (Fig. 2.8.).

The diastolic compliance of the affected myocardium is low, therefore a high EDp is necessary to keep an elevated EDV. The continuously high ventricular EDp causes continuous stretch of the ventricular wall and deteriorates the oxygen supply of the myocardium, particularly that in the subendocardial parts (ch. 2.6.1.). Due to the elevated filling pressure the preload is much higher than normally, while the afterload does not decrease (the amount of muscles is smaller and its vessels are continuously exposed to catecholamines).

PROCESS AND MECHANISMS OF COMPENSATION

In sum, any increase of the cardiac output (or maintaining it at a relatively high level) is possible exclusively by the help of some „compensatory" mechanisms. Such compensatory mechanisms (Fig. 2.9.):

1) high catecholamine level (with tendency for tachycardia and vasoconstriction),
2) higher blood volume, enhanced salt- and water-retention, increased venous return, venous congestion,
3) continuous stretch of the ventricular wall.

1) High catecholamine level, increased ***sympathetic activity***: This causes a tendency for tachycardia vasoconstriction, increases contractility, enhances the venous tone and helps venous return. In contrast to other compensatory steps this is not unequivocally positive step, since vasoconstriction also increases the afterload and makes the work of heart more difficult.

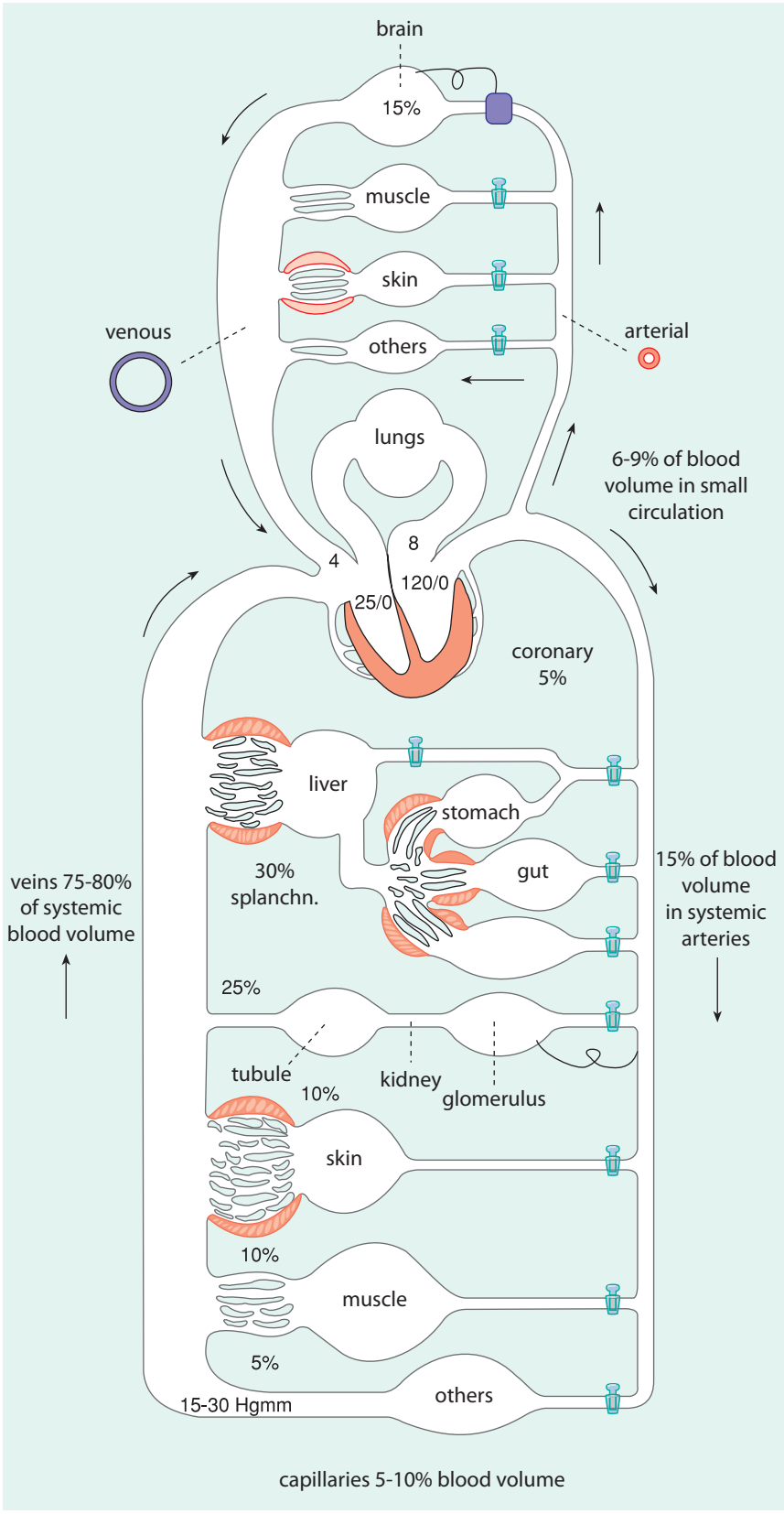

Fig. 2.7.: Distribution of cardiac output at rest. Please note the pressure values in the heart and capillaries, and the blood content of different areas.

*2) High blood volume, with **salt- and water-retention,*** increased venous return, venous congestion. The most important step is the activation of the renin-angiotensin-aldosterone system (RAAS) mainly due to maldistribution of the cardiac output and hypoperfusion of the kidney: the secondary hyperaldosteronism leads to salt- and water-retention. The consequent volume rise affects mainly the venous side, the so-called „effective arterial volume" is rather low – this is responsible for RAAS activation and contributes to the sympathetic activation. At the same time, the venous congestion tends to cause anasarca (high hydrostatic pressure in the capillaries of the leg), or dyspnea (pulmonary congestion and decreased pulmonary compliance). Besides, the stretch of the atria and ventricles (high EDV) may explain the overproduction of natriuretic peptides (ANP, BNP) – the decreased tubular reabsorption at rest will explain the nocturia (preventing an unlimited retention of salt and water). Elevation of these peptides in the plasma has a diagnostic value. In case the secondary hyperaldosteronism is not sufficient to normalize the arterial volume, vasopressin (ADH) is also activated, causing vasoconstriction and water (but not salt!) retention. However, this may result in **hyponatremia** and hypotonicity (ch. 6.1.4.1.) with severe consequences, particularly in elderlies and in late stage of heart failure.

*3) A continuously high **stretch of the ventricular wall.*** Stretch is a consequence of increased filling (for high EDV high EDp is necessary, increasing the wall-

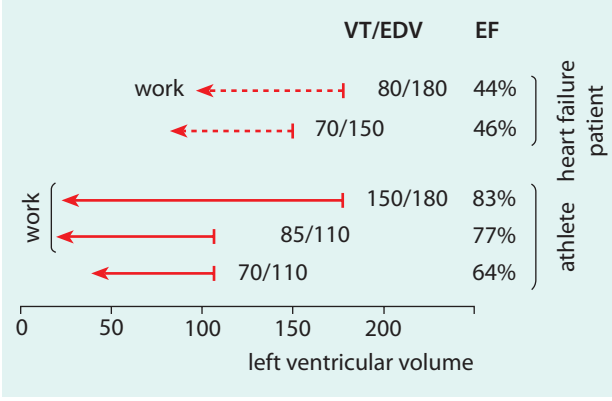

Fig. 2.8: Association of ejection fraction (EF) and cardiac output (CO) in athletes and in patients with failing heart. Stroke volumes and changes of EF are designated by arrows (continuous in healthy and interrupted in diseased patients).

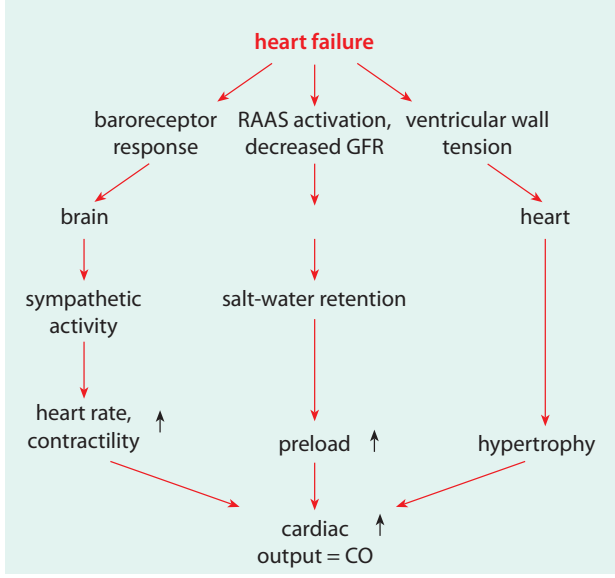

Fig. 2.9.: Mechanisms of compensating heart failure.

stretch). For the first sight it is advantageous: allows enhancement of stroke volume. However, it also increases the oxygen need of the ventricles, whilst the coronary perfusion decreases. The stretch (increased pressure and/or volume) enhances the production of proinflammatory cytokines (e.g. TNF-α, IL-1, IL-6), natriuretic peptides, growth factors, endothelin (by oxidative stress and endothelial dysfunction), as does infarction, ischemia, inflammation of the ventricle. Concentration of these substances is elevated also in the systemic circulation. All these contribute to remodeling of the myocardium and development of ventricular hypertrophy. With rising pressure, by the effect of *C-fos* and *C-myc* proto-oncogenes the myocardial fibers multiply in parallel order, the wall thickness increases, concentric hypertrophy develops with rearrangement of fibers and architecture. At filling, the extension energy becomes distributed between several sarcomeres and the wall stretch decreases, while the new sarcomeres resemble the fetal ones, they have better efficacy, their energy and oxygen need is relatively smaller. At the beginning this helps the ventricular contraction (as a compensating factor), later the thick-walled ventricles have to be overfilled. By then the volume-induced burden will dominate, what leads to increase in fiber numbers in serial-type arrangement, to large diastolic volume and excentric type of hypertrophy – this can no more be a good compensation, and easily leads to diastolic dysfunction (decrease of ventricular compliance), to late-stage decreased contractility and rhythm abnormalities. (Excentric type of hypertrophy may also develop as a primary abnormality.) Experimentally antiinflammatory immunoglobulins may improve the functional capacity of the damaged heart.

Since the high sympathetic activity and high preload alter the fiber-structure of the myocardium and increase its oxygen need, these effects should be attenuated. This is mainly an important duty of the natriuretic peptides: by inhibiting the vasomotor center they decrease the catecholamine release, inhibit the peripheral effects of catecholamines, decrease TPR and promote salt- and water-excretion (= decrease the volume). However, with time, this counter-regulation becomes less sufficient, ANP depletion/resistance may develop. Due to lasting ventricular dilation the hypertrophic ventricular wall becomes thinner and more rigid, some myocardial fibers necrotize, the advantageous effect of stretch is lost, the Frank-Starling curve flattens (this is accompanied by down-regulation of beta-1 receptors), sympathetic overweight and lasting sympathetic excitements dominate. Increase of preload has small effect, while changes of afterload have strong ones on the hemodynamics of the heart. Peripheral vasoconstriction and salt- and water-retention are characteristic, together with a rise of blood pressure (including the diastolic pressure). Thus, in a way this is a vicious circle, the dysfunction of the heart becomes less and less compensated – increasingly severe clinical symptoms can be expected.

The compensating mechanisms aim primarily the maintenance of stroke volume, eventually (at early stages, during work) also its moderate elevation – they try to secure a normal (or rather somewhat increased) diastolic filling of the ventricles. In case the compensating mechanisms are insufficient (e.g. heart rate cannot be increased, severe arrhythmia, salt and water loss, negative inotropic effects), decompensation develops faster. During compensation the *distribution* of cardiac output also changes, thereby the resting or slightly enhanced perfusion of some tissues/organs (brain > functioning muscles) temporarily secures their resting or slightly enhanced perfusion on the account of perfusion of other tissues/organs. Thus, the perfusion of the brain (except in the most severe acute cases) is relatively maintained during decompensation.

In less severe cases the compensating mechanisms may allow significant rise of cardiac output, but this is smaller than in healthy athletes and the clinical symptoms appear upon relatively big exercise. In contrast, in the most severe cases the reserve-capacity is zero, even maintenance of the resting cardiac output becomes difficult and needs the help of compensating mechanisms – in the end-stage even the resting cardiac output cannot be secured, i.e. at this stage (but only now!) the resting cardiac output really significantly decreases. With maldistribution, this stage can be maintained for a while, but the process clearly leads to cardiogenic shock, because the perfusion of tissues becomes severely insufficient in a generalized, lasting way. Failure of pump function may cause relative or transient hypoperfusion of certain tissues even at earlier stages: this can explain the „forward failure symptoms". The compensatory mechanisms themselves (venous congestion and its consequences) will be responsible for the „backward failure symptoms", while the ventricular stretch may contribute to the development of angina pectoris.

The „**subcompensation**" expression refers to a stage when in the **symptomless** (not healthy, but still compensated) patient the **transient/relative insufficiency of either the cardiac output or its distribution exhibits noticeable symptoms**. These may be early exhaustion because of ineffective muscle perfusion, daytime oliguria combined with nocturia (together: symptoms of forward failure), or the **compensatory mechanisms themselves** (e.g. venous congestion and its consequences, dyspnea, tendency for tachycardia, angina pectoris due to ventricular stretch, prolonged rise of blood pressure upon exercise).

2.1.1. CAUSES OF DEFECTIVE VENTRICULAR FUNCTION

1) insufficient filling of the ventricle,
2) defective contractile force of the ventricular muscles (this is the most frequent),
3) inhibition of ventricular emptying,
4) various combinations of these disturbances (Fig. 2.10/1-4.).

Increased venous pressure is unavoidable for maintenance of the stroke volume, first to keep the normal EDV, later to increase the EDp and EDV. The role of high diastolic filling can be understood by the Frank-Starling mechanism: in case of high end-diastolic volume the stroke volume can be maintained or even slightly elevated in cases of large end-diastolic volume, high peripheral resistance or decreased contractility and decreased EF. High EDV is able to compensate falls of EF to about 25-30%. However, in extreme increase of volume („myogenic dilatation") the fibers are extremely expanded, the EF and the cardiac function decreases. Below about EF 20% the probability of cardiogenic shock increases.

ad 1) Insufficient filling of the ventricle: In case of the right ventricle, defective venous return may occur e.g. in cases of decreased blood volume, thrombosis/compression of v. cava, liver cirrhosis, tricuspid narrowing, high intrathoracic or intrapleural pressure (PTX) or rigid ventricular wall. Filling of the left ventricle may be disturbed in mitral stenosis, in hypertrophy – rigidity – thickening of the left ventricular wall, in cases of altered shape (septum-shift into the lumen due to right ventricular dilation), lack of energy (ischemia and diastolic deficiency), pericardial fluid accumulation or constrictive pericarditis. Restrictive and some hypertrophic type primary cardiomyopathies also belong here. Filling disturbances of the left ventricle cause congestion in the pulmonary vessels. In cases of mitral/tricuspid insufficiencies regurgitation prevents normal filling and function of the ventricle. In primary disorders of ventricular filling the atrial volume and stretch necessarily increase, causing a tendency for atrial fibrillation. (Low blood volume may prevent filling in both ventricles, or pulmonary embolism prevents it for the left ventricle, but these are not primary abnormalities of the given ventricle and do not necessarily cause venous congestion.) If not low blood vol-

ume is the cause of disturbance, the filling pressure always increases.

ad 2) Defective contractile force of the ventricular muscles: Decreased ventricular contractility (systolic deficiency) may be evoked by either exogenous or endogenous negative inotropic factors (Fig. 2.2.). Most frequent causes: degeneration due to ischemia or other (toxins, vitamin-deficiency, starvation, storage disorders, fibrosis, etc.) degenerative disorders, but also the dilation following hypertrophy. Necrotic areas of the ventricle do not contract, and an area with aneurysm rather expands instead of contraction (dyskinesia) (Fig. 2.3.4.). Besides, the surrounding zone has hypokinesia, akinesia – contraction will be the difficult duty of the surrounding normal myocardial tissues. Much increase the venous filling pressure is not necessary. In degenerative changes, the tyrosine hydroxylase enzyme is defective, thus the local noradrenaline release decreases; this is one cause of decreased contractility, but a decrease of receptor sensitivity may also contribute to it. The secondary ventricular hypertrophy (e.g. due to hypertension) allows transient increase in contractility. With time, however, the contractility decreases due to degenerative changes. Besides the more frequent secondary dilative cardiomyopathies,

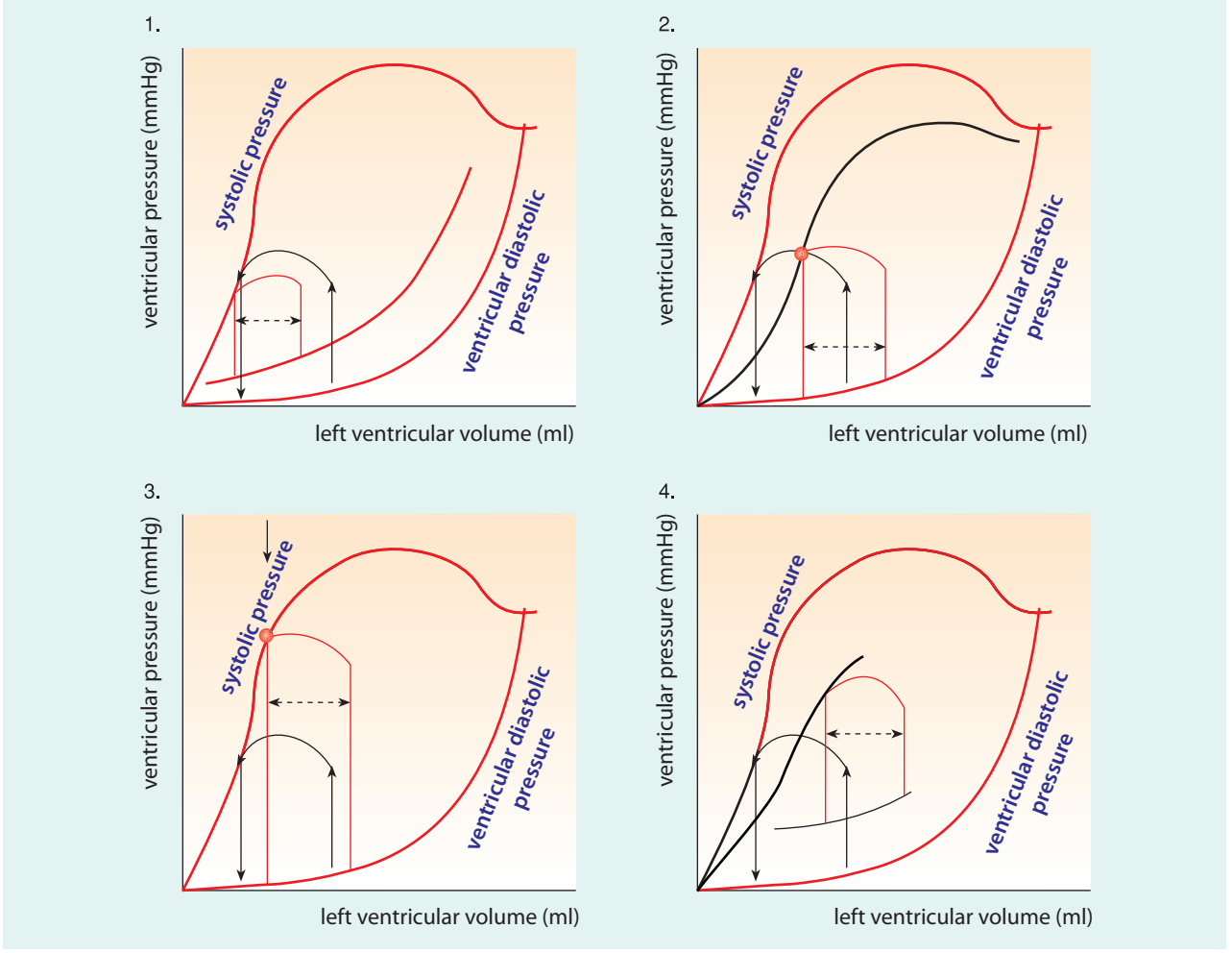

Fig. 2.10.: Pathological forms of ventricular pressure-volume connections (interrupted loops). In case "1" the diastolic expansion decreases, thus higher venous pressure is needed to reach a given EDV; despite this the diastolic filling is also poorer and the stroke volume decreases even with normal EF, the heart rate soon increases or the cardiac output falls. In case "2" the ventricular contractility decreases, with normal diastolic filling this results in earlier finish of systole and decrease of stroke – in order to avoid this, the diastolic filling is enhanced, (for this the blood enters from the veins with higher pressure), but as a result of this despite the low EF the stroke volume is normal. In case "3" the resistance of the vessels is higher (hypertonia), with normal diastolic filling the systolic emptying starts and finishes at higher pressure, the stroke volume decreases – to overcome this the diastolic filling is higher again and the filling pressure is high. In case "4" the combination of the previous cases is shown, this is characteristic for heart function in the elderly.

the congestive-type primary cardiomyopathies also belong here.

ad 3) Inhibition of ventricular emptying, or increased afterload: Emptying the right ventricle is difficult in pulmonary stenosis, pulmonary hypertension. In these cases, the vascular resistance increases, due to decrease of total vascular diameter (of either thromboembolic, or vasoconstrictor origin, e.g. the constriction of vessels in alveolar hypoxia, destruction of pulmonary tissue and vessels in emphysema), or with veno-occlusive cause in left atrial congestion (e.g. adjoining left ventricular failure). In tricuspid insufficiency only a fraction of the emptying is normal, the enlarged ventricle emits large amount a part of which gets back to the right atrium. Emptying of the left ventricle is inhibited mainly by high TPR (hypertension!), narrowing of large arteries or the aortic valves. The forwarded stroke volume is continuously higher than normal, in mitral insufficiency and aortic insufficiency, since emptying takes place only partly in the normal direction or the emptied blood returns to the ventricle. In certain cases of high output cardiac failure, the afterload may also be high due to volume anomalies, in polycythemia due to high viscous resistance. Whether the afterload is increased due to pressure/resistance or volume, it will cause lasting stretch of ventricular wall, and hypertrophy affecting the ventricles either together or independent of each-others. In cases of absolutely or relatively low cardiac output the adrenergic mechanisms of compensation lead to elevation of peripheral resistance, thereby to increase of afterload – both suppressing the cardiac performance. Elevation of EDV, EDp and venous pressure is a general feature.

ad 4) Combinations of these disturbances appear characteristically in some age-related and late ischemic heart failures. Combined disturbances may be derived from pressure- or volume-overburdening. The pressure-burden (e.g. hypertension, aortic-narrowing) characteristically causes concentric hypertrophy, with thick ventricular walls – at the beginnings this results in contractility, but later the large muscle mass cannot be supplied by the coronary perfusion, in the ischemic phase the contractility decreases. Finally, the ventricle dilates (the EDV and EDp increase), in the muscle degenerative foci (pathology: „tiger-heart") are formed. The volume-burden forms (mitral-, or aortic insufficiency, anemia, hyperthyroidism, etc.) cause excentric hypertrophy: the ventricle dilates with unchanged thickness, but since its total mass is high, the oxygen supply is not sufficient. The hypertrophic ventricular wall is more rigid, its filling is difficult and its contractility is low. It is important that a hypertrophy of the left ventricle also leads to mitral or aortic insufficiency, thereby causes further volume overload (similar changes may also happen in the right ventricle).

CARDIOMYOPATHIES (CMP):
In a narrow sense only the myocardial damages of unknown origin are called cardiomyopathies (CMP-s). In the general practice, however, several primary (based on genetic or unknown origin), even secondary (coupled to know disease) CMP forms are also differentiated in the literature.

- *Dilatative (congestive) CMP*:
- *Primary*: Genetic factors are in the background (frequent association of autoimmunity-related HLA DR4 type). In presence of autoantibodies enterovirus (Coxsackie) infections non-replicating (modifying the DNS of the patient) forms are thought to be causative factors. A disease of relatively frequency (20-40/10 000 persons) and quick progression (death rate is 35% within 5-y, 70% in 10-y). During its development the ventricular wall becomes thinner, thereby the EF may decrease to 20-15%, the cardiac output quickly falls, symptoms (rhythm abnormalities, ventricular wall thromboses) of congestive heart failure appear at early phase.
- *Secondary*: (rather frequent abnormality, with slower progression)

  Old age (complex etiological factors)

  Deficiencies (thiamine-deficiency, Se-deficiency, protein-calorie malnutrition)

  Toxicoses (chronic alcohol, cocaine, amphetamine, Co, cyclophosphamide- and antracycline-type cytostatic substances)

  Metabolic diseases (diabetes mellitus, gout)

  Endocrine disorders (pheochromocytoma, hyperthyroidism, gigantism-acromegaly)

  Ischemic CMP (= coronary disease, ischemic heart disease)

  Infections (rheumatic fever, tuberculosis, syphilis, spirochetes, rickettsia)

  Pregnancy (develops peripartally, may appear repeatedly in new pregnancy)

  Neuromuscular, connective tissue, autoimmune diseases (Duchenne dystrophy, systemic lupus erythematodes = SLE, progressive systemic sclerosis = PSS)

- *Hypertrophic CMP*: It may join severe septal hypertrophy (asymmetric, obstructing ejection), or may be generalized non-obstructive hypertrophy. The ventricular compliance (and diastolic filling) is low in both forms, high EDp and venous pressure are necessary for ventricular filling. Its occurrence is usually familiary type, but it may also develop secondarily adjoining GH overproduction. Most often it affects males over 30-y, occasionally in latent form. The contraction force is high (EF near 100%), the ventricular pressure, usually together with the systolic blood pressure, are high. Ischemic ECG-signs or angina pectoris may be present even at rest. Apart from a tendency for collapse, rhythm abnormalities and fatal ventricular fibrillation may adjoin, although the progression is slow.

  Besides the primary (genetic) forms the secondary forms (hypertension, aortic stenosis, mitral insufficiency, aortic insufficiency) are more frequent.
- *Restrictive CMP*: Due to a rigid endo-/myocardium the diastolic filling is insufficient, an increase of filling pressure (venous congestion) is unavoidable. The primary form is rare (in Africa it is relatively more frequent). It is usually accompanied by eosinophilia. Necrotic, thrombotic, fibrotic forms are known. Secondarily infiltrative abnormalities (e.g. tumor, collagen, amyloidosis, sarcoidosis, hemochromatosis, carcinoid, irradiation) are its most frequent causes. Resembling constrictive pericarditis, the disease has very quick progression (mortality rate is about 35-50% within 2-y). Ventricular congestion and frequent thrombus formation make the prognosis even poorer.
- *Arrhythmogenic right ventricular dysplasia*: It is an inherited fatty/fibrotic degeneration of the right ventricle. It might be associated with sudden cardiac death (arrhythmia) of seemingly healthy sportsmen under the age of 25-y.

RATE AND RHYTHM DISORDERS OF THE HEART (cf. ch. A1):

Besides stroke volume, the other determinant of cardiac output is heart rate. Its abnormalities may be due to changes of frequency (bradycardia, tachycardia), or to anomalies of rhythm (arrhythmias).

- Disorders of heart rate that limit cardiac output: In case of extreme **bradycardia** the stroke volume cannot be increased proportionally to normalize and even less to increase cardiac output. A 25-30 heart rate may produce enough cardiac output at most for survival in supine position, but not for any physical activity (e.g. Adams-Stokes syndrome). In contrast, extreme **tachycardia,** due either to hyperactivity of a nomotopic or heterotopic pacemaker center (e.g. pheochromocytoma, nodal/ventricular tachycardia, ventricular flutter), or to a reentry mechanism (e.g. paroxysmal tachycardia in WPW syndrome). Such tachycardia may suppress the time and extent of ventricular filling. Besides, due to the short diastolic time the coronary blood flow decreases and the myocardial contractility becomes weaker. All these decrease the stroke volume as well as the cardiac output and blood pressure. Maldistribution of the cardiac output leads to severe muscle weakness. The maintained venous return and poor ventricular filling lead to congestion in the big veins, including the pulmonary vein and thereby induce dyspnea. Due to dyspnea, the alveolar ventilation increases, hypocapnia develops – this, together with the hypotension will be responsible for the concurrent brain dysfunctions.
- Simple disorders of **rhythm** do not necessarily limit the cardiac output, but they produce uneven stroke volume. In extrasystole the contraction of the early beat is stronger but the corresponding stroke volume is smaller (this is not necessarily noticed). During compensatory pause bigger filling, bigger stroke volume and noticeably stronger pulse are characteristic. In conduction abnormalities a missing ventricular beat may also remain unnoticed, the greater stroke volume (and pulse) will be noticed at the next beat. Unless these appear in great numbers, these usually do not influence the cardiac output. Very frequent abnormalities, however, (e.g. absolute arrhythmia) lead to uneven cardiac output and disordered character of the circulation.
- Combined disorders of rate and rhythm (e.g. tachyarrhythmia absoluta) may result in severely defective cardiac output. The most serious case is ventricular fibrillation (the individual ventricular myocardium fibers exhibit continuous incoordinated contractions without ventricular contraction and stroke volume) leads to a complete stop of circulation – this is the most frequent cause of acute heart failure and cardiac death. The other frequent cause is diastolic stop of heart function (no sinus pacemaking, no escape rhythm, and the circulation stops in diastole).

2.1.2. HEMODYNAMIC CHANGES IN HEART FAILURE

Although the hemodynamic changes in various forms of heart failure are similar to a great extent, (differences are obvious rather in the extent of increase of sympathetic tone and the measures of manifestations) these changes can be demonstrated most simply in the context of decreased contractility: due to a decreased EF the stroke volume would decrease and as a compensation increased diastolic filling soon becomes necessary. The diastole becomes prolonged, the early fast (active) dilation phase becomes insufficient, the role of the atrial contraction becomes more important and the blood must enter the heart with a higher pressure from the veins. The high venous pressure is partly the effect of increased level of circulating catecholamines, partly a consequence of increased blood volume (on the long run increased salt- and water-retention and increased formation of blood elements are to be expected). Despite the enhanced venous return and higher filling pressure, the defective contraction forwards only less blood to the arterial side (decrease of the „effective arterial volume"). At the same time the peripheral resistance in the arterial vessels increases (partly due to circulating catecholamines, partly due to activation of the vasoconstrictor RAAS system due to decreased renal perfusion and consequent salt- and water-retention – a part of salt and water, together with Ca are deposited in the vascular wall), decreasing the capacity for vasodilation. The rise in peripheral resistance (afterload) does not help the work of the ventricles, it makes it rather difficult. Upon even mild physical exercise not only the systolic, but also the diastolic pressure increases. The resting blood pressure tends to be higher and decreases only when – at the end-stage – the cardiac output is explicitly insufficient. The circulating catecholamines have stronger effect on pacemaker activity than on contractility and tachycardia easily develops. The speed of tissue perfusion becomes slower, stagnation type hypoxia may develop with cyanosis, although the gas composition of the arterial blood is normal for long, or the pulmonary congestion may cause dyspnea and the consequent respiratory changes may even induce hypocapnia.

2.1.3. CLINICAL SYMPTOMS IN HEART FAILURE

The clinical consequences of heart failure form two main groups: *backward failure* and *forward failure* symptoms. The symptoms of backward failure are due to increased venous pressure and congestion. The explanation of the forward failure symptoms lays in (transient, mild, or sometimes more severe) hypoperfusion. The actual symptom always varies depending on which ventricle is affected (Fig. 2.11.).

In the clinical practice the symptoms often appear in a mixed fashion, although sometimes with different severity. The explanation lays in the interdependence of the two ventricles, or simultaneous (though not necessarily similarly severe) damage of the two ventricles.

In case of *backward failure of the right ventricle* the high pressure is pronounced in veins of the systemic circulation. The symptoms of venous congestion are congested big liver and spleen (meteorism, anorexia, nausea, cachexia, ascites, hypersplenic hemolytic anemia, jaundice may join) and also edema (anasarca) of the lower extremities (in bedridden patients this may be in the sacral region). The explanation of edema development: the high venous pressure is transmitted without difficulty to the capillaries, the high intracapillary hydrostatic pressure causes imbalance of intra- and peri-capillary hydrostatic and oncotic pressures and enhances salt and water extravasation. So much fluid enters the interstitial space that the lymphatic system cannot carry this away, cannot compensate. Salt and water accumulate in the interstitium, resulting in pitting edema. In order to notice it, about 1-1.5 L fluid accumulates. Since this volume is missing from the plasma, it would be important to refill the plasma space by enhanced salt- and water-retention (decreased renal blood flow, decreased GFR and enhance tubular reabsorption by secondary hyperaldosteronism). In contrast, in supine position (at night) the intracapillary hydrostatic pressure decreases, the direction of flow is altered: more fluid returns to the capillaries and the atria, activating the ANP, BNP and causing nocturia and decrease of edema. The problem of edema is that in edematous tissues the transport of oxygen and nutrients from the capillary to the tissues becomes inhibited, also the backward transport of waste-products. On the calf and distal parts of the body even bullous edema may develop with necroses and infections. The congestion is also observed in the areas of v. portae and it may severely inhibit the absorption of nutrients.

Backward failure of the left ventricle leads to high pressure in the pulmonary veins and this, due to characteristics of the lung vessels, (ch. 2.6.6.) causes increased pressure in the whole pulmonary circulation. The pulmonary congestion enhances the elastic resistance of the lung, the work of breathing, the excitation

of juxta-alveolar stretch-sensitive J-receptors and causes dyspnea. Development of dyspnea does not necessitate presence of arterial hypoxia or hypercapnia, moreover, the feeling of dyspnea increases ventilation and often causes hyperventilation-induced hypocapnia and alkalosis. Dyspnea quickly worsens even for moderate muscle activity, since the necessity to increase circulation needs disproportionally high acute diastolic ventricular extension and increase in venous congestion. At capillary level salt- and water-efflux is also present: most of it remains in the interstitium, some gets into the alveoli, causing bronchial rales („wet lung"). In chronic pulmonary congestion cells may also get into the interstitium (induratio brunea pulmonum), but this is still not pulmonary edema. The good lymphatic system prevents salt- and water-accumulation. Wet lung is not equal with real acute pulmonary edema. In real pulmonary edema (cf. ch.3.) the capillary permeability also increases (local or central neurogenic factors, local toxic effects, etc.): in this case protein and many cellular elements leave the capillaries, the edema fluid becomes foamy and colored, it cannot be carried away by the lymph, the fluid gets into the alveoli and causes acute respiratory failure. On the basis of left ventricular failure this dangerous situation develops only on the basis of extremely severe acute or end-stage chronic heart failures (these usually cause also cerebral hypoxia). In left ventricular failure an early and frequent disorder of the regulation of respiration is Cheyne-Stokes breathing (and sleep-apnea syndrome) (ch. 3.1.) – these might be explained by the congestion in pulmonary capillaries, poor alveolo-capillary gas exchange, and also the fact that due to the longer circulation time changes of the composition of the alveolar air provide only slowly some signals to be corrected by the activity of the respiratory center.

Forward signals of the right ventricular failure cannot be appreciated by themselves, since they are necessarily coupled with insufficient filling of the left ventricle and clinically show the symptoms of forward failure of the left ventricle. Eventual decrease of pulmonary circula-

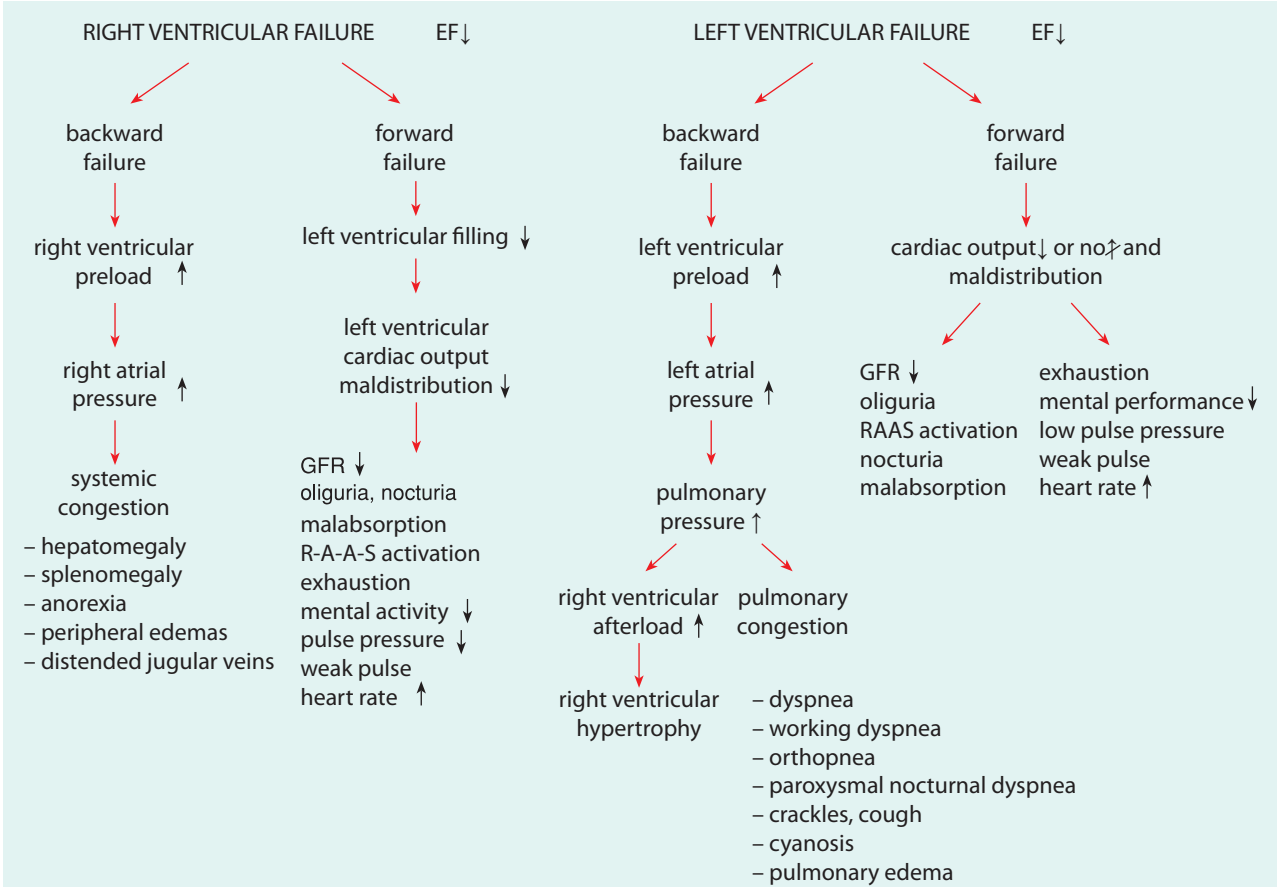

Fig. 2.11.: Backward and forward symptoms of right- and left-sided heart failure. Due to interdependence in practice these symptoms appear in mixed forms: tiredness, dyspnea, nocturia, anasarca simultaneously, but with different severity.

tion causes disturbances only in case of significant shift in ventilation/perfusion ratio, thereby leading to respiratory failure. Lasting deficiency leads to chronic cor pulmonale.

Forward failure symptoms of left ventricular failure derive from the fact that the level of cardiac output cannot be adjusted to the actual need. Some territories remain temporarily hypoperfused. This is promoted by the altered distribution of cardiac output: at some regions (muscle, kidney, splanchnic area, skin) the perfusion significantly decreases. The O_2-content of the mixed venous blood is lower than normal (the O_2-utilization increases) particularly during muscle exercise. Perfusion of the working muscles cannot increase according to the actual need, what is an important component in the deterioration of working capacity. The muscle weakness is particularly pronounced if the volume of circulating blood also decreases (diuretic effect, water lack, sweating, etc.), or if the distribution is abnormal (e.g. in a warm environment the perfusion in the skin increases instead of the muscle). In cases of acute worsening this easily leads to fainting-like symptoms: pronounced weakness in the postural muscles, with collapse, but without unconsciousness. Very characteristic is the daytime oliguria with nocturnal polyuria (= nocturia; due to daytime activity the renal perfusion and glomerular filtration decrease, the tubular reabsorption increases – in the inactive period renal perfusion and filtration are normalized, most of the anasarca returns to the circulation, thereby the venous return and atrial filling increase and natriuretic mechanisms are activated). Due to hypoxia of the villi of the gut the absorption decreases. The brain perfusion may also decrease slightly, although this can be explained partly by the hyperventilation and hypocapnia due to pulmonary congestion/dyspnea. Hypoperfusion of the skin (particularly if coupled with edema) increases the tendency for pressure ulcers.

In heart failure for enhanced salt-and water-reabsorption the RAAS is activated by constriction of the renal artery (high sympathetic tone), decreased renal perfusion, and participation of angiotensin II (AII).

In decompensated (combined) heart failure both the forward and the backward symptoms may be connected with the abnormalities of water spaces. Regulation of the water spaces is mainly the duty of the kidneys. The functional connection of the kidneys and the heart, the maladaptation by which in their abnormalities they respectively deteriorate the function of each-others, is described by the **cardiorenal syndrome.**

Activation of the *RAAS,* constriction of the renal artery, lasting decrease of renal perfusion and the participation of AII consequently evoke the production of reactive free radicals (ROS) in the kidneys, but these may cause damage to the parenchyma, the endothelial cells and the tubules. By the activated angiotensin-1-receptors the AII stimulates the NF-κB (nuclear transcription factor κB), that influences the proliferation and apoptosis of cells. By the mediation of all these and other growth factors the AII induces inflammatory changes of vessels, thereby induces chemotactic and adhesion molecules, inflammatory cytokines (TNF-α, IL-6, IL-1β) and further ROS production. Similarly, as the participating IL-1β, the RAAS enhances the sympathetic activity, too. The ROS inhibits the favorable effects (vasodilation, natriuresis) of NO. IL-6 enhances the production of angiotensin-1-receptor, and the cytokines may also stimulate renin secretion, too. In this cardiogenic state, that is finally a chronic systemic inflammation all these together and in interaction cause damage to renal functions.

The *sympathetic activity* which is also enhanced in heart failure increases renin secretion, and this, together with ROS leads to thickening of the intrarenal vessels. Noradrenaline also increases the production of cytokines, as well as the production of strongly vasoconstrictor NPY. These also contribute to the deterioration of renal functions.

AII is also produced in the heart. In the process of heart failure development, simultaneously with the deterioration of renal function, similar mechanisms induced by AII result in hypertrophy of the myocardium (remodeling process), also in morphological and functional damage of vascular smooth muscle and myocardial cells, and thereby contributing to the progression of heart failure.

In primary renal failure more or less the same systems are activated and promote the defective function of myocardium (ch. 5.5.2.). More and more data suggest that similar processes, with chronic systemic inflammation and simultaneous functional disorder of small vessels stands in the background of the progression of several organ dysfunctions, and in these processes the RAAS system is also involved.

2.1.4. FORMS OF HEART FAILURE

2.1.4.1. RIGHT-SIDED AND LEFT-SIDED HEART FAILURE

Failure of the two sides of the heart may happen in isolated form, in such cases the forward and backward failure symptoms of the given side appear in a combined way. Hypertension, ischemic heart disease, myocardial infarction and its late consequences, any vitium of the left side,

affect primarily the left ventricle. In contrast, pulmonary abnormalities (e.g. fibrosis, COPD = chronic obstructive pulmonary disease) and anomalies of pulmonary circulation (e.g. pulmonary embolism, any vitium of the right ventricle) will affect the right ventricle (cor pulmonale). The frequent situation that chronic failure of one heart side is rather quickly followed by failure of the other side is called *interdependence*. Left ventricular failure causes pulmonary congestion, pulmonary hypertension, finally exhaustion and failure of the right ventricle – in such cases the dyspnea as the originally dominant symptom is more and more accompanied by anasarca. Primary contractility or emptying insufficiency of the right ventricle leads to right ventricular hypertrophy and/or dilation, therefore the ventricular septum becomes shifted and pressed into the left ventricle, the shape and filling of the left ventricle becomes disturbed, excentric hypertrophy of the left ventricle develops, finally the left ventricle also fails and its EDV increases. Symptoms of the failure of the two ventricles often appear in a mixed form (although the severities may be different) the patient may have dyspnea and anasarca simultaneously. In such cases the decrease of pulmonary blood content and attenuation of dyspnea appears to be more important – the patient sits on the edge of the bed, supported by cushions, with legs hanging by the bedside: according to an old saying „better to have a wet foot than a wet lung".

2.1.4.2. SYSTOLIC AND DIASTOLIC HEART FAILURE

Basically, the cases of decreased contractility are called as systolic heart failure, those of filling abnormalities due to difficult expansion called as diastolic ones. With increasing age first usually the diastolic expansion decreases (decreased compliance), the filling pressure becomes high, later follows the decrease of contractile force. An appropriate filling pressure is important mainly in diastolic heart failure: in these cases, the attenuation of central venous pressure (e.g. deceasing the blood volume by diuretics) leads to decrease of cardiac output. Substances that increase the contractility can attenuate the systolic deficiency.

2.1.4.3. STAGES OF HEART FAILURE

In most cases the stage according to the classification of the New York Heart Association ("NYHA") is considered, according mainly to left ventricular failure:

- healthy person: good tolerance of exercise, dyspnea only during extreme work
- work induces dyspnea, palpitation, exhaustion, eventually angina pectoris – at the beginnings these are moderate, but they become more pronounced even at small work (NYHA I-III categories are used to judge working ability)
- resting dyspnea, symptoms without physical exercise (NYHA IV)
- orthopnea: dyspnea at supine position, the patient sits at the edge of the bed, and uses accessory respiratory muscles
- paroxysmal dyspnea (usually during night), „asthma cardiale": severe acute states, pulmonary edema is possible

It is rather inaccurate how the **„decompensation"** expression is used in the clinical practice: the severity is judged according to the consequences of venous congestion in the circulation, to the level of dyspnea, and to the measure of decrease in physical working capacity (generally the forward- and backward-failure symptoms). The expression indicates that in „compensated" state there is already a basic abnormality that could limit the cardiac output, but the patient can still compensate this (e.g. by increasing the EDV) without having severe forward or backward failure symptoms upon moderate physical activity. In the process of decompensation these symptoms become increasingly severe at moderate work („subcompensation"), finally they will be severe even at rest. If the capacity for compensation is insufficient (e.g. need for very high cardiac output, negative inotropic effects, hypoxia, decreased venous congestion due to volume loss), decompensation develops. This becomes critical with lasting and significant fall of the cardiac output below normal level (cardiogenic shock can be expected), or the pulmonary congestion is severe enough to cause pulmonary edema (in this case even the brain perfusion may decrease or brain hypoxia of other origin can provide neurogenic component for increased permeability of pulmonary capillaries).

***Muscle work** in subcompensated patients:* The earlier compensated patient starts exhibiting symptoms of decompensation. The preload increases (due to the venous tone and the rise of circulating volume). The sympathetic activity also increases, but it elevates the frequency rather than the contractility, and contributes to a rise in afterload and to increase in TPR that cannot be resolved by vasodilation. The cardiac output hardly increases, but

systolic and diastolic (!) blood pressure rise strongly and normalizes slowly after work. If the venous return is high already at rest and cannot increase sufficiently, or some vasodilator effect attenuates the venous return, the cardiac output cannot increase despite tachycardia (this tachycardia ceases slowly after work), the rearrangement of the decreasing cardiac output quickly leads to muscle hypoxia, exhaustion and consequent collapsing follows. This is not the same as the vasovagal syncope (ch.2.2.1.), rather collapsing due to muscle weakness (brain blood flow is less affected): lasting orthostatic type blood distribution is not necessary, unconsciousness is not characteristic – in fact the forward failure becomes more pronounced.

Exhaustion is one limit of muscle work. The other, slightly earlier observed limit is *dyspnea*. This is due to fast increase of diastolic left ventricular volume that is needed even for a minimal increase of stroke volume, therefore the pulmonary congestion steeply increases. (N.B. dyspnea may develop also in athletes, but much later, when the ventilation and respiratory work is elevated without severe congestion in pulmonary vessels). Since the work of the heart increases, but not its oxygen supply, during muscle work diffuse oxygen lack of the myocardium (affecting mainly the subendocardial layer) may develop often causing *angina pectoris*.

FROM COMPENSATION TO DECOMPENSATION

Without compensation, failure of the ventricles would lead to severe decrease in cardiac output. In order to survive, the EDV needs to be increased together with the EDp. This is secured by an increased venous pressure and congestion in the central veins, and it means the first step in compensation: the drop of cardiac output is prevented. However, the distribution of blood in the circulatory system is altered. More blood is congested in the venous system, due to the congestion the intracapillary hydrostatic pressure increases leading to edema formation. On the other hand, at the arterial side the effective circulating volume decreases, inducing maldistribution of cardiac output (decreased flow to muscle, skin, kidney, splanchnic system, with activation of the sympathetic system) and also increasing volume retention by secondary hyperaldosteronism. This would lead to extreme hypervolemia and edema formation. In order to counteract this, during rest in supine position (at night) the venous congestion and edema formation decrease, interstitial fluid enters the capillaries, the increased blood volume and venous return act at the atria/ventricles, activate ANP and BNP and suppress tubular reabsorption, thereby the total blood volume becomes normalized.

This suggests a balance between volume retaining (RAAS, catecholamines) and volume loosing (ANP, BNP) mechanisms, securing a compensated state. Nevertheless, the cardiac output cannot be increased as much as normally, the balance cannot secure normal heart functions (= subcompensation). With time, however, an imbalance develops: the level/efficacy of the ANP/BNP system becomes insufficient and in the gradually deteriorating decompensation muscle weakness, edema, dyspnea and other symptoms become more and more severe (= decompensation).

Progression of subcompensation symptoms with the development of decompensation:

- at the beginning, with normal lifestyle there are no symptoms, these appear upon greater physical exercise (e.g. anasarca, dyspnea, early exhaustion)
- there are symptoms (e.g. anasarca) even at normal life activity, but at rest they disappear (e.g. nocturia antagonizes anasarca)
- the symptoms do not disappear even at rest, but pharmacologically can be treated (inotropic agents, diuretics)
- even pharmacological treatment is without effect

2.1.4.4. CHRONIC/ACUTE HEART FAILURE

So far the more frequent chronic forms of failure have been dealt with, when the capacity of heart function decreases gradually and the symptoms of decompensation develop step by step. In the clinical practice the most frequent causes of ***chronic heart failure***:

- ischemic cardiomyopathy
- ventricular hypertrophy due to high afterload (hypertension)
- thorax- and lung-abnormalities, pulmonary hypertension
- disorders of filling/emptying (e.g. forms of vitium), with or without hypertrophy
- degenerative abnormalities of myocardium (toxic, inflammatory, metabolic, etc.)
- primary cardiomyopathies

In cases of ***acute heart failure,*** the cardiac output and perfusion of tissues falls suddenly. The cause is either lack of filling (right: v. cava occlusion; left: pulmonary thrombo-, air-, fat-embolization), or because the ventricular contraction acutely becomes insufficient (diastolic stop of heart, III-degree a-v block, ventricular fibrillation, acute valvular damage, toxic/metabolic

myocardium damage, myocardial infarction, ventricular aneurysm), in other cases occlusion of the aorta, rupture of aneurysm, (dissecant aneurysm). Acute disorders of pacemaking or conduction are frequent causes of acute heart failure. The consequences depend on the severity of the disorder:

- severe brain hypoxia may lead to death within a few minutes (diastolic stop, ventricular fibrillation, Adams-Stokes syndrome)
- in less rapid cases (e.g. extensive myocardial infarction, toxic myocardium damage, extreme ventricular brady-, or tachycardia, extreme arrhythmia, subtotal pulmonary embolism) – in contrast to chronic heart failure – extreme acute muscle weakness and dyspnea may be followed by pulmonary edema and loss of consciousness
- in still less dramatic cases (particularly in acute myocardial infarction) „only" cardiogenic shock can be expected
- in the least severe form the forward failure symptoms of heart failure may be acutely worsening: e.g. in subcompensated patient a sudden decrease of circulating volume (bleeding, exsiccosis, strong diuretic-effect, heat-induced congestion in the skin = heat decompensation) evokes severe muscle weakness (collapse) with relatively moderate cerebral circulatory disorder (provided that the brain vessels are normal). It has to be distinguished from the ordinary fainting (collapse): this is the more severe abnormality in which simple change in body position (to supine) is not enough, the decompensation must be treated.

2.1.4.5. HEART FAILURE WITH LOW OR HIGH CARDIAC OUTPUT

Until now the mainly the ***low-output cardiac failure*** was analyzed. This is the most frequent form of heart failure, when increasing or even maintaining the cardiac output is difficult and its compensation is the primary problem to be solved.

There are, however, other forms, too: in ***„high-output cardiac failure"*** a continuously high cardiac output has to be maintained with the help of progressively deteriorating myocardial functions. In some cases, the *decrease of afterload* (e.g. vasodilation and hypotension in beri-beri or anemia), or *increase of preload* (e.g. shunt) induces continuously high stroke volume and high cardiac output. For this, higher pulse rate, and (at the beginnings) hypertrophy-induced high contractility may be coupled (in late phase the contractility rather decreases). With or without hypertrophy (but never with increasing compliance) rising EDV and EDp are characteristic. These are coupled with consequent venous congestion and signals of backward failure, although the cardiac output remains higher than normal for long, the arterial gas tensions remain normal, and the tissue oxygen-utilization is rather low as compared to normal. This – in some cases – may be coupled with redistribution of cardiac output and relative hypoperfusion of some tissues/organs (e.g. skin, muscle in anemia), as signs of forward failure. The most characteristic forms:

Anemia: In case of suddenly developing anemia the pulse rate increases, later rather the stroke volume. The way of increase in stroke volume: the tissue hypoxia and metabolic products (e.g. lactate, adenosine) induce vasodilation, and together with decreased viscosity it results in decreased peripheral resistance and speed-up of circulation (the decreased blood pressure must be compensated by enhancement of cardiac output). Due to the high venous return the ventricular filling also increases (dilation), as well as the stretch of the ventricular wall – this gradually leads to eccentric ventricular hypertrophy, increase of contractility and EF. However, in late phase the hypertrophy already results in relative ischemia (besides the anemic hypoxia), leading to degenerative changes and decreasing contractility. Still, the high cardiac output at rest must be kept up, and this (on top of increased cardiac output) must be maintained by further rise in EDV and EDp, as in heart failure by the Frank-Starling mechanism.

Shunt-circulation (congenital hemorrhagic teleangiectasia mainly in the liver, lung; obtained a-v fistula formation adjoining Wilms tumor; implanted fistula for hemodialysis): The hyperdynamic circulation is elicited primarily by the increase of venous return (the cardiac output may be two to three times higher than the resting cardiac output). Maintaining the high cardiac output takes place by the similar mechanisms as in the previous cases.

Beri-beri: Thiamine-deficiency causes vasodilation, faster circulation and enhanced venous return due to functional disorder of smooth muscles of vessels and sympathetic nuclei. In alcoholic cardiomyopathies and in cardiomyopathies refractory to digitalis/diuretics thiamine-deficiency has to be considered.

Hyperthyroidism: Vasodilation is caused by enhanced tissue oxygen need and enhanced need of heat loss. At the beginnings it may be coupled with high contractil-

ity, later the increase of EDV is more pronounced. Due to relative insufficiency of coronary blood flow, angina pectoris may adjoin. It is characteristic that in hyperthyroidism of elderly patients not the typical symptoms of hypermetabolism and tachycardia, but rhythm abnormalities, atrial fibrillation and decompensated heart failure dominate as first signs of the disease.

Pregnancy: In expectant women the resting cardiac output is about 40% above the normal resting value. In cases of pre-existing compensated heart failure, this may lead to decompensation.

Heat effect: Due to skin vasodilation the peripheral resistance may decrease, the circulation becomes hyperdynamic. In otherwise compensated patients the defense against heat may evoke acute decompensation.

Hypoxia: In chronic pulmonary diseases the low O_2-tension leads to polycythemia and hypervolemia, these cause moderately increased venous return. This is already not characteristic for cor pulmonale.

Liver diseases, cirrhosis: Shunts (e.g. porto-caval anastomoses) may develop in the liver and systemically. Vasodilator substances may also accumulate.

Obesity: Blood volume is great, also the venous return and the cardiac output is continuously high. It may be combined with decreased distensibility of the ventricle.

In these cases, apart from extreme situations (e.g. heat stroke), the clinical symptoms of heart failure are not accompanied by generalized insufficiency of circulation.

2.1.5. BASIC CONSIDERATIONS IN TREATMENT OF HEART FAILURE

Preferably the cause of the abnormality should be treated. It is important to normalize the rhythm. Depending on the abnormality the afterload may be decreased (ACE-blockers, Ca-channel blockers, central/peripheral antiadrenergic medication, direct vasodilators), in other cases the strength of contraction has to be increased (digitalis, β-adrenergic stimulants), and, if necessary, influencing the venous influx. In chronic heart failure diuretic drugs affect only the symptoms, they have no effect on the cause: salt and water will be lost not only from the interstitium but also from the plasma, thereby the venous return and the efficacy of the heart gets worse. They should not be used as primary factors of treatment. These drugs do decrease the venous congestion and the preload, but the high preload would be necessary for diastolic (over)filling to secure stroke volume. During diuretic effect, improving the symptoms of congestion are coupled with worsening the symptoms of forward failure (decrease of cardiac output, even cardiogenic shock). Diuretics may still be important in additional treatment: some salt and water may be lost from the arterial walls helping the decrease of peripheral resistance, besides decreasing the edema makes oxygenation of tissues easier. Recently in the clinical practice greater emphasis is put on decreasing the afterload (thereby decreasing the myocardial burden and oxygen need), and it appears paradoxical to use also β-adrenergic inhibitory substances (beside ACE-blockers). In severe *acute* cases, naturally most important may be the quick decrease of congestion and venous return (venesection, diuretics, etc. may be necessary).

2.1.6. AGE-RELATED CHANGES IN HEART FUNCTIONS

Similarly, as the peripheral muscles, although in a different degree, the myocardial muscles also show signs of atrophy: its structure becomes more fibrotic and there is lipid-accumulation. Both the contractility (EF) and the compliance may be negatively affected. As a result, increase of the filling pressure and the EDV can be expected. This may explain the frequent occurrence of exercise-induced dyspnea and anasarca (backward failure) and atrial fibrillation in elderly persons. If a decreased contractility dominates, more pronounced is the decreased capacity for physical exercise (forward failure) without anasarca. Although the pacemaker activity of the sinus node decreases with aging, the enhanced sympathetic activity that is used in compensation of the failing heart may lead to fast increase in heart rate or to slightly enhanced resting pulse rate, and due to the increased vascular resistance to elevation of blood pressure (both systolic and diastolic), which normalizes slowly and sometimes only partially after physical exercise. More frequent are the disorders of formation and conduction of impulses, and more common is the insufficiency of coronary blood flow.

2.2. PERIPHERAL CIRCULATORY FAILURES

Despite absolutely normal heart pump functions, the perfusion of peripheral tissues may still be insufficient due to some functional disorder of the peripheral part

of the cardiovascular system. The two main forms of these are collapse and circulatory shock. Both of them are acute abnormalities. In collapse the transient disorder of cerebral functions dominates, while in shock lasting and generalized circulatory disorder of other organs is characteristic, while the brain perfusion is less affected until the very end.

2.2.1. FAINTING (COLLAPSE), VASOVAGAL SYNCOPE, ORTHOSTATIC HYPOTENSION

Fainting is an acute circulatory failure with unconsciousness. It may be normalized spontaneously, *provided* that the orthostatic (upright) position of the body is ended. The evoking factors are multiple: pain, fear, unpleasant sensory effects, hyperventilation (and consequent hypocapnia-induced brain vasoconstriction, ch. 2.6.2) – these act not alone, the simultaneous orthostatic body position is absolutely necessary („in supine position fainting is practically impossible").

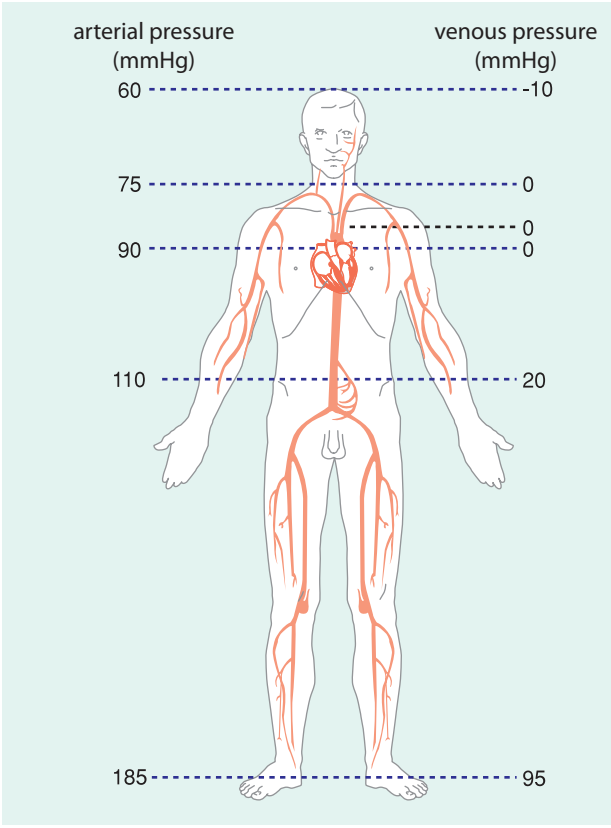

Fig. 2.12.: The vaso-vagal (vago-vagal) reflex. Inhibition of the vasomotor center activates the parasympathetic efferent mechanisms. The inhibition may be initiated from higher cerebral regions.

Quick and effective vascular adaptation to an orthostatic position is absolutely necessary both at the arterial and the venous side. In upright position the blood column produces a pressure gradient both in the arteries and the veins: the mean intracranial arterial pressure is significantly lower (about 60-80 mmHg) than 120/80 mmHg (at the level of the heart, i.e. 90-100 mmHg mean arterial pressure) while it is much higher (180-190 mmHg) in the arteries of the lower extremities (Fig. 2.12.). At the feet, and the legs such pressure without unchanged vascular tone would extend the thin-walled veins and would cause accumulation and decreased venous return of blood in the distal parts of the legs, causing a rapid decrease of cardiac output, arterial pressure and particularly that of the perfusion in the cerebral vessels.

Provided that the vascular tone changes quickly enough (Fig. 2.13.), such decrease in venous return and cerebral circulatory disorder should not happen. The adaptation must take place both at the arterial and the venous side by the help of fast sympathetic reflex-mechanisms originating from the appropriate baroreceptors.

Circulatory abnormality may be expected, however, if the adaptation capacity decreases for any reason (e.g. adaptation to immobilization, vessels of elderly persons), in various forms of idiopathic hypotension, and in any situation with physiologically low blood pressure (e.g. in pregnancy the normal blood pressure is 110/70 mmHg). In such cases in orthostatic position the brain perfusion can easily become insufficient and fainting may happen easily.

In the classic form of *vasovagal syncope* upon an increased pressure in the carotid sinus („vaso-") the afferent fibers of the vagal and glossopharyngeal nerves provide an afferent signal to inhibit – by reflex through

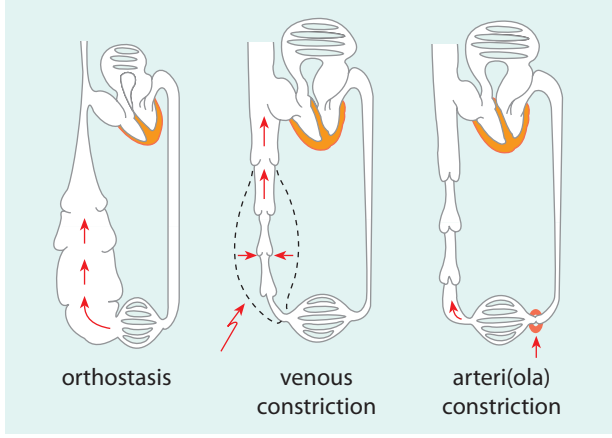

Fig. 2.13.: Variations of the arterial and venous pressure in orthostatic position.

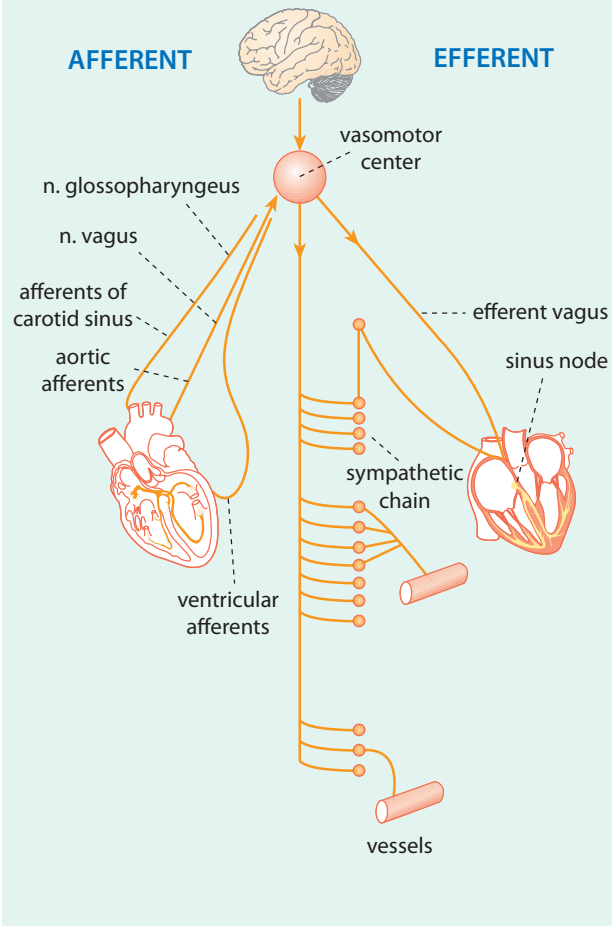

Fig. 2.14.: Adaptation of circulation to orthostatic position.

the vasomotor center – the efferent vagal fibers („-vagal") and induce a parasympathetic activation (bradycardia, vasodilation, drop of blood pressure, filling the blood reservoirs, decreased venous return). Syncope is a consequence of cerebral hypoperfusion due to pronounced acute hypotension (Fig. 2.14.). In other cases, the efferent part of the reflex may be activated by other afferentation: psychogenic effect from the cortex may activate the efferent part of the reflex (e.g. unexpected news from the death of a close relative may induce collapse) and big pain, various sensory effects may also evoke collapse.

Standing erect (soldiers!) for longer time, or upon stop following an exhausting physical activity with muscle vasodilation in a hot environment (which causes strong skin vasodilation) collapse may easily happen. Some reflexes, e.g. Valsalva (coughing, micturition, weight-lifting), carotid-compression, carotid-hypersensitivity usually act by altering the blood distribution (through parasympathetic activation). In other cases, decrease of circulating blood volume (hypovolemia), or anatomical blockade of venous return (varicosity, pregnancy) helps the development of collapse. Similar result can be observed if the sympathetic adaptability decreases due to defective pressor reflex, e.g. lasting bed-rest, immobilization (= desadaptation to orthostatic position), autonomic neuropathies (old age, alcoholics, diabetes mellitus, uremia, etc.), sympathectomy. Antihypertensive, diuretic and antidepressant drugs or starvation may also contribute to the development of orthostatic hypotension or collapse. The venous return and blood pressure decrease in all cases.

In the pathomechanism of the most frequent forms of collapse the decrease of intravascular volume and/or maldistribution of blood due to decreased venous return (with consequent decrease of tone in atria and big vessels) are the most important causative factors. Just prior to collapsing (prodromal phase of callapse) this induces decrease of stroke volume, blood pressure and cardiac output – while the reflexes originating from the stretch of vessel walls cause tachycardia, vasoconstriction, rise of TPR via sympathetic activation (without normalizing blood pressure), together with sweating of sympathetic origin. This hemodynamic state is accompanied by altered distribution of cardiac output and accumulation of blood in certain parts of the vascular system (capacity vessels, splanchnic vessels). Beside skin hypoperfusion (pale skin) the oxygen supply in organs of big oxygen need also decreases – this is particularly important in the skeletal muscles and the brain, resulting in weakness and disorientation. It is assumed that the brain hypoxia activates the efferent part of the vasovagal reflex (under other circumstances this would be activated by the intracarotid pressure and the excitation of afferent vagus), and this activation of the efferent vagus induces sudden vasodilation and bradycardia without improving the venous return (Fig. 2.15.). Thus, cardiac output remains low and in the dilated vessels the blood pressure starts falling precipitously (instead of the previous slow fall) – as a result weakness turns to collapse, disorientation to unconsciousness (when the brain tissue oxygen tension falls below 20 mmHg). Normalization of blood distribution (position change from orthostatic to supine one) and improvement of venous return (by the help of the normal heart) leads to quick normalization of circulatory parameters, improvement of brain perfusion to regaining consciousness. Lasting damage is not expected, except if the brain perfusion cannot be normalized (e.g. fainting in a fix orthostatic position) – in this case the most vulnera-

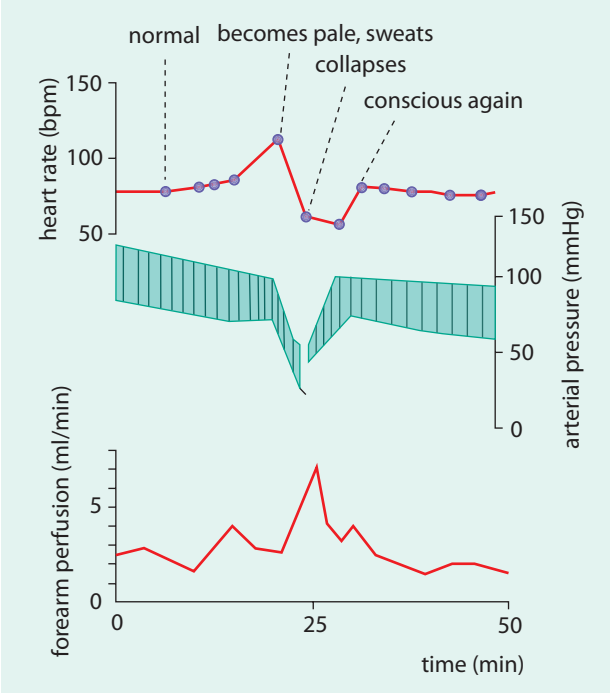

Fig. 2.15.: Hemodynamic changes in pre-collapse and collapse. Consciousness is lost when the slowly decreasing blood pressure starts falling suddenly. The parasympathetic activation is shown by skin vasodilatation (forearm perfusion rises) and bradycardia.

ble brain region, the cortex will be damaged and lasting decortication syndrome develops. Severe cerebral atherosclerosis may speed up the process, brain perfusion may decrease because of insufficient autoregulation. In patients with insufficiently treated hypertension the „set-point" of blood pressure regulation is shifted upwards and orthostatic collapse may develop at relatively higher absolute values of blood pressure.

While pain, psychological and sensory impulses promote the development of collapse by reflex mechanisms, in hyperventilation hypocapnia causes constriction of cerebral vessels and brain hypoxia, with early disorientation gradually growing to unconsciousness. In most cases this is also accompanied by parasympathetic activation and bradycardia. In hypoxic environment collapse develops more easily: increased ventilation and decreased peripheral vasoconstrictor tendency adjoins hypoxia (e.g. crammed, stuffy environment).

Quickly developing brain hypoxia and unconsciousness, resembling the orthostatic syncope, may also develop in cardiogenic disorders: in Adams-Stokes syndrome (3rd-degree a-v block, sinus arrest) and longer asystolia (the unconsciousness is often combined with convulsions and release of closing muscles), ventricular fibrillation, cardiac tamponade, acute valve disorders (e.g. prolapse of mitral valve due to rupture of papillary muscles in myocardial infarction), pulmonary embolism, etc. In these cases, the cardiac output, blood pressure and brain perfusion fall so much that the patient may die before the hypodynamic circulation could turn into shock. These should not be mixed up with simple fainting.

2.2.2. CIRCULATORY SHOCK

Circulatory shock means a dramatic decrease of tissue perfusion, thereby a capillary level deficiency of oxygen- and nutrient-supply and waste-product elimination, which may cause functional failure even in organs of life importance. Important clinical topics of the problem are also dealt with in ch. A10. The basis of ***circulatory shock*** is in most cases a pronounced and lasting decrease or maldistribution of cardiac output, with severe acute hypotension. The main feature of this abnormality is an insufficiency of peripheral circulation, that may develop in presence of intact heart functions, but may also be a consequence of severely defective pump function of the heart. In contrast to fainting this cannot be normalized spontaneously: without appropriate treatment it is lethal. Another difference from collapse that until the very end it is not coupled with unconsciousness: although in shock the blood pressure is low, but the patient is usually maintained in horizontal position and the brain perfusion is relatively safe.

2.2.2.1. EVOKING CAUSES AND FORMS OF SHOCK

- hypovolemic shock (blood loss, exsiccoses, fluid accumulations, burns, operation, trauma, anaphylaxis, etc.)
- obstructive shock (occlusion of big veins or arteries, pulmonary embolism, aortic aneurysm, pneumothorax with high pressure, pericardial tamponade)
- distributive shock (sepsis, shunt-circulation, acute pancreatitis, anaphylaxis, heat stroke, medullary damage, trauma /particularly polytrauma, ch. A10//, head-trauma, too fast removal of ascites fluid)
- cardiogenic shock (acute myocardial infarction, end-stage chronic/acute heart failure, severe abnormalities of rhythm, diphtheria toxin, cardiotoxins, cardiomyopathies, pericarditis)

2.2.2.2. PROCESS OF SHOCK DEVELOPMENT

The process can be well demonstrated by the example of hemorrhagic shock. Following relatively **smaller bleedings,** the blood pressure may transiently decrease, what is followed by increase in catecholamine levels, vasoconstriction, tachycardia, emptying of blood reservoirs and capacity-vessels, fluid movement from the interstitium to the plasma, faster return of venous blood, while the activation of RAAS also leads to salt- and water-retention – all these normalize blood pressure after the initial hypotension (Fig. 2.16.). The distribution of the temporarily low cardiac output characteristically changes: it decreases strongly in the skin, less in the muscle, kidney, splanchnic region, but there is hardly any fall in the coronaries and the brain. In the letter organs there is rather vasodilation, in contrast to the very strong vasoconstriction in the earlier mentioned areas (in these areas vasoconstriction – for a short period – may develop without causing severe consequences).

Short-term severe bleeding may remain without consequences in case of immediate transfusion, while even less severe (but not mild) blood loss may cause irreversible shock if the transfusion comes too late. In the latter cases hypovolemia and hypotension activate the same defense mechanisms as in case of small bleedings (Fig. 2.16.), but now more strongly and ineffectively: despite the vasoconstriction the blood pressure cannot be normalized (although tachycardia develops). Both vasoconstriction and hypotension remains for long. The main disturbance is caused in the microcirculation: through the narrow arterioles, with low pressure hardly any blood gets into the microcirculation, to the capillaries – generalized ischemia develops.

In circulatory shocks of other origin, the microcirculation and disorder of tissue metabolism change similarly as in hemorrhagic shock, proving that the basic process in all cases can be explained by the microcirculatory changes in the periphery (Fig. 2.17.).

2.2.2.3. PHASES OF SHOCK (Fig. 2.18.)

1. *Reversible:* Practically the same steps as in cases of small bleeding. Due to arteriolar constriction less blood gets into the capillaries and further to the veins. The venules are still open, at the capillary level the hydrostatic pressure is rather low, allowing fluid influx from the interstitium. *At the time being* there are *no severe consequences* of the slow microcirculation.

2. *Compensated (late reversible):* Gradually more and more, finally all capillaries dilate simultaneously in the microcirculation – this is due to tissue hypoxia and the accumulation of metabolic products (lactate, CO_2, adenosine, K^+, etc. leads to opening of precapillary sphincters, or even to some shunt-vessels). Thus, the total capillary cross-section may be even 10-times above normal, while due to the low blood pressure and arteriolar constriction significantly less blood reaches the capillaries. The intracapillary circulation is extremely slow, stagnating, the venules are narrowing. On the one hand, this leads to further decrease of venous return, on the other hand to intracapillary and pericapillary disorders.

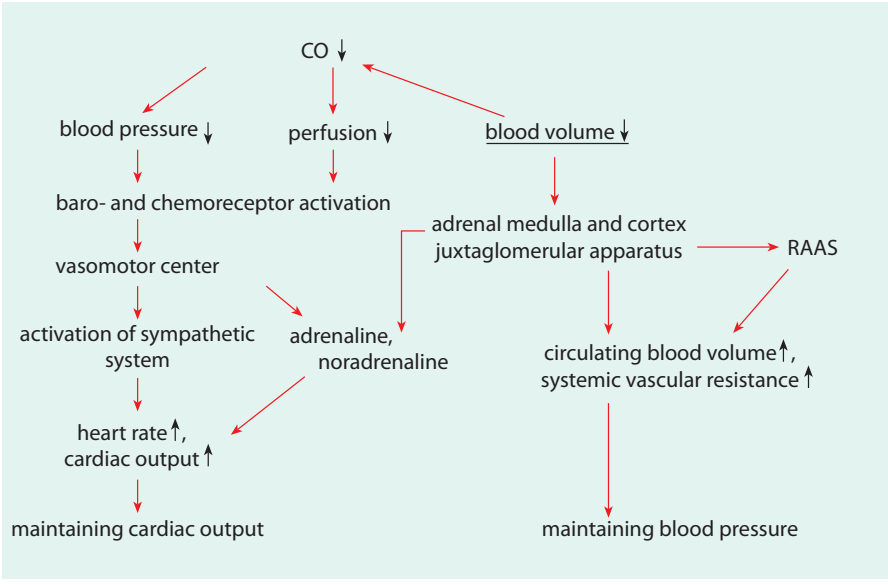

Fig. 2.16.: Modes of compensation of blood loss. The blood distribution also changes. (SVR = systemic vascular resistance)

3. *Progressive (refractory)*: The capillary endothelial-cells are damaged, and this induces local coagulation process. This is made easier because thickening of the blood in the capillaries (through the damaged capillary wall of high permeability salt and water gets into the interstitium, later macromolecules and cellular elements). The coagulation abnormality corresponds to disseminated intravascular coagulation (DIC). The microthrombi (sludge) obstruct the capillaries and further worsen the microcirculation. The pericapillary cells are hypoxic, the acidic products of anaerobic glycolysis accumulate, lysosomal enzymes are released from the damaged cells, macromolecules are split, osmotically active substances accumulate and draw water from the capillaries. The number of necrotic cells increases.

   Due to the fibrinolytic activity the capillary thrombi may be dissolved, but the released hemoglobin is not suitable for oxygen transport. Some of the locally released tissue metabolites have vasodilator effect, the so far constricted arterioles dilate, the normally closed shunt-vessels open up. Thereby the little blood reaching the microcirculation can quickly reach the venous side (this, at some places like the brain still secures some perfusion), but practically surrounds the local/peripheral capillaries. There is an inverse relationship between the amount of microthrombi and the reversibility of the process.

4. *Irreversible phase:* Besides the precapillary shunt-formation and postcapillary obstructions, the high capillary permeability, tissue ischemia, toxic substances (lysosomal enzymes, free radicals, cytokines, etc.), the coagulopathies (DIC + consumption coagulopathy; ch. 4.) and severe endothelial- and tissue-damages make the situation increasingly difficult. Death is result of parallel and interactive insufficiency of several vital organs („multiorgan failure") (see organ/tissue damages in shock). Exhaustion of the adrenal gland or additional infection may speed up worsening of the process.

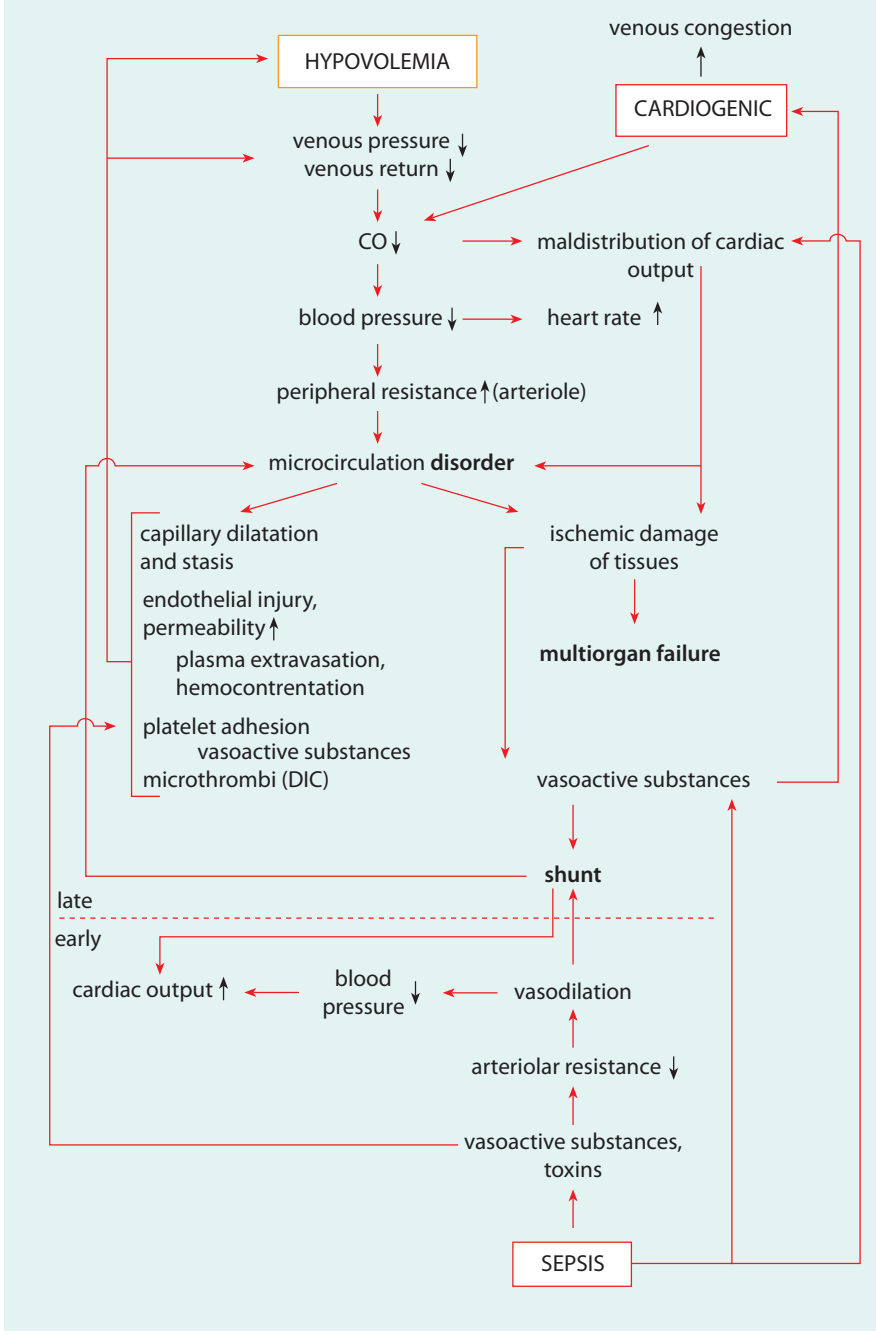

Fig. 2.17.: Hemodynamic and tissue changes in various forms of shock.

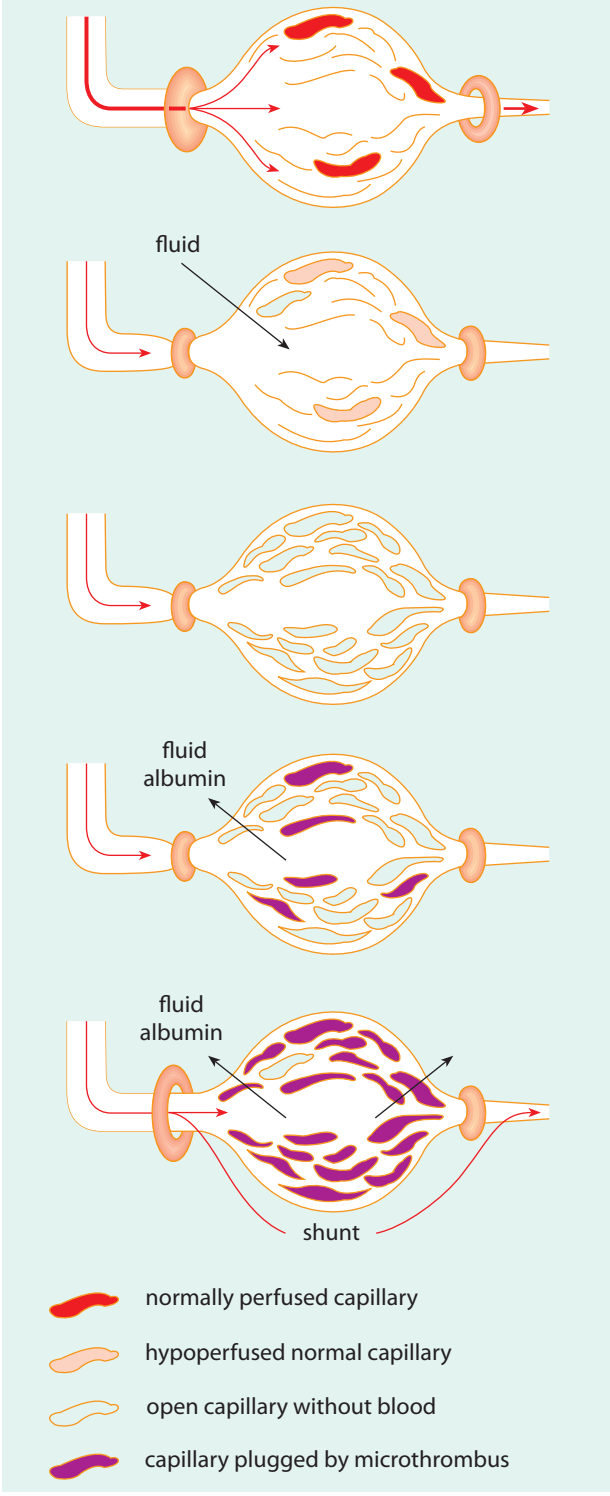

Fig. 2.18.: Changes of microcirculation in various phases of shock: Normally the arteriole is open, but only a few capillaries are perfused (in changing order), precapillary sphincters close the others, the venous outflow is not inhibited. In the first phase: arteriole constriction, the capillary perfusion and venous outflow decrease. In the 2nd phase the precapillary sphincters open up, but there is hardly any flow in the open capillaries. In the 3rd phase, due to the capillary congestion, some microthrombi appear, while in the 4th phase the microthrombi dominate, occlude perfusion – although the arterioles dilate, the blood gets to the veins through the opening shunt-vessels.

2.2.2.4. METABOLIC AND TISSUE DISORDERS IN SHOCK

Both supply of oxygen and nutrients for the cells and the cellular utilization of these are disordered. Tissue hypoxia leads to anaerobic glycolysis, acidosis, decreased ATP-formation and dysfunction of the energy-dependent enzymes (Fig. 2.19.).

Intermediary metabolism: The tissue glucose uptake decreases due to inhibition of insulin effects (catecholamines, cortisol, GH), while the gluconeogenesis and glycogenolysis increase, altogether the blood glucose level is high. The main source of gluconeogenesis is protein, the increased proteolysis is important mainly in the case of myocardium and respiratory muscles. Lipolysis is also enhanced, in the circulation the level of free fatty acids and that of triglycerides is elevated. Polyunsaturated fatty acids derive from the phospholipids of destroyed membranes – they can be peroxidated easily. Due to disorders of ion-transport Na^+ and Ca^{++} can easily enter the cells, while K^+ rather leaves the cells. The acidosis due to anaerobic metabolism enhances the disorders.

The *Na/K pump* disorder due to ischemia causes pathological change of resting and action potentials of cells, particularly in muscle and neural tissues. Besides Na, water also enters the cells and this further decreases the extracellular volume, while the intracellular „swelling" causes damage of cell membrane and lysosomes. The released *lysosomal enzymes* in the local and surrounding cells, in the interstitium and via the circulation even in faraway places can cause tissue damage and induce functional disorders. Rise of the *intracellular* Ca^{++}-level helps the activation of phospholipase and protease enzymes, thereby causes further *membrane-damage*, and worsens the mitochondrial ATP production, while the Ca^{++}-ATPase increases the ATP utilization. Disorder of mitochondrium-functions and damage of cell membranes by products of cell-damage induce ***inflammatory reaction***, and the phospholipase enzymes act similarly by local production of prostaglandins, thromboxanes, leukotrienes.

On top of this, the electron-transport in mitochondria is disconnected due to ischemia, the ischemia-induced rise of AMP and xanthine-oxidase activity promotes the production of ***reactive oxygen free radicals*** (ROS), while due to insufficient activity of superoxide dismutase and glutathione-peroxidase the elimination of these radicals becomes defective. The complement

activated in the ischemic tissues induces phagocyte accumulation and production of further free radicals. The lipid peroxidation products (arachidonic acid + lipoxygenase peroxides, leukotrienes, etc. produced by the help of free radicals) contribute to the destruction of intracellular and cell-wall membranes, mitochondrial damage, while prostaglandins and thromboxanes of the cyclooxygenase pathway contribute to the local inflammatory reaction in forms of endoperoxides. The free radicals influence the conformation of proteins, help formation of disulfide bridges and protein aggregation, inhibit the function of enzymes and other specific proteins. In case of carbohydrates cross-bridges are formed resembling glycosylation. Damages of DNA may destroy cells or may turn them to autoantigens.

Permeability is increased at different levels (cell/interstitium, capillary-permeability). In the interstitium besides lysosomal enzymes osmotically active degradation products and water, the interstitial edema extends the diffusion route for nutrients and gases. Phagocytes accumulate (together with free radicals, enzymes, vasoactive/inflammatory substances, proliferation factors). Increasing amount of protein-containing fluid leaves the capillaries, there is a further decrease of plasma volume and capillary perfusion. Local vasodilator substances (histamine, bradykinin, serotonin, thromboxanes) also enhance the capillary permeability. Worsening the capillary perfusion, hemoconcentration, local acidosis and hypoxia promote the damage of endothelial cells and the increase of capillary permeability – the damaged capillary surface contributes to the attachment of platelets and the intravascular activation of the **coagulation cascade**, production of microthrombi (sludge, DIC, ch. 4.4.3.2.). This, together with the cellular swelling contributes to the *inflammatory response* and leads to further effect of lysosomal enzymes.

In fact, there are positive feedback circles, in which changes of the coagulation cascade, decrease of circulating blood volume and the lysosomal enzymes, free radicals, inflammatory processes enforce the effect of each other and worsen the state of the patient.

2.2.2.5. DYSFUNCTIONS OF ORGANS/ORGAN-SYSTEMS/TISSUES IN SHOCK

Due to alteration of cardiac output the extent of damage in tissues/organs is not uniform. More severe are those damages that develop at areas of stronger vaso-

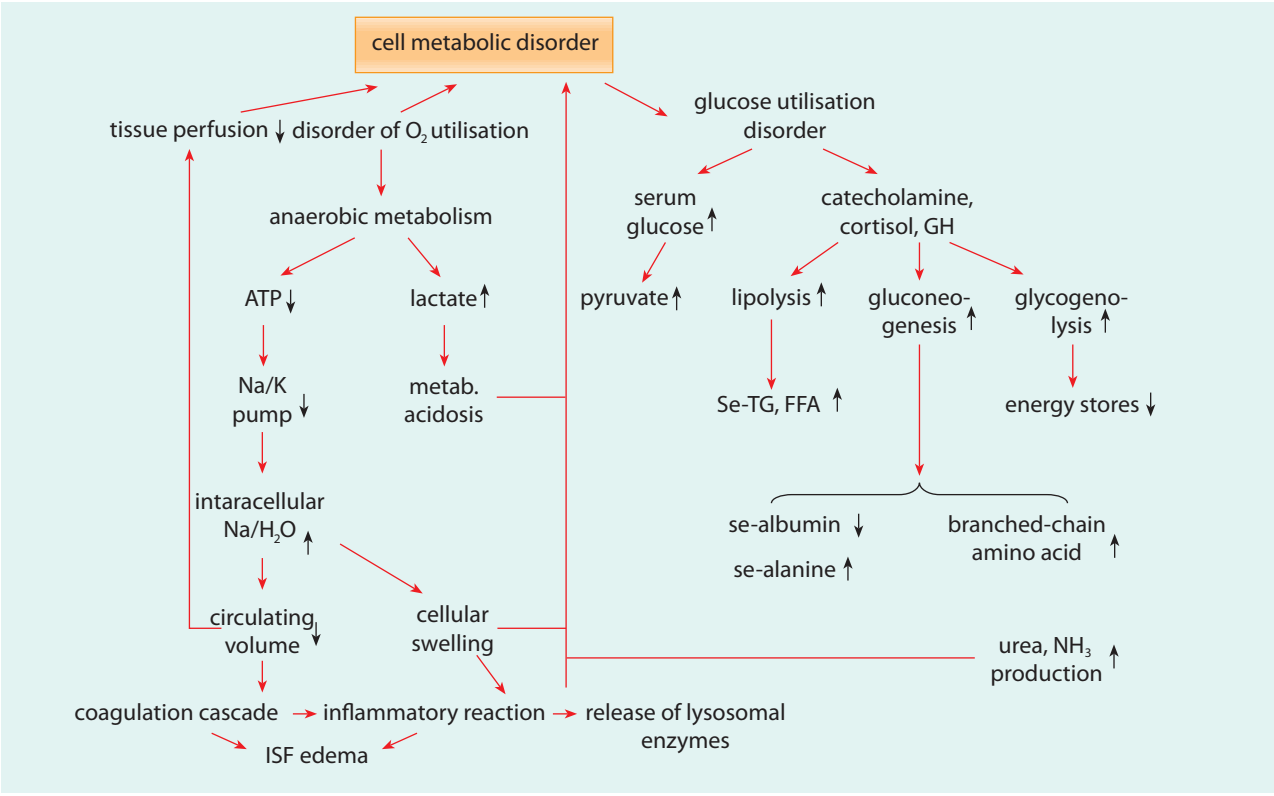

Fig. 2.19.: Alterations of tissue metabolism and their effects in shock.

constriction. ***Neither morphological, nor severe functional abnormalities develop in the brain*** (except if the vessels cannot dilate due to pre-existing sclerosis or if the patient remains in orthostatic position), thus, consciousness may be maintained until the end (except in shock adjoining direct cranial or brain damages). The coronary perfusion and heart performance are damaged also at late stages. In contrast, at other regions the disproportionally pronounced vasoconstriction leads to abnormalities earlier, particularly in the skin, the muscular system, the kidney, and the splanchnic system – from these areas significant amount of blood can be transferred to replace the blood lack at other regions.

More organs and organ systems may be damaged simultaneously, by different degrees, according to the origin of shock. These negatively counteract with the function of each-others, not only decreasing the possibility of compensatory steps, but eliciting vicious circles (positive feedback circles). For example, the low blood pressure and low cardiac output decrease the pancreatic perfusion, while from the hypoperfused pancreas substances are released that decrease cardiac contractility, this is followed by decreased heart function and cardiac output, etc. In the treatment of shock-induced multiorgan dysfunction/insufficiency (multiple organ dysfunction syndrome = ***"MODS"***, cf. ch. A.9. and A10.) there is a great importance of securing appropriate *ventilation*, *infusion* and *pump-function* (V.I.P.).

Gastrointestinal system, liver:
Almost one third of the resting cardiac output perfuses the gastrointestinal system and the liver – a significant part of it can be redirected during the redistribution of cardiac output. Similar redistribution may also be observed during physical exercise, but in shock this appears earlier, becomes more severe and more lasting.

The perfusion of the gastrointestinal system decreases, but due to the characteristic change of microcirculation the mucosa appears to be congested with smaller bleedings in the mucosa and submucosa. The congestion and slow perfusion rate particularly strongly affects the apical parts of the villi (Fig. 2.20.), with less influence on the secretion in the Lieberkühn-crypts, therefore the secretion may be maintained, but not the absorption. This initiates significant loss of fluid towards the lumen, in the congested bowel-content bacteria and toxins may accumulate. At the beginning this bowel congestion is coupled with high motility, with large amount of occasionally bloody diarrhea, later rather the ischemia-induced hypomotility dominates (cf. non-occlusive mesenterial ischemia, Fig. 7.10.). The changes may be particularly pronounced in elderly patients, when the sclerosis of the mesenterial arteries worsens the situation. Such alterations of the gastrointestinal tract may turn lethal the otherwise non-lethal shock. Passive translocation of bacteria and passive entry of endotoxins through the ischemic gut wall further aggravate the clinical picture.

Decreased pancreatic perfusion may increase the release of protease enzymes. The myocardial depression factor (MDF) oligopeptide from the local destruction of proteins gets into the circulation, decreases the cardiac contractility and initiates a vicious circle, bringing a cardiogenic component into the peripheral circulatory failure.

In the liver centrilobular necrotic zones are formed due to this hypoperfusion induced hypoxia. Further damaging lysososomal enzymes may also be released from here. The detoxifying function of the liver (including detoxification of MDF) decreases, the bilirubin metabolism is abnormal, liver failure, subicterus (mild jaundice) may develop.

Kidneys:
The renal blood flow (RBF) has ca. 20-25% participation from resting cardiac output. In everyday life (exercise, heat exposure, etc.) this may transiently be decreased without morphological or significant functional damage. In shock, however, decreased perfusion of

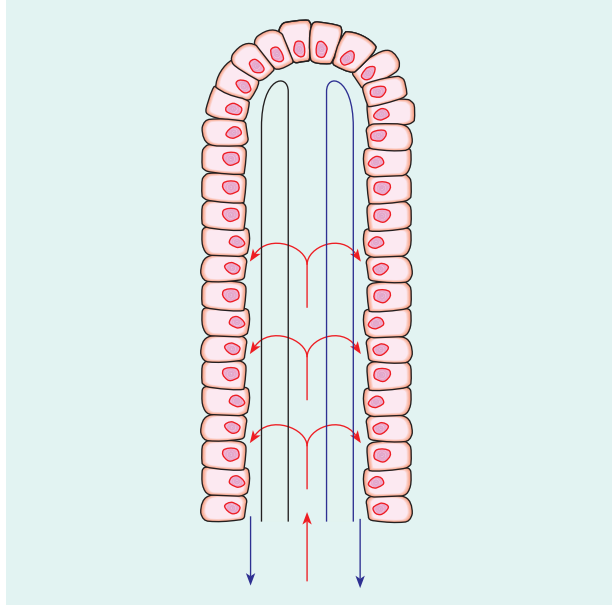

Fig. 2.20.: In case of slow villus perfusion the oxygen diffuses from the central artery to the veins (countercurrent flow), as shown by the arrows, the blood reaches the tip of the villus, but without enough oxygen – there is severe hypoxia at the tip of the villus.

the kidneys (particularly the cortex) may appear earlier, may be more lasting, stronger, and may cause functional and morphological damages (Fig. 2.21).

For the development of shock-kidney the decrease of renal circulation is severe and affects not only the glomerular filtration (although this is strongly affected, with shunt formation between the vas afferent and vas efferent), but the tubular oxygen supply in the region of the second capillarization is also defective. Due to tubular damage, obstruction and backleaking, most of the filtrate gets back passively to the systemic circulation – oligo-anuria follows with hyposthenuria due to tubular damage, and with insufficiency of renal excretory function. Therefore, in the clinical practice this is often named *extrarenal uremia*, pointing to the the fact that the kidney is originally normal, uremia still develops. The pathological picture corresponds to the acute tubular nephropathy (ATN) (ch. 5.5.3.3.): the cortical zone appears to be more strongly affected (it is practically bloodless), while in the medullary zone symptoms of congestive microcirculation abnormality dominate. The morphological changes of glomeruli may be moderate. The tubular disorder may also be reversible, provided there is no damage of the basement membrane (tubulorrhexis) – in such cases the tubular cell regeneration may be reached, but in the meantime dialysis treatment is necessary. In the course of such normalization of tubular functions first hyposthenuric polyuria develops (= sign of normal glomerular filtration with defective tubular function), later practically normal renal excretory function may be seen, demonstrating normalization of tubular functions.

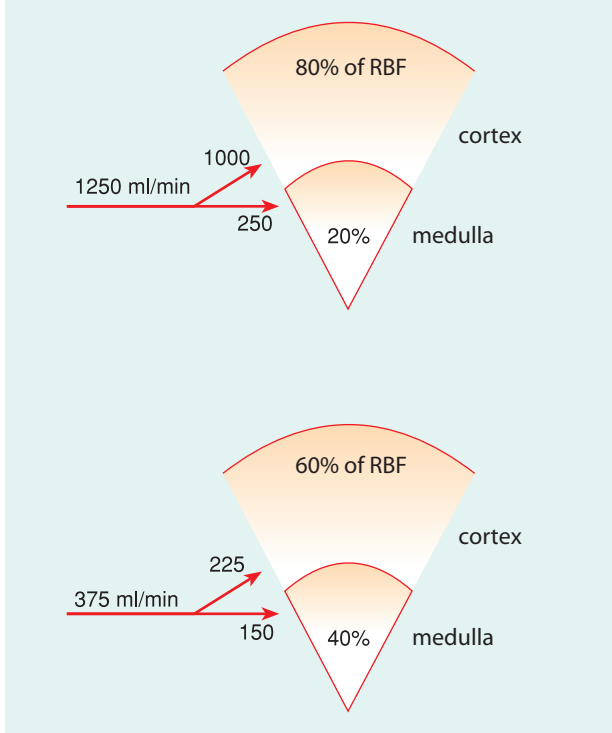

Fig. 2.21.: Renal blood flow normally (A) and in shock (B) when the RBF decreases and the distribution between the cortex and medulla changes: particularly big decrease in the cortex.

Heart muscle:

If the mean arterial pressure falls below 70 mmHg (and the diastolic pressure below 60 mmHg), the coronary blood flow decreases (cf. dependence of coronary perfusion on diastolic pressure and time), the coronary perfusion decreases even in non-cardiogenic shock. In the process of shock this is a relatively late step. At the beginnings coronary vasodilation compensates the fall in blood pressure, although the shorter diastolic time (due to tachycardia) is not favorable. Finally, the coronary blood flow still falls, causing first defective oxygen supply to the endomyocardial areas, later the ischemia is transmural, finally small subepicardial bleedings may develop. The MDF accumulating in the plasma, together with lysosomal enzymes and eventually some direct toxic substances (e.g. diphtheria toxin) inhibit the contractility. Similar consequences can be expected from a decrease in number of β-receptors, what is characteristic in cases of lasting myocardial ischemia.

The fall in coronary perfusion induced by hypotension and tachycardia and the consequent ischemia decreases the amount of contractile myocardial mass, further suppressing the left ventricular function, further decreases blood pressure and coronary blood flow, i.e. forms a vicious circle, making the situation more severe by further disturbing the microcirculation of the coronary region (Fig. 2.22., Braunwald spiral).

In cardiogenic shock the process is *ab ovo* accompanied by a decreased contractility, either acute myocardial infarction, either ventricle-aneurysm is in the background, or end-stage chronic heart failure. The EF is very low and normal cardiac output cannot be secured even with extreme EDV, thus the perfusion of peripheral tissues has a lasting deficiency.

Lungs:

Although the perfusion of the bronchial artery decreases, this is not the main explanation of the shock-induced pulmonary changes, which may develop even without direct damage (eventually shock-inducing burning trauma, smokes, chlorine-gas, etc.) of the lung (Fig. 2.23.).

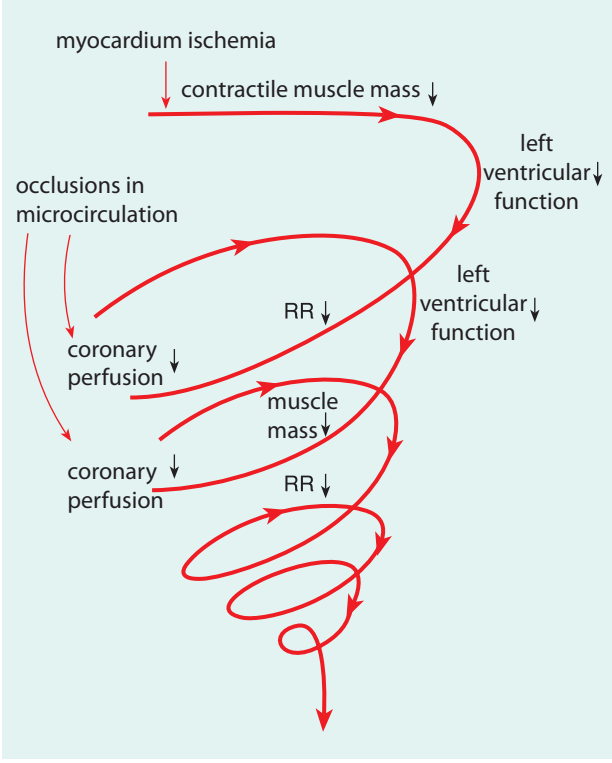

Fig. 2.22.: Worsening of coronary-perfusion and contractility leads to vicious circle (Braunwald spiral).

In early phase of shock (due to lactate accumulation?) tachypnea develops, due to the superficial breathing the dead-space and slightly also the alveolar ventilation increases. However, since in superficial ventilation the number of alveoli with atelectasis increases, the ventilation/perfusion mismatch becomes more pronounced. At this level there is maximum *partial* respiratory failure: the carbon dioxide tension rather decreases, while hypoxia develops.

By the pulmonary artery, from the circulation phospholipase enzymes, prostaglandins, thromboxanes, leukotrienes, lipid-peroxidation products, cytokines, vasoactive substances (bradykinin, histamine, serotonin) and substances derived from DIC can get here. These damage mainly the capillaries of the pulmonary circulation, inducing obstructions, dilations, endothelial damage, permeability increase, local inflammatory reactions. In the pulmonary capillaries there are microthrombi and platelet aggregation. Endotoxins reaching this region act particularly strongly, partly explaining that in septic shock the pulmonary changes are very pronounced, though in sepsis the amount of other humoral factors is also high.

Upon the gradual rise of the permeability of alveolo-capillary membrane protein-rich fluid accumulates first in the interstitium, then in the alveoli. The water content of the pulmonary tissue increases, the compliance decreases, the irritability of stretch-sensitive receptors becomes high and breathing becomes even more superficial. Cellular migration (mainly phagocytes) starts towards the pulmonary tissue, tissue degrading enzymes, cytokines, free radicals and lipid-peroxides accumulate. In the interstitium cells, collagen and elastic fibers are destroyed. Complement activation, locally produced and accumulated kinins and histamine quickly enhance fluid extravasation, they increase the number of atelectasic alveoli, increase the diffusion route and worsen the ventilation/perfusion ratio. This enhances the functional shunt circulation with *global* respiratory failure. Due to damaged endothelium, the aggregation of platelets follows and this leads to further accumulation of thromboxanes and prostaglandins, to capillary obstruction and DIC-equivalent local intravascular coagulation with hypoxia, increase in free radicals and hypoxia-induced vasoconstriction, with the rise of pulmonary resistance. Pneumocyte destroyment, phospholipase enzyme and the free radicals lead to decreased production and/or enhanced elimination of surfactant, thereby they further deteriorate the capillary permeability and decrease the compliance of pulmonary tissue. Pulmonary edema may be manifested, but already before this state the lung is more rigid, the respiration is fast, superficial and has a high rate, but functionally insufficient: this is the adult respiratory distress syndrome (ARDS; ch. 3.).

In the interstitium relatively quickly fibrosis develops due to destroyed tissue elements, phagocytes, proliferation factors – artificial ventilation with oxygen makes the situation worse (it enhances the amount of free radicals). The fibrosis may remain progressive even if the respiratory failure and shock can be improved or cured – the fibrotic change is lasting and progressive.

In the therapy of ARDS caution is needed with volume replacement (tendency for pulmonary edema), with oxygen administration (surfactant destroyment), the often applied high-pressure artificial respiration may make venous return more difficult (this would be important in shock).

Hypophysis:
The portal perfusion of hypophysis (particularly that of sensitized during pregnancy) may be easily damaged by DIC accompanying to shock or causing it. The local hypoxic tissue damage may initiate lasting hypophysis insufficiency. One example of this is *Sheehan syndrome*: in this the deficiency of prolactin and gonadotropic hormones dominates, but lack of other hormones may adjoin (cf. ch. 10.).

Fat tissue:
In fat tissue the perfusion particularly decreases (practically stops), anaerobic processes together with lactic acid and lipase accumulation are characteristic, many fat cells necrotize. Besides tissue acidosis, complement and the coagulation system are activated (tendency for DIC). Reperfusion damage is frequent. In obese patients the prognosis of shock is worse than in non-obese ones.

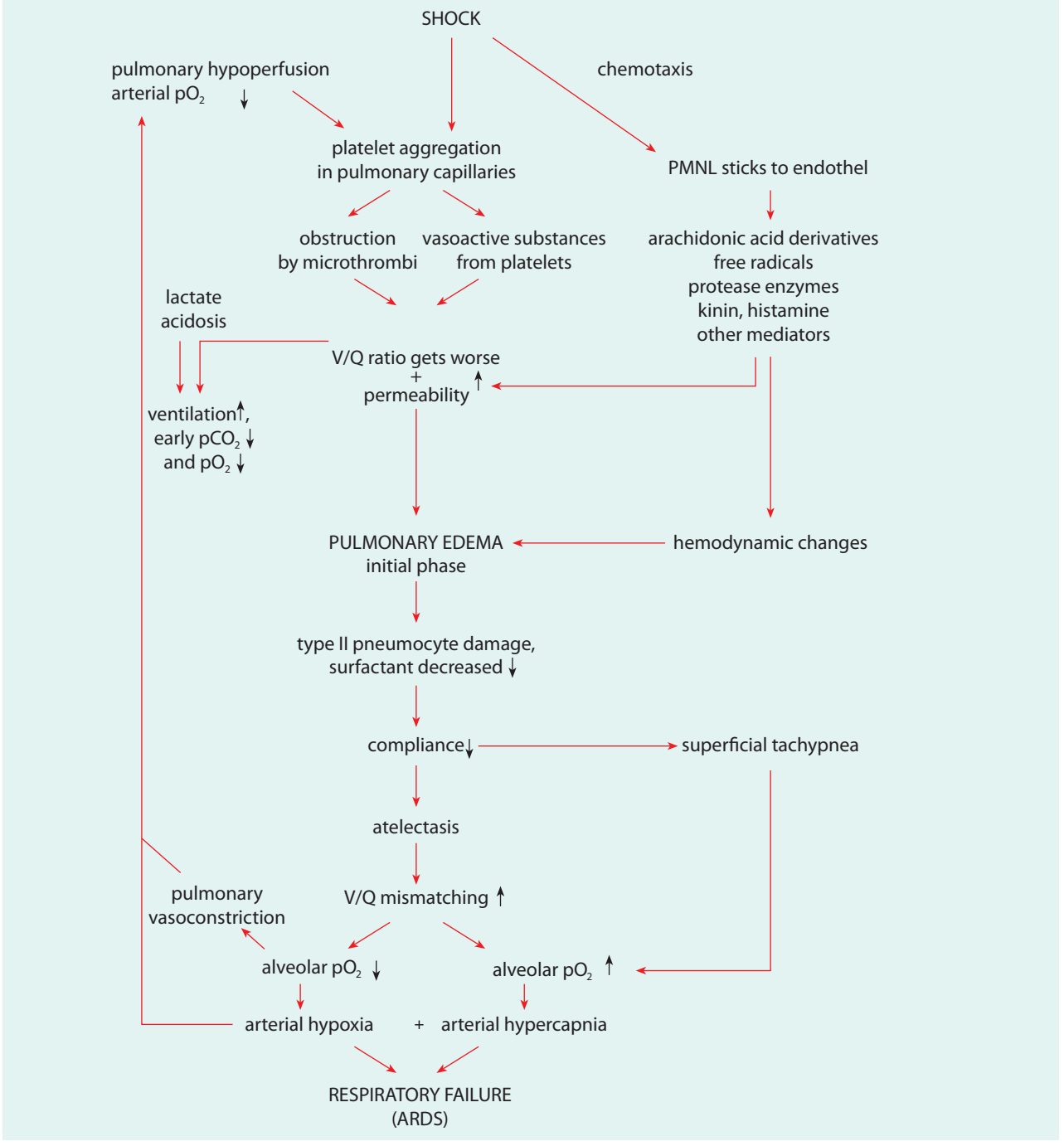

Fig. 2.23.: Development of ARDS in shock.

2.2.2.6. TYPES OF SHOCK

Hypovolemic shock

Causes:

- blood loss
- operation, trauma (often with bleeding, maldistribution of blood)
- burns (plasma loss, often with infection, trauma)
- exsiccosis, dehydration (the most frequent cause, particularly in babies and in elderlies) (diarrhea, vomiting, sweating, polyuria e.g. in diabetes mellitus, diabetes insipidus, early /polyuric/ chronic renal failure, Addison disease, overdose of diuretics)
- fluid loss to „third water space" (e.g. ileus), large edema/ascites formation, or end-stage heart failure, in late stage of traumatic shock loss towards the interstitium
- anaphylaxis (acute hypersensitivity reaction, huge angioneurotic edema, often combined with disturbance of blood distribution)

Pathomechanism: blood volume ↓, venous return ↓, central venous pressure ↓, end-diastolic ventricular volume/pressure ↓, stroke volume ↓, cardiac output ↓, arterial pressure ↓, heart rate ↑, TPR ↑, circulation time ↑, speed if circulation is decreased.

Possible compensation: tachycardia, increase of TPR, emptying blood stores, and enhanced salt- and water-retention.

Obstructive shock

Characteristically the aorta, or the pulmonary artery is occluded (thrombus, air, fat), or pericardial tamponade, myxoma, occlusion of big veins, or other occlusion may be the cause. In its mechanism it corresponds to the hypovolemic form: filling of the ventricles is not sufficient, therefore the forwarded and effectively circulating blood volume decreases. Occlusion of the aorta resembles rather the cardiogenic shock.

Cardiogenic shock

Causes:

- acute myocardial infarction (contractile force ↓ + dyssynergy + arrhythmias)
- obstructions, acute valve-insufficiency, mechanic damage
- cardiomyopathy (primary hypertrophic obstructive, toxin, sepsis)
- end-stage of heart failure, ventricular-aneurysm (contraction deficit)
- extreme arrhythmias (with tachy-, or bradycardia), a-v block

Pathomechanism: EDV and EDp ↑, central venous pressure ↑ (later this may return or even decrease since hypovolemia also develops by fluid loss towards the damaged tissues), stroke volume ↓, cardiac output ↓, blood pressure ↓, heart rate ↑, peripheral resistance ↑ (or normal, since the vasomotor reflexes are mixed, overstretch of the ventricle induces pathological reflexes and vasodilation), blood volume (at beginning) normal (not the distribution!), circulation time ↑, circulation speed decreased. In late (irreversible) stage the blood is stuck in the microthrombi, the venous return cannot be secured, the central venous pressure also decreases.

Trials of compensation: in infarction it would be important to enhance the contractility of the remaining normal myocardium, however due to the necrosis the contractile force decreases even at faraway regions. Due to poor contractility (despite decreased diastolic compliance) the end-diastolic ventricular filling and venous pressure are high (due to heart failure – this is specific for this type of shock), but the cardiac output and blood pressure still cannot be normalized. Besides the reflex vasoconstriction abnormal reflexes from the stretched ventricular wall may initiate abnormal vasodilator reflexes and the combination of the two effects will determine the final peripheral resistance. The dilatory effects refer to overstretched ventricular muscles and have a poor prognosis.

The greater the lost muscle amount, the worse is the prognosis:

Whatever is the origin of shock, the altered circulation will affect the coronaries, too: the worsening coronary circulation causes further formation of hypoxic/ischemic myocardial regions with decreased contractility, it further worsens the cardiac output and with this also the coronary perfusion. In end-stage heart failure the consequences of lasting systemic venous congestion and decreased contractility of the left ventricle are combined. The venous congestion (and additional tissue hypoperfusion) results in lasting tissue ischemia and massive edema, and these finally decrease also the circulating blood volume – by now the edema persists even without signs of venous congestion. The decreased contractility would lead even without this to worsening of the cardiac output, to diffuse tissue hypoperfusion, by now the defective venous return may speed up the process.

Distributive shock ("neurogenic", "vasogenic")
There is no primary abnormality of blood volume, rather the blood distribution is abnormal: it is „disclosed intravascularly" from the systemic circulation, in some vessels or tissues the blood „gets stuck", it accumulates there, („the patients is bleeding into his/her own vascular system"), or from some parts the return of blood is too fast, while the perfusion is insufficient at other parts. In the background of extreme and widespread vasodilation a decrease of sympathetic tone may stand, or enhanced NO-production by inflammatory cytokines, hyperthermic skin vasodilation, or an extensive release of vasodilator substances from the damaged tissues.

Causes:

- transverse lesion of the medulla, spinal anesthesia, ganglionic blockade (widespread vasodilation)
- overdose of narcotics or central depressants (widespread vasodilation)
- high intracranial pressure, brain-edema, cranial trauma, cerebral ischemia
- polytraumatisation (early phase – it occurs frequently in accidents!)
- anaphylaxis
- heat stroke, inflammatory changes of chemical/mechanical origin
- acute pancreatitis
- sepsis (it is regarded as shock since 1950, its occurrence increases; ch. A10.)

Pathomechanism: In distributive (particularly in septic) shock, as a result of all these, the energy balance increases (fever and mild hyperventilation are characteristic), while for the compensation of widespread vasodilatation the increase of cardiac output becomes disproportionately high.

Table 2.3.

The extension of myocardial injury influences the severity of functional damage

if the necrosis/ischemia	8%	→	diastolic compliance decreases
	10%	→	EF and contractility decreases
	15%	→	EDV and EDp increase
	25%	→	clinical heart failure
	40%	→	shock
	50-60%	→	acute heart failure, pulm. edema

Pathomechanism of forms of distributive shock:

In septic shock (Table 2.4.), besides the infection-induced high energy balance (fever and mild hyperventilation) and for the compensation of widespread vasodilation a still higher cardiac output can be expected. However, doe to a-v shunts mainly ineffective circulation (avoiding the capillaries) ("warm shock" = high skin perfusion), together with low blood pressure, in some regions capillary-level microthrombi and obstructions develops. The cellular oxygen supply may be inefficient, but many cytotoxic factors contribute to the tissue damages. This is made more pronounced by the edema due to increased permeability. Such edema decreases the originally normal plasma volume, and with time the vasodilator factors become mixed with increasing number of vasoconconstrictor effects (catecholamines, angiotensin, vasopressin). This leads to abnormality in distribution of cardiac output, to diffuse-patchy maldistribution with increasingly severe hypoxia, diffuse necroses and hemorrhages. By now the cellular damages, hypometabolism and hypovolemia dominate the picture („cold shock", Table 2.5.), with functional disturbances of various organs, particularly those of the lung and the heart. The patients subjectively feel both phases and in the cold phase they often understand the coming end.

In anaphylactic shock upon the effect of the released vasoactive substances (mainly histamine) generalized, massive vasodilation develops (with abnormal blood distribution) and circulatory failure develops, despite the fact that no blood is lost. In this type of shock, the picture may be modified by quickly developing severe and extensive edema (eventually it can be directly noticed how the lips of the patient become swollen, his

Table 2.4.

Hemodynamic characteristics in phases of septic shock

Hemodynamics	Early phase („warm")	Late phase („cold")
blood volume	normal	decreased
vascular resistance	low	high
blood pressure	low	very low
stroke volume	ca. normal	low
heart rate	high	very high
cardiac output	high	low
centr.venous pressure	normal/low	very low
EDV, EDp	normal	low
speed of blood flow	increased	slow

eyes swell, etc.) – these are consequences of increased capillary permeability and cause massive acute hypovolemia.

Traumatic shock (e.g. car accident), *or transverse medullary lesion:* The maldistribution of cardiac output develops quickly by neurogenic mechanism: at some regions strong vasodilatation, at others vasoconstriction may be observed. The total peripheral resistance may decrease, thus the blood pressure gradually decreases, in the dilated regions the blood is congested, the return becomes slower, thus the cardiac output falls (according to old saying „the patient bleeds out into his own vascular system").

As a compensation the sympathetic system becomes activated, in the hypoperfused regions the vasoconstriction is more and more pronounced – but the blood reaches these regions with low pressure, the tissue perfusion corresponds to microcirculation seen in shock, with intravascular microthrombus formation. The blood that still reaches here forms increasingly more clots (DIC), thereby decreases the amount of effectively circulating blood, the area of hyperperfused regions gradually decreases, finally vasoconstriction and shock-equivalent tissue circulation develops everywhere. The process is speeded up by edema-formation – this is responsible for the trauma-related but late- and slowly-developing shock (e.g. beating up the whole body, crush – these are connected neither with severe damage of individual organs nor with bleeding).

Acute pancreatitis (ch. 7.5.1.): due to tissue damage the released susbstances that cause vasodilatation and increase permeability (e.g. kinins, histamines) initiate the maldistribution of circulation and induce fluid loss (these are coupled with hypovolemia and decreased ventricular contractility). MDF also suppresses heart function.

Clinically the most frightening and rather frequent consequences of sepsis and other forms of distributive shock are DIC, decrease of myocardial contractility and the shock-lung – these are most difficult to prevent or treat and these are responsible for the great mortality.

Due to their frequent occurrence and clinical importance, the (poly)traumatisation and sepsis deserve separate mentioning (ch. A10).

2.3. ABNORMALITIES OF THE ARTERIAL BLOOD PPRESSURE

A stabile blood pressure has a basic importance for securing standard tissue perfusion. However, it is of similar importance to be able to change it, according to the changing actual need of tissue perfusion. The value of

Table 2.5.

Hemodynamic changes in various types of shock

	Hypo volemia	Obstruction	Cardiogenic	Septic		Anaphylactic
				early	late	
blood volume	↓	N	N	N	↓	↓(N)
venous return	↓	↓	↑	↑	↓	↓
centr. venous pressure	↓	depends on location	↑	N	↓	↓
filling of ventricles	↓	depends on location	↑	N	↓	↓
EDV	↓	depends on location	↑	N	↓	↓
EDp	↓	depends on location	↑	N	↓	↓(N)
EF	N	N	↓	N	↓	N
stroke volume	↓	↓	↓	N	↓	↓
cardiac output	↓	↓	↓	↑	↓	↓
blood pressure	↓	↓	↓	↓	↓	↓
heart rate	↑	↑	↑	↑	↑	↑
TPR	↑	↑	↑	↓	variable	↓
tissue perfusion time	↑	↑	↑	variable	↑	↑

blood pressure can be analyzed only in view of cardiac output and TPR, these together determine blood pressure (arterial blood pressure = cardiac output x TPR, i.e. the arterial blood pressure is directly proportional to cardiac output and to vascular resistance).

Control of arterial blood pressure happens by means of rapid (baroreceptor reflexes), mid-term (sympathoadrenal system) and long-term mechanisms. The latter ones, like volume regulation, are affecting the salt- and water-retention or -excretion: RAAS, natriuretic systems, and intrarenal mechanisms (primarily the changes of angiotensin level, which allow adjustment of salt- and water-excretion to intake even at stable blood pressure/renal perfusion and glomerular filtration; Fig. 2.24.). In pathological cases, changes of renal blood flow and pressure-diuresis are added to the controlling factors of blood pressure.

Arterial blood pressure is continuously affected by renal pressor and depressor mechanisms.

The cardiopulmonary receptors of the low pressure system (atria, lungs) carry information about blood volume via the vagal and sympathetic afferents, before changes in the arterial blood pressure, which could be sensed by the baroreceptors of the arterial side. Upon their activation, the renal salt- and water-excretion increases, the distribution of intravascular and interstitial spaces is shifted to the latter one (by means of decreased sympathetic tone causing release of arteriolar sphincters and increased intracapillary pressure). Besides, the blood content of the blood stores and capacitance vessels will also be altered, partly due to the previous mechanisms, partly by the secretion of hormones affecting the size of the extracellular space (ADH, RAAS, atriopeptins).

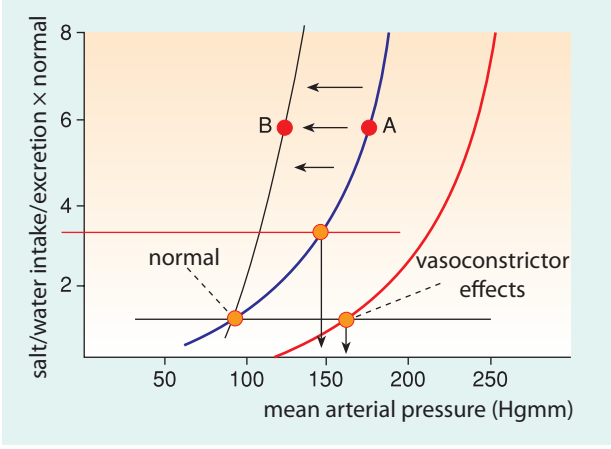

Fig. 2.24.: Pressure-diuresis curves: normal kidney at normal salt intake excretes this salt at about 100 mmHg mean arterial pressure. At acute consumption of more salt (thin red line) the salt balance can be established at around 150mmHg pressure. The compensatory decrease of RAAS has not started as yet, while in lasting salt excess due to the decreasing RAAS the salt excess can be excreted at relatively lower blood pressure: A®B curve. In case the kidney is under primary vasoconstrictor effect (red line) even the normal salt intake can be excreted and salt balance maintained only at higher blood pressure.

Baroreceptor reflexes from the high-pressure system (e.g. carotid sinus) ensure quick but not very accurate counter-regulation, which is characterized by adaptation to the new pressure (this phenomenon partly explains the set-point shift in prolonged changes of blood pressure).

It should be emphasized that the factors maintaining arterial blood pressure outnumber those factors aiming to decrease a too high pressure (sympathetic efferents plus RAAS vs. the low efficacy natriuretic systems). It is likely that in phylogenesis life-threatening acute hypovolemia (bleeding, diarrhea, vomiting, etc.) occurred more frequently and the mechanisms to elevate blood pressure (vasoconstriction and rise of blood volume) exceed the opposite mechanisms. This might explain the phenomenon that an arteriolar constriction in massive bleeding is still maintained (primarily to save normal level of blood pressure) when it is leading to further impairment of the already existing hypoperfusion in the microcirculation. In affluent societies the volume-decreasing abnormalities are relatively rare (except for traumas, accidents), which might explain that their population has a tendency for hypertension.

The optimal blood pressure in adults, at the level of the heart, is a value between 120/80 and 110/70 mmHg. The mean (integrated) arterial pressure is about 100 mmHg. The high normal value is 130/85 mmHg, above 140/90 mmHg hypertension is diagnosed. Increasing age does not affect these limits. Although with aging the blood pressure appears to rise, only the number of hypertensive patients is greater among the elderly. In contrast, in children and pregnant women the blood pressure is lower. Physical activity, emotions, stress situations may affect blood pressure temporarily, and the diurnal changes are also significant: at daytime the blood pressure is higher, at night-time sleep it is lower. These are not pathological phenomena, rather a lack of them might signal abnormality. Patients with normal diurnal blood pressure changes are designated as „dippers", while those not showing this phenomenon are „non-dippers". In hypertension the blood pressure can even be higher at night than during the day.

There are postural variations in blood pressure: in erect position, the mean arterial pressure is 180 mmHg at the level of the ankles, and about 60-70 mmHg at the top of the head (Fig. 2.12.) – the vessels must continuously adapt to these postural changes. In the analysis of organ perfusions (e.g. brain) this factor must also be considered.

2.3.1. STATES ASSOCIATED WITH HYPOTENSION

Hypotension is characterized by a blood pressure lower than 110/70 mmHg in adults. There are different types of hypertension: severe acute (shock, syncope), moderate, or mild (fever, drug effect, alcohol, etc.) forms, and there are states with prolonged hypotension.

There is a need for rapid circulatory adaptation to the orthostatic position both on the venous and on the arterial side (Fig. 2.13.). Without this, in upright position pooling of blood and markedly decreased venous return would be expected, that would lead to diminished and inadequate cardiac output and to cerebral hypoperfusion. With normal adaptation capacity such disorders do not occur. However, if the adaptability decreases for any reason, the orthostatic posture predisposes to orthostatic hypotension, to fall in brain blood flow and to syncope. In supine position brain blood flow is insufficient only if the mean arterial pressure level is below 60-70 mmHg.

Chronic orthostatic hypotension is possible in various forms:

- *idiopathic:* It is usually without consequence, apart from weakness and tendency for collapse, but sometimes presents as part of complex neural degeneration (gut, bladder, cardiovascular and sexual disorders). It positively affects life expectancy, but in case of sclerotic cerebral vasculature (= small capacity for vasodilation) it also bears the risk of repeated cerebral hypoperfusion, brain hypoxia and vascular dementia.
- *secondary:* autonomic neuropathies (diabetes mellitus, old age, uremic, hepatic and other metabolic disorders, toxins, alcohol, encephalo-/neuropathies)
  - adrenal insufficiency
  - pituitary insufficiency
  - hypothyroidism
  - sympathectomy
  - drug (side)effects
  - starving, malabsorption, some vitamin-deficiencies (e.g. beri-beri)
  - prolonged decrease of intravascular volume (prolonged dehydration)
  - aortic stenosis, bicuspid stenosis, constrictive pericarditis
  - cardiomyopathies (with decreased contractility)

In judging blood pressure one has to be cautious: in chronic hypertensive patients a sudden decrease to 120/80 mmHg might seem normal, but this can already be below the zone of autoregulation of brain blood flow for the given patient, and may lead to cerebral hypoperfusion and hypoxic stroke (i.e. to severe consequences of acute hypotension, with apparently normal blood pressure).

2.3.2. HYPERTENSION DISEASE

A blood pressure which at rest chronically is exceeding 140/90 mmHg, is pathologically high (although recently 135/85 is denominated as „high normal"). It is an irksome definition: hypertension is not diagnosed if the resting blood pressure is normal, even if the patient gives a hypertensive response to stimuli or on exertion, and concomitantly spends his entire life with an elevated blood pressure. In these patients, definite hypertension appears later more frequently – this should be probably perceived as a „pre-hypertension state". The prevalence of hypertension is different in various populations, it varies between 5% and 30%. In developed countries the prevalence is high. Hypertension is a very frequent disease, sometimes without symptoms for long, therefore the diagnosis is often late. It can be well controlled, but the untreated cases might lead to severe, sometimes lethal consequences, ruin the quality of life, and shorten the expected life-span.

ETIOLOGY AND CLASSIFICATION OF HYPERTENSIONS

According to the clinical course, benign and malignant (rapidly progressing) hypertensions are distinguished. By appearance, systolic and diastolic hypertensions are possible, from which the diastolic hypertension is more the dangerous (usually referring to arteriolar vasoconstriction). This is usually combined with systolic hypertension, but there are isolated systolic hypertensions, as well, either originating from the increase

in the volume of blood propelled by the heart (aortic insufficiency, a-v shunts, hyperthyroidism, fever, hyperkinetic circulation, etc.), or from the stiffness of the great vessels (e.g. sclerosis). „White coat hypertension" is also distinguished (this hypertension presents only in hospitals, surgeries), and there are other forms, like hypertension associated with pregnancy (even if it just reaches 120/80 mmHg; cf. ch. A13).

The main classification of hypertensions is based on their pathophysiology: primary or essential (without any known reason), or secondary (with well-defined pathomechanism, like pheochromocytoma, adrenal hyperactivity, etc.).

2.3.2.1. SECONDARY HYPERTENSIONS (with known cause; 5-10% of all cases)

Renovascular hypertension – renal parenchymal hypertension (Fig. 2.25.)

In animal experiments, a unilateral stricture (not occlusion!) of one renal artery leads to a drop in the intrarenal pressure of this kidney, with concomitant increase of the activity of the juxtaglomerular apparatus (JGA), and activation of the renin-angiotensin-aldosterone system (RAAS). This is also observed in human individuals upon unilateral stricture of the renal artery (e.g. sclerosis, external compression). The mechanism of the pressor effect is twofold: angiotensin II (ATII) is a direct, potent vasoconstrictor and increases salt uptake, acting on AT_1 receptors, while aldosterone leads to salt- and water-retention and increased intravascular volume. Angiotensin converting enzyme (ACE) inhibitors can temporarily inhibit the development of hypertension (by blocking ATI → ATII conversion), but cannot normalize the circulation and function of the affected kidney. In case of re-dilation (re-vascularization) or complete removal of this kidney (experimentally, not in humans!), the blood pressure becomes normal, because the initiating disorder is eliminated.

In prolonged stenosis, depending on its degree, the salt- and water-excretion of the affected kidney will be decreased by its dependence on intrarenal pressure, and due to the hypervolemia, the blood pressure remains high. This is not strongly affected by the RAAS, although the high salt- and water-content of the vascular walls (and the rigidity of the connective fibers) causes sustained elevation of TPR. In the contralateral kidney the salt- and water-excretion will increase (secondarily to pressure diuresis, and sometimes even over-compensating the stenotic kidney, causing decrease of extracellular volume /ECV/), inhibiting the decrease in the activity of the RAAS. Therefore, the ECV and the cardiac output will return to its normal value or even below this value, while the absolutely or relatively high RAAS keeps TPR and blood pressure at a high level. This blood pressure will be independent of renin, so ACE inhibitors are less useful in the treatment, but removal of the kidney of such animals may be still effective.

In case of too late removal of the stenosed kidney of the animal, the blood pressure remains high, proving that the hypertension is no more maintained by the original cause. In case of dilating the stenosis and removing the contralateral kidney, the blood pressure will normalize. Stenosis protected the affected kidney, but not the contralateral one, from the deteriorating effects of hypertension. The cause of maintaining hypertension is the exhaustion of depressor functions of the contralateral kidney, which suffers parenchymal injury. The depressor function is dual: on the one hand, renal parenchyma secretes vasodilator prostacyclins and kinins, on the other hand, it produces renomedullary lipids, which increase the tubular salt- and water-excretion and cause ECV depletion. If only this kidney remains with exhausted depressor mechanisms, the depressor depleted kidney is responsible for the sustained hypertension (whether or not the originally stenotic kidney is normalized or removed). However, if the stenosed kidney is normalized and the contralateral kidney is removed, the blood pressure can be normalized.

Depressor-deficiency may develop simultaneously in both kidneys if the hypertension is triggered not renovascularly, but by some other (e.g. primary or neurogenic) factors. In case of decreased renal parenchyma, less and less depressor will enter the circulation, and this maintains the hypertension without primary abnormality of renal circulation. If both kidneys are removed in animal experiments, hypertension will develop despite eventual hemodialysis (= renoprive hypertension), because of complete lack of depressor mechanisms – in humans this can be observed in end-stage renal failure: lack of vasodilator substances and lack of volume decreasing mechanisms results in hypertension. Since it is known, that any form of hypertension, irrespective of its mode of development, can impair re-

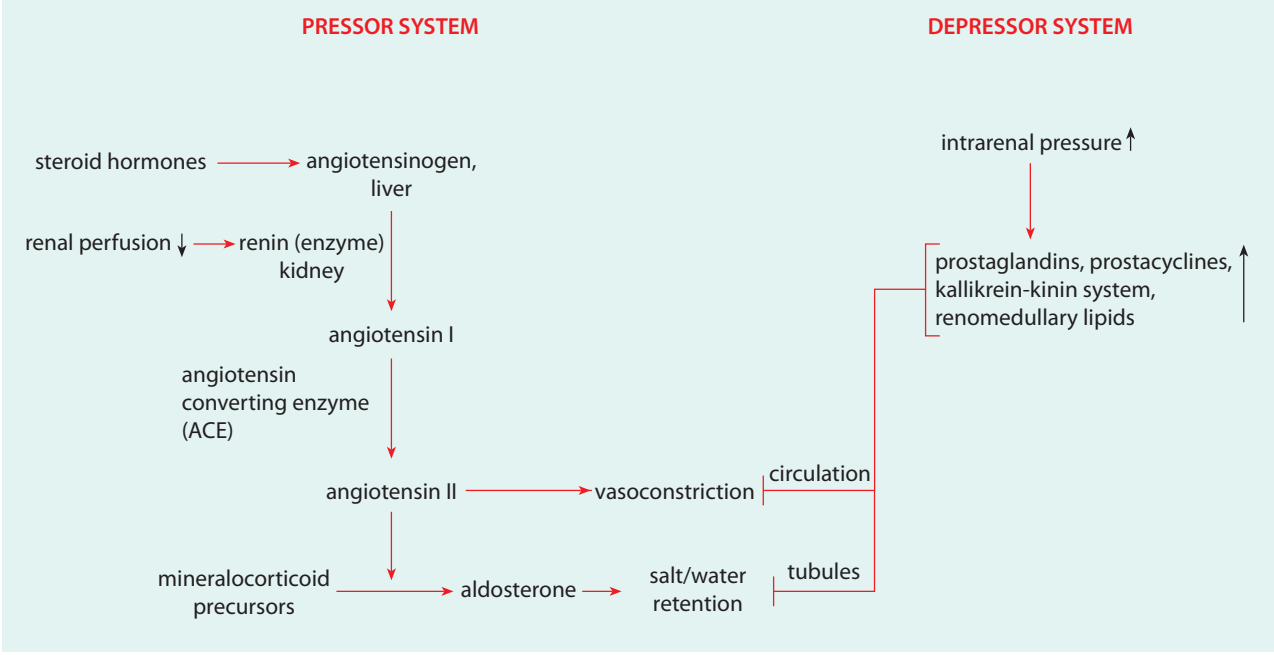

Fig. 2.25.: Pressor and depressor systems of the kidney. Earlier ACE production was supposed to happen in the lung only, now it is obvious that the endothelium also has a role.

nal parenchyma – accordingly, the kidneys have a role in sustaining any type of hypertension.

Endocrine hypertensions

Hypertension can be caused by ***mineralocorticoid*** excess in primary hyperaldosteronism (Conn syndrome), or by deficient 11β-, or 17α-hydroxylase enzyme (ch. 10.8.4. and 10.8.5.). In adrenogenital syndrome adrenal hypertrophy may develop due to the enzyme-deficiency and disturbance of cortisol synthesis deficiencies, which goes along with great overproduction of (otherwise weak) mineralocorticoid precursors. The 11β-hydroxysteroid dehydrogenase enzyme in healthy subjects neutralizes cortisol effect on the mineralocorticoid receptors in the kidneys – the lack of this enzyme causes hypertension. The salt- and water-retention, developing in such cases, increases plasma volume. Since there was no change in the hydrostatic/oncotic pressures at the capillary level, the retained salt and water does not move to the interstitium, it will increase mainly or exclusively the plasma volume. This will result in temporarily and moderately increased venous return, higher stroke volume and cardiac output. To prevent tissue hyperperfusion, the autoregulation (which is present at some level in all tissues) will react with arteriolar constriction (increased TPR/afterload), therefore the cardiac output will be normalized, but hypertension will develop.

These hypertensions are usually moderate and react to salt restriction. Escape mechanisms, like production of natriuretic hormones in the overextended atria will inhibit extreme salt- and water-retention and development of edema (escape from the effect of aldosterone to cause salt- and water-retention). Although thereby the hypervolemia is limited, but it will remain constant, and will lead to volume-hypertension, which causes lasting stimulus on renal depressor functions and on arterial wall. The increasing blood pressure will, independently from natriuretic factors, increase salt- and water-excretion and this also limits volume overload. However, due to the chronic hyperaldosteronism, K loss will also be observed, and there is no escape mechanism for this.

Cortisol (e.g. in Cushing disease, or in the course of glucocorticoid treatment) can partly increase blood pressure by occupying the mineralocorticoid receptors („spillover" mechanism), partly by increasing hepatic angiotensinogen synthesis, therefore also the RAAS activity: the ATII produced in such a way has a direct vasoconstrictor effect. In addition, cortisol can increase catecholamine sensitivity.

Oral anticoncipients have the same mechanism in the liver, and increase the catecholamine level and ATII sensitivity (differences depending on age, body weight and genetic background may be important). In normal pregnancy, the ATII sensitivity is decreased (ch. A13), explain-

ing the physiological decrease in blood pressure (despite higher cardiac output), while in toxemic pregnancy the sensitivity remains at the pre-pregnant level, supposedly due to insufficient placental prostaglandin production.

Pheochromocytoma: Hypertension is caused by increased production and release of adrenal catecholamines, usually by benign, or sometimes a malignant tumor (less than 1% of all hypertensions). Besides the overproduction, the normal noradrenaline/adrenaline ratio of 1:5 is skewed towards the noradrenaline (might reach 1:1), this makes understandable the strong α-receptor effect, and the increase in vasoconstriction. Characteristically, this hypertension presents as an attack, from near normal level the arterial blood pressure can shoot up even to 300/150 mmHg, accompanied by sweating, tachycardia, nausea, angina and sometimes hypertensive encephalopathy. However, 2/3 of the patients have continuously high blood pressure, and in 10% there is no hypertension (as yet). The diagnosis is based on measurement of vanillylmandelic acid (VMA, catecholamine metabolite) in 24-h collected urine and the therapy is based on removal of the tumor and on administration of α-adrenergic blockers.

Hyperthyroidism causes mainly systolic hypertension, while in *hypothyroidism* the diastolic pressure increases due to the rigidity of the arterial wall (the pulse pressure decreases).

In ***acromegaly*** hypertension is caused by the increased salt- and water-retention induced by growth hormone and by the increased cardiac output, and appearance of digitalis-like materials in the circulation.

Hyperinsulinism: In 2DM insulin causes renal salt- and water-retention and increased catecholamine sensitivity.

Diseases associated with ***hypercalcemia:*** The blood pressure usually increases, but the plasma free Ca^{2+} *per se* is not responsible for this (on a Ca^{2+}-rich diet the blood pressure rather decreases). However, the intracellular Ca^{2+} in vascular cells plays a pivotal role in maintaining hypertension. Ca^{2+}-channel blockers can control such hypertension.

Hypertensions of hemodynamic origin

- Coarctation of the aorta causes hypertension proximally to the stenosis. The set-point of the baroreceptor reflexes is relatively easily shifted upwards – this phenomenon is also important in the control of hypertensions of other origin.
- In severe atherosclerosis, the systolic blood pressure is elevated if large vessels are affected. However, if smaller arterioles are sclerotic or rigid, the diastolic pressure will increase. (In case of rigid large vessels the heart can forward the stroke volume only with greater systolic pressure – the diastolic pressure is determined by the distribution of the blood via the arterioles.) With aging, the vessels normally loose from their elasticity, the hypertension (particularly the systolic form) is more frequent (Fig. 2.27.). Hypertension of such origin presents as a „non-salt-sensitive" type, the renal salt excretion more or less follows the changes in salt intake, only always at a higher blood pressure in the systemic vessels and the kidney (Fig. 2.28. cf. Fig. 5.19.).
- Increased plasma volume (e.g. disproportionate infusion in renal failure, or extreme infusion even without renal damage) may acutely evoke a rise in tension. In chronic cases relatively small excess of volume hypertension may also be sustained (e.g. primary excess of aldosterone or salt). The peripheral resistance becomes elevated even in these cases, and with time this will maintain the pressure at high level (Fig. 2.26.).
- In polycythemia the increased blood viscosity results in a high resistance and hypertension, which is further worsened by the moderate increase in blood volume. Androgen hormones, chronic hypoxemic hypoxia facilitate the development of hypertension.

Neurogenic factors in hypertension

The importance of baroreceptor reflexes is underlined by the fact that their denervation induces hypertension. Lesions in the nucleus of the solitary tract (NTS), or in the lateral hypothalamus result in neurogenic hypertension, unlike a lesion at the ventral part of the 3rd ventricle (AV3V region) which lesion prevents these hypertensions.

Blood pressure is affected by increased intracranial pressure (ICP), or exciting the vasomotor region. In earlier animal experiments kaolin suspension was injected into the cerebral ventricles to demonstrate this. Clinically it is observed as the Cushing reflex (compression of the brain vessels decreases cerebral perfusion, what is compensated by a rise in blood pressure, initiated from the vasomotor center; ch. 2.6.2.4.): parallel with the increasing intracranial pressure, the systolic

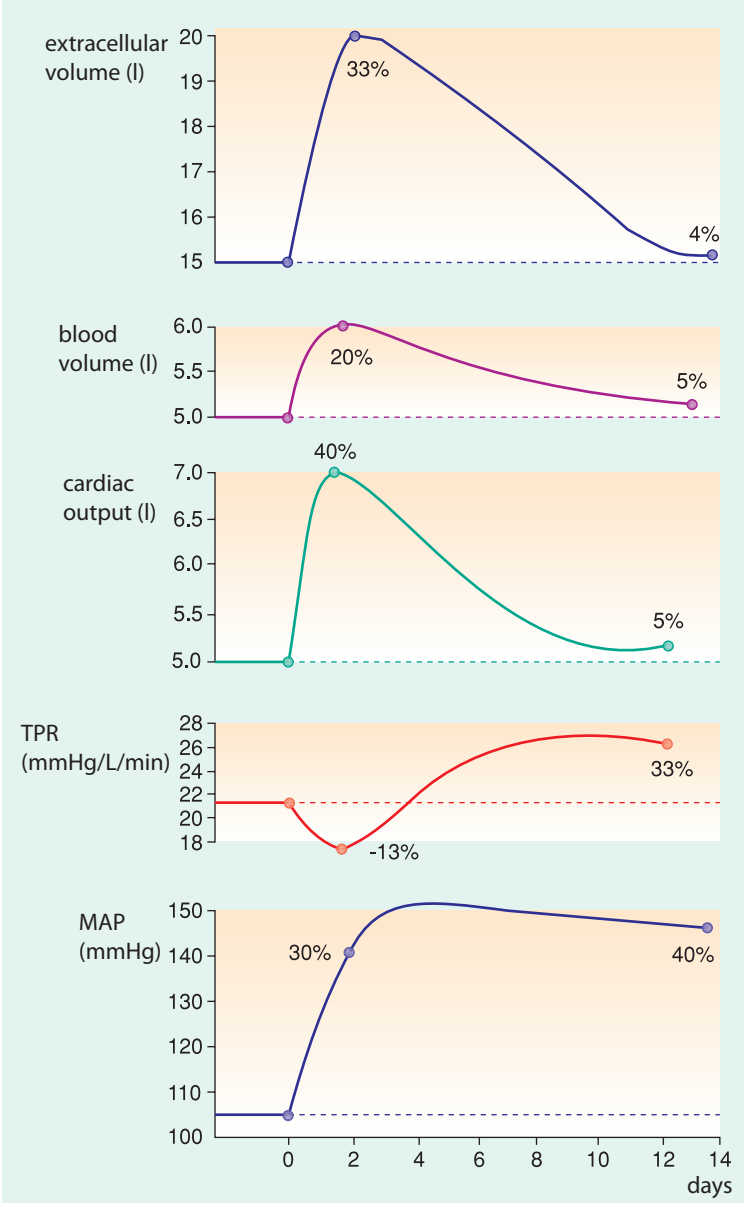

Fig. 2.26.: Increase of ECV (e.g. due to aldosterone, or salt-intake) transiently increases hypertension: blood volume and cardiac output increase, what is not fully compensated by decreased TPR. After few days to prevent further hyperperfusion, due to the autoregulation, change of the vessel wall structure, and the increase of TPR, the tissue perfusion declines. Although the ECV and plasma volume remain high, the cardiac output is already only minimally higher than the starting level and the high TPR keeps blood pressure at a high level. At this stage – due to the vasoconstrictor effect and relatively high RAAS only a higher blood pressure secures the intake-related salt excretion.

and diastolic pressures become markedly elevated, along with bradycardia. In severe cases this can lead to death by asystolia.

Lasting hypertension of any origin eventually results in shift of the „set-point" of blood pressure, along with resetting the baroreceptor reflexes. After this, any blood pressure lower than the newly set limits will be perceived as hypotension. This may affect the autoregulation zones of various organs: a seemingly normal blood pressure of 120/80 mmHg might result in cerebral hypoperfusion and hypoxia. Eventually, in the maintenance of hypertension of any origin an increased sympathetic tone and catecholamine overproduction participate.

Various stress-situations increase blood pressure by neural mechanisms, but this may be more important in essential hypertension (see below).

2.3.2.2. PRIMARY (ESSENTIAL) HYPERTENSIONS (the evoking factor is not known)

About 90-95% of all hypertensive patients belong here. Although the exact cause is not known, genetic and environmental factors are generally accepted to be responsible for the development.

Due to the familiar accumulation, inheritance is supposed to be a factor. More than one gene might play a role, but these determine rather the zone of blood pressure setting than a fix blood pressure value. In general, some genetic malformations manifest only under special environmental/acquired circumstances (like malignant hyperthermia, hemophilia, etc.), this is particularly true for hypertension. Along with genetic determinants, environmental and acquired factors are also of importance – these can be influenced more easily.

Genetic factors

Gene defects were detected on chromosome 10, which is related to production of ACE and angiotensinogen. Functions associated with regulation of blood pressure are associated with chromosomes 1, 2, 6, 7, 16 – the inheritance is polygenic.

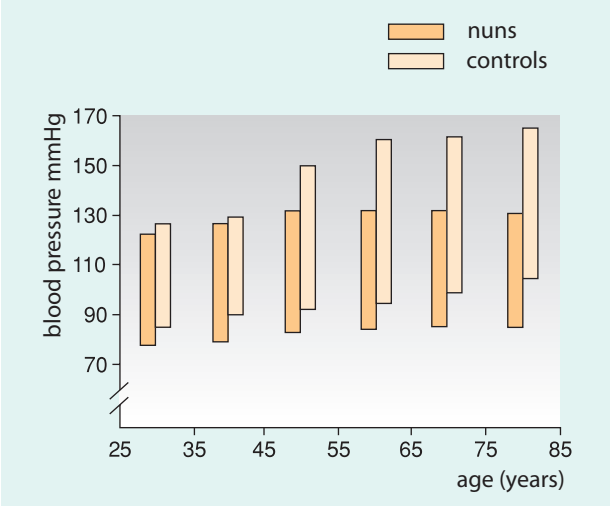

Fig. 2.27.: Blood pressure values in urbanized women and in nuns at different ages. The age-related rise of blood pressure suggests a role of lifestyle factors.

It may be difficult to distinguish racial differences from environmental effects. Black Americans have a higher incidence of hypertension than their white counterparts (this would suggest a role for some genetic factor), but in the African countries where they originated from, the prevalence of hypertension is low.

In experimental animals there are some rat and mouse strains which spontaneously develop hypertension at some stage of their life (SHR = spontaneously hypertensive rat).

Possible manifestations of genetic disorders:

- abnormal Na-excretion
- membrane Na-transport (Na^+/K^+ exchange decreased, Na^+/Li^+ exchange increased; but these are "genetic markers" in hypertension rather than causes)
- disorders of intracellular Ca^{++} metabolism
- abnormal responses to sympathetic stress and stimuli (personality types: different drivers, cold-pressor test differences, manager-type, etc.)

Some genetic forms of human hypertension:

1. *Glucocorticoid sensitive hyperaldosteronism*
   Hypertension with autosomal dominant inheritance, in which – along with 11β-hydroxylase and aldosterone synthase – there is another enzyme that produces aldosterone in the fasciculate zone. This process is sensitive to ACTH, therefore administration of physiological amounts of cortisol that decrease ACTH production (via negative feedback), can lower aldosterone secretion and blood pressure. The aldosterone released from the fasciculate zone does not respond to renin (otherwise the renin activity is low, like in primary hyperaldosteronism).
2. *"Virtual aldosterone excess" syndrome*
   Normal cells producing aldosterone are protected from the stimulating effects of cortisol by 11β-hydroxysteroid dehydrogenase enzyme, since it degrades cortisol to inactive cortisone. Otherwise, cortisol concentration is at least one magnitude higher than the aldosterone concentration. In this autosomal recessive abnormality the 11β-hydroxysteroid dehydrogenase activity is insufficient, so cortisol can bind to the aldosterone receptors even in normal concentration and can stimulate them. Concomitantly, hypertension will develop due to salt- and water-retention, yet without hyperaldosteronism.
3. *Liddle-syndrome*
   It is an inborn defect that causes hyperactivity of the amiloride-sensitive renal Na-channel and leads to volume hypertension, without hyperaldosteronism or abnormality of the aldosterone-receptors and/or the fasciculate zone: this leads to volume hypertension.

Environmental (acquired) factors:

Nutritional factors:

- Epidemiological investigations reveal that *high salt-intake* is one of the most common factors to cause hypertension. In Hungary and many developed countries, the average salt-intake is 12 g/day, what is 5-times more than required. With high salt-intake, salt- and water-balance may still develop and blood pressure will increase only moderately, provided that the renal function and renal parenchyma are intact, and the angiotensin effect can be suppressed. If this is not provided, salt- and water-excretion still occurs, but only with increasing blood pressure, and a concomitant volume hypertension will develop. Blood pressure lowering effect of diuretics (= saluretics) underlines the importance of this mechanism.
- Intake of K and Ca has an opposite role to salt-intake: these counteract the development of hypertension.
- Hypertension almost inevitably develops in obesity. Higher body weight does not account for this, since the mean arterial pressure is around 100

mmHg in species of very different body weights (from mouse to elephant). In pregnancy, too, the body weight increases, but the blood pressure normally decreases. The main factors in the development of hypertension in obese subjects are: insulin resistance and hyperinsulinism (with salt- and water-retention), increased cardiac output, increased sympathetic activity and TPR. Later the rigidity of vessels may contribute to all these. Physical inactivity is a frequent accompanying phenomenon. Higher food intake predisposes to hypertension even without weight gain, and caloric restriction attenuates hypertension before significant fall in body weight.

Increased fiber intake can prevent not only the development of obesity, but also the hypertension – the mechanism is still unknown.

- Chronic alcohol intake is frequently associated with hypertension. Although the direct, acute effect of alcohol is vasodilation, some direct vasoconstrictor effect is seen in different areas (umbilical vessels, possibly in coronary arteries). Besides the hormonal changes (large fluctuations in ADH level, ACTH/cortisol increase, enhanced catecholamine secretion) associated with higher fluid intake and loss, a decreased vagal tone and increased intracellular Ca^{++} uptake (and consequent rise in vascular tone) are important factors in the development of hypertension in alcoholics. In rat experiments, chronic alcohol intake induced renal changes: hypertrophy, decreased glomerular filtration rate, dilation of distal tubules, acidosis, increased Na-level and hyperosmolarity as a sign of dehydration.

Stressors:

- Chronic/repeated psychological stress, frustration, anxiety, usually genetically determined „manager-type" A-personality (with aggressiveness), all can provoke hypertensive states, or can lead to fixation of hypertension.
- Repeated strong physical stimuli (sound, light, cold, etc.) are demonstrated to be responsible for triggering and maintaining hypertension. In nuns and those living in rural areas the mean arterial pressure increases to a smaller extent with age than in those living in urban areas (Fig. 2.27.).
- Social factors: e.g. overcrowded places, coffee and smoking help the development of hypertension. Alcohol should also be noted.
- Physical activity diminishes the susceptibility to hypertension: vasomotor changes are functioning well also in the direction of vasodilation, and the vascular activity is maintained – in case of inactivity/immobilization the tendency for hypertension is greater.

Other factors:

- vascular wall hyperreactivity
- vascular changes associated with old age (not only sclerosis)
- toxemic pregnancy (ch. A13.)
- oral contraceptives
- sleep apnea syndrome (ch. 3.1.)

In the pathogenesis of essential hypertension Page emphasizes the *mosaic-theory,* i.e. a multifactorial development (with interaction between the components) instead of one single genetic or pathogenetic factor.

It is essential to remember that a *shift of the set-point* of the baroreceptor-level regulation and the *renal involvement* are important in the development of hypertension of any origin. A common characteristic feature is the *ineffective modulation of the RAAS*: in the so-called „low-renin" hypertension the angiotensin sensitivity is increased, in other types the NaCl is unable to affect the kidneys and adrenal glands in relation of angiotensin production (the angiotensin level remains high), while in „high-renin" hypertension blood pressure itself is unable to affect renin production and adrenal activity. Another common feature is the *high vascular sensitivity* to noradrenaline, most likely due to the increased arterial smooth muscle mass. The structural changes of the vessels are similar, and they promote the maintenance of hypertension.

2.3.2.3. CONSEQUENCES OF HYPERTENSION

While the systolic pressure depends on the strength of the left ventricular contraction and the aortic/large-vessel (and valvular) resistance, the diastolic pressure is mainly dependent on the arteriolar resistance. Ultimately both values depend on the ventricular activity (in case of ventricular arrest blood pressure drops to zero). It is understandable that a constant high blood pressure leads to myocardial dysfunction and damage. On the other hand, untreated hypertension leads to vascular changes as well. In fact, all complications of hypertension are associated with the hypertension-induced cardiovascular changes.

According to the Framingham-study (a study lasting for decades in the American city of Framingham), the risk of cardiovascular morbidity and mortality doubles if the blood pressure is 160/95 instead of 140/90 mmHg. At the beginning of the 20th century, the newly, but obviously late diagnosed (and untreatable) hypertension forecasted a maximal survival of 4-16 months. Regular checkups and control of blood pressure started only in the years of 1920–1930. The Hungarian writer (and M.D.), László Németh wrote his book "Letters about Hypertension" analyzing his own, still hardly treatable hypertension in the 1950-s. Today, with an early diagnosis and adequate treatment, the morbidity and mortality data are significantly better, but they are still poorer than in the normotensive population. Within the remaining fatalities, the cause of death is different (Table 2.6.).

It is proven that an increase in the pressure itself is the *cause* of vascular complications. In case of an arterial stenosis, atherosclerosis always develops proximally to this malformation. In pulmonary hypertension (but only in this case!) sclerosis may occur in the pulmonary artery. Nephrosclerosis associated with hypertension affects only the supposedly healthy (non-stenosed) kidney (see: renal hypertensions, Fig. 2.25).

Characteristics of vascular changes *(Figs. 2.28, 2.29.):* Pressure and friction cause intima damage mainly at arterial branchings with steep connection. Volume overload helps the accumulation of Na^+, Ca^{++} and water, and the increase of vascular tone. Humoral factors (thromboxanes, PG-s, angiotensin, catecholamines, and tissue factors of local damage/ischemia) might increase vascular tone, and can also be toxic to the vascular wall. Intima damage results in protein exudation and hyalinic degeneration in the vessel wall. Interstitial fibrosis, mucopolysaccharide accumulation and lymphocytic infiltration are also characteristic. Sclerotic plaques develop easily in the damaged vessel wall. Hypertrophy of the muscular layer contributes to the enlargement of the wall and to stenosis of the lumen. In arteries, media degeneration and thinning or cystic transformation of the collagen and elastic fibers may lead to aneurysm formation (in the aorta, celiac trunk, renal artery, etc.: e.g. dissecting aneurysm of the aorta) and to widening of the aortic root.

The endothel may also be damaged in the microcirculation, mainly in capillaries and venules of some regions (kidney, coronaries, etc.), causing increased permeability and local tendency for coagulation, thereby decreasing the tissue oxygen and nutrient supply.

In *malignant hypertension* a more pronounced endothelial damage and exaggerated permeability are characteristic. These are coupled with platelet adhesion and intravascular thrombus formation, with smooth muscle degeneration and fibrinoid necrosis in the vessel wall, with lymphocytic infiltration, occasionally with signs of periarteritis. Intima hyperplasia is more pronounced and atherosclerosis is characteristic. Widening of the vascular wall is accompanied by a narrower lumen. Often a RAAS overactivity is in the background.

Hypertensive angiopathies of the peripheral vessels include stenosis with ischemic changes of the affected region, what may lead e.g. to intermittent claudication (pain and crural spasm upon walking), chest pain (angina pectoris), or abdominal angina.

Effects on the heart *(Fig. 2.30.):*

- left ventricular hypertrophy: The *concentric hypertrophy* initially increases the contractility, and therefore it improves pump function. Later the ventricular compliance decreases (according to *hypertrophic cardiomyopathy*), along with increase in EDV, even with still normal ejection fraction – this is followed by massive dilation of the degenerated myocardium, with left-sided congestive heart failure (ch. 2.1.4.1.).
- coronary sclerosis and its consequences (ischemic heart failure, acute coronary syndrome /ACS/, angina pectoris, *myocardial infarction*); – these are the most frequent fatal complications.
- the degenerated myocardium might act as a source of dangerous dysrhythmias

Table 2.6.

Most important causes of death in untreated and treated hypertensive patients. In the treated ones the total mortality is smaller, death comes later and in other forms

UNTREATED	32 %	CNS	23 %	TREATED
	22 %	congestive heart failure	6 %	
	21 %	coronary disease	42 %	
	2 %	uraemia	10 %	
	23 %	else	19 %	

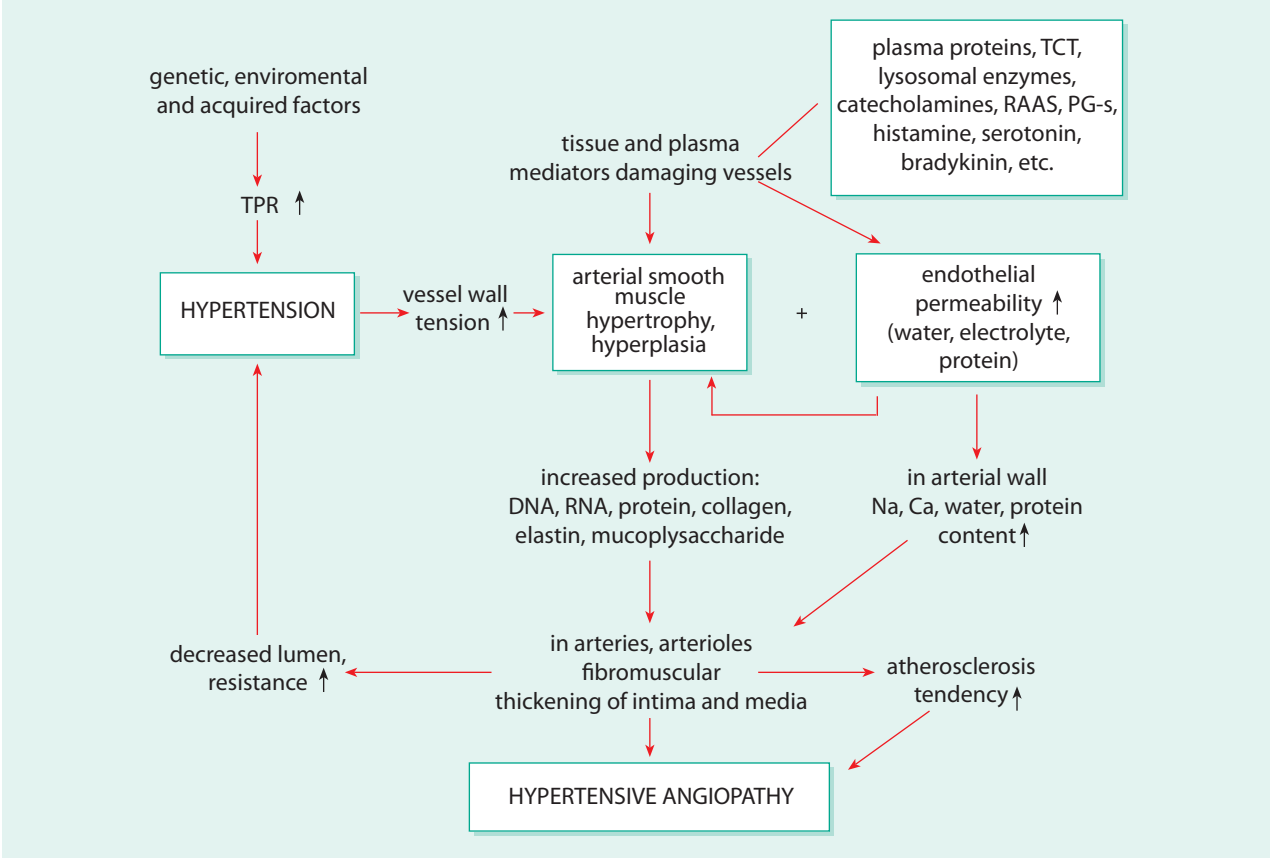

Fig. 2.28.: Development of hypertensive vascular damage.

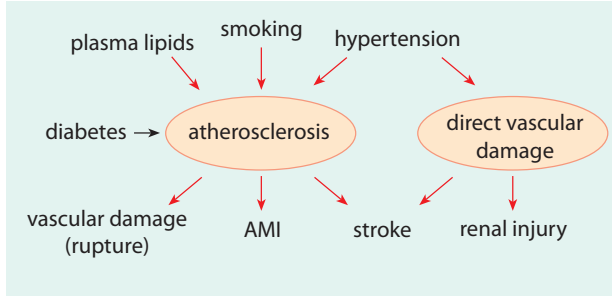

Fig. 2.29.: Role of hypertension in the damage of certain vascular regions

Cerebral involvement:

At about every 10 mmHg rise in blood pressure, the risk of stroke increases by 10%. Cerebral complications rank second in the lethal complications of hypertension. Systolic and diastolic pressures are equally important in its development. The most frequent consequences are cerebral atherosclerosis, fibrinoid necrosis with asymmetric aneurysms in the arterial wall, cerebral embolism – these can cause primary intracerebral hemorrhage (hemorrhagic stroke), subarachnoid bleeding, hypoxic stroke, encephalomalacia, with acute symptoms. At post mortem investigations lacunar brain degeneration (several trabecular cavities of 0.5 -1.5 mm diameter), as sign as earlier symptom-free or hardly noticed small infarctions in deep brain regions, is a frequent finding.

An acute rise in blood pressure may be responsible for *hypertensive encephalopathy*. The quick rise breaks through the autoregulation of cerebral blood flow, the intracranial pressure suddenly increases, with headache, nausea, vomiting, incoordination, falls, visual disturbances (e.g. scintillation), fits, loss of consciousness, coma, stroke, paraplegia. An ocular symptom is papillary edema, with exudate and retinopathy. Regional cerebral vasodilation and constriction, along with increased permeability, are thought to be pathogenetic factors.

Renal consequences:

- Vascular: the wall thickness of the afferent arteriole increases, the smooth muscle is swollen, there is hypertrophy, hyperplasia and fibrinoid necrosis.
- Glomerular: there is thickened capillary basement membrane, scar formation, hyaline produc-

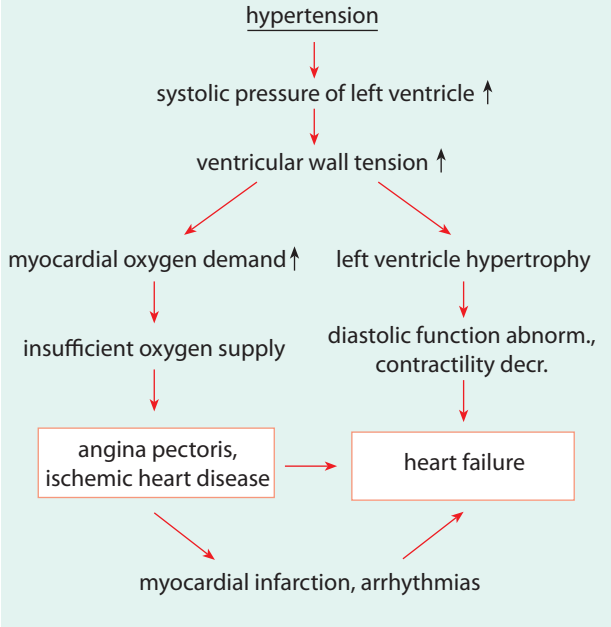

Fig. 2.30.: Heart damage in hypertension.

tion, increased permeability (this will give rise to proteinuria).

- Functional: decreased renal plasma flow with gradually decreasing GFR, despite increased filtration fraction. Non-selective proteinuria is an early sign. The speed of progression to chronic renal failure is variable, it also involves parenchymal damage.

Skin and muscles:
Prolonged changes in skin vessels (arterial stenosis, particularly in smokers) may lead to the formation of ischemic leg ulcers, accompanied by intermittent claudication.

2.3.2.4. BASIC PRINCIPLES IN THE TREATMENT OF HYPERTENSION

Causative treatment is indicated, if possible. Early recognition and treatment are of paramount importance, unfortunately there are lots of undiagnosed or mistreated (under- or over-treated) cases. Normalizing blood pressure too rapidly may lead to brain hypoperfusion and its consequences, because of the reset range of autoregulation of brain blood flow. The blood pressure should be lowered gradually, and kept at this lower level continuously.

Along with lifestyle and environmental recommendations, pharmacological therapy aims at decreasing the plasma volume by salt restriction, diuretics, plus the decrease of sympathetic tone by ACE inhibition, AT-receptor blockers, adrenergic (α and β) inhibition, Ca-channel blockers, vasodilator central adrenergic (α_2) blockers. Prevention of possible complications (secondary/tertiary prevention) should also be kept in mind.

2.4. DISORDERS OF VENOUS CIRCULATION

Factors ensuring venous backflow:
In upright position, secondary to addition of hydrostatic pressure, the venous pressure increases in the lower part of the body (Fig. 2.12.). Although the venous wall is elastic, significant amount of blood is not pooling in the veins. A reactive arteriolar constriction is accompanied by venous constriction (Fig. 2.13.), while closure of venous valves, muscle pump of the calf and negative intrathoracic pressure help venous return to the heart – without these the blood would accumulate in the lower parts of the body.

Venous varicosity: chronic venous insufficiency. The veins are dilated, convoluted, the venous tone is low, and the valves are insufficient. The velocity of blood flow is significantly decreased, and since under these circumstances the plasma flow is faster than the flow of corpuscles, thus, hemoconcentration occurs. The oxygen supply of the venous wall is impaired, and these changes predispose to thrombus formation (phlebothrombosis). Inflammatory changes of the already thrombotic vein (i.e. thrombophlebitis) may also develop, without concomitant bacterial infection. A retrograde pressure due to congestion affects the capillaries, the tissue oxygen supply is impaired and local edema develops. In superficial veins the congestion may be alleviated by collateral vessels, but the inflammation may still cause edema. If the thrombus is released and carried away by the blood (quite frequent event in case of deep venous thrombosis /DVT/ of the legs) it will enter the pulmonary circulation and pulmonary embolism develops. Depending on its size, it may even be fatal. Varicosity presents most commonly on the lower parts of the body, secondary to obesity, systemic venous congestion, or due to large vein compression. Immobilization of the extremity, increased viscosity, tumors, lower

extremity and hip operation, lower abdominal surgery are additional important causative factors in thrombus formation.

Thrombosis in other parts of the body is much less frequent. These are usually results of compression, with local edema, stagnation, and insufficient tissue O_2 supply.

Thrombosis, or *compression* of central veins obstructs filling of the heart and causes circulatory insufficiency. Increase in intrathoracic pressure (e.g. mechanical ventilation) carries the same risk. In cardiac failure there is congestion in the central veins – this impairs venous return. The consequences of this (anasarca, dyspnea, congestion of the portal vein, etc.) are discussed in connection with the venous circulation of the specific areas. Unlike in cardiac failure, the central venous pressure is lower in peripheral circulatory failures (except in the early phase of cardiogenic shock), and the backflow from the peripheral parts is insufficient.

The venous return can be improved by elastic bandaging of the lower extremities (elastic stockings), or by active mobilization (or even passive kinetics) of the limb ("muscle pump") which induce periodic compression of veins. Lack of muscle pump, immobilization promote the development of thrombosis (but a consecutive pumping may mobilize the thrombus). It is presumed (and used at some places) that a dry immersion of the legs into a cold, CO_2-rich air-bath (= mofetta: CO_2 released from earth in deep parts of caves, it does not reach upper parts of the body) increases the venous tone and enhances the venous return.

2.5. THE LYMPHATIC SYSTEM AND ITS ABNORMALITIES

Functional structure of the lymphatic system

The lymphatic system is a specialized system consisting of lymphatic vessels and lymphoid tissue. Lymphatic circulation is closely linked to the vascular system and forms an integral part of it. It does not form such a closed network as the vascular system, but the lymphatic capillaries begin as blind pouches deep in the connective tissue. One purpose of the lymphatic system is to return the fluid leaking from the vascular system to the interstitial space back into the circulation, *ensuring the stability of the interstitial fluid volume*. The liquid flowing out of the capillaries based on the balance of the intracapillary and pericapillary hydrostatic and oncotic pressures: it can reach up to two to four liters per day. This volume must be continuously returned to the systemic circulation. The lymph vessels are located very close to the capillaries; the fluid diffuses between the capillaries, the interstitium and the lymphatic vessels. Lymph itself is defined as blood plasma without its protein content. After this lymph has been filtered through the lymph nodes, it already contains lymphocytes and immunoglobulins. The lymph drains from the lymphatic vessels into a particularly low-pressure area of venous circulation through the thoracic duct and truncus lymphaticus dexter to the angulus venosus at the intersection of internal jugular vein and subclavian vein. Lymph circulation plays a role also in *the fight against pathogens, in the removal of toxins and in the absorption of fats.*

2.5.1. LYMPHATIC VESSELS

Lymphatic vessels have thin wall resembling mostly to the wall of the veins. Lymphatic capillaries are linked by thin filaments to the surrounding interstitial fibers. These connective tissues are anchored to the lymphatic capillaries and are likely to contribute to the enlargement of lymph capillaries during periods of increased lymph production. High permeability of lymph capillaries is due to larger gaps between endothelial cells and lack of basement membrane. Lymph capillaries form bigger lymphatic vessels, which contain valves similar to those of the veins. Due to their high permeability, lymphatic vessels may also take up particles of much larger size than capillaries such as macromolecules, large proteins, and bacteria leaked out from damaged tissue. In the walls of the larger lymphatic vessels, there is a concentrically located smooth muscle layer, where muscle fiber contractions are synchronized by their own pacemaker cells as a driving force for lymphatic flow. The more a lymph vessel is filled, the more marked the smooth muscle contractions are. The external pressure on the lymph vessels helps the lymph flow. The pulsating movement of the arteries drives the lymph to the direction of the heart, which is also assisted by respiratory-related chest pressure changes (negative pressure in the mediastinum) and by the positive abdominal pressure. Lymph circulation accelerates during physical activity, partly due to increased blood pressure and respiratory rate.

Unlike most organs of the body, cerebral interstitial fluid is not diffused from the blood plasma (blood-liquor barrier). The cerebral interstitial fluid is the se-

cretory product of endothelial cells. However, cerebral interstitial and cerebrospinal fluid are already in a relationship allowing diffusion.

2.5.2. REGULATION OF THE LYMPH CIRCULATION

Fluid exchange between the blood and the interstitial fluid is a process controlled by hydrostatic and oncotic, i.e. colloid-osmotic pressure variations inside and outside the capillary, thus physiologically the Starling forces and the effective filtration pressure play a leading role. Always slightly more fluid is filtered out on the arterial side of the capillaries as taken up on the venous side; this difference is the interstitial fluid, which is returned to the venous side of the circulation through the lymphatic vessels. When tissue pressure is increased, the loose endothelial cells lining the lymph capillaries as a shingle on a roof are separated by the increased pressure and free flow of liquid can occur through the gap between them. In the case of heavily filled, dilated lymph capillaries, the internal pressure closes the endothelial cells and like a valve they prevent further fluid intake. In the case of extremely enlarged lymphatic vessels, however, due to the large internal pressure, the endothelial cells are separated, large gaps are formed on the wall of the lymph vessel, the fluid can travel freely in both directions, so the interstitium and the lymphatics will have the same internal pressure.

2.5.3. CHANGED LYMPH FLOW, TYPES OF EDEMA

Physiologically, the interstitial fluid volume is constant. However, if much more fluid flows out of the capillaries and the increased lymphatic flow cannot keep pace, **dynamic** lymphatic disorder, tissue fluid accumulation, **edema formation** occurs. Edema formation can be the result of either an increased hydrostatic pressure in the venous part of the capillaries (e.g., in a congestive heart failure, opening of the arterioles in beri-beri or hot environment) or reduced colloid osmotic pressure of plasma proteins (e.g. in hypoalbuminemia). The increase in vessel permeability in inflammations of different origin means a further pathogenic factor. In addition to the above reasons, damage to the lymphatic system itself can cause edema by **obstruction**, which is called **lymphedema**; in this case, even the transport of the normal lymph volume is disturbed.

Lymphedema: etiology and pathogenesis

Primary lymphedema develops due to a congenital disorder; it is a relatively rare disease. The edema formation based on other diseases or any edemas from an iatrogenic origin are called secondary, since their cause can be identified. Worldwide, the most common cause of the secondary form is the filariasis of the lymphatic system, where worms migrate to the lymph nodes and hinder the lymphatic flow. In developed countries, obstruction of the lymphatic drainage is most often the result of surgical removal or irradiation during treatment of cancerous diseases. After mastectomy, edema occurs in 24 to 49%, and after lumpectomy, in 4 to 28% of the cases. Other causes of the secondary form include tumor infiltration, mechanical compression, lymphangitis or lymphadenitis caused by viral, bacterial or fungal infection or immune complex formation. Traumas, post-operative scars, and venous diseases (varicose veins, obstructed veins) may also coexist. In the case of paralysis caused by different reasons, edema can be formed due to lack of muscle pump.

2.5.4. CLINICAL MANIFESTATION AND DIAGNOSIS

The lymph accumulates in the interstitium, which presents in acute cases in the form of a pitting edema and it is reversible in this stage. In chronic cases, it leads to an inflammatory response, it is transformed to connective tissue, and the skin becomes dough-like.

In tumorous patients, due to the more common occurrence of coagulation disorders, in case of an often unilateral limb swelling, deep vein thrombosis should be considered, because beside the typical thrombotic signs, it is often associated with secondary edema. Before diagnosing primary lymphedema, the secondary causes should be excluded, as contrast media itself causes obstruction of the lymphatic system, as well as aggravation of the symptoms in contrast lymphangiography. *In the case of an edema of unknown origin, our main goal should be exclusion of tumor diseases and deep vein thrombosis.*

2.5.5. COMPLICATIONS OF EDEMAS

In the presence of any edema, tissue microcirculation is severely impaired. Congestion of the affected limb and the edema fluid increases the diffusion route leading to hypoxia of the limb. The visible alteration of the skin is papillomatosis due to connective tis-

sue and epithelial tissue proliferation. The limb with lymphedema becomes susceptible to *infections*, in the form of recurrent fungal infections, erysipelas, or cellulitis. As a result of inflammations, scar tissue results in decreased lymph drainage, leading to limb elephantiasis. In severe cases, the lymph can form bullae on the skin, or lymph can be excreted through lymphatic fistulas, leading to significant protein loss. This is another source of infection. If the protein loss is more severe, hypoproteinemia exacerbates the edema by decreasing the oncotic pressure. Chronic edema may lead to the development of malignant lymphangiosarcoma.

Disturbance of the lymphatic circulation greatly contributes to the injury to the inflamed area. The experimental obstruction of the coronary sinus in itself does not cause serious changes in the myocardium, but when the lymphatic vessels are simultaneously obstructed, the ECG shows a typical acute myocardial infarction. Injury of the lymphatic system of the lung contributes to the development of pulmonary edema, hinders the absorption of the exudate in case of pneumonia and contributes to the subsequent development of fibrosis. Beside healthy lymphatic circulation, occlusion of renal pelvis does not damage irreversibly the kidney for weeks, but if the inflammation damages and blocks the lymphatic circulation, the kidney will perish within a few days.

The location of edema is also important concerning the complications. Further discussion of this and the pathological consequences of edema is described in ch. 6.1.2.2. Ascites (ch. 7.6.1.7.) deserve particular attention, which is due to the dynamic failure of the lymphatic circulation in the liver.

2.5.6. THERAPEUTIC CONSIDERATIONS

To improve venous circulation, *compression products* (stockings, socks), lymphatic massage and physical activity are recommended. While lymphatic flow is minimal in an inactive limb, *active or passive movement of the limb* instantly increases lymphatic flow. There is currently no official medication for the improvement of lymphedema. The *use of diuretics* may yield minimal results, but their use **is** *not recommended* because the relative increase in interstitial fluid protein content stimulates fibroblasts to promote fibrotic remodeling of the edema. Surgical treatment is possible by removing the subcutaneous tissue and creating an artificial lymph-vein anastomosis.

2.6. CIRCULATORY DISORDERS OF SPECIFIC ORGANS

2.6.1. CORONARY CIRCULATION

2.6.1.1. CHARACTERISTICS AND DISORDERS OF CORONARY CIRCULATION

The metabolism in the myocardium is aerobic, therefore, when compared to its mass, the coronary circulation is excessive, even at rest (approx. 80 ml/100g/min) and the O_2 extraction is nearly maximal (up 10-14%). The O_2 consumption is 8-15 ml/100g/min. In the event of an increased workload, the oxygen supply can match demands if proportionately increased perfusion is provided. Without this, the contractility decreases and the pump-function fails. Optimally, in physiological conditions, the demand and supply are in balance.

Coronary arteries enter the ventricular wall from the pericardium. They divide into smaller branches while they penetrate the myocardium from the outside toward the subendocardial area. Due to their anatomical position, the subendocardial regions of the left ventricular muscle receive its blood supply only in diastole owing to the rise of intraventricular pressure and ventricular contraction in systole. In these areas, the circulation diminishes or ceases during systole, and, at its peak within certain areas, begins to flow backwards (the often referred, *slosh-phenomenon*, Fig. 2.31.). Therefore, regarding coronary circulation, both diastolic time and intracavital pressure are of high importance. The right ventricular O_2 supply is regarded as fair, even in systole, since the thinner ventricular wall and lower intraventricular pressure do not compromise blood flow. A coordinated regulation must assure the proper adjustment of coronary blood flow to the actual needs.

The capillary density in the myocardium is nearly 2000/mm^3, with half of them continuously open. Increasing the number of open capillaries constitutes a *capillary reserve,* that is important in *ischemic preconditioning* (please note below).

α_2 adrenergic activity decreases coronary flow, while hypoxia, adenosine, K^+, lactate, NO and PGI_2 increase it; correctly, the intact epithelium inhibits the constrictor effect of endothelin upon the vascular smooth mus-

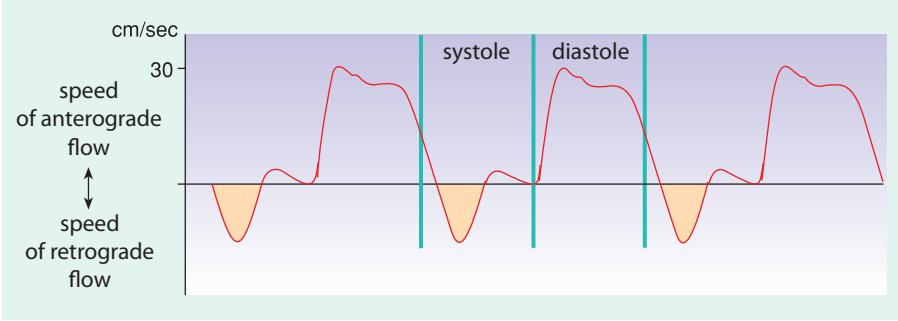

Fig. 2.31.: Blood flow in smaller coronary vessels during systole and diastole (the slosh-phenomenon).

cle cells (VSCM). Endothelial damage, on the other hand, leads to VSCM contraction upon endothelin action. Upon its binding to intact endothelium, endothelin indirectly leads to dilation, since it induces $NO^{\bullet}$ synthesis. Angiotensin II and ADH/vasopressin are vasoconstrictors administered in pharmaceutical doses.

Factors of myocardial oxygen supply and demand under normal/abnormal conditions:

Factors affecting O_2 demand:
Work of heart:

1. The effort against blood pressure (an important factor, determines the *pressure performance*) and is dependent upon the systolic peak pressure (determined substantially by TPR) and upon the cardiac output (i.e. stroke volume x heart rate).
2. Kinetic work: it accelerates as it pumps out the blood. Normally, a non-dominant segment of the effort of heart. Largely, it is dependent upon blood viscosity, state of aortic valve and ejection time. It is increased in valvular insufficiency.

Hemodynamic parameters:

1. heart rate
2. contractility
3. ventricular wall tension (strain)

According to the **LaPlace law: Pi × Ri / 2 × h**

- directly proportional to intraventricular pressure (Pi)
- directly proportional to internal radius of left ventricle (Ri)
- indirectly proportional to wall thickness × 2 (2 × h)

Two pathophysiologically important conclusions can be drawn from the LaPlace law:

– mild increase in left ventricular wall thickness (e.g. mild hypertrophy seen in athletes) is advantageous by decreasing wall tension and oxygen demand.

- on the contrary, left ventricular dilation (e.g. late phase of heart failure) increases wall tension, hence, myocardial oxygen demand.

Factors affecting oxygen supply:
Myocardial oxygen extraction is near maximal, even at rest, and a significant increase cannot be achieved even by exertion. This means, that even without exertion, the myocardium functions at the edge of hypoxia.

Coronary perfusion is dependent upon *perfusion pressure* (aortic diastolic pressure – coronary sinus pressure) and *coronary resistance* (normally, very small). The perfusion of the left ventricle is affected by EDp, in which elevated EDp primarily impairs perfusion of subendocardial myocardium regions.

Table 2.7.

Factors of myocardial oxygen need and oxygen supply under normal and pathological conditions

NORMAL CONDITIONS	
MYOCARDIAL OXYGEN NEED = MYOCARDIAL OXYGEN SUPPLY	
heart rate	coronary circulation
contractility	– perfusion pressure
ventricular strain	– coronary resistance
– ventricle size	myocardial oxygen extraction
– intraventricular pressure	
work of the heart (pressure, kinetic)	
PATHOLOGICAL CONDITIONS	
MYOCARDIAL OXYGEN NEED >> MYOCARDIAL OXYGEN SUPPLY	
reversible ---------- myocardial ischemia ---------- symptoms	
(angina pectoris)	thoracic pain
	left ventricle contractility ↓
irreversible	local metabolic disorders
(sudden cardiac death)	electrophysiological changes
(AMI)	

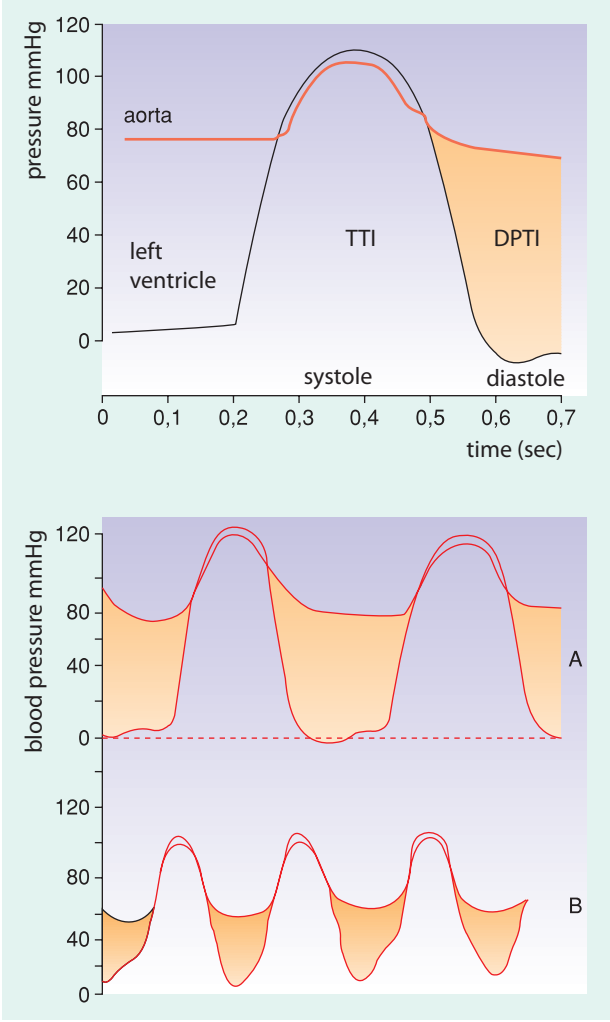

Fig. 2.32.: The DPTI/TTI ratio is used to assess the viability. Compared to a normal (A) situation, tachycardia and an increase in EDp (B) impair the ratio.

Viability of myocardium (what is based on the balance of oxygen supply and oxygen demand) can be assessed by a demonstrative graphical method, and this is the value of the **DPTI/TTI ratio.** The value of diastolic pressure-time index, DPTI, is proportional to the myocardial O_2 supply. The tension-time index, TTI, (referring to systole) is proportional to the myocardial O_2 demand. Viability improves with the increase of the ratio (DPTI/TTI).

Fig.2.32. defines further correlations:

1. Increasing heart rate shortens the diastolic time, what typically leads to a diminished blood supply of the left ventricle
2. EDp increase (due to the Frank-Starling mechanism) observed in heart failure and possibly at excessive exercise, negatively affects the left ventricular oxygen supply and viability.

Causes of decreased coronary reserve:

Decreased diameter of coronary vessels:

1. atherosclerotic plaque causes ca. ≥75% stenosis of the lumen and inevitably results in ischemic symptoms (e.g. stable angina with or without exercise). For specific details on the development of atherosclerosis (ch. 9.3.2.).
2. coronary spasm (without plaque formation, e.g., the spasm of the subepicardial coronaries) causes Prinzmetal angina.
3. thrombus formation refers to a rupture of an unstable plaque, rich in lipids, or the formation of thrombus on top of a late complicated plaque, which can occlude the coronary lumen with concomitant myocardial ischemia. If spontaneous recanalization via local activation of fibrinolysis does not ensue quickly, or not at all, consequently, the result is acute myocardial infarction (AMI, and/or, necrosis of the myocardium). In the event of recanalization following a short (< 30 min.) temporary occlusion, instable angina sets in and wanes with no perceptible signs of permanent muscle damage. N.B.: therapeutic recanalization either by percutaneous catheter intervention (PCI) or by thrombolytics inevitably improves the outcome if performed within 4 hours following the onset of occlusion.
4. An embolism in the coronaries is very rare, due to the anatomical conditions, such as, the emboli expelled at a high speed from the left ventricle upon opening of the aortic valve in systole has a much higher chance to move (centrifugally) through big vessels of the neck toward branches of the cerebral arteries, than compared with turning back and finding their way into orifices of main coronary arteries behind the pouches of the aortic valve. Emboli may originate from the left atrium (e.g. in atrial fibrillation), the left ventricle (from a wall thrombus after an AMI) or rarely (in the case of a foramen ovale apertum) from the venous side.

Without decreased diameter of coronaries:

1. generalized hypoxic states, e.g., severe anemia
2. extreme workload (excessive exercise) (demand increases)
3. increased blood viscosity, e.g. (in polycythemia vera, polyglobulia, as seen in Cushing's disease)
4. increased coagulability (thrombophilia)
5. diseases of the small vessels (vasculitis)

2.6.1.2. ACUTE MYOCARDIAL ISCHEMIA

Consequences of myocardial ischemia:

Sequence of events following a 0.5-1 min ischemia is demonstrated in Fig. 2.33.

1. approx. 5 s: active diastolic relaxation is impaired
2. approx. 8 s: impaired systolic function (low contractility)
3. approx. 15 s: hemodynamic changes, e.g. decreased EF, stroke volume, high EDp
4. approx. 18 s: ECG changes (typically ventricular premature beats or ventricular tachycardia/flatter/fibrillation)
5. approx. 25 s: angina pectoris sets on (constricting type chest pain)

Consequences according to the type of changes:

1. Electric: The surface of the damaged myocardial fibers is increasingly more electro-negative at rest than when compared with their normal counterparts. This generates the well-known effect, "*current of injury*" typically leading to the appearance of ST changes upon the ECG, reentry, arrhythmias and ventricular fibrillation may develop (see details in the ECG, ch. A1.).
2. Mechanical: Wall kinetics may be deranged in the affected area (Fig.2.34.): Hypokinesia, akinesia and dyskinesia may all likely be seen, occasionally, with the ventricular wall rupture hemopericardium and cardiac tamponade. The increased contractility of adjacent intact ventricular areas may partially compensate regarding the hypokinesia of the damaged myocardium.
3. Biochemical:
   a) local hyperkalemia is triggered by the release of K^+ from necrotizing cells, consequently peaked, and tall T-wave is seen on the ECG.
   b) enzymes are liberated from the damaged myocardium several hours afterwards, e.g. creatine-kinase (CK) myocardial band (MB) or CK-MM_3 type, or myofibrillar components, like troponin T, troponin C, myoglobin (Fig. 2.35.)
4. Structural: Although as seen in animal experiments, irreversible damage can be demonstrated already 15-30 min following occlusion of the coronary branch, histopathological signs are observed only a few hours later (see. Fig. 2.36.: the cup or plate shape "necrosis

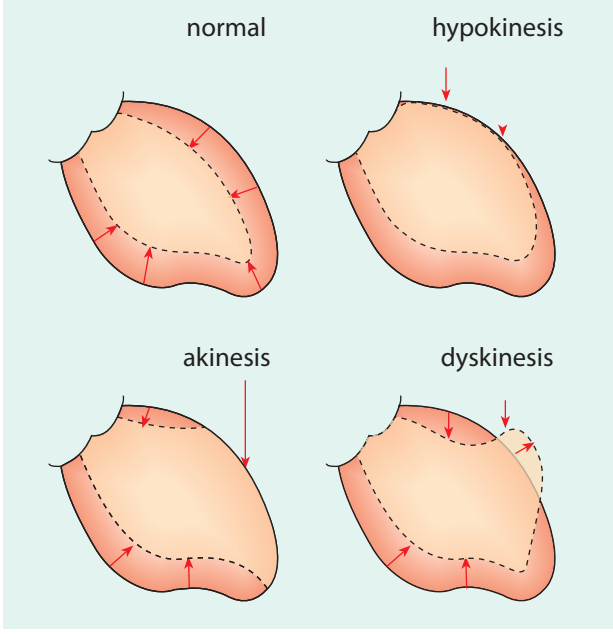

Fig. 2.34.: Ventricular wall kinetics (continuous line in diastole, dashed line in systole), in normal, hypokinetic, akinetic and dyskinetic states.

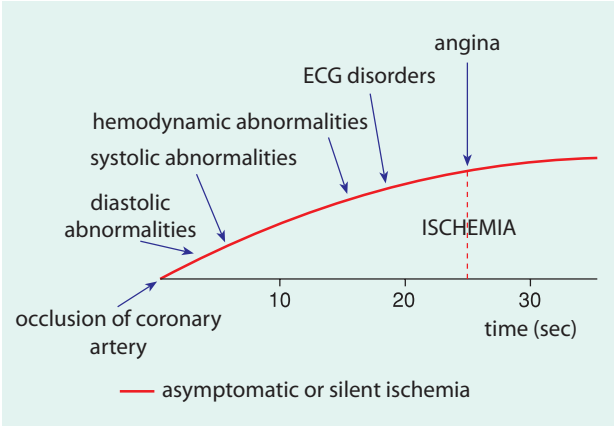

Fig. 2.33.: Cascade of ischemic changes in the function of time

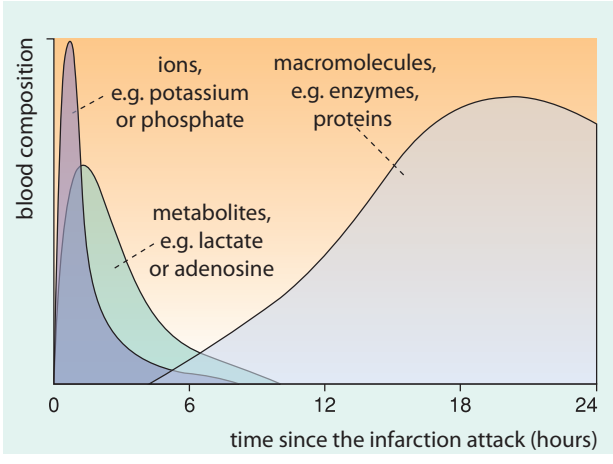

Fig. 2.35.: Biochemical changes following myocardial infarction.

wave" travels from the endocardium to the epicardium. Within 45 minutes, ca. ¼, following 3 hours ½, within 6 hours ¾, and within approx. 24 hours, the entire thickness of the left ventricular wall will be necrotized. The picture of the patchy papillary necrosis is also time-dependent, yet partial necrosis (and the concomitant papillary rupture) may develop prior to the transmural wall necrosis. Transmural necrosis is seen in the form of a Q-wave on the ECG (ch. A1.2.3.).

CLINICAL CONSEQUENCES:

Acute coronary syndrome (ACS) is the clinical term currently used to sum up all conditions in which myocardial ischemia is lurking in the background, should it be reversible (angina) or irreversible (infarction/AMI).

Reversible ischemia – angina pectoris (chest pain)

a) *Stable angina – effort angina* – It is set upon a standard level of exercise, in which a stable plaque causing more than 75% coronary stenosis is in the background.)
b) *Unstable angina* – Independent of exercise/exertion, develops on the grounds of coronary lumen stricture of variable degree. There are unstable, supposedly ruptured, fat-rich plaques in the background, with periodic transient occlusion and recanalization of the lumen. It usually presents a few days prior, or following myocardial infarctions.)
c) *Prinzmetal angina / angina varians* – Presents itself typically upon rest, in the form of transient, constricting chest pain. Subepicardial coronary spasm is in the background.
d) *Mixed angina* – Includes the characteristics of all the previous forms.
e) *"Silent" angina/ischemia* – It can be diagnosed by ECG alterations, however, it is not accompanied with chest pain. It presents itself frequently in autonomic neuropathies, as seen in DM. ACS of inferior localization may sometimes be accompanied with vomiting, yet without the characteristic type of pain associated with angina pectoris.
f) *„Walk through" angina* (An angina that presents at a certain level of the exercise tolerance test, but ceases with the continuation/increase of workload. Often explained by a delayed utilization of the coronary reserve in course of the test.)

The clinical perspective regarding ACS can present itself in three primary types:

1: ACS without ST elevation
- 1/1: Unstable angina pectoris (reversible subendocardial ischemia)
- 1/2: Infarct without ST-elevation (NSTEMI: non-ST-elevation myocardial infarct)

2: ACS with ST elevation (STEMI ST-elevation myocardial infarct)

3: Sudden cardiac death due to ischemia (e.g. ventricular fibrillation developing early in the course of ACS)

Irreversible ischemia – acute myocardial infarction (AMI) and its potentially lethal complications:

a) ventricular fibrillation (frequent, particularly in the first few hours)
b) cardiogenic shock (presents when at least 40% of the ventricular myocardial mass is necrotic, the mortality is near 60%)
c) ventricular wall rupture, cardiac tamponade
d) papillary muscle rupture, leading to valvular insufficiency
e) wall thrombus implies a high risk of cerebral embolization > stroke (note the chapter referencing cerebral circulation, ch. 2.6.2.)
f) ischemic cardiomyopathy is defined as ischemic heart disease

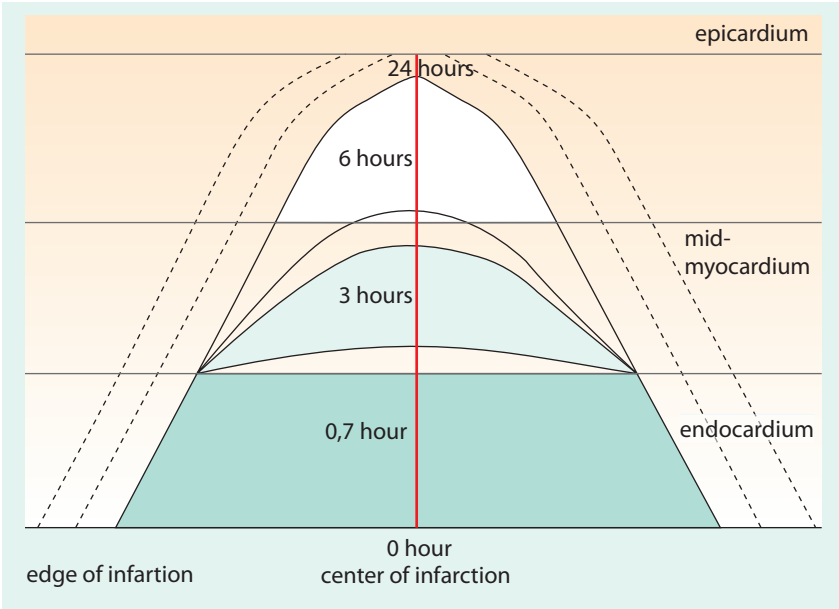

Fig. 2.36.: Advancement of necrosis in myocardial infarction (necrosis wave).

(IHD) (multiple, small infarctions destruct the myocardium, including the phenomenon of remodeling /see below/).

REPERFUSION AND REPERFUSION DAMAGE (cf. ch. A9.)

1. Reperfusion is essential for the survival of the affected area or in the very least, a part of it. Early reperfusion in the clinical practice (within 1-3 hours) is the main goal of therapy and always considerably beneficial. Reperfusion within 4-6 hours may diminish the area of necrosis in the affected areas. It is supposed that reperfusion within 12 hours is still beneficial from the point of remodeling.
2. Reperfusion following a lengthier ischemic period may be, on the other hand, harmful:
   a) during ischemia, the level of antioxidant free radical scavengers in the myocardium significantly decreases, while the xanthine-oxidoreductase enzyme converts to **xanthine-oxidase**, which is an enzyme capable to create the free radical superoxide. Reoxygenation during reperfusion is therefore, followed by **free radical damage** (often referred to as *oxygen paradox*).
   b) the **Ca^{++}** content of reperfused fibers initially shows an oscillating change (Ca^{++} is released from the sarcoplasmic reticulum), which can trigger arrhythmias, **ventricular fibrillation,** and, during reperfusion, the Ca^{++} may accumulate intracellularly, which can contribute to the maintenance of **"stunned" myocardium** (= despite reperfusion, myocardial contractility is markedly depressed). H^+ wash-out through reperfusion generates H^+ efflux from the cells which is replaced by a Ca^{++} influx into the myocardial cells (commonly referred to as *Ca-paradox*)
   c) **hibernation** is also associated with reperfusion (decreased myocardial function during prolonged, abnormally low perfusion): normalizing perfusion possibly improves the situation.
   d) during the **no-reflow** phenomenon, the microcirculation will not restart, despite recanalization of larger arterial branches. Ischemic swelling, or possibly death and flaking of endothelial cells are supposed to be in the background, including the inflammatory activation of circulating white blood cells (leukocytes) which adhere to the capillary endothelium.
3. Mild, repeated ischemia may be useful in the long term:
   a) **remodeling:** The rearrangement of muscle fibers may beneficially compensate for the dysfunction of damaged fibers (although it can also be harmful in contributing to the ischemic cardiomyopathy).
   b) preconditioning: Mild ischemic episode may activate **tissue defense mechanisms** (e.g. heat shock protein 70 /HSP-70/ expression).
   c) mild ischemia may **open previously closed capillaries**, thus, **collateral circulation** may evolve.
   d) the **patient may change his/her lifestyle** following complaints of angina (healthy diet, sports, less cholesterol consumption, cessation of smoking, attaining optimal body weight, etc.), which, according to latest results, might lead to a decrease of volume and fat-content of already developed plaques, hence, decreasing the risk of infarction and cardiomyopathy.

CIRCADIAN OCCURRENCE OF ACUTE CARDIOVASCULAR EVENTS

Unlike nightly cumulating, mainly acute circulatory events (e.g. paroxysmal nocturnal dyspnea), the severe, acute coronary syndromes (AMI, sudden cardiac death, angina pectoris) are most frequent in the early hours of the day, following or just prior to waking up. During the day, the frequency is relatively decreased, yet is still higher than when compared to that of the night. There is an "AMI peak" in the afternoon (Fig. 2.37.), as well.

The circadian changes may be attributed to the increased sympathetic tone in the morning and early evening (Fig. 2.38.). Daily fluctuations in cortisol levels, as well as the hemorheological parameters (blood viscosity) may also have a role. Thrombotic tendency is also higher in the morning.

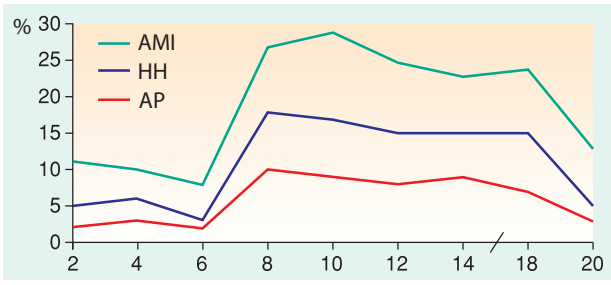

Fig. 2.37.: Circadian occurrence of AMI, sudden cardiac death, and angina.

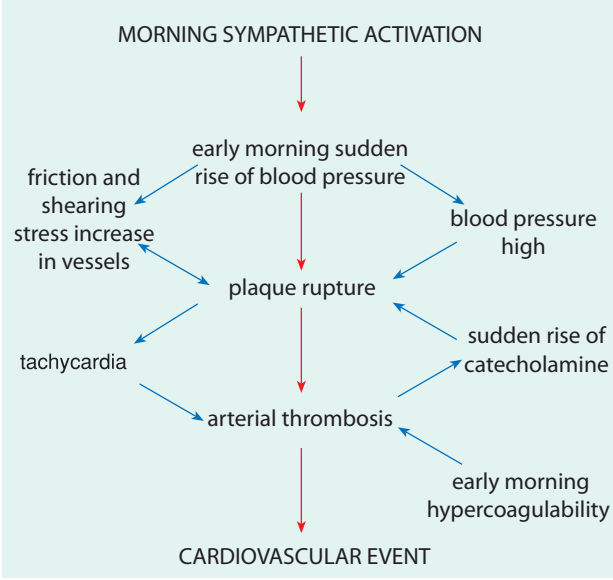

Fig. 2.38.: Role of activation of morning sympathetic activity in the explanation of acute coronary syndromes.

PREVENTION AND THERAPY OF ACUTE CORONARY SYNDROMES:

Primary prevention: Develop and maintain a healthy lifestyle.

- stop smoking
- normalization of hypertension and dyslipidemia (ideal weight, regular exercise, optimal diet)

Therapy:

- instrumental (catheter plus stent)
- pharmaceutical: thrombolysis and anticoagulants
- bed rest, β-blockers, ACE-inhibitors to decrease myocardial oxygen demand
- administration of O_2 may prove beneficial
- nitrates ($NO^{\cdot}$ donors) are effective in angina, yet may not be helpful in AMI
- inhibition of platelet aggregation (aspirin, clopidrogel)

The significance in eliminating risk factors is supported by statistics in the US, due to a successful campaign in the 1960s and '70s, which brought about changes in lifestyle, participation in sports, the decrease of risk factors, and, perhaps ingesting antibiotics which prevent latent chronic infections. Today, "only" 600 000/y individuals succumb to stroke or AMI. In contrast, unfortunately, the cardiovascular mortality scored steeply upwards in Hungary since the 1970s and '80s. Simultaneous presence of more risk factors increases the cardiovascular mortality (Fig. 2.39.).

2.6.1.3. CHRONIC MYOCARDIAL ISCHEMIA

Chronic ischemia causes diffuse degenerative/fibrotic transformation of the heart muscle tissue, particularly in the endomyocardial areas. Eventually, it

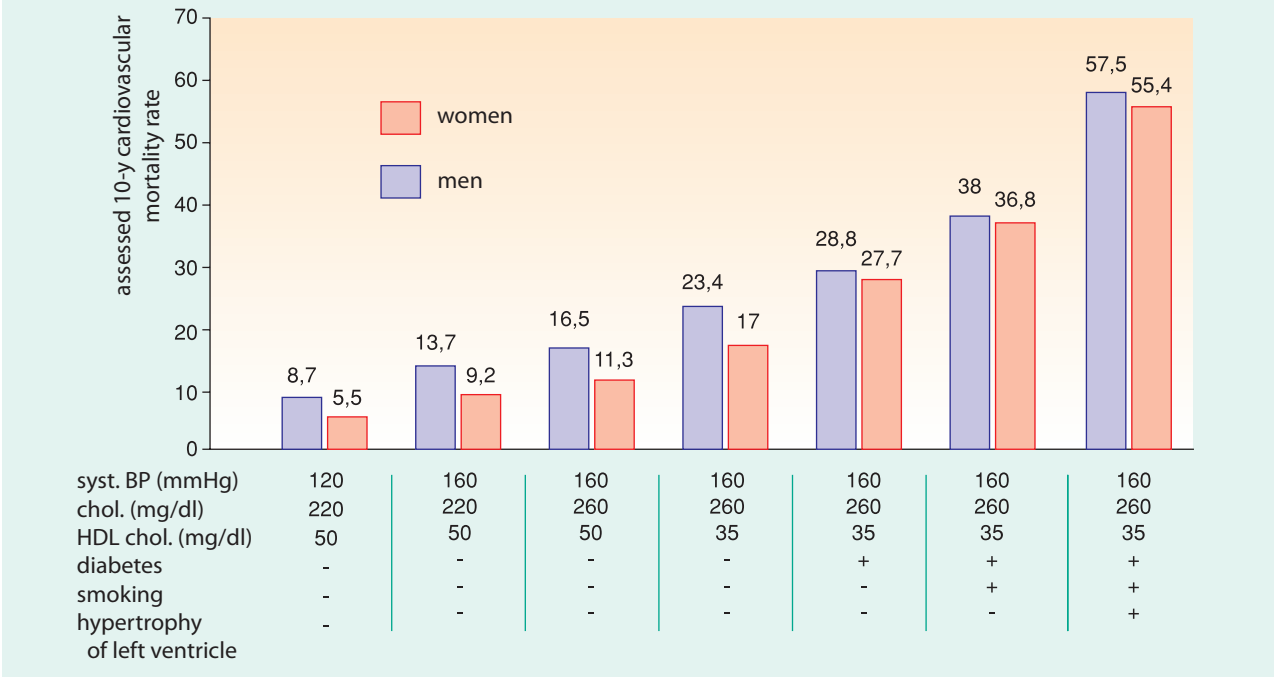

Fig. 2.39.: Role of cumulation of risk factors in the development of risk factors in the development of cardiovascular events based on coronary disease of men and women (10-years average).

leads to compromised contractility, yet even prior to, it interferes with the diastolic compliance of the ventricle (diastolic dysfunction/decreased lusitropy). This leads to raised levels of EDp which, in turn, impairs endomyocardial oxygen supply yet even more. The tendency for angina pectoris increases substantially, however, the risk of AMI (transmural necrosis) may be alleviated by the ischemic preconditioning. The impaired ventricular pumping ability and consequential rise in intraventricular EDp causes increased atrial wall stretch, which is a major risk factor regarding atrial fibrillation with arrhythmia absoluta. (N.B.: the risk and peril regarding atrial ball thrombus and embolization!) The dilation of the left ventricle leads to insufficiency of the mitral valve, consequently resulting in the further deterioration of the pumping efficiency. Degenerative foci of the myocardium may be the source of ventricular premature beats, or might even generate ventricular fibrillation. The damage of impulse conducing fibers running underneath the endomyocardium may lead to bundle branch blocks, AV-blocks or even Adams-Stokes syndrome. In summary, progressive failure of both systolic and diastolic ventricular functions, with angina, various impulse-formation and -conduction anomalies are the main hallmarks of chronic myocardial ischemia.

2.6.2. CEREBRAL CIRCULATION

2.6.2.1. CHARACTERISTICS OF THE CEREBROVASCULAR SYSTEM

Cerebrovascular emergencies rank at the third level in the Western world, following coronary and malignant diseases. According to its origin, a **stroke** can be either **hemorrhagic** (*apoplexy*/bleeding or *aneurysm rupture*), or **ischemic** (can be *brain infarct* with necrosis if permanent, or transient ischemia if temporary).

The weight of the brain (approx. 1.5 kg) represents only 2% of the entire body weight. Despite this, at rest, the brain receives 15% of cardiac output, consumes 25% of all oxygen, and 70% of all glucose. There are no energy stores in the neurons, therefore circulatory arrest results in loss of consciousness (LOC) after several seconds, and irreversible changes are seen following 3-5 minutes. In the brain, no advantages of ischemic preconditioning are yet known (c.f. coronary circulation). Neurons can utilize not only glucose, but lactate as well, originating from glucose and presented by the glia cells (peripheral lactate will not reach neurons). Apart from this function, (astro)glia can neutralize excitatory neurotransmitters (glutamate→glutamine transformation), stores glycogen, produces heat, and it is also responsible for certain immune functions. Their ratio to the neurons in the adult brain is 10:1 (the size of the neurons is much larger, hence, the weight ratio for glia:neuron is ca. 1:1).

Parameters of cerebral blood flow – CBF:

1. CBF: 700-800 ml/min, it is **a relatively constant** value and cannot be increased, even by robust activity, due to the enclosed space (the flow can accelerate), except as seen in epileptic fits. The cerebral circulation is a**utoregulated** in a range of 50-150 mmHg of mean arterial pressure, in which the CBF is constant. This means the normal CBF can be maintained even at a mean arterial pressure of 60-70 mmHg, provided the patient is in a supine position. The brain perfusion can adjust to the changing demands by intracerebral rearrangement of the circulation (Roy-Sherrington principle). The shifting of the ratios of circulation between areas can be monitored through the use of diagnostic procedures (PET-CT, infracam) to deduce local activity in which, characteristically, perfusion rises.
2. Another parameter of CBF is flow, referred to 100 g tissue. On average, it is **60 ml/100g/min** (cortical flow is 80 ml/100g/min). If this value decreases to 20 ml/100g/min, functional abnormalities are expected, below 10 ml/100g/min irreversible changes will be observed.
3. Average O_2 consumption of the cerebral tissue is 3.5-4 ml/100g/min (higher in the grey matter and lower in the white). The cerebral O_2 extraction is relatively constant: the O_2 content of cerebral venous blood is 8-10 ml/100 ml. In REM sleep, epileptic fits and in the early phase of head injury the metabolism of the entire brain increases, and in contrast, in a coma state or in the event of sedative overdose, it decreases.

The sympathetic and parasympathetic nervous system portrays little role in the regulation of cerebral circulation. However, some metabolic products possess *high vasodilator activities*, and these are CO_2, H^+ (pH), K^+, adenosine, $NO^{\cdot}$ and the decrease of pO_2. Vasoconstrictor effect is attributed to decreased $\mathbf{pCO_2}$ or alkalosis.

Intracranial fluid spaces (Fig. 2.40.):

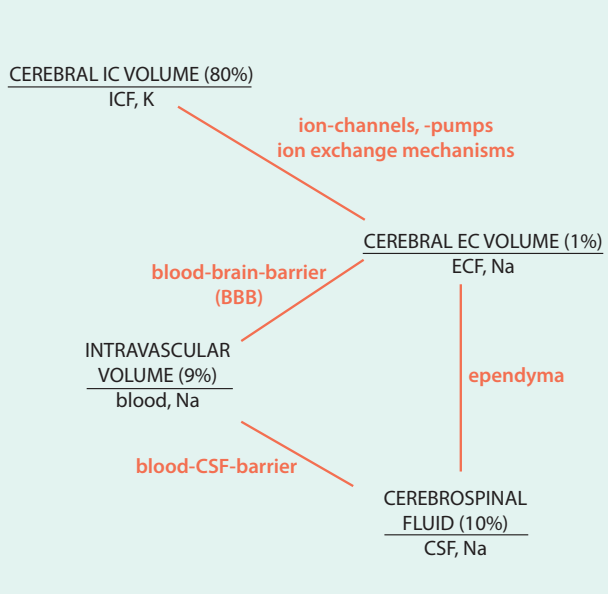

Fig. 2.40.: Intracranial fluid spaces.

2.6.2.2. CEREBRAL ISCHEMIA, ISCHEMIC STROKE

According to their localization, forms of cerebral ischemia are classified in the following manner.

1. *Global*
   a) Adams-Stokes syndromes: e.g. 3rd degree sino-auricular or atrioventricular block, sinus arrest and/or ventricular fibrillation.
   b) *Very* late phase of circulatory shock, e.g. severe hemorrhage and/or cardiogenic shock (cerebral perfusion during shock is maintained almost up to the end, due to redistribution)

2. **Regional (local)**
   a) Atherosclerosis: Characteristically severe, more than 60-70 percent stenosis regarding the vessels supplying the brain (carotid arteries and/or vertebral arteries). Stenosis or obliteration of a single artery in the neck will not necessarily result in cerebral ischemia, provided other arteries are intact/patent, since blood distributed through the *circulus arteriosus Willisii* is able to provide satisfactory perfusion of the brain. N.B.: *circulus arteriosus Willisii* is incomplete, i.e., it does not form a full ring in about 15-20% of the population, hence, these individuals are more vulnerable regarding the risk of brain ischemia. The branches of cerebral arteries, however, are end-arteries, and their stenosis or obliteration causes ischemia to brain areas supplied by them. *Subclavian steal syndrome*[1] is an interesting yet rare circulatory anomaly affecting brain perfusion.
   b) Cerebral embolus (derived from ventricular or atrial thrombus, carotid plaque thrombus, etc.)

TYPES OF CEREBRAL ISCHEMIA IN THE CLINICAL SETTING:

Reversible forms:

1. *Transient ischemic attack (TIA)*: Reversible ischemia, presenting with symptoms which last from 5-30 minutes up to 24 hours. Likely associated with a spasm or occlusion and quick (within 5 minutes) recanalization of a smaller cerebral vessel often found in the background. An MRI of the brain detects no tissue damage following this event. Within two years after a TIA, the occurrence of a stroke with permanent consequences is high, due to the shared risk factors. Today, less cited forms include the following: *Reversible ischemic neurological deficit (RIND)*: Presents with symptoms lasting up to 7-10 days, and characteristically, the longest regarding spontaneous improvement. *Prolonged reversible ischemic neurological deficit (PRIND)*: Presents with symptoms that last longer than 7-10 days, but with spontaneous improvement waning within a couple of weeks. The brain MRI in these latter cases tends to detect some tissue damage, hence, these actually qualify as mild strokes affecting small areas
2. *Prolonged ischemia*: Rapidly, or slowly developing, progressing, irreversible ischemia with permanent complications: *Ischemic stroke* (brain infarct)

CONSEQUENCES OF CEREBRAL ISCHEMIA:

1. The brain does not tolerate ischemia. Nevertheless, in vitro neural and glia cells are able to survive for several minutes, in vivo irreversible changes occur after already 1.5 minutes of circulatory arrest. Cortical functions may return if perfusion is restored within 4-5 minutes following the arrest.

[1] *Steal syndrome* on the great cervical vessels: if the left subclavian artery is stenotic directly distally from the origin of the carotids, upon moving of the left arm the increased demand for blood is met only by *"stealing" blood [at least partially, through the ipsilateral vertebral artery (the direction of flow is reversed)] from the cerebral circulation*

2. The ischemic tolerance is impaired by an increased level of the excitatory neurotransmitter glutamate (Glu) (moderately decreased release and severely damaged energy-dependent reuptake), which increases O_2 consumption and worsens cellular damage. Glu activity increases cellular Ca^{++} uptake, Na^+ influx, elevates the extracellular K^+-level, prolonging depolarization time of the neurons. Inhibition of Glu-receptors (by inhibiting NMDA /N-methyl-D-aspartate/ -dependent Ca^{++}-influx, and kainite- and AMPA /amino-methyl-isoxazolepropionic acid/ -induced monovalent cation fluxes) may help cellular survival. The level of acetylcholine rapidly decreases, followed by a fall in the level of dopamine and noradrenaline. The ischemia tolerance of the brainstem is much better, it can survive up to 20-30 minutes of circulatory arrest, which explains cases with decortication syndrome.

Process of damage:

1. **Induction**
   The glucose supply diminishes, pO_2 is decreased, and the Glu activity increases (due to low reuptake). Ca^{++} channels open due to the activity of NMDA receptors, monovalent cation channels are activated by kainate receptors. Na^+ enters and K^+ leaves the cells. These will result in an enhanced excitability of the neurons, and their cell-swelling (a type of *brain edema*).
2. **Amplification**
   The Ca^{++} influx continues, the IP3 (inositol-triphosphate) and DAG (diacyl-glycerine) systems are activated and the glutaminase activity is increased. DNA and phospholipid damages occur.
3. **Expression**
   DNA, protein and phospholipid damage (e.g. peroxidation) progresses and expands. The arachidonic acid metabolism is accelerated, the free radical activity is high, membrane damage ensues and vascular obstructions aggravate the process in the form of a vicious circle.
4. **Reparation**
   The functionality of those areas only partially affected by ischemia may improve. Most of the *penumbra*[2] may regenerate, and the vitality of previously edematous areas may also improve. Thrombolysis may positively affect the patient's condition. Other parts of the brain can resume responsibility regarding several functions over the long term (explained by the often referred to, "*neuronal plasticity*").

Factors affecting penumbra regeneration:

1. Glu receptor antagonists (in experimental phase): Seemingly advantageous for the oxygen need and may help survival of the penumbra.
2. "Cold head": Regarding tissue hypothermia, the O_2 demand and metabolism decreases. Experimental results do not meet expectations, as of yet. However, a concurrent fever must be treated.
3. Sedation and/or anesthesia may be useful in decreasing the metabolism.
4. Osmotic dehydration of the cells (mannitol).

2.6.2.3. HEMORRHAGIC STROKE

Types:

1. Parenchymal bleeding
2. Subarachnoideal bleeding (ruptured aneurysm): Partially characterized due to pressure damage, partially due to tissue destruction.
   N.B.: Epi- and sub-dural bleeding is extra-cerebral bleeding, caused by trauma, not by circulatory pathology

The two types of stroke, ischemic and hemorrhagic, often combine with one another and cerebral edema often develops in both cases.

a) Bleeding destructs tissues, and the molecules liberated due to bleeding may cause vasoconstriction and ischemia.
b) Ischemic stroke often becomes hemorrhagic due to the collateral circulation or thrombolytic therapy.

Nearly 85% of the aneurysms are usually found in the anterior half and ca. 15% in the posterior half of the circulus arteriosus Willisii. They develop through the bulging of the arterial wall triggered by hemodynamic forces. Up to 15% of patients possess multiple aneurysms. Contrary to the ischemic stroke, the aneurysm rupture (AR) attacks more often at a younger, professionally active age of the individual.

The leading symptom of AR: Sudden-onset, strong head- or neck- ache and/or loss of consciousness, stiffness in the neck, falls, light illusions and ventilatory

[2] **Penumbra:** the phenomenon observed during an eclipse, a halo around the moon. Here it refers to a partially injured area surrounding the necrosis. With progression, the central necrosis expands, and as a result, the penumbra diminishes. The earlier perfusion is restored by therapeutic intervention, while the larger part of the penumbra can be saved, hence, the lost functions may (in part) return with time.

Table 2.8.

Types and characteristics of cerebral edema

Type	Pathogenesis	Edema-fluid	Localisation	Causes
Vasogen ic	BBB-disorder	water, Na, prot.	EC	focal lesion
Cytotoxic	disordered cellmetabolism	water, Na IC	IC	anoxia, toxins
Osmotic	osmotic gradient	water, Na	IC & EC	water-intoxication hypotonicity
Hydrostatic	pressure gradient	water, Na	EC (CSF)	hypertension hydrocephalus

arrest. These symptoms may appear simultaneously or 1-2 hours following the onset of bleeding. AR may occur after the commonly referred to, prodromal sign, i.e., a strong yet transient headache episode (parallel with the warn-bleeding[3]), however, it can manifest in full well-being without any anticipatory signs.

Immense, complex statistics do not support the notion in which, whether during exercise or a hypertensive episode, AR occurs more frequently. Nevertheless, hypertensive patients do suffer more frequently AR (e.g.: upon their rest when they have normal BP). Perhaps, it is either because they develop more aneurysms or those are more prone to rupture.

2.6.2.4. TYPES AND CHARACTERISTICS OF INTRACRANIAL FLUID SPACES (Fig. 2.40.)

Vasogenic: Impairment of the blood-brain-barrier (BBB) is in the background. Na^+, H_2O and proteins accumulate secondary to increased permeability. Possible clinical causes include, focal lesions like tumors and/or local ischemia.

Cytotoxic: In consideration of a wide range of cellular metabolic disorders in the background, it can manifest itself in multiple conditions. The function of the Na^+/K^+ ATPase becomes insufficient, the cells swell up secondary to the influx of Na^+ and water and the Ca^{++} channels are activated. Another cause of Na^+ influx is acidosis, in which the IC Na^+ level is increased via the upsurge of Na^+/H^+ exchange. Most frequent causes include ischemia, other types of hypoxias, toxins and metabolic disorders (e.g., hypo- and hyperglycemia, uremia and/or hepatic failure).

Osmotic: The osmotic gradient is changed. Hypotonicity develops in the EC space and water enters the cells. Causes: Water intoxication, SIADH (excessive ADH, syndrome of inadequate ADH). While treating severe hyperglycemic states (diabetic comas), cerebral edema may develop if the EC hypertonicity is corrected too rapidly (infusion plus insulin), while the IC osmotic concentration remains high (removal of idiogenic osmoles is a slow process).

Hydrostatic: Pathophysiological changes of some pressure gradients are in the background. For example, in hypertensive crisis, the mean arterial pressure may exceed the upper limit of autoregulation, and the result is, brain perfusion increases, including an increase in the EC salt/water content, and the intracranial pressure is high. During chronic hypertension, the limits of autoregulation are gradually shifted upwards and CBF may be normal at higher mean arterial pressures. In these cases, too drastic correction in the blood pressure may result in cerebral hypoperfusion, even at "normal" levels of mean arterial pressure. Cerebrospinal fluid (CSF) accumulation also produces hydrostatic cerebral edema. Typically, CSF flow is obstructed in such cases, the intracranial pressure increases and hydrocephalus develops.

Cytotoxic and osmotic edemas do not exactly meet the criteria regarding authentic edema, i.e., fluid excess is accumulated primarily not in the EC but in the IC space. Nevertheless, the consequences of all types of cerebral edemas are the same.

Since cerebral edema develops in a closed space, the intracranial pressure (ICP) will increase in all cases. **(Monroe-Kelly principle states: Expansion of a fluid compartment within the skull will compress the oth-**

[3] Warn-bleeding unfortunately often does not draw appropriate attention and evaluation. It begins with a very strong ("It has never been like this before") headache in the beginning, shifting into an annoying, yet no longer an alarming type head- or neck -ache. Within the next couple of days, or 1-2 weeks afterwards, a serious relapse, in the form of an AR will follow! Relapse bleeding poses a high risk since it may lead to as high as 70% mortality rate! In the background, over-activity of the local endogenous fibrinolytic system is suspected, which prevents proper coagulation at the site of a ruptured aneurysm.

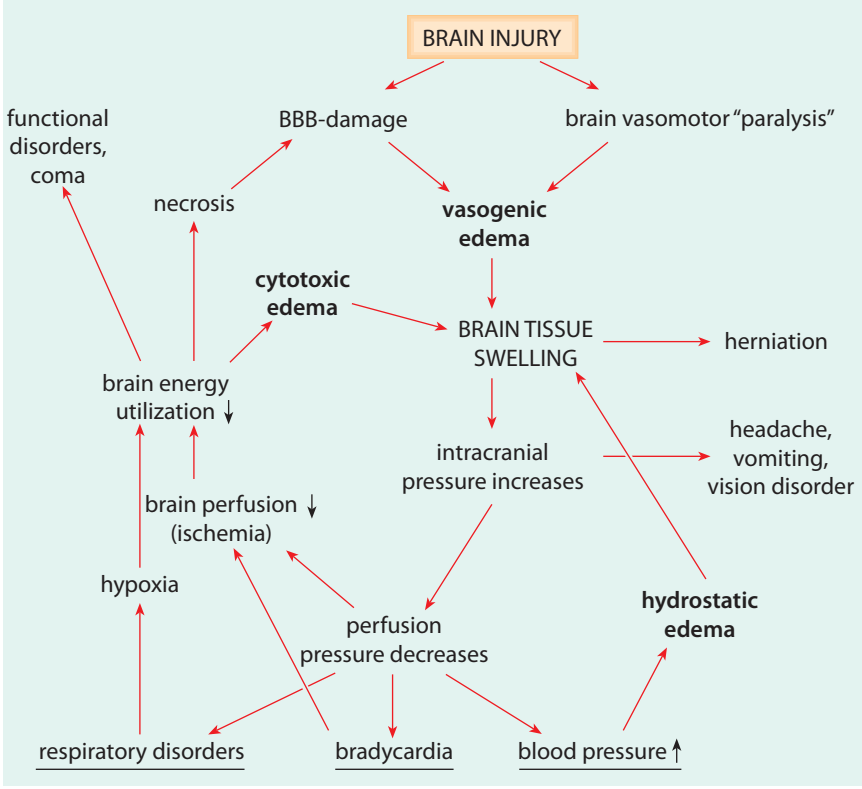

Fig. 2.41.: Edema associated with cerebral injury and concomitant functional lesions.

ers). Symptoms include headache, nausea, vomiting, visual disturbances, incoordination, **Cushing reflex** (bradycardia and increased blood pressure)[4], pathological breathing patterns (e.g. apneusis), confusion, convulsions and coma. In the most severe cases, the cause of death is cerebral herniation with circulatory and ventilatory failure Fig.2.41.).

2.6.3. RENAL CIRCULATION

Compared to their size, renal blood flow is extreme: 20-25% of resting cardiac output perfuse them, while their mass is only 0.5% of the total body mass. The O_2 extraction is only one third to one half when compared to other organs (Fig. 2.7.). This abundant circulation does not only serve O_2 supply, but rather the formation of adequate amount of glomerular filtrate, and, it is processing the filtrate in the tubules (i.e. transport of solutes) which consumes energy and requires oxygen. The anatomical basis of this dual function is the dual capillarization, meaning, filtration takes place in the glomerular capillaries, while the tubular oxygenation is provided by the peritubular capillaries originating from the vas efferents of glomeruli.

The intrarenal distribution of renal blood flow is also important. Normally, the cortex receives disproportionately higher amount of blood than the medulla (Fig. 2.21.). In the regulation of this distribution, vasodilator renal prostaglandins and other local vasoactive substances play a role. Decreased renal circulation (shock kidney, cardiac failure, NSAIDs inhibiting prostaglandin synthesis) affects the circulation of the internal cortical zone to a significantly higher extent.

The anatomical arrangement explains, while even at a significant decrease in renal circulation, will not result in an increase of O_2 extraction (Fig. 5.2.): Processing less tubular filtrate requires less oxygen, the tubules utilize less oxygen yet will not become hypoxic (although prerenal azotemia might develop as a complication, see at acute renal failure, ch. 5.5.3.). However, a significant hypoperfusion at the level of the second capillaries will provoke tubular hypoxia-ischemia, and acute tubular nephropathy (ATN, "shock kidney"). Since kidneys tolerate hypoperfusion to this degree, (even down to 50% of the normal blood flow) without serious pathological consequences, redistribution will not acutely affect them, once blood is diverted toward other parts of the body which require more blood. Basic circulatory reflexes regularly affect renal blood flow.

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[4] Cushing reflex: Increased ICP interferes with cerebral perfusion, which is compensated by increased perfusion pressure. This is ideal in compensating for a hypovolemic decrease of CBF. Since the brain cannot distinguish between causes of hypoperfusion, the CBF decrease due to increased ICP will also result in increased blood pressure.

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Autoregulation of the kidney aims at stabilizing renal perfusion, and ensuring independence of actual blood pressure (Fig.5.3.). In a zone of 60-160 mmHg mean arterial pressure, the filtration and circulation of the kidneys are independent of blood pressure *in vitro*, yet this can be affected *in vivo* through formerly discussed reflexes. However, these do not affect the circulation of transplanted kidneys. The mechanism of autoregulation serves the needs of stable intrarenal (and filtration) pressures.

Stenosis of the renal arteries causes a decrease of intrarenal pressure and triggers the activation of pressor mechanisms (RAAS), therefore, the intrarenal pressure and the excretory function will normalize. In cases of constriction of the afferent vessel associated with systemic circulatory disorders, the renal blood flow will decrease, just as in the case of severe hypotension. Via stagnation type tissue hypoxia tubular dysfunction may occur in congested kidneys (e.g. in cardiac failure). This may be a factor in the often referred to as *cardiorenal syndrome*.

Since moderate changes in renal blood flow do not induce tissue hypoxia, they bear little influence regarding erythropoietin synthesis. This is dependent upon the composition (hypoxemia and/or anemia) of perfusing blood. Venous congestion, causing stagnation hypoxia, may also increase erythropoietin synthesis, however, significant prolonged venous stagnation may impair tubular functions and cause hypoxic parenchymal damage.

2.6.4. SPLANCHNIC CIRCULATION

Circulation of the bowel, liver, pancreas and spleen comprehensively receives a significant amount of the cardiac output, and it is approx. 1300-1400 ml/min, and from this, 300-350 ml is received by the hepatic artery.

Adequate blood supply is essential in maintaining normal bowel motility and adequate secretion-absorption. Increased circulation evoked by food intake is regulated by gastrointestinal peptide hormones (CCK, secretin, VIP) along with kinins synthesized in the gut wall. Decreased pO_2 and a parallel rise in local adenosine levels will increase gastrointestinal circulation. Sympathetic vasoconstriction seemingly bears a major role in view of neural control, which does not only affect arterial, but also the mesenteric venous aspect.

Absorption will be deranged first, once gastrointestinal circulation is impaired (either by ischemia or congestion), since the apical parts of bowel mucosa villi will become increasingly hypoxic due to their characteristic countercurrent flow, whereas these ones are mainly responsible for the absorption (Fig.2.20.). Malabsorption will ensue with maintained secretion and initially increased motility. Later, motility will decelerate, with a tendency to develop subileus, sometimes with Weber positive, or macroscopically bloody diarrhea. In the case of celiac artery sclerosis/stenosis, periumbilical pain following a meal (the well-known, "abdominal angina") is frequently observed indicating inability of perfusion to satisfy increased need, but often times it also occurs in chronic congestion.

Pancreas-ischemia may deliberate proteolytic enzymes and may lead to the production of pathological peptides (e.g. MDF = myocardial depressing factor).

The liver receives, apart from the hepatic artery, approximately, an additional 1000-1100 ml/min blood through the portal circulation. Therefore 30% of cardiac output flows through the branches of the

hepatic veins, therefore, relatively small changes of this amount will largely affect the filling of the heart. Congestive and hypoxic liver develops both, morphological and functional anomalies (e.g. in the detoxification of substances, such as MDF, intermediary metabolism). Decreased arterial circulation leads to centrilobular hypoxia, and, in congestion, there is evidence of the formation of ascites originating from the surface of the liver.

Either physiologically or pathologically redistributed circulation (e.g. in extreme workload or in shock/heart failure, accordingly) may result in a highly diminished splanchnic blood flow. A rare example is the transient Weber positive stool of Marathon runners following the race which normalizes quickly, yet similar findings among circulatory pathologies indicates serious bowel ischemia.

2.6.5. CIRCULATION OF MUSCLES, SKIN AND OTHER AREAS

The perfusion of muscles is a magnitude higher in activity than when compared to at rest. Therefore, insufficient circulation, independent of its cause, will only manifest during exercise and will be responsible for well-known muscle weakness. Severe hypoperfusion of postural muscles, on the other hand, may not simply interfere with physical activity, but also compromise the ability to keep the erect position, hence, it may lead to falls due to the loss of balance (e.g. in acutely worsening circulatory failure and in heat-decompensation, in paroxysmal tachycardia, in myocardial infarct or in acute volume loss etc.). Splanchnic and renal perfusion are both hindered in these conditions, yet symptoms associated to these organ dysfunctions will manifest later than fast evolving signs of muscular hypoperfusion.

Skin perfusion and its O_2 demand are low at rest. In a warm environment, thermoregulation requires substantially increased cutaneous perfusion (vasodilation). In extreme heat, skin perfusion can exceed 5-6 liter/min, reaching 2/3 of the actual cardiac output. In such situations, subpapillary plexus of the skin can contain a considerable amount of blood which can predispose to orthostatic hypotension/collapse due to the decreased venous return. If the cutaneous circulation is insufficient, then thermoregulation against heat will be deranged, this may lead to hyperthermia, and, heat-stroke may easily develop among patients with partially compensated circulatory failure. In contrast, as seen in heart failure patients, skin vasodilation triggered by thermoregulatory response may spark acute circulatory decompensation by decreasing the effective circulating blood volume, and, as a result, symptoms of forward failure will be predominant, since limited pump function is not able meet the need for an increased cardiac output. A mild decrease in the resting perfusion of the skin may not lead to serious consequences, however, any further local anomalies impairing skin blood flow will result in local necrosis, e.g.: pressure sores and leg ulcers. Tissue oxygenation in the skin is also affected by anemia, interstitial edema and hypothyroidism.

Extreme rises of skin blood flow (reminiscent of shunts) occur in hyperdynamic circulatory conditions straining the heart not only in decompensated patients, but also in high cardiac output circulatory failure.

For other tissues, specific features of their circulation are less well understood. Autoregulation is ubiquitously present up to a certain degree. In the case of primary increase of cardiac output or a rise in blood pressure, local vasoconstriction will prevent tissue hyperperfusion and, vice versa, if oxygen demand rises, vascular resistance decreases. Notably, these aspects demonstrate relevance in the regulation of the blood pressure. Autoregulation is extremely important in the control of cerebral and renal blood flow.

2.6.6. PATHOPHYSIOLOGY OF PULMONARY CIRCULATION

2.6.6.1. CHARACTERISTICS AND REGULATION OF PULMONARY CIRCULATION

- The same amount of blood enters the pulmonary circulation as its systemic counterpart, although the amount of blood residing in the pulmonary vessels is far from the amount stored in the systemic circulation (normally 6-9% of total blood volume, pathologically up to 20 %).
- Bronchial circulation, originating from the systemic circulation, is responsible for the parenchymal blood supply of the lungs, with a comparably much smaller volume.
- The pressure in the pulmonary artery is **20/12 mmHg**, much less than when compared to that

in the systemic circulation. The cardiac output of the right ventricle, equal to the left ventricle, assumes pulmonary vascular resistance (PVR) is much less (about 1/5th) than systemic TPR, and the arterioles are much more distensible. In pulmonary circulation, vascular resistance cannot be explained by the resistance of a single segment (whereas the precapillary arterioles are mainly responsible for TPR in the systemic circulation), hence, both arterial/arteriolar vasoconstriction (e.g. in alveolar hypoxia), venous congestion (in left ventricular failure) and the decreased total capillary diameter (emphysema, micro-embolization, fibrosis) translates into a higher perfusion pressure leading to pulmonary hypertension, in which the extent of the rise in the mean arterial pressure exceeds its counterpart in the systemic circulation (at least proportionally: it may increase even 5-fold above the normal pressure). Pulmonary hypertension is diagnosed once the mean arterial pressure exceeds 25 mmHg in pulmonary arteries, at rest, or higher than 30 mmHg during exercise.

- The **contact time** of blood and alveolar air is **0.7-0.8 s at rest, during exercise, with accelerated circulation, it is nearly 0.3 s, which is still sufficient for diffusion under normal conditions.**

Control of pulmonary circulation

- **Hypoxia, unlike in the systemic circulation, triggers vasoconstriction in the lungs.** Hypoxia primarily is defined as the decrease of alveolar oxygen tension. During regional bronchoconstriction and alveolar hypoventilation of the affected area, the blood is steered towards well perfused areas, equalizing ventilation/perfusion ratio, which is a distinct advantage (ch. 3.2.). Compensation regarding CO_2 is typically adequate, yet the O_2 uptake of the blood cannot be increased due to the maximal saturation of Hb. In widespread chronic hypoxia of the lungs (e.g. in alveolar hypoventilation), pulmonary hypertension develops via pulmonary vasoconstriction, which characterizes its disadvantage.
- Effect of sympathetic/parasympathetic innervation is moderate in the pulmonary circulation, humoral factors, however, play a major role. Circulating catecholamines are constricting pulmonary veins, thus increasing the filling of the left heart. Parasympathetic predominance causes vasodilation.
- The systemically vasodilator **serotonin**, **histamine**, and several **PGs,** are vasoconstrictors in the pulmonary circulation. In liver failure, on the other hand, excessive action of vasodilators not properly eliminated by hepatocytes may impair alveolo-capillary diffusion abnormalities, thereby leading to hypoxemia. These include glucagon, $NO^{\cdot}$, CGRP /calcitonin-gene-related peptide/, VIP, substance P and ANP.)
- Pulmonary blood flow is influenced by posture (orthostatically, the lungs are less, while in a supine position, are more congested), and due to pressure correlations caused by both inspirations and expirations. In consideration of inspiration, the negative intrathoracic pressure increases the pulmonary circulation, while during expiration, lung perfusion somewhat decreases.

2.6.6.2. ETIOLOGY OF PULMONARY HYPERTENSION (primary or secondary)

Pulmonary hypertension (PAH: Pulmonary arterial hypertension) is diagnosed once the mean arterial pressure of the pulmonary artery reaches or exceeds 25 mmHg, while at rest. According to its etiology, it is classified as either primary or secondary, the latter being by far more frequent.

Primary pulmonary hypertension:
Primary pulmonary hypertensions may develop upon the basis of fibromuscular hyperplasia of the pulmonary vessel wall inherited in some families, yet can jump generations, in which sporadic cases are also detected, therefore, it is considerably a very rare disease. Though once commonly thought to affect typically young women, it occurs in both sexes and among all age groups. Most frequently, it presents between the ages of 30 to 40. The male:female ratio is 1:1.7. Previously healthy individuals develop dyspnea of an unknown origin, and is chiefly, the first sign, although at this point, the disease is considerably at an advanced stage. The average survival rate characteristic of the diagnosis is 2-3 years. The cause of death is due to the right ventricular insufficiency. Familiar PAH is inherited at an autosomal dominant trait with unequal penetrance between sexes. A mutation of the Bone Morphogenic Protein Receptor II (BMPR2) gene, which codes a member of the TGFß signal superfamily, is detected in nearly 50-67% of PAH cases among affected families, while only in ca. 12% of sporadic

(non-hereditary) cases. Since PAH is a multifactorial pathology, other factors may also have a role in its development, whether of other genetic or environmental origins.

Currently, there is no effective treatment. Introduction of bed rest, Ca^{++}-channel blockers, other vasodilators, diuretics have been implemented, yet the decrease in systemic blood pressure limits their use. New, experimental treatment is the administration of PGI_2, or $NO^{\cdot}$ inhalation, including the phosphodiesterase inhibitor, Sildenafil. Following lung- (or combined heart-lung-) transplantation, the disease does not recur.

Secondary pulmonary hypertension:
Three main pathophysiological mechanisms are in the background:

Vasoconstrictive:

- Chronic, diffuse alveolar hypoxias
  - High altitudes
  - Sleep apnea syndrome and the other very frequent types of alveolar hypoventilation (e.g. COPD, restrictive disorders)
  - V/Q mismatch
- Other arterial stenoses
  - Inhalation of toxic gases (chlorine, mustard)
  - Vasculitis
  - Pulmonary artery stenosis
  - Eisenmenger syndrome (e.g. persistent Botall duct, left-to-right shunt)
  - Decreased capillary diameter
- Emphysema (damage of interalveolar septa and capillaries, bulla formation)
- Lung fibroses (tuberculosis, silicosis, sarcoidosis, autoimmune alveolitis, progressive systemic sclerosis and late consequences of Gramoxone/Paraquat intoxication)
- Microembolism (e.g. ARDS, after-effect of DIC and/or thrombotic tendencies)

Veno-occlusive

- Left heart failure (backward failure, pulmonary venous congestion, and/or increased PVR)

In some cases, the pathomechanism is combined. Some "slimming pills" (fenmetrazine - Gracidine, or fenfluramine + phentermine combinations – Fen-Phen) actually have been retracted from the market due to this side-effect. The administration of several "antihunger" drugs (serotonin agonists) can also cause PAH.

Regarding the potential consequences, causes can be classified upon the basis whether or not they trigger pulmonary congestion/edema.

1. **Precapillary**
   Pulmonary wedge pressure[5] is normal (5-12 mmHg). There is no congestion or edema, the vasoconstrictive and thromboembolic forms are aligned here.
2. **Postcapillary**
   Pulmonary wedge pressure is increased (> 24 mmHg). There is a danger of pulmonary edema. The veno-occlusive forms are aligned here.

SEQUEL OF PULMONARY HYPERTENSION

1. There is an increase in the right ventricular effort, and characteristic of its small muscle mass, the ventricle will dilate and becomes insufficient much earlier than typical regarding the left ventricle (*cor pulmonale chronicum*). The right atrium is also enlarged, P pulmonale may present itself upon the ECG. Pressure can acutely increase during the pulmonary circulation, and most frequently during pulmonary embolism. This is referred to as, cor pulmonale acutum, and does not belong to the chronic forms of pulmonary hypertensions.
2. The functions of the two ventricles are interdependent. Forward failure of the right ventricle prevents adequate left ventricular filling, as seen in the right ventricular hypertrophy, does so by bulging into the left ventricle. Inevitably, both sides will fail.

[5] **The Swan-Ganz catheter:** Used since the 50-ies the balloon-flotation catheter is suitable for monitoring pulmonary venous pressure, the left ventricular function, and hence the risk of pulmonary edema. It is **especially useful e.g. in MODS. Introduced through a central vein (v. subclavia, v. jugularis interna etc.) it** will float with the bloodstream to the right atrium, the right ventricle, then, to one of the pulmonary artery branches. Its tiny balloon will eventually get stuck (wedge) into a small pulmonary artery. The tip of the catheter is equipped with a pressure sensor that measures the "***wedge-pressure***" behind the wedged balloon. Its normal value is 5-12 mmHg that reflects pressure in pulmonary veins, which is essentially almost the same as the left ventricular filling pressure. Hence, according to the Frank Starling Mechanism, stroke volume depends on it, and rises in left ventricular failure. An intact valvular system is the prerequisite for proper analysis of pressure values obtained by this catheter.

3. On the grounds of vascular damage triggered by increased pressure, atherosclerosis may develop, which is absolutely uncharacteristic in consideration of the pulmonary circulation.

2.6.6.3. PULMONARY EMBOLISM

A most frequent cause of a pulmonary artery obstruction is thromboembolism. Either deep vein thrombosis (DVT) of the lower limbs or those of the pelvic veins is in the background, in which the risk increases regarding prolonged immobilization, obesity, some forms of oncological pathologies, thrombophilia, or anticoncipient (progesterone effect). A single large embolus or multiple small emboli can both occur, often alternating. A total obstruction is nearly always lethal, however, subtotal obstruction or multiplex micro-embolization are much more likely to occur. In less severe cases, symptoms are not always conspicuous, yet repeated supraventricular tachycardia may lead to suspicion of pulmonary embolism. Respiratory and circulatory derangements dominate the clinical picture. Sudden-onset dyspnea may be explained due to the increased effort regarding breathing, due to the higher dead-space ventilation, additionally hypoxia is frequent, yet not always present, while hypocapnia is typical. Global respiratory failure with a rise in pCO_2 is found only in the most severe cases. Stabbing, stinging-like pain presents itself in nearly 10% of the cases and indicates concomitant pulmonary infarct. Thromboembolic vascular obstruction releases vasoconstrictive substances (e.g. platelet-derived serotonin). Obstruction leads to acute cor pulmonale with rapid dilation of the right ventricle compromising left ventricular filling, along with right atrial congestion, retrograde jugular pulse and cyanosis mostly pertaining in the area drained by the superior vena cava (the well-known, "*collar-cyanosis*"). The stretch of the right ventricular wall increases the risk of ischemia which likely leads to angina. Changes of blood pressure and cardiac output may rapidly cause muscle weakness and possibly fainting. Embolectomy or adequate thrombolysis may potentially prevent circulatory shock (obstructive type of shock).

Lipid-emboli likely emanate from the bone marrow following traumatic fractures or after a large blunt trauma to fat tissue. Symptoms usually begin after 12-36 hours of the triggering incident, brought on by a sudden onset and includes dyspnea, tachypnea, tachycardia, hypotension, ARDS, DIC, delirium and/or a coma with a high mortality rate. Lipid aggregates obstruct the small pulmonary arteries and the fatty acids released cause toxic vasculitis. Air emboli are generated by the puncture of big (central) veins (e.g. subclavia) close to the heart. Amniotic fluid emboli primarily generate DIC, and in the course of DIC pulmonary, micro-embolization follows.

2.7. ALTERATIONS OF CARDIOVASCULAR FUNCTIONS IN THE ELDERLY

Both spontaneous activity of the sinus-node and its capacity to raise frequency declines with age, therefore, resting and maximal heart rate both decreases. The chronotropic effect of catecholamines also wanes, though resting catecholamine levels tend to be higher and also rise steeper upon stimuli, than compared with youth. Myocardial fibers gradually degenerate, though at an individually different rate. The fibrotic transformation of the ventricular wall first translates into the deterioration of compliance and diastolic dysfunction, followed by impairment of contractility. Catecholamines are also becoming less effective towards increasing contractility due to age. An ensuing rise in EDV leads to the dilation of the annulus fibrosus with partial insufficiency of the atrioventricular valves. Consequently, myocardial oxygen supply further deteriorates, leading to the further degeneration of myocardial fibers, in particular, those in the endomyocardial region. Therefore, conduction disorders (AV- and bundle branch blocks) and arrhythmias (blocks, premature beats) develop regularly. Degenerative foci may serve as sources of serious impulse formation abnormalities including ventricular paroxysmal tachycardia or even ventricular fibrillation.

Essentially, the clinical picture of ischemic heart disease dominates, and is often complicated regarding ventricular hypertrophy due to hypertension, which is not properly controlled through the use of antihypertensives. A slow, gradual decline of resting cardiac output can reach 1% rate annually, and the capability to increase heart performance on demand also becomes more and more limited, though regular physical activity may curb this tendency by maintaining vascular reactivity (dilation), hence, keeping peripheral resistance low at periods of bodily work. A high EDP also elevates intra-atrial pressure, therefore, it increases atrial wall stress which is a main trigger of atrial fibrillation, a major risk factor for atrial ball thrombus formation, and, a

likely source of emboli causing stroke (left side) or pulmonary embolism (right side). Atrial pressure rise will lead to venous stagnation with edema formation. The highest risk in the arteries is progression of atherosclerosis with age, though fibrotic transformation in place of elastic fibers of vessel wall in big arteries itself impairs the distensibility of these vessels at a significantly advanced age. As a result, the attenuative function of the aorta against pressure swings during the pulse surge diminishes. Systolic pressure rises steeper and higher during the expulsion of the stroke volume, while the pressure after closure of the aortic valve drops faster and sometimes deeper than normal. Therefore, pulse pressure widens due to higher systolic and normal or only moderately elevated diastolic pressures. Dilation of the aortic bulb may lead to aortic valvular insufficiency with lowered diastolic pressure and impaired coronary perfusion. In conditions associated with hypotension (e.g. volume loss), sinking of blood pressure may be accompanied with low diastolic values, which can severely compromise both coronary and cerebral perfusion.

The structural rebuilding of arterial walls may lead to the formation of aneurysms. The vasomotor capability of vessels is diminished, and, due to neuropathy, frequency rise may also prove insufficient in the case of a need, therefore, the chance of orthostatic hypotension is high. The adaptive functionality of autoregulation is narrowed, so even mild, accidental hypotensive periods may lead to brain ischemia, or, consequently, the transient upsurge of blood pressure may easily cause elevated intracranial pressure. At the onset of physical exertion, or robust exercise, blood pressure (dominantly systolic) elevates quicker 'as in' youth and diastolic pressure also grows since the adaptive drop of afterload typical in youth is missing. Following exercise, the normalization of both pressure and frequency is slower.

The resistance in support of the wall of big veins diminishes. Venous valves often develop insufficiency, muscular pump is weaker as well, due to less activity and the loss of muscle mass. The slowing of venous blood flow increases thrombotic tendency with a vast array of pathologic consequences. Venous stagnation leads to stagnation-type tissue hypoxia and triggers edema formation. Pulmonary venous stagnation leads to dyspnea.

Capillary basement membrane structural rebuilding leads to weakening of the collagen mesh. Increased capillary wall fragility may lead to senile purpura in the skin, but also to micro-aneurysms and their thrombosis/rupture in the retina. Increased permeability of the capillary wall might also contribute to edema formation.

Further readings:

Approach to Internal Medicine: A Resource Book for Clinical Practice (Eds: Hui D, Leung AA, Padwal R), Springer, 2015

Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine (by Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF), Elsevier, 2015

Cecil Medicine (Eds: Goldman L, Ausiello DA), Saunders Elsevier, 2008

Harrison's Principles of Internal Medicine. I., II., 19th Edition. McGraw-Hill, 2015

Katz AM, Konstam MA: Heart Failure: Pathophysiology, Molecular Biology and Clinical Management. 2nd Edition, Lippincott, Williams and Wilkins, 2009