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Alteration in diurnal and nocturnal melatonin serum level in patients with chronic heart failure

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Abstract

Introduction: Melatonin is best known for its influence on circardian physiology. The circulating levels of the hormone vary in a daily cycle, allowing the regulation of the circadian rhythms of several biological functions. Melatonin is now considered as a cardioprotective factor and its secretion might be influenced by the clinical course of CHF.

Objective: Assessment of the alteration in diurnal and nocturnal melatonin serum levels in patients with chronic heart failure.

Material and methods: The study group consisted of 32 patients diagnosed with CHF according to ESC criteria. The study group was divided into two subgroups: patients in NYHA class II (n=21, 8 women) and patients in NYHA class III (n=11, 6 women). In all patients, serum melatonin levels at 02:00 and at 07:00 were determined using competitive enzyme immunoassay technique. High-sensitive C-reactive protein (HsCRP) was determined with nephelometric method.

Results: Mean hsCRP level was 0.368 (0.195; 0.794) mg/l and 0.54 (0.128; 1.04) mg/l in the group NYHA II and NYHA III patients, respectively; the difference was not statistically significant. NTproBNP levels were higher in NYHA III group than in the group NYHA II [2300 (1509;6317) pg/ml vs 7157 (4155; 13339) pg/ml]; the difference was substantial and approached the level of statistical significance (p=0.057). In both subgroups, higher levels of melatonin at 02:00 than at 07:00 was noticed; however, the differences were not statistically significant (p>0.05). In NYHA III subgroup lower levels of melatonin were observed at both time points; the difference was not statistically significant.

Conclusion: The study results suggest that in patients with advanced heart failure (NYHA III but not NYHA II), nocturnal melatonin secretion is negatively correlated with NTproBNP.

Key words

melatonin, chronic heart failure, NYHA.

INTRODUCTION

Chronic heart failure (CHF) is reported to show an increasing prevalence in western countries posing a great health burden both in terms of healthcare costs and the mortality. In individuals aged 55, almost 1 in 3 will develop heart failure during their remaining lifespan [1]. With approximately 14 million people in the United States and 7 million in Europe suffering from CHF, this condition represents 1–2% of the entire health costs in western countries [1]. The contemporary working hypothesis is that heart failure is a progressive ventricular remodeling with impaired myocardial performance due to neurohormonal changes. The most important neurohormonal systems activated in course of heart failure are:

1) the natriuretic peptide system;
2) adrenergic nervous system;
3) vasopressin system;
4) renin-angiotensin-aldosterone (RAA) system;
5) endothelin system [2].

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Melatonin, N-acetyl-5-methoxytryptamine, is best known for its influence on circardian physiology. The circulating levels of the hormone vary in a daily cycle, allowing the regulation of the circadian rhythms of several biological functions. Due to this key biological property, melatonin is best known for its efficacy in combatting sleep disorders [3, 4]. It has also been attributed with beneficial effects on the immune system, the process of aging and in obesity [5]. The latest promising publications prompt the consideration of melatonin as a novel cardioprotective agent [6, 7, 8]. The protective action of melatonin on the heart occurs at two levels. The former involves classic melatonin membrane receptors (MT1 and MT2) present in the heart and throughout the vascular system [9, 10]. The latter refers to its function as a potent anti-oxidant and free radical scavenger, resulting in diminishing molecular damage resulting from elevated oxidative stress [11]. Additionally, melatonin has been shown to reduce catecholamine concentrations and relax smooth muscles in the blood vessels. Recent findings from research on melatonin and cardiac pathology has given rise to claims of melatonin's beneficial effects on attenuation of the arterial hypertension severity [12, 13], protective role on myocardial infarction, limitation of myocardial damage, prevention of oxidative injury to the ischemic/reperfused heart [14], heart protection from anthracyclines toxicity [15] and reduction of cardiac hypertrophy and remodeling [16].

It is assumed that changes in the adrenergic nervous system and the vasopressin system in the course of CHF may have great influence on the secretion of melatonin. This presumption is based on the fact that the main mechanism of melatonin synthesis is initiated by the binding of norepinephrine to the adrenergic b1 receptor that causes activation of adenylate cyclase (AC), with subsequent increase of cAMP level which in turn activates NAT [17].

To the author's knowledge, only one study concerning melatonin level variations in patients with CHF has been published to date. This fact prompted the presented study to investigate the possible association between melatonin and cardiovascular diseases. The above-mentioned single study suggests a low urinary 6-sulfatoxymelatonin levels in patients with severe congestive CHF [18], which gives a rise to the claim that the presented study is of prime importance in this area.

MATERIALS AND METHOD

Patients. The study group consisted of 32 patients diagnosed with CHF according to ESC criteria. The exclusion criteria were: myocardial infarction in last three months, unstable angina pectoris, infections, maligancies, neuropsychiatric disorders, usage of sleeping pills, antidepressants or neuroleptics. The study group consisted of two subgroups: patients with NYHA class II (n=21, 8 women) and patients with NYHA class III (n=11, 6 women).

Laboratory tests. In all patients, serum melatonin levels at 02:00 and at 07:00 were determined using competitive enzyme immunoassay technique (USCN Life Science Inc., Wuhan, China; Polish distributor – Immuniq). High-sensitive C-reactive protein was determined with the nephelometric method. Other tests were performed by routine methods in a hospital laboratory.

Statistical analysis. The results were expressed as mean and standard deviation if distribution was normal, or as median 25 and 27 quartile (median, 25Q; 75Q) in the cause of variable distribution differing from normal. To investigate whether variables have a normal distribution, Shapiro-Wilk's test was used. To determine the relationship between the study variables, Pearson's test or Spearman's rank correlation test were used, depending on the type of distribution. The statistical significance of differences between groups were tested by t-Student's or Wilcoxon's test. p-value <0.05 was considered statistically significant.

RESULTS

The mean age of patients was 70 ± 12 yr. The hsCRP concentration was 0.512 (0.166; 1.040) mg/l, [0.368 (0,195; 0,794) mg/l and 0.54 (0.128; 1.04) mg/l in the group NYHA II and NYHA III patients, respectively; the difference was not statistically significant]. NTproBNP level was higher in the group NYHA III than in the group NYHA II [2300 (1509; 6317) pg/ml vs 7157 (4155; 13339) pg/ml]; the difference was substantial, but yet not statistically significant (p=0.057). In both subgroups, higher melatonin concentrations were noticed at 02:00 than at 07:00; however, the observed difference was not significant (p>0.05). In the NYHA III subgroup, lower levels of melatonin were observed at both times points; the difference, however, was not statistically significant (Tab. 1).

Table 1. Basic characteristic of study group in total and according to NYHA functional class. Results presented as median (25 quartile; 75 quartile).

	Study group		
	Total (n=32)	**patients with NYHA II (n=21)**	**patients with NYHA III (n=11)**
Melatonin at 7 am (pg/ml)	379.8 (321.6; 475)	424.7 (345.6; 475.9)	368.8 (267.5; 472.2)
Melatonin at 2 am (pg/ml)	399.9 (263.2; 503.4)	422.1 (231.6;503.4)	372.142 (265.4; 470.3)
Δ Melatonin (pg/ml)	4.3 (-27.2; 39.2)	6.1 (-33.6;44.1)	4.2 (-9.4; 32.8)
NTproBNP (pg/ml)	4243 (1649; 7174)	2300 (1509;6317)	7157 (4155; 13339)
hsCRP (mg/l)	0.512 (0.166; 1.040)	0.368 (0,195; 0,794)	0.54 (0.128; 1.04)

Further analysis revealed that in the NYHA II class patients there was a strong negative correlation between plasma hsCRP and serum melatonin at 07:00 (r=-0.62; p=0.017). Similarly, the correlation between hsCRP levels and melatonin at 02:00 was observed, although in this case, the difference was not of statistical significant (p=0.067).

Very strong negative correlations between the NTproBNP level and serum melatonin concentrations at 02:00 (r=-0.83; r=0.005) and 07:00 (r=-0.72; p=0.03) were observed in the NYHA class III patients. There were no similar correlations for NYHA class II patients (Tab. 2, Tab. 3).

Table 2. Correlation between serum melatonin, NTproBNP and hsCRP in patients with NYHA II functional class.

	NTproBNP	**hsCRP**
Melatonin at 7am (pg/ml)	r=0.02, NS	r=-0.62; p=0.017
Melatonin at 2 am (pg/ml)	r=-0.14, NS	r=-0.5, NS (p=0.067)
Δ Melatonin (pg/ml)	r=0.14, NS	r=-0.18, NS

Table 3. Correlation between serum melatonin, NTproBNP and hsCRP in patients with NYHA III functional class.

	NTproBNP	**hsCRP**
Melatonin at 7am (pg/ml)	r=-0.72, p=0.03	r=-0.41; NS
Melatonin at 2 am (pg/ml)	r=-0.83, p=0.005	r=-0.35, NS
Δ Melatonin (pg/ml)	r=-0.12, NS	r=-0.11, NS

DISCUSSION

Melatonin concentrations are influenced by numerous factors and conditions; therefore, the presented study compares two chronic heart failure patient groups, according to NYHA functional class after careful clinical assesment with

respect to exclusion criteria, with well-established impact on melatonin secterion.

Patients with heart failure (HF) commonly complain about disrupted sleep, reduced sleep efficiency, and a feeling of fatigue; however, they do not demonstrate sleepiness when measured in the conventional manner [19]. This phenomenon is thought to be caused by HF-related elevations in sympathetic nervous system activity (SNA) that impair the sleep quality at night.

The presented study investigates night-time pineal melatonin production in patients with chronic heart failure. Very strong negative correlation between the NTproBNP level and the serum melatonin concentration at 07:00 (r=-0.72; p=0.03) and 02:00 (r=-0.83; r=0.005) were noted in the subgroup of NYHA class III patients, but not in NYHA II class.

BNP levels are highest in patients with decompensated heart failure, and lowest in those without heart failure or LV dysfunction. Intermediate levels were present in those patients with known LV dysfunction but no cardiac decompensation [20]. Among patients with chronic heart failure, higher levels of BNP correlate with increased mortality and this correlation were found to be independent of age, New York Heart Association (NYHA) class, prior myocardial infarction (MI), and left ventricule ejection fraction LVEF [21].

The mechanisms involved in the reduction of melatonin production in CHF patients remain to be defined. The hyperadrenergic activity seen in CHF could down-regulate pineal adrenergic receptors. In congestive heart failure, prolonged exposure to high plasma catecholamine concentrations may reduce the adrenergic system responsiveness to physiological stimuli by beta-adrenergic receptors down-regulation in the myocardium [22]. This down-regulation of beta-adrenergic receptors results in decreased affinity to noradrenaline and observed in the myocardium may also occur in the pineal gland. This hypothesis appears to be corroborated by the fact that noradrenergic neurons are activated in the brain in the course of congestive heart failure [23].

Girotti et al. assessed the urinary 6-sulfatoxymelatonin excretion in a group of CHF patients and compared it with the excretion observed in a group of healthy volunteers [19]. Melatonin, the principal product of the pineal gland, is metabolized in the liver mainly to 6-sulfatoxymelatonin. As this substance is mostly excreted by urine, urinary 6-sulfatoxymelatonin is considered to be an useful index of melatonin production. 6-Sulfatoxymelatonin levels were significantly lower in CHF patients than in controls. A significant decrease in 6-sulfatoxymelatonin excretion occurred with age. There were no significant differences in urinary 6-sulfatoxymelatonin levels between chronic and acute CHF patients.

In the final stages of CHF, an immune activation occurs and some circulating cytokines, notably interleukin 1 and 6 and TNFα, increase considerably and may lead to melatonin synthesis inhibition [24].

C-reactive protein (CRP) plasma concentrations are typically increased in patients with acute coronary syndrome (ACS). Elevated CRP plasma concentrations are now recognized as a prognostic factor, both in subjects with ST elevation ACS (STE-ACS) and with unstable angina (UA) – non-ST elevation ACS (NSTE-ACS) [25]. CRP levels are conditioned by seasonal or daily variability. Dominguez-Rodriguez et al. demonstrated that in patients with ST elevation myocardial infarction (STEMI), CRP plasma concentrations measured early in the morning were significantly higher than that in the dark phase of day [26].

Melatonin levels are related to CRP concentration in patients with STEMI. As suggested by recent reports, circadian changes of melatonin may be responsible, at least in part, for the light/dark variations of endogenous CRP production in patients with STEMI [27].

CONCLUSIONS

It should be noted that the presented study showed that in patients with advanced heart failure (NYHA III but not NYHA II), nocturnal melatonin secretion is negatively correlated with NTproBNP. It can be assumed that reduced melatonin concentrations may result from melatonin synthesis inhibition due to neurohormonal activation (especially adrenergic system overactivity). These preliminary results are promising and indicate clearly that further studies are required to determine the pathogenic as well as prognostic importance of melatonin synthesis and secretion disturbances in patients with chronic heart failure.

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