Cytokines and heart rate variability in patients with chronic heart failure

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Abstract

Introduction: Heart rate variability (HRV) analysis is a non-invasive method of assessment of the autonomic nervous system's effects on heart function. In chronic heart failure (CHF), decreased HRV correlates with the progression of the disease. It is also known that in CHF increased levels of proinflammatory cytokines are present. Because these molecules are believed to influence the nervous system at both the central and peripheral levels, their potential role in HRV reduction in the course of CHF has been proposed.

Aim: The study was designed to verify potential relations between cytokines and HRV parameters in CHF patients. The concept of the study was driven by the recognition of controversies in this field and the paucity of published reports.

Methods: Forty-four patients with CHF and stable NYHA class I-IV symptoms and 15 healthy controls were enrolled in the study. Time-domain HRV analysis was performed based on of 24-hour Holter ECG monitoring. Plasma concentrations of soluble TNFα receptors sTNF-RI and sTNF-RII and interleukin 6 (IL-6) were measured using commercially available ELISA kits (Quantikine, R&D Systems).

Results: In patients with CHF, HRV indices included in the analysis were significantly decreased, and the levels of cytokines increased in comparison with the control group. In the whole study population, both in the CHF patients and the control group, significant negative correlations were observed between sTNF-RI level and long-term HRV indices such as SDNN (r=-0.44; p=0.0006), SDANN (r=-0.44; p=0.0005) and short-time index SDNNI (r=-0.37; p=0.004). Similar negative correlations were found between sTNF-RII level and SDNN (r=-0.35; p=0.007), SDANN (r=-0.34; p=0.01), and SDNNI (r=-0.31; p=0.02), as well as between IL-6 level and SDNN (r=-0.41; p=0.001), SDANN (r=-0.44; p=0.0005) and SDNNI (r=-0.34; p=0.009).

Conclusions: Significant negative correlations between TNF-α soluble receptors sTNF-RI, sTNF-RII and IL-6 levels and time-domain HRV parameters were observed in the study. Because the results of investigations conducted so far do not elucidate the cause-effect relationship, further studies are needed to clarify the mechanisms of HRV depression in CHF and the role of cytokines in this severe clinical condition.

Key words: cytokines, heart failure, heart rate variability

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Introduction

Chronic heart failure (CHF) is a clinical syndrome with complex and not fully understood pathogenesis. The role of proinflammatory cytokines in the pathophysiology of CHF has been widely discussed in recent years. TNFα and IL-6 are two of the most important ones; elevated levels of them are observed in CHF patients. By various mechanisms, they can contribute to the progression of left ventricular (LV) dysfunction [1].

Abnormalities in autonomic control with sympathetic overactivity and parasympathetic withdrawal are also characteristic of CHF. A non-invasive, widely used method

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of autonomic function assessment is the analysis of heart rate variability (HRV) [2]. Depressed HRV is observed in CHF patients and it correlates with disease progression. Some of the HRV parameters can be used in prognosis prediction [3]. HRV depression might be related to the imbalance between the sympathetic and parasympathetic activation, modifications in β-adrenergic receptor numbers and function, inappropriate baroreceptor activity and disturbed central autonomic regulation [4-7]. Because cytokines are believed to influence the nervous system at both the central and peripheral levels, their potential role in HRV reduction in the course of CHF has been proposed [8, 9].

The concept of the study was driven by the recognition of controversies in this field and the paucity of published reports. The study was designed to verify potential relations between cytokines and HRV parameters in CHF patients.

Methods

Patients

Forty-four patients with CHF and stable symptoms were enrolled in the study. All of them were referred to our institution in order to evaluate their exercise capacity and, when necessary, to consider heart transplantation. The inclusion criterion was the presence of CHF with systolic dysfunction, documented by LV ejection fraction (LVEF) of less than 45% on echocardiography. Exclusion criteria included: severe renal dysfunction (serum creatinine concentration >250 µmol/l), significant pulmonary disease, the presence of acute infection symptoms, chronic infectious diseases or a malignant process.

Time-domain HRV analysis was performed based on recordings in patients with sinus rhythm. Recordings with atrial fibrillation, paced rhythms, and with >10% arrhythmias in 24-hour Holter monitoring were excluded. All patients were stable, and received optimal medical treatment for at least two weeks preceding the examinations; treatment included angiotensin-converting enzyme inhibitors – 41 (93%) patients; β-blockers – 33 (75%); digoxin – 21 (48%); amiodarone – 16 (36%); statins – 21 (48%); acetylsalicylic acid – 27 (61%); and spironolactone – 19 (43%). The patients were classified according to the New York Heart Association (NYHA) functional scale: 6 patients were in class I, 19 in class II, 16 in class III and the remaining 3 in class IV.

In all patients coronary angiography was performed. Ischaemic cardiomyopathy (ICM) was diagnosed in patients with significant stenotic lesions in the epicardial coronary arteries (>50% reduction of the diameter). In 21 (48%) patients ICM and in 23 (52%) patients dilated cardiomyopathy (DCM) were diagnosed.

Table I. CHF patients and healthy controls – clinical characteristics

	CHF patients (n=44)	Healthy controls (n=15)	p
Age [years]	51.7±9.3	49.9±11.3	ns
Gender (F/M) [%]	2/42 (0.05/99.5%)	2/13 (15/85%)	ns
LVEF [%]	26.3±7.3	67.6±2.8	0.0000
Creatinine [µmol/l]	86.9±17.8	76.9±8.2	0.03
ICM/DCM [%]	21/23 (48/52%)		
Diabetes	6 (10%)		
NYHA I/II/III/IV [%]	6/19/16/3 (14/43/36/7%)		
NYHA class [mean]	2.4±0.8		

CHF – chronic heart failure; LVEF – left ventricular ejection fraction; HR – heart rate; ICM – ischaemic cardiomyopathy; DCM – dilated cardiomyopathy

The control group consisted of 15 healthy subjects with similar age and gender distribution and no history of cardiac disease (patient history, physical examination, ECG, echocardiography). General characteristics of the study groups are shown in Table I.

Cytokine assays

Venous blood samples for cytokine measurements were drawn after the patient had remained in the supine position for at least 30 minutes, prior to any breakfast, during the morning. Blood was immediately centrifuged; plasma was frozen and stored at -70°C till the time of measurement. The plasma concentration of soluble TNFα receptors sTNF-RI and sTNF-RII and interleukin 6 (IL-6) were measured using commercially available ELISA kits (Quantikine, R&D Systems).

HRV analysis

Time-domain HRV analysis was performed according to the published guidelines [2, 4] using the Excel-2 system, model 7.5 Oxford based on 24-hour Holter recordings. The following time-domain variables, calculated based on the duration of normal RR intervals were included in the analysis: SDNN – standard deviation of all normal RR intervals; SDANN – standard deviation of all 5-min mean RR intervals; SDNNI – mean of the standard deviations of all RR intervals for all 5-min segments. The square root of mean squared differences of successive RR intervals (rMSSD) and percentage of RR intervals with >50-msec variation (pNN50) were assessed based on the variation between adjacent RR intervals.

The study protocol was approved by the Ethics Committee at the University of Medical Sciences in

Table II. Time-domain HRV indices in CHF patients and in healthy controls

	CHF patients	Healthy controls	p
HR average [1/min]	75.1±12	78.0±11	ns
HR min [1/min]	51.9±9.6	50.4±8	ns
SDNN	100.1±23.6	147.4±42.8	0.0001
SDANNI	88.6±23.3	137.1±40.7	0.00007
SDNNI	42.6±16.7	55.1±19.1	0.01
rMSSD	27.5±13.5	29.2±13.7	ns
pNN50	6.5±7.3	9.1±10.1	ns

Abbreviations as defined in the text

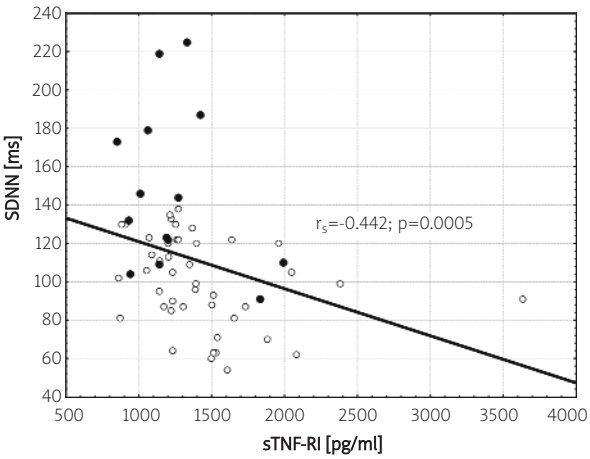

Figure 1. Relationship between SDNN and sTNF-RI level in CHF patients and healthy controls
white dots – CHF patients; black dots – healthy controls

Poznań (number 233/01) and written consent from all the patients was obtained.

Statistical analysis

Values of studied parameters are given as mean ± standard deviation and percentage. Chi-square test and Mann-Whitney test were used to compare the difference between the groups. Spearman's test was used to measure correlations between variables.

A p value <0.05 was considered significant.

Results

The following HRV parameters were significantly lower in the study group than in the controls: SDNN, SDANN, SDNNI (Table II). There were no significant differences in rMSSD and pNN50 values between the two groups. With respect to CHF aetiology, analysis of HRV parameters, as well as LVEF values, revealed no statistically significant differences between patients with ICDM and DCM (Table III). The mean plasma levels of sTNF-RII and IL-6 were significantly higher in CHF patients than in the controls (Table IV); sTNF-RI level was also higher but the difference was only of borderline significance.

Evaluation of HRV parameters with respect to cytokine concentration levels revealed a significant negative correlation between sTNF-RI level and SDNN, SDANN and SDNNI (r=-0.41; p=0.006; r=-0.40; p=0.007; r=-0.34; p=0.02, respectively), as well as a trend to a negative correlation between sTNF-RII level and SDNN (r=-0.26; p=0.09) and between IL-6 level and SDNN and SDANN (r=-0.25; p=0.09 and r=-0.28; p=0.07, respectively). Similarly to Malave et al. [8], these correlations were analysed in the whole study population, both in the patients and in the control group. Significant negative correlations were observed between sTNF-RI level and long-term HRV indices such as SDNN (r=-0.44; p=0.0006, Figure 1), SDANN (r=-0.44; p=0.0005, Figure 2) and short-time index SDNNI (r=-0.37; p=0.004) (Figure 3), as well as between the sTNF-RII level and SDNN (r=-0.35; p=0.007), SDANN (r=0.34; p=0.01) and SDNNI (r=-0.31; p=0.02) and between the IL-6 level and SDNN (r=-0.41; p=0.001, Figure 4), SDANN (r=-0.44; p=0.0005, Figure 5) and SDNNI (r=-0.34; p=0.009, Figure 6). No correlation was found between cytokine levels and indices of parasympathetic modulation (rMSSD, pNN50).

There was no correlation between calculated time-domain HRV indices and the age of patients or LVEF. A significant negative correlation was observed between NYHA class and long-term HRV index SDNNI (r=-0.26; p=0.048). No relationship between indices of parasympathetic modulation (rMSSD, pNN50) and NYHA class was observed.

Discussion

The influence of autonomic control on the cardiovascular system has been for many years the

Table III. Time-domain HRV indices and LVEF in ICM and DCM patients

	SDNN	SDANN	SDNNI	rMSSD	pNN50	LVEF [%]
ICM (n=21)	101±22.8	86.9±22.2	45.7±19.5	28.2±12.2	7.1±7.8	27.5±6.8
DCM (n=23)	99.2±24.7	90.2±24.7	39.8±13.4	26.8±14.8	6±6.9	25.3±7.7
p	ns	ns	ns	ns	ns	ns

subject of interest of many investigators. Despite the fact that HRV analysis does not reflect directly the activity of the sympathetic and parasympathetic nervous system, it shows the net effect of both these systems on the sinus node cells. Time-domain analysis provides information about HRV over long periods of time, and some of its parameters (rMSSD, pNN50) indirectly reflect the tone of the parasympathetic system [2]. SDANN corresponds to VLF (very-low-frequency spectral power), which reflects long-term variability, whereas rMSSD and pNN50 correspond with HF (high-frequency spectral power), reflecting short-term variability [3].

The prognostic value of HRV has been demonstrated in selected diseases, particularly in patients after acute myocardial infarction. In the last few years, the prognostic value of HRV in patients with CHF has been discussed [3, 10, 11]. Reduced HRV is observed in CHF, as confirmed also in our study. Markedly depressed HRV is observed in patients with more advanced stages of CHF [12, 13], which was also demonstrated in our study by the presence of a significant correlation between the HRV parameters and NYHA class. Whether depressed HRV in CHF is a marker of the severity of the disease, or whether it just reflects the sympathetic activation, as suggested by other authors, remains a matter of discussion [3].

Mechanisms responsible for depression of HRV in CHF are still not completely understood. In CHF patients, unlike in healthy individuals, a relationship between gender, age and HRV indices is not observed [14-16], which was also noted in our study. The activity of baroreceptors and respiratory disturbances seem to play an important role. Evaluation of the ventilatory response to exercise and HRV in CHF patients, carried out by Ponikowski et al. [12], revealed the relationship between depressed HRV and peak oxygen consumption (peak VO_2) and VE/VCO_2 slope, which reflects increased ventilation during exercise in CHF patients. A significant correlation between peripheral chemoreceptor activity and HRV indices was also relevant in these studies. In their authors' opinion, such a relationship may create a potential link between the functional severity of CHF and the autonomic imbalance.

The relationship between HRV and CHF aetiology was also investigated. In the study referred to [12], significantly depressed HRV was observed in ICM patients in comparison with DCM patients. In a few other studies, similarly to ours, significant differences between HRV values in ICM and DCM patients were not found [12, 13].

In the last decade the role of the inflammatory process in the development and progress of symptomatic CHF has been widely discussed. In many reports elevated levels of proinflammatory cytokines and their receptors were described in CHF patients [17-19]. Among them,

Table IV. Cytokine levels in analysed groups

	CHF patients	Healthy controls	p
sTNF-RI [pg/ml]	1428.7±473.6	1235.2±316.4	0.051
sTNF-RII [pg/ml]	2777.8±960.1	2179.3±570.6	0.018
IL-6 [pg/ml]	6.3±4.7	2.1±1.6	0.0006

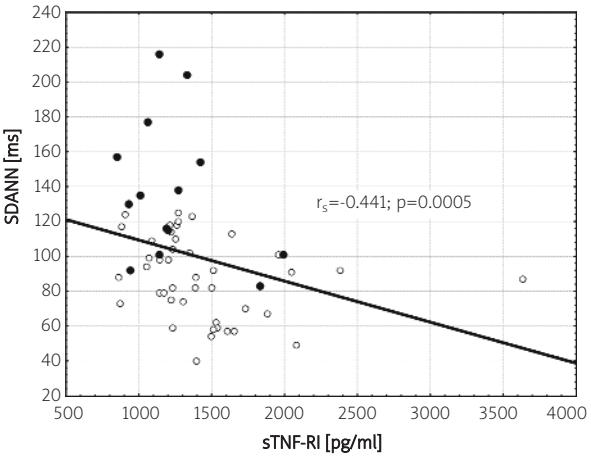

Figure 2. Relationship between SDANN and sTNF-RI level in CHF patients and healthy controls
white dots – CHF patients; black dots – healthy controls.

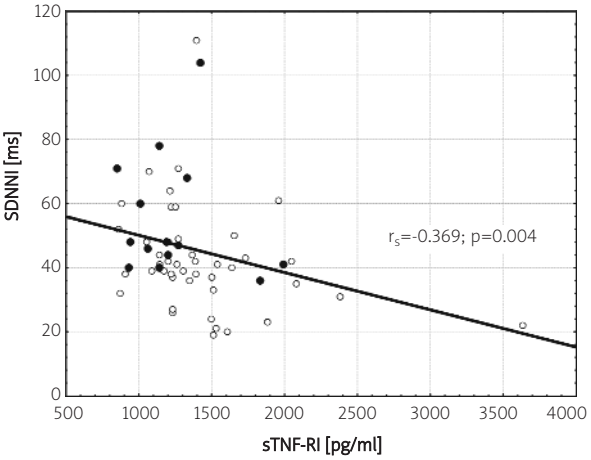

Figure 3. Relationship between SDNNI and sTNF-RI level in CHF patients and healthy controls
white dots – CHF patients; black dots – healthy controls

TNFα and its soluble receptors sTNF-RI and sTNF-RII, as well as interleukin 1 and 6, are the most extensively investigated [1, 20, 21]. It was found that the concentration of many of them correlates with the stage of CHF, estimated using the NYHA scale and values of peak oxygen consumption (peak VO_2) [17-19]. The

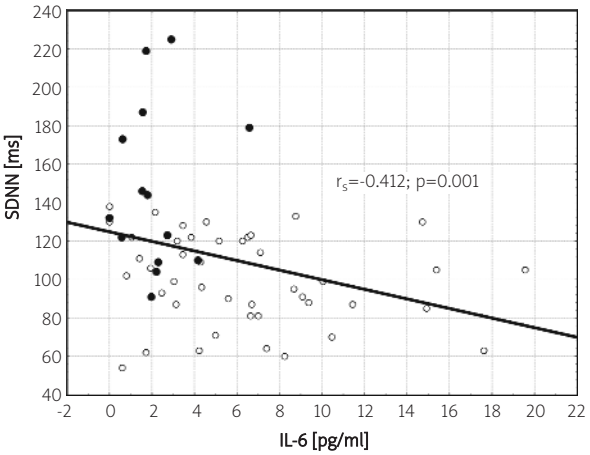

Figure 4. Relationship between SDNN and IL-6 level in CHF patients and healthy controls
white dots – CHF patients; black dots – healthy controls

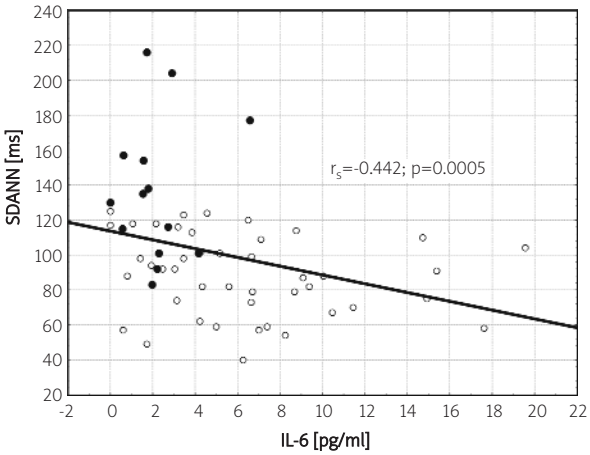

Figure 5. Relationship between SDANN and IL-6 level in CHF patients and healthy controls
white dots – CHF patients; black dots – healthy controls

prognostic value of IL-6 [22, 23], sTNF-RI [24], sTNF-RII [25] has been documented.

Some suggested that TNFα could contribute to HRV depression in CHF patients [8]. Experimental studies showed that TNFα changed β-adrenergic signal transduction in isolated cell culture models [26, 27]. Malave et al. [8] investigated the correlation between TNFα, noradrenalin levels and HRV indices in stable, mild or moderately severe CHF (NYHA class I-III). In their opinion, an excessive TNFα expression, resulting in the loss of β-adrenergic signal transduction, can contribute to HRV depression observed in CHF. Investigators observed a significant negative relationship between both TNFα and noradrenalin concentration and indices of time-domain HRV analysis SDNN and SDANN, as well as between indices of frequency-domain analysis: TNFα with LF and HF, and noradrenalin with LF. A significant negative relationship between TNFα soluble receptors sTNF-RI and SDNN and also SDANN, as well as between sTNF-RII and SDNN, SDANN and also HF, were also observed. Multivariate analysis confirmed that TNFα is an independent index of HRV depression, stronger than noradrenalin.

In the present study the level of TNFα was not measured but the concentration of its soluble receptors was assessed. There are two opinions about the role of soluble TNFα receptors. According to one of them, TNFα soluble receptors act as a reservoir of slowly released TNFα, and thus intensify its unfavourable effects. The other one is that soluble receptors neutralise TNFα by binding its molecules. Their concentrations are less variable than those of TNFα. The measurement of TNFα soluble receptors is thought

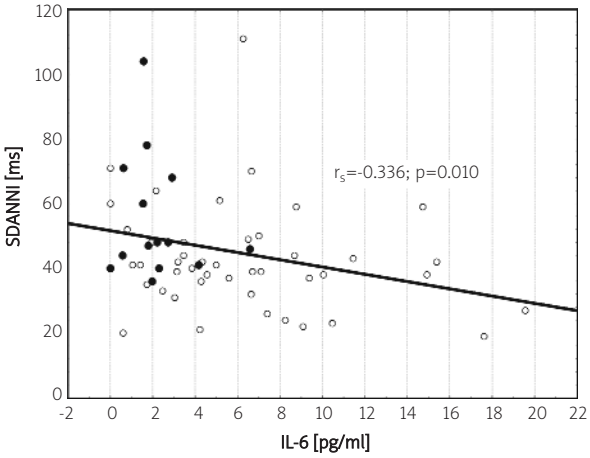

Figure 6. Relationship between SDNNI and IL-6 level in CHF patients and healthy controls
white dots – CHF patients; black dots – healthy controls

to be a more specific index of TNFα activity than direct measurement of TNFα itself [20].

The results of our study including stable patients in NYHA class I-IV were similar to those previously mentioned. A significant negative relationship between concentrations of TNFα soluble receptors sTNF-RI and sTNF-RII and SDNN, SDANNI and SDNNI was observed. Additionally, a significant negative correlation between IL-6 concentrations and SDNN, SDANN, and also SDNNI, was noted. However, noradrenalin concentrations were not measured.

Contrary to the above-mentioned results, Aronson et al. [9] did not confirm the correlation between TNFα

concentrations and HRV indices. However, they investigated patients with decompensated CHF (NYHA III and IV). Thus, their group was more homogeneous, and, as they reported, cytokine levels were higher than usually observed in patients with stable CHF. The authors observed a significant negative relationship between IL-6 level and time-domain HRV indices SDNN and SDANN, as well as between IL-6 level and frequency-domain HRV indices TP (total power spectrum) and ULF. A significant negative correlation between noradrenalin concentration and HRV indices was also reported. Multivariate analysis confirmed significant correlations between IL-6 level and indices of long-term HRV. Multivariate analysis did not confirm a correlation between noradrenalin level and HRV indices. In the authors' opinion, in patients with decompensated CHF increased levels of IL-6 can lead to the reduction of HRV indices.

As mentioned before, the results of the present study confirm a significant negative correlation between HRV indices and TNFα soluble receptors TNF-RI and sTNF-RII levels in patients with stable CHF of various stages (NYHA I-IV). The relationship between HRV and IL-6 level is an additional important observation, and has not been previously reported in available medical literature. However, these results do not allow assessment of the cause-effect relationship of the phenomenon. One might speculate that it is an epiphenomenon. Low cytokine concentrations are observed in healthy subjects, whereas elevated levels, in proportion with disease progression, are observed in CHF patients [19]. Similarly, high HRV indices are observed in healthy individuals, decreasing with the progression of the disease. Thus, there is probably a correlation between the index, which is normal in the healthy and varies in the affected subjects according to the progress of the disease, and the indices of similar characteristic. According to Malave et al. [8], overexpression of TNFα may be one of the many possible mechanisms leading to the attenuation of β-adrenergic responsiveness in the reaction to sympathetic activation in the failing heart. Another argument suggesting a direct relation between TNFα and HRV is that TNFα is a stronger predictor of depressed HRV than noradrenalin, which in turn is an accepted marker of decreased HRV in CHF.

Another explanation of the relationship between HRV and cytokines is also possible, assuming that increased cytokine production is a result of changes in the sympathetic innervation within the heart. In experimental studies, the regulation (inhibition) of cytokines production by activation of heart β-adrenergic receptors was shown [28, 29]. Scintigraphy with 123-I-metaiodobenzylguanidine (MIBG), a noradrenalin analogue, allows for visualisation of the adrenergic innervation. The correlation between cardiac MIBG uptake and plasma level of TNFα and its soluble receptors sTNF-RI and sTNF-RII, and IL-6, was investigated [30]. The studies revealed a significant relationship between increased cytokine levels and reduction of MIBG uptake, the parameter of reduced cardiac sympathetic innervation. In the authors' opinion, this may suggest a potential proinflammatory effect of the autonomic system via modulation of cytokine production in the heart.

Mabuchi et al. [31] presented in their study more arguments for a relationship between sympathetic system activity and production of cytokines. They investigated the relation between IL-6 production in the lung and pulmonary vascular resistance in patients with CHF. An independent relationship between IL-6 production in the lung and noradrenalin plasma level was demonstrated, as well as an independent negative relationship between IL-6 production in the lung and treatment with β-blockers.

Conclusions

Significant negative correlations between TNFα soluble receptors sTNF-RI, sTNF-RII and IL-6 levels and time-domain HRV parameters were observed in the study. Because the results of investigations conducted so far do not elucidate the cause-effect relationship, further studies are needed to clarify the mechanisms of HRV depression in CHF and the role of cytokines in this severe clinical condition.

References

1. Blum A, Miller H. Role of cytokines in heart failure. *Am Heart J* 1998; 135: 181-6.
2. Piotrowicz R, Baranowski R, Dąbrowski A. Zmienność rytmu zatokowego. *Elektrofizjologia i Stymulacja Serca* 1998; Supl. II: 30-4.
3. Karcz M, Rużyłło W. Zmienność rytmu zatokowego jako potencjalny czynnik rokowniczy w kardiomiopatii rozstrzeniowej. *Folia Cardiol* 2001; 8: 85-9.
4. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; 93: 1043-65.
5. Malik M, Camm AJ. Components of heart rate variability-what they really mean and what we really measure. *Am J Cardiol* 1993; 72: 821-2.
6. Murray DR. What is „heart rate variability" and is it blunted by tumor necrosis factor? *Chest* 2003; 123: 664-7.
7. Pawlak-Buś K, Kołodziejczyk-Feliksik M, Czerwiński-Mazur P, et al. Zmienność rytmu zatokowego – interpretacja patofizjologiczna i metodologia pomiarów. *Folia Cardiol* 2003; 6: 719-26.
8. Malave HA, Taylor AA, Nattama J, et al. Circulating levels of tumor necrosis factor correlate with indexes of depressed heart rate variability: a study in patients with mild-to-moderate heart failure. *Chest* 2003; 123: 716-24.

9. Aronson D, Mittleman MA, Burger AJ. Interleukin-6 levels are inversely correlated with heart rate variability in patients with decompensated heart failure. *J Cardiovasc Electrophysiol* 2001; 12: 294-300.
10. Ponikowski P, Anker SD, Chua TP, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997; 79: 1645-50.
11. Szabo BM, van Veldhuisen DJ, van der Veer N, et al. Prognostic value of heart rate variability in chronic congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. *Am J Cardiol* 1997; 79: 978-80.
12. Ponikowski P, Chua TP, Piepoli M, et al. Ventilatory response to exercise correlates with impaired heart rate variability in patients with chronic congestive heart failure. *Am J Cardiol* 1998; 82: 338-44.
13. Musialik-Łydka A, Średniawa B, Pasyk S. Zmienność rytmu zatokowego w przewlekłej niewydolności serca. *Kardiol Pol* 2003; 58: 14-16.
14. Wachowiak-Baszyńska H, Ochotny R. Zmienność rytmu zatokowego w chorobie niedokrwiennej serca. Część I: Wybrane czynniki ryzyka miażdżycy a wartości parametrów zmienności rytmu zatokowego u osób zdrowych i ze stabilną chorobą niedokrwienną serca. *Folia Cardiol* 2001; 8: 109-17.
15. Stein PK, Freedland KE, Skala JA, et al. Heart rate variability is independent of age, gender, and race in congestive heart failure with a recent acute exacerbation. *Am J Cardiol* 1997; 79: 511-12.
16. Antelmi I, de Paula RS, Shinzato AR, et al. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. *Am J Cardiol* 2004; 93: 381-5.
17. Straburzyńska-Migaj E, Leśniewska K, Ochotny R, et al. Wyniki testu spiroergometrycznego i wartości wybranych wskaźników odczynu zapalnego u chorych z przewlekłą niewydolnością serca. Porównanie chorych z kardiomiopatią niedokrwienną i rozstrzeniową. *Pol Arch Med Wewn* 2004; 111: 693-701.
18. Koller-Strametz J, Pacher R, Frey B, et al. Circulating tumor necrosis factor-alpha levels in chronic heart failure: relation to its soluble receptor II, interleukin-6, and neurohumoral variables. *J Heart Lung Transplant* 1998; 17: 356-62.
19. Torre-Amione G, Kapadia S, Benedict C, et al. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol* 1996; 27: 1201-6.
20. Bolger AP, Anker SD. Tumour necrosis factor in chronic heart failure: a peripheral view on pathogenesis, clinical manifestations and therapeutic implications. *Drugs* 2000; 60: 1245-57.
21. Berry C, Clark AL. Catabolism in chronic heart failure. *Eur Heart J* 2000; 21: 521-32.
22. Orus J, Roig E, Perez-Villa F, et al. Prognostic value of serum cytokines in patients with congestive heart failure. *J Heart Lung Transplant* 2000; 19: 419-25.
23. Tsutamoto T, Hisanaga T, Wada A, et al. Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. *J Am Coll Cardiol* 1998; 31: 391-8.
24. Rauchhaus M, Doehner W, Francis DP, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. *Circulation* 2000; 102: 3060-7.
25. Ferrari R, Bachetti T, Confortini R, et al. Tumor necrosis factor soluble receptors in patients with various degrees of congestive heart failure. *Circulation* 1995; 92: 1479-86.
26. Chung MK, Gulick TS, Rotondo RE, et al. Mechanism of cytokine inhibition of beta-adrenergic agonist stimulation of cyclic AMP in rat cardiac myocytes. Impairment of signal transduction. *Circ Res* 1990; 67: 753-63.
27. Gulick T, Chung MK, Pieper SJ, et al. Interleukin 1 and tumor necrosis factor inhibit cardiac myocyte beta-adrenergic responsiveness. *Proc Natl Acad Sci USA* 1989; 86: 6753-7.
28. Guirao X, Kumar A, Katz J, et al. Catecholamines increase monocyte TNF receptors and inhibit TNF through beta 2-adrenoreceptor activation. *Am J Physiol* 1997; 273: E1203-8.
29. Hasko G, Nemeth ZH, Szabo C, et al. Isoproterenol inhibits Il-10, TNF-alpha, and nitric oxide production in RAW 264.7 macrophages. *Brain Res Bull* 1998; 45: 183-7.
30. Parthenakis FI, Patrianakos A, Prassopoulos V, et al. Relation of cardiac sympathetic innervation to proinflammatory cytokine levels in patients with heart failure secondary to idiopathic dilated cardiomyopathy. *Am J Cardiol* 2003; 91: 1190-4.
31. Mabuchi N, Tsutamoto T, Wada A, et al. Relationship between interleukin-6 production in the lungs and pulmonary vascular resistance in patients with congestive heart failure. *Chest* 2002; 121: 1195-202.

Cytokiny a wskaźniki zmienności rytmu serca w przewlekłej niewydolności serca

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Streszczenie

Wstęp: Analiza zmienności rytmu serca (HRV) jest nieinwazyjną metodą oceny wpływu układu autonomicznego na czynność serca. W przewlekłej niewydolności serca (CHF) obniżona HRV koreluje ze stopniem zaawansowania choroby. Wiadomo również, że w CHF podwyższony jest poziom cytokin prozapalnych. Ponieważ uważa się, że cytokiny mogą oddziaływać na układ nerwowy, zarówno obwodowo jak i centralnie, wysunięto koncepcję, że być może przyczyniają się one do obniżenia HRV w przebiegu CHF.

Cel: Wobec istniejących wokół tego zagadnienia kontrowersji i tylko nielicznych publikacji podjęto badania mające na celu ocenić czy istnieją powiązania pomiędzy cytokinami a wskaźnikami HRV.

Metody: Badaniami objęto 44 chorych z wyrównaną CHF w klasie I – IV wg NYHA i 15 osób grupy kontrolnej. Analizę czasową przeprowadzono w oparciu o 24-godzinną rejestrację ekg metodą Holtera. Pomiaru osoczowego stężenia rozpuszczalnych receptorów TNF-α: sTNF-RI i sTNF-RII oraz IL-6 wykonano używając standardowych zestawów ELISA (Quantikine, R&D Systems).

Wyniki: Analizowane wskaźniki HRV były istotnie niższe, a stężenia cytokin wyższe w grupie chorych z CHF niż w kontrolnej. W całej badanej grupie: chorych i kontrolnej, stwierdzono istotną ujemną korelację między stężeniem sTNF-RI i SDNN (r=-0,44; p=0,0006), SDANN (r=-0,44; p=0,0005) oraz SDNNI (r=-0,37; p=0,004), między stężeniem sTNF-RII i SDNN (r=-0,35; p=0,007), SDANN (r=-0,34; p=0,01) i SDNNI (r=-0,31; p=0,02) oraz między stężeniem IL-6 i SDNN (r=-0,41; p=0,001), SDANN (r=-0,44; p=0,0005) oraz SDNNI (r=-0,34; p=0,009).

Wnioski: W przedstawianych badaniach zaobserwowano istotne ujemne korelacje pomiędzy stężeniem rozpuszczalnych receptorów TNFα: sTNF-RI i sTNF-RII oraz IL-6 ze wskaźnikami analizy czasowej HRV. Ponieważ wyniki dotychczasowych obserwacji nie pozwalają na określenie zależności przyczynowo-skutkowych konieczne są dalsze badania nad mechanizmami obniżenia HRV w CHF i wyjaśnieniu roli cytokin w tym ciężkim stanie chorobowym.

Słowa kluczowe: cytokiny, niewydolność serca, zmienność rytmu serca

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