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Cardiac Resynchronization Therapy and AV Optimization: A Hemodynamic Evaluation with Non-Invasive Techniques

Kardiyak Resenkronizasyon Tedavisi ve AV Optimizasyonu: Non-İnvaziv Tekniklerle Hemodinamik Değerlendirme

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ABSTRACT

Aim: This study aimed to evaluate the impact of atrioventricular (AV) optimization of biventricular pacemakers on cardiac hemodynamic parameters, particularly mitral inflow and aortic valve velocity-time integral (VTI), using impedance cardiography (ICG) and echocardiography in patients with symptomatic systolic heart failure and left bundle branch block unresponsive to cardiac resynchronization therapy.
Material and Methods: The study included 20 patients, 10 (50%) males and 10 (50%) females, aged between 18 and 80 years, who had undergone biventricular pacemaker implantation and did not have aortic stenosis, decompensated heart failure, or echocardiographically optimized AV interval measurements. Hemodynamic values were calculated following ICG measurements.
Results: The mean AV delay time did not change after AV optimization (p=0.685). However, optimization led to a statistically significant increase in mitral inflow VTI and aortic valve VTI (both p<0.001). No significant post-optimization variations were observed in hemodynamic parameters obtained by ICG compared to baseline measurements. There was a statistically significant decrease in heart rate when compared to the pre-optimization values (p=0.003).
Conclusion: This study identified a significant enhancement in echocardiographic parameters attributable to AV optimization. The results obtained with AV optimization were consistent with those of large-scale randomized studies. However, further comprehensive studies are needed to assess the individual patient responses and long-term outcomes.
Keywords: Cardiomyopathy; cardiac resynchronization therapy; artificial pacemaker; impedance cardiography; echocardiography.

ÖZ

Amaç: Bu çalışmada, semptomatik sistolik kalp yetmezliği ve kardiyak resenkronizasyon tedavisine yanıt vermeyen sol dal bloğu olan hastalarda, biventriküler kalp pillerinin atriyoventriküler (AV) optimizasyonunun, özellikle mitral doluş ve aort kapak hız-zaman integrali (VTI) olmak üzere, kardiyak hemodinamik parametreler üzerindeki etkisinin impedans kardiyografi (ICG) ve ekokardiyografi (ECHO) kullanarak değerlendirilmesi amaçlanmıştır.
Gereç ve Yöntemler: Çalışmaya, biventriküler kalp pili implantasyonu yapılmış olan ve aort darlığı, dekompanse kalp yetmezliği bulunmayan veya daha önce ekokardiyografik olarak AV interval optimizasyonu yapılmamış yaşları 18 ile 80 arasında, 10 (%50) erkek ve 10 (%50) kadın olmak üzere 20 hasta dahil edildi. Hemodinamik değerler, ICG ölçümlerini takiben hesaplandı.
Bulgular: AV optimizasyonu sonrası ortalama AV gecikme süresi değişmemiştir (p=0,685). Bununla birlikte, optimizasyon, mitral doluş VTI ve aort kapak VTI bakımından istatistiksel olarak anlamlı bir artışa neden olmuştur (her iki p<0,001). ICG ile elde edilmiş olan hemodinamik parametrelerde, başlangıç ölçümleri ile karşılaştırıldığında optimizasyon sonrası anlamlı bir değişim gözlenmemiştir. Kalp hızında ise optimizasyon öncesi değerler ile karşılaştırıldığında istatistiksel olarak anlamlı bir azalma olduğu saptanmıştır (p=0,003).
Sonuç: Bu çalışma, ekokardiyografik parametrelerde AV optimizasyonuna atfedilebilecek önemli bir iyileşme tespit etmiştir. AV optimizasyonu ile elde edilen sonuçlar, büyük ölçekli randomize çalışmalar ile tutarlılık göstermektedir. Bununla birlikte, bireysel hasta yanıtları ve uzun vadeli etkiler açısından değerlendirmek için daha kapsamlı çalışmalara ihtiyaç vardır.
Anahtar kelimeler: Kardiyomiyopati; kardiyak resenkronizasyon tedavisi; yapay kalp pili; empedans kardiyografi; ekokardiyografi.

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INTRODUCTION

Heart failure (HF) is a major cause of morbidity and mortality worldwide (1). Despite the implementation of optimal medical therapy (OMT), cardiac resynchronization therapy (CRT) has emerged as the preferred treatment modality for patients with symptomatic systolic HF accompanied by left bundle branch block (LBBB) (2). The 2021 European Society of Cardiology (ESC) guidelines further underscore the role of CRT in patients with left ventricular ejection fraction (LVEF) ≤35%, sinus rhythm, and QRS duration ≥150 ms, in conjunction with OMT (3). Moreover, based on robust evidence from multiple clinical trials, current guidelines advocate CRT for patients with an anticipated survival of at least one year, LVEF ≤35%, QRS duration ≥120 ms, and LBBB morphology. Notably, CRT is also recommended for patients with sinus rhythm and QRS duration ≥150 ms, irrespective of LBBB morphology (4-12). CRT represents a significant advancement in the management of chronic heart failure (CHF) and offers an effective therapeutic alternative, particularly for patients with advanced disease refractory to pharmacological interventions (13). Nevertheless, approximately 20-30% of patients do not exhibit a favorable response to CRT, despite the high success rates reported in large randomized controlled trials. In this context, clinical guidelines suggest considering biventricular pacemaker optimization in non-responders, based on findings from smaller randomized and observational studies (14,15). CRT is principally delivered via biventricular pacing (BiVP), wherein the left ventricular lead is typically positioned in the lateral or posterolateral tributary of the coronary sinus (4). Optimization of atrioventricular delay (AVD) through echocardiographic methods has been shown to enhance left ventricular filling in patients with biventricular pacemakers, while further adjustment of interventricular delay (VVD) has demonstrated additional improvements in cardiac output (CO). AVD optimization is a component of all major CRT trials and is endorsed in clinical practice guidelines (13). Although invasive techniques remain the gold standard for optimization, non-invasive methods are increasingly preferred owing to their practicality, safety, and cost-effectiveness (15).

In the present study, atrioventricular (AV) optimization was performed using echocardiographic techniques in patients who had previously undergone CRT device implantation. Hemodynamic changes resulting from the optimization process were subsequently evaluated using impedance cardiography (ICG), a non-invasive assessment method. It was hypothesized that AV optimization would exert a positive effect on hemodynamic parameters in patients with biventricular pacemakers following CRT. This study aimed to investigate the impact of echocardiographically guided AV optimization on hemodynamic performance assessed using ICG. By focusing on a non-invasive and accessible approach, this research seeks to contribute to the growing body of evidence regarding the role of device optimization in enhancing outcomes among CRT non-responders. Furthermore, the study highlights the potential utility of echocardiographic AVD and VVD optimization methods in improving cardiac function and underscores the value of non-invasive techniques as practical, cost-effective alternatives in clinical practice.

MATERIAL AND METHODS

The study included 20 patients, consisting of 10 (50%) males and 10 (50%) females, aged between 18 and 80, who had previously undergone biventricular pacemaker implantation. Ethics committee approval was received from Mersin University Clinical Research Ethics Committee with the decision number 2015/127. In this study, informed consent was obtained from all individual participants. Respondents were assured that their original data would be kept confidential and not shared. The study was conducted in accordance with the Principles of the Declaration of Helsinki. Patients with decompensated HF, aortic stenosis, or those who had undergone AV interval optimization via echocardiography (ECHO) were excluded. Additionally, individuals who did not sign the informed consent form were also excluded. The sample size calculation was performed using the G*Power 3.1.9.4 software. As no directly comparable prior study was identified in the literature to determine an empirical effect size for the primary outcome, the calculation was based on a medium effect size (0.50) in accordance with Cohen's convention (16). A priori power analysis was conducted with a significance level (α) of 0.05, power (1-β) of 0.80, and a one-tailed paired t-test, given that the hypothesis was directional, anticipating an improvement in cardiac hemodynamic parameters, particularly aortic valve velocity-time integral (VTI), following AV optimization. The minimum sample size was determined as 20 patients. AV interval measurements were performed using ECHO by experienced cardiologists, and ICG was recorded by experienced biophysicists at Mersin University Faculty of Medicine in a controlled clinical setting. The demographic and baseline parameters of all eligible patients were recorded following transthoracic ECHO and ICG assessments. During the study, all participants remained in a supine resting position. Among the total patients, 5 were diagnosed with ischemic cardiomyopathy, while 15 had non-ischemic cardiomyopathy. Based on these data, functional capacities were classified according to the New York Heart Association (NYHA) classification.

Echocardiography (ECHO)

The Philips Sonograph (HD 11XE, Eindhoven, The Netherlands) with a 3 MHz transducer was used to perform two-dimensional ECHO. Images of the heart were obtained in the standard parasternal long-axis, short-axis, and apical four-chamber planes. Left ventricular end diastolic and systolic dimensions and left atrial diameter were measured using M-mode echocardiograms in the parasternal long axis, according to the American Society of Echocardiography standards.

During apical 4-chamber imaging, the mitral diastolic filling time (in milliseconds), mitral E and A waves were recorded using PW by measuring the aortic valve VTI (in centimeters), which is an indicator of CO. Diastolic mitral insufficiency, the shape and size of the A wave in relation to the E wave were evaluated. Mitral E and A durations were measured. Patients with an evident but uninterrupted A wave and optimal diastolic filling time were considered optimized and excluded from the study (Figures 1 and 2).

Impedance Cardiography (ICG)

Hemodynamic parameters obtained non-invasively through ICG using the BIOPAC MP100 system were recorded with EBI 100C, DA 100C, and ECG100C

modules. Parameters such as Z_0 (base impedance), dZ_{max}/dt (maximum rate of change in impedance), left ventricular ejection time (LVET), and heart rate (HR) were measured (Figure 3). These parameters were utilized to calculate additional hemodynamic values, including thoracic fluid content (TFC), thoracic fluid content index (TFCI), total peripheral resistance (TPR), total peripheral resistance index (TPRI), contractility index (or inotropy index, IC), stroke volume (SV), stroke index (SI), CO, cardiac index (CI), and rate pressure product (RPP or myocardium oxygen consumption index, MVO_2I) (17). Four electrodes were strategically placed on the left side of the neck and thorax for impedance measurement, applying high-frequency (70 kHz) and low-amplitude current (2.5 mA) externally (18). The impedance changes were related to volume and tissue conductivity properties, and Bernstein's equations were used to derive SV (19). TFC was derived as $1/Z_0$, and total thorax conductivity was calculated as $1000/Z_0$. Volume of electrically participating thoracic tissue (VEPT), on the other hand, is the thorax volume that is included in an electrical manner. It is calculated by using the L3/4.25 ratio. Here, L (cm) is the distance between internal electrodes. The method involved recording mitral and tricuspid valve activities (S1), as well as aorta and pulmonary valve activities (S2), using a band-permeable filter and a heart sound microphone. LVET was determined from the time between S1 and S2 heart sounds, and the heartbeat rate was recorded using three ECG electrodes (20). Impedance changes due to body movements and respiration were eliminated during the 60-second recording, and maximum waveforms were used to obtain HR, Z_0, dZ_{max}/dt, and LVET. SV was calculated using the $SV = VEPT \times LVET / Z_0 \times dZ_{max}/dt$ Bernstein equation, and CO was $CO = SV \times HR$ (19). Ejection velocity index (EVI) and thoracic fluid index (TFI) are respectively referred to as dZ_{max}/dt and Z_0. The IC was

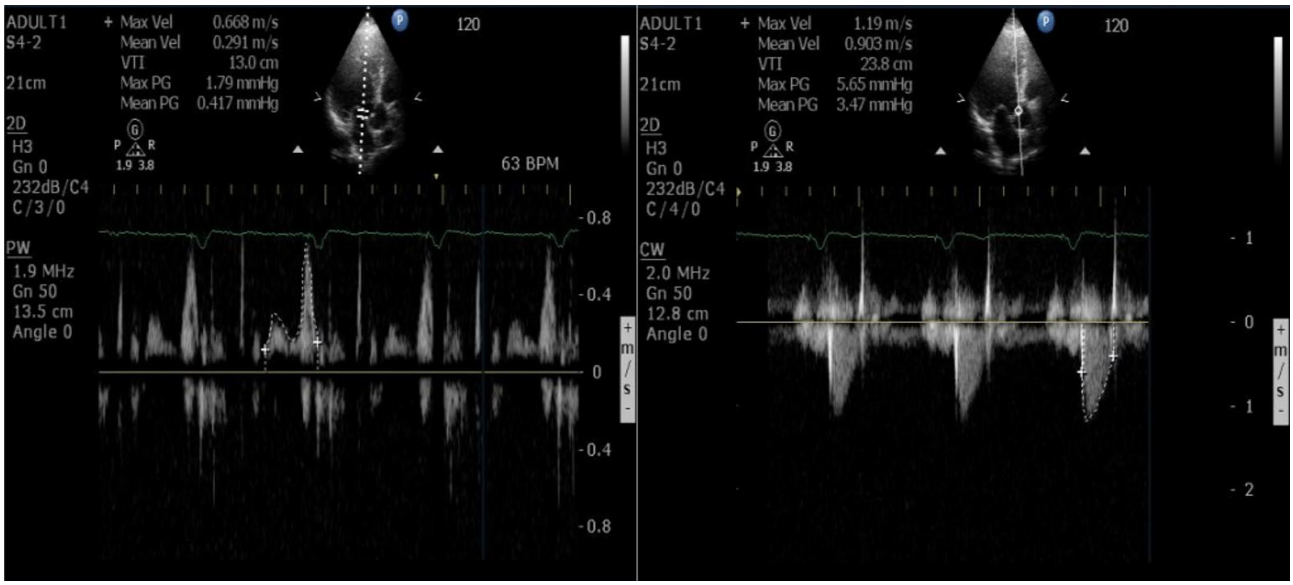


Figure 1. The echocardiography images of one of the patients included in the study

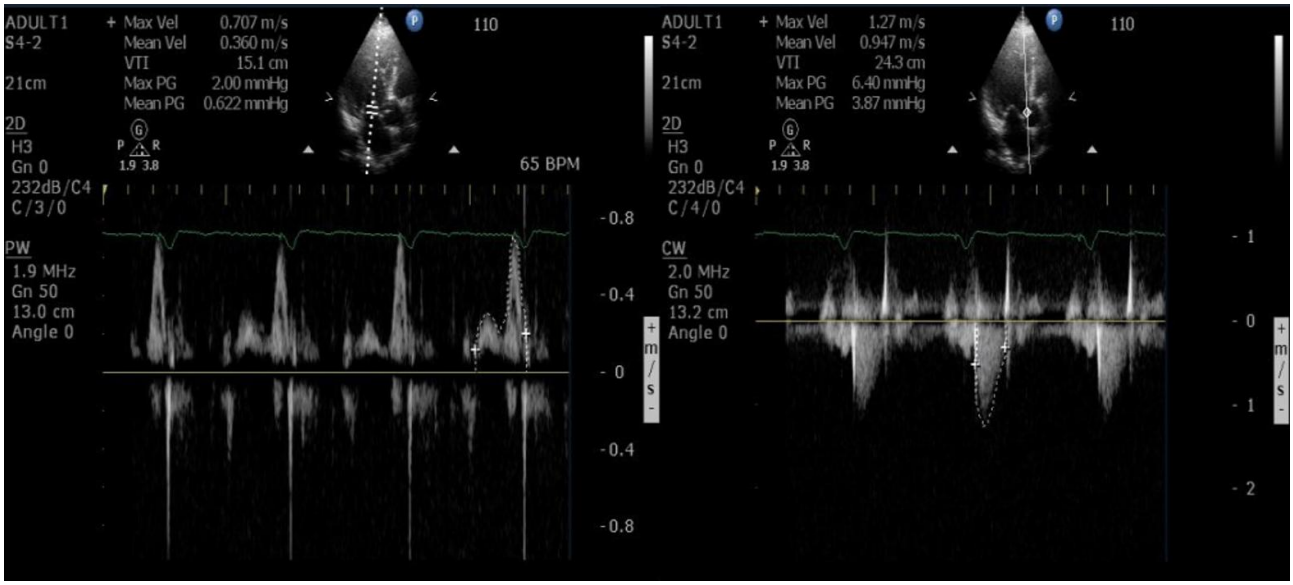


Figure 2. The echocardiography images of the same patient, belonging to atrioventricular delay (AVD) time from which the maximum aorta velocity-time integral (VTI) and mitral EA values were taken

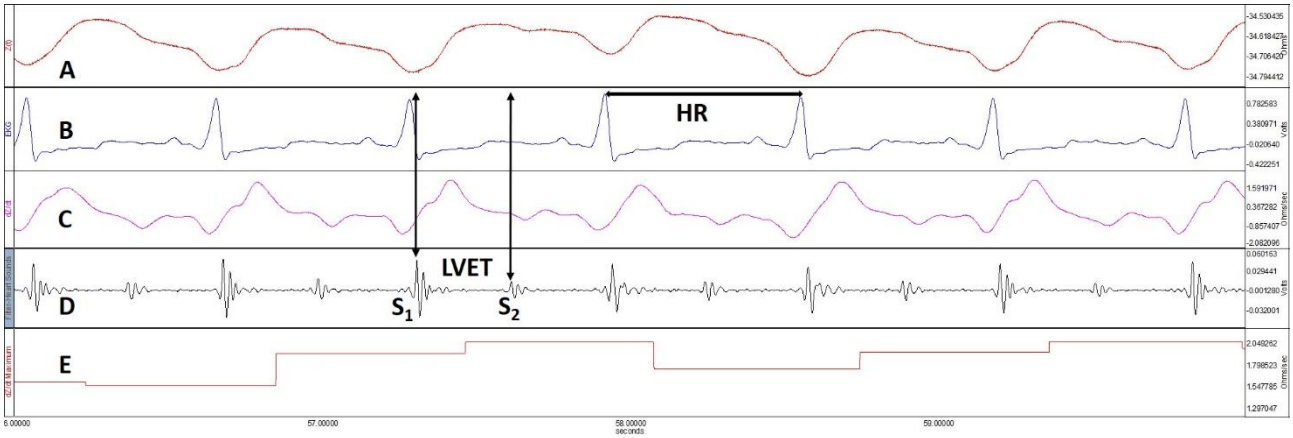


Figure 3. The impedance cardiography (ICG), electrocardiogram (ECG) and heart sounds were recorded simultaneously, **A)** Z_0, base impedance, **B)** ECG, heart rate (HR) was determined by measuring R-R, **C)** impedance change rate, **D)** heart sounds, left ventricular ejection time (LVET) was determined as the time of the electro-mechanical systole, and measured by using the pulses that trigger heart sounds as the time between the first heart sound S1 and second heart sound S2, **E)** dZ_{max}/dt, the maximum rate of change in impedance

derived from thoracic impedance, including TFI and EVI, using the formula IC = EVI / TFI (19). Diastolic arterial blood pressure (DABP) and systolic arterial blood pressure (SABP) are found using the blood pressure monitor. Mean arterial pressure (MAP) was determined by MAP = ((2 × DABP) + SABP) / 3. TPR was calculated as TPR = MAP / CO. RPP (or MVO_2I) was computed as RPP = SABP × HR. CI, SI, TFCI, and TPRI were calculated by dividing CO, SV, TFC, and TPR by body surface area (BSA). BSA was calculated by Mosteller's formula (21). All evaluations were objective, unbiased, and accompanied by explanations for technical terms.

Statistical Analysis

The assumptions of normality of the data were tested by the Shapiro-Wilk test. Descriptive statistics were given as mean±standard deviation. All hemodynamic parameters before and after optimization were assessed using the paired-samples t-test. Categorical data were determined as percentages for descriptive statistics. Statistical analyses were performed using the IBM SPSS software version 21. A $p \leq 0.05$ was considered statistically significant.

RESULTS

The study group comprised patients diagnosed with cardiomyopathy (ischemic/non-ischemic) who had received a biventricular pacemaker implant. Demographic and baseline echocardiographic parameters of the patients were presented in Table 1. The study included 20 patients with a biventricular pacemaker, 10 (50%) of whom were male and 10 (50%) were female. The mean age was 56.95±8.91 years. Of the patients, 15 (75%) were diagnosed with non-ischemic cardiomyopathy and received CRT, and 5 (25%) were diagnosed with ischemic cardiomyopathy and received CRT. All patients received a biventricular implantable cardioverter-defibrillator. CRT was administered to 12 patients within the past year and 8 patients more than a year ago.

Doppler ECG was used to detect AV dyssynchronization based on the status of mitral E and A waves. AVD times were found to be very long in 6 (30%) patients, extremely short in 4 (20%), and very short in 10 (50%) patients. The AVD times were adjusted between 100-140 ms before optimization. The AVD times that produced the highest values were adjusted as optimization values using the iterative method and the mitral EA VTI and aorta VTI methods simultaneously. The adjusted AVD times were found to be between 100-130 ms. The mean AVD time was 116.50±13.86 ms before optimization and 118.00±8.33 ms after optimization, indicating no statistically significant difference (p=0.685). The Aorta VTI showed a significant increase from 22.00±1.11 cm to 25.49±1.12 cm after optimization (p<0.001). Similarly, the mitral EA VTI increased from 16.46±0.95 cm to 18.32±1.11 cm after optimization significantly (p<0.001, Table 2).

Table 1. Demographic, basal echocardiographic, and electrocardiographic parameters of patients

Age (year)	56.95±8.91
Body Surface Area (m^2)	1.879±0.033
QRS duration (ms)	121.40±2.80
LVEF (%)	42.25±1.68
LVEDD (cm)	6.155±0.215
LVEDDI (cm/m^2)	3.274±0.097
Cardiomyopathy, n (%)	
Ischemic cardiomyopathy	5 (25)
Non-ischemic cardiomyopathy	15 (75)
MR Severity, n (%)	
None (Grade 0)	5 (25)
Mild (Grade 1)	11 (55)
Mild to Moderate	1 (5)
Moderate (Grade 2)	2 (10)
Moderate to Severe	1 (5)
NYHA Classification, n (%)	
Class I	1 (5)
Class II	15 (75)
Class III	4 (20)
Hypertension, n (%)	17 (85)
Hyperlipidemia, n (%)	2 (10)
Diabetes Mellitus, n (%)	5 (25)
Smoke, n (%)	3 (15)

BSA: body surface area, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end diastolic diameter, LVEDDI: left ventricular end diastolic diameter index, MR: mitral regurgitation, NYHA: New York Heart Association

The CO values were 4.00±0.79 l/min before optimization and 4.05±0.67 l/min after optimization, indicating no statistically significant difference (p=0.893). There was a slight increase in the CI from 2.11±0.37 l/min/m^2 to 2.15±0.32 l/min/m^2, and this was not statistically significant (p=0.825).

In the subgroup analysis, after optimizing treatment for 5 patients received CRT due to ischemic cardiomyopathy, the mitral EA VTI increased from 15.90±2.72 cm to 18.18±2.77 cm, and this increase was found statistically significant (p=0.012). There was no statistically significant increase in the aorta VTI value, which rose from 23.62±1.54 cm to 27.00±2.26 cm (p=0.055). The ischemic cardiomyopathy group did not show any significant increase in CO (p=0.622) or CI (p=0.605) values. In the non-ischemic cardiomyopathy group, the mitral EA VTI increased from 16.64±0.95 cm to 18.37±1.22 cm after optimization, which was statistically significant (p=0.008). Similarly, the aorta VTI increased from 21.46±1.38 cm to 24.98±1.30 cm, which was also significant (p<0.001). For the non-ischemic cardiomyopathy group, the increase in CO value from 3.50±0.59 l/min to 3.61±0.37 l/min was not significant (p=0.808). Similarly, the increase in CI value from 1.91±0.33 l/min/m^2 to 1.99±0.26 l/min/m^2 was also not statistically significant (p=0.739).

The hemodynamic parameters of the patients before and after optimization were determined using ICG (Table 3). No statistically significant differences were found for the Z_0, dZ_{max}/dt, LVET, VEPT, MAP, TFC, TFCI, TPR, TPRI, IC, SV, SI, CO, CI, and RPP parameters of the patients who received a biventricular pacemaker. However, a significant difference was observed in HR (p=0.003).

Table 2. Comparison of standard transmittal Doppler echocardiographic parameters before and after optimization

	Before (n=20)	After (n=20)	p
Mitral VTI	16.46±0.95	18.32±1.11	**<0.001**
Aorta VTI	22.00±1.11	25.49±1.12	**<0.001**

VTI: velocity-time integral

Table 3. Comparison of ICG parameters before and after optimization

	Before (n=20)	After (n=20)	p
Z_0 (ohm)	33.96±1.67	33.61±1.85	0.849
dZ_{max}/dt (ohm/s)	1.77±0.25	1.59±0.19	0.933
LVET (s)	0.308±0.007	0.311±0.009	0.516
VEPT (l)	3.137±0.237	3.201±0.213	0.377
MAP (mmHg)	89.03±3.16	84.33±2.97	0.170
HR (beat/min)	77.66±2.04	74.17±1.95	**0.003**
TFC ($kohm^{-1}$)	31.20±1.98	31.98±2.34	0.787
TFCI ($kohm^{-1}/m^2$)	16.66±0.93	17.67±1.97	0.579
TPR (mmHg.min/l)	31.95±3.62	27.00±2.65	0.088
TPRI (mmHg.min/l/m^2)	17.15±1.89	14.58±1.49	0.077
IC (s^{-1})	0.050±0.006	0.053±0.005	0.443
SV (ml/beat)	50.00±8.75	54.51±8.77	0.274
SI (ml/beat/m^2)	26.43±4.21	28.87±4.14	0.271
CO (l/min)	4.00±0.79	4.05±0.67	0.893
CI (l/min/m^2)	2.11±0.37	2.15±0.32	0.825
RPP (mmHg×beat⁄min)	9182±442	8403±468	0.061

ICG: impedance cardiography, Z_0: base impedance, dZ_{max}/dt: maximum rate of change in impedance, LVET: left ventricular ejection time, VEPT: volume of electrically participating thoracic tissue, MAP: mean arterial pressure, HR: heart rate, TFC: thoracic fluid content, TFCI: thoracic fluid content index, TPR: total peripheric resistance, TPRI: total peripheric resistance index, IC: contractility index (or inotropy index), SV: stroke volume, SI: stroke index, CO: cardiac output, CI: cardiac index, RPP: rate pressure product (or myocardium oxygen consumption index, MVO_2I)

DISCUSSION

CRT is an effective treatment for HF with reduced LVEF and a wide QRS complex. Large randomized controlled trials have demonstrated that CRT improves symptoms, quality of life, and left ventricular remodeling and reduces morbidity and mortality in this population (22). However, CRT has a significant rate of non-response. However, there is no universally accepted definition for CRT response, and the rate of non-response is largely dependent on the definition used (23). In a real-life prospective study, the non-response rate reached 31% at 6 months (24). In a study by Moulin et al. (25), the non-response rate was 49%. Poor response to CRT can be attributed to various factors, including suboptimal programming, suboptimal lead position, and residual desynchrony in atrial or ventricular rhythms. AVD and VVD times can be used to enhance cardiac hemodynamic performance and reduce CRT failure rates (26,27). The use of Doppler ECG for optimizing intracardiac delays has been discussed by the ESC (28). Echo techniques optimize AVD and VVD by measuring the maximum aortic VTI. However, echo-based methods are not integrated into routine clinical practice because of their time-consuming nature (29). The aim of optimization in CRT is to adjust the AV interval and the stimulation timing of both ventricular electrodes to maximize their contribution to left ventricular function (30,31). This study aimed to investigate patients who had undergone CRT and were suspected of having an inadequately adjusted AVD based on a literature review. Echocardiographic methods, mitral EA VTI, aorta VTI, and the iterative method, which were reliable and easy to implement were used. The noninvasive method of ICG was used to measure CO after optimization. Although invasive thermodilution is considered the gold standard for measuring CO, non-invasive methods can also be used as alternatives. According to a study conducted by Dupuis et al. (32) in 75 patients, CO measurement with ICG was found to be reliable when compared to the Fick method and thermodilution obtained by right heart catheterization. A correlation was found between CO measurements using thermodilution and ICG methods in a study by Guha et al. (33) involving 15 patients who underwent coronary bypass surgery. In another study by Kim et al. (34) of 16 patients who underwent liver transplantation, ICG showed a more significant correlation with arterial waveform analysis than thermodilution and arterial waveform analysis for CO measurement. The study results indicate a statistically significant increase in aorta VTI and Mitral EA VTI after optimization. Although measurements with ICG showed a slight increase in CO after AV optimization compared with baseline, a statistically significant increase was not observed. Therefore, this study suggest that AV interval optimization has no impact on CO as measured using ICG. The findings are consistent with those of large, randomized trials. For instance, in the SMART-AV trial,

which involved 1014 patients, no superiority of SmartDelay and echocardiographic optimization over the fixed AVD set at 120 ms was observed. Although the study did not recommend routine AV optimization based on its results, it excluded non-responsive patients (35). In a study by Moulin et al. (25), which involved echocardiographic CRT optimization in 227 CRT patients who did not respond to treatment, one-third of the patients showed improvement in the clinical composite score. However, this improvement was not associated with better clinical outcomes in the non-responsive group. Routine AV-VV optimization in patients with CRT devices was not supported by the 2013 ESC CRT guidelines. However, the guidelines suggest that AV and VV optimization could be considered to correct suboptimal device settings, especially in non-responsive patients and those with ischemic heart disease (36). In light of these recommendations, it is important to evaluate how AV optimization may differentially impact patient subgroups. The findings of the present study are consistent with the general trends reported in comprehensive evaluations in the literature. Previous studies have emphasized that AV optimization in patients undergoing CRT may yield more pronounced clinical and hemodynamic benefits in cases of non-ischemic cardiomyopathy. This has been attributed to the better-preserved myocardial structure and the more effective achievement of synchronization in non-ischemic patients, whereas the presence of scar tissue in ischemic cardiomyopathy may limit the potential for mechanical resynchronization (37). In the present study, the improvement observed following optimization was more evident in the non-ischemic group, while it was more limited in the ischemic group. Here, the term improvement refers to the statistically significant increases in mitral EA VTI and aortic VTI values after optimization, as these parameters serve as volumetric indicators of ventricular filling and ejection, thereby reflecting the acute hemodynamic benefit achieved through optimization. In this regard, the findings align with the evaluations reported in the literature. The 2021 guidelines do not support CRT optimization for routine use in non-responsive patients. However, they recommended specialized centers for close and multidisciplinary follow-up (38).

Among the limitations of this study, the focus on a specific patient group may restrict the generalizability of the results. Methodologically, CO measured using ICG was compared with invasive thermodilution, in addition to echocardiographic methods, as in previous studies. However, this study exclusively utilized non-invasive methods, which may have affected the measurement accuracy. The AV interval optimization methods employed in this study were conducted using specific echocardiographic parameters, and we were unable to compare these methods with other optimization approaches. In addition, the study had a limited follow-up period, with measurements taken within a specific timeframe. A more extended follow-up period may be necessary to evaluate long-term outcomes. Furthermore, we assessed the impact of CRT optimization on the AV interval, neglecting other factors (e.g., VV interval optimization), which limits the scope of this study.

CONCLUSION

This study identified a significant enhancement in echocardiographic parameters attributable to AV interval optimization. Nevertheless, the augmentation in CO, as assessed via ICG, did not achieve statistical significance. These findings align with those observed in extensive randomized controlled trials. Furthermore, CRT optimization may not substantially improve clinical outcomes in non-responsive patients, a result that concurs with existing literature. Additionally, the findings revealed a discrepancy with the 2021 guidelines. Presently, these guidelines do not advocate for routine CRT optimization but recommend its consideration for adjusting device settings in unresponsive patients, particularly those with ischemic heart disease.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Mersin University (30.04.2015, 127).

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