The interplay between peripheral organs and the heart in heart failure

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Abstract
Heart failure (HF) is a clinical syndrome with a high prevalence and significant mortality characterized by frequent hospitalizations, poor quality of life, and complex treatment regimens. Comorbidities have a huge impact on its course. Meanwhile, management of patients presenting with HF and concomitant diseases continues to be challenging. Therefore, understanding the interaction between the heart and peripheral organs is pivotal in tailoring therapy. The pathophysiological mechanisms underlying the associations between comorbidities, such as renal failure, thyroid disorders, liver diseases, diabetes mellitus, lung diseases, body composition abnormalities, and HF remain not fully understood. The proper treatment of peripheral organ diseases is important also in the context of HF prognosis. ■Heart Metab. 2018;77:4-8

Keywords: comorbidities; heart failure; peripheral organs

Introduction
Two main types of heart failure (HF) have been portrayed: HF with reduced ejection fraction (HFREF), also known as systolic HF; and HF with preserved ejection fraction (HFPEF), previously known as diastolic HF. Very recently, the European Society of Cardiology proposed a third type: HF with mid-range ejection fraction (HFMEF).1 The pathophysiological mechanisms underlying the associations between comorbidities, such as diabetes mellitus, thyroid diseases, lung diseases, renal failure, liver diseases, body composition abnormalities, and HF remain unclear (Figure 1). They are partially associated with systemic inflammation; Paulus et al hypothesize that chronic inflammation leads to endothelial dysfunction, myocardial hypertrophy, fibrosis, and diastolic dysfunction.2 Other proposed pathophysiological mechanisms include abnormal hemodynamics, metabolic dysregulation, and neurohumoral activation.2 Even results of basic routine laboratory tests, such as hyponatremia, hyperglycemia, and impaired estimated glomerular filtration rate (eGFR), performed on admission in the emergency department are independently associated with in-hospital death in patients with acute HF.3
Cardiorenal syndrome

Cardiorenal syndromes (CRS) were established as a theoretical model to guide clinicians on the complex interplay between the heart and kidneys and to allow for better grouping of patients along clinical variables, both in acute and chronic settings. The effective classification of CRS proposed in a Consensus Conference by the Acute Dialysis Quality Group essentially divides CRS into two main groups: cardiorenal and renocardiac CRS, on the basis of primum movens of disease (cardiac or renal); both cardiorenal and renocardiac CRS are then divided into acute and chronic according to disease onset.

The development of renal dysfunction in patients with HF is multifactorial. The role of reduced renal perfusion and venous congestion, as well as increased venous pressure and activation of multiple neurohormonal systems have been acknowledged. Also a number of pathobiological processes contribute to initiating and perpetuating kidney insufficiency, including endothelial and epithelial cell death, disruption of membrane and transporter integrity, as well as immunological and inflammatory processes and apoptosis/necrosis. On the other hand, renal impairment causes metabolic and systemic derangements in circulating factors, causing an activated systemic inflammatory state and endothelial dysfunction, which may lead to cardiomyocyte stiffening, hypertrophy, and interstitial fibrosis via cross talk between the endothelium and cardiomyocyte compartments. Renal function is protected over a wide range of renal perfusion by means of renal autoregulation. However, when renal perfusion drops below a certain level, GFR will eventually decrease despite maximum autoregulatory compensation. In studies by Gori et al and Unger et al, chronic kidney disease (CKD) was independently associated with abnormal cardiac mechanics, which may explain why HFPEF patients with CKD have worse outcomes. CKD-associated mortality is worse in patients with HFPEF compared with patients with HFREF even after controlling for covariates. At present, there is no evidence-based intervention specifically targeted at preservation and/or restoring of renal (dys)function.

Dysthyroidism and HF

Dysthyroidism represents a relevant problem, especially in the aging patients with chronic HF worldwide. The thyroid gland greatly affects many cardiovascular activities and its dysfunction may worsen a chronic HF condition. The thyroid hormones are critical regulators of cardiac growth and development, and their homeostasis is essential for optimal function of the cardiovascular system. The defining biochemical features of euthyroidism, subclinical hypothyroidism (SCH), and hypothyroidism are summarized in Table I. Based on data from the SCD-HeFT trial (Sudden Cardiac Death in Heart Failure Trial), abnormal thyroid function in patients with symptomatic HF and an ejection fraction ≤35% was associated with a significantly increased risk of death, even after controlling for known mortality predictors. Moreover, recent studies revealed that expression of thyroid hormones biosynthesis machinery in the heart and total tissue levels of triiodothyronine (T3) and thyroxine (T4) are altered in

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**Abbreviations**

- BNP: brain natriuretic peptide
- CKD: chronic kidney disease
- COPD: chronic obstructive pulmonary disease
- CRS: cardiorenal syndromes
- eGFR: estimated glomerular filtration rate
- FEV1: forced expiratory volume in 1 second
- HF: heart failure
- HFMEF: HF with mid-range ejection fraction
- HFREF: HF with preserved ejection fraction
- NAFLD: nonalcoholic fatty liver disease
- SCD-HeFT trial: Sudden Cardiac Death in Heart Failure Trial
- SCH: subclinical hypothyroidism
- SICA-HF study: Studies Investigating Comorbidities Aggravating Heart Failure
- TSH: thyroid-stimulating hormone

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**Fig. 1** Pathophysiological associations between frailty and cardiovascular disease.
patients with dilated cardiomyopathy, which provides a basis for new gene-based therapeutic strategies for treating this disease. Hyperthyroidism causes high cardiac output and left ventricular hypertrophy in the early stage and biventricular dilatation and congestive HF in the late stage. Atrial fibrillation and pulmonary arterial hypertension also add to the increased morbidity of untreated hyperthyroidism. Controlling atrial fibrillation and preventing thromboembolic events are very important aspects of hyperthyroidism treatment. Early and effective treatment of hyperthyroidism is fundamental in preventing thyrotoxic cardiomyopathy.

Several recent studies have demonstrated an association between dysthyroidism and adverse effects on cardiovascular and bone health, especially in older populations. Nanchen et al analyzed a large group of patients with dysthyroidism and found a higher incidence of heart failure hospitalizations in older patients, particularly in those with lower levels of serum thyroid-stimulating hormone (TSH) <0.1 mIU/L. More importantly, results from recent large retrospective studies have shown a significant association between SCH and all-cause mortality and cardiovascular events, with heart failure as the leading cause of increased major adverse cardiac events. In recently released clinical guidelines, the European Thyroid Association recommends treating subclinical hyperthyroidism with serum TSH <0.1 mIU/L in patients >65 years old and to consider treating milder grades in the presence of heart disease or other significant comorbidities or risk factors. Hypothyroidism has a relatively high prevalence in patients with HF and it plays a key role in influencing HF onset, progression, and prognosis. The reduced production of thyroid hormones results in adverse cardiac effects, represented by reduced contractility with impaired left ventricular systolic function on exercise, impaired ventricular filling (diastolic dysfunction) associated with increased systemic vascular resistance and diastolic hypertension.

Consistent with this, levothyroxine replacement therapy has been shown to improve cardiovascular performance and ventricular remodeling in experimental models of hypothyroidism. Among 25,390 participants in the study performed by Gencer B et al, 2068 (8.1%) were found to have SCH. Risks of HF events were increased with higher TSH levels, particularly for TSH levels ≥10 mIU/L. The potential mechanisms responsible for diastolic dysfunction of the left ventricle in SCH are connected with endothelial dysfunction, arterial stiffness, inflammatory state, and are driven by TSH apoptosis-derived microparticles. The impact of SCH on left ventricular systolic function is still controversial; it is related not only with cardiac remodeling, but also with predisposition of patients with SCH to the conditions leading to HF. Levothyroxine replacement for TSH levels <10 mIU/L should be considered according to patient-specific and age-specific characteristics, as well as clinical symptoms consistent with hypothyroidism.

**Diabetes and HF**

HF is a particularly common complication of diabetes, with poor outcomes and 5-year survival rates <25%. Poorer glycemic control (hazard ratio [HR], 1.32 per percentage point of HbA1c) is an important predictor of HF development. The diabetic heart is characterized by metabolic disturbances that are often accompanied by local inflammation, oxidative stress, myocardial fibrosis, and cardiomyocyte apoptosis. Overall changes result in contractile dysfunction, concentric left ventricular hypertrophy, and dilated cardiomyopathy, which together affect cardiac output and eventually lead to heart failure, the foremost cause of death in diabetic patients. The proper treatment of diabetes is important also in the context of HF prognosis.

<table>
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<tr>
<th>TSH</th>
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<th>Interpretation</th>
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<td>Nonthyroidal illness</td>
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*Table I* Diagnosis of thyroid function.

Abbreviations: T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.
Liver dysfunction and HF

Liver dysfunction in HF is common and usually clinically significant. Lesions are caused by an impaired hepatic circulation due to congestion and hypoperfusion. Congestive lesions are characterized by dilatation of the central vein with fibrotic changes in the surrounding areas on histological examination. Isolated ischemic lesions are rare and occur due to severe and prolonged ineffective perfusion, often accompanied by hypoxemia. Increased total bilirubin and decreased albumin in patients without a history of primary liver disease who were admitted to the hospital for acute HF were associated with a higher risk of rehospitalization and death in the following months. The recognition of liver dysfunction also affects patient management. The congestive phenotype should be treated with diuretics or elimination therapy. However, if the ischemic/hypoxic phenotype is dominant, it is appropriate to initiate or intensify the therapy aimed to increase the perfusion and oxygenation. Liver stiffness is a useful index for assessing systemic volume status and predicting the severity of HF, and that the presence of liver congestion at discharge is associated with worse outcomes in those patients. Increased total bilirubin and decreased albumin in patients without a history of primary liver disease who were admitted to the hospital for acute HF were associated with a higher risk of rehospitalization and death in the following months. The NAFLD score (NFS; based on the aspartate aminotransferase to alanine aminotransferase ratio, platelet counts, and albumin), a novel indicator of liver fibrosis, correlated with circulating systemic markers of fibrosis and congestion, such as procollagen type III peptide, type IV collagen 7S, hyaluronic acid, and brain natriuretic peptide (BNP), was independently associated with higher all-cause mortality in HFPEF patients. In patients with HF and impaired hepatic function, drug hepatotoxicity and the role of the liver in the drug effects and degradation should be considered.

Lung diseases and HF

Up to 50% of all patients with chronic HF have chronic obstructive pulmonary disease (COPD), which is up to seven times higher than the general population. The forced expiratory volume in 1 second (FEV1) is used to evaluate the severity of airflow limitation. Honda et al revealed that a decrease in percent predicted FEV1 (FEV1/expected predicted) was independently associated with the poor cardiac outcomes in patients with HF. The study of Alter et al showed that the airway obstruction and lung hyperinflation were significantly associated with cardiac diastolic filling in patients with COPD, suggesting a decreased preload rather than an inherently impaired myocardial relaxation itself. This result hints that a reduction in obstruction and hyperinflation could help to improve cardiac filling.

Possible pathophysiological mechanisms of both diseases are smoking, chronic low-grade inflammation, hypoxia, oxidative stress, systemic inflammation, and sympathetic nerve system dysfunction. HF might be caused or worsened by an increase in pulmonary blood pressure, as observed in patients with COPD. Moreover, reduced lung volume due to cardiomegaly, pulmonary edema, interstitial fibrosis, and respiratory muscle weakness are also likely pathophysiological and common determinants of HF and COPD.

Cachexia and sarcopenia in chronic HF

The multinational SiCA-HF study (Studies Investigating Comorbidities Aggravating Heart Failure) showed that muscle wasting is a frequent comorbidity among patients with chronic HFREF and associated with worse exercise capacity in treadmill performance and in walking exercise tests. Cachexia in HF can be diagnosed and defined as involuntary nonedematous weight loss ≥6% of the total body weight within the previous 6 to 12 months. While sarcopenia means loss of skeletal muscle mass and strength that predominantly affects postural rather than nonpostural muscles, cachexia means loss of muscle and fat tissue that leads to weight loss. The wasting continuum in HF implies that skeletal muscle is lost earlier than fat tissue and may lead from sarcopenia to cachexia.

The causes of sarcopenia and cachexia are multifactorial. They may include proinflammatory immune activation, neurohormonal derangements, poor nutrition and malabsorption, impaired calorie and protein balance, anabolic hormone resistance, reduced anabolic drive, prolonged immobilization, and physical deconditioning, which, taken together, is characterized by catabolic/anabolic imbalance. Patients with HF associated with sarcopenia have impaired endothelial function. Lower vasodilatation had a negative impact on exercise capacity, which is particularly prevalent in patients with sarcopenia.
Summary

Multimorbidity in HF, defined as HF of any etiology and multiple concurrent conditions that require active management, represents an emerging problem within the aging population of patients with HF worldwide. Understanding the interaction of the heart and peripheral organs is pivotal for tailoring therapy. There are confirmed associations between comorbidities, such as renal failure, thyroid disorders, liver diseases, diabetes mellitus, lung diseases, body composition abnormalities, and HF. The pharmacological management of HF complicated by comorbidities is essential to improve survival. Pharmacological and nonpharmacological therapies are therefore required to prevent the development of these illnesses and reduce the combined effects of these diseases on morbidity and mortality in the population.

REFERENCES


BIELECKA-DABROWA AND OTHERS

Interplay between peripheral organs and the heart

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