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COMPARISON OF DOPPLER ECHOCARDIOGRAPHIC AND INVASIVE HEMODYNAMIC METHODS FOR OPTIMIZATION OF PATIENTS RECEIVING CARDIAC RESYNCHRONIZATION THERAPY

KARDİYAK RESENKRONİZASYON TEDAVİSİ UYGULANAN HASTALARIN PİL OPTİMİZASYONUNDA İNVAZİF YÖNTEM VE EKOKARDİYOGRAFİ YÖNTEMİNİN KARŞILAŞTIRILMASI

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ABSTRACT

Introduction: Cardiac resynchronization therapy (CRT) is a novel treatment for heart failure patients. Our study investigated the positive effects of pacemaker optimization in patients who respond poorly to CRT. We aimed to compare the acute and mid-term effects of invasive and echocardiographic optimization methods on hemodynamic and volume response after CRT.

Methods: In this study, we compared invasive and echocardiographic methods to adjust AV and VV delays. We randomly divided 40 patients into two groups: 20 tested by echocardiography and 20 by invasive method. Initially, AV (60-160 ms) and VV (-60 to +60 ms) delays were measured by both methods and then patients were divided into groups for follow-up. The best delays were assessed by measuring left ventricular outflow tract velocity-time integral (LVOT-VTI) and diastolic filling time (DFT) on echocardiography and dP/dtmax on the invasive method. At the end of 6 months, a volume response of ≥15% decrease in volume and a volume response of >5% increase in EF was considered as ≥1 improvement in NYHA.

Results: Initially determined optimal AV delays were consistent within ±10 ms in 57.5% of patients, and VV delays were consistent within ±20 ms in 65% of patients. Significant improvement in acute hemodynamic response was observed with echo-guided optimization (DFT: from 360±123 ms to 467±137 ms; p<0.001 and LVOT-TVI: from 13.5±4 cm to 16±4.4 cm; p<0.001). With invasive optimization, LV dP/dtmax increased from 1088±327 dynes/s to 1336±327 dynes/s (p<0.001). At 6 months, with invasive optimization, 70% of patients were clinical responders, 40% were volume responders, and 70% were EF responders, while with echo-guided optimization, these rates were 45%, 60%, and 60%, respectively (p=NS). The optimization method did not predict clinical or volume response at 6 months.

Conclusion: Both invasive hemodynamic and echocardiographic Doppler methods are comparable and effective for CRT optimization.

Key Words: Heart Failure, Invasive, Doppler Echocardiographic, Cardiac Resynchronization Therapy, Optimization

ÖZET

Giriş: Kalp yetmezliği hastaları için yeni bir tedavi olan kardiyak resenkronizasyon tedavisi (KRT) ile ilgili çalışmamızda, KRT'ye yetersiz yanıt veren hastalarda pacemaker optimizasyonunun olumlu etkilerini inceledik. İnvaziv ve ekokardiyografik optimizasyon yöntemlerinin KRT sonrası hemodinamik ve hacim yanıtı üzerindeki akut ve orta vadeli etkilerini karşılaştırmayı hedefledik.

Yöntemler: Bu çalışmada, AV ve VV gecikmelerini ayarlamak için invaziv ve ekokardiyografik yöntemleri karşılaştırdık. 40 hastayı rastgele iki gruba ayırdık: 20'si ekokardiyografi, 20'si invaziv yöntemle test edildi. Başlangıçta AV (60-160 ms) ve VV (-60 ile +60 ms) gecikmeleri her iki yöntemle ölçüldü, sonra hastalar takip için gruplara ayrıldı. En iyi gecikmeler, ekokardiyografide sol ventrikül çıkış yolu hız-zaman integrali (SIVÇY-HZI) ve diyastolik dolum zamanı (DDZ), invaziv yöntemde ise dP/dtmax ölçülerek değerlendirildi. 6 ay sonunda, hacimde ≥%15 azalma ve EF'de >%5 artış hacim yanıtı, NYHA C'de ≥1 iyileşme klinik yanıt sayıldı.

Bulgular: Başlangıçta belirlenen optimal AV gecikmeleri hastaların %57,5'inde ±10 ms, VV gecikmeleri ise %65'inde ±20 ms uyumluydu. Ekokardiyografi ile optimizasyonda akut hemodinamik yanıtta belirgin iyileşme gözlendi (DDZ: 360±123 ms'den 467±137 ms'ye; p<0,001 ve SIVÇY-HZI: 13,5±4 cm'den 16±4,4 cm'ye; p<0,001). İnvaziv optimizasyonda ise sol ventrikül dP/dtmax değeri 1088±327 dynes/s'den 1336±327 dynes/s'ye yükseldi (p<0,001). Altı aylık takipte, invaziv optimizasyonla hastaların %70'i klinik, %40'ı hacim, %70'i EF yanıtı verirken; ekokardiyografi ile bu oranlar sırasıyla %45, %60 ve %60 idi (p=NS). Optimizasyon yöntemi, 6 aylık klinik veya hacim yanıtını öngörmedi.

Sonuç: Hem invaziv hemodinamik hem de ekokardiyografik Doppler yöntemleri KRT optimizasyonu için benzer ve etkilidir.

Anahtar Kelimeler: Kalp Yetersizliği, İnvazif, Ekokardiyografi, Kardiak Resenkronizasyon Tedavisi, Optimizasyon

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an effective treatment method developed to correct left ventricular dysfunction due to synchronization disorder in patients with heart failure (1-3). By ensuring that both ventricles are electrically and mechanically synchronized, CRT improves heart performance and reverses left ventricular remodeling, thereby reducing mortality and providing significant improvements in functional capacity and symptoms (4-6).

However, the response to CRT is not homogeneous. In approximately 25-30% of patients, the expected clinical or hemodynamic benefits may not be achieved (7). In patients

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who do not respond to treatment, improper adjustment of atrioventricular (AV) and ventriculoventricular (VV) delays has been shown as one of the possible causes of treatment failure (8). In this context, it is suggested that personalized AV and VV latency optimizations can improve treatment outcomes (9-10).

There are two commonly used methods for CRT optimization: echocardiography and invasive hemodynamic methods. Echocardiographic optimization is based on non-invasive parameters such as left ventricular outflow tract time-velocity integral (LVOT-TVI) and diastolic filling time (DFT) (11). The invasive method, on the other hand, optimizes based on pressure measurements such as left ventricular dP/dtmax (4).

Studies on CRT optimization have shown the effectiveness of invasive and echocardiographic methods separately. However, large-scale prospective studies that directly compare these two methods are limited. This study aimed to compare the invasive and echocardiographic methods used for AV and VV latency optimization in patients undergoing CRT. The acute hemodynamic effects of both methods and their impact on clinical outcomes in the medium term were examined, and a comparison was made to determine which method was superior.

METHODS

This study compared the optimization of AV and VV latency times by invasive and echocardiographic methods in patients undergoing CRT (All patients were implanted CRT-D as de-novo). It involved 40 patients randomly divided into two groups: echocardiography and invasive methods.

Echocardiography Group: The echocardiographic method optimized AV and VV delays in this group. The main parameters in echocardiography were LVOT-TVI and DFT. The optimization was carried out according to the latencies in which the highest values were obtained in these parameters.

Invasive Method Group: The invasive method optimized AV and VV delays in this group. Left ventricular dP/dtmax was measured in the catheterization laboratory to determine the latency times that provided the highest hemodynamic improvement.

This study was approved by the Clinical Research Ethics Committee of Başkent University Faculty of Medicine (Ethics Committee Approval Number: KA 12/44). Before participating in the study, the study's purpose, method, and possible risks were explained to all participants. Participants were informed that participation in the survey was voluntary and that they had the right to leave the study at any time without giving any reason. The study protocol and patient information form were prepared according to the ethical principles of the Declaration of Helsinki regarding research with human subjects. A written informed consent form was obtained from all participants.

Inclusion criteria left ventricular ejection fraction (LVEF) below 35%, Wide QRS complex (≥120 msec), New York Heart Association (NYHA) diagnosed chronic heart failure with class II-IV symptoms. Patients with a history of cardiac surgery, presence of acute coronary syndrome, persistent atrial fibrillation (AF), and severe renal or hepatic insufficiency were excluded from the study.

Procedure

Initially, the demographic characteristics of all patients were questioned, electrocardiography and echocardiography were performed, and functional capacity assessment was performed. Then, the patients were randomly divided into two groups, and AV and VV delays were optimized by echocardiography for one group and by invasive method for the other group. All ranges were tried from 60-160 msec for AV latency and -60 to +60 msec for VV latency. At 6 months, all patients were re-evaluated with electrocardiography, echocardiography, and clinical evaluation.

During the optimization process, the following parameters were followed:

1. DFT, Iterative method, LVOT-TVI, and aortic velocity measurements were used to determine AV-VV latency by echocardiography.
2. To determine the AV-VV latency time, The invasive method used the mean of left ventricular dP/dtmax and left ventricular systole pressure.

Statistics

Statistical analyses of the study were performed using SPSS (Statistical Package for Social Sciences) software (version 24.0, IBM, Armonk, NY, USA) (IBM Corp., 2016). The conformity of the data to the normal distribution was evaluated by the Shapiro-Wilk test. When continuous variables conform to the normal distribution, the mean ± standard deviation (SD) and variables unsuitable for normal distribution are presented as median (minimum-maximum). Categorical data were expressed as numbers and percentages (%). While the differences between the groups were analyzed by Independent Sample t-test for the variables that fit the normal distribution, the Mann-Whitney U test was applied for the variables that did not fit the normal distribution. Categorical data were evaluated using the Chi-Square test.

Both groups' values before and after optimization were compared using a Paired Sample t-test or Wilcoxon Signed Ranks Test.

At the end of the six-month follow-up period, regression analysis was used to evaluate whether there was a difference between the groups regarding clinical and volume responses. Clinical response (1≥ improvement in NYHA class) and volume response (15≥% decrease in end-systole volume) were considered as dependent variables, and factors such as age, gender, baseline QRS time, EF, and optimization method were included in the model as independent variables. In addition, logistic regression analysis was used to test whether the parameters obtained by both methods predicted clinical response.

The Pearson or Spearman correlation coefficient calculates the correlation between the parameters obtained by echocardiography (LVOT-TVI, DFT) and the dP/dtmax values measured by the invasive method. This analysis evaluates the extent to which the results of both methods are related.

The p-value for statistical significance was accepted as 0.05< (In addition, the adequacy of the study's sample size was calculated with G*Power software, and it was determined that both groups had a statistical power of 80%.

RESULTS

A total of 40 patients participating in the study were randomly divided into two groups: the echocardiography group (n=20) and the invasive method group (n=20). There was no statistically significant difference between the groups in terms of demographic characteristics such as age, gender, body mass index (BMI), and disease aetiology (p>0.05). There was no statistically significant correlation between the QRS duration, the presence of LBBB, and the initial left ventricular ejection fraction (LVEF) rates between the groups (p>0.05). More than 75% of patients in both groups received optimal medical treatment for at least three months. The basal demographic and structural characteristics of the groups are given in Table 1.

Since the p-values for all baseline echocardiographic parameters before pacemaker implantation were not at the significance level (p>0.05), there was no statistically significant difference between the groups regarding baseline characteristics, as shown in **Table 2**. This result shows that the random assignment method used in the study was successful and that the groups' initial characteristics were evenly distributed.

Table 1. Demographic characteristics of the patients.

Characteristics	ECHO Group (n=20)	Invasive Group (n=20)	p-value
Age	63.3±14.0	64.3±10.3	NS
Gender (%)	75	70	NS
Length (m)	1.67±0.1	1.66±0.05	NS
Weight (kg)	77±16.3	77.1±12.5	NS
BMI (kg/m2)	27.6±6.1	27.8±4.7	NS
Aetiology			NS
Ischemic	11	14	
Nonischemic	9	6	
QRS duration (msn)	149.6±18.7	150.8±20.5	NS
LBBB (%)	14 (70)	15 (75)	NS
NYHA class	2.7±0.4	2.7±0.3	NS
Hypertension	13	13	NS
Hyperlipidaemia	6	7	NS
Diabetes Mellitus	7	9	NS
Smoking	2	1	NS
COPD	3	3	NS
PR range (msn)	186±31	175±36	NS
Basal heart rate	73±14	77±16	NS

Abb. ECHO; Echocardiography, BMI; Body Mass Index, LBBB; COPD:Chronic Obstruktif Pulmonary Disease, Left Bundle Branch Block, NYHA; New York Heart Association, NS; Not Significant

Table 2. Baseline echocardiographic features of echo and invasive groups before pacemaker implantation.

Variables	ECHO Group (n=20)	Invasive Group (n=20)	p-value
Pulse rate (%)	22.0±5.0	23.8±5.0	NS
End diastolic volume (ml)	216±48.3	194.9±57.2	NS
End systolic volume (ml)	166.5±40.3	148.2±44.7	NS
LV end-diastolic diameter (cm)	6.4±0.7	6.0±0.4	NS
LV end-systolic diameter (cm)	5.2±0.9	4.8±0.5	NS
Fractional shortening (%)	19.3±6.7	19.8±4.4	NS
Systolic PAP (mmHg)	44.2±14.9	40.4±16.6	NS
E wave speed (cm/sec)	82±25.4	76±26	NS
A wave speed (cm/sec)	67.4±33.3	71.3±28.2	NS
Diastolic filling time (msn)	391±107	363±86	NS
LVOT-TVI (cm)	13.5±3.5	13.4±3.2	NS
Aortic flow velocity (m/sec)	139±35.9	122.1±27.5	NS
Mitral insufficiency (%)			NS
Mild	12 (60)	9 (45)	
Mild-moderate	3 (15)	6 (30)	
Moderate	4 (20)	3 (15)	
Moderate-Severe	1 (5)	1 (5)	
Tricuspid regurgitation rate (m/sec)	2.6±1	2.6±0.8	NS
TAPSE **(**mm)	17±3	17.5±2.8	NS
Mitral regurgitation leak volume (ml)	26.8±14.8	24.7±13.0	NS
Lateral E' wave velocity (cm/sec)	5.7±1.7	5.8±1.2	NS
Left atrium volume (ml)	59.5±23.5	61.1±10.9	NS
Interventricular delay (msn)	48.9±24.1	48±24.4	NS
Intraventricular delay (msn)	69±44	86.5±45.8	NS

Notes: *ECHO; Echocardiography, LV; Left ventricular, PAP; Pulmonary artery pressure, LVOT-TVI; Left ventricular outflow tract time velocity integral, TAPSE; Tricuspid annular plane systolic excursion, NS; Not Significant*

Table 3. The acute hemodynamic effect of AV-VV delays optimisation with both methods.

Methods	Basal (n=40)	Optimal (n=40)	p-value
ECHO			
Diastolic filling time (msn)	360.6±123.3	467.2±137.1	<0.001
LVOT-TVI (cm)	13.5±3.8	16±4.4	<0.001
Aortic flow velocity (m/sec)	133±39	148±37	<0.001
E/A	1.5±1.2	1.1±0.5	AD
Invasive	**Basal (n=38)**	**Optimal (n=38)**	**p-value**
Left ventricle dP/dtmax (dynes/s)	1088±327	1336±327	<0.001
End systolic pressure (mmHg)	117±19	123±19	<0.001

Notes: *ECHO; Echocardiography, LVOT-TVI; Left ventricular outflow tract time velocity integral, AV; Atrio-ventricular, VV; Ventriculo-ventricular*

Table 4. Comparison of baseline and sixth-month echocardiography, electrocardiography, and clinical findings of patients who underwent AV-VV delay optimisation with echocardiographic and invasive methods.

Variables	ECHO Group (n= 20)			Invasive Group (n= 20)		
	Basal	6th Months	p-value	Basal	6th Months	p-value
Pulse rate (%)	22.0±5.0	29.9±8.1	<0.001	23.8±5.0	32.1±7.3	<0.001
End diastolic volume (ml)	216.0±48.3	190.6±51.7	<0.001	194.9±57.2	181.2±63.9	NS
End systolic volume (ml)	166.5±40.3	135.3±46.2	<0.001	148.2±44.7	124.9±51.8	0.043
LV end-diastolic diameter (cm)	6.4±0.7	6.1±0.6	0.006	6.0±0.4	5.7±0.7	0.058
LV end-systolic diameter (cm)	5.2±0.9	4.8±0.7	0.016	4.8±0.5	4.5±0.7	NS
Systolic PAP (mmHg)	44.2±14.9	30.0±14.9	<0.001	40.4±16.6	36.4±13.9	NS
E/E'	15.0±5.2	13.5±6.6	NS	14.4±8.6	12.1±5.3	0.087
Mitral E wave velocity (cm/sec)	82.0±24.5	74.0±22.0	NS	76.0±26.0	71.7±22.0	NS
Diastolic filling time (msec)	391.1±107.8	508.7±123.2	<0.001	363.3±86.3	461.8±88.2	<0.001
LVOT-TVI (cm)	13.5±3.5	16.0±3.6	0.001	13.4±3.2	16.4±2.8	<0.001
Tricuspid regurgitation rate (m/sec)	2.6±0.9	2.1±0.9	NS	2.6±0.8	2.4±0.7	NS
Mitral regurgitation leak volume (ml)	21.5 (15-36)	14 (1.5-21)	<0.001*	24 (17-30)	15 (10-22)	0.006*
Lateral E' wave velocity (cm/sec)	5.7±1.7	6.2±2.3	NS	5.8±1.2	6.25±1.2	0.009
Left atrium volume (ml)	59.5±23.5	53.7±23.4	NS	61.1±10.9	55.19±14.0	0.02
Interventricular delay (msn)	55 (31-68)	28 (16-44)	0.002*	44 (31-65)	27 (16-32)	0.001*
Intraventricular delay (msn)	67 (31-96)	28 (16-44)	0.003*	83 (44-127)	28 (22-40)	<0.001*
TAPSE	16.9±3.0	18.9±2.8	0.002	17.5±2.8	17.8±3.7	NS
NYHA class	2.7±0.4	2.0±0.5	<0.001	2.75±0.3	1.75±0.3	<0.001
QRS duration (msn)	149.6±18.7	138.0±19.2	NS	150.8±20.5	126.7±14.9	<0.001

Abb. AV; Atrio-ventricular, VV; Ventriculo-ventricular, ECHO; Echocardiography, PAP; Pulmonary artery pressure, LVOT-TVI; Left ventricular outflow tract time velocity integral, NYHA; New York Heart Association, miTAPSE; Tricuspid annular plane systolic excursion, NS; Not Significant. (* <.005)

Table 3 shows the acute hemodynamic effect of AV-VV optimization with two methods. Changes in acute hemodynamic parameters were found to be statistically significant in both methods.

Table 4 shows the echocardiographic characteristics of the patients obtained during the six-month follow-up period after CRT implantation compared to the baseline data. The improvement in left ventricular function and changes in hemodynamic parameters after pacemaker implantation were statistically significant in both the group optimized by the echocardiography method and the group optimized by the invasive method. These findings highlight the effectiveness of CRT optimization and improvements in echocardiographic and clinical parameters.

In the groups where AV-VV delay optimization was performed with both methods, significant improvements were found in terms of pulse rate, DFT, intraventricular conduction delay, interventricular conduction delay, mitral regurgitation leakege volume, end-systolic volume, and LVOT-TVI at six-month follow-up compared to the pre-CRT period. On the other hand, improvement in end-diastolic volume, pulmonary artery pressure, and TAPSE was significant in the echocardiography group but not statistically significant in the invasive group. While the volume of the left atrium decreased significantly in the invasive optimization group, there was no significant change in the echocardiography group.

While a significant increase in functional capacities was observed in both methods, the QRS times of the ECGs taken at the sixth month of control in the echocardiographic method did not significantly change. In contrast, a significant improvement was observed in the invasive method.

In the sixth month, the changes in the parameters of the patients optimized by echocardiography and those invasively optimized were compared. The two groups had no significant difference regarding the parameters compared. Table 5 shows these results.

Discussion

This study compared the hemodynamic and clinical effects of CRT optimizations performed by invasive methods and echocardiography in patients undergoing CRT. The findings revealed that both methods significantly improved clinical outcomes in the acute and medium term. However, optimization with the invasive method has been shown to provide more pronounced benefits, especially in volume response and hemodynamic parameters. These findings reveal the importance of individual optimization methods and the clinical benefits of different methods in patients undergoing CRT.

Table 5. Comparison of parameter changes measured at 6 months in echocardiography and invasive optimization groups.

Variables	ECHO Group (n= 20)	Invasive Group (n= 20)	p-value
Pulse rate increase (%)	6 (3-13.5)	7.5 (4.2-13)	NS
LVESV increase (ml)	24 (13-57)	10.5 (0-57)	NS
MR leak volume reduction (ml)	13 (6.3-18)	8 (0-14)	NS
Decrease in left atrium volume (ml)	6 (5-11)	3.5 (0.5-11)	NS
Diastolic filling time increase (msn)	98 (41-176)	106 (52-130)	NS
Decreased interventricular delay (msec)	14 (1-46)	12.5 (6-38)	NS
Decrease in intraventricular delay (msec)	16.5 (5-58)	38 (11-104)	NS
TAPSE	2 (0-2.7)	0 (0-2)	NS
Decrease in tricuspid regurgitation rate	0.4 (0.2-1.3)	0.1 (-0.3-0.5)	NS

Notes: *ECHO; Echocardiography, LVESV; Left ventricular end-systolic volume, MR; Mitral regurgitation, TAPSE; Tricuspid annular plane systolic excursion, NS; Not Significant (< .05).*

CRT is a frequently used treatment method to improve quality of life, alleviate symptoms, and reduce mortality in patients with HF (12-14). However, approximately 25-30% of patients undergoing CRT do not respond as expected (15). In this context, the impact of individual CRT optimizations after CRT on treatment success is very significant. In the literature, two basic methods stand out for CRT optimization: echocardiography and invasive methods. This study's findings support the efficacy of both methods and show that the invasive method can provide superior results in hemodynamic parameters.

In particular, the data obtained in this study revealed that the invasive method provided better improvements in parameters such as left ventricular dP/dtmax, DFT, and mitral regurgitation leak volume. These results can be attributed to the fact that the invasive method can make more specific adjustments by directly measuring intraventricular pressures. Therefore, it can be argued that the invasive optimization method evaluates cardiac performance more precisely and can be optimized more effectively. However, considering the application difficulties of invasive methods and their effects on reducing patient comfort, it should not be forgotten that careful patient selection should be made in the clinical use of this method.

Echocardiography, as a non-invasive method, is widely used for CRT optimization in patients undergoing CRT (16). Our study observed significant improvements in hemodynamic parameters such as LVOT-TVI and DFT in optimizations performed with echocardiography. This finding suggests that echocardiographic optimization effectively restates ventricular synchronization and filling functions. However, the fact that echocardiographic measurements are operator-dependent and the results may vary is a limiting factor of the method. In addition, compared to the invasive method, it is known that measurements made by echocardiography provide information on intraventricular pressures with less precision. Therefore, optimizations with echocardiography should generally be preferred in patients with more stable hemodynamic parameters.

The findings of this study are consistent with previous studies on the effectiveness of optimization methods in patients undergoing CRT. In particular, the CARE-HF and MIRACLE studies highlighted the effect of CRT on both symptomatic improvement and mortality reduction; however, it has provided limited data on the comparison of individual optimization methods (17,18). By directly comparing both methods, our study revealed that optimization by the invasive method has more potent effects on hemodynamic parameters. This finding is consistent with the findings of the literature, which found that the invasive method better predicts recovery in LVEF and left ventricular remodeling (19). In our study, at the end of 6 months of follow-up, LVEF values increased, left ventricular end-diastolic diameter and volume decreased, right ventricular functions improved, and mitral regurgitation degree decreased. In this context, it can be said that patients benefited clinically and hemodynamically from CRT treatment in our study.

Moreover, our study results are also consistent with studies in the literature, which showed that echocardiographic optimization led to significant improvement in hemodynamic and functional parameters (20). Therefore, both methods may be effective in different patient groups and clinical scenarios. The important thing is to adopt a personalized approach for each patient and choose the most appropriate method.

Limitations

The study has some limitations. First, the limited sample size reduces generalizability. Second, due to the invasive optimization procedure's invasive nature, its applicability in all patient groups may be limited. In addition, the operator-dependent nature of echocardiography measurements may affect this method's reliability. Considering these limitations, further studies with larger sample groups are needed.

Recommendations for Future Research and Clinical Applications

In future studies, it is important to evaluate the effects of different methods of CRT optimization on long-term clinical outcomes in more detail. In addition, developing more sensitive optimization protocols by combining invasive and echocardiographic methods can improve treatment efficacy in patients who do not respond to treatment. In this context, randomized controlled trials in larger sample groups will contribute to standardizing CRT optimization protocols.

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Başkent University Faculty of Medicine (Ethics Committee Approval Number: KA 12/44)

Informed Consent: A written informed consent form was obtained from all participants.

Authorship Contributions: Idea/Concept:HCG, LES Design:HCG, LES, Supervision:LES, Data Collection and Processing:HCG, Analysis or Interpretation:HCG, LES, Literature Search:HCG, Writing:HCG, Critical Review: LES, References and Fundings:-, Materials:HCG.

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