

Cell Growth and Cell Adaptation

In the middle of the 19th century Rudolf Virchow first conceived of his idea of *cellular pathology*, i.e., that disease is a disorder of the physiological life of the **cell**. The cell is the smallest unit of the living organism (Wilhelm Roux), i.e., the cell (and not any smaller entity) is in a position to fulfill the basic functions of the organism, namely *metabolism*, *movement*, *reproduction* and *inheritance*. The three latter processes are made possible only through **cell division**, although cells that can no longer divide can be metabolically active and are in part mobile.

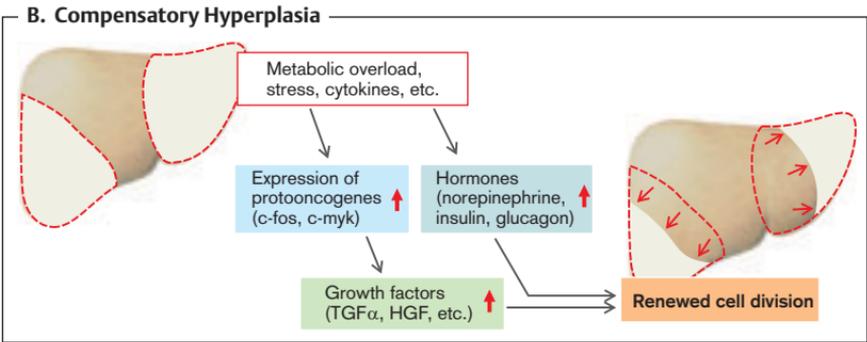
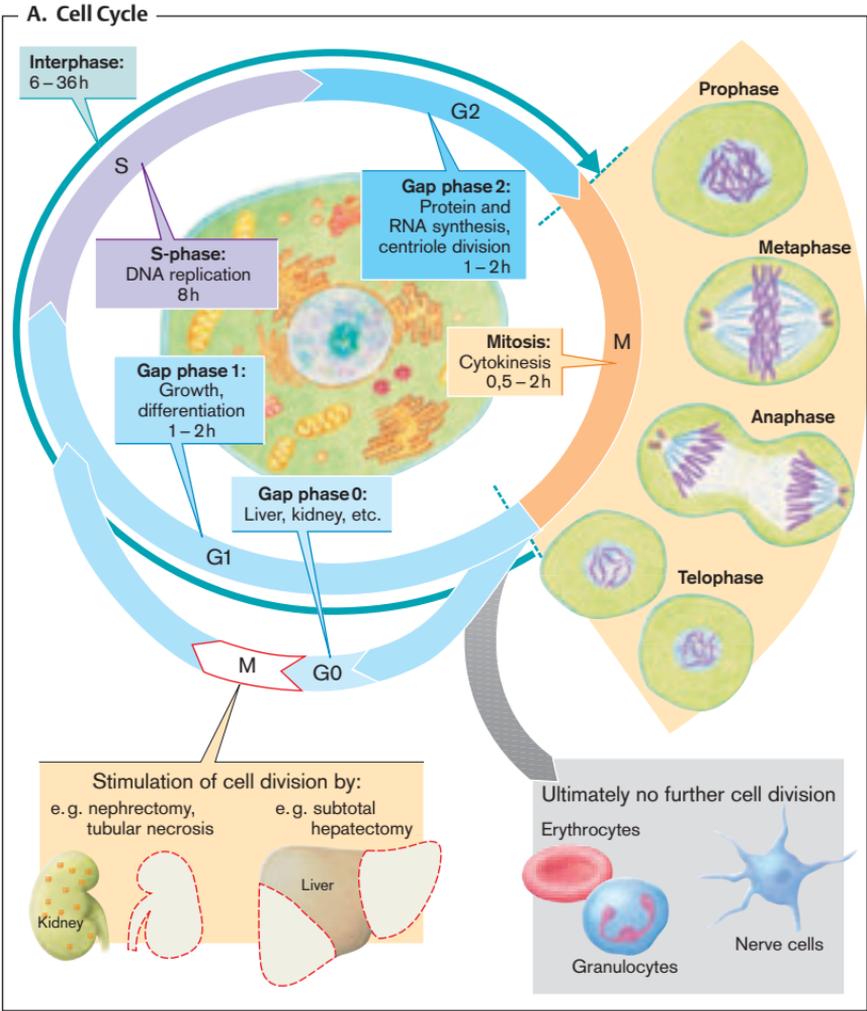
With the exception of the germ cells, whose chromosome set is halved during meiotic division (*meiosis*), most cells divide after the chromosome set has first been replicated, i.e., after mitosis (so-called indirect division of the nucleus) followed by division of the cell (*cytokinesis*). In this process every cell capable of mitosis undergoes a **cell or generation cycle** (\rightarrow A) in which one mitosis (lasting ca. 0.5–2 h) is always separated from the next one by an **interphase** (lasting 6–36 h, depending on the frequency of division). Most importantly, the cell cycle is governed by certain cycle phase-specific proteins, the *cyclines*. They form a complex with a protein kinase, called *cdc2* or *p34^{cdc2}*, which is expressed during all phases. When cytokinesis is completed (= end of telophase; \rightarrow A), cells that continually divide (so-called labile cells; see below) enter the *G₁ phase* (**gap phase 1**), during which they grow to full size, redifferentiate and fulfill their tissue-specific tasks (high ribonucleic acid [RNA] synthesis, then high protein synthesis). This is followed by the *S phase*, which lasts about eight hours. During this phase the chromosome set is doubled (high DNA synthesis). After the subsequent *G₂ phase*, which lasts about one to two hours (high protein and RNA synthesis; energy storage for subsequent mitosis; centriole division with formation of the spindle), the next **mitosis** begins. The *prophase* (dedifferentiation of the cell, e.g., loss of microvilli and Golgi apparatus; chromosomal spiraling) is followed by the *metaphase* (nuclear envelope disappears, chromosomes are in the equatorial plane). Then comes the *anaphase* (chromo-

some division and migration to the poles) followed by the *telophase* (formation of nuclear envelope). *Cytokinesis* begins in the late stage of the anaphase with development of the cleavage furrow in the cell membrane. After this a new *G₁* phase begins.

Cells with a short life-span, so-called **labile cells**, continually go through this cell cycle, thus replacing destroyed cells and keeping the total number of cells constant. Tissues with labile cells include surface epithelia such as those of the skin, oral mucosa, vagina and cervix, epithelium of the salivary glands, gastrointestinal tract, biliary tract, uterus and lower urinary tract as well as the cells in bone marrow. The new cells in most of these tissues originate from division of poorly differentiated stem cells (\rightarrow p. 32 ff.). One daughter cell (stem cell) usually remains undifferentiated, while the other becomes differentiated into a cell which is no longer capable of dividing, for example, an erythrocyte or granulocyte (\rightarrow A). Spermatogenesis, for example, is also characterized by such *differentiated cell division*.

The cells of some organs and tissues do not normally proliferate (see below). Such **stable** or **resting cells** enter a resting phase, the *G₀ phase*, after mitosis. Examples of such cells are the parenchymal cells of the liver, kidneys, and pancreas as well as connective tissue and mesenchymal cells (fibroblasts, endothelial cells, chondrocytes and osteocytes, and smooth muscle cells). Special stimuli, triggered by functional demand or the loss of tissue (e.g., unilateral nephrectomy or tubular necrosis; removal or death of portions of the liver) or tissue trauma (e.g., injury to the skin), must occur before these cells re-enter the *G₁* phase (\rightarrow A, B). Normally less than 1% of liver cells divide; the number rises to more than 10% after partial hepatectomy.

The conversion from the *G₀* phase to the *G₁* phase and, more generally, the trigger for **cell proliferation** requires the binding of growth factors (GFs) and growth-promoting **hormones** (e.g. insulin) to specific receptors that are usually located at the cell surface. However, in the case of steroid receptors these are in the cytoplasm or in the cell nucleus (\rightarrow C). The GF re-



Acute Respiratory Distress Syndrome

The acute respiratory distress syndrome (ARDS) is a life threatening impairment of pulmonary function.

Causes of ARDS include among others severe sepsis, bacterial pneumonia, near-drowning, inhalation of toxic vapors, intoxications, pulmonary contusion, severe trauma (particularly thorax, head trauma, multiple bone fractures), burns, multiple transfusions, aspiration of gastric content, and pancreatitis. ARDS may further develop after surgery with cardiopulmonary bypass. The risk to develop ARDS is increased by the coincidence of more than one of the causes. For instance, the incidence of ARDS increases from 25% in patients with severe trauma to 56% in patients with severe trauma and sepsis.

The clinical course of ARDS is characterized by three phases:

In the initial **exudative phase** of ARDS, injury of the pneumocytes and pulmonary endothelial cells is paralleled by the release of several inflammatory mediators including interleukin 1 (IL-1), interleukin 8 (IL-8), tumor necrosis factor (TNF- α), and leukotriene B₄ (LTB₄). Leukocytes (especially neutrophils) invade the pulmonary tissue. The injury of the pneumocytes and endothelial cells as well as the influence of the inflammatory mediators lead to loss of the barrier function between capillaries and alveoli with entry of plasma proteins and fluid into the alveolar space. Cellular debris, plasma proteins, and defective surfactant aggregate in the alveolar lumen to hyaline membranes, thus impairing the ventilation of the affected alveoli. The occlusion of airways may lead to the development of atelectases. The lung compliance is decreased, and the work of breathing increased accordingly. The loss of contact between capillaries and ventilated aveoles leads to vascular shunting with decreased oxygenation of blood and thus to hypoxemia. The decrease of the alveolar O₂ concentration leads to pulmonary vasoconstriction, which increases pulmonary vascular resistance and thus results in the development of pulmonary hypertension. The pulmonary vascular resistance is further increased by microvascular occlusions. The disruption of contact between alveoli and pulmonary capillaries leads to an increase of

the dead space. Despite the increased dead space, breathing is typically shallow and frequent and the patient feels unable to inhale sufficient air. The impairment of gas exchange results in hypoxemia, hyperkapnia, and dyspnea.

Typically, after some 7 days, the **proliferative phase** develops. During this phase, the neutrophil leukocytes in lung tissue are largely replaced by lymphocytes. The type II alveolar epithelial cells may proliferate, produce surfactant, and differentiate into type I alveolar epithelial cells. In this phase the patient may gradually recover. However, the hypoxemia, tachypnea, and dyspnea frequently disappear only slowly. In many patients recovery is observed within 3–4 weeks from the initial injury.

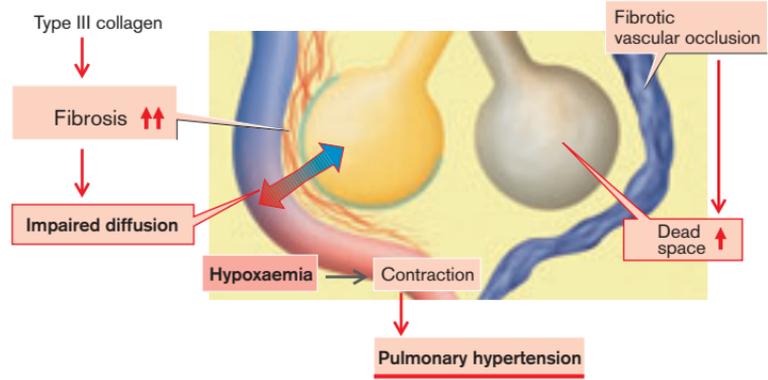
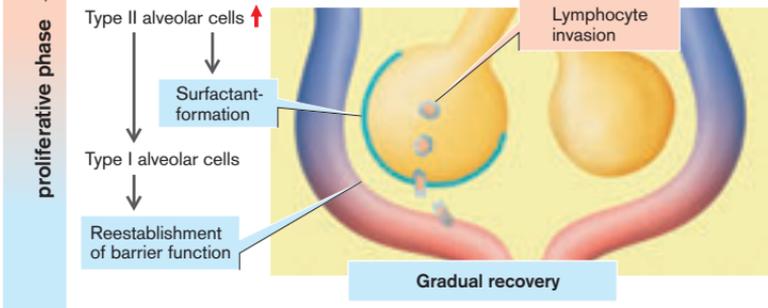
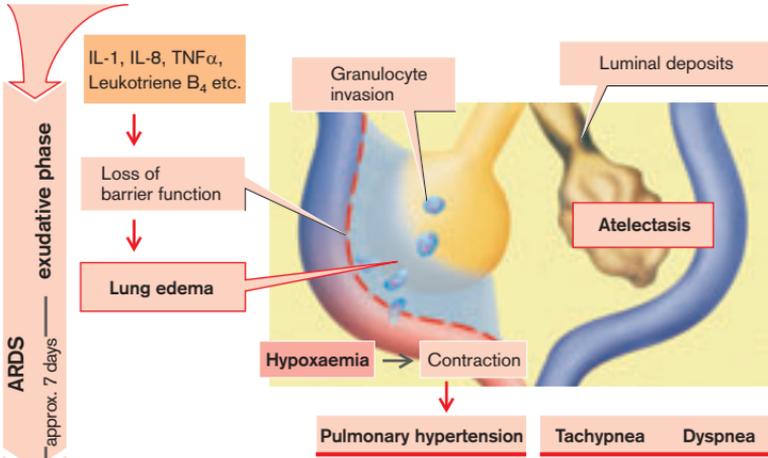
In a subset of patients, signs of fibrosis develop during the proliferative phase, which may be followed by a **fibrotic phase**. In those patients, alveolar edema and exudate are followed by massive formation and deposition of matrix proteins in the interstitial space and the airways. Fibrotic lung tissue typically produces type III procollagen peptide, which is thus a diagnostic indicator for the development of pulmonary fibrosis. The presence of this peptide points to a protracted clinical course of ARDS and is associated with enhanced mortality of the affected patients. Due to the fibrosis, the delicate lung architecture is disrupted with the appearance of widened alveoli (“bul-lae”) similar to emphysema. The compliance is decreased and the dead space increased. The patient is at an increased risk of developing pneumothorax. The lumen of pulmonary microvessels is decreased by intimal fibroproliferation and by compression due to perivascular fibrosis. The occlusion of the vessels increases the pulmonary vascular resistance with development of pulmonary hypertension. The patients suffering from this course of ARDS are left with substantial loss of pulmonary function.

A. Acute Respiratory Distress Syndrome (ARDS)

Sepsis
near drowning
transfusions

pneumonia
toxic vapours
aspiration

lung injury
poisoning
pancreatitis



approx. 14 days

ARDS fibrotic phase

Pathophysiology of Bone

Bone consists of connective tissue or bone matrix (including type I collagen [$> 90\%$], thrombospondin, osteopontin, fibronectin, osteocalcin, proteoglykanes), minerals (alkaline salts of Ca^{2+} , phosphate, Na^+ , CO_3^{2-} , Mg^{2+} , K^+ , and F^-) and cells (osteocytes, osteoblasts, and osteoclasts).

Osteocytes are mechanosensitive and adjust the bone architecture to the mechanical requirements by influencing osteoblasts and osteoclasts.

Osteoblasts develop under the influence of BMPs (bone morphogenetic proteins) from mesenchymal progenitor cells. BMPs stimulate through the transcription factor CBFA1 (core binding factor A1) the expression of, among others, type I collagen, osteocalcin, osteopontin, and RANKL (receptor activator of NF κ B ligand). Osteoblasts are stimulated by growth factors (TGF- β , FGF, PDGF, IGF) and form alkaline phosphatase, which fosters the mineralization by cleaving pyrophosphate. The plasma concentration of alkaline phosphatase reflects the osteoblast activity (\rightarrow A).

The osteoblasts release RANKL, a mediator that stimulates the formation of **osteoclasts** from hematopoietic progenitor cells. The development of osteoclasts is inhibited by RANKL-binding osteoprotegerin and is fostered by the antiapoptotic M-CSF (macrophage colony-stimulating factor). The osteoclasts are inhibited by calcitonin. Osteoclasts degrade bone by proteolysis (proteinases such as cathepsin K) and by H^+ secretion (H^+ ATPase, carbonic anhydrase II [Ca II], Cl^- channel). The osteoclast activity is apparent from the plasma concentrations of type I collagen degradation products (peptides).

In children bone develops from cartilage, which is generated by **chondrocytes**. Those cells are under the control of parathyroid hormone (PTH), PTHrP (PTH-related peptide), FGF (fibroblast growth factor), growth hormone, glucocorticoids, and estrogens. High phosphate concentrations stimulate the apoptosis of chondrocytes.

Bone is constantly remodeled to meet the mechanical requirements. Following bone fractures, infections, and ischemia, dead bone is degraded, the blood supply improved by angiogenesis, and new bone is synthesized. Unstable

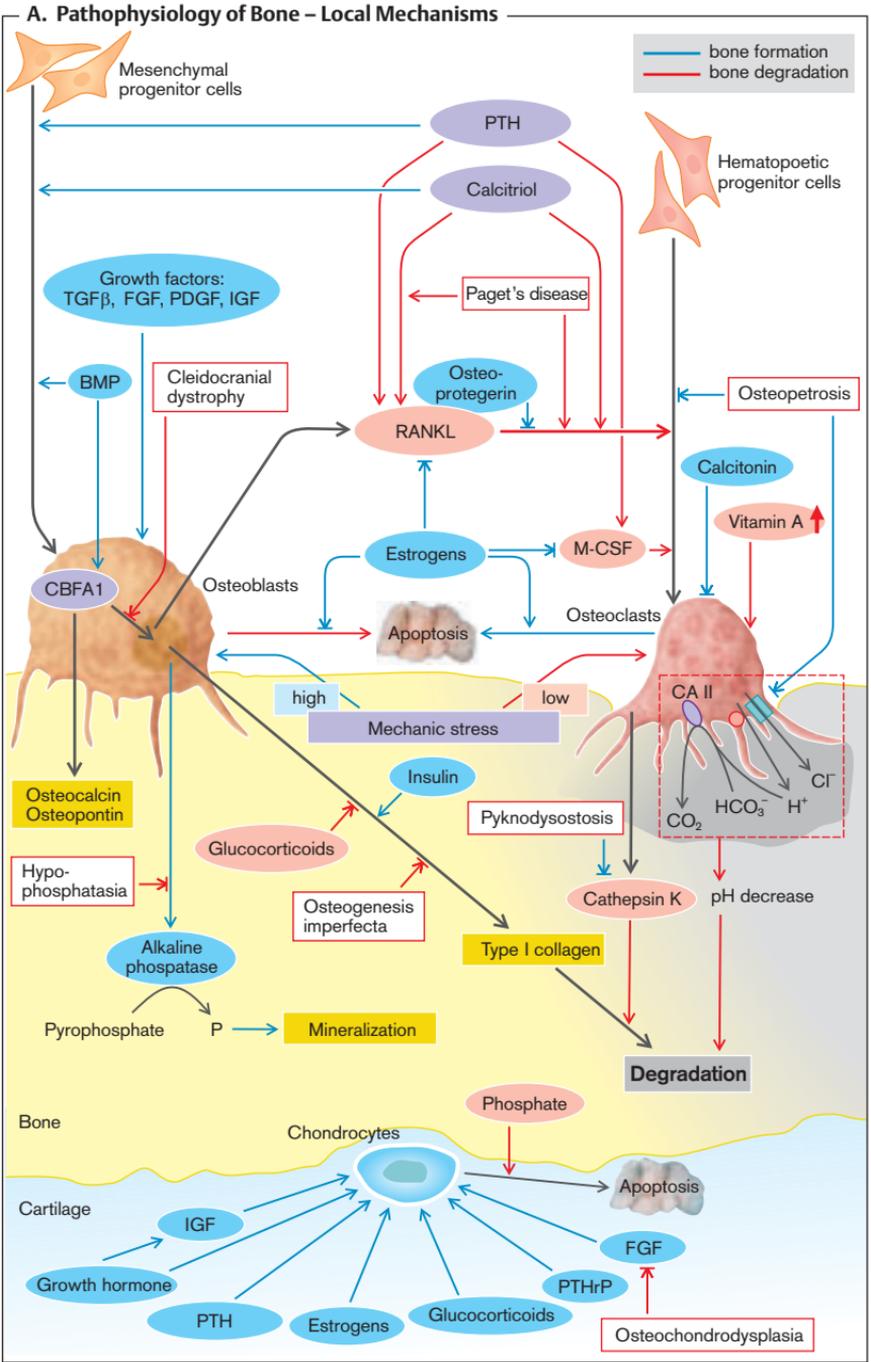
links stimulate the formation of connective tissue and of cartilage.

The **regulation of bone structure and mineralization** is a function of *mechanical use*, plasma Ca^{2+} and phosphate concentrations as well as of PTH and calcitriol.

The release of **PTH** is stimulated by hypocalcemia (\rightarrow p. 138) and inhibited by calcitriol (\rightarrow B). PTH stimulates the remodeling of bone and increases the number of osteoblasts and (via RANKL and M-CSF) of osteoclasts. Intermittent administration of PTH stimulates bone formation; continuous increase of PTH leads to bone resorption.

PTH further influences bone metabolism by stimulation of **calcitriol** ($1,25(\text{OH})_2\text{D}_3$) formation (\rightarrow A1, \rightarrow p. 138): Exposure of the skin to UVB radiation stimulates the generation of vitamin D_3 from 7-dehydrocholesterin. Vitamin D_3 is converted to $25(\text{OH})\text{D}_3$ in the liver and by the enzyme 1α -hydroxylase to the active hormone $1,25(\text{OH})_2\text{D}_3$ mainly in the kidney. The enzyme is stimulated by PTH and growth hormone and inhibited by excess of Ca^{2+} and phosphate, by FGF23 and by KLOTHO (\rightarrow p. 100). $1,25(\text{OH})_2\text{D}_3$ is further produced in macrophages and lymphocytes, which synthesize the hormone irrespective of PTH and calcium phosphate metabolism. Stimulation of macrophages (e.g., at sarcoidosis and tuberculosis) or lymphocytes (e.g., lymphomas) thus leads to inadequate formation of $1,25(\text{OH})_2\text{D}_3$. A vitamin D-24-hydroxylase inactivates $1,25(\text{OH})_2\text{D}_3$. Calcitriol stimulates via the vitamin D receptor (VDR) the formation of bone matrix proteins, osteocalcin, osteopontin, and RANKL. Calcitriol stimulates via RANKL and M-CSF the formation of mature osteoclasts. Calcitriol thus stimulates both bone formation and bone resorption. The VDR is stimulated not only by $1,25(\text{OH})_2\text{D}_3$ but also by excessive $25(\text{OH})\text{D}_3$ concentrations.

Glucocorticoids inhibit the formation and action of calcitriol and thus foster bone resorption. **Insulin** stimulates the formation of bone matrix. **Estrogens** (mainly estradiol) inhibit the apoptosis of osteoblasts and stimulate the apoptosis of osteoclasts. They inhibit via RANKL and M-CSF the formation of mature osteoclasts and thus the bone resorption. **Thyroid hormones** increase the bone remodeling. Bone



Heart Failure

Heart failure (HF) is the state of reduced myocardial performance and mainly affects the *left ventricle (LV)*. Its most common causes (\rightarrow **A**) are coronary heart disease (\rightarrow p. 232 ff.) and hypertension (\rightarrow p. 222 ff.), which account for some three-quarters of all cases. However, nearly all other forms of cardiac disease (valvular defects, cardiomyopathies; \rightarrow **A**) as well as certain extracardiac diseases can result in HF. In particular, *right ventricular failure* may result from pulmonary hypertension (\rightarrow p. 228) in addition to right heart defects and shunts (\rightarrow p. 216 ff.). The right ventricle (RV) may also be affected secondarily by decreased function of the left ventricle (mitral stenosis, left HF). Usually HF only becomes manifest initially on *severe physical work* (when maximal O_2 uptake and maximal cardiac output is decreased, but otherwise without symptoms; stage I of the NYHA [New York Heart Association] classification). However, symptoms later develop progressively, at first only on ordinary physical activity, later even at rest (NYHA stages II–IV).

In principle, a distinction is made between HF with *systolic dysfunction* and HF with *diastolic dysfunction*. At a **systolic dysfunction** ventricular contractility is decreased (\rightarrow **A**, **C1**: $U \rightarrow U'$), the ventricles are not sufficiently emptied during contraction, the end diastolic volume (EDV) increases and the stroke volume (SV) decreases (\rightarrow **C1**). As a result the *ejection fraction* ($EF = SV/EDV \rightarrow$ p. 192) decreases. The most frequent **cause** of a systolic dysfunction is *cardiac infarction*. Depending on its localization it is the LV or the RV that is affected, whereby a HF of the LV frequently results in a secondary RV failure. Systolic failure involves disorders of energy supply and utilization, cardiac excitation, contractile apparatus, and regulation of cytosolic Ca^{2+} .

The **ventricular filling** is a function of the magnitude and speed of ventricular **relaxation**, which is an ATP-dependent process. The time course of relaxation depends, in part, on the decline of cytosolic Ca^{2+} , i.e., the rapidity of the Ca^{2+} reuptake into the sarcoplasmic reticulum (SERCA_{2A}) and the interstitium (sarcolemmal Ca^{2+} -ATPases). Beyond that, the passive stiffness of the myocardium is modulated by phosphorylation of the titin “tension

springs” by protein kinase G (PKG). Moreover, the relaxation is accelerated by phosphorylation of phospholamban during β -adrenergic myocardial stimulation (positive lusitropy).

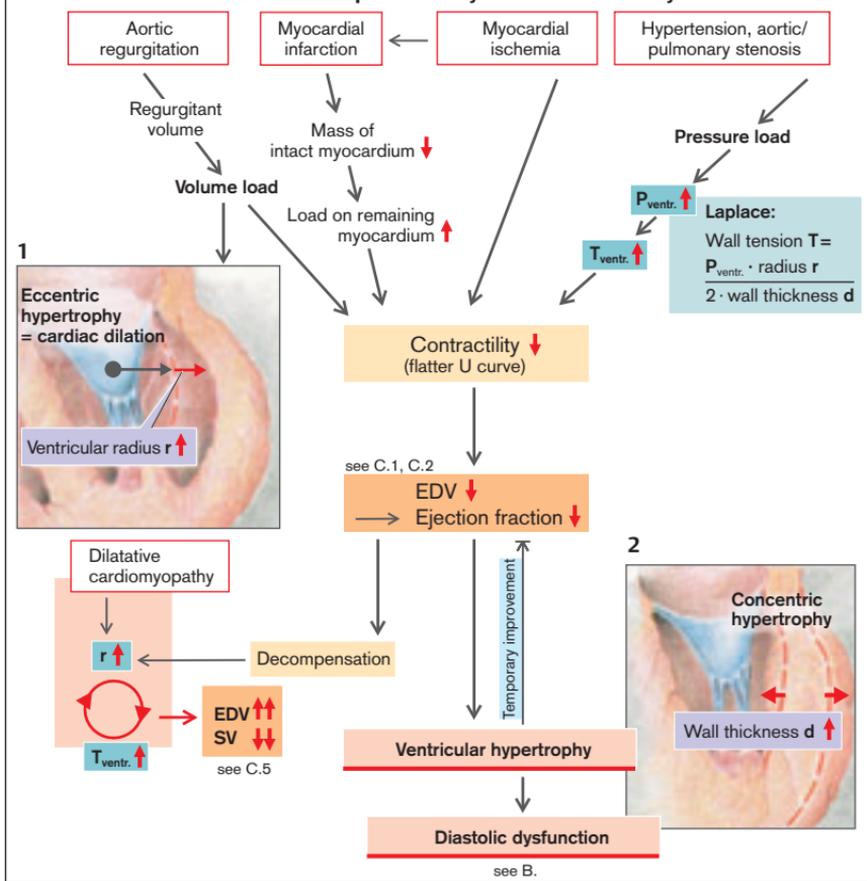
At **diastolic dysfunction** the ventricular filling is decreased, which frequently ($\varphi > \sigma$) results from *insufficient relaxation*, for instance due to decreased Ca^{2+} -pump rate as a result of ATP deficiency during ischemia. Further causes of a diastolic dysfunction include enhanced stiffness of the ventricular wall and an impairment of ventricular distension by:

- ◆ *cardiac hypertrophy* due to a hypertrophic cardiomyopathy or due to a) pulmonary or systemic hypertension and b) enhanced ventricular pressure at stenosis of the pulmonary or aortic valve (impairment of ejection, \rightarrow pp. 212, 216);
- ◆ *interstitial myocardial deposition of collagen* during aging, of *amyloid* in amyloidosis (\rightarrow p. 274), or of Fe in hemochromatosis (\rightarrow p. 270);
- ◆ *restrictive cardiomyopathy*
- ◆ *constrictive pericarditis* or pericard tamponade (\rightarrow p. 244).

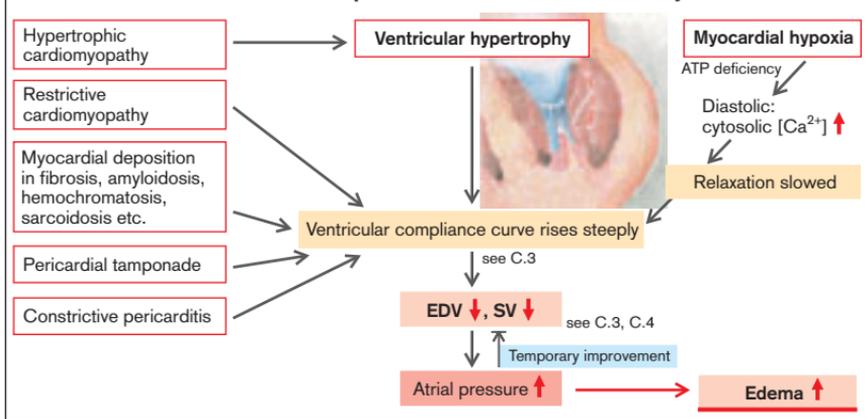
A **consequence** of diastolic dysfunction is a decrease of both stroke volume and enddiastolic volume (EDV) (\rightarrow **C3**), while the ejection fraction (EF) rather remains constant or even increases, in order to maintain the cardiac output despite insufficient ventricular filling. Nevertheless, a substantial decrease of LV filling may lead to a decline of cardiac output with the respective clinical consequences (see below). An *increase of the pressure in the respective atrium* enhances the ventricular filling but may, by the same token, lead to edema in the respective upstream capillary bed (see below).

HF caused by myocardial disease: In *coronary heart disease* (ischemia; \rightarrow p. 232) and after *myocardial infarction* (\rightarrow p. 234) the load on the noninfarcted myocardium increases and causes a *systolic dysfunction* (see above) with reduced cardiac contractility and decreased stroke volume (\rightarrow **A**). Hypertrophy of the remaining myocardium, a stiff myocardial scar as well as the diminished Ca^{2+} pump rate in the ischemic myocardium further lead to *diastolic dysfunction*. Finally, a compliant infarct scar may bulge outward during systole (dyski-

A. Causes and Mechanical Consequences of Systolic Ventricular Dysfunction



B. Causes and Mechanical Consequences of Diastolic Ventricular Dysfunction



Pathophysiology of Nerve Cells

In order to fulfill their function, neurons must be able to receive information from other cells and then pass it on to yet other cells. As a rule the information is received via **membrane receptors** that are activated by neurotransmitters. The activity of ionic channels is influenced directly or via intracellular mechanisms of transmission. Thus, in suitable target cells acetylcholine (ACh) opens nonspecific cation channels that will then allow the passage of Na^+ and K^+ . This will lead to depolarization of the cell membrane and thus to opening of the voltage-gated Na^+ and Ca^{2+} channels. Ca^{2+} ions then mediate the release of neurotransmitters by the target cell. In the long term, cell metabolism and gene expression of the target cell, and thus the formation of synapses and the synthesis and storage of neurotransmitters are also regulated.

Abnormalities can interfere with each element of this cascade (\rightarrow A). For example, receptor density can be reduced by down-regulation. Also, certain mechanisms of intracellular transmission can be blocked. An example is the blocking of G proteins by, among others, pertussis toxin (\rightarrow A1). Ionic channels can be blocked by drugs, or their activity changed by Ca^{2+} , Mg^{2+} , or H^+ . Furthermore, their effect on the membrane potential can be distorted by a change in ionic gradients, such as an increase or a decrease in the intracellular or, more importantly, extracellular K^+ concentration. Both occur when Na^+/K^+ -ATPase is inhibited, for example, due to energy deficiency. Axonal transport as well as formation, storage, release, and inactivation of neurotransmitters (\rightarrow A2) can be impaired, for example, by genetic defects or drugs. **Functional abnormalities** can be reversible once the damage is no longer effective.

Lesions may also lead to **irreversible destruction of neurons**. Thereby neurons could die by direct damage (necrosis, e.g., due to energy deficiency or mechanical destruction), or by apoptosis (\rightarrow A3 and p. 14). Apoptosis plays a major role in neurodegenerative disease (e.g., Alzheimer's disease, Huntington chorea, amyotrophic lateral sclerosis, infantile spinal muscle dystrophy), and contributes to cell death during ischemia. Neuronal apoptosis is fostered by a wide variety of disorders including lack of NO synthase (NOS), of poly-ADP-ribose poly-

merase (PARP), or of superoxide dismutases (SOD). In the adult brain, the replacement of dead neurons is hardly possible (in the hippocampus and olfactory bulb). Neuronal death thus leads to mostly irreversible loss of function even if other neurons can partly take over the function of the dead cell.

Deleterious substances must pass the **blood-brain barrier** if they are to reach the neurons of the central nervous system (CNS) (\rightarrow B). An intact blood-brain barrier impedes the passage of most substances and prevents pathogens and immunocompetent cells entering (\rightarrow p. 378). However, some toxins (e.g., pertussis and botulinus toxins) reach neurons in the spinal cord through **retrograde axonal transport** via peripheral nerves, and thus avoid the blood-brain barrier (\rightarrow p. 378). Some viruses also reach the CNS in this way.

If an **axon is transected** (\rightarrow C), the distal parts of the axon die (**Waller degeneration**). **Axons of central neurons** as a rule do not grow outward again, rather the affected neuron dies by apoptosis. Causes include absence of the nerve growth factor (NGF), which is normally released by the innervated, postsynaptic cell and, via the axon, keeps the presynaptic cell alive. The axonal regeneration is inhibited by extracellular macromolecules, such as chondroitin sulfate, oligodendrocytic myelin glycoprotein (OMGP), myelin-associated protein (MAG), and Nogo. Interruption of the retrograde axonal transport in an otherwise intact axon also leads to death of the neuron. The proximal stump of the **peripheral axon** can grow out again (\rightarrow C2). The proteins that are necessary for this to happen are formed within the cell body and are transported to the place of injury by axonal transport. A possible reason for survival of the affected cell is that macrophages migrating into the peripheral nerve, via the formation of interleukin 1, stimulate the Schwann cells to produce NGF. Macrophages are not, however, able to enter the CNS.

Transection of an axon not only causes death of the primarily damaged neuron (\rightarrow C1), the absence of innervation often leads to death of the target cell (**anterograde transneuronal degeneration**) and sometimes also of cells that innervate the damaged cell (**retrograde transneuronal degeneration**).

