DOCTORAL THESIS – SUMMARY

Endothelial dysfunction in heart failure with reduced ejection fraction

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1. INTRODUCTION, WORKING HYPOTHESIS, OBJECTIVES

Cardiovascular disease is the leading cause of death worldwide, with arterial stiffness and endothelial dysfunction representing major cardiovascular risk factors. Macrovascular function is a less common phenomenon studied in heart failure (HF); however, it is well-known that arterial stiffness (AS) has a consistent effect on central hemodynamics, affecting left ventricular function by altering ventricular-arterial coupling.

The aim of our research was to evaluate the prevalence and clinical correlations between AS biomarkers in subjects with systolic heart failure (sHF). Therefore, we determined serum osteoprotegerin (OPG), receptor activator of nuclear factor kappa-β ligand (RANKL), sclerostin, and another Wnt signaling pathway inhibitor, Dickkopf-1 (DKK-1) concentrations, in a cohort of patients with sHF and different comorbidities, and established regression models for pulse wave velocity (PWV) determinants as a significant AS indicator.

The following general objectives were established:

- determination of clinical and diagnostic parameters associated with increased AS in patients with sHF;
- analysis of the association of electrocardiographic characteristics with elevated PWC values in patients with sHF;
- identification of echocardiographic parameters associated with increased AS in patients with sHF;
- investigation of laboratory parameters and biomarkers associated with increased PWV in patients with sHF;
- highlighting the correlations between PWV values and clinical and paraclinical parameters.

2. MATERIALS AND METHODS

78 patients with sHF were enrolled in a prospective study (21 women - 26.9%; 57 men - 73.1%; mean age 65.80 ± 1.41 years). Between 2017-2020 patients were admitted to the Cardiology Department of the Mureș County Clinical Hospital, Târgu Mureș, Romania. The inclusion criteria were as follows: willingness to participate in the study, left ventricular ejection fraction <45%, hemodynamic stability (in terms of blood pressure, pulse, heart rate and congestive signs), sinus rhythm. Exclusion criteria for the current study were applied: acute phase of cardiac decompensation (in terms of clinical condition and therapy), also technical difficulties in determining AS.

The registration of the data fully complied with the Helsinki Declaration, all patients signed an informed consent regarding participation, and the study was approved by the Ethics Committee of the Mureș County Clinical Hospital (3865 / 01.03.2016).

All patients underwent an assessment of the stage and etiology of HF, paraclinical investigations were also carried out including electrocardiography, cardiac and carotid echocardiography, determination of the ankle-brachial index, measurement of arterial stiffness (PWV), laboratory tests, dosing of biomarkers for arterial stiffness and endothelial dysfunction.

Data processing was performed using Microsoft Excel 2016, GraphPad Prism 9.01, and IMB SPSS Statistics 22 software (IBM Corporation USA). Several linear regression models were established to determine PWV as a continuous variable in the whole group of patients, and in the normal PWV subgroup. Finally, nonlinear logistic regression models were created to predict high PWV values. P values <0.05 were considered statistically significant.

3. RESULTS/CONCLUSIONS

- Patients with elevated PWV were older than patients with normal PWV.

- Increased PWV was significantly more common among men compared to women.

- Blood pressure was significantly higher in patients with elevated AS.

- No association was identified between different cardiovascular diagnoses and increased PWV.

- Frequent coffee consumption was more prevalent in the normal PWV group compared to the increased one.

- Electrocardiographic characteristics were similar in both groups.

- There was a significant difference with respect to certain echocardiographic parameters, such as left ventricular telediastolic diameter, ejection fraction (EF), pseudonormal diastolic ventricular filling pattern, intima-media thickness, and thickened pericardium, between patients with pathological AS and patients with normal AS.

- Glomerular filtration rate (GFR) was significantly lower among patients with increased PWV compared to patients with normal PWV values.

- Among patients with elevated PWV blood glucose levels were higher compared to the group with normal PWV.

- OPG concentrations were significantly higher among patients with elevated AS.

- Increased PWV showed correlation with age, body mass index, EF, GFR, C-reactive protein (CRP), blood glucose, OPG, sclerostin and intima-media thickness.

- Among patients with EF <30% there was a significant correlation between PWV and age, left ventricular telediastolic diameter, GFR and serum sclerostin.

- Among patients with EF >30% there was a significant correlation between PWV and age, blood glucose, GFR and OPG.

Carotid intima-media thickness and OPG were the factors most associated with AS in patients with sHF. Serum OPG levels were significantly elevated in patients with pathological AS, while sclerostin concentrations were similar in patients with elevated and normal PWV. In our study, serum sclerostin levels were associated with AS only in patients with normal PWV values.

Biomarkers correlating with AS in HF may provide prognostic information. Further studies targeting elderly patient populations are needed to confirm the role of OPG and sclerostin in sHF.