The influence of cardiac resynchronization therapy on selected inflammatory markers and aldosterone levels in patients with chronic heart failure

The aim of the study was to assess the influence of cardiac resynchronization therapy (CRT) on a series of humoral parameters crucial for the pathophysiology of chronic heart failure such as aldosterone or the inflammatory markers. Thirty eight consecutive patients (aged 66.3 ± 9.6 years, 31 men - 82%) with chronic heart failure (57.9% with ischaemic background and 42.1% of non-ischaemic etiology) in stable for at least 3 months, NYHA class III - IV despite optimized pharma- cotherapy, with left ventricular ejection fraction (LVEF) < 35% and wide QRS complex (> 120 ms) had the blood serum tested for the concentrations of interleukin-6 (IL-6), interleukin-18 (IL-18), C-reactive protein (CRP) and aldosterone before and 12-16 weeks after CRT introduction. In the study group aldosterone concentrations were significantly reduced. Among the inflammatory markers the level of IL-6 decreased, IL-18 concentrations showed a falling trend (445.1 ± 225.7 pg/ml vs 418.4 ± 229.6 pg/ml, p=0.052), whereas no change of CRP serum contain was noted. It was showed that cardiac resynchronization therapy had an impact on systemic inflammation and hormonal status in patients with chronic heart failure during short-term observation.

Introduction
Symptomatical chronic heart failure (CHF) affects over 15 million people in >900 million European population and nearly 1 million in Poland alone. It is a problem of increasing gravity regarding social and economical aspects [2]. Despite the development of the treatment of coronary artery dis- ease and hypertension, main causes of CHF, prognosis in advanced forms of CHF remains worse than in many malignant neo- plasms [11].

Cardiac resynchronization therapy (CRT) has achieved a well established po- sition in the management of patients with drug-refractory CHF [3]. CRT has been shown to improve prognosis, physical capacity and the quality of life but the effects of biventricular stimulation not always strictly correlate with the changes of mechani- cal heart performance [16]. The other facets of CHF pathophysiology that are influenced by CRT, including neurohormonal activity, general inflammation and endothelium function are postulated to play a crucial role in this phenomenon. Little is known about the impact of biventricular stimulation on the inflammatory markers and mineralocortico-
The aim of the study was to evaluate the changes of the levels of selected inflammatory markers like interleukin-6 (IL-6), interleukin-18 (IL-18), C-reactive protein (CRP) and aldosterone serum concentrations in patients with CHF in the course of CRT.

Material and methods
Thirty eight consecutive patients (aged 66.3 ± 9.6 years, 31 men - 82%, 7 women - 18%) with chronic heart failure in stable for at least 3 months, NYHA class III - IV despite optimized pharmacotherapy with left ventricular ejection fraction (LVEF) < 35% and wide QRS complex (≥ 120 ms) were involved in the prospective study.

Exclusion criteria comprised the presence of unstable angina, acute myocardial infarction, coronary artery bypass graft or percutaneous coronary intervention within 3 months; continuous or intermittent intravenous inotropic drug therapy, an estimated life expectancy of less than 12 months, a mechanical right-side heart valve, heart transplant, pregnancy or a concurrent enrolment in a study thought to confound the results.

All patients undergoing CRT had had a coronography done. An ischaemic background of CHF was diagnosed when there was at least 50% stenosis of one or more coronary artery branches or a patient had a history of coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) [4].

Patients in sinus rhythm received atrio-biventricular stimulator (DDD BIV - n = 25), while individuals with permanent atrial fibrillation - biventricular device (VVIIR BIV - n = 13). Patients with history of cardiac arrest and/or malignant ventricular arrhythmias received the system with combined cardioverter-defibrillator function - CRT-D (16 cases). During CRT procedure all leads were implanted transvenously. Left ventricular lead, guided by venogram, was placed in coronary sinus tributary in a stable lateral or postero-lateral position, with a <3.5 cm capture threshold. The right ventricular lead was placed in the septal or outflow tract (RVOT) position. Leads’ tips positions were verified on frontal and sagittal chest X-ray. Atrioventricular (AV) delay remained standard (340 – 410 ms). In those patients AV was shortened till ventricles were paced (4 cases). Interventricular (VV) liming left nominal 5 ms, unless no signs of biventricular stimulation in the body surface ECG were observed. VV was changed then to elicit the picture of QRS fusion beats in ECG lead V1 (4 cases).

In patients with permanent atrial fibrillation (n = 13) ventricles’ rate control with beta-blockers, digoxin and amiodarone was assessed. Pharmacologic effect was assessed at one month of the follow-up considering the ablation of atrioventricular junction (if biventricular stimulation was <95%). All patients with permanent atrial fibrillation achieved the goal, none required the ablation. Given inflammatory markers including CRP (nephelometric method, Behring), IL-6 (ELISA method, Immunotech), IL-18 (ELISA method, MBL) and hormonal parameter - aldosterone (RIA method, Immunotech) were determined before CRT implementation and after 3 months of the follow-up.

Statistical analysis was performed with SAS System 9.1 (SAS Institute Inc., Cary North Carolina, USA). All parameters were tested for normal distribution with the Schapiro-Wilk test. The Student’s t-test was applied to determine if the parameters’ averages before and after the CRT introduction are significantly different. Statistical significance was considered when p < 0.05.

In the studied group 25 patients (65.8%) were in sinus rhythm, among them 9 individuals had the history of paroxysmal atrial fibrillation. Thirteen participants (34.2%) had permanent fibrillation. Clinical characterisation of the study group is summarized in table I. Patients’ pharmacotherapy comprised: angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker - 89.5%, β-blocker - 100%, loop diuretic - 86.8%, potassium-sparing diuretic - 81.6%, digoxin - 13.2%, amiodarone - 13.2%, statin - 89.5%, acetylsalicylic acid - 89.5%.

Table I
Clinical data of the study group (n = 38) - data presented as mean value with standard deviation (SD) or patients’ percentage share (%).

| Age (years) | 66.3 ± 9.6 |
| Body mass index (BMI - kg/m2) | 28.4 ± 5.1 |
| Male gender, n (%) | 31 (82%) |
| Ischaemic background of heart failure | 57.9% |
| Non-ischaemic heart failure origin | 42.1% |
| Diabetes | 44.7% |
| Hypertension | 68.4% |
| History of stroke | 10.5% |
| Chronic obstructive pulmonary disease | 13.2% |
| Hypercholesterolaemia | 84.2% |
| Hypertension | 23.7% |
| Hiponatraemia | 21.1% |
| Smoking | 13.2% |
| History of coronary artery bypass graft (CABG) | 2.6% |
| History of percutaneous coronary intervention (PCI) | 23.7% |

Table II
Selected inflammatory markers and aldosterone levels in patients before and 3 months after cardiac resynchronization therapy introduction (CRT).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before CRT (n = 38)</th>
<th>3 months after CRT (n = 38)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone [pg/ml]</td>
<td>291.9 ± 207.1</td>
<td>236.3 ± 204.0</td>
<td>0.024</td>
</tr>
<tr>
<td>IL-6 [pg/ml]</td>
<td>10.1 ± 19.7</td>
<td>5.4 ± 10.6</td>
<td>0.036</td>
</tr>
<tr>
<td>IL-18 [pg/ml]</td>
<td>445.1 ± 225.7</td>
<td>418.4 ± 229.6</td>
<td>0.052</td>
</tr>
<tr>
<td>CRP [mg/l]</td>
<td>10.0 ± 22.3</td>
<td>5.4 ± 6.8</td>
<td>0.145</td>
</tr>
</tbody>
</table>

IL-6 - interleukine-6, IL-18 - interleukine-18, CRP - C-reactive protein

Results
None of the participant died in the 3-month follow-up. Five patients were hospitalized during the observation period: two participants due to CRT-D high energy intervention in response to sustained ventricular tachycardia, one due to pulmonary embolism, one because of CHF exacerbation. One patient required left ventricular lead reposition due to its dislocation - his follow-up was prolonged to reach the 3-month period between the effective CRT introduction and control visit. All prescriptions remained stable through the study.

In the whole study group aldosterone concentrations were significantly reduced. Among the inflammatory markers the level of IL-6 decreased, IL-18 concentrations showed a falling trend (445.1 ± 225.7 pg/ml vs 418.4 ± 229.6 pg/ml, p = 0.052), whereas no change of CRP serum contain was noted (table II).

Discussion
CHF has been associated with chronic inflammatory status, which accompanies heart muscle destruction, serves originally with its healing properties but eventually leads to the aggravation of CHF [12]. Moreover, coronary artery disease and dilated cardiomyopathy are believed to be of an inflammatory origin. Proinflammatory cytokines including tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), IL-6 and IL-18 alter myocyte function and structure, participate in the process of hypertrophy, contractile dysfunction, myocyte apoptosis and extracellular matrix remodeling [7].

IL-6 with the family of IL-6 related proteins participate in the control of proliferation, growth, differentiation, survival and apoptosis signals in various tissues [5]. IL-6 has a negative inotropic action, its elevated levels in patients with compromised left ventricular systolic function were associated with the increased preload and heart rate. IL-18 based on INF-γ inducing action and a wide variety of INF-γ independent mechanisms was also demonstrated to have cardiodepressive effects [17]. It served as a predictor of future events in patients with acute coronary syndromes [6]. IL-18 mediated cardiac fibrosis and diastolic dysfunction.
tion in mice model of heart failure [19]. CRP - an acute phase-protein has been shown to have an independent prognostic value in CHF [8,18].

Aldosterone not only regulates ion homeostasis through stimulation of sodium retention and potassium excretion in the kidney, but also has many other effects. It induces heart muscle fibrosis, intensifies endothelial dysfunction, oxidative stress, inflammation and impairs fibrinolysis. All these effects lead to CHF progression and have pro-arrhythmogenic results with an increased rate of cardiovascular events altogether [10]. As RALES and EPHESUS studies have shown, the inhibition of aldosterone action with its antagonists, either spironolactone or eplerenone, reduces remarkably morbidity and mortality related to CHF [13,14]. In our study CRT decreased aldosterone concentrations, what has to be stressed, without changes in drug therapy during the follow-up period. This is an interesting result, indicating another possible effect of biventricular stimulation - involvement of mineralocorticoids. Interestingly, the only observation to date on 32-person CHF patients group involving aldosterone levels determination conducted by Boriani et al. [1] showed no changes of the hormone level after 3 months of CRT [1].

We have noted a decrease of IL-6 and a falling trend of IL-18, but not CRP, indicating still that CRT affects the intensity of systemic inflammation. IL-6 and IL-18 have been shown to be implicated in CHF pathophysiology, whereas CRP is the least specific for this disease. Similar observations on decreasing IL-6 levels in CRT patients come from the study of Lappegard [9]. Conversely, IL-6 serum contain was not changed within 12-month observation in the aforementioned study of Boriani et al. [1]. The systemic inflammation assessed with high sensitivity CRP was improved in the study of Shinohara et al. in responders to CRT (defined as the ones presenting ≥ 15% reduction of left ventricular systolic volume) during 6-month observation [15]. It only implicates the heterogeneity of inflammatory processes associated with CHF. It might be the background of CHF that affects the inflammatory cytokines profile [7]. Additionally, the involvement of different functional neurohormonal status, like the level of aldosterone in our study, might have its impact on particular cytokines concentration. To date, no large trial basing on the complex treatment targeting cytokine system with the net outcome assessment has been performed. The influence of CRT on neurohormones and inflammatory markers, and the significance and prognostic value of this impact is definitely a field for future research.

Conclusions
Cardiac resynchronization therapy has an impact on systemic inflammation and hormonal status in patients with chronic heart failure during short-term observation.

Study limitations
The study group was small and heterogeneous but highly reflected clinical profile of patients undergoing CRT. The follow-up was short.

References