Effect of elevated bilirubin levels on the long-term outcome in patients with chronic heart failure due to hypertension

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Abstract: Introduction. Data on the elevated plasma bilirubin level as a predictor of adverse cardiac events in patients with heart failure are scarce, and there are no reports in this regard concerning hypertension-related heart failure. **Objectives.** The aim of the study was to evaluate the frequency of death and composite end point (MACE) in patients with normal (group A) and elevated (group B) plasma bilirubin levels. **Patients and methods.** We evaluated prospectively 124 patients (83% males, mean age 50.1 ±7.7 yrs) in the NYHA class II and III with hypertension-related chronic heart failure. Hypertension was defined as BP >140/90 mmHg documented clinically for at least 5 years before the onset of heart failure symptoms. All patients were on standard medical therapy for heart failure. All of them underwent coronary angiography to exclude coronary artery disease as a cause of heart failure. The primary end point was the frequency of death due to cardiovascular causes and the secondary end point was the frequency of MACE (including death, urgent heart transplantation and readmission to hospital due to heart failure progression). **Results.** Groups A and B comprised 77 and 47 patients, respectively. The mean bilirubin level in group A was 0.8 ±0.17 mg%, and 1.7 ±0.61 mg% in group B ($p < 0.0001$). The groups were similar with respect to age, sex, the duration of chronic heart failure, and the NYHA class, echocardiographic parameters, baseline sodium concentration, alanine and aspartate aminotransferase activity and the therapy used. Patients in group B had higher concentrations of NT-proBNP ($p = 0.001$) and fibrinogen ($p = 0.04$) along with longer prothrombin time ($p = 0.02$) as compared to patients in group A. In the 2-year follow-up the death rate was 5.2% in group A, and 23.4% in group B ($p = 0.002$), and the frequency of MACE 18.2% and 42.6% in groups A and B ($p = 0.003$), respectively. **Conclusions.** Associated with higher incidence of death and adverse cardiac events during the two-year follow-up in patients with hypertension-related chronic heart failure. The elevated bilirubin level may be used as a simple prognostic factor in this group of patients.

Key words: arterial hypertension, bilirubin level, chronic heart failure

INTRODUCTION

Mortality and morbidity in patients with chronic heart failure (CHF) are high. Assessment of prognosis in an individual subject is based on a variety of tests such as measurements of the transpulmonary gradient, pulmonary vascular resistance, oxygen consumption stress tests as well as plasma concentrations of endothelin, natriuretic peptides (brain natriuretic peptide [BNP] and N-termind pro-brain natriuretic peptide [NT-proBNP]) or catecholamines [1-5]. Therefore, it is essential to find simple screening tests that enable the identification of the CHF patients at an increased mortality risk who would require the broader diagnostics and modification of treatment strategy.

As the CHF might be associated with clinical, biochemical and histopathological features of liver failure, there is a growing interest in laboratory tests reflecting liver function [6,7].

In a high percentage of the CHF patients the enlargement of the liver on physical examination, increased total bilirubin, alanine and aspartate transaminase levels and mild prolonga-

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tion of prothrombin time are found [6-9]. These simple tests are common and available in general practice.

There are three probable mechanisms responsible for anatomical and functional hepatic changes: 1) insufficient oxygenation of liver cells due to slow blood flow within are liver and reduced arterial blood saturation as a result of lung damage; 2) venous hypertension with fluid overload and intercellular matrix oedema and, in consequence, impaired oxygen diffusion; 3) reduced cardiac output [8,10].

Additionally, blood hemolysis in ischaemic and damaged peripheral tissues, particularly within infarcted lung, may also be responsible for increased plasma bilirubin [7] as well as effect of pharmacotherapy [11].

There is little data regarding the prognostic value of elevated plasma bilirubin in patients with CHF [3,11]. Therefore, we sought to determine the frequency of death and combined end point (MACE) in patients with normal (group A) and elevated (group B) plasma bilirubin levels.

PATIENTS AND METHODS

One hundred and twenty-four consecutive patients with CHF in NYHA II (85%) and III (15%) and hypertension were prospectively studied between January 2003 and May 2004. All patients in 4–6 months prior to admission were treated with increasing doses of the following medications: angiotensin-converting enzyme inhibitor (ACEI), β-blocker (metoprolol CR 50–150 mg/d or carvedilol 50–75 mg/d), spironolacton 25 mg/d, furosemide 40–80 mg/d. Patients with the ACEI intolerance were treated with angiotensin II receptor antagonist (5.6% of patients). Digoxin was administered in 68.6% of patients. The aim of the treatment was to achieve optimal neurohormonal inhibition [12] and regression of heart failure signs and symptoms. The medication doses had not been changed for at least 4 weeks before the study entry.

Inclusion criteria:

1) symptomatic systolic heart failure for at least 2 years
2) hypertension (documented ≥2 episodes of systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg for at least 5 years prior to the onset of symptoms of heart failure)
3) left ventricle (LV) dilation and reduced ejection fraction (LVEF) <45% on transthoracic echocardiography
4) no coronary artery disease on coronary angiogram.

Exclusion criteria:

1) confirmed coronary artery disease and/or history of myocardial infarction
2) valvular or congenital heart disease or any other disease which may result in structural or functional myocardial damage apart from relative mitral and/or tricuspid regurgitation
3) immunosupressive treatment in the last 3 months before inclusion in the study
4) confirmed connective tissue disease and/or cancer
5) any endocrine disease
6) any liver disease
7) any kidney disease
8) no informed consent.

In all patients history was taken and physical examination, laboratory tests, transthoracic echocardiography, coronary angiogram, electrocardiogram at rest, the assessment of quality of life and frequency of depression episodes were performed. In the last 3–6 months before entry into the study, the ambulatory blood pressure monitoring (ABPM) was performed in all patients. Blood pressure values exceeding 135/85 mmHg were considered abnormal [13].

Transthoracic echocardiography (M-mode, 2D, Doppler) was performed with Vingmed VIVID-5 (General Electrics). All data were registered on magneto-optic discs in order to enable off-line analysis and assessment of intra- and inter-observer variability. Echocardiographic calculations were performed using commercially available software ComPACS (Medimatic). Echocardiographic measurements included the following parameters: LV end-diastolic (EDD) and end-systolic (ESD) diameter, intraventricular end-diastolic diameter, LV posterior wall end-diastolic diameter (LVPWD), LV mass index, LV end-diastolic (EDV) and end-systolic (ESV) volume, LV ejection fraction (EF) and right ventricular systolic pressure (RVSP).

Quality of life was assessed by the SF-36 test [14] which consists of 36 questions reflecting the status of eight human life areas: physical functioning, limitations due to physical health – physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning and mental health. Physical functioning, physical role functioning, bodily pain and general health are the components of the Physical Component Summary (PCS). Vitality, social functioning, emotional role functioning and mental health form the Mental Component Summary (MCS). The rate of occurrence of depression episodes was evaluated by the Beck Depression Inventory. Depression was diagnosed if the result of the Beck test exceeded 12 points [15].

Long-term clinical observation began on the patient's admission to the hospital. Long-term follow-up data were achieved during control visits, through questionnaires and telephone contact. The questionnaire inquired about cardiac adverse events (death, heart transplantation, hospitalization due to exacerbation of chronic heart failure).

Statistical analysis

All values were expressed as mean ± SD. Differences between the study groups were evaluated by Student's unpaired test for continuous variables with normal distribution and by the Mann-Whitney test for variables without normal distribution. Discreet variables were estimated by the χ^2 test. Yates' correction was applied for low-number population groups. The influence of analyzed parameters on mortality and combined end-point occurrence was assessed by univariate and multivariate logistic regression. A P value <0.05 was required to fulfil

statistical significance. All calculations were performed using a commercially available statistical package STATISTICA PL 6.0 (StatSoft Inc.).

RESULTS

Groups of patients with normal (A) and increased plasma bilirubin (B) did not differ in regard to age, gender, duration of heart failure and hypertension and concomitant diseases such as diabetes and gout. No significant differences were found between the groups in echocardiographic parameters or in a daily dose of loop diuretics. In patients with elevated plasma bilirubin concentration, prothrombin time and the NT-proBNP were significantly increased and total cholesterol and triglicerides levels reduced compared to patients with normal plasma bilirubin. Quality of life in both groups was similar at baseline and in the 2-year follow-up. Results are given in table 1.

Cardiac death and unfavourable cardiac events were significantly more common in patients with increased plasma bilirubin. In the population with increased bilirubin concentration 11 patients died of massive pulmonary embolism (n = 2), electromechanical dissociation (n = 1), pulmonary oedema as a result of hypertonic crisis (n = 1) and sudden cardiac death (n = 7). In the group of patients with normal bilirubin concentrations, 5 subjects died because of sudden cardiac death.

The NT-proBNP (per 1000 U) (odds ratio [OR] = 2.48; 95% CI: 1.29–4.76, p = 0.005) and the PCS (per 10 points) (OR = 0.81; 95% CI: 0.66–0.99, p = 0.03) have been identified as independent risk factors of cardiac death, and age (per 10 yrs) (OR = 1.3; 95% CI: 0.1–1.8, p = 0.04), the NT-proBNP (per 1000 U), (OR = 3.69; 95% CI: 1.02–3.69, p = 0.04) and the result of the Beck test (OR = 1.51; 95% CI: 1.02–2.5, p = 0.01) as independent risk factors of the MACE in patients with elevated plasma bilirubin.

In patients with normal plasma bilirubin the NT-proBNP (per 1000U) (OR = 2.64; 95% CI: 1.31–5.32, p = 0.006) and the MCS (per 10 U) OR = 0.91; 95% CI: 0.85–0.98, p = 0.01) have been shown as independent risk factors of the MACE. Uni- and multivariate analysis of factors influencing cardiac death was not performed in patients with normal plasma bilirubin as death events were infrequent in this group of patients (n = 4).

DISCUSSION

The goal of the present study was to compare the prognosis regarding cardiac death and the MACE in patients with hypertension and systolic heart failure without concomitant coronary artery disease in relation to plasma bilirubin concentration.

In the 2-year follow-up patients with increased plasma bilirubin were more frequently affected by cardiac death, need for heart transplantation and re-hospitalization due to exacerbation of heart failure symptoms.

Our results are in accordance with reports by Masson et al. and Batin et al. [3,16].

Masson et al. have shown that elevated plasma bilirubin, creatinine and the BNP were associated with the increased plasma concentration of endothelin-1 precursor. The endothelin precursor (so called "great" endothelin) is recognized as a prognostic factor of cardiac death and the MACE [3]. Batin et al. defined plasma bilirubin and aspartate transaminase as prognostic factors of cardiac adverse events [16]. In our patient population, we have not found any significant differences in transaminase plasma concentration between patients with normal and increased plasma bilirubin. However, Batin et al. evaluated patients with heart failure mainly due to coronary artery disease and cardiomyopathy. Hypertensive etiology of heart failure in this group of patients was marginal. Increased levels of transaminases are common in patients with myocardial infarction and episodes of hypotension or cardiogenic shock as a result of ischaemic damage to the liver [17]. The majority of patients analyzed by Batin et al. were in the NYHA class III and IV, while patients in our study group presented the NYHA class II and III. The follow-up of patients reported by Batin et al. is much longer than ours (13 yrs). It also should be pointed out that Batin et al. carried out their study in the 1980s when heart failure treatment standards were different and not as effective as nowadays.

According to Lau et al. [17] liver dysfunction with elevated cholestatic parameters (bilirubin, alcalic phosphatase, gamma glutamyl transpeptidase) in patients with chronic heart failure is potentially reversible, if the liver ultrasonic image is normal. Therefore, the intensification of heart failure treatment may result in the improvement of liver function. This conclusion combined with the results of the present study has some practical implications. A simple measurement of bilirubin plasma concentration enables the assessment of prognosis in individual subjects and helps introduce changes in treatment strategies in order to reduce the risk of cardiac death or unfavourable cardiac events.

Some of the investigators suggest that the severity of liver dysfunction is related to the degree of hemodynamic disturbances due to heart failure [6,17]. Lau et al. have shown that the degree of tricuspid regurgitation, severity of pulmonary hypertension and the LV dysfunction were independent factors of increased plasma bilirubin [17]. Kubo et al. have proved that the liver dysfunction degree was inversely related to the cardiac index [6]. In the present study this finding was not confirmed as doses of diuretics necessary to maintain appropriate fluid load and echocardiographic parameters did not differ between patients with normal and increased plasma bilirubin. It is likely, however, that plasma bilirubin is a better marker of patients` clinical conditions than hemodynamic parameters. It shows the consequences of chronic heart failure for the cellular level with ischaemia and oedema of liver cells, contrary to hemodynamic and echocardiographic measurements which

Table. Baseline characteristics and results of the two-year follow-up

Parameter	Group A (n = 77)	Group B (n = 47)	p
Age (years)	49 ±7	49 ±9	NS
Duration of CHF (years)	3 (1.8–4.2)	3.3 (1.6–3.9)	NS
Duration of HA (years)	8.8 ±6	8.9 ±4.5	NS
Men	61 (79.2%)	42 (89.4%)	NS
Alcohol	8 (10.4%)	4 (8.5%)	NS
Caries	15 (19.5%)	11 (23.4%)	NS
Depression on admission (>12 points)	48 (62.3%)	33 (70.2%)	NS
Diabetes	7 (9.1%)	7 (14.9%)	NS
Gout	10 (13%)	3 (6.3%)	NS
NYHA class III	8 (10.39%)	10 (21.28%)	NS
Fibrinogen (mg/dl)	373.6 ±78.2	409.2 ±96.4	0.036
Prothrombin time (s)	13.57 ±1.54	14.04 ±1.35	0.02
Activated partial thromboplastin time (s)	35.9 ±5.7	36.2 ±6.9	NS
Potassium (mEq/l)	4.5 ±0.5	4.5 ±0.5	NS
Sodium (mEq/l)	139.5 ±4.1	137 ±3.3	0.003
D-dimer (μg/ml)	0.37 ±0.31	0.39 ±0.26	NS
Erythrocytes (106/μl)	4.78 ±0.43	4.78 ±0.52	NS
Hemoglobin (mmol/l)	9.14 ±0.83	9.28 ±2.68	NS
Hematocrite (%)	43.4 ±3.9	42.4 ±4.8	NS
Leukocytes (103/μl)	7.86 ±5.4	7.9 ±2.1	NS
Platelets (103/μl)	192.5 ±59.6	214.41 ±90.4	NS
Creatinine (μmol/l)	85.6 ±19.5	88.0 ±15.1	NS
CK-MB mass (ng/ml)	2.1 ±1.13	3.8 ±9.3	NS
Total Bilirubin (μmol/l)	13.6 ±2.9	28.9 ±10.4	<0.0001
NT-proBNP (pg/ml)	959.6 ±953.9	1801.4 ±1526.7	0.001
AspAT (U/l)	27.6 ±10.7	28.5 ±13.9	NS
AlAT (U/l)	36.1 ±20.9	34.7 ±23.2	NS
Total Cholesterol (mmol/l)	5.6 ±1.1	5.0 ±1.2	0.006
Triglycerides (mmol/l)	2.3 ±1.5	1.6 ±0.8	<0.001
LVEF (%)	31.7 ±7.8	30.2 ±7.4	NS
IVSD (mm)	11.6 ±1.7	11.5 ±1.8	NS
EDDLV (mm)	65.8 ±7.7	67.5 ±6.5	NS
LVPWD (mm)	11.3 ±1.7	11.4 ±1.1	NS
ESDLV (mm)	50.5 ±8.9	52.46 ±8.4	NS
EDVLV (ml)	205.7 ±71.2	215.55 ±60.34	NS
ESVLV (ml)	141.4 ±57.5	149.35 ±54.85	NS
LA (mm)	42.1 ±4.9	44.03 ±4.74	NS
RV (mm)	26.0 ±4.8	28.1 ±5.1	NS
Mass index LV (g/m^2)	177.4 ±44.1	178.5 ±39.1	NS
RVSP (mmHg)	34.0 ±4.8	35.1 ±5.08	NS
Mean arterial pressure values in ABPM			
Mean systolic pressure (mmHg)	144.7 ±6.1	144.3 ±5.5	NS
Mean diastolic pressure (mmHg)	97.7 ±4.0	95.4 ±4.9	0.006
Quality of life according to health status (SF-36)			
Total physical health on admission	32.2 ±4.75	33.7 ±8.3	NS
Total mental health on admission	30.73 ±11.3	28.6 ±14.3	NS
Total physical health on admission – 2-year follow-up	36.24 ±10.0	30.3 ±17.5	NS
Total mental health on admission – 2-year follow-up	36.99 ±12.6	29.89 ±18.5	NS

Table. Baseline characteristics and results of the two-year follow-up – cont.

Parameter	Group A (n = 77)	Group B (n = 47)	p
End-points			
Death	4 (5.19%)	11 (23.4%)	0.002
MACE	14 (18.18%)	20 (42.55%)	0.003

ABPM – ambulatory blood pressure measurement, AIAT – alanine aminotransferase, AspAT – asparagine aminotransferase, CHF – chronic heart failure, CK-MB – creatine kinase MB, EDDLV – left ventricle end-diastolic diameter, EDVLV – left ventricle end-diastolic volume, ESDLV – left ventricle end-systolic diameter, ESVLV – left ventricle end-systolic volume, HA – arterial hypertension, IVSD – intraventricular end-diastolic diameter, LA – left atrium diameter, LV – left ventricle, LVEF – left ventricle ejection fraction, LVPWD – left ventricle posterior wall end-diastolic diameter, MACE – major adverse cardiac events, NS – not significant, RV – right atrium diameter, RVSP – right ventricular systolic pressure

enable the evaluation of real time heart function but do not bring any information on other organs condition [18]. It has to be taken into consideration that our patient population, contrary to patients analyzed by Kubo, consisted of subjects only in the NYHA class II and III. They were consecutively enrolled in our study having fulfilled the inclusion and exclusion criteria. Different treatment strategies were also applied in both groups of patients. Due to the developments in the CHF treatment in the past years it is possible to prevent patients with the long time CHF more effectively from progression of the disease. The CHF duration in patients with increased and normal plasma bilirubin was similar. However, Felder et al. reported in 1950 that elevated plasma bilirubin was more common in patients with a longer history of CHF [7].

We have shown in our study the prognostic value of quality of life (QOL) assessment in patients with increased plasma bilirubin and the CHF due to hypertension. The well validated SF-36 questionaire has been used in our study in order to examine general physical and mental health as regards physical functioning, bodily pain, the role of limitation because of physical and emotional problems, emotional well-being, social functioning, energy or fatique and general health perceptions. Contrary to the NYHA stratification the QOL brings information not only on patients` physical but also mental functioning. It is composed of questions related to a point scale which enables the presentation of the quantitative results of the questionaire. However, it has to be taken into account that the patient's functioning is mainly dependent on the presence of the CHF symptoms, therapy efficacy and side-effects and the patient's expectations. Therefore, the discrepancy between the CHF symtoms, myocardial dysfunction and tissue metabolic disorders is often observed. Nonetheless, the maintenance of a good quality of life, which affects the long-term outcome of the CHF treatment, is one of the priorities in this treatment.

In patients with elevated plasma bilirubin the PSC was identified as an independent risk factor of death, and the presence of depression according to the Beck Depression Inventory as an independent risk factor of combined end-point. It is known that depression affects the functioning of hypothalamo-pituitary-suprarenal feedback and autonomic system as well as patients' adaptation to restrictions in their lifestyle. It may also be augmented by the medications and their

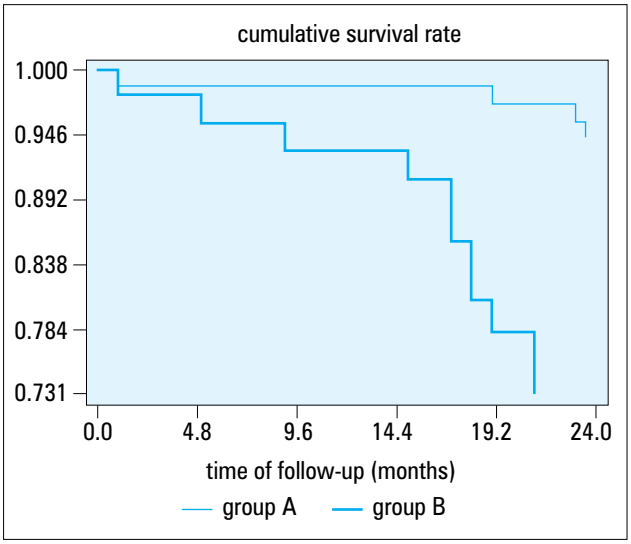

Fig. 1. Kaplan-Meier curves showing survival during follow-up ($P_{log\ rank}$ = 0.02).

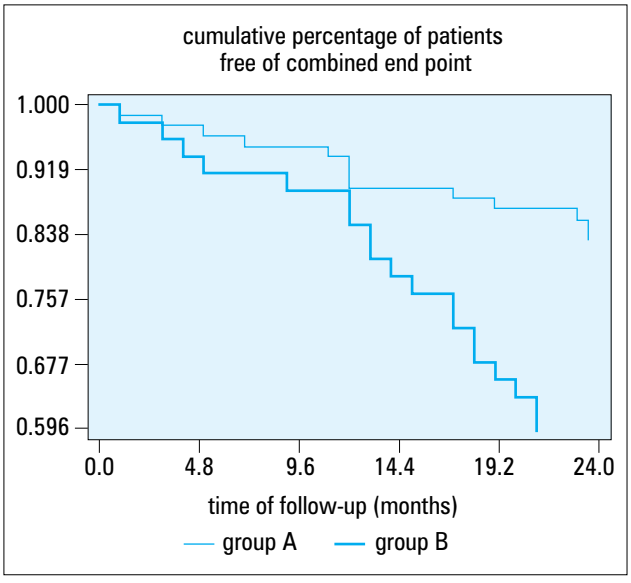

Fig. 2. Kaplan-Meier curves showing subjects free of combined end point $P_{log\ rank}$ = 0.003.

side-effects. In patients with normal plasma bilirubin the MCS was proved to be an independent risk factor of the composite end-point. Our results show that the improvement in the quality of life of the CHF patients achieved by psychotherapy and pharmacological treatment may influence prognosis particularly in patients with increased plasma bilirubin.

The age of the CHF patients with elevated plasma bilirubin was also shown to be the MACE risk factor. Our findings are in accordance with other studies showing the worse CHF prognosis in elderly patients [18-20].

We also proved in both study groups that the increased plasma NT-proBNP was associated with the increased risk of MACE, which had already been reported [2,3,10].

In our study hyponatremia as a result of fluid overload was found more severe in patients with elevated plasma bilirubin. Plasma natrium levels reflect the activation of renin-angiotensin-aldosteron system and are inversely related to plasma renin activity [21].

In the patients with increased plasma bilirubin reduced cholesterol levels were noted compared to the patients with normal plasma bilirubin. However, both groups of patients were treated with statins. Despite the fact that statin doses and the number of patients treated with statins did not differ significantly between both groups, this finding should be treated cautiously due to the different baseline cholesterol levels and response to treatment with statins.

The prolongation of prothrombin time in patients with abnormal plasma bilirubin was explained not by liver dysfunction but the common warfarin intake.

We consider a low number of subjects just in the NYHA class II and III being diagnosed and treated in one centre as the study limitation. However, our patient population was homogenous in regard to hypertensive etiology of the CHF.

The elevated plasma concentration of the NT-proBNP, the reduced PCS result and the presence of depression assessed by Beck's test affect the long-term prognosis in patients with increased plasma bilirubin and chronic heart failure due to hypertension. In patients with normal bilirubin plasma concentration, death and cardiac adverse events are associated with the increased NT-proBNP level and the decreased PCS result. The elevated plasma concentration of total bilirubin is associated with increased occurrence of death and cardiac adverse events and may serve as a prognostic factor in this group of patients.

REFERENCES

1. Cohn JN, Johnson GR, Shabetai R, et al. For the V-HeFT VA Cooperative Studies Group. Ejection fraction, peak oxygen consumption, cardiothoracic ratio, ventricular arrythmias, and plasma norepinephrine as determinants of prognosis in heart failure. Circulation. 1993; 87 (Suppl VI): 5-16.
2. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). Eur Heart J. 2005, 26: 1115-1140.
3. Masson S, Latini R, Anand IS, et al. The prognostic value of big endothelin-1 in more than 2,300 patiens wih heart failure enrolled in the Valsartan Heart Failure Trial (Val-HeFT). J Cardiac Fail. 2006; 5: 375-380.
4. McKie PM, Rodeheffer RJ, Cataliotti A, et al. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide: biomarkers for mortality in a large community-based cohort free of heart failure. Hypertension. 2006; 47: 874-880.
5. Keogh AM, Baron DW, Hickie JB. Prognostic guides in patients with idiopathic or ischaemic dilated cardiomyopathy assessed for cardiac transplantation. Am J Cardiol. 1990; 65: 903-908.
6. Kubo SH, Walter BA, John DHA et al. Liver function abnormalities in chronic heart failure. Arch Intern Med. 1987; 147: 1227-1230.
7. Sherlock S. The liver in heart failure: relation of anatomical, functional and circulatory changes. Br Heart J. 1951; 13: 273-293.
8. Felder L, Mund A, Parker JG. Liver function tests in chronic congestive heart failure. Circulation. 1950; 2: 286-297.
9. Schalm L, Hoogenboom WAH. Blood bilirubin in congestive heart failure. Am Heart J. 1952; 44: 571-580.
10. Ware A. The liver when the heart fails. Gastroenterology. 1978; 74: 627-628.
11. Giallourakis CC, Rosenberg PM, Friedman LS. The liver in heart failure. Clin Liver Dis. 2002; 6: 947-967.
12. Roik M, Starczewska MH, Stawicki S, et al. Wpływ optymalnego hamowania neurohormonalnego na rokowanie odległe u pacjentów z przewlekłą niewydolnością serca. Pol Arch Med. Wewn. 2006, 115: 321-328.
13. Pickering TG et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Circulation. 2005, 111: 697-716.
14. Ware JE. Hypertension – when is the clinical problem solved. When quality of life is secured. Cardiology. 1994; 85 (Suppl 1): 65-70.
15. Beck AT, Stear RA, Garben MG. Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. The Beck Depression Inventory. Boston, Hougton Mifflin, 1985.
16. Batin P, Wickens M, McEntegart D, et al. The importance of abnormalities of liver function tests in predicting mortality in chronic heart failure. Eur Heart J. 1995; 16: 1613-1618.
17. Lau GT, Tan HC, Kritharides L. Type o f liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. Am J Cardiol. 2002; 15: 1405-1409.
18. Kistorp C, Raymond I, Pedersen F, et al. N-terminal pro-brain natriuretic peptide, c-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. JAMA. 2005; 293: 1609-1616.
19. Likoff MJ, Chandler SL, Kay HR. Clinical determinants of mortality in chronic congestive heart failure secondary to idiopatic dilated or ischemic cardiomyopathy. Am J Cardiol. 1987; 59: 634-638.
20. Huges CV, Wong M, Johnson G, et al. Influence of age on mechanisms and prognosis of heart failure. Circulation. 1993; 87 (Suppl VI): 111-117.
21. Lee WH, Packer M. Prognostic importance of serum sodium concentration and it's modification by angiotensin converting-enzyme inhibition in patients with severe chronic heart failure. Circulation. 1986; 73: 257-267.