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"Pathological Physiology of Heart Failure"

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Annotation: Heart failure is an epidemic disease which affects about 1% to 2% of the population worldwide. Both, the etiology and phenotype of heart failure differ largely. Following a cardiac injury (e.g., myocardial infarction, increased preload or afterload) cellular, structural and neurohumoral modulations occur that affect the phenotype being present. These processes influence the cell function among intra- as well as intercellular behavior. In consequence, activation of the sympathoadrenergic and renin-angiotensin-aldosterone-system takes place leading to adaptive mechanisms, which are accompanied by volume overload, tachycardia, dyspnoea and further deterioration of the cellular function (vicious circle). There exists no heart failure specific clinical sign; the clinical symptomatic shows progressive deterioration acutely or chronically. As a measure of cellular dysfunction, the level of neurohormones (norepinephrine) and natriuretic peptides (e.g., NT-pro BNP) increase. For the diagnosis of heart failure, noninvasive (echocardiography, NMR, NT-proBNP) and invasive (heart catheterization, biopsy) diagnostic procedures are implemented. Modulation of the activated systems by ß-blocker, ACE-inhibitors and ARNI improve outcome and symptoms in heart failure patients with left ventricular dysfunction. Interventional and surgical therapy options may be performed as well. The understanding of the underlying pathophysiology of heart failure is essential to initiate the adequate therapeutic option individually for each patient. Furthermore, prevention of cardiovascular risk factors is essential to lower the risk of heart failure.

Keywords: Heart failure, pathophysiology, HFpEF, HFrEF, treatment of heart failure.

Heart failure is a clinical syndrome characterized by typical symptoms (e.g., dyspnoea, ankle swelling, fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, peripheral oedema) caused by a structural and/or functional cardiac abnormality, leading to a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress (definition according to the European Society of Cardiology, ESC 2016). Heart failure is present only when symptoms are apparent.

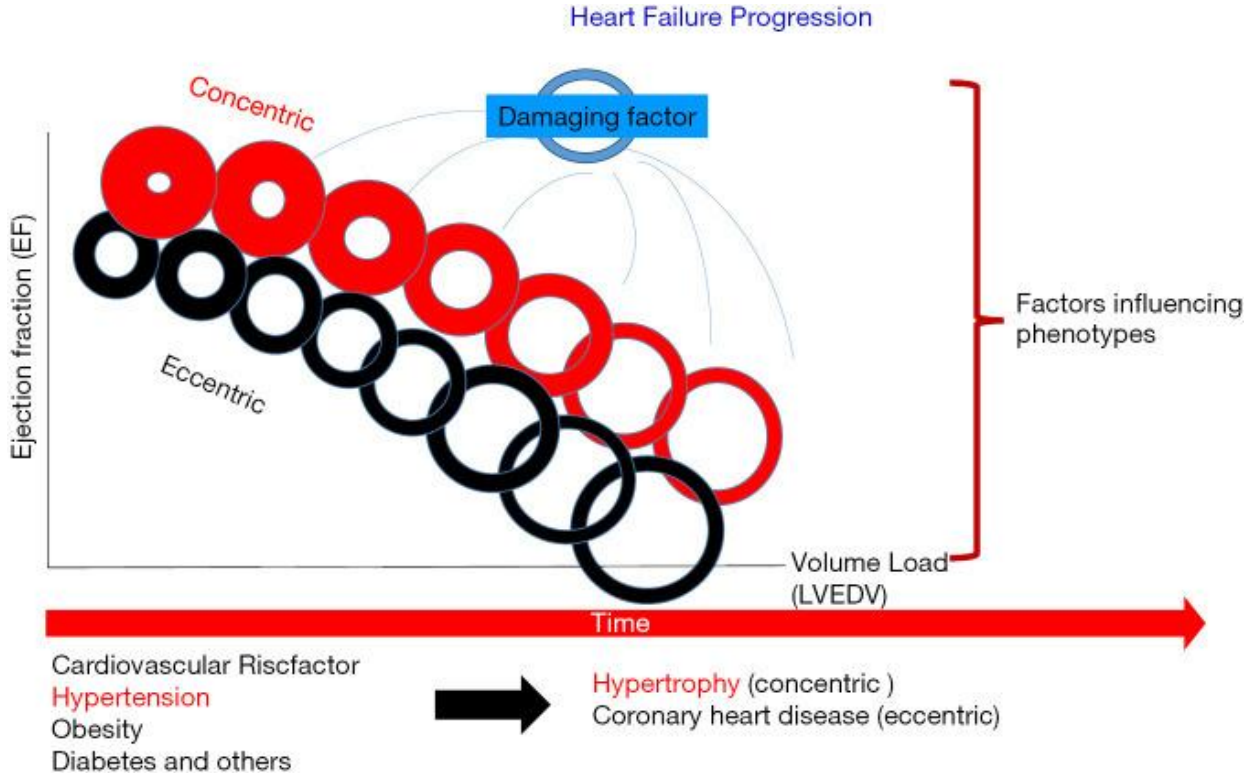
The demonstration of an underlying cardiac dysfunction is essential for the diagnosis of heart failure. This is usually a cardiac abnormality (e.g., myocardial infarction) causing systolic and/or diastolic ventricular dysfunction. Abnormalities of the valves (stenosis, regurgitation), pericardium, endocardium, heart rhythm/conduction or a combination of these alterations may also initiate heart failure. Identification of the pathophysiological mechanism leading to heart failure is crucial to choose adequate therapeutic options i.e., valve repair, treatment of rhythm disorders, pharmacological treatment.

The clinical severity of heart failure is graded according the New York Heart Association (NYHA) on the basis of clinical symptoms at various degrees of physical activity of the patient. The American College of Cardiology (ACC) and the American Heart Association (AHA)

introduced a classification which combines clinical symptoms and the concomitant disease and risk factors to develop heart failure.

The lifetime risk to develop heart failure is about one in five for a 40-year-old man in Europe or North-America and increases with age. Main risk factors are coronary heart disease, hypertension, diabetes mellitus, a family history of heart disease, obesity, chronic pulmonary diseases, inflammation or chronic infection, metabolic diseases, treatment with cardiotoxic agents (cocaine, anthracycline therapy in oncology e.g., doxorubicin, trastuzumab in treatment of breast cancer) or alcohol abuse. Cardiotoxic agents may induce cardiotoxicity acutely, early-onset chronically or late-onset chronically. Anthracycline-containing therapy leads to cardiotoxicity mostly within the first year and is associated with the given dose and the LVEF at the end of treatment. Early detection (echocardiographic strain imaging; cardiac biomarker troponin) and early treatment (ACE-I, ß Blocker, change in cancer treatment) of depressed cardiac function after anthracycline induced cardiotoxicity is crucial for recovery of the heart function. Heart failure is a progressive disease with an annual mortality rate of about 10%. The main causes of death are sudden cardiac death (>50%) or organ dysfunction due to hypoperfusion.

Patients with heart failure may present with low or reduced ejection fraction (HFrEF: EF <40%; also systolic heart failure), preserved ejection fraction (HFpEF: EF >50%; also diastolic heart failure) or mid-range (HFmrEF: EF 40–49%) ejection fraction. Patients with HFpEF are more often older, female, and obese with a history of hypertension and/or atrial fibrillation. No evidence-based therapy to improve outcome can be offered for patients with HFpEF. HFrEF patients show up more often with coronary heart disease (myocardial infarction), valve disease (aortic stenosis, mitral regurgitation) or uncontrolled hypertension; these more exactly defined underlying diseases in HFrEF are to be treated more effectively via medication, surgery or intervention. The main structural alteration in HFrEF is eccentric remodeling accompanied with chamber dilatation and often volume-overload leading to forward failure typically as consequence of large anterior myocardial infarction. The volume overload is most often the result of permanent neurohumoral activation (RAA-System). HFpEF shows impaired ventricular relaxation and/or filling, increased ventricular stiffness and thus elevated filling pressure accompanied by pressure overload. These hearts show concentric remodeling and/or ventricular hypertrophy accompanied by pressure overload and often backward failure.



The phenotype of the heart may be predominantly excentric (e.g., following volume overload, myocardial infarction), concentric (e.g., following pressure overload, aortic stenosis) or a combination of both. The adaptive remodeling (change in LV mass, volume, structure) is influenced by the phenotype, comorbidities (e.g., diabetes), risk factors (e.g., hypertension) and by the damaging factors (e.g., myocardial stress following volume load after NSAR treatment; high heart rate). The left ventricular ejection fraction depends on filling pressure and volume. Permanent overload initiates structural remodeling with chamber dilatation and shift of the pressure-volume relationship which further deteriorate cardiac function.

Heart failure may present acutely (de novo) e.g., as a consequence of acute myocardial infarction or hypertensive emergency, or in otherwise stable patients with stable heart failure symptoms for months, who can also decompensate acutely (e.g., NSAR treatment; increased fluid intake; high heart rate in atrial fibrillation). Acute decompensation of chronic heart failure is the most common type of clinical presentation of acute heart failure.

Heart failure may be also classified according to the affected circulatory system (right–sided; left- sided) or the underlying pathophysiological factor leading to cardiac dysfunction (pressure-induced: aortic stenosis, hypertension; volume-induced: ASD, VSD, mitral regurgitation). Excessive preload, excessive afterload or pump failure may lead to low output heart failure. High-output failure results from a mismatch of cardiac output (stroke volume, heart rate) and circulatory oxygen demand (e.g., high heart rate in anemia).

Only in HFrEF but not in HFpEF evidence-based therapy offers improvement in symptoms and prognosis. These differences highlight the need for understanding the differences in the pathophysiology between HFrEF and HFpEF which might also influence treatment -targets. A common fact for both is the increasing incidence and high mortality. Differences in pathological development of HFrEF and HFpEF, have been reported for aspects of inflammation and endothelial function, cardiomyocyte hypertrophy and death, alterations in the giant spring titin, and fibrosis and other aspects. HFpEF is characterised by structural and cellular alterations leading to an inability of the left ventricle to relax properly, e.g., cardiomyocyte hypertrophy, intercellular fibrosis, altered cardiomyocyte relaxation and inflammation. HFpEF is often connected with chronic comorbidities, such as arterial hypertension, type 2 diabetes mellitus (T2DM), obesity, renal insufficiency, pulmonary disease, liver disease, sleep apnoea, gout, and cancer. The inflammatory process in HFpEF is often linked to these comorbidities e.g., diabetes which also exert activation of inflammation. Endothelial cells represent about 60% of non-cardiomyocytes and endothelial dysfunction seen early in cardiovascular disease is more often present in HFpEF than HFrEF. Endothelial dysfunction can be the result of various adaptive mechanisms following reduced cardiac output e.g., neurohumoral activation, vasoconstriction, increased oxidative stress, imbalance of nitric oxide or energy bioavailability. But endothelial dysfunction (initiated by comorbidities) may be precursor of cardiac dysfunction in HFpEF also. HFpEF shows a broad spectrum of heterogeneity. Some comorbidities and risk factors are shared but some are different between HFrEF and HFpEF. Patients with HFpEF are older and show a two-fold predominance of females. The predominance of men in HFrEF might be connected to a higher incidence in myocardial infarction. HFrEF is characterized by a substantial cardiomyocyte loss acutely or chronically, resulting in the development of systolic dysfunction; e.g., myocyte loss following myocardial infarction, a genetic mutation, myocarditis with cell loss, or valvular disease with cell death due to overload (apoptosis antigen 1 activation) followed by inability of the left ventricle to contract properly. In consequence eccentric remodeling with excessive fibrotic tissue may be seen; in HFpEF concentric cardiomyocyte hypertrophy is the predominant face. In addition, cardiomyocytes are thinner; more elongated, and show lower myofibrillar density in HFrEF. Cardiac titin and calcium levels are differently affected in HFrEF and HFpEF also. HFmrEF can progress into either HFrEF or HFpEF, but its phenotype is dominated by coronary artery disease, as in HFrEF.

Genetic contribution to expression of heart failure is heterogenous and complex. Genomic variants and genetic predisposition influence the prevalence of risk factors (e.g., hyperlipidaemia, hyperglycaemia etc.) and causes of heart failure like coronary heart disease or dilated or hypertrophic cardiomyopathy (HCM). As genetic testing is more available and cheaper (next generation sequencing, NGS) it is also part of routine work up in special cases (e.g., HCM, familial heart failure syndrome). More than 100 genes have been identified to be connected with the occurrence of cardiomyopathies. Due to the specific morphological and functional phenotypes, cardiomyopathies can be clinically divided in five different groups, i.e., dilated cardiomyopathy (DCM), HCM, restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and non-classified cardiomyopathies as the left ventricular non-compaction cardiomyopathy. These forms may occur as familial (genetic) or non-familial (non-genetic) entity. Genetic profiles may influence risk and prognosis as well as therapeutic options of heart failure e.g., defibrillator implantation in high risk mutations for hypertrophy. Heart failure patients should also be asked for family history of the disease or the occurence of sudden death. In the current ESC-guidelines genetic testing is recommended when the prevalence of detectable mutations is sufficiently high and consistent to justify routine targeted genetic screening.

The clinical manifestation of heart failure is largely influenced by the primary side of dysfunction as left sided, right sided or biventricular. Left ventricular dysfunction (volume or pressure overload) increases pulmonary pressure (backward failure; increased PCWP) and consequently pulmonary congestion occurs leading to dyspnoea and tachypnoea (fluid transudation, pulmonary crackles). As the peripheral circulation is reduced (forward failure), renal dysfunction, peripheral malperfusion and malabsorption of nutrition with the signs of cardiac cachexia develop. In a chronic state, the permanent activation of neurohumoral systems (compensatory mechanisms) lead to further volume overload [liver congestion, ascites, edema (ankle, pretibial)], peripheral vasoconstriction (acrocyanosis), increased heart rate at rest and during exercise, and to a further deterioration of the cardio-renal system. Anemia, increased pulmonary pressure and muscle fatigue (diaphragm, peripheral muscles) deteriorate the symptoms of dyspnoea as well. Overload (pressure, volume) of the heart leads to enlargement of the heart itself and as a measure the cardiothoracic index increases with leftward shift of the palpable cardiac pulsation. Mostly in volume overload situations filling volume of the ventricle increases periodically and a typical 3rd or 4th heart sound as protodiastolic gallop occurs (known as “the heart cries for digitalis” in the digitalis treatment epoche some years ago). In consequence, heart failure influences almost all organ systems and thus heart failure is a systemic disease or a syndrome with a broad clinical spectrum.

Moderate anemia (haemoglobin concentration <13 g/dL in men and <12.0 g/dL in women) is often prevalent in patients with heart failure regardless of HFrEF or HFpEF. The incidence is higher in women, elderly and diabetic patients as well as in patients with renal failure. Increased blood loss in patients treated with oral anticoagulants (atrial fibrillation), aspirin or both (triple therapy in patients with coronary stent implantation and atrial fibrillation) as well as decreased absorption of vitamin (B12) and/or iron may favor anemia. Similar as in other chronic illnesses iron deficiency is common in heart failure and may influence prognosis worse. Whether anemia and/or iron deficiency are markers of heart failure severity or whether they affect outcome of heart failure disease and thus should be treated is not entirely clear. In patients with heart failure with as well as without anemia intravenous ferric carboxymaltose has improved quality of life and NYHA class but not prognosis.

Heart failure and chronic kidney disease (CKD: eGFR <60 mL/min/1.73 m2 and/or present albuminuria >30 mg albumin/1 g of urine creatinine) frequently coexist and share many risk factors (diabetes, hypertension, hyperlipidaemia) also. CKD worsen prognosis in heart failure patients; however, patients with severe CKD often have been excluded from randomized clinical trials and thus there is limited evidence-based therapy available.

Both, dysglycaemia and diabetes are very common in heart failure and impaire functional status and prognosis. Interventions which reduce mortality and morbidity in heart failure patients are similar effective in the presence or absence of diabetes. Glucose control with metformin has been shown to be safe and effective in heart failure also; it is contraindicated in patients with severe renal or hepatic impairment as of the risk of lactic acidosis. Recently, sodium-glucose cotransporter (SGLT2) inhibitors have been shown to reduce morbidity and prolong life in patients with heart failure with as well as without diabetes. This may favor the hypothesis that mitigation of glycemia-related cardiotoxicity by SGLT2 inhibitors slows the progression of heart failure.

Comorbidities and aging via influencing cognitive and self-care ability affect management of heart failure patients. Also, polypharmacy is present often. In addition, frailty [frailty scores] is common in these patients. In consequence, a multidisciplinary team is needed to take care especially for older heart failure patients to reduce hospitalizations and improve outcome.

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