The effects of cardiac resynchronization treatment on autonomic functions aside from functional status in heart failure

Kardiyak resenkronizasyon tedavisinin otonom sistem üzerine fonksiyonel kapasite ötesinde etkileri

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Abstract

Objective: Cardiac resynchronization therapy (CRT) improves heart rate variability (HRV) and heart rate turbulence (HRT) parameters. Herein, our aim was to compare these parameters with intracardiac- cardioverter defibrillator (ICD) patients with similar functional status to detect possible additional benefits of CRT on autonomic functions.
Methods: Patients who had systolic HF (NYHA class II and III) with an ejection fraction <35% were enrolled in this observational, cross-sectional study. These patients were implanted either an ICD or a CRT device. A 24-hour Holter recording was obtained to assess HRV and HRT parameters in 2 groups. Unpaired t-test and Chi-square test were used for comparisons between 2 groups. Logistic regression analysis was performed to determine the variables affecting functional status.
Results: Of 105 patients included in the study; 55 had CRT and 50 had ICD device. The baseline characteristics of the patients were similar in both groups. SDNN, SDANN, SDNN index, and LFnu were similar in both groups; however, RMSSD, pNN50, HFnu, LF/HF ratio, turbulence slope and albeit to a non-significant value turbulence onset were better in CRT group. When the HRV and HRT parameters were compared according to functional status, patients in functional class II had significantly better HRV and HRT parameters when compared to the ones in class III (p<0.05 for all). Regression analysis showed that only SDNN was associated with functional class [OR: 0.89 (95% CI: 0.80-0.98), p=0.03]. After the covariance analysis to eliminate the effects of functional status on HRV and HRT parameters; the parameters mostly related with the parasympathetic system activity, namely RMSSD, pNN50, HFnu, LF/HF ratio, turbulence onset and turbulence slope were still better in CRT group.
Conclusion: The most striking finding in our study is that HRV and HRT values related with parasympathetic activation are better in CRT patients when compared to ICD patients with similar functional status. Therefore, upgrading to CRT may have additional benefits on autonomic functions, which needs further investigation. *(Anadolu Kardiyol Derg 2013; 13: 439-45)*
Key words: Heart failure, heart rate variability, heart rate turbulence, cardiac resynchronization therapy, functional status, regression analysis

Özet

Amaç: Kardiyak resenkronizasyon tedavisinin (KRT) kalp yetersizliği (KY) hastalarında kalp hızı değişkenliği (KHD) ve kalp hızı türbülansını (KHT) düzelttiği bilinmektedir. Bu çalışmada amacımız KRT'nin fonksiyonel kapasiteyi düzelterek oluşturduğu KHD ve KHT düzelmesinin üzerine olası ek faydasını incelemektir. Bu amaçla intrakardiyak kardioverter defibrilatörü (İKD) olan KY hastalarındaki KHD ve KHT parametrelerini KRT'li hastalarla karşılaştırdık.
Yöntemler: Ejeksiyon fraksiyonu <%35 olan sistolik kalp yetmezlikli (NYHA sınıf 2-3) hastalar bu gözlemsel ve kesitsel çalışmaya dahil edildi. Bu hastalara İKD veya KRT cihazı implante edilmişti. Yirmi dört saatlik Holter EKG kayıtlarından KHD ve KHT parametreleri karşılaştırıldı. T-testi ve χ^2 testi, gruplar arasındaki karşılaştırmalarda, lojistik regresyon analizi, değişkenlerin fonksiyonel kapasiteye etkilerini değerlendirmek için kullanıldı.
Bulgular: Çalışmaya alınan 105 hastanın 55'inde CRT, 50'sinde İKD cihazı mevcuttu. Hastaların bazal özellikleri benzerdi. SDNN, SDANN, SDNN indeks, ve LFnu her 2 grupta farklılık göstermezken RMSSD, pNN50, HFnu, LF/HF oranı, türbülans eğimi ve her ne kadar anlamlılığa ulaşamasa da türbülans

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Accepted Date/Kabul Tarihi: 25.12.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 10.05.2013

doi:10.5152/akd.2013.138

başlangıcı KRT grubunda daha iyiydi. Fonksiyonel kapasitelerine göre hastalar karşılaştırıldığında fonksiyonel kapasitesi sınıf 2 olan hastalarda daha iyi KHD ve KHT parametreleri izlendi. Regresyon analizi sonuçlarına göre sadece SDNN fonksiyonel kapasite ile ilişkili bulundu [OR: 0,89 (%95 CI: 0,80-0,98), p=0,03]. Fonksiyonel kapasitenin KHD ve KHT parametelerine etkisini azaltmak için yapılan kovariyans analizi sonrası parasempatetik aktivite ile daha ilişkili olan RMSSD, pNN50, HFnu, LF/HF oranı, türbülans başlangıcı ve türbülans eğimi KRT grubunda yine daha iyi bulundu.
Sonuç: Bu çalışmadaki en önemli bulgu, parasempatetik aktivasyonla ilişkili olan HRV ve KHT değerlerinin, benzer fonksiyonel statusa sahip KRT hastalarında IKD hastalarından daha iyi olduğudur. Sonuç olarak KRT tedavisine yükseltmenin otonom fonksiyonlara düzeltici ek etkisi olabilir.
(Anadolu Kardiyol Derg 2013; 13: 439-45)
Anahtar kelimeler: Kalp hızı değişkenliği, kalp hızı türbülansı, kalp yetersizliği, kardiyak resenkronizasyon tedavisi, fonksiyonel status, regresyon analizi

Introduction

Heart rate variability (HRV) and heart rate turbulence (HRT) have been studied extensively in systolic heart failure (HF). Impairment of both of these parameters is associated with poor prognosis in HF (1-3). Some drugs, which are used in HF in order to improve survival and functional capacity have been also shown to improve the HRV parameters (4-6). Recently, cardiac resynchronization therapy (CRT), by improving functional capacity and prognosis in severe HF, has become an essential treatment in selected HF patients and evidence supports that CRT improves both HRV and HRT parameters (7-9).

The functional status of the patients is one of the most important determinants of HRV and HRT parameters in severe HF (10-12). In studies, which investigated HRV and HRT parameters in CRT patients, improvement of functional capacity was accompanied with the improvement of HRV and HRT parameters in good responders to CRT (13-16). However, we do not know whether there is an additional benefit of CRT on autonomic functions independent from the improvement in functional capacity.

In this study, our aim was to compare the HRV and HRT parameters in 2 groups [CRT patients vs. patients with intracardiac-cardioverter defibrillator (ICD) having clinical indications for CRT] with similar functional status in order to detect a possible additional benefit of device upgrade to CRT on autonomic functions assessed by HRV and HRT parameters.

Methods

Study design

This is a single-center, observational, cross-sectional study.

Study population

Patients with implantable devices, admitted to our outpatient clinics between January 2011 and November 2011 were included. These patients had systolic HF with a left ventricular ejection fraction (LVEF) ≤35% and had been implanted either an ICD or a CRT device with or without cardioversion-defibrillation feature (CRT-D or CRT-P) according to the relevant guidelines (17, 18) at least 6 months before their inclusion to the study. The CRT and ICD patients were age and sex matched with functional classes II or III according to New York Heart Association criteria to avoid any major differences between groups.

The ICD patients were selected from the ones having clinical indications for CRT according to the most recent guideline (19). They had ischemic or non-ischemic cardiomyopathy in sinus rhythm with NYHA functional class III with QRS duration ≥120 msec or NYHA functional class II with QRS duration ≥150 msec. These patients were pace-independent, whose lower rate limit was adjusted to 40/min and had a sense of ventricular beats >99%.

The CRT patients had biventricular pacing >99% since time of implantation. At the implantation time, CRT patients had had HF (LVEF≤35%) with NYHA functional class III-IV [20 (36.3%) with class III HF, 35 (63.7%) with class IV HF], sinus rhythm and QRS duration≥120 msec (mean QRS duration: 0.14±0.02 sec).

Exclusion criteria included atrial fibrillation because HRV and HRT measurement could not be done. Atrial sense <90% in CRT patients was another exclusion criterion to eliminate the direct effects of pacemaker functioning on HRV and HRT parameters.

The study protocol was approved by the institutional ethical committee and written informed consent was obtained from all patients.

Indications for ICD and CRT

Two major indications had been present for ICD implantation (18). For primary prevention, ICD had been implanted to patients with LV dysfunction due to prior myocardial infarction who had been at least 40 days post-MI or non-ischemic dilated cardiomyopathy, had had an LVEF ≤35%, in NYHA functional class II or III, receiving optimal medical therapy, and who have a reasonable expectation of survival with good functional status for >1 year. ICD therapy for secondary prevention had been applied for survivors of ventricular fibrillation and also for patients with documented hemodynamically unstable VT and/or VF with syncope, a LVEF≤40%, on optimal medical therapy, and with an expectation of survival with good functional status for >1 year.

The indications for CRT had been as follows: Heart failure (LVEF≤35%) due to ischemic or non-ischemic cardiomyopathy with NYHA functional class III-IV, sinus rhythm and QRS duration≥120 msec.

Study protocol

Baseline characteristics, functional status, vital signs and medications history of the patients were assessed at the time of inclusion. HRV and HRT parameters were collected and they were compared between 2 groups: ICD and CRT group.

A 24-hour electrocardiogram (ECG) Holter recording was obtained to assess HRV and HRT parameters in 2 groups.

All patients underwent conventional echocardiography at the time they were included in the study at the same center, using a GE-Vingmed Vivid 7 system (GE-Vingmed Ultrasound AS, Horten, Norway) with a phased array transducer 2.5 to 4 MHz. LVEF was obtained by the modified biplane Simpson's method. The time-frame between the EF measurements and the Holter test was at most 7 days.

Heart rate variability and heart rate turbulence measurements

The analysis of HRV and HRT was performed similar to our previous study (20). 24-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 were manually preprocessed. Recordings lasting for at least 18 hours and of sufficient quality for evaluation were included in the analysis. In case these criteria were not achieved, the recordings were repeated.

Time-domain HR variability indices, namely 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-minute NN intervals over the entire recording), the SDANN (standard deviation of the average NN intervals calculated over 5-minute periods of the entire recording) and the pNN50 (proportion of adjacent R-R intervals differing by >50 milliseconds in the 24-hour recording) were 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 (1).

The frequency-domain analysis of HRV included the total power, high frequency (HF) component (0.15-0.40 Hz), low frequency (LF) component (0.04-0.15 Hz) and very low frequency (VLF) component (0-0.04 Hz). The normalized HF power (HFnu=100xHF power/total power), normalized LF power (LFnu=100xLF power/total power) and low/high frequency power ratio (LF/HF ratio=LF power/HF power) were measured to give the relative changes in the frequency-domain. Spectral analysis was performed with short-segments with averaging of parameters.

Heart rate turbulence parameters were calculated using an algorithm adapted from the Web page popularizing the noncommercial use of HRT (http://www.h-r-t.org). The turbulence onset which is a measure of the expected normal early sinus acceleration after a ventricular premature beat and the turbulence slope which is a measure of late sinus deceleration after a ventricular premature beat constitute the two components of HR turbulence. After manual review of the 24-hour Holter tracings, turbulence onset and turbulence slope were determined according to the previously published method (2, 21). A turbulence onset value below 0 % indicates early sinus acceleration and is considered normal and a turbulence slope value above 2.5 ms/R-R interval indicates the normal expected late deceleration.

Statistical analysis

The SPSS statistical software (SPSS for windows 15, Inc., Chicago, IL, USA) was used for all statistical calculations. Continuous variables are given as mean±SD; categorical variables were defined as percentages. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Continuous variables of normally and non-normally distributed data were compared with an independent samples t-test and Mann-Whitney U test, and the χ^2 test was used for the categorical variables. Logistic regression analysis was used to detect effects of study variables on functional status. The HRV and HRT variables which showed difference between the 2 groups were then subjected to analysis of covariance (ANCOVA) to verify the influence of CRT on results obtained in the parametric tests (independent t-test). All tests of significance were two-tailed. Statistical significance was defined as p<0.05.

Results

Baseline characteristics

One hundred and five patients according to the above-mentioned criteria were included in our study. Of these 105 patients; 55 had a CRT and 50 had an ICD device. The baseline characteristics of these patients are summarized in Table 1.

Among ICD patients with HF, 29 (58.0%) received the device for primary prevention, the rest 21 (42.0%) for secondary prevention (clinically significant cardiac arrhythmias or sudden cardiac death). When we look through the CRT patients, 10 (18.2%) had CRT devices without cardioversion-defibrillation feature (CRT-P). Among the patients with CRT-D, 17 (30.9%) had significant cardiac arrhythmias before implantation and 28 (50.9%) had the defibrillation feature for primary prevention. No significant difference was observed between groups by means of cardioversion-defibrillation indication (secondary prevention, p=0.4).

HRV and HRT parameters in both groups

The comparison between HRV and HRT parameters in 2 groups was also shown in Table 1. SDNN, SDANN, pNN50, and LFnu were similar in both groups, however RMSSD, pNN50, HFnu, LF/HF ratio, TS (p<0.05 for all) and albeit to a non-significant value TO were better in CRT group when compared with the ICD patients.

HRV and HRT parameters according to functional status

When the HRV and HRT parameters were compared according to functional status, patients in functional class II had significantly better parameters when compared to the ones in class III (p<0.05 for all) (Table 2). After the ANCOVA analysis was performed to eliminate the effects of functional status of the

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Table 1. Baseline characteristics and heart rate variability and heart rate turbulence parameters of the study population

Variables		ICD patients (n=50)	CRT patients (n=55)	*p
Age, years		62.9±7.8	62.7±9.4	NS
Male, n (%)		39 (78.0)	45 (81.8)	NS
Ischemic etiology, n (%)		37 (74.0)	39 (70.9)	NS
NYHA	Class II	35 (70.0)	40 (72.7)	NS
	Class III	15 (30.0)	15 (27.3)	NS
Hypertension, n (%)		29 (58.0)	29 (53.7)	NS
Diabetes mellitus, n (%)		11 (22.0)	15 (27.8)	NS
Smoking history, n (%)		16 (32.0)	14 (25.5)	NS
Medications				
ACE inhibitors/ARB's, n (%)		47 (94.0)	52 (94.5)	NS
β-blockers, n (%)		45 (90.0)	50 (90.1)	NS
Statins, n (%)		39 (78.0)	45 (81.8)	NS
Nitrates, n (%)		48 (96.0)	54 (98.2)	NS
Aspirin/Clopidogrel, n (%)		9 (18.0)	8 (14.5)	NS
Diuretics, n (%)		43 (89.6)	48 (87.3)	NS
SBP, mm Hg		118.7±18.5	121.7±16.4	NS
DBP, mm Hg		75.1±10.7	76.6±9.4	NS
Pulse, beats/min		73.2±12.4	72.6±15.4	NS
LVEF, %		26.5±5.1	25.4±4.2	NS
Time from implantation of device, months		20.2±10.3	19.7±12.4	NS
Mean RR interval, msec		815.0±139.1	829.6±116.8	NS
Time-domain heart rate variability parameters				
SDNN, msec		90.6±30.1	93.5±27.5	NS
SDANN, msec		78.2±27.2	78.5±28.0	NS
SDNN index, msec		43.1±11.9	44.0±11.1	NS
RMSSD, msec		27.7±9.6	37.5±11.6	<0.001
pNN50, %		5.8±5.4	12.4±7.8	<0.001
Frequency-domain heart rate variability parameters				
LFnu		29.1±18.6	29.9±16.2	NS
HFnu		10.6±9.8	15.9±11.2	0.011
LF/HF ratio		4.9±4.3	2.8±2.1	0.002
Heart rate turbulence parameters				
Turbulence onset		0.4±1.4	-0.4±2.5	0.06
Turbulence slope, msec/RR		2.2±1.6	4.0±2.4	<0.001

Data are expressed as mean±SD and number of patients and percentages.
*t-test for independent samples and Chi-square test for categorical variables
ACE - angiotensin converting enzyme, ARB - angiotensin II receptor blocker, SBP-Systolic blood pressure, CRT - cardiac resynchronization therapy DBP - diastolic blood pressure, HF - high frequency power, HFnu - normalized high frequency power, ICD - intracardiac-cardioverter defibrillator, LFnu -normalized low frequency power, LF - low frequency power, LVEF - left ventricular ejection fraction, NS-not significant, NYHA - New York Heart Association, pNN50 - proportion of adjacent R-R intervals differing by >50 milliseconds in the 24-hour recording, 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 2. Heart rate variability and heart rate turbulence parameters according to the functional status of the patients

Variables	NYHA class II (n=75)	NYHA class III (n=30)	*p
Mean RR interval, msec	835.6±114.6	790.4±152.4	0.10
Time-domain heart rate variability parameters			
SDNN, msec	103.6±23.9	63.4±17.1	<0.001
SDANN, msec	88.8±24.5	52.3±14.5	<0.001
SDNN index, msec	46.7±10.8	35.7±9.1	<0.001
RMSSD, msec	34.3±11.7	29.2±11.0	0.04
pNN50, %	10.2±7.8	7.8±6.2	0.03
Frequency-domain heart rate variability parameters			
LFnu	26.6±16.3	36.9±17.6	0.005
HFnu	14.1±11.2	11.6±9.9	0.26
LF/HF ratio	3.3±3.3	5.1±3.8	0.02
Heart rate turbulence parameters			
Turbulence onset	-0.3±2.3	0.6±1.5	0.04
Turbulence slope, ms/RR	3.4±2.2	2.4±2.1	0.02

Data are expressed as mean±SD and number of patients and percentages.
*t-test for independent samples
HF - high frequency power, HFnu - normalized high frequency power, LF - low frequency power, LFnu - normalized low frequency power, NS - not significant, NYHA - New York Heart Association, pNN50 - proportion of adjacent R-R intervals differing by >50 milliseconds in the 24-hour recording, RMSDD - square root of the mean squared differences of successive normal-to-normal intervals, 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

patients, the HRV and HRT parameters which were different from each other in 2 groups, namely RMSSD, pNN50, HFnu, LF/HF ratio, TO and TS were still significantly better in CRT group ($p<0.05$ for all) (Table 3).

Determinants of functional status in both groups

The effects of study variables (CRT or ICD implantation, baseline characteristics, HRV and HRT parameters) on functional status were also studied with logistic regression analysis (Table 4). In this analysis, only SDNN was found to be significantly related with functional status [OR: 0.89 (95% CI: 0.80-0.98), p=0.03].

Discussion

The main finding of our study is that HRV and HRT parameters mostly affected from parasympathetic system (RMSSD, pNN50, HFnu, TO and TS) are better in the CRT group however those parameters mainly related to sympathetic system activation (SDNN, SDANN, SDNN index and LFnu) are similar in CRT and ICD patients who had similar functional capacity. Accordingly, it may be understood that upgrading to CRT may have an additional benefit on autonomic functions (mainly the parasympathetic system) aside from the improvement of the HRV and HRT parameters in concordant with recovered functional capacity.

Table 3. Some heart rate variability and heart rate turbulence parameters in 2 groups after adjustment for functional capacity of the patients

Variables	ICD patients (n=50)	CRT patients (n=55)	*p
Time-domain heart rate variability parameters			
RMSSD, msec	27.8±1.5	37.4±1.4	<0.001
pNN50, %	5.9±0.9	12.3±0.9	<0.001
Frequency-domain heart rate variability parameters			
HFnu	10.6±1.5	15.9±1.4	<0.001
LF/HF ratio	5.0±0.5	2.9±0.4	<0.001
Heart rate turbulence parameters			
Turbulence onset	0.4±0.3	-0.4±0.3	0.025
Turbulence slope, msec/RR	2.2±0.3	4.0±0.3	<0.001

*Data are expressed as mean ± SD and number of patients and percentages.
Adjustment for functional status of the patients was performed with analysis of covariance (ANCOVA).
CRT - cardiac resynchronization therapy, HF - high frequency power, HFnu - normalized high frequency power, ICD - intracardiac-cardioverter defibrillator, LF - low frequency power, RMSDD -square root of the mean squared differences of successive normal-to-normal intervals, pNN50 - proportion of adjacent R-R intervals differing by >50 milliseconds in the 24-hour recording

Table 4. The effects of study parameters on functional status of patients after logistic regression analysis

Variables	Odds Ratio (95% C.I.)	p
SDNN, msec	0.89 (0.80-0.98)	0.03
SDANN, msec	0.98 (0.89-1.09)	0.75
SDNN index, msec	0.95 (0.84-1.07)	0.37
RMSSD, msec	1.10 (0.86-1.33)	0.35
pNN50, %	0.75 (0.52-1.09)	0.13
LFnu	1.05 (0.99-1.11)	0.08
HFnu	0.96 (0.87-1.06)	0.44
Turbulence onset	1.35 (0.87-2.09)	0.18
Turbulence slope, msec/RR	1.01 (0.65-1.56)	0.97
Age	0.96 (0.87-1.06)	0.38
Diabetes mellitus	3.57 (0.47-27.4)	0.22
Hypertension	0.60 (0.07-4.81)	0.63
Ischemic etiology	0.98 (0.13-7.53)	0.98
Ejection fraction	1.09 (0.90-1.33)	0.36
ICD or CRT implantation	0.55 (0.05-5.90)	0.62

HFnu-normalized high frequency power, LFnu-normalized low frequency power, pNN50- proportion of adjacent R-R intervals differing by >50 milliseconds in the 24-hour recording, 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

HF is a disease characterized by sympathetic activation and sympatovagal disturbance resulting in autonomic dysfunction. It is a well-known fact that the level of sympathetic activation is both a cause and a marker of the hemodynamic status and symptomatology of HF patients (22). Blocking the sympathetic system activation by drugs like beta- blockers improves functional status and prognosis. These drugs have been also shown to improve the HRV and HRT parameters (4, 6) which are closely related with the prognosis and degree of sympathovagal imbalance. In addition to beta- blockers, some drugs used in HF treatment have been also shown to improve HRV and HRT parameters (5, 23, 24).

In the literature, it was disclosed that CRT improved HRV and HRT parameters which were calculated with either ambulatory Holter monitoring or the CRT device itself (7-9, 13-16). In these studies, patients who were clinically good responders to CRT (improved functional capacity, improved ejection fraction, etc) had an improvement in the HRV and HRT parameters and those patients whose HRV and HRT parameters were not improved, did not get better by means of symptoms. In this study, we enrolled patients who were good responders to CRT and compared the HRT and HRV parameters with the patients with NYHA class II-III symptoms who were implanted ICDs.

Among the time-domain HRV parameters, SDNN, SDANN and SDNN index were found to be similar in both groups. The effect of short term respiratory variations in heart rate which is assumed to be vagally mediated is very low and these parameters are thought to be mostly effected by the sympathetic system activity (25). LFnu, a frequency-domain HRV parameter well-known to reflect sympathetic activity, was also similar in both groups. One of the most reliable parameters, SDNN, was not different between the ICD and CRT groups. However, this parameter was the only parameter, which was found to be related with functional status of the patients after regression analysis. We thought that SDNN was similar in both groups because the study population was selected from the patients with similar functional status. Thus, it might be said that the sympathetic activation of both CRT and ICD groups were alike and this might be a consequence of the same functional status in both groups. We postulated this relationship in concordance with the previous studies (11, 12) and in our study; we also disclosed that those parameters related to sympathetic nervous system activation were significantly different between groups when patients were categorized according to their NYHA functional class. However, a prospective study in which the effects of CRT on both functional capacity and HRV and HRT parameters would be more valuable to prove this relationship.

TO denotes the acceleration of sinus rate immediately after a ventricular premature beat and is known to be due to vagal withdrawal (26). Delayed sympathetically mediated vasomotor response to the initial loss of cardiac output after ventricular extrasystole produces systolic blood pressure overshoot that subsequently induces vagally mediated late heart rate deceleration. This deceleration is denoted as TS. TO, albeit to a statistically non-significant degree and TS were both found to be improved in CRT group when compared with the ICD group. HFnu, a frequency-domain HRV parameter mostly related to

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parasympathetic activity, was also found to be higher in CRT group. Among the time-domain HRV parameters, RMSSD and pNN50, which are supposed to be quite robust parameters of vagally mediated HRV, were also significantly higher in the CRT group. These findings constitute evidence for the advanced parasympathetic system activation in patients with CRT. Why these parameters were found to be better in CRT group should be explained by further studies.

Study limitations

Due to the cross-sectional design of our study, it has some limitations. As we did not know the initial HRV and HRT parameters in CRT patients, we assumed that they had been improved with functional status. This assumption was strongly supported with the previous studies (13-16) showing improved HRV and HRT parameters in CRT responders. Similarly, an improvement might be achieved in ICD patients with a placebo effect. By including ICD patients instead of HF patients without implantable devices, we thought that the placebo effect of the implantable devices might be eliminated. Besides, as we described above, because of the cross-sectional design of this study, we cannot clearly say that, upgrading to CRT improves HRV and HRT parameters as a result of the improvement of functional capacity with CRT. Therefore, a prospective study in which the effects of CRT on both functional capacity and HRV and HRT parameters would be more valuable.

Conclusion

The most striking finding in our study is that HRV and HRT values related with parasympathetic activation are better in CRT patients when compared to ICD patients with similar functional status. Therefore, upgrading to CRT may have additional benefits on autonomic functions, which needs further investigation.

Conflict of interest: None declared.

Peer-review: External peer-review.

Authorship contributions: Concept - U.A., M.M.B., İ.K.; Design - U.A., M.M.B., T.Ç.; Supervision - U.A., A.T.; Resource - S.K., A.T.; Materials - T.Ç., İ.K., S.K.; Data collection&/or Processing - T.Ç., U.A., İ.K.; Analysis &/or interpretation - U.A., M.M.B., A.T.; Literature search - U.A., T.Ç., S.K.; Writing - U.A., M.M.B., İ.K.; Critical review - U.A., A.T.

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