The preserved autonomic functions may provide the asymptomatic clinical status in heart failure despite advanced left ventricular systolic dysfunction

Korunmuş otonomik fonksiyonlar ileri sol ventrikül sistolik disfonksiyonuna rağmen kalp yetersizliğinde asemptomatik klinik durumu sağlayabilir

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ABSTRACT

Objective: Autonomic dysfunction is an important marker of prognosis in congestive heart failure (CHF) and may determine the symptoms and progression of CHF. The aim of our study was to investigate whether preserved autonomic function assessed by heart rate variability (HRV) analyses is related to absence of CHF symptoms despite prominently reduced systolic function.

Methods: The study had a cross-sectional observational design. Fifty patients with left ventricular ejection fraction (EF) below 40% were enrolled. The patients were divided into two groups according to their CHF symptomatic status as Group 1 (NYHA functional class I, asymptomatic group) and Group 2 (NYHA functional class≥ II, symptomatic group). Plasma C-reactive protein (CRP), N-terminal proB-type natriuretic peptide (NT-proBNP) levels, echocardiographic parameters and HRV indices were measured while the patients were clinically stable in each group. Possible factors associated with the development of CHF symptoms were assessed by using multiple regression analysis.

Results: Baseline clinical characteristics and left ventricular EF were similar in the two groups. Serum CRP (15±21 vs 7±18 mg/L, p=0.011) and NT-proBNP levels (1935±1088 vs 1249±1083 pg/mL, p=0.020) were significantly higher in symptomatic group. The HRV parameters (SDNN: 78±57 vs 122±42 ms, p=0.001; SDANN: 65±55 vs 84±38 ms, p=0.024; SDNNi: 36±41 vs 70±46 ms, p<0.001; triangular index [Ti]: 17±12 vs 32±14, p<0.001) were also significantly depressed in symptomatic group. When multiple regression analysis was performed, only HRV indices of autonomic function were significantly associated with the asymptomatic status (SDNN, OR: 1.016, 95%CI: 1.002-1.031, p=0.028; SDNNi, OR: 1.030, 95%CI: 1.008-1.052, p=0.006; TI, OR: 1.088, 95%CI: 1.019-1.161, p=0.011).

Conclusion: Preserved autonomic functions were shown to be associated with absence of CHF symptoms independently of angiotensin converting enzyme inhibitor/angiotensin receptor blocker's treatment and BNP levels and may be protective against the development of CHF symptoms despite advanced left ventricular systolic dysfunction. *(Anadolu Kardiyol Derg 2010 December 1; 10(6); 519-25)*

Key words: Heart rate variability, systolic heart failure, preserved autonomic function, autonomic dysfunction, clinical symptoms, regression analysis

ÖZET

Amaç: Otonomik disfonksiyon konjestif kalp yetersizliğinde (KKY) prognozun önemli bir belirleyicisidir ve KKY'nin semptomlarını ve ilerlemesini öngörebilir. Çalışmamızın amacı belirgin olarak azalmış sistolik fonksiyonu olan hastalarda kalp hızı değişkenliği (KHD) ile belirlenen korunmuş otonomik fonksiyonun KKY semptomlarının yokluğu ile ilişkili olup olmadığının araştırılmasıdır.

Yöntemler: Çalışma gözlemsel ve enine- kesitli olarak planlandı. Sol ventrikül ejeksiyon fraksiyonu (EF) %40'ın altında 50 hasta çalışmaya alındı. Hastalar KKY semptomatik durumlarına göre; Grup 1 (NYHA sınıf I, asemptomatik grup) ve Grup 2 (NYHA sınıf>=II, semptomatik grup) olmak üzere iki gruba ayrıldılar. Hastaların plazma C-reaktif protein (CRP), N-terminal pro-B tip natriüretik peptit (NT-proBNP) düzeyleri, ekokardiyografik ölçümleri ve KHD parametreleri hastalar klinik olarak stabil iken ölçüldü. Konjestif kalp yetersizliği semptomlarının gelişimi ile ilgili olası faktörlerin bağımsızlığı çok değişkenli regresyon analizi ile değerlendirildi.

Bulgular: Bazal klinik özellikler ve sol ventrikülün EF'si her iki grupta benzerdi. Serum CRP (15±21 ve 7±18 mg/L, p=0.011) ve NT-proBNP düzeyleri (1935±1088 ve 1249±1083 pg/mL, p=0.020) semptomatik grupta anlamlı olarak yüksekti. Kalp hızı değişkenliği parametreleri (SDNN: 78±57 ve 122±42 ms, p = 0.001; SDANN: 65±55 ve 84±38 ms, p=0.024; SDNNi: 36±41 ve 70±46 ms, p<0.001; triangüler indeks [Ti]: 17±12 ve 32±14, p< 0.001) semptomatik grupta anlamlı olarak baskılanmıştı. Çok değişkenli analiz gerçekleştirildiğinde, sadece KHD parametreleri asemptomatik klinik durum için

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bağımsız öngörücü idi (SDNN, OR: 1.016, %95GA: 1.002-1.031, p=0.028; SDNNi, OR: 1.030, %95GA: 1.008-1.052, p=0.006; TI, OR: 1.088, %95GA: 1.019-1.161, p=0.011).
Sonuç: Korunmuş kardiyak otonomik fonksiyonlar ileri sol ventrikül sistolik disfonksiyonuna rağmen KKY semptomlarının yokluğu ile anjiyotensin dönüştürücü enzim inhibitörü/anjiyotensin reseptör bloker tedavisi ve BNP düzeylerinden bağımsız olarak ilişkili saptandı ve KKY semptomlarının gelişimine karşı koruyucu olabilir. *(Anadolu Kardiyol Derg 2010 Aralık 1; 10(6); 519-25)*
Anahtar kelimeler: Kalp hızı değişkenliği, sistolik kalp yetersizliği, korunmuş otonomik fonksiyon, otonomik disfonksiyon, klinik semptomlar, regresyon analizi

Introduction

Congestive heart failure (CHF) is a clinical syndrome that is frequently associated with neurohormonal dysregulation and cardiac autonomic dysfunction. Systolic HF is a complex neurohormonal condition in which activation of the renin-angiotensin-aldosterone and sympathetic systems (1) and a reduction of the parasympathetic tonus contribute to CHF progression and its poor prognosis.

Heart rate variability (HRV) indices derived from 24-hour Holter electrocardiogram recordings reflect the autonomic balance and autonomic nervous system (ANS) functionality (2). Heart rate variability is known to be disturbed and associated with increased mortality in CHF. Autonomic dysfunction is an important marker of prognosis in CHF and may determine the symptomatic status and the progression of heart failure in patients with reduced left ventricular systolic function.

The aim of our study was to investigate whether preserved autonomic functions assessed by HRV analyses are related to absence of CHF symptoms despite prominently reduced systolic function.

Methods

Patient population and Study protocol

The study had a cross-sectional observational design. Fifty patients (37 male, mean age: 63±13 years) with left ventricular ejection fraction (EF) below 40% were enrolled. Those who had NYHA (New York Heart Association) functional class I symptoms made up Group 1 (n=20, asymptomatic group) and those with NYHA class II or higher symptoms formed the Group 2 (n=30, symptomatic group).

Patients with acute infections, acute coronary syndromes, typical stable angina pectoris, decompensated heart failure requiring intravenous therapy, hyper-or hypothyroidism, atrial fibrillation, concomitant valvular diseases and active malignancy were excluded from the study. Both ischemic and non-ischemic cardiomyopathies were eligible. Although decompensated heart failure requiring intravenous therapy is exclusion criteria, if these patients were clinically stable for at least 1 week after compensation were also included and then their study parameters were obtained just before hospital discharge. In this study, the assignment of patient groups and collection of patient data were performed by investigators who were totally blind to this study.

The local Ethical Committee approved the study protocol and all patients gave written informed consent. All patients were evaluated in our cardiology clinic between June 2007 and March 2008.

Laboratory analyses

All eligible patients were hospitalized and researched for advanced left ventricular systolic dysfunction. Blood samples were drawn by venipuncture to perform routine blood chemistry after fasting for at least 8 hours. Fasting plasma glucose, blood urea nitrogen (BUN), creatinine, Na, K, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, hemoglobin, leukocytes, platelets, troponin-T, creatine phosphokinase (CPK), creatine phosphokinase-MB (CK-MB), plasma C-reactive protein (CRP) and N-terminal pro-B type natriuretic peptide (NT-proBNP) levels were obtained in hospital.

After recording the baseline clinical characteristics, venous blood samples were drawn from an antecubital vein and placed in tubes with ethylenediaminetetraacetic acid. The specimens were centrifuged for 1 hour and plasma was frozen at -80°C until analysis. NT-proBNP was measured by an electrochemiluminescence immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany) (Reference range: 0.0-125.0 pg/mL). Plasma CRP levels were determined by nephelometric method (Reference range: 0.0-5.0 mg/L).

Heart rate variability analyses

All patients underwent a 24-hour Holter recording to assess HRV parameters. Twenty-four hour Holter evaluations were performed by an experienced physician who was totally blind to the study population. Holter ECG was performed on a 3-channel digitized recorder (Del Mar Reynolds Medical Ltd, Hertford, UK). Before analyzing the data they were manually preprocessed. Recordings lasting for at least 18 h and of sufficient quality for evaluation were included in the analysis. In case these criteria were not achieved, the recordings were repeated. The time domain HRV indices were analyzed by using statistical and geometrical methods. By using statistical methods, the RMSSD [the square root of the mean squared differences of successive normal-to-normal (NN) intervals], the SDNN (the standard deviation of all NN intervals), the SDNN index (the mean of the deviation of the 5 min NN intervals over the entire recording), the SDANN (standard deviation of the average NN intervals calculated over 5 min periods of the entire recording), and the pNN50 (proportion of adjacent R-R intervals differing by 50 ms in the 24 h recording) were measured. By using geometrical methods, the HRV triangular index (TI) (total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 7.8125 ms (1/128 s) was measured. Also mean R-R interval was calculated. All of

them were measured according to the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (2).

Echocardiography

All patients underwent complete transthoracic echocardiographic studies including two-dimensional, color flow and pulsed Doppler with a GE-Vingmed Vivid 7 system (GE-Vingmed Ultrasound AS, Horten, Norway) using a 2.5-3.5 MHz transducer. Two-dimensional, Doppler echocardiographic examinations and M-mode measurements were taken according to the recommendations of the American Society of Echocardiography (3).

Statistical analysis

The SPSS statistical software (SPSS 15.0 for windows, Inc, Chicago, IL, USA) was used for all statistical calculations. Continuous variables were given as mean±standard deviation and median (minimum-maximum); categorical variables were defined as percentages. Continuous variables were compared by Mann-Whitney U Test and the Chi-square test was used for the categorical variables between two groups. Spearman's rank correlation coefficient was used for correlation analysis. All demographical and clinical properties, total biochemistry, CRP and pro-BNP levels, medications, HRV indices and echocardiographic parameters were firstly evaluated in univariate analysis and then the parameters which were statistically significantly different between two groups or clinically possible confounding factors for symptomatic status were also included in multiple regression analyses. Therefore, logistic regression with stepwise method (Forward: LR) was used for analysis of independent variables including hemoglobin, creatinine levels, HRV indices, CRP values, pro-BNP levels, ACE inhibitor/ARB and Digoxin use. All tests of significance were two-tailed. Statistical significance was defined as $p<0.05$.

Results

The baseline clinical characteristics were similar in the two groups, except for a higher rate of angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker's (ARB) use in Group 1 and digoxin use in Group 2 (Table 1).

In Group 2, CRP (p=0.011), NT-proBNP (p=0.020) and plasma creatinine levels (p=0.013) were significantly higher and hemoglobin levels (p=0.028) were significantly lower as compared to Group 1 (Table 1). Echocardiographic parameters were not statistically different between two groups (Table 2).

Plasma CRP levels were positively correlated with NT-proBNP level (r=0.385, p=0.006) and negatively correlated with HRV indices (for TI, r=-0.404, p=0.007) in the whole study population. In Group 2, the HRV indices (SDNN, p=0.001; SDANN, p=0.024; SDNNi, p<0.001; RMSSD, p=0.04; Ti] p<0.001) were significantly depressed as compared to Group 1 (Table 2).

When multiple logistic regression analysis was performed, the only parameters found to be independent negative predictors for the presence of NYHA class II or higher symptoms of heart failure status were HRV indices, namely 1) SDNN (OR: 1.016, 95%CI: 1.002-1.031, p=0.028); 2) SDNNi (OR: 1.030, 95%CI: 1.008-1.052, p=0.006); 3) RMSSD, (OR: 1.019, 95%CI 1.004-1.034, p=0.011) and 4) TI (OR: 1.088, 95%CI: 1.019-1.161, p=0.011) (Table 3).

Discussion

The main finding of this study was that impaired sympathovagal balance as determined by depressed HRV independently was related to presence of heart failure symptoms in patients with systolic left ventricular dysfunction. An interesting finding of our study was that some patients with prominent reduced systolic function and similar baseline characteristics had the preserved autonomic functions with no symptom of heart failure.

The processes contributing to the progression of systolic HF are complex. A primary pathophysiological mechanism in systolic HF is impaired cardiac function, associated with ongoing remodeling, inflammation, neurohormonal activation, and impaired ANS function. An abnormally activated sympathetic and altered parasympathetic tonus associated with increased concentration of circulating norepinephrine (NE), profound peripheral vasoconstriction, attenuated cardiovascular reflexes, and down-regulation of adrenergic nerve terminals play a pivotal role in the progression of pump failure (4-6). Sympathetic nervous system activation in heart failure, as indexed by elevated NE levels, higher muscle sympathetic nerve activity and reduced HRV, is associated with pathologic ventricular remodeling, increased arrhythmias, sudden death, and increased mortality (7-14).

HRV indices can reflect the activity of the ANS. Heart rate variability quantifies alteration in intervals between sinus heartbeats as the heart rate oscillates around a mean value. These oscillations are modulated by the ANS and can be analyzed by different measures. Autonomic nervous system functionality and autonomic imbalance in CHF have been indexed by HRV analyses. Heart rate variability is a standardized tool for examining ANS activity in various disease states such as hypertension, diabetes mellitus, coronary artery disease, as well as myocardial dysfunction. Similar to studies post-myocardial infarction, CHF is characterized by a decrease in time-domain indices of HRV, which correlates with the severity of left ventricular dysfunction (2, 15-17).

Heart rate variability is known to be depressed in CHF (2) and depressed HRV predicts hemodynamic compromise, sudden death and death from progressive pump dysfunction (16, 18-20). SDNN has been shown to be strongly predictive of mortality in CHF; in the UK-HEART study, SDNN <50 ms was associated with >50% mortality compared to only 5.5% in the group with SDNN >100 ms (20). In our study, patients with prominent reduced sys-

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Table 1. Baseline clinic characteristics of two groups according to clinical symptoms in patients with reduced systolic function

Clinical characteristics	Group 1 (NYHA I) (n=20)		Group 2 (NYHA≥II) (n=30)		*p
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Age, years	65±12	68(39-85)	62±13	62(28-86)	0.336
Gender, male, n (%)	14 (70)		23 (77)		0.599
Height, cm	166±11	169(148-186)	167±7	168(151-178)	0.874
Weight, kg	75±20	68(50-127)	72±13	70(46-101)	0.960
Waist, cm	96±14	97(70-132)	96±10	96(73-115)	0.744
Hip, cm	101±9	101(82-114)	100±10	98(82-130)	0.263
Waist hip ratio	0.94±0.08	0.92(0.85-1.18)	0.96±0.07	0.98(0.78-1.07)	0.118
BMI, kg/m2	27±5	26(18-40)	26±5	26(17-35)	0.797
Systolic dysfunction (duration, years)	5.0±4.5	3(1-15)	5.0±5.4	3(1-25)	0.709
Systolic dysfunction, n (%) (etiology, ischemic)	15 (75)		22 (73)		0.895
Hypertension, n (%)	9 (45)		17 (57)		0.419
Diabetes mellitus, n (%)	9 (45)		17 (57)		0.419
Dyslipidemia, n (%)	13 (65)		14 (47)		0.203
Family history for CAD, n (%)	1 (5)		2 (7)		0.808
Smoking, n (%)	8 (40)		17 (57)		0.248
Biochemistry					
Fasting plasma glucose, mg/dl	122±45	101(77-228)	126±36	125(64-197)	0.458
BUN, mg/dl	24±13	22(14-78)	32±25	27(4-145)	0.113
Creatinine, mg/dl	1.2±0.5	1.1(0.8-3.1)	1.3±0.4	1.3(0.8-2.6)	0.013
AST, U/L	22±7	20(12-38)	26±16	26(1-67)	0.620
ALT U/L	23±14	16(6-55)	27±21	19(6-100)	0.455
Na, mmol/L	138±3	139(133-143)	139±5	139(128-148)	0.557
K, mmol/L	4.5±0.5	4.6(2.8-5.2)	4.4±0.6	4.3(3.2-5.5)	0.234
Total cholesterol, mg/dl	158±34	159(89-216)	155±41	160(87-221)	0.765
LDL, mg/dl	93±30	97(36-146)	92±30	96(51-170)	0.800
HDL, mg/dl	42±10	43(25-64)	41±15	38(21-85)	0.427
Triglyceride, mg/dl	109±53	97(23-249)	101±52	92(11-282)	0.597
Hemoglobin, mg/dl	13.5±1.6	14(11-16)	12.6±2.4	13(10-23)	0.028
Leukocytes, $10^3/mm^3$	8.3±1.9	9(4-11)	8.1±2.4	8(3-12)	0.721
Platelets, $10^4/mm^3$	229±71	236(116-381)	249±78	257(75-462)	0.357
Troponin-T, ng/mL	0.02±0.04	0.01(0-0.13)	0.01±0.02	0.01(0-0.05)	0.951
CPK, U/L	86±44	82(25-168)	189±173	146(25-594)	0.097
CK-MB, U/L	24±19	21(5-70)	31±24	21(6-84)	0.612
CRP, mg/L	7.8±18.0	0(0-66)	15±21	9(0-96)	0.011
NT-proBNP, pg/mL	1249±1083	733(19-3000)	1935±1088	1945(62-3000)	0.020
Medications					
ASA, n (%)	15 (75)		23 (77)		0.892
Clopidogrel, n (%)	2 (10)		2 (7)		0.670
ACE inhibitor/ ARB, n (%)	18 (90)		17 (57)		0.012
Statin, n (%)	9 (45)		15 (50)		0.729
Beta-blocker, n (%)	13 (65)		13 (43)		0.133
CCB, n (%)	1 (5)		3 (10)		0.523
Furosemide, n (%)	7 (35)		15 (50)		0.295
Thiazide, n (%)	7 (35)		8 (27)		0.529
Spironolactone, n (%)	7 (35)		14 (47)		0.413
Digoxin, n (%)	7 (35)		21 (70)		0.015
Oral nitrates, n (%)	5 (25)		3 (10)		0.156
Oral anticoagulants, n (%)	3 (15)		4 (13)		0.868

Continuous variables are given as mean ± standard deviation and median (min–max); categorical variables are presented as percentages
* Mann-Whitney U test and Chi-square test
ACEI- angiotensin converting enzyme inhibitor, ARB-angiotensin II receptor blocker, ASA- acetylsalicylic acid, ALT- alanine aminotransferase, AST-aspartate aminotransferase, BUN- blood urea nitrogen, CCB- calcium channel blocker, CK-MB- creatine phosphokinase-MB, CPK- creatine phosphokinase, CRP- C-reactive protein, HDL- high-density lipoprotein, LDL- low-density lipoprotein, NT-proBNP- N-terminal pro-B type natriuretic peptide, NYHA-New York Heart Association Functional Class

Table 2. Heart rate variability and echocardiographic measurements in two groups

Variables	Group 1 (NYHA I) (n=20)		Group 2 (NYHA≥II) (n=30)		*p
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
HRV variables					
Mean R-R interval, ms	819±105	795(654-1041)	756±166	755(427-1267)	0.062
SDNN, ms	122±42	121(54-211)	78±57	61(10-234)	0.001
SDANN, ms	84±38	83(32-185)	66±55	51(4-258)	0.024
SDNN index, ms	70±46	47(27-163)	36±41	25(5-182)	<0.001
RMSSD,ms	73±43	32(9-214)	39±50	19(6-204)	0.040
Triangular index	32±14	32(16-72)	17±12	15(1-52)	<0.001
Echocardiographic variables					
Ejection fraction %	31±8	30(15-40)	30±7	30(12-40)	0.307
Stroke volume, cm^3	57.3±14.5	55(36-82)	53.4±11.6	54(23-75)	0.476
LVEDD, cm	6.0±1.0	6(4-8)	6.1±1.0	6(4-8)	0.641
IVSD, cm	1.1±0.2	1.1(0.8-1.5)	1.1±0.2	1.1(0.7-1.4)	0.680
PWD, cm	1.0±0.2	1(0.7-1.4)	1.0±0.1	1(0.8-1.3)	0.326
LVEDV, cm^3	189±65	180(83-334)	188±60	180(65-352)	0.976
LVESV, cm^3	129±57	110(47-252)	136±56	125(20-286)	0.547
Left atrial dimension, cm	4.5±0.6	4.5(3.3-6.0)	4.6±0.7	4.6(3.2-6)	0.642
Aorta dimension, mm	31.4±2.37	32(27-35)	29.90±2.96	30(23-36)	0.050
Pulmonary artery pressure, mmHg	45±17	40(30-75)	50±12	50(30-80)	0.188

Continuous variables are given as mean ± standard deviation and median (min–max); categorical variables are presented as percentages

*Mann-Whitney U and Chi-square test

HRV- heart rate variability, IVSD- interventricular septal thickness, LVEDD-left ventricular end-diastolic diameter, LVEDV- left ventricular end-diastolic volume, LVESV- left ventricular end-systolic volume, NYHA-New York Heart Association Functional Class, PWD- posterior wall thickness, RMSDD-square root of the mean squared differences of successive normal-to-normal intervals, SDNN-standard deviation of all normal-to-normal intervals, SDANN-standard deviation of the average normal-to-normal intervals calculated over 5-minute periods of the entire recording

Table 3. Multiple logistic regression analysis of the predictors of heart failure symptomatic state

Independent variables	p	Wald	Symptomatic state	Asymptomatic state
			Odds Ratio (OR) (Confidence Interval 95%)	1/OR (Confidence Interval 95%)
SDNN	0.028	4.8	0.984 (0.970-0.998)	1.016 (1.002-1.031)
SDANN	0.762	0.1	0.998 (0.984-1.012)	1.002 (0.988-1.016)
SDNN index	0.006	7.4	0.971 (0.951-0.992)	1.030 (1.008-1.052)
RMSSD	0.011	6.4	0.981 (0.967-0.996)	1.019 (1.004-1.034)
Triangular index	0.011	6.5	0.919 (0.861-0.981)	1.088 (1.019-1.161)
CRP	0.861	0.0	0.997 (0.960-1.034)	1.003 (0.967-1.042)
NT-proBNP	0.431	0.6	1.000 (1.000-1.001)	1.000 (0.999-1.000)

Logistic regression analysis with stepwise method (Forward: LR)

Independent variables included in the model: hemoglobin, creatinine, HRV indices, CRP, pro-BNP, ACE inhibitor/ARB and digoxin use

ACEI-angiotensin converting enzyme inhibitor, ARB-angiotensin II receptor blocker, CRP- C-reactive protein, NT-proBNP- N-terminal pro-B type natriuretic peptide, SDANN-standard deviation of the average normal-to-normal intervals calculated over 5-minute periods of the entire recording, SDNN-standard deviation of all normal-to-normal intervals, RMSDD- square root of the mean squared differences of successive normal-to-normal intervals

tolic function and good functional capacity had a mean SDNN value of 122±42 ms, which means that they were low-risk patients according to the results of the UK-HEART study.

In our study, CRP was positively correlated with NT-proBNP and negatively correlated with HRV indices. Although the CRP levels were significantly higher in group 2 patients, it failed to be an independent determinant of the presence of NYHA class 2 or higher symptoms in the multiple regression analysis. Other than CRP, the possible confounding factors which were different between two groups were included in multiple regression analysis.

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The HRV is regulated by central nervous signals sent to the heart via sympathetic and parasympathetic nerves. A recent study demonstrated that the central nervous system can decrease cytokine production via parasympathetic or vagal nerve activity. Stimulation of the vagus nerve significantly inhibits tumor necrosis factor-α (TNF α) release in animals (21). Furthermore, experimental models studying sepsis, myocardial ischemia and pancreatitis have documented an inhibition of cytokine activity through vagus nerve stimulation (22-24). Only a small fraction of the vagus nerve innervates the heart and other ANS innervations may play a more important role in development of symptoms and progression of heart failure. For example, the beta-blockers with high lipid solubility, which can pass the blood-brain barrier can provide a more central blockage of sympathetic nervous system and have a more potent effect on heart failure. More central and selective blockage of sympathetic nervous system may provide more potent modulation on heart and peripheral vascular system than peripheral affected drugs in heart failure patients.

Standard life-prolonging neurohormonal blockers for CHF, including ACEIs, ARBs, beta-blockers and aldosterone antagonists, have been shown to improve HRV parameters in patients with CHF (25-36), and the success in treating CHF by pharmacological neurohumoral antagonists underscores the importance of modulating the neurohumoral axis to improve clinical outcome (37, 38).

Despite advances in our understanding of CHF pathophysiology and treatment, mortality rate in CHF is still high. Cardiac mortality is often associated with gradual worsening of CHF (progressive pump dysfunction), although sudden death is common (39, 40). In our study, development of heart failure symptoms was independently related with the impairing process of autonomic functions. This finding supports that ANS which has functional effects on heart and peripheral vascular system may play a more important role in the progression of heart failure. The patients with moderately or severely reduced systolic function may have different autonomic and inflammatory responses to the situation with reduced systolic pump function by genetically determined mechanisms or environmental factors. For example, some situations such as type-A personality, depressive mood and psychiatric disorders may chronically affect the ANS activity. The mechanisms of different responses may be important in the treatment of heart failure. Furthermore, those different responses may provide us the mechanisms of action and modulation of the autonomic nervous system in CHF. Further studies are needed to clarify the mechanisms of individual different autonomic responses to the situation with reduced systolic pump function.

Study limitations

There are several limitations of our study. Firstly, the population size is small because our aim was to study the HRV in patients with prominent reduced systolic function, a patient subset is not so easy to find. Nevertheless, significant differences were found between the groups. Secondly, we do not have a long follow-up and mortality data for CHF and therefore, additional analyses of the end-points were not performed.

Conclusion

Preserved autonomic functions were shown to be associated with absence of CHF symptoms independently of ACE inhibitor/ARB treatment and BNP levels and may be protective against the development of CHF symptoms despite advanced left ventricular systolic dysfunction.

Conflict of interest: None declared.

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