GEORGE EMIL PALADE UNIVERSITY OF MEDICINE, PHARMACY,
SCIENCE AND TECHNOLOGY OF TÎRGU MUREŞ

DOCTORAL SCHOOL OF MEDICINE AND PHARMACY

PhD THESIS SUMMARY

Psycho-neuro-immunological aspects in heart failure

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Introduction:

Heart failure (HF) is linked to increased mortality, frequent hospitalizations, and poor quality of life (QoL), showing a significant increase in age-adjusted prevalence. The characteristic clinical presentation of HF includes dyspnea, fatigue, reduced physical capacity, and edema, which are the consequence of congestion and low cardiac output (causing hypoperfusion), the main pathophysiological features of HF. Although currently available evidence-based treatment has significantly reduced patient morbidity and mortality, HF still remains a complex clinical syndrome difficult to tackle. Since it was first hypothesized in 1984, abundant and strong evidence emerged proving that sustained neurohormonal activation may exert deleterious effects and impose serious hemodynamic consequences. Updated clinical practice guidelines on HF drug therapy highlight the importance of targeting the sympathetic nervous system, the renin-angiotensin-aldosterone system, the natriuretic peptide system, and the sodium-glucose cotransporter-2 pathway. Despite currently available pharmacological and implantable device therapy, disease progression suggests unexplored underlying pathophysiological mechanisms. In 1990, Levine et al. proposed the involvement of inflammation in the pathogenesis of HF, linking elevated levels of tumor necrosis factor-alpha to cardiac cachexia. Ever since, accumulating preclinical and clinical data on local and systemic inflammation in the promotion and progression of HF has been witnessed. The relationship between inflammation and HF is bidirectional and intricately entwined – left ventricular (LV) systolic and diastolic dysfunction enhances local and systemic inflammation, whereas an increased inflammatory response promotes myocardial fibrosis and adverse ventricular remodeling.

Aim:

Considering the above, the aim of the applied research was to measure circulating levels of proinflammatory cytokines, macrophage migration inhibitory factor 1 (MIF-1) and interleukin 6 (IL-6), in patients with HF with reduced (HF-rEF) and mildly reduced ejection fraction (HF-mrEF), in order to better understand systemic inflammation in HF. We also aimed to evaluate the prevalence and patient perception of symptom burden caused by emotional distress in HF-rEF and HF-mrEF. Ultimately, it was deemed necessary to identify markers of depression and anxiety in HF-rEF and HF-mrEF, to find subgroups of patients at higher risk of developing mental health conditions for future targeted screening. The third study focused on the relational analysis between established biomarkers in HF – vitamin D (25-hydroxyvitamin D, 25(OH)D), uric acid, and serum albumin – and LV systolic function evaluated by echocardiography in patients with HF-rEF and HF-mrEF. We also determined the predictive value of these markers in different logistic regression models.

Material and methods:

The research presented in the doctoral thesis is based on the clinical study entitled "Psycho-neuro-immunological aspects in heart failure", having a cross-sectional design. The study recruited patients with HF and LVEF < 50%, who registered at the Cardiology Department of the Clinical County Hospital Mureș, in Târgu Mureș, Romania. Participants were recruited either from ambulatory care or were inpatients, and evaluated before discharge. We applied the following inclusion criteria: existing HFrEF or HFmrEF according to the 2021 ESC guidelines, New York Heart Association (NYHA) functional class I–III, and overall clinical stability (regarding heart rate, blood pressure, and clinical congestion). Patients were excluded from the study if they showed signs and/or symptoms of infection, had diagnosed cancer, autoimmune disorders, liver disease, and poor kidney function (with estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation). Routine demographic, clinical, laboratory (routine tests, inflammatory markers such as MIF-1 and IL-6, 25(OH)D), and ultrasound (heart and lung (LUS)) data were collected from each participant. Patients were screened for symptoms of depression (Patient Health Questionnaire 9, PHQ-9) and anxiety (Generalized Anxiety Disorder 7, GAD-7) using validated questionnaires. Health-related QoL was also evaluated (Minnesota Living with Heart Failure Questionnaire, MLHFQ).

The study was conducted in accordance with the Declaration of Helsinki; the Ethics Committee approved the study protocol (7716/02.07.2021, Clinical County Hospital Mureș; 2281/13.04.2023, George Emil Palade University of Medicine, Pharmacy, Science and Technology of Targu Mures), and all patients provided written informed consent before enrollment.

Results:

Study 1: Implications of macrophage migration inhibitory factor 1 in heart failure with reduced and mildly reduced ejection fraction

Circulating MIF-1 can be detected in patients with HF-rEF and HF-mrEF. MIF-1 also shows significant correlations with different markers of inflammation and clinical and paraclinical parameters of disease severity. MIF-1 proved to be a significant predictor of the lower tertile of LVEF even after correcting for potential confounding factors, such as 25(OH)D tertiles, patient history of atrial fibrillation and myocardial infarction. The large number of interactions between MIF-1, IL-6, and established biomarkers in HF denotes the active involvement of systemic inflammation and the monocyte-macrophage system in the complex pathophysiology of HF. Further in vivo and in vitro studies are needed to draw solid conclusions regarding the implications of MIF in HF, in order to pharmacologically block MIF and obtain potential benefits associated with cardiovascular morbidity and mortality.

Study 2: Comparative assessment of psychological factors in heart failure with reduced and mildly reduced ejection fraction

Symptoms of depression and anxiety are common among patients with HF-rEF and HF-mrEF, affecting mental health, well-being, QoL, and the prognosis of heart disease through multiple interactions. MLHFQ scores are significantly higher in HF-rEF compared to HF-mrEF, indicating reduced QoL and a greater symptom burden associated with HF symptoms. Dyspnea proved to be a significant predictor of depression symptoms and QoL in HF with LV systolic dysfunction. C-reactive protein was the only inflammation parameter showing statistically significant correlations with depression and QoL scores. A large number of parameters showed significant associations with PHQ-9 and MLHFQ scores, thus identifying a subgroup of patients more vulnerable to developing depression, which may facilitate targeted screening in the future.

Study 3: Metabolic biomarkers for the prediction of left ventricular ejection fraction in heart failure with reduced and mildly reduced ejection fraction

Vitamin D, uric acid, and serum albumin are extensively studied prognostic biomarkers in HF. 25(OH)D has been shown to be an independent marker of LVEF in univariate and multiple regression analyses. We identified significant correlations between LVEF, 25(OH)D, uric acid, and serum albumin, suggesting similar molecular interactions. Although there is currently a plethora of information regarding vitamin D deficiency in HF, its precise mechanism, clinical impact, and management still need clarification. Our findings are mostly hypothesis generating, and further research needs to provide missing information on possible interconnections regarding vitamin D, in order to implement a multimodal approach in HF.

Originality:

The originality of the thesis lies in the triple correlation of soluble mediators of inflammation, functional indicators, and echocardiographic parameters of LV systolic function, along with standardized scores of depression and anxiety. The detection of circulating cytokines, MIF-1 and IL-6, was performed while evaluating patients with HF-rEF and HF-mrEF, and considering a significant number of clinical (6MWT) and paraclinical parameters (routine laboratory tests, LUS, echocardiographic parameters, all within a comprehensive exploration protocol). The impact of MIF-1 in HF with LV systolic dysfunction has not been previously documented by analyzing such thorough data.