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HYPERCAPNIC CHEMOSENSITIVITY IN PATIENTS WITH HEART FAILURE: RELATION TO SHIFTS IN TYPE-1 INSULIN-LIKE GROWTH FACTOR AND SEX HORMONE-BINDING GLOBULIN LEVELS

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In patients suffering from heart failure (HF), autonomic imbalance develops even at early stages along with derangements of cardiopulmonary reflex control and abnormalities in metabolism of several hormones. In 34 men with stable systolic HF, we investigated hypercapnic chemosensitivity (HCS, liter/min·mm Hg) measured using the rebreathing method and defined as the slope of the regression line relating minute ventilation (VE, liter/min) to end-tidal carbon dioxide concentration ($PETCO_2$, mm Hg). Serum levels of testosterone, dehydroepiandrosterone sulfate, type-1 insulin-like growth factor (IGF-1), sex hormone-binding globulin (SHBG), estradiol, and cortisol were measured using immunoassays. We found that there were no associations between HCS and clinical variables, applied therapy, and co-morbidities (all $P > 0.2$). Augmented HCS was accompanied by increased serum SHBG (when expressed in nM, $r = 0.43$, $P < 0.05$; when expressed as percentage of the age-matched reference values, $r = 0.62$, $P < 0.001$) and the reduced serum IGF-1 (when expressed in ng/ml and as percentage of the above-mentioned values, $r = –0.49$, $P < 0.05$, and $r = –0.47$, $P = 0.007$, respectively). The HCS was not related to serum levels of all the remaining analyzed hormones (all $P > 0.2$). Thus, it may be suggested that the hormone stimuli can noticeably modify the reflex mechanisms in cardiorespiratory control in the clinical setting of cardiovascular pathology.

Keywords: hypercapnic chemosensitivity, IGF-1, SHBG, heart failure.

INTRODUCTION

The complex pathophysiology of systolic heart failure (HF) involves, in addition to hemodynamic abnormalities, the dysfunction of most body organs, including the autonomic nervous and endocrine systems [1, 2]. Augmented hypercapnic chemosensitivity (HCS) reflects considerably deranged cardiopulmonary reflex control [3, 4] manifested, in particular, in patients with HF [2, 5, 6]. This phenomenon is linked to exercise intolerance and poor outcome and mostly occurs at early stages of HF [2, 5, 7].

Men with systolic HF are characterized by derangements within the functioning of several endocrine glands [8] and demonstrate deficiencies in, e.g., circulating testosterone, dehydroepiandrosterone sulfate (DHEAS), and insulin-like growth factor type 1 (IGF-1), which, independently of each other and of other clinical prognosticators, unfavorably affect the long-term prognosis [9]. A reduced level of serum testosterone is related to a diminished lean tissue mass [10], severe depressive symptoms [11], exercise intolerance [12, 13], and anemia [14]. Moreover, IGF-1 deficiency in this group of patients is associated with further reduction in both exercise capacity [12] and hemoglobin level [14], whereas DHEAS deficiency is linked with augmented depressive symptoms [15]. We have also demonstrated that both low and high circulating estradiol (E_2) levels are related to increased mortality in men with systolic HF, which may suggest that some optimum E_2 levels are advantageous for these patients [16].

The autonomic nervous and endocrine systems are tightly linked to each other due to the anatomical contiguity of the hypothalamic–hypophyseal–

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endocrine gland axis and CNS structures [17]. Sympathetic and parasympathetic neurons within both central and peripheral nervous systems are characterized by the presence of receptors specific for androgens, estrogens, mineralocorticoids, and glucocorticoids [17, 18]. On the other hand, both gonads and adrenal glands are innervated by autonomic nerve fibers [19].

Hence, taking into consideration these close interplays between the hormonal and autonomic nervous mechanisms [17, 20] and experimental evidence that, e.g., estrogens modulate the central autonomic balance [21], we hypothesized that there would be associations between the hormone status (assessed based on circulating levels of certain hormones) and central HCS (reflecting the efficiency of reflex control of respiration). This hypothesis was tested on the patients with systolic HF at the early stage of heart disease.

METHODS

Examined Group. The recruitment phase of the study was conducted in the Center for Heart Diseases, Military Hospital (Wroclaw, Poland) among patients with systolic HF attending the outpatient HF clinic.

The criteria for study inclusion were: (i) age between 18 and 75 years, (ii) male gender, (iii) a documented history of HF for more than 6 months preceding the study, (iv) HF symptoms corresponding to the functional class (New York Heart Association, NYHA) I-II, (v) clinical stability (i.e., unchanged severity of the signs and symptoms of HF along with unchanged medications) for minimum 3 months preceding the study, and (vi) left ventricular ejection fraction (LVEF) ≤45%.

The exclusion criteria were as follows: (i) acute coronary syndrome and/or coronary revascularization within 3 months preceding the study, (ii) unplanned hospitalization due to HF deterioration or any other cardiovascular reason within 3 months preceding the study, (iii) atrial fibrillation, a pacemaker rhythm, and/or frequent ectopics, and (iv) any hormonal dysfunction and/or hormonal therapy (either in the time of the study or in the past).

The study protocol was approved by the local Ethics Committees, and all subjects gave written informed consent. The study was conducted in accordance with the Helsinki Declaration.

Study Protocol. In all patients, venous blood samples were taken in the morning after a supine rest of at least 15 min. After centrifugation, the serum was collected and frozen at –70°C until further analyzed.

The serum levels of total testosterone (TT, ng/ml), DHEAS (ng/ml), E_2 (pg/ml), sex hormone-binding globulin (SHBG, nM), and cortisol (nM) were assessed using electrochemiluminescence techniques (Elecsys 2010, Roche Diagnostics, Germany). The serum IGF-1 level (ng/ml) was assessed using an immunochemiluminescence technique (Immulite 2000/2500, Diagnostic Products, USA).

The inter- and intraassay variability coefficients for TT, DHEAS, E_2, SHBG, cortisol, and IGF-1 were taken as 3 and 4%, 2 and 4%, 5 and 4%, 2 and 4%, 1 and 2%, and 3 and 6%, respectively.

The deficiencies of TT, DHEAS, and IGF-1 were defined prospectively as a serum hormone level less than or equal to the 10th percentile calculated for the equivalent age categories in the cohort of healthy men, as previously described [9]. Serum TT, DHEAS, and IGF-1 were referred to values assessed among the population of healthy men living in Wroclaw, Poland [9]. Medians of the analyzed serum hormone levels in the age groups 51 to 60, 61 to 70, and older than 71 years were as follows: TT, 4.20, 3.90, and 4.40 ng/ml, DHEAS, 1648, 989, and 936 ng/ml, and IGF-1, 290.1, 268.5, and 229.0 ng/ml [9].

According to DeGroot and Jameson [22], the E_2 excess in men with systolic HF was defined as serum $E_2 \geq 50$ pg/ml, and the E_2 deficiency as serum $E_2 \leq \leq 10$ pg/ml. The following cut-off values of serum SHBG and cortisol were considered as excess of these hormones: ≥50 and ≥700 nM, respectively [22].

The level of plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP, pg/ml) was measured using an electrochemiluminescence technique (Elecsys 1010/2010, Roche Diagnostics, Germany). The renal function was assessed based on the estimated glomerular filtration rate (GFR; ml/min×1.73 m^2) [22]. Serum high-sensitive C-reactive protein (hsCRP, mg/liter) was assessed using immunonephelometry (Dade Behring, Marburg, Germany) [22].

HCS Assessment. The HCS assessments (allowing us to estimate the peculiarities of respiration control) were carried out between 9 and 12 a.m. in an air-conditioned room. All subjects were asked to avoid strenuous physical activity for 24 h before each test and to avoid smoking, eating, or consuming caffeine for 3 h prior to the study. The tests were preceded by 30 min of resting in a quiet environment.

The HCS was assessed with a re-breathing method

[23, 24] using a 5-liter bag containing almost 100% oxygen initially and room air in the remaining volume. During the entire test, minute ventilation (VE; liter/min) and end-tidal carbon dioxide concentration ($PETCO_2$, mm Hg) were measured breath by breath using the gas exchange system (BREEZE EX, Cardiorespiratory Diagnostic Software 1991-1996, Medical Graphics, USA). Subjects were wearing a nose clip. The test was divided into three parts: (i) resting recording (3 min), (ii) re-breathing within a closed circuit (using a 5-liter bag), and (iii) recovery (3 min). During both resting and recovery stages, subjects were breathing with room air. At the beginning of the second stage, subjects were switched unnoticeably to breathing within a closed circuit. During the re-breathing stage, subjects were exhaling CO_2 to a 5-liter bag, which resulted in a steady increase in the CO_2 concentration within this bag, and, subsequently, in inhaling a gas mixture with a continuously increasing CO_2 concentration in peripheral blood. As a consequence, hypercapnia developed in the subjects, which in turn induced hyperventilation in a reflex manner. This stage was stopped when a subject became either breathless (and informed the staff by tagging at a table), or $PETCO_2$ exceeded 70 mm Hg. The HCS was defined as the slope of the regression graph relating VE to $PETCO_2$ concentration measured during the re-breathing stage of the test (expressed in liter/min·mm Hg) [23, 24].

Statistical Analyses. Normally distributed continuous variables were presented as means ± s.d. The intergroup differences were tested using the Student's *t*-test. Variables with a skewed distribution were expressed as medians with lower and upper quartiles and were log-transformed, which enabled normalization of these distributions. Categorical variables were expressed as numbers with percentages. Intergroup differences were tested using the χ^2 test. Relationships between continuous variables were calculated using the Pearson's correlation coefficient for variables with a normal distribution or the Spearman's rank correlation coefficient for variables with a skewed distribution.

In intergroup comparisons, values of $P < 0.05$ were considered significant.

RESULTS

Baseline clinical and laboratory parameters are shown in Table 1. Mean values of the serum levels of analyzed hormones along with the prevalence of hormonal abnormalities in men with mild systolic HF are shown in Table 2.

Table 1. Baseline Clinical and Laboratory Characteristics of Examined Patients with Mild Systolic Heart Failure (HF)

Т а б л и ц я 1. Вихідні клінічні та лабораторні характеристики досліджених пацієнтів з помірною систолічною серцевою недостатністю

Conditions for examination of patients with mild systolic HF	Variables
Inclusion criteria	
Age	61 ± 10 years
BMI	28.6 ± 4.0 kg/m^2
NYHA class I/II	21/79%
Etiology (CAD)	65%
Hypertension (yes)	62%
DM (yes)	24%
LVEF	31 ± 7%
LVEDD	66 ± 8 mm
Hemoglobin	14.4 ± 0.9 g/dl
hsCRP	1.23 (0.98 – 2.27) mg/liter
GFR	82.0 ± 13.6 ml/min·1.73 m^2
Na	141 ± 3 mEq/liter
NT-proBNP	655 (263 – 942) pg/ml
Treatment	
ACE inhibitor and/or ARB	89%
β-Blocker	100%
Aldosterone antagonist	12%
Loop diuretic	47%
Thiazide diuretic	35%
Digoxin	24%
Statin	88%
Acetylsalicylic acid	82%

Footnotes. Data are presented as means ± s.d., medians with lower and upper quartiles, or percentage where appropriate. BMI, body mass index; NYHA, New York Heart Association; CAD, coronary artery disease; DM, *diabetes mellitus*; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; hsCRP, high-sensitivity C-reactive protein; GFR, glomerular filtration rate; NT-proBNP, plasma N-terminal pro-B-type natriuretic peptide; ACE, angiotensin converting enzyme; and ARB, angiotensin receptor blocker.

The mean value of HCS in examined men with mild systolic HF was 0.68 (0.43-0.95) liter/min·mm Hg, and was higher than the reference values assessed in our laboratory ($P < 0.01$).

There were no associations between HCS and clinical variables (including the plasma NT-proBNP level), applied therapy, and co-morbidities (in all cases, $P > 0.2$).

The augmented HCS was accompanied by an increased serum SHBG level, when expressed both in nM ($r = 0.43$, $P < 0.05$, Fig. 2) and when normalized

Table 2. Serum Hormone Levels and Frequency of Cases of Hormone Deficiency or Excess in Examined Patients with Mild Systolic Heart Failure (HF)

Т а б л и ц я 2. Рівні гормонів у сироватці крові та частота випадків дефіциту або надлишку гормонів у досліджених пацієнтів з помірною систолічною серцевою недостатністю

Analyzed hormones	Patients with mild systolic HP (n = 34)		
	mean values of the serum hormone levels	hormone deficiency (%)	hormone excess (%)
TT	5.00 (4.30 – 5.80) ng/ml	9	–
DHEAS	558 (96 – 1214) pg/ml	47	–
IGF-1	114.5 (103.0 – 141.0) ng/ml	91	–
SHBG	46.3 (38.5 – 57.3) nM	–	38
E_2	29.4 (25.1 – 31.8) pg/ml	0	0
Cortisol	613 (517 – 718) nM	–	30

Footnotes. Data are presented as medians with lower and upper quartiles or percentages where appropriate. TT, total testosterone; DHEAS, dehydroepiandrosterone sulfate; IGF-1, type-1 insulin-like growth factor; SHBG, sex hormone binding globulin, and E_2, estradiol.

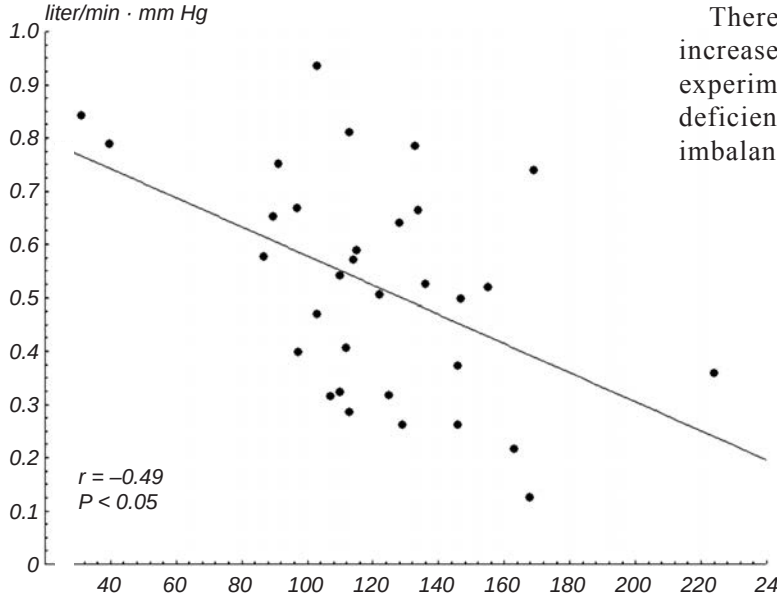
with respect to the age-matched reference values (r = 0.62, $P < 0.001$), and the reduced serum IGF-1 level, also when expressed in both ng/ml (r = –0.49, $P < 0.05$, Fig. 1) and as percentage of age-matched reference values (r = –0.47, $P = 0.007$).

The HCS was not related to serum levels of all the remaining analyzed hormones (in all cases, $P > 0.2$).

DISCUSSION

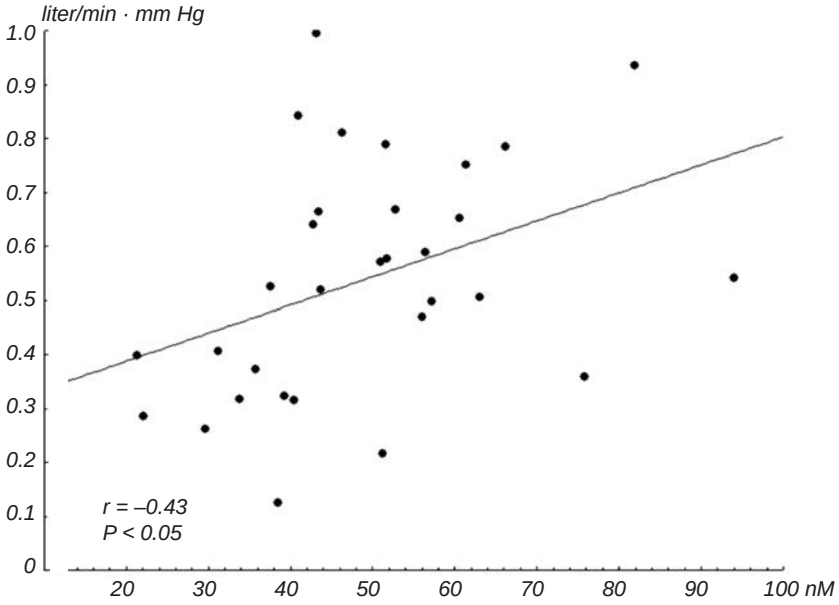
In our study, we have demonstrated that men with mild systolic HF treated according to current guidelines manifest noticeably augmented central hypercapnic chemoreceptor sensitivity. Our observation confirms that reflex mechanisms controlling the functioning of the cardiopulmonary system are deranged at early stages of the heart disease, and therapies counteracting the overactivated renin-angiotensin-aldosterone and adrenergic systems do not bring these mechanisms to normalization [2]. It should be emphasized that we have not found any associations of the chemosensitivity with any clinical and laboratory parameters, applied treatment, and co-morbidities in men with mild systolic HF. In particular, at the early stage of heart disease, augmented hypercapnic chemoreceptor sensitivity reflects neither the HF severity, the magnitude of inflammation (expressed using serum hsCRP), the neurohormonal activation (measured using plasma NT-proBNP), and the presence of major co-morbidities, such as anemia, renal dysfunction, and *diabetes mellitus*.

There is evidence that androgens are responsible for increased ventilatory force in men [25]. Also, in an experimental rodent model of cerebral ischemia, the E_2 deficiency was found to be linked with the autonomic imbalance, which can be at least partly restored



F i g. 1. Relationship between the serum level of insulin-like growth factor type 1 (abscissa, ng/ml) and hypercapnic chemosensitivity (ordinate, liter/min·mm Hg) in patients with mild systolic heart failure.

Р и с. 1. Взаємовідношення рівнів інсуліноподібного фактора росту типу 1 у сироватці крові (вісь абсцис, нг/мл) та хемочутливості до гіперкапнії (вісь ординат, л/хв·мм рт. ст.) у пацієнтів з помірною систолічною серцевою недостатністю.



F i g. 2. Relationship between the serum level of sex hormone-binding globulin (abscissa, nM) and hypercapnic chemoreceptor sensitivity (ordinate, liter/min·mm Hg) in patients with mild systolic heart failure.

Р и с. 2. Взаємовідношення рівнів глобуліну, що зв'язує статеві гормони (вісь абсцис, нМ), та хемочутливості до гіперкапнії (вісь ординат, л/хв·мм рт. ст.) у пацієнтів з помірною систолічною серцевою недостатністю.

during E_2 supplementation [21]. However, although anticipated [25], we did not find relations between hypercapnic chemoreceptor sensitivity and circulating levels of neither TT nor E_2. In this context, it is very intriguing that we have found the other relationships, i.e., between augmented HCS and low IGF-1 together with high SHBG levels in men with systolic HF. Although anticipated, we did not record any relations between the chemosensitivity and cortisol level in examined patients.

Although it is not commonly acknowledged, IGF-1 is an important modulator of the functions of the autonomic nervous system [26, 27]. Cachectic patients with HF, on the one hand, develop abnormal functioning of the growth hormone-IGF-1 axis [28], and, on the other hand, demonstrate a severe autonomic imbalance and overactivation of central chemoreceptors [28]. Moreover, we showed earlier that men with systolic HF along with IGF-1 deficiency develop exercise hyperpnea [12]. Therefore, the relationship between an overactivated chemoreflex and reduced circulating IGF-1 levels reported here might at least partly explain the previously observed phenomena.

It should be taken into account that SHBG not only is an agent responsible for the transport of steroid hormones in the circulation but also is considered a separate hormone that, through its interaction with specific receptors, can modify the metabolism of target cells, including the autonomic structures within the CNS [29]. Patients with HF demonstrate increased serum levels of SHBG accompanied by high plasma NT-proBNP, low LVEF, and low BMI levels [30]; this constitutes an independent factor for unfavorable prognosis [30]. In other clinical settings, SHBG has been linked with the nutrition status, metabolic syndrome, hyperinsulinemia, and insulin resistance [31-33]. Our observations are the first report relating the circulating SHBG level to the efficacy of reflex control of cardiorespiratory functioning in the clinical setting of a cardiovascular disease. This relationship may be expected because the autonomic nerve centers reveal a high affinity to SHBG, and SHBG has been shown to modify the functioning of these structures in experimental studies [29].

Our study has certain limitations. The first one is the relatively low number of examined subjects with systolic HF, which is mainly due to the very laborious and time-consuming character of physiological measurements (in particular, that of HCS). Second, we would like to point out that we have assessed in our study the functioning of endocrine glands (gonads, adrenals) using baseline circulating levels of produced and released hormones without the comprehensive and dynamic assessment of the entire hypothalamic-hypophyseal-gonadal and hypothalamic-hypophyseal-adrenal axes. We believe that the latter information is not obligatory for full interpretation of the results, as the hormone parameters analyzed in our study are considered standard hormone measures used in everyday clinical practice.

Finally, we need to acknowledge the observational character of our study, as we have not assessed the

precise mechanism responsible for the observed relationships. The above interesting and intriguing results need further experimental studies.

Thus, men with systolic HF at the early stage of heart disease demonstrate augmented HCS that is particularly increased in subjects with reduced serum IGF-1 and higher serum SHBG levels. Thus suggests that some hormones with the respective receptors in the autonomic centers may modify the reflex mechanisms of cardiorespiratory control in the clinical setting of cardiovascular pathology. Hence, modified levels of SHBG and IGF-1 may be a factor responsible for augmented ventilation and subjective feeling of dyspnea in patients with HF.

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ХЕМОЧУТЛИВІСТЬ ДО ГІПЕРКАПНІЇ У ПАЦІЄНТІВ ІЗ СЕРЦЕВОЮ НЕДОСТАТНІСТЮ: КОРЕЛЯЦІЯ ЗІ ЗМІЩЕННЯМИ РІВНІВ ІНСУЛІНПОДІБНОГО ФАКТОРА РОСТУ ТИПУ 1 ТА ГЛОБУЛІНУ, ЩО ЗВ'ЯЗУЄ СТАТЕВІ ГОРМОНИ

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Р е з ю м е

У пацієнтів із серцевою недостатністю (СН) навіть на ранніх стадіях захворювання розвивається автономний дисбаланс паралельно з розладами контролю серцево-судинної системи та відхиленнями метаболізму деяких гормонів від норми. Ми досліджували хемочутливість до гіперкапнії (*HCS*) у 34 чоловіків із СН, використовуючи метод зворотного дихання. Така чутливість визначалась як нахил лінії регресії при співставленні хвилинного об'єму вентиляції (л/хв) та кінцевої концентрації двооксиду вуглецю (мм рт. ст.). Рівні тестостерону, дигідроепіандростерону сульфату, інсулінподібного фактора росту типу 1 (*IGF-1*), глобуліну, що зв'язує статеві гормони (*SHBG*), естрадіолу та кортизолу визначали в сироватці крові, використовуючи імунологічні методики. Як виявилося, зв'язки між рівнем *HCS*, з одного боку, та клінічними показниками, застосованою терапією та супутніми захворюваннями – з другого, були відсутніми (в усіх випадках $P > 0.2$). Підвищена *HCS* супроводжувалася підвищеними рівнями *SHBG* (для концентрацій у наномолях на 1 л r = 0.43, $P < 0.05$, а для нормованих значень, наведених щодо певної вікової групи, r = 0.62, $P < 0.001$) та низькими рівнями *IGF-1* (для концентрацій у нанограмах на 1 мл та для наведених нормованих значень r = –0.49, $P < 0.05$ та r = –0.47, $P = 0.007$ відповідно). Значення *HCS* не виявляли будь-яких зв'язків з рівнями всіх досліджених гормонів у сироватці. Це дозволяє думати, що гормональні стимули можуть помітно модифікувати рефлекторні механізми контролю серцево-судинної системи у клінічних випадках її патологій.

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