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Plasma Hemoxygenase-1 and Cardiac Enlargement in Chronic Heart Failure Patients

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Abstract

Introduction: Heme oxygenase-1 (HO-1) is a stress protein that is involved in protection of cardiac diaseases from diffrent noxious stimuli.

Objective: We investigated whether plasma HO-1 is changed in cronic heart failure (CHF) patients and whether plasma HO-1measurements provide a peripheral biomarker of the disease.

Methods: Plasma HO-1, were measured in 24 normal controls (NEC) and in 53 consecitive patients with CHF admitted to the Clinic of Cardiology over the period May 2010 - January, 2011. Systolic dysfunction was defined at left ventricle ejection fraction (LVEF) < 40%. Standardised protocol was used for colecting information on the investigated variables of interest. Plasma HO-1 and Brain natriuretic peptide (BNP) were measured with immunoassays. Depending on the distribution variables are reported with mean and median. Associations of the variables with HO-1 were investigated with linear regression analyses.

Results: Plasma HO-1 concentrations (ng/ml) were significantly lower in CHF patients (median 2.58, range 0.5-7.3) compared with NEC (median 5.2 range 1.2-12.2) ($p < 0.01$). Circulating BNP levels were not significantly correlated with plasma HO-1 levels. There was a significant negative correlation between HO1 and serum total bilirubin ($p<0.05$). A negative weak correlations were also observed with functional class ($p<0.05$) and atrial fibrillation ($p<0.05$). Plasma levels of HO-1 showed a significant considerable positive correlation with left ventricle (LV) dimensions values. Independent predictive effects on HO-1 levels in multiple regression analysis ($F=8.2$, $p<0.01$) were explored for the values of the LV end-diastolic volume and artrial fibrillation.

Conclusion: Plasma HO-1 are decreased in patients with CHF. Levels of HO-1 are independently correlated to the degree of cardiac enlargement. Further studies are needed on the concrete mechanisms of the deranged HO-1 regulation in CHF patients.

Keywords: Chronic heart failure; Heme oxygenase – 1; Brain natriuretic peptide subheading: Relationship between plasma hemoxygenase-1

Introduction

Chronic heart failure (CHF) may be considered as the fatal finishing line of all cardiovascular disease (CVD). Despite advances in the understanding and treatment, it still has a poor prognosis. The antioxidant enzyme Heme oxygenase-1 (HO-1) is also a stress protein (Hsp32) that catalyzes the degradation of heme to iron, carbon monoxide and biliverdin and is involved in protection of cardiac muscle from diffrent harmful stimuli [1]. It is known that the protective HO-1 role is provided by the antioxidant activity of bilirubin [2], antifibrinolytic, and vasodilative effect of CO [3-5]. The positive biological effects exerted by this enzyme have gained attention, as anti-inflammatory, antiapoptotic, angiogenic, and cytoprotective functions are also attributable to its producs mentioned above. The physiological induction of HO-1 may be an adaptive and beneficial response to a variety of factors, including heme itself, suggesting a potentially autoprotective and autodefensive role in several pathophysiological states such as acute coronary syndromes and stroke [6-8]. The characteristic of the physiologic induction of HO-1 in CHF as a common final pathway of all CVD have not been investigated and known till now. There is extensive experimental evidence from *in vitro* and animal experiments, that CHF could be considered as a state of oxidative stress. Moreover, in animal models, the development of CHF is accompanied by changes in the antioxidant defense mechanisms of the myocardium as well as evidence of oxidative myocardial injury. No information is, however available on the peripheral levels of the accepted as an antioxidant enzyme HO-1 and, whether raised or lowered levels are present in patients with chronically impaired cardiac function, a condition with a frequently discussed oxidative pathogenetic mechanism.

It is also unknown, if plasma HO-1 levels correlate with other components of the HO- 1 – carbon monoxide system and how it interrelate to the the neurohormonal response to heart damage and its strongest plasma biomarker for CHF, such as brain natriuretic peptide (BNP) for instance [9-11]. The growing interest in HO-1 is also related to the suggestions that the induction of the HO-1 gene may be a new opportunity to target the pathophysiology of CVD, with therapeutic implications for management [12].

We aimed to investigate whether plasma HO-1 are changed in CHF patients and whether plasma HO-1 measurements provide a peripheral biomarker of the disease.

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Methods

Patient population and study protocol

Plasma HO-1, was measured in 24 normal middle aged to elderly controls (NEC) and in 53 consecutive patients with CHF, between 48 and 81 years, (mean age 69.3±7.9 years), admitted to the Clinic of Cardiology, Department of Internal Medicine, University Hospital Alexandrovska, Medical University of Sofia over the period May 2010 - January, 2011. Cases were eligible for inclusion in the study if they were older than 18 years and have CHF of NYHA functional class II-IV. A diagnosis of CHF was given in cases where typical signs and symptoms (at least one of the following: raised jugular venous pressure, peripheral edema, third heart sound, pulmonary congestion at clinical examination), pulmonalry congestion at X-ray, and considerable clinical response to the conducted therapy were found. Systolic dysfunction was defined as left ventricular ejection fraction (LVEF) ≤ 40%. Additional exclusion criteria for inclusion in the study included patients with primary pulmonary hypertension, congenital cardiac malformations, patients awaiting cardiac transplantation, having suffered stroke within three months, with any disease of less than a one-year time period of expected survival, known history of alcohol or drug abuse or severe disability due to any cause.

Ischaemic etiology is defined in the case of angiographic confirmation (37.1%) and/or history of the coronary event and angina pectoris with the corresponding electrocardiographic (ECG) and clinical pattern.

All patients underwent a detailed clinical examination and interview according to the standard protocol, to collect information on biologic and demographic data including age, gender, cardiovascular risk factors and blood pressure. All information on medical history and medication was documented. Most part of the interview consisted of questions on clinical characteristics and included queries on the etiology of CHF, comorbidity, NYHA functional class, heart rate and rhythm, and clinical signs of CHF.

The study was approved by the local Ethical Committee at the Medical University of Sofia. Informed consent was obtained from the subjects before they were recruited into the study.

Instrumental assessment

Instrumental assessment was conducted at admission for the cases and included:

- Standard ECG obtained from 12 leads;

- Radiographic examination assessed for the signs of left chamber enlargement, pleural effusion, pulmonary vascular congestion and cardiothoracic ratio (<0.6 / ≥0.6).

Transthoracic echocardiography was undertaken with the patient in the left lateral decubitus position using a 3.5 MHz transducer and Phillips HD 11XE equipment. Standard M-mode was applied for obtaining left ventricle end-diastolic (LVEDD) and end-systolic diameters (LVESD). Standard two-dimentional images were examined off-line. Left ventricular end-systolic volumes (LVESV) and end-diastolic volumes (LVEDV) as well as the LVEF (%) were quantified using manual planimetry of conventional two- and four-chamber views and Simpson's technique [13].

Control group: The control group consisted of healthy subjects. Mean age of control subjects was 68.7±7.9 years, 16 were female (all p>0.01, compared to patients). All the subjects were questioned and carefully examined to exclude concomitant pathologic conditions. Only those subjects who were free from any history of the disease and medication were eligible. The total number of controls for analyses and comparisons with the cases under study was 24.

Biochemical tests: Blood samples were taken at admission from both patients and controls, for biochemical analyses. Blood investigations included information on blood count, serum electrolytes (sodium and potassium), creatinine, enzymes, lipid status total serum bilirubin (TBR), serum ferritin and iron. Plasma HO-1 and brain natriuretic peptide (BNP) were measured with immunoassays. Blood samples for BNP and HO-1 were taken at discharge. Plasma BNP was analyzed in the laboratory of Medicobiologic Investigations, Institute of Molecular Biology, Bulgarian Academy of Sciences, through the enzyme related immunosorbent method (ELISA), using the commercially available kit (BNP-32, IBL Hamburg). Blood samples were collected with Vacutainer (Beckton Dickinson, NJ, USA) in EDTA containing tubes. Samples were centrifuged up to 1 hour after sampling, and plasma and serum were stored at -20° until assayed. The analyses were done on the ELISA reader of Biolab. The sensitivity of the assay has been determined to be 4 pg/ml. Intraassay coefficient of variation was assessed as 5%, whereas the interaassay variation was <14%. The concentrations of plasma HO-1 protein were investigated by Enzyme Immunoessay (EIA- ELISA assay) of Stressgen's StressXpressTM on the ELISA reader Trinitron in the Institute of Biology and Immunology of Reproduction at the Bulgarian Academy of Sciences, Sofia, Bulgaria. The sensitivity of the assay Human HO-1 ELISA has been determined to be 0.78 ng/ml.The Intra-Assay Coefficient of variation of the Stressgen HO-1 ELISA test has been determined to be <10%. The Inter-Assay Coefficient of variation of the Stressgen HO-1 ELISA has been determined to be <10%.

All other serum and plasma parameters were measured as part of routine clinical testing in the central laboratory of the Alexandrov's University Hospital.

Statistical analysis: The data were tabulated in terms of frequencies and percentages for categorical variables, and by mean and standard deviations (SD) for continuous variables. Normally distributed variables were reported with mean and skewed variables with median and range of values. Group comparisons were made with the independent t-test, Mann-Whitney U-test and $\chi 2$-test, where appropriate. Univariate associations of the variables with HO-1 were investigated with linear regression analyses. Natural logarithmic transformation was used for skewed variables, including HO-1 and BNP. Multiple linear regression was used to investigate the independent relations to HO-1. Multivariate linear regression models were conducted, including variables with a univariate level of significance of p<0.010.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), endsystolic volume (ESV), end-diastolic volume (EDV), end-systolic diameter (ESD), and end-diastolic diameter (EDD) values were entered as continuous independent variables in the linear regression analyses. The independent laboratory variables including parameters of the blood count, liver indices, creatinine, electrolytes and BNP were also measured on a continuous measurement scale. Independent categorical variables include: age, gender, history of diabetes mellitus and arterial hypertension, etiology of CHF, atrial fibrillation (AF), pulmonary congestion and therapy. Reference categories for the set of the independent categorical variables were defined as age ≤ 65 years, male gender, non-diabetics, normotensives, non-ischemic etiology, sinus rhythm, negative data for pulmonary congestion, LVEF ≤ 40%, and no treatment with ACE/ARB blockers and β-blockers.

Statistical analyses were done on the SPSS version 13.0 (SPSS Inc, Chicago, IL).

Results

Comparison between the groups

The detailed characteristics of the CHF patients are listed in Table 1. Biochemical parameters and comparisons between cases and controls are shown in Table 2.

The patients and control group differed significantly in the values of hemoglobin, total serum cholesterol (TSCH), blood glucose, creatinine and serum sodium levels. Statistically significant differences between groups were also observed for the measured levels of BNP and HO-1.

Plasma HO-1 concentrations were significantly lower in CHF patients (median 2.58, range 0.5-7.3), compared with controls (median 5.2 range 1.2-12.2) ($p < 0.01$) ($p=0.006$).

The associations between HO-1 and demografic variables as well as the comorbidity, etiology and clinical signs were statistically not significant (Table 3).

Relationship between HO-1, functional class, instrumental parameters and BNP

The results did not show a significant relationship between HO-1 and the degree of LV dysfunction. All measures of the LV size, including LV diameters and volumes were significantly and positively correlated to the plasma HO-1 (Table 4). Patients of the third and forth NYHA functional class were with lower HO-1 levels as compared to the patients of NYHA class II and controls ($p=0.007$) (Figure 1).

Variable	No. (%) / Mean (SD)/ Median (range)
Age≥ 65 years	36 (67.9)
Women	23 (43.4)
Comorbidity and risk factors	
Arterial hypertension	44 (83.0)
Diabetes mellitus	11 (20.8)
History of peripheral vessel diseases	5 (9.4)
COPD	9 (17.0)
Ischaemic etiology	24 (45.3)
Myocardial infarction	21 (39.6)
Clinical signs	
Chronic AF	26 (49.1)
SBP (mmHg)	130 (110-180)
DBP (mmHg)	80 (50-100)
Pulmonary congestion	34 (64.2)
Peripheral edema	28 (52.8)
NYHA Functional class	
II	18 (34.0)
III/IV	20 (37.7)/15 (28.3)
Instrumental data	
Radiographic data for pulmonary congestion	30 (56.6)
Echocardiography	
LVEDV (ml)	137 (58-456)
LVESV (ml)	88 (36-311)
LVEF <40%	24 (45.3)
PPmax (mmHg)	49 (30-90)
Therapy at admission	
ACE/ARB	29 (54.7)
β-blockers	37 (69.8)
Acetysal	14 (26.4)
Statins	15 (28.3)

*Inhibitors of angiotensin converting enzyme/angiotensin receptor blockers; maximal pressure in a. pulmonalis

Table 1: Characteristics of chronic heart failure patients.

Variables	Patients *n*=53	Controls *n*=24	*P*
BNP (pg/ml)	650 (401-5974)	57 (35-118)	<0.05
HO-1(ng/ml)	2.58 (0.52-13.3)	5.1 (1.2-12.2)	<0.01
TSCH (mmol/l)	4.6 (0.7)	5.3 (0.6)	<0.05
Fasting blood glucose (mmol/l)	6.4 (2.3)	5.4 (0.8)	<0.05
Hemoglobin (g/l)	126.5 (19.7)	144 (19.4)	<0.05
Serum iron (μmol/l)	17.1 (8.8)	20.2 (8.1)	NS
Serum ferritin (μmol/l)	74.8 (67.8)	80.9 (42.8)	NS
TBR *(μmol/l)*	17.2 (13.5)	16.2 (9.0)	NS
Creatinine *(μmol/l)*	126.5 (45.7)	97.7 (35.4)	<0.05
Sodium (mmol/l)	140 (3.7)	144 (3)	<0.05

Notes: The values are presented as mean with SD, median with range, depending on the type of data; Mann-Whitney U-test

Table 2: Comparison of biochemical test in chronic heart failure patients and healthy subjects.

Variable	**R^2**	**F**	**B**	**P**
Age >65 years	0.002	0.12	-0.08	NS
Women	0.03	1.19	0.23	NS
Comorbidity				
Diabetes mellitus	0.01	0.353	0.15	NS
Arterial hypertension	0.01	0.046	-0.08	NS
Ethiology of HF				
Ishaemic	0.00	0.00	-0.001	NS
Clinical signs				
AF (chronic)	0.067	3.38	-0.379	0.072
SBP (mmHg)/	0.057	2.84	0.35	NS
DBP (mmHg)	0.002	0.10	0.08	NS

Table 3: Univariate linear-regression analysis for the investigated demographic and clinical variables.

Variable	**R^2**	**F**	**B**	**P**
Instrumental data				
Radiologic data for pulmonary congestion	0.012	0.56	-0.172	NS
Echocardiography				
LVEDV (ml) /				
LVESV (ml)	0.22	4.74	0.76	**0.044**
LVESD (mm)/	0.22	4.87	0.77	**0.041**
LVEDD (mm)	0.12	4.70	0.53	**0.037**
LVEF (%)	0.12	4.52	0.52	**0.041**
Ppmax	0.01	0.57	-0.16	NS
	0.00	0.01	0.14	NS
Therapy				
ACE/ARB	0.005	0.225	0.105	NS
B-blocker	0.004	0.167	0.096	NS

Table 4: Univariate linear-regression analysis for the investigated instrumental variables and therapy.

There was observed a weak non significant negative relationship between HO-1 and BNP (Table 5). Independent predictive effect on HO-1 levels in multiple regression analysis ($F=8.2$, $p<0.01$) were explored for the values of the LVEDV and AF (Table 6).

Relationship between HO-1 and the products of HO-1 carbonmonoxide system

We obtained a significant negative correlation between the dependent variable HO-1 and TBR ($p<0.05$). The investigated relationships with the serum feritin and iron failed to reach statistical significance (Table 5).

Discussion

The pattern of pathophysiologic induction of HO-1 in CHF as a final common pathway of all CVD has not been currently investigated and known. The results from our study show lower levels in patients

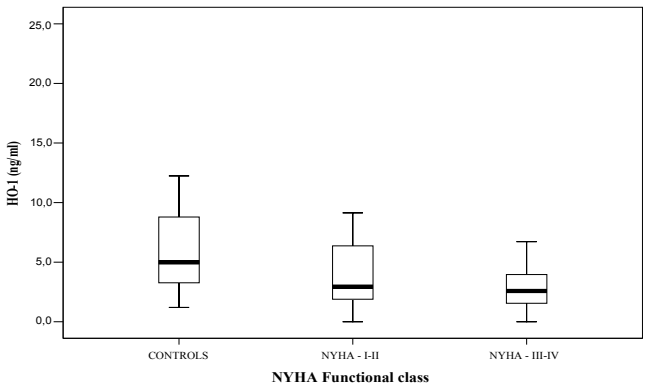

Figure 1: Plasma HO-1 by functional class and in comparison with controls.

Variable	R^2	F	B	P
Blood count				
Hemoglobin (g/l)	0.008	0.38	-0.003	NS
Hematocrit	0.009	0.37	-1.25	NS
Serum iron (μmol/l)	0.001	0.33	0.003	NS
Serum feritin (μmol/l)	0.011	0.34	-0.001	NS
Liver indices				
ASAT (U/l)	0.001	0.56	0.001	NS
ALAT (U/l)	0.002	0.08	0.002	NS
TBR *(μmol/l)*	0.137	4.28	-0.023	0.048
Creatinin (μmol/l)	0.006	0.25	-0.001	NS
Sodium (mmol/l)	0.009	0.41	0.018	NS
Potasium (mmol/l)	0.008	0.38	-0.149	NS
BNP (ng/ml)	0.005	0.25	-0.049	NS

Table 5: Univariate linear regression models for laboratory variables.

Variable	R^2	F	B	p
Atrial fibrillation (chronic)			-1.985	0.04
Functional class	0.916	8.179	1.38	NS
Total serum BR			0.046	NS
LVEDV (ml)			0.006	0.04

Table 6: Multivariate linear regression model.

with CHF as compared to healthy controls. This finding is in support to the protective role of HO-1 previously proved by the experimental animal and human genetic studies. The inclusion of HO-1 in cardiac pathology in CHF seems to be more complex, supported by the observed in our study significant negative correlation between HO-1 and TBR but not with serum ferritin and iron. It is accepted that the potential benefit of TBR is beyond the unfavourable effects of the iron and that consideration is in close relation to our understanding for the role of HO-1 in the CHF. It should, here, also be noticed the lack of significant relationship between the plasma HO-1 and the values of the maximal pulmonary pressure, a target point for the effect of CO, the other also important product of HO-1.

According to our results the investigated demographic factors including age, gender and co-morbidity as well as the investigated clinical characteristics do not contribute to the pattern of plasma profile of HO-1 in CHF patients. The most important finding from our study is the observed strong relationship between the LV dimensions and HO-1. This novel finding together with the observed negative correlation between HO-1 and TBR, suggest participation of HO-1 antioxidant potential in the LV remodeling in CHF. The latter raise the interesting hypothesis that the oxidative pathway of HO-1 may be modulated through selective pharmacologic targets, and that the complex signaling pathways of cardiac dilatation may mutually regulate in HF.

Left ventricular remodeling is a critical pathophysiologic process in the development and progression of systolic HF. Experimental and clinical studies have demonstrated that neurohormonal derangements mediate maladaptive LV remodeling and correspond to the subsequent increase in the neurohormonal activation manifested by the increase also in BNP, the strongest diagnostic and prognostic biomarker of HF. The latter determines the importance of the investigation of the relationship between HO-1 and BNP in our study. The observed weak negative relationship between the BNP and HO-1 corresponds with our assumption for the utilisation of HO-1 in the intensive pathologic processess in CHF as lower HO-1 levels mean higher neurohormonal activation and more advanced HF, and vice versa. Although the precise reasons for the lack of statistical significance of that result are unknown, differences in the responsible mechanisms for changes in HO-1 and BNP, important characteristic in patient population and background, and conducted over hospitalisation pharmacotherapies may account for this result. We also only indirectly measured only the HO-1 abundance rather than its enzymatic activity and that could also affect the received result.

Previous studies of patients with CVD have reported increase in gene expression of HO-1. In confirmation Li et al found statistically significant diffrences in the HO-1 expression in mono- and lymphocytes from patients with myocardial infarction, unstable and stable angina. The highest expression was reported in the group of patients who have experienced myocardial infarction, followed by the group with unstable angina and patients with stable angina. In patients with angiographically proven coronary artery disease the highest gene expression was observed in the group of patients with the most significant coronary lesions.

Morsi et al. gave more promising data, investigating endothelial cells from patients with advanced or initial coronary lesions as well as from free of lesions vessels [14]. The expression of HO-1 and its biological activity expressed as an amount of BR per mg protein were established only in the cells from advanced atherosclerotic lesions. The decreased expression of HO-1 gene promoter in this study was an independent prognostic marker for stenosis after the percuteaneous coronary intervention and stent implantation [15].

The received in our study results together with the results from the reported studies raise two possible considerations on the involvement of HO-1 in the pathophisiology of CHF and corresponding to it plasma HO-1 profile. Firstly, patients with CHF could have higher compensatory HO-1 expression, consistent with the cell biology and results from the studies described above. Low plasma levels found in cases result from utilisation in the intensive pathologic processes in CHF, supported by the observed the strong relationship between HO-1 and LV dimensions, and symptoms.

The second option for the observed in our study plasma profile of HO-1 concerns the expression of a deficient type of HO-1 gene expression CHF patients, which is, however, less likely possible as it would correspond with low HO-1 and TBR levels in contrast to the explored in our study negative correlation between HO-1 and TBR.

Heart failure is a syndrome, rather than a primary diagnosis, which results from cardiac disorders that impair the ability of the heart to support the circulation. Unfortunately, there is no single diagnostic test for CHF, and the accuracy of diagnosis and risk stratification depend on the availability of biomarkers of either risk or disease. There is an increasing interest in the development of new biomarkers, and a great number of laboratory tests have been recently proposed [16]. Actually

among the laboratory tests together with imaging and functional instrumental tests, however, only the BNP/ NT-proBNP assays are recommended by international guidelines for diagnostic evaluation and risk stratification of patients with CHF as a marker of the chronic imbalance in the neurohormonal control of circulation [17,18]. Despite the observed in our study significant positive relationship between the HO-1 and cardiac enlargement and a plausible biological link with CHF pathophisiology, associated with response to heart damage, further studies are needed, in selected, large populations, to test the efficacy of HO-1 as new, oxidative stress marker within a multi-marker strategy for patient management [19,20].

Limitations of the Study

The present study has several limitations. Our modest sample size may have afforded limited power to detect potentially weaker correlations that exist. Since this study was cross-sectional study, we cannot draw conclusions on a proposed cause and effect relation between HO-1 and the course of CHF. The generalizability of our findings needs also to be confirmed. We also do not have information on plasma HO-1 as a prognostic factor in CHF and this is would be addresed in future research . However our data support the biologically plausible role for HO-1, directed towards restriction of pathologic processes in CHF patients. Further, the gene expression has not been measured in paralell to plasma levels and the current study could not give the answer to the question about the pattern of induction of the enzyme in CHF but only describes the pattern of plasma profile in CHF patients. The study is also limitet to a single measurement of HO-1 whereas there is a necessity of serial measurements of HO-1 over the development of asymptomatic LV dysfunction and its progression towards the advanced systolic dysfunction and the relation of these measuremets to BNP as well.

Conclusions

Plasma HO-1 are decreased in subjects with CHF. Levels of HO-1 are independently correlated with the degree of cardiac enlargement, expressed by the observed effect of EDLV measures, and that relationship is independent also of the marker of neurohormonal activation BNP. Further studies are needed on the concrete mechanisms of the HO-1 regulation in CHF patients. Independently on the increasing data on the role of HO-1 the exact relationship between the enzyme and CVD remains still unclear.

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