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Using Cornell Product to Predict Echocardiographic Response of Left Bundle Branch Area Pacing

Sol Dal Alan Pacing Tedavisine Ekokardiyografik Yanıtı Göstermede Cornell Product'ın Değeri

ABSTRACT

Objective: Cardiac resynchronization therapy with left bundle branch area pacing (LBBAP) is a novel resynchronization technique that serves as an alternative to biventricular pacing. This study investigated the predictive value of electrocardiographic Cornell Product (CP) in identifying super-responders to LBBAP among heart failure patients with left bundle branch block (LBBB).

Method: This retrospective study included 32 patients who underwent LBBAP, had a left ventricular ejection fraction (LVEF) ≤ 35%, were in sinus rhythm with LBBB and a QRS duration ≥ 150 ms, and had been receiving optimal medical therapy for at least three months. CP was calculated from baseline 12-lead electrocardiography (ECG) using the following formula: CP (mm x ms) = [(RaVL + SV3) x QRS duration]. Super-response was defined as an increase of at least 15% in LVEF six months after the procedure. Patients were classified as super-responders or non-super-responders, and their clinical, electrocardiographic, and echocardiographic parameters were compared.

Results: Among the 32 patients, 53% (n = 17) were identified as super-responders. The mean age of participants was 65.2 ± 9.9 years, and 46.9% were female. Based on baseline 12-lead ECG, CP was significantly lower in the super-responder group (3788.4 [3222.4-4569.6] mm*ms vs. 5174.0 [4516.4-5296.0] mm*ms, P = 0.044). Additionally, multivariate analysis revealed that systolic pulmonary artery pressure (odds ratio [OR]: 1.08; P = 0.041) and CP (OR: 1.01; P = 0.036) were independent predictors of super-response to LBBAP.

Conclusion: CP, a simple and readily applicable electrocardiographic parameter, can serve as a predictor of which patients will benefit from LBBAP.

Keywords: Cardiac resynchronization, Cornell Product, heart failure, left bundle branch area pacing

ÖZET

Amaç: Sol dal alanı uyarımı ile kardiyak resenkronizasyon (LBBAP), biventriküler uyarıma alternatif olan yeni bir resenkronizasyon tekniğidir. Çalışmamızda, sol dal bloğu (LBBB) olan kalp yetersizliği hastalarında LBBAP'ye süper yanıtı göstermede elektrokardiyografik bir parametre olan Cornell product'ın (CP) prediktif değerini araştırdık.

Yöntem: Çalışmaya LBBAP uygulanan, sol ventrikül ejeksiyon fraksiyonu (LVEF) ≤%35 olan, sinüs ritminde ve LBBB'si olan, QRS süresi ≥150 ms olan ve en az 3 aydır optimal medikal tedavi kullanan 32 hasta retrospektif olarak dahil edildi. Bazal EKG'den CP değeri hesaplandı: CP (mm x ms) = [(RaVL + SV3) X QRS süresi]. LBBAP'ye süper yanıt, işlemden sonraki altıncı ayda LVEF'de minimum ≥ %15 artış olarak tanımlandı. Hastalar süper-yanıt verenler ve süper-yanıt vermeyenler olarak sınıflandırıldı ve klinik, elektrokardiyografik ve ekokardiyografik özellikler karşılaştırıldı.

Bulgular: Çalışmaya dahil edilen hastaların %53,1'i (n=17) süper-yanıt veren grupta idi. Tüm hastaların %46,9'u kadındı ve ortalama yaşı 65,2 (SD=9,9) idi. Süper yanıt veren grupta bazal EKG'de hesaplanan CP anlamlı derecede daha düşüktü (3788,4 [3222,4-4569,6] mm*msn vs. 5174,0 [4516,4-5296,0] mm*ms, P = 0,044). Ayrıca, çok değişkenli analiz; sistolik pulmoner arter basıncı (OR: 1.08, P = 0,041) ve CP (OR: 1.01; P = 0,036) değerlerinin LBBAP'ye süper yanıtı göstermede bağımsız prediktörler olduğunu ortaya koydu.

Sonuç: Basit ve uygulanabilir bir elektrokardiyografik parametre olan CP, LBBAP'den fayda görecek hastaları tahmin edebilir.

Anahtar Kelimeler: Kardiyak resenkronizasyon, Cornell Product, kalp yetersizliği, sol dal alan pacing

ORIGINAL ARTICLE
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Heart failure (HF) is a chronic syndrome that requires innovative treatment approaches, including device therapies, in addition to pharmacotherapy, to improve patient outcomes.[1,2] Cardiac resynchronization therapy (CRT) has been shown to enhance both clinical and echocardiographic outcomes by reversing ventricular remodeling in HF patients with ventricular conduction disturbances and low left ventricular ejection fraction (LVEF).[3] Biventricular (BiV) pacing, which involves epicardial pacing from coronary sinus branches and endocardial pacing from the right ventricle, has been a widely used resynchronization method for many years.[4] However, left bundle branch area pacing (LBBAP) has emerged as an alternative pacing technique and has been suggested as an alternative to right ventricular pacing and CRT. This approach not only offers lower pacing thresholds and higher success rates[5] but it also provides a more physiological pattern of ventricular activation than BiV pacing. As a result, LBBAP can lead to improved outcomes and is becoming the preferred method for many clinicians managing HF patients, especially those with left bundle branch block (LBBB).

LBBAP has been demonstrated to alleviate HF symptoms, enhance LVEF, and reduce hospital admission rates over the long term.[6] However, the response to LBBAP varies significantly among individuals. Additionally, there is a subset of patients, referred to as "super-responders," who experience a substantial improvement in LVEF. The predictors of response to LBBAP are poorly understood, and electrocardiographic features have not been widely evaluated as potential predictors of LBBAP success.

The Cornell Product (CP) is an electrocardiographic marker that has demonstrated high sensitivity in identifying left ventricular hypertrophy (LVH).[7,8] Additionally, elevated CP values have been associated with the onset of diastolic dysfunction.[9] However, no studies have examined the correlation between preoperative CP values and echocardiographic response in patients undergoing LBBAP. Understanding this relationship could provide valuable insights into potential predictors of a successful therapeutic response and long-term prognosis in this patient population.

The aim of this retrospective study was to analyze the correlation between preoperative CP measurements and echocardiographic response following LBBAP. Additionally, the study sought to identify independent predictors that may indicate a "super-response" to this intervention.

Materials and Methods

This retrospective, observational study was conducted in accordance with the Declaration of Helsinki and received approval from the Eskişehir Osmangazi University Non-Interventional Clinical Trials Ethics Committee (Approval Number: E-25403353-050.04-240208494, Date: 28.11.2024). Artificial intelligence-assisted technologies were not used in the production of this study.

Study Patients

Between February 2023 and February 2024, 32 consecutive patients who underwent LBBAP were included in the study. The inclusion criteria were as follows:

1. Patients with heart failure with reduced ejection fraction (HFrEF) who had New York Heart Association (NYHA) class II to ambulatory class IV HF symptoms despite optimal medical therapy.
2. Optimal use of guideline-directed medical therapy for HF.
3. Patients with LVEF ≤ 35% for at least three months.
4. Sinus rhythm and LBBB with a QRS duration ≥ 150 ms.

ABBREVIATIONS

BiV	Biventricular
CP	Cornell Product
CRT	Cardiac resynchronization therapy
ECG	Electrocardiography
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
LA	Left atrial
LAO	Left anterior oblique
LBBAP	Left bundle branch area pacing
LV	Left ventricular
LVAT	Left ventricular activation time
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
PSA	Pacing system analyzer
RV	Right ventricular
SPAP	Systolic pulmonary artery pressure

Electrocardiogram

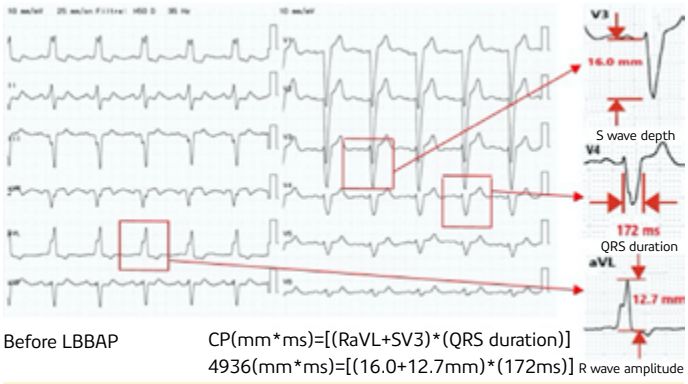
A standard 12-lead electrocardiogram (ECG) was obtained for each patient at admission and after the procedure. The same ECG machine (Mortara ELI 250, Milwaukee, Wisconsin, USA) was used, calibrated to 25 mm/s and 1 mV/cm. The 12-lead ECGs recorded before and after the procedure were transferred to digital media, and ECG measurements were performed by an experienced cardiologist using these digital PDF records. The following parameters were analyzed: heart rate, QRS voltage, QRS duration, S wave depth in V3 (SV3), and R wave amplitude in aVL (RaVL). The CP was calculated using the formula: CP (mm x ms) = [(RaVL + SV3) x QRS duration][9] (Figure 1).

Echocardiography

Echocardiographic evaluations were conducted at baseline and at a six-month follow-up using a commercially available system (EPIQ 7C, X5-1 transducer, Philips Medical Systems, Andover, MA, USA). Measurements of left atrial (LA) and left ventricular (LV) dimensions were performed according to the guidelines of the American Society of Echocardiography.[10]

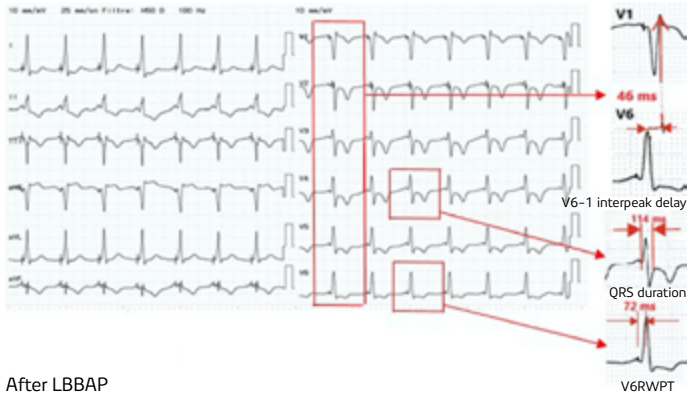
LBBAP Procedure

All patients underwent left bundle branch area pacing with cardiac resynchronization therapy and either a defibrillator (LBBAP-CRT/D) or a pacemaker (LBBAP-CRT/P) implantation. After accessing the left axillary or subclavian vein, the defibrillator lead was first implanted into the right ventricular (RV) apex with active fixation. The Solia S60 (Biotronik, Berlin, Germany) ventricular lead was prepared by activating the helix on the operating table.[11] Under fluoroscopy guidance, the Selectra 3D 55-39 (Biotronik, Berlin, Germany) delivery sheath was advanced into the RV over a guidewire. A continuous 12-lead ECG recording was performed throughout the procedure using the Philips Allura Xper FD20 X-ray system. Additionally, continuous intracardiac electrogram (EGM) recordings were obtained with a pacing system analyzer (PSA) (Renamic Neo programmer, Biotronik) using a modified three-lead ECG connection. After the delivery sheath was



Before LBBAP CP(mm*ms)=[(RaVL+SV3)*(QRS duration)]
4936(mm*ms)=[(16.0+12.7mm)*(172ms)]

Figure 1. Method of calculating the Cornell Product (CP) before left bundle branch area pacing (LBBAP).



After LBBAP

Figure 2. Measurement of V6 R-wave peak time (V6RWPT), V6–1 interpeak delay, and QRS duration after left bundle branch area pacing (LBBAP).

positioned correctly at the right anterior oblique (RAO) 30º view, unipolar pace-mapping ECG parameters were checked. Lead penetration into the interventricular septum was performed in the left anterior oblique (LAO) 40º view at the appropriate anatomical location, where optimal unipolar pace-mapping characteristics were observed. During septum penetration, the fluoroscopic advancement of the electrode, unipolar impedance, and the progressive change from a W pattern to a terminal r/R wave in lead V1 were actively monitored. Once the terminal r/R wave was observed in V1, V6 R wave peak time (V6RWPT) and V6–1 interpeak delay measurements were performed (Figure 2).

Then, unipolar/bipolar pacing threshold, impedance, R wave amplitude values, and current of injury pattern were evaluated. The depth of the lead in the septum was assessed using septography with contrast injection through the sheath. LBBAP confirmation was performed according to the most recent European Heart Rhythm Association (EHRA) consensus paper.[12] Once LBBAP was confirmed, the generator was connected to the leads and placed in the pacemaker pocket. The procedure was completed by closing the subcutaneous tissues and skin according to anatomical guidelines. At the end of the procedure, appropriate pacemaker settings were adjusted based on left ventricular activation time (LVAT), V6–1 interpeak delay, and QRS durations. Following the procedure, patients were transferred to the coronary care unit for monitoring.

Patient Follow-Up and Determination of Super-Response

The CP was obtained from each patient's baseline pre-procedural 12-lead ECG. LVEF was measured at baseline and at the six-month follow-up. Patients were then categorized into two groups: super-responders and non-super-responders, based on the change in LVEF. Super-responders were defined as patients who achieved a minimum 15% increase in LVEF.[13]

Statistical Analysis

Continuous variables were reported as mean ± standard deviation or median (25^{th}–75^{th} percentile), with normality assessed using the Kolmogorov-Smirnov test. Categorical variables were presented as frequencies and percentages. Univariate logistic regression was initially performed, followed by multivariate logistic regression analysis to identify independent predictors of super-response. Logarithmic transformation was applied to the CP and systolic pulmonary artery pressure (SPAP) values used in the analysis. Receiver operating characteristic (ROC) curves were utilized to determine optimal cut-off values for continuous variables in predicting super-response. A two-sided P value of < 0.05 was considered statistically significant. Analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics 21.0 software (IBM Corp., released in 2012, Armonk, NY, USA).

Results

Baseline Characteristics of the Study Patients

The study included 32 patients who underwent LBBAP-CRT and were classified into super-responders (n = 17) and non-super-responders (n = 15). All patients had LBBB on electrocardiogram. The mean QRS duration was 156 ms (151–165 ms), and the mean LVEF was 24.6 % (standard deviation [SD] = 5.9).

Comparison of Super-Responders and Non-Super-Responders

There was no significant difference between the super-responder and non-super-responder groups in terms of age and gender (P = 0.307, P = 0.464) (Table 1). There was also no difference in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels between the two groups (P = 0.597) (Table 2). QRS duration was similar between super-responders and non-super-responders. Notably, the CP was significantly lower in the super-responder group (3788.4 [3222.4–4569.6] mm*msn vs. 5174.0 [4516.4–5296.0] mm*ms, P = 0.044) (Table 3). Additionally, there was no correlation between CP and left ventricular end-diastolic diameter (LVEDD) in all patients (P = 0.858, Pearson R = -0.033). When the groups were evaluated separately, no correlation was found between the CP and LVEDD in either the super-responders (P = 0.478, Pearson R = 0.185) or the non-super-responders (P = 0.336, Pearson R = -0.267).

Procedural Outcomes

Successful LBBAP was achieved in all patients. The procedural outcomes of LBBAP were analyzed based on procedure duration, pacing parameters, and complications, as summarized in Table 4. Among all patients, 31 patients underwent CRT-defibrillation (CRT-D) implantation and one patient underwent CRT-pacing (CRT-P) implantation. Favorable pacing parameters were observed, including an R wave amplitude of 17.2 ± 5.7 mV, impedance of 624 ± 124.8 Ω, and a mean capture threshold

Table 1. Baseline Characteristics of Super-Responders and Non-Super-Responders

Characteristics	Total Population (n = 32)	Super-Responders (n = 17)	Non-Super-Responders (n = 15)	P
Age, years	65.2 ± 9.9	64.0 ± 10.3	67.6 ± 8.2	0.307
Female sex, n (%)	15 (46.9%)	9 (52.9%)	6 (40.0%)	0.464
Hypertension, n (%)	23 (71.9%)	13 (76.5%)	10 (66.7%)	0.699
Diabetes, n (%)	17 (53.1%)	10 (58.8%)	7 (46.7%)	0.492
Non-ischemic etiology, n (%)	18 (56.3%)	10 (58.8%)	8 (53.3%)	0.755
Ischemic etiology, n (%)	14 (43.8%)	7 (46.7%)	7 (41.2%)	0.755
Previous PCI, n (%)	6 (18.8%)	4 (23.5%)	2 (13.3%)	0.539
Previous CABG, n (%)	8 (25%)	3 (17.6%)	5 (33.3%)	0.306
ACE-I/ARB/ARNI, n (%)	24 (75%)	13 (76.5%)	11 (73.3%)	0.838
Beta-blockers, n (%)	28 (87.5%)	14 (82.4%)	14 (93.3%)	0.603
MRA, n (%)	24 (75.0%)	23 (76.5%)	11 (73.3%)	0.838
SGLT-2 inhibitor, n (%)	11 (34.4%)	5 (29.4%)	6 (40.0%)	0.798
Diuretics, n (%)	27 (84.4%)	15 (88.2%)	12 (80.0%)	0.645

Values are presented as mean ± SD, median (range), or n (%). ACE-I, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin II Receptor Blocker; ARNI, Angiotensin Receptor-Neprilysin Inhibitor; CABG, Coronary Artery Bypass Graft; MRA, Mineralocorticoid Receptor Antagonist; PCI, Percutaneous Coronary Intervention; SD, Standard Deviation; SGLT-2, Sodium-Glucose Cotransporter-2.

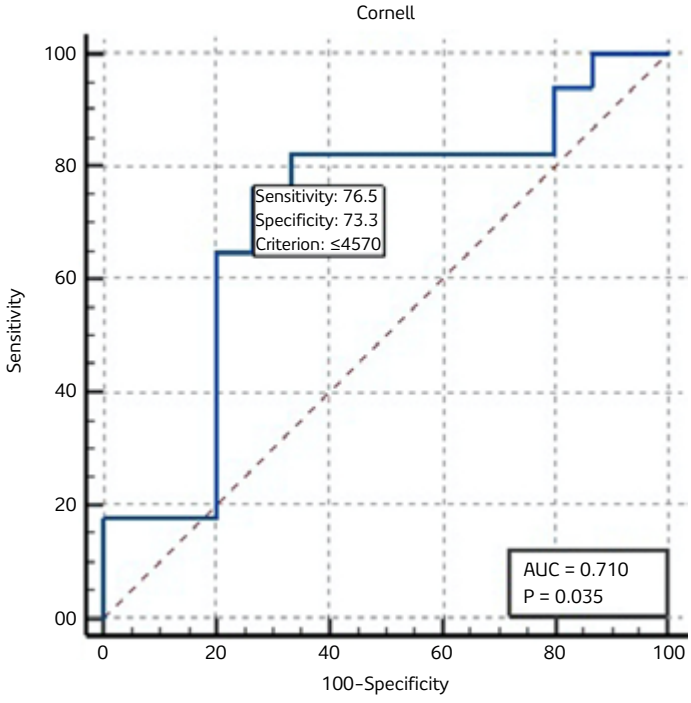


Figure 3. Receiver operating characteristic (ROC) curve demonstrating the predictive performance of the Cornell Product for super-response to left bundle branch area pacing (LBBAP).

of 0.6 ± 0.2 V. Complications were minimal, with no cases of pneumothorax, pericardial effusion, stroke, or left ventricular (LV) perforation. However, one case of atrial lead dislodgement was noted, though there was no loss of LBBAP capture. The atrial lead dislodgement was identified and successfully repositioned the following day. In the patient who developed pneumonia after LBBAP, an appropriate antibiotic regimen was initiated and completed, leading to full resolution of the infection.

Comparison of Baseline and Follow-up Echocardiographic and Biomarker Characteristics of Patients

QRS duration significantly decreased in both super-responders and non-super-responders following LBBAP. In super-responders, the mean QRS duration decreased from 155 ± 19.9 ms at baseline to 119.0 ± 8.4 ms at follow-up (P < 0.001). Similarly, in non-super-responders, the mean QRS duration decreased from 165.2 ± 19.9 ms at baseline to 128.2 ± 11.4 ms at follow-up (P < 0.001). For super-responders, LVEF improved markedly from 24.5 ± 6.2% at baseline to 44.3 ± 8.9% at follow-up (P < 0.001). Similarly, significant reductions were observed in LVEDD, decreasing from 60.5 ± 7.1 mm to 50.9 ± 4.8 mm (P < 0.001), and in left ventricular end-systolic diameter (LVESD), which decreased from 51.5 ± 7.8 mm to 37.1 ± 6.7 mm (P < 0.001). In contrast, non-super-responders demonstrated more modest improvements. LVEF increased from 24.5 ± 6.1% to 28.8 ± 6.3% (P = 0.005), while LVEDD and LVESD showed slight reductions from 60.9 ± 5.8 mm to 57.0 ± 7.2 mm (P = 0.005) and from 51.5 ± 6.9 mm to 46.6 ± 7.7 mm (P = 0.002), respectively (Table 5).

Univariate and Multivariate Analysis of Variables Predicting LBBAP Response

Based on univariate analyses, systolic pulmonary artery pressure (odds ratio [OR]: 1.06; P = 0.047), QRS duration (OR: 1.05; P = 0.048), and CP (OR: 1.01; P = 0.036) were identified as predictors of super-response to LBBAP in all patients. Multivariate analyses demonstrated that SPAP (OR: 1.08; 95% confidence interval [CI]: 1.01–1.16, P = 0.041) and CP (OR: 1.01; 95% CI: 1.00–1.02, P = 0.036) were independent predictors of super-response to LBBAP (Table 6). The optimal cut-off value for CP was determined to be 4570 mm x ms, with 76.5% sensitivity and 73.3% specificity in predicting super-response to LBBAP (area under the curve [AUC] = 0.710; P = 0.035) based on ROC curve analysis (Figure 3).

Table 2. Comparison of Baseline Laboratory and Echocardiographic Features in Super-Responders Versus Non-Super-Responders

Characteristics	Total Population (n = 32)	Super-Responders (n = 17)	Non-Super-Responders (n = 15)	P
LVEF, %	24.6 ± 5.9	24.7 ± 6.0	24.5 ± 6.1	0.952
LVEDD, mm	60.7 ± 6.4	60.5 ± 7.1	60.9 ± 5.8	0.883
LVESD, mm	51.5 ± 7.3	51.5 ± 6.9	51.5 ± 7.8	0.999
IVSd, mm	10.9 ± 2.0	11.2 ± 2.5	10.7 ± 1.6	0.533
LA diameter, mm	42.4 ± 5.2	42.0 ± 5.1	43.0 ± 5.4	0.598
RA diameter, mm	36.0 (34.0-41.0)	35.5 (34.0-38.0)	37.0 (35.0-45.5)	0.129
TAPSE, mm	19.5 (18.0-23.5)	21.0 (19.0-23.0)	18.0 (16.5-22.0)	0.153
SPAP, mmHg	29.5 (25.0-42.5)	28.0 (25.0-35.0)	33.0 (26.5-55.0)	0.105
E/a ratio	0.6 (0.4-1.4)	0.7 (0.4-1.2)	0.6 (0.6-1.7)	0.846
E/e' ratio	12.9 (10.0-16.9)	13.5 (10.6-15.6)	12.3 (9.1-19.4)	0.894
Hemoglobin, g/dL	12.9 ± 2.0	12.5 ± 1.6	13.4 ± 2.6	0.239
NT-proBNP, pg/mL	2110 (485-5280)	1480 (409-4946)	2270 (585-4098)	0.597
Albumin, g/dL	4.0 ± 0.4	4.0 ± 0.3	4.0 ± 0.5	0.746
Creatinine, mg/dL	1.0 (0.8-1.4)	1.0 (0.8-1.3)	1.1 (0.7-1.6)	0.602
AST, U/L	20.5 (17.0-23.5)	20.0 (18.5-21.0)	21.0 (16.0-25.0)	0.852
ALT, U/L	15.0 (11.5-20.0)	16.0 (12.0-20.0)	14.5 (12.0-20.0)	0.861

Values are presented as mean ± SD, median (range), or n (%). ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; IVSd, Interventricular Septal Thickness Diameter; LA, Left Atrium; LV, Left Ventricle; LVEDD, Left Ventricular End-Diastolic Diameter; LVEF, Left Ventricular Ejection Fraction; NT-proBNP, N-Terminal Pro-B-Type Natriuretic Peptide; RA, Right Atrium; SPAP, Systolic Pulmonary Artery Pressure; TAPSE, Tricuspid Annular Plane Systolic Excursion.

Table 3. Baseline Electrocardiographic Features of Super-Responders and Non-Super-Responders

Characteristics	Total Population (n = 32)	Super-Responders (n = 17)	Non-Super-Responders (n = 15)	P
RaVL, mm	7.1 ± 3.1	6.4 ± 2.8	8.0 ± 3.3	0.155
SV3, mm	18.0 (13.5-24.0)	17.0 (12.0-21.0)	21.2 (14.0-25.5)	0.278
QRS duration, ms	156 (151-165)	154 (151-160)	160 (155-175)	0.093
Cornell Product (mm*msn)	4468.8 (3313.7-5286.0)	3788.4 (3222.4-4569.6)	5174.0 (4516.4-5296.0)	0.044

Values are presented as mean ± SD, median (range), or n (%).

Discussion

This study highlights the value of the CP, an electrocardiographic marker, in predicting procedural success in patients with HF who undergo LBBAP. Our findings demonstrate that CP is a valuable tool for predicting echocardiographic super-response to LBBAP. Furthermore, among patients with HF and LBBB, CP on electrocardiography and SPAP on echocardiography emerged as the most significant predictors of super-response, underscoring their importance in guiding clinical decisions.

Electrical conduction abnormalities play a key role in the pathophysiology of HF patients and are traditionally treated with BiV pacing. However, conduction system pacing techniques, such as His bundle pacing and LBBAP, have emerged as novel alternatives to conventional BiV pacing. The first successful case of LBBAP for CRT in an HF patient with LBBB was reported in 2017.[14] Since then, research into predictors of LBBAP-CRT response has become increasingly common. Vijayaraman et al.[15] conducted a study evaluating the feasibility of LBBAP in patients eligible for CRT and reported a significant echocardiographic response (≥ 5% improvement in LVEF) in 73% of patients. They identified baseline LBBB morphology and LVEDD as predictive parameters for echocardiographic response. Different studies have used various cut-off values for LVEF improvement as an echocardiographic response criterion. In our study, we defined super-response as an improvement of more than 15% in LVEF, and the echocardiographic super-response rate was 53%.

In another study investigating 59 HF patients who underwent LBBAP therapy, the association between paced QRS morphology in lead V1, QRS axis, and V6 R-wave peak time with echocardiographic response was assessed.[16] The study concluded that paced qR morphology and transition during threshold testing predicted greater improvement in LVEF, whereas loss of terminal R in lead V1 and prolongation of R-wave peak time on follow-up predicted nonresponse to LBBAP. This study highlights that the ability to obtain appropriate post-procedure electrocardiographic features serves as an important predictor of response to LBBAP. In the present study, we aimed to evaluate whether a parameter different from classical ECG markers obtained from baseline ECG is associated with echocardiographic response. For this purpose, we examined the relationship between the CP value on the

Table 4. Procedural Characteristics, Pacing Parameters, and Complications of Patients Undergoing Left Bundle Branch Area Pacing (LBBAP)

Procedural Outcomes		Complications	
Procedure duration (minutes)	120 ± 37	Pneumothorax (n)	0
Fluoroscopy duration (minutes)	30 ± 12	Pericardial effusion (n)	0
Type of device implanted		Device infection (n)	0
CRT-P (n)	1	Stroke (n)	0
CRT-D (n)	31	LV perforation (n)	0
Pacing characteristics		Lead dislodgement (n)	1
R-wave amplitude (mV)	17.2 ± 5.7	Loss of left septal capture (n)	0
Impedance (Ω)	624 ± 124.8		
LBBAP threshold (V at 0.5 ms)	0.6 ± 0.2		

CRT, Cardiac Resynchronization Therapy; CRT-D, Cardiac Resynchronization Therapy - Defibrillator; CRT-P, Cardiac Resynchronization Therapy - Pacemaker; LBBAP, Left Bundle Branch Area Pacing; LV, Left Ventricle.

Table 5. Baseline and Follow-up Echocardiographic and Biomarker Characteristics of Super-Responders and Non-Super-Responders

	Super-Responders (n = 17)			Non-Super-Responders (n = 15)		
Characteristics	**Baseline**	**Follow-up**	**P**	**Baseline**	**Follow-up**	**P**
QRS duration, mean ± SD	155 ± 19.9	119.0 ± 8.4	<**0.001**	165.2 ± 19.9	128.2 ± 11.4	<**0.001**
LVEF, %, mean ± SD	24.5 ± 6.2	44.3 ± 8.9	<**0.001**	24.5 ± 6.1	28.8 ± 6.3	**0.005**
LV EDD, mm, mean ± SD	60.5 ± 7.1	50.9 ± 4.8	<**0.001**	60.9 ± 5.8	57.0 ± 7.2	**0.005**
LV ESD, mm, mean ± SD	51.5 ± 7.8	37.1 ± 6.7	<**0.001**	51.5 ± 6.9	46.6 ± 7.7	**0.002**
NT-proBNP, pg/mL	1480 (409-4946)	1193 (403-2013)	**0.004**	2270 (585-4098)	2379 (568-4571)	0.972

LV EDD, Left Ventricular End-Diastolic Diameter; LVEF, Left Ventricular Ejection Fraction; LV ESD, Left Ventricular End-Systolic Diameter; NT-proBNP, N-Terminal Pro-B-Type Natriuretic Peptide.

Table 6. Univariate and Multivariate Logistic Regression Analyses of Predictors of Super-Response

	Univariate Analysis		Multivariate Analysis	
Variables	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Age	1.04 (0.96-1.12)	0.298		
Gender	0.59 (0.14-2.41)	0.465		
LVEF	0.99 (0.88-1.12)	0.950		
TAPSE	0.84 (0.67-1.05)	0.132		
SPAP	1.06 (1.00-1.13)	0.047	1.08 (1.01-1.16)	0.041
NT-proBNP	1.00 (1.00-1.00)	0.306		
Creatinine	1.68 (0.52-5.42)	0.381		
RaVL	1.19 (0.93-1.52)	0.157		
SV3	1.03 (0.95-1.10)	0.416		
QRS Duration	1.05 (0.99-1.11)	0.048		
Cornell Product	1.01 (1.00-1.03)	0.036	1.01 (1.00-1.02)	0.036

CI, Confidence Interval; LVEF, Left Ventricular Ejection Fraction; NT-proBNP, N-Terminal Pro-B-Type Natriuretic Peptide; OR, Odds Ratio; SPAP, Systolic Pulmonary Artery Pressure; TAPSE, Tricuspid Annular Plane Systolic Excursion. Logarithmic transformation was performed for the Cornell Product (CP) and systolic pulmonary artery pressure (SPAP) values evaluated in the analysis.

pre-procedural 12-lead ECG and echocardiographic response. Cornell Product is a well-studied and widely recognized electrocardiographic criterion for left ventricular hypertrophy.[17-19] However, several studies have explored the predictive value of the CP on ECG in clinical fields beyond its traditional role in reflecting LVH. In a study comparing healthy individuals, hypertensive patients, and HF patients with preserved ejection fraction (HFpEF), CP was found to be higher in HFpEF patients compared to both healthy individuals and hypertensive patients. Moreover, CP distinguished HFpEF from hypertension with an optimal cut-off value of ≥ 1800 mm*ms. This study also demonstrated that CP predicts a poor prognosis in HFpEF patients, reflecting the severity of diastolic dysfunction and LVH.[20]

In another study investigating the relationship between ECG and echocardiographic parameters and cardiovascular outcomes in elderly patients with stage B-HF, CP was found to be a predictor of outcomes in non-ischemic stage B-HF patients, independent of age, gender, and comorbidities.[21] Otaki et al.[22] examined whether CP could be used for risk stratification and predicting cardiac events in patients with chronic HF. This study demonstrated that higher CP values in chronic HF patients were strongly associated with reduced LVEF, increased LVEDD, and an etiology of dilated cardiomyopathy. Additionally, the study found that lower CP values were associated with a left ventricular geometry resembling normal conditions, whereas higher CP values were linked to eccentric hypertrophy.[22]

Ischemic or non-ischemic etiology may also influence the response to LBBAP. Unlike our study, Vijayaraman et al.[15] emphasized non-ischemic etiology as a predictor of super-response to LBBAP in their univariate analysis. However, a key difference between their study and ours is that the echocardiographic super-response

criterion for LVEF improvement was set at 5%. The number of patients included in the study and the criteria used to define super-response may influence the results when assessing the impact of etiology on response.

Additionally, one of the major causes of non-ischemic cardiomyopathy is LBBB-induced cardiomyopathy.[23-26] Data on super-response to CRT and improvement in ejection fraction (EF) in some patients with LBBB-induced cardiomyopathy suggest that LBBB may be the underlying cause of cardiomyopathy in certain cases.[26] In clinical practice, identifying the relationship between LBBB and cardiomyopathy can be challenging, particularly when dilated cardiomyopathy is detected alongside LBBB. One indicator supporting LBBB-induced cardiomyopathy is the presence of LBBB before the onset of cardiomyopathy. The recommended diagnostic approach for LBBB-induced cardiomyopathy is exclusion of other causes of dilated cardiomyopathy.[23-26] Our study did not specifically investigate this etiology, but future studies evaluating patients with LBBB-induced cardiomyopathy in terms of their response to LBBAP-CRT will provide valuable insights.

Considering this finding, one possible explanation for why patients with lower CP values benefited more from LBBAP in our study may be their better ventricular geometry. Some studies have demonstrated that CP is associated with diastolic dysfunction, reflects left ventricular geometry, and correlates with worse outcomes and functional capacity in HF patients.[19-21] Although there are studies investigating the prognostic value of CP in HF patients, there is a lack of research on electrocardiographic and echocardiographic predictors for this new CRT modality. Our results indicate that CP measured on ECG can predict super-response in HF patients undergoing LBBAP. Notably, this study is the first to establish the prognostic value of CP in predicting super-response to LBBAP therapy, marking its potential as a novel and practical tool for guiding clinical decisions and optimizing therapeutic outcomes. In addition to well-known classical parameters, CP, which can be measured simply and objectively from a 12-lead ECG, may aid in patient selection for LBBAP.

Limitations

This study has certain limitations. The primary limitations include its retrospective design and relatively small sample size. Another limitation is that post-procedural ECG parameters were not evaluated. Additionally, further investigation into the relationship between CP and other cardiac parameters, as well as its impact on long-term outcomes, could provide deeper insights into its prognostic role.

Conclusion

In HF patients with LBBB, CP is associated with echocardiographic outcomes following LBBAP. Our findings, supported by existing literature, suggest that CP has the potential to optimize patient selection and improve therapeutic outcomes. However, further large-scale and long-term studies are necessary to better understand its clinical utility and prognostic significance.

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