Insulin-like growth factor type 2 is better than insulin-like growth factor type 1 a survival marker in patients after acute decompensation of heart failure.

Keywords
heart failure, type 2, insulin-like growth factor

Abstract
Introduction
A decreased IGF-1 has been found in heart failure (HF). There are no reports assessing IGF-2 in HF, although in vitro study has shown, that IGF-2 stimulates cardiomyocyte proliferation more than IGF-1. The study aim was to compare the IGF-1 and IGF-2 concentration depending on HF exacerbation and annual survival.

Material and methods
Among 75 patients hospitalized due to newly diagnosed or exacerbated HF, the following tests were determined: anthropometric measurements, basic laboratory tests, heart echocardiography, the IGF-1 and IGF-2 concentration. The annual survival was assessed. The participants were divided into NYHA II and NYHA III/IV groups. They did not differ in age, gender, BMI, WHR, HbA1c, HDL-cholesterol, and triglycerides, but differed in echocardiographic parameters, BNP, total cholesterol (TC) and LDL-cholesterol levels. Nine patients (12%) died during the 12-month follow-up.

Results
There were no differences in IGF-1 between NYHA groups and depending on the BMI, carbohydrate metabolism disorders and annual survival. A significantly lower IGF-2 concentration was found in NYHA III/IV vs. NYHA II: 583.71 (162.35) vs. 676.08 (172.09), p=0.02, and in those who died: 501.47(172.89) vs. 645.31(166.17) nmol/l, p=0.04. There was a positive correlation between IGF-2 and TC: r=0.28, p=0.015 and LDL: r=0.29, p=0.011 in the whole group and among patients with BMI ≥25 kg/m2: respectively for TC (r=0.31, p=0.014) and LDL (r=0.28, p=0.028). No IGF-1 correlation was found.

Conclusions
Reduced IGF-2 concentration better than low IGF-1 can characterize patients with more advanced HF and a higher one-year death risk. It secretion can depend on the cholesterol concentration.

Main text

Introduction

Insulin growth factors (IGF), also called somatomedins, are synthesized under the influence of growth hormone (GH) and form with it the somatotropin axis, which plays a key role in the regulation of growth-related processes. So far, two somatomedins have been discovered: IGF-1 and IGF-2. According to biochemical background they belong to the proteins related to insulin [1]. Both IGFs are composed of single polypeptide chains structurally similar to insulin [2,3]. IGF-1 consists of 70 amino acids, while IGF-2 is 67 amino acids long and has a 65% homology to IGF-1 [4]. They show cytophysiological activities, i.e., activation of DNA replication and RNA transcription, protein synthesis (e.g., collagen and proteoglycans), regulation of cell division and growth (e.g., chondroblasts and chondrocytes).

IGF-1 influences the sulphates absorption into cartilage and bone, bone mineralization and an increase in the kidney the process of phosphate reabsorption, influencing mainly bone growth on length [5], whereas, IGF-2 shows a strong (stronger than IGF-1) mitogenic effect mainly on muscle cells, influencing their differentiation and maturation [5,6].

Since IGFs have a structure similar to insulin, they exert also comparable effects through insulin receptors. However, they are 16 times weaker. IGFs via the insulin receptor lead to inhibition of lipolysis, increased transport of glucose to adipocytes, glucose oxidation, and a reduction in the release of free fatty acids [2]. It has also been confirmed that insulin deficiency itself is associated with decreased IGF-1 values [7].

IGFs are mainly synthesized in the liver. In addition, they can be found in fibroblasts, myoblasts, chondroblasts, osteoblasts, brain cells, gastrointestinal epithelium, kidneys and adipose tissue. Their production depends on many factors, such as: age, sex, circadian rhythm, genetic factors and the presence of chronic diseases [7,8]. In chronic liver disease, the IGF-1

production is reduced, while chronic renal failure leads to a decrease in the bioavailability of this molecule, despite its normal or sometimes elevated levels [9,10,11].

The major observation of researchers was finding the correlation and a significant influence of reduced IGF-1 concentrations on the development of cardiovascular diseases. Also the negative correlation has been documented between somatomedin and fibrinogen and homocysteine concentrations, which are independent coronary heart disease and stroke risk factors [12,13,14,15]. Patients with chronic, impaired IGF-1 production also show endothelial dysfunction and premature atherosclerosis, and those suffer from serious vascular clinical events, such as heart attack or stroke. [16,17,18].

Previous studies in the HF patients assessed mainly IGF-1. An overwhelming number of researchers have mostly observed a significant reduced IGF-1 concentration in HF. No previous studies assessed the IGF-2 in patients with chronic HF despite reports indicating its stronger mitogenic effect on cardiomyocytes. We decided to evaluate the IGF-1 and IGF-2 concentration depending on the severity of HF and annual mortality.

Methods and patients

Methods.

The study included patients consecutively admitted to the Department of Cardiology, Multispecialty Hospital in Inowroclaw with new diagnosed or worsening HF. The exclusion criteria were a history of active neoplastic disease (< 5 year), acute HF requiring catecholamines treatment, acute infection, advanced chronic obstructive pulmonary disease, renal and liver dysfunction (creatinine concentration over 2 mg/dl and transaminase 2-3 times above normal)

and mental illness. The condition for participation in the study was signing the informed consent form.

Each participant was examined with the the following measurements during the admission to the hospital: height, weight, waist and hip circumference and blood pressure; blood collection for routine/ base laboratory tests including the natriuretic peptide (BNP) and glycated hemoglobin (HbA_{1c}) concentrations. During the blood collection for routine laboratory tests, 2 ml of peripheral venous blood were additionally collected for IGF-1 and IGF-2 determinations. During the first 48 hours after admission all patients were performed echocardiography examination (ECHO) in accordance to the guidelines of the Echocardiography section of the Polish Cardiac Society [19].

All routine laboratory tests, BNP and HbA_{1c} concentations were performed at the Central Laboratory of Multispecialist Hospital in Inowrocław. BNP concentration was measured with the Human brain natriuretic peptide ELISA kit from Sigma Aldrich and HbA_{1c} with the Human Glycated Hemoglobin A1c ELISA kit from MyBioSource, using the Sysmex XN-1000 automated analyzer. IGF-1 concentration was determined by enzyme immunoassay using IGF-1 600 Elisa from DRG, IGF-2 was assessed using IGF-II Human ELISA from BioVendor. Both parameters were measured at the Department of Laboratory Medicine, Collegium Medicum UMK in Bydgoszcz.

The transthoracic ECHO examination was performed at rest, in the lying position on the left side with calm breathing pattern in one-dimensional and two-dimensional presentation, using Doppler pulsation method and the Vivid 7 pro equipped with a mechanical probe (2.5 MHz frequency). The image of the heart was obtained in the following views: the parasternal in the long axis of the left ventricle, the parasternal in the short axis of the left ventricle, and the

apical four-chamber projection. The following echocardiographic parameters were analyzed: the left atrium size (LA), the left ventricle size (LV), and the ejection fraction of the left ventricle (EF) using the biplane technique Simpson method.

One year follow up after hospitalization, participants or their designated representatives were contacted by phone to obtain information on survival. The causes of deaths were verified based on the provided medical documentation.

The study was approved by the Bioethical Committee of the Collegium Medicum Nicolaus Copernicus University in Toruń, number KB 466/2014 of June 26, 2014. **Ok**

Patients

The study included 75 patients (64% of men). The mean (SD) age of researched subjects was 67.11 (13.56) years, body mass index (BMI) - 30.18 (6.17) kg/m^2 and waist-to-hip ratio (WHR) - 0.99 (0.11). Most of patients had excessive body weight: 41% were overweight, 43% were obese. 42 patients (56% of all subjects) were diagnosed with carbohydrate metabolism disorders prior hospitalization (51% with type 2 diabetes, and 5% with prediabetes). The mean [interquartile range] HbA_{1c} was 44.0 mmol/mol [40.0 – 51.0], EF: 41% [26 – 55] and BNP 517.27 pg/ml [235.41 – 1566.34]. Ischemic HF ethiology was found among 43% of patients, due to arrhythmia in 41%, and due to valvular defects in 16% of patients. In the research group, 26 (34.7%) patients presented HF with preserved ejection fraction, 13 (17.3%) presented HF with midrange ejection fraction and 36 (48%) had HF with reduced ejection fraction [20].

All participants have been classified according to functional class II to IV in addition to *New York Heart Association* (NYHA) classification. The subjects were divided into two groups depending on the severity of HF. One group enrolled the patients with NYHA class II, while

the second included patients with classes III and IV. Characteristics of the study group according to the NYHA classification presented in the Table 1. Patients from both groups did not differ in: age, sex, BMI and WHR indexes, glycemia, HbA_{1c}, creatinine, high-density lipoprotein (HDL) and triglycerides concentrations and glomerular filtration rate (eGFR) value. However, they differed significantly in echocardiographic parameters, the BNP, total cholesterol (TC) and low-density lipoprotein (LDL) concentration. NYHA II patients presented significantly smaller LA and LV dimensions and it was also observed a significantly higher EF value. NYHA III/IV patients had significantly higher BNP level and lower TC and LDL concentration compared to NYHA II, despite the fact that they were treated with statin significantly less frequently and therapy with an aldosterone receptor antagonist was introduced more regularly for this group. (Tab. 1).

Nine patients (12%) died during the 12-month follow-up. All deaths were due to cardiovascular causes.

Statistical methods.

The summary statistics for normally distributed continuous variables that are presented as mean and (SD) and as a median with interquartile range [IQR] for non-normally distributed variables. Categorical variables are presented as frequencies.

Differences between continuous normally distributed variables were analyzed by the t test for independent samples or by ANOVA together with the adjustment for multiple testing. In the case that data was not normally distributed, differences were tested by the Wilcoxon and Kruskal-Wallis test. When multiple patient groups were compared, multiple testing corrections were also applied. Differences for categorical variables were tested using the chi-square or Fisher exact test for independence. Pearson's r correlation coefficient was used to test the

strength of the correlation between the selected continuous-type variables. To identify independent death risk factors a statistic regression model was used.

The results were considered as statistically significant when the p-value was less than 0.05. The statistical analysis was performed with the use of the R-software, version 3.0.3.

Results

We found IGF-1 concentration that was no statistically significant among patients with various HF severity according to the NYHA classification, BMI value and carbohydrate metabolism disorders presence. It was also not different in the surviving patients compared to the patients who died during the 12-month follow-up.

There were also no statistically significant differences in IGF-2 concentrations depended to BMI value and the presence of carbohydrate metabolism disorders. The group of patients with more advanced HF (NYHA III/IV) showed significantly lower IGF-2 concentration compared to NYHA II patient. Also, lower values of the somatomedin were characteristic for people who died during the 12-month follow-up (Tab. 2).

We assessed the correlations between IGF-1 and IGF-2 concentration and: age, gender, BMI and WHR index, heart rate in the ECG record, echocardiographic parameters, i.e., LA, LV, and EF as well as the glycemia, creatinine, TC, HDL, LDL, triglycerides, BNP and HbA_{1c} concentration. There were no significant correlations for the IGF-1. We stated a positive correlation between IGF-2 and TC concentrations ($r = 0.28$, $p = 0.01$) and the LDL fraction concentration ($r = 0.29$, $p = 0.011$) (Fig. 1). We found similar correlations in the group NYHA III/IV patients only. In this group IGF-2 positively correlate with concentrations of: the TC ($r = 0.42$, $p = 0.008$), the LDL ($r = 0.43$, $p = 0.007$) and also triglycerides ($r = 0.35$, $p = 0.031$) (Fig. 2). We have not found such correlations in NYHA II patients.

In the groups divided depending on the BMI, among patients with BMI ≥ 25 kg/m^2, IGF-2 concentrations correlated positively with the TC (r = 0.31, p = 0.014) and LDL level (r = 0.28, p = 0.028) (Fig. 3). There were no significant correlations of IGF-1 concentration in these groups.

To identify independent annual death risk factors the regression model was used. Table 3 presents the estimation results of the models with a single explanatory variable (Model I) and with multiplevariable model (Model II). The concentration of IGF-2 and HbA_{1c} as well as the LA size has an impact on the mortality of patients with chronic HF during the 12-month follow-up.

Discussion

In HF patients the vast majority of researchers have so far observed GH deficiency and decrease of IGF-1 concentrations [21,22]. Jankowska et al. stated in 64% of HF patients reduced IGF-1 values [23]. In this group of patients, it was found that low IGF-1 concentration correlates positively with the degree of systolic dysfunction, the presence of cachexia and skeletal muscle weakness, as well as interacts with neurohormonal activation (synthesis of cortisol and natriuretic peptides) and proinflammatory cytokines [24,25]. Some researchers have shown that low IGF-1 concentration mainly affect patients with cardiac cachexia. Anker et al. did not find a decreased IGF-1 concentration in HF patients without cachexia, however, along with the symptoms of malnutrition, the values of this protein decreased significantly [26]. Studies by Petrett et al. indicate that low IGF-1 values in relation to GH with simultaneous high NT-proBNP concentration may be take into consideration as independent death predictors in HF patients without cachexia [27].

Experimental studies explaining the mechanism of the IGF-1 beneficial effect on the heart muscle function and patient survival indicated the influence of this somatomedin on the cardiomyocyte apoptosis processes inhibition. This has been documented by activating the PI3k/Akt (*phosphatidylinositol 3-kinase and AKT protein kinase*) signaling pathway and feedback inhibition of the SOCS (*suppressors of cytokine signaling*) pathway, which are the mechanisms of apoptosis process [28,29]. Repetto et al. showed that IGF-1 also participates in the vascular endothelium proper functioning by stimulating the nitric oxide production, thus exerting an antiatherosclerotic effect [30], and it may explain the beneficial effect of the protein on the cardiomiocytes functions and, consequently, the patients survival.

In our study, however, we did not find significant differences in IGF-1 levels depending on the HF severity according to NYHA qualification, but we observed statistically significantly lower IGF-2 levels in patients with advanced (NYHA III/IV) HF that are compared to patients with the NYHA II.

Most of the existing studies focus only on IGF-1, while data on IGF-2 in HF patients are insufficient. Influence of IGF-2 on the survival of HF patients has not been documented in the trial. The experimental studies which evaluated the effect of this somatomedin on the cardiomyocyte apoptosis inhibition, indicate influence similar to IGF-1, (by activating similar metabolic pathways) [29]. Additionally, it emphasizes, that IGF-2 has a very strong mitogenic effect on muscle cells growth and differentiation. The IGF-2 mitogenic activity based on influence on the cascade mechanism of tyrosine kinase activation signal transduction and it is stronger than IGF-1 [5,6]. Since in our studies, we found not only higher IGF-2 levels among patients with less advanced HF, but also the IGF-2 concentration was significantly lower in the patients who died during the 12-month follow-up compared to living patients. We hypothesize that perhaps the "beneficial" IGF-2 effect on cardiomyocytes is more significant than IGF-1.

This is also confirmed in the univariate regression model. We determined that lowered IGF-2 concentration is one of the parameters with an established effect on the death risk. We have not shown such an effect to IGF-1.

The published studies have shown that the levels of IGFs are influenced by cholesterol concentration [7]. In the conducted study, we also found that in the group NYHA III/ IV patients IGF-2 concentration positively correlates with the total cholesterol and triglycerides concentration - Figure 2. Similar relationship was also observed in patients with BMI ≥ 25 kg/m^2. In this patients group IGF-2 concentration positively correlates with total cholesterol and the LDL fraction (Figure 3). Such dependencies have not been found for IGF-1.

Our results confirm, that increased serum lipids correlate with enhanced IGF-2 secretion. Fatty acids are a proven significant energy source for cardiomyocytes [31,32]. We can speculate that IGF-2 secretion takes place only if the energy cells reserves are properly "secured", because lipids are an important energy source and building material for cardiomyocytes growth and differentiation. **k**

In the relation of low values of total and LDL cholesterol, which characterized patients from the NYHA III/IV group [33], the IGF-2 secretion increased only with enhanced concentration of these lipids. This relationship, can be explanation why in the malnourished and cachectic patients with low serum lipids we observe lower values of somatomedins, which may be the reason for a development of more advanced HF and a higher mortality of such patients [34].

Recently, it has also been shown that IGF-2 reduces the concentration of glucose in the plasma more strongly than IGF-1 [35]. Since IGFs are structurally identical to insulin, they can exert in the same metabolic effects through specifically located receptors. This includes enhancement of glucose transport to cells, glucose oxidation, and reduction of free fatty acid

release. This effect can take place both through the IGF and the insulin receptors [31,35]. Perhaps, also due to the mechanism of a greater glycemia decrease, IGF-2 also positively influences the prognosis of patients. However, in the conducted study, we did not find significant differences in IGF-2 levels among patients with and without carbohydrate disturbances.

We ~~also s~~peculate that IGF-2 plays a role in the "obesity paradox" in HF, which means a better prognosis for HF patients with excess body weight [36,37]. The positive correlation of IGF-2 with TC and LDL concentration that was observed among patients with BMI ≥ 25 kg/m^2, often characterized by hyperlipidemia, may be responsible for a stronger effect on the growth and multiplication of muscle cells in this group.

It can be suggested that IGF-2 have a stronger influence on the processes of cellular metabolism (carbohydrates and lipids) than IGF-1, which participates mainly in GH-controlled growth processes. This is a hypothesis that requires confirmation in studies on a larger group of patients and verification in experimental researches.

Study limitations

The main project limitation is the small size of the study group and the results large dispersion. The mean IGF-2 concentration in patients from NYHA groups and those who died vs. survived was significantly different, but the SD values of the compared groups overlapped widely. In this situation single value in individual patient can not be considered clinically meaningful or significant. The correlation between IGF-2 and TC and LDL have wide dispersion along the regression line too, that this is only indicating a dependence suggestion. The study results require confirmation in a larger patients group for future research and follow

up studies. The study limitation are also the results ECHO examination, because intraobserver and interobserver echocardiographic reproducibilities were not calculated.

Summary

Based on the obtained results it can be assumed that reduced IGF-2 concentration can be better than low IGF-1 concentration a marker of patients with more clinical advanced HF and a higher death risk of in one-year follow-up. It seems that IGF-2 can stimulate the metabolic processes in heart muscle cells more strongly than IGF-1 and its secretion may be associated with the serum lipids level.

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IGF-2 is better than IGF-1 a survival marker in patients with chronic heart failure.

Parametr		IGF-1, nmol/l mean (SD)	P	IGF-2, nmol/l Mean (SD)	P
Total study group		12.07 (6.22)		82.11 (22.53)	
NYHA classification	NYHA II	11.11 (3.63)	0.19	88.39 (22.50)	0.02
	NYHA III/IV	12.96 (7.85)		76.31 (21.23)	
BMI, kg/m^2	< 25.0	10.56 (3.76)	0.20	79.43 (17.04)	0.59
	≥ 25.0	12.36 (6.57)		82.62 (23.51)	
	≤ 27.0	10.54 (2.98)	0.06	82.43 (24.51)	0.94
	> 27.0	12.79 (7.18)		81.96 (21.79)	
	< 30.0	11.83 (7.40)	0.68	81.31 (23.36)	0.72
	≥ 30.0	12.39 (4.26)		83.18 (21.70)	
Carbohydrate metabolism disorders	Absent	10.86 (3.89)	0.12	83.89 (19.41)	0.54
	Present	13.02 (7.48)		80.71 (24.85)	
12-month survival	Yes	11.22 (3.61)	0.18	84.37 (21.72)	0.04
	No	18.29 (14.24)		65.56 (22.60)	