Received: 19 September 2021 | Revised: 27 December 2021 | Accepted: 2 January 2022

DOI: 10.1111/pace.14445

PACE WILEY

DEVICES

Septal flash correction with His-Purkinje pacing predicts echocardiographic response in resynchronization therapy

Margarida Pujol-López MD[1,2] | Rafael Jiménez Arjona MD[1] | Eduard Guasch MDPhD[1,2,3] | Adelina Doltra MDPhD[1,2] | Roger Borràs MSc[1,2,4] | Ivo Roca Luque MDPhD[1,2] | María Ángeles Castel MDPhD[1,2,3] | Paz Garre BEng[1] | Elisenda Ferró BEng[5,6] | Mireia Niebla RN[1] | Esther Carro RN[1] | Elena Arbelo MDPhD[1,2,3] | Marta Sitges MDPhD[1,2,3] | José M. Tolosana MDPhD[1,2,3] | Lluís Mont MDPhD[1,2,3]

[1] Institut Clínic Cardiovascular (ICCV), Hospital Clínic, Universitat de Barcelona, Catalonia, Spain

[2] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Catalonia, Spain

[3] Centro de Investigación Biomédica en Red Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain

[4] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain

[5] Medtronic Iberica, Barcelona, Spain

[6] Fundació Clínic per a la Recerca Biomèdica (FCRB), Barcelona, Catalonia, Spain

Correspondence
Margarida Pujol-López, MD and Lluís Mont, MD, PhD, Institut Clínic Cardiovascular (ICCV), Hospital Clínic, Catalonia, Spain. C/ Villarroel 170, 08036 Barcelona, Catalonia, Spain.
Email: mapujol@clinic.cat and lmont@clinic.cat

Lluís Mont and José M. Tolosana share the senior authorship.

Funding information
"Grant of the Catalan Society of Cardiology, 2019": Resynchronization therapy with hisian pacing; Research Grant Josep Font 2019, Hospital Clínic de Barcelona

Abstract

Background: His-Purkinje conduction system pacing (HPCSP) has been proposed as an alternative to Cardiac Resynchronization Therapy (CRT); however, predictors of echocardiographic response have not been described in this population. Septal flash (SF), a fast contraction and relaxation of the septum, is a marker of intraventricular dyssynchrony.

Methods: The study aimed to analyze whether HPCSP corrects SF in patients with CRT indication, and if correction of SF predicts echocardiographic response. This retrospective analysis of prospectively collected data included 30 patients. Left ventricular ejection fraction (LVEF) was measured with echocardiography at baseline and at 6-month follow-up. Echocardiographic response was defined as increase in five points in LVEF.

Results: HPCSP shortened QRS duration by 48 ± 21 ms and SF was significantly decreased (baseline 3.6 ± 2.2 mm vs. HPCSP 1.5 ± 1.5 mm $p < .0001$). At 6-month follow-up, mean LVEF improvement was 8.6% ± 8.7% and 64% of patients were responders. There was a significant correlation between SF correction and increased LVEF ($r = .61$, $p = .004$). A correction of ≥1.5 mm (baseline SF – paced SF) had a sensitivity of 81% and 80% specificity to predict echocardiographic response (area under the curve 0.856, $p = .019$).

Conclusion: HPCSP improves intraventricular dyssynchrony and results in 64% echocardiographic responders at 6-month follow-up. Dyssynchrony improvement with SF correction may predict echocardiographic response at 6-month follow-up.

KEYWORDS
His-Purkinje conduction system pacing, intraventricular dyssynchrony, left ventricular ejection fraction, physiological pacing, septal flash

1 | INTRODUCTION

His-Purkinje conduction system pacing (HPCSP) has been proposed as an alternative to Cardiac Resynchronization Therapy (CRT). His bundle pacing (HBP) and left bundle branch pacing (LBBP) are physiological pacing modes, as the myocardial depolarization occurs through the specialized conduction system. Since 2018, HBP is indicated in the American Guidelines[1] as an alternative to biventricular CRT in patients with AV block and left ventricular (LV) dysfunction. The *His-Sync* randomized study showed that HBP is comparable to biventricular CRT in echocardiographic and electrocardiographic response achieved[2] and non-randomized studies support LBBP as an alternative to biventricular CRT.[3–6] Wu *et al*.[7] observed greater improvement in symptoms and increase in LV function with LBBP and HBP than were seen in patients treated with biventricular CRT. However, no predictors of echocardiographic response have been described in patients with HPCSP.

Septal flash (SF)[8,9] is a fast pre-ejection leftward movement of the interventricular septum, immediately followed by a paradoxical rightward movement when the late-activated LV lateral wall starts to contract; it serves as an echocardiographic marker of LV dyssynchrony. It was first described in 1973 by McDonald as a characteristic abnormality of motion of the interventricular septum, visualized by echocardiography, in patients with left bundle branch block (LBBB).[10] In 2009, Parsai *et al*.[8] applied the concept of abnormal septal motion in the field of CRT as a marker of dyssynchrony in patients with LBBB. The SF excursion was quantified by the amplitude of the early inward motion (measured from QRS onset to maximal inward motion). The presence of SF was confirmed with an excursion ≥1 mm, quantified using M-mode in parasternal short and long axis views.[11]

The reported prevalence of SF among patients with LBBB ranges from 45% to 63%.[12,13] Right ventricular (RV) pacing elicits SF in 77% of patients[14] (a higher percentage than in LBBB) and the presence of SF has shown to be a robust predictor of CRT response.[9,13,15] Doltra *et al*[9] observed SF in 53% of patients undergoing CRT; the therapy corrected SF in 93% of the cases and resulted in an 80% rate of echocardiographic response at 1 year of follow-up.

An improvement of dyssynchrony is expected after physiological pacing. Cai *et al*[16] showed that LBBP could preserve LV synchrony in patients with dual chamber pacemaker implantation. Furthermore, in patients with LBBB and LV dysfunction, Moriña-Vázquez *et al*[17] described an early increase (at 1 month) in left ventricular ejection fraction (LVEF) and LV resynchronization. The use of HPCSP has the potential advantage of a simple procedure, avoiding the potential difficulties of coronary sinus catheterization and LV electrode deployment.

We present a retrospective analysis of prospectively collected data. The aim was to analyze whether HPCSP corrects SF and if correction of SF predicts LV echocardiographic response.

2 | METHODS

2.1 | Study population

The study is a retrospective analysis of prospectively collected data; it included prospectively 30 consecutive patients with CRT indication who underwent HPCSP (December 2018–February 2020; the first 30 patients implanted with HPCSP at our center). The included patients had CRT indication according to ESC guidelines: a) heart failure, optimal medical treatment, LVEF ≤35%, and a QRS width ≥130 ms with LBBB or b) heart failure, LV dysfunction (LVEF ≤45%), and ventricular pacing indication due to high degree AV block. LBBB criteria were: QRS duration ≥130 ms; broad notched or slurred R wave in leads I, aVL, V5, and V6; QS or rS in leads V1 and V2; and absent Q waves in leads I, V5, and V6. All patients had CRT indications according with ESC guidelines.

Patients were followed up after the implant in the CRT clinic by a nurse and an electrophysiologist at 15 days, 45 days, and at 6 months. Medication was titrated by a heart failure specialist during the follow-up. Echocardiography was performed at baseline, 15 days (to study correction of cardiac asynchrony) and 6 months follow-up. SF assessment was performed at 15 days follow-up in order to ensure that the His capture was correct (previous ECG and device check) and performed in the echocardiography laboratory to have good image quality. A ≥95% percentage of resynchronization with HPCSP was pursued.

The study protocol was approved by our *Research Ethics Committee*, and all patients provided signed informed consent (for device implantation and for the study). The investigation conforms to the principles outlined in the Declaration of Helsinki.

2.2 | Device implant

SelectSecure 3830 pacing lead (Medtronic), delivered via a fixed-curve C315-His sheath, was used in all the cases. During HBP and LBBP, intracardiac electrograms were recorded along with 12 lead ECG in order to guide the implant (Figure S1). The His signal was found with the use of unipolar sensing with the lead and the position on x-ray. HBP was the first approach in all patients[18]; if HBP could not be achieved due to high pacing thresholds (>3.5V/1ms) or inability to correct left bundle branch block, LBBP was attempted.

The location for LBBP was 1–1.5 cm distal to the His signal. At this site, the unipolar paced QRS morphology before fixation showed a "W" pattern in V1. The sheath was rotated counterclockwise to maintain the lead tip perpendicular to the septum. The pacing lead was rapidly rotated clockwise, controlling impedance. Since there are no specific algorithms universally accepted, we have applied the following LBBP criteria based on previous publications[19,20]: all patients should fulfill *criteria 1* (paced morphology of right bundle branch block in V1); and at least one the following additional: 2)

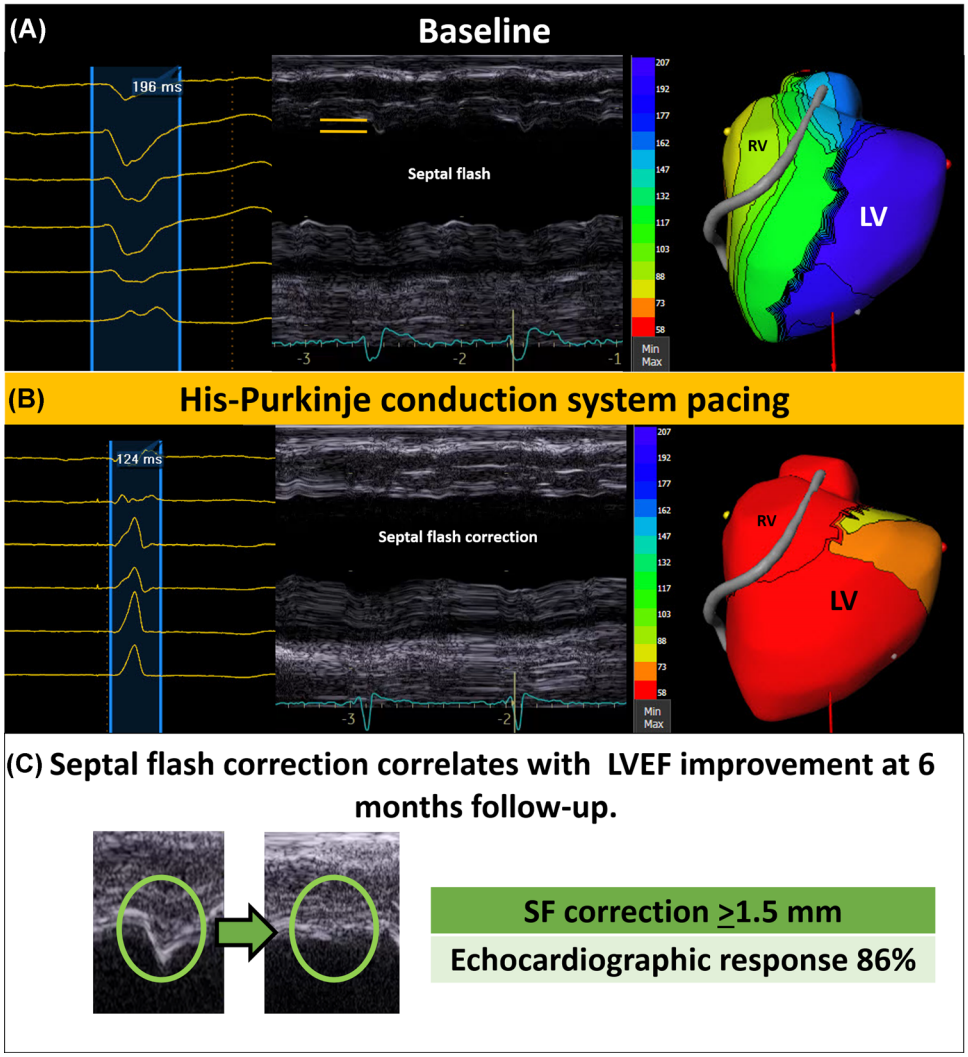

FIGURE 1 Central Illustration. Correction of septal flash (SF) with His Purkinje conduction system pacing (HPCSP). (A) Left bundle branch block with QRS width of 196 ms and SF of 5 mm; electrocardiographic imaging showed a ventricular activation pattern with late activation of the lateral left ventricle (in blue) and a left ventricular activation time (LVAT) of 82 ms. (B) HPCSP with left bundle branch pacing with AV optimization (AV 90 ms) obtained QRS of 124 ms, abolition of SF, and fast ventricular activation (red) with LVAT of 41 ms. (C) The adjusted probability prediction for LVEF response showed that the probability of response was 86% if SF correction was ≥1.5 mm

selective capture defined as an isoelectrical segment between the pacing spike and the QRS onset[21]; 3) left ventricular activation time in V6 ≤85 ms[21]; 4) left bundle branch potential recorded; 5) programmed pacing by visualization of both components of the paced QRS complex: selective paced left bundle branch QRS and myocardial-only paced QRS.[22]

The HPCSP thresholds provided in the study are those that correct the QRS due to all patients have LV dysfunction and resynchronization therapy indication. That is, in them it is necessary to capture the conduction system and not only the muscle.

Optimization was done with 12-lead ECG in the Electrophysiology Laboratory in patients with LBBP. The AV interval was optimized with ECG fusion – similar to the FOI method[23] in CRT – in patients with no AV block and no atrial fibrillation. The aim of the optimization with ECG was to shorten the QRS with prolongation of the AV delay to synchronize intrinsic RV activation with LBBP. As an example of ECG optimization, Figure 2 shows LBBP optimization of the patient depicted in Figure 1.

2.3 | Echocardiographic evaluation

Standard Doppler echocardiography was performed using a commercially available system (Vivid E95, GE-Vingmed, Milwaukee, Wisconsin). All the echocardiograms were performed by one operator (RJ) specialized in echocardiography and resynchronization therapy; a second senior echocardiographer (AD) reviewed all the studies.

The presence of ventricular dyssynchrony was analyzed by 2D-echocardiography baseline and at 15 days post-implant. Intraventricular dyssynchrony was evaluated with SF excursion measurement, as SF has been shown to be a robust and dominant predictor of CRT response.[15] Using M-mode in parasternal short and long axis views,

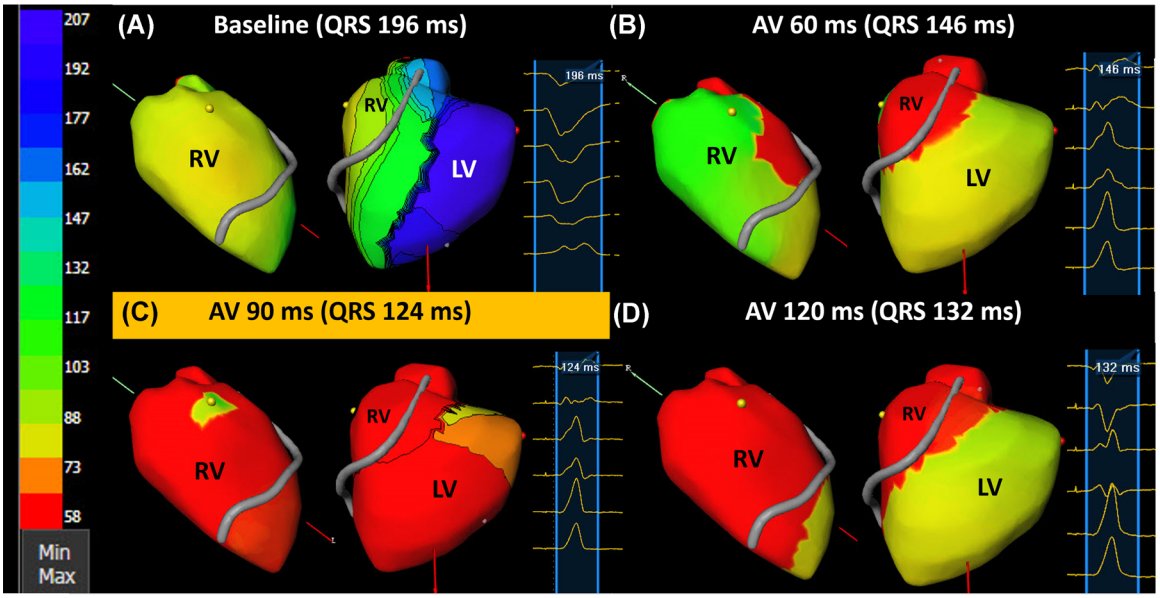

FIGURE 2 Left bundle branch pacing (LBBP) optimization with fusion. Early activation shown in red, late activation in blue. (A) Baseline activation with left bundle branch block (QRS 196 ms); electrocardiographic imaging showed ventricular activation pattern with late activation of the lateral left ventricle (in blue). (B) LBBP with short AV (60 ms), achieving a QRS of 146 ms. (C) Prolongation of the AV delay allows coordinating the stimulation of the left branch with the intrinsic activation of the right branch, normalizing the activation time and pattern (both ventricles in red); AV 90 ms allows the shortest QRS (124 ms). (D) With AV 120 ms, right ventricle is preactivated (red), obtaining a QRS of 132 ms

SF was quantified as the highest amplitude of the early inward motion (measured from QRS onset to maximal inward motion).[11] Baseline SF excursion was determined during intrinsic rhythm, or RV pacing if patient had AV block, and final SF was obtained during HPCSP. The pair of SF measures (baseline and HPCSP) taken at the axis with the highest baseline SF was selected in each patient. HPCSP could correct or abolish SF (Figure 3). In order to reduce variability, SF measurements for each patient (i.e., before and after pacing) were done in the same location and the same echocardiographic view. SF was considered present if its excursion was ≥1 mm.[11]

SF can be assessed visually in 2D echo, without need of complex post-processing, with good reproducibility.[12] In previous studies from our group, Doltra *et al*[9] reported a good agreement between two observers regarding the presence of SF (Kappa = 1, misclassification error = 0); and on the other hand, Gabrielli *et al*[11] showed good intra- and interobserver SF reproducibility.

LVEF was calculated (baseline and 6-month follow-up) by the Simpson rule from two- and four-chamber apical views. Echocardiographic response was defined as increase in five points in LVEF at 6-month follow-up. Left ventricular end systolic (LVESV), left ventricular end-diastolic volume (LVEDV), and mitral regurgitation (MR) were evaluated at baseline and at 6-month follow-up. Patients were classified as superresponders if they had LVEF ≥50% and functional recovery at 6 months follow-up.

2.4 | Electrocardiographic measurements

ECG measurements were obtained by two experienced researchers before and after device implantation (with final programming) in the Electrophysiology Laboratory at a screen speed of 300 mm/s. QRS measurements were performed using computerized recordings that were digitally stored (EP-TRACER, Schwarzer CardioTek). QRS onset was considered to be the start of fast deflection, as reported previously.[24]

ECGI was performed (CardioInsight Mapping Vest-Medtronic) in two patients, one with LBBP (Figures 1 and 2) and the other with HBP, to validate ventricular activation shortening and to study the basal and HPCSP activation pattern. ECGI maps were obtained in both patients: baseline without pacing and with HPCSP.

2.5 | Statistical analysis

The χ^2 test (categorical variables) and Student's *t*-test (continuous variables) were used to determine differences between two groups (HBP and LBBP). McNemar test (categorical variables) and paired Student's *t*-test were used for related data. Spearman correlation coefficient was applied to assess correlation between continuous variables. A univariate analysis of seven possible predictive variables of LVEF response at 6-month follow-up was performed using a logistic regression. Odds ratio was also computed. The area under the receiver operating characteristic (ROC) curve was calculated for SF correction; the value of SF correction of the ROC curve with the best sensitivity and specificity to discriminate between those with and without echocardiographic response was chosen. Statistical analysis was performed using R software for Windows (R Project for Statistical Computing).

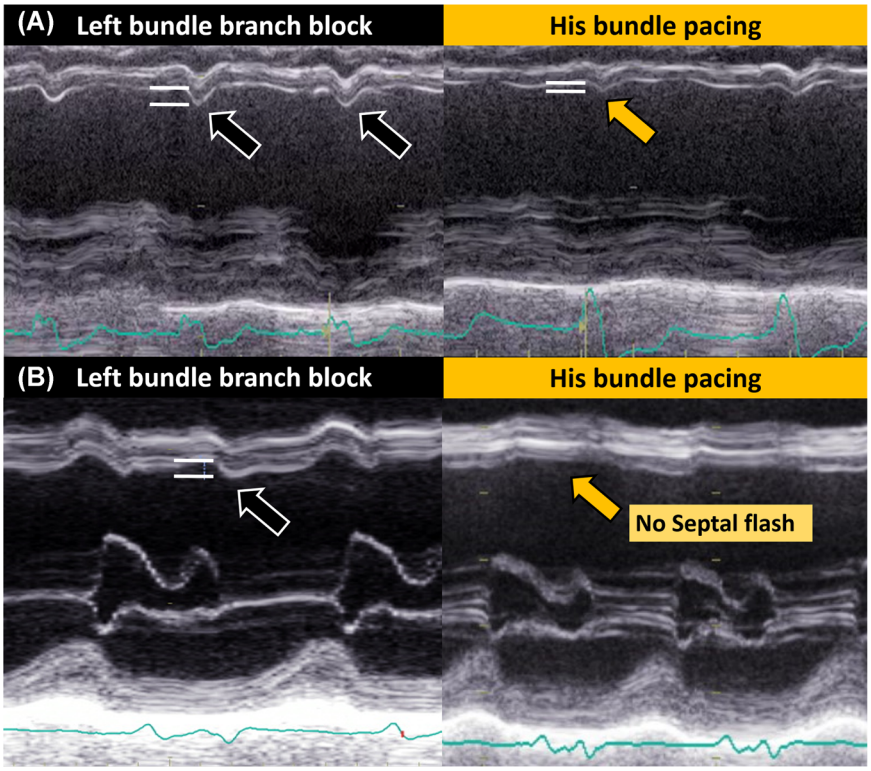

FIGURE 3 Septal flash correction with His Purkinje conduction system pacing. Activation in patients with left bundle branch block produces septal flash (SF), a marker of intraventricular dyssynchrony. Black arrows point to SF in two patients (A and B), a fast contraction and relaxation of the septum occurring during the isovolumetric contraction period. SF was corrected (yellow arrow, A) or abolished (yellow arrow, B) with His bundle pacing [Color figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

A cohort of 30 consecutive patients with CRT indication who underwent HPCSP was analyzed. Baseline patient characteristics are shown in Table 1. HPCSP included HBP and LBBP: 22 (73%) patients received HBP and 8 (27%) received LBBP. Defibrillator was implanted in 10 patients (30%). Acute implant pacing thresholds were 1.96V ± 1.20V (pulse width 0.95 ± 0.15 ms) in patients with HBP and 0.99V ± 0.45V (pulse width 0.5 ± 0.27 ms) in patients with LBBP ($p = .035$). The type of capture was 17% selective and 83% non-selective. Baseline echocardiographic characteristics are shown in Table 2.

Eight patients received LBBP. Fifty percent presented selective capture. All patients have right bundle branch block on the final ECG in V1. One patient presented left bundle branch potential. The mean spike-R (V6) in non-selective patients was 81 ms (80–85 ms). Mean QRS shortening with LBBP was −62 ± 16 ms. In Table SA there is detailed information on a case-by-case basis for all LBBP patients.

Mean total procedure time was 105 ± 37 min (minimum 60 min, maximum 225 min); the conduction system lead implant time was 29 ± 16 min and the total X-ray time was 20 ± 9 min. In relation to how much time was additionally needed for the HPCSP approach, in our center the mean coronary sinus lead implant time during the last 24 months was 33 ± 17 min; it was similar to the HPCSP lead implant time (29 ± 16 min) ($p = .23$). The mean total X-ray time with biventricular pacing in our center was 20 ± 8 min (no differences between HPCSP and biventricular pacing, $p = .93$).

There were two complications: an early HBP lead dislodgement <24 h that was repositioned successfully (threshold 0.5V, 1 ms; final QRS

TABLE 1 Baseline characteristics

	His-Purkinje conduction system pacing % ($n = 30$)
Age, years	73 ± 8
Women	23% ($n = 7$)
Ischemic heart disease	27% ($n = 8$)
Glomerular filtration (ml/min)	64 ± 19
Hypertension	90% ($n = 27$)
Diabetes	43% ($n = 13$)
Sinus rhythm	80% ($n = 24$)
Permanent atrial fibrillation	20% (n = 6)
Baseline rhythm	
* LBBB	47% ($n = 14$)
* Upgrades from RV pacing	23% ($n = 7$)
* "de novo" AV block	30% ($n = 9$)
Concomitant medications	
Beta-blockers	83.3% (25)
ACEI/ARB/ARNI	80% (24)
Aldosterone antagonist	63.3% (19)

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; LBBB, left bundle branch block; RV, right ventricular.

TABLE 2 His Purkinje conduction system outcomes: Acute and chronic

	Baseline	Acute ($n = 30$)	p
Septal flash excursion (mm)	3.6 ± 2.2	1.5 ± 1.5	<.0001
* LBBB	4.3 ± 2.3	1.8 ± 1.6	
* Upgrades from RV pacing	3.1 ± 2.6	1.0 ± 1.1	
* "de novo" AV block	2.9 ± 1.8	1.3 ± 1.8	
QRS (ms)	174 ± 24	125 ± 24	<.0001
* LBBB	175 ± 22	129 ± 21	
* Upgrades from RV pacing	187 ± 24	123 ± 24	
* "de novo" AV block	162 ± 24	121 ± 28	
	Baseline	**Chronic (6-month follow-up, $n = 27$)**	**p**
LVEF	30 ± 9%	40 ± 11%	<.0001
LVESV (ml)	97 ± 52	82 ± 52	.012
LVEDV (ml)	146 ± 57	130 ± 61	.017
NYHA functional class	2.6 ± 0.95	1.6 ± 0.49	<.0001
* NYHA III-IV	50%	0%	
Mitral regurgitation (%)	87%	48%	.002
* mild (I)	50%	37%	
* moderate (II)	27%	11%	
* moderate-severe (III)	3%	0%	
* severe (IV)	7%	0%	

116 ms). Another patient suffered a late atrial lead dislodgment at 6 months follow-up; the atrial lead was repositioned without complications.

3.1 | Acute changes in QRS width and SF with HPCSP

HPCSP significantly shortened the QRS from 174 ± 24 ms to 125 ± 24 ms (delta QRS −48 ± 21 ms; QRS shortening of 28%) ($p < .0001$; 95% CI −56.4, −40.7). At baseline, SF was present in 25 patients (83.3%) and mean SF excursion was 3.6 ± 2.2 mm. After HPCSP, this was reduced to 1.5 ± 1.5 mm; the mean SF reduction was 2.1 ± 1.7 mm (95% CI 1.4, 2.7; $p < .0001$) with a median of 2 mm (min, max −1, 5; range 6). There were no differences between the SF reduction between the patients with selective and non-selective capture (1.8 ± 1.6 mm vs. 2.1 ± 1.8 mm reduction, respectively; $p = .68$). Figure 4 shows the box-and-whisker plot representation of the change between baseline and final SF with HPCSP. In seven patients (7/25, 28%), HPCSP totally abolished SF; examples of SF abolition with LBBP and, with HBP are shown in Figures 1B and 3B, respectively. In relation to QRS narrowing, patients with SF abolishment showed significantly more QRS shortening than patients with no SF abolishment (−65 ± 15 ms vs. −44 ± 21 ms, respectively; $p = .03$, 95% CI −39.0, −2.1). There were no differences in SF correction between the HBP and LBBP group (2.1 ± 1.9 mm vs. 2.0 ± 1.5 mm respectively; 95% CI −1.4, 1.6; $p = .85$).

3.2 | Pacing follow-up at 6 months

The median percentage of ventricular pacing with HPCSP at 6-month follow-up was 97% and there was a significant decrease in pacing thresholds (1.82 ± 1.2V vs. 1.26 ± 1.05 V, $p = .002$). Baseline LBBP thresholds were significantly lower compared to HBP (0.99 ± 0.45 V vs. 1.96 ± 1.20 V; $p = .035$, 95% CI 0.07, 1.87). One patient received AV node ablation 4 months after the device implant due to AF with fast ventricular rate.

Polymorphic ventricular tachycardia was not detected in any patient. One patient with ischemic dilated cardiomyopathy (LVEF 17%) received two appropriate shocks due to sustained monomorphic ventricular tachycardia in ventricular fibrillation zone.

3.3 | Clinical and echocardiographic response at 6-month follow-up

During the 6 months of follow-up, three patients died (10%); one death was due to myocardial infarction and two were of non-cardiac etiology (COVID-19 pneumonia and colorectal cancer metastasis). At 6 months, NYHA functional class significantly decreased, from 2.6 ± 0.95 to 1.6 ± 0.5 with HPCSP ($p < .0001$). All 27 survivors remained in NYHA class I or II at 6 months post-implant. There were three hospital admissions due to heart failure.

Baseline LVEF was 30% ± 9%, increasing to 40% ± 11% among survivors at 6 months of follow-up (delta LVEF 8.6% ± 8.7%; 95% CI 4.9, 12.2; $p < .0001$) (Table 2). Echocardiographic response was defined as increase in five points in LVEF at 6 months. The percentage of echocardiographic responders was 64% in the total cohort (36% nonresponders, including the three patients who died). There was no difference in echocardiographic response rate between the HBP and LBBP groups (64% vs. 67%, respectively, $p = .89$). Echocardiographic response was observed in 71% of the nonischemic cohort and in 43% of the ischemic patients. Among survivors, 26% of the patients had normalized LVEF (≥50%) and functional recovery at 6 months, defined as "superresponders."

Finally, MR decreased with HPCSP (Table 2). At 6 months, the percentage of patients with moderate or severe MR decreased from 37%

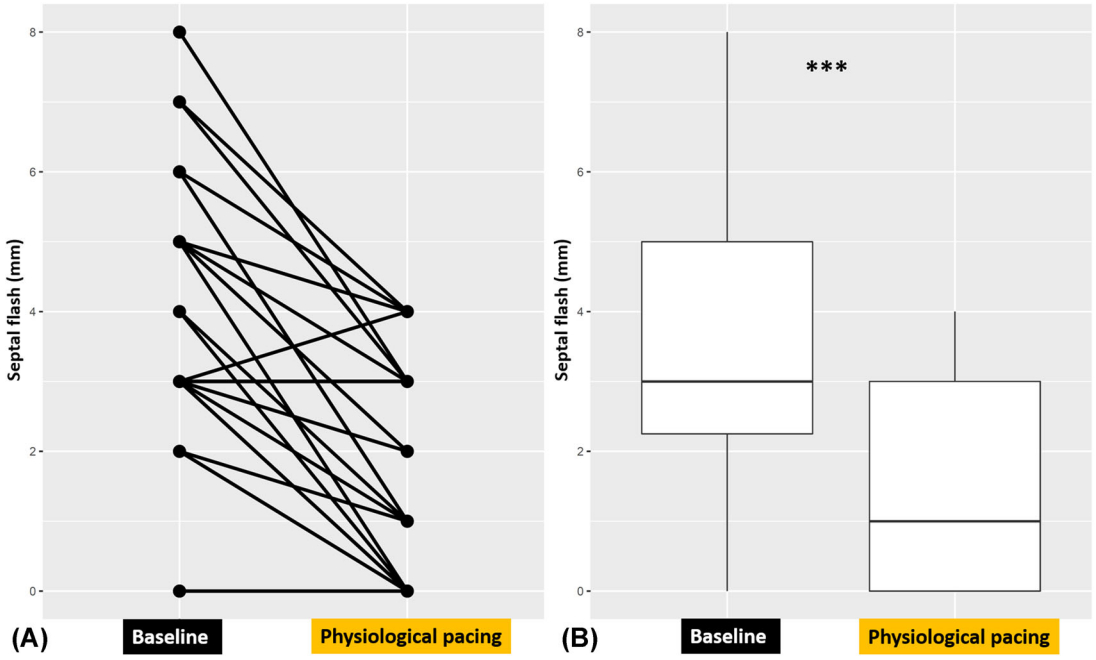

FIGURE 4 Baseline and physiological pacing septal flash (SF). Representation of SF values at baseline and with physiological pacing, in each patient ($n = 30$) (A) and Box plot diagram (B) [Color figure can be viewed at wileyonlinelibrary.com]

($n = 11$) to 11% ($n = 3$). Two patients (7%) had severe MR at baseline that decreased to moderate MR during follow-up.

3.4 | Prediction of echocardiographic response with SF

Ability to predict echocardiographic response was analysed in 25 patients with baseline SF (SF ≥1 mm) to test the hypothesis that patients would achieve echocardiographic response if intraventricular asynchrony was present and HPCSP could correct it. There was a significant correlation between the reduction in SF excursion and QRS shortening after HPCSP ($r = .41$, $p = .04$). Furthermore, correction of SF correlated with LVEF increase at 6 months ($r = .61$, $p = .004$) (Figure 5A).

In the patients with baseline SF ($n = 25$), the best SF correction value to predict echocardiographic response at 6 months was a 1.5 mm reduction in SF excursion (Figure 5B). Acute SF correction (Baseline SF – Paced HPCSP SF) ≥1.5 mm had a sensitivity of 81% and specificity of 80% to predict echocardiographic response at 6-month follow-up (area under the curve 0.856, $p = .019$). The adjusted probability prediction for LVEF response showed 86% probability if SF correction was ≥1.5 mm; otherwise, if SF correction was <1.5 mm, the probability of response was 45% ($p = .032$). The only patient who presented with worsened SF was an echocardiographic non-responder.

In the five patients with baseline SF of 0 mm (no SF), the HPCSP indications were upgrade to CRT from a previous conventional pacemaker (2/5, 40%) and "de novo" complete AV block with LVEF ≤45% (3/5, 60%). Only one of these five patients had echocardiographic response; this patient (3rd-degree AV block and LVEF 35%) had received a transcatheter aortic valve replacement due to severe aortic stenosis and 15 days after the procedure had normalized LVEF. This rapid increase in LVEF was likely due to the disappearance of the obstruction caused by the aortic stenosis. None of the other four patients showed sufficiently increased LVEF to be considered responders to HPCSP.

TABLE 3 Univariate analysis for prediction of LVEF response

	Univariate OR	95% CI	*p* value
Men	1.54	.24 – 9.90	.65
Ischemic	3.33	.57 – 19.59	.18
Permanent AF	2.14	.34 – 13.42	.42
Δ SF	.42	.21 – .86	.02
Baseline SF	.29	.04 – 2.15	.23
Baseline QRS width	.99	.96 – 1.03	.7
LBBB	.34	.07 – 1.78	.20

Abbreviation: AF, atrial fibrillation; LBBB, left bundle branch block; SF, septal flash.

In univariate analysis of predictors of echocardiographic response at 6-month follow-up (Table 3), only correction of SF (delta SF) was a significant predictor (OR.42, $p = .02$, 95% CI .21,.86). Baseline SF presence and LBBB showed a trend toward prediction of echocardiographic response, while trending predictors of non-response were male sex, ischemic etiology of LV dysfunction, and permanent AF. The small size

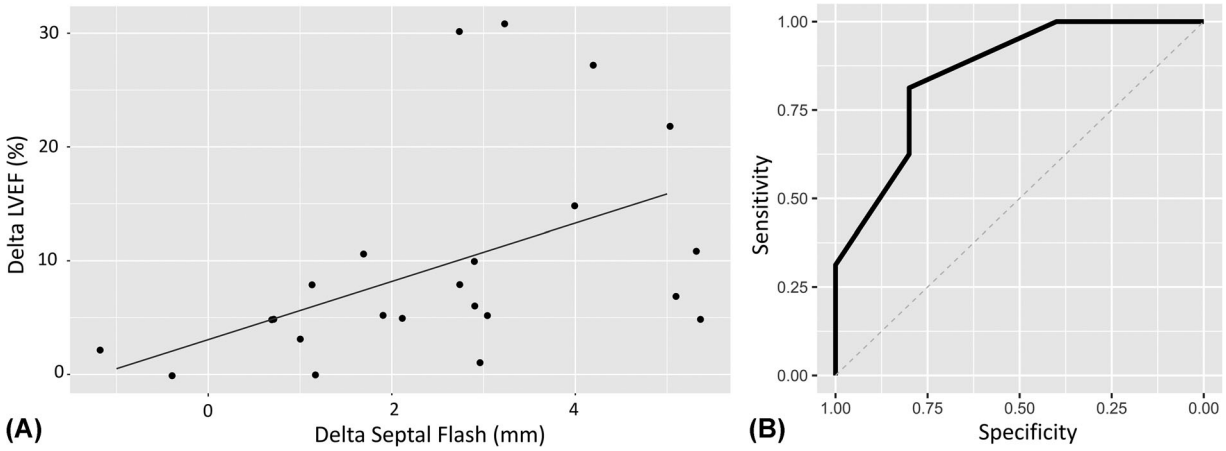

FIGURE 5 (A) Increase of left ventricular ejection fraction (LVEF) as a function of delta Septal flash. Correction of SF correlated with LVEF increase at 6 months ($r = .61$, $p = .004$). (B) Receiver operating characteristic (ROC) curve illustrates the classifying ability of SF correction to predict **echocardiographic response**. A value of SF correction ≥1.5 mm had 81% sensitivity and 80% specificity to predict echocardiographic response at 6-month follow-up (area under the curve 0.856, $p = .019$)

of the cohort may explain the lack of statistical significance of these variables.

The response analysis taking into account reduction in LVESV also showed that those patients with correction of SF≥1.5 were more likely to respond to therapy. The adjusted prediction for response with LVESV reduction ≥10% as the criterion, showed 67% probability if SF correction was ≥1.5 mm versus 29% if SF correction was <1.5 mm (OR of response = 5.0; $p = .08$; 95% CI .74, 33.8). With LVESV reduction ≥15% as the criterion, the probability was 44.4% vs 28%, respectively (OR of response 2.0; $p = .47$; 95% CI .3, 13.1).

3.5 | SF: Agreement and correlation with strain curves

We have analyzed SF with speckle-tracking longitudinal strain curves (dichotomous variable) and septal rebound stretch (quantitative variable) in the population of the study as a cooperative synchronization testing to confirm the sensitivity and specificity of SF. Kappa coefficient was k = 0.64 ($p < .001$) showing substantial agreement between SF and SF with speckle-tracking longitudinal strain curves. Sensitivity of SF was 100%; specificity 56%; positive predictive value was 84% and negative predictive value 100%. SF excursion and septal rebound stretch showed a significative correlation ($r = .63$, $p < .001$).

4 | DISCUSSION

In 1925, Wiggers[25] proposed that the more muscle was activated before excitation of the Purkinje system, the greater the asynchrony and the weaker and less effective the resulting contraction. HBP has been proposed as an alternative to conventional CRT in three randomized studies to date.[2,26,27] However, HBP has some limitations: high pacing thresholds, low R-wave amplitude, or heart block distal to the His.[3] LBBP is a more recent pacing technique with potential advantages including lower thresholds and less precision required during the implant. The combination of these techniques -HPCSP- could provide ventricular resynchronization in a wider range of patients if high thresholds are required with HBP or the block is more distal.

The main finding of our study was that physiological pacing with HPCSP improved acute intraventricular dyssynchrony and achieved echocardiographic response in 64% of cases at 6-month follow-up. Moreover, the dyssynchrony improvement with SF correction was predictive of echocardiographic response at 6 months.

4.1 | Acute SF correction predicts echocardiographic response

Our study showed that a decrease of 1.5 mm in SF excursion has 81% sensitivity and 80% specificity to predict echocardiographic response; moreover, probability of response was 86% if SF correction was ≥1.5 mm. Acute correction of asynchrony would therefore be a predictor of patient response at 6 months. Correction of SF showed moderate correlation with LVEF increase at 6 months ($r = .61$, $p = .004$), suggesting the presence of a continuum gradient between degree of SF reduction and response. Our results showed that correcting SF ≥1.5 mm could obtain echocardiographic response. Total abolition was not as important as the degree of SF change; the greater the SF correction, the more the LVEF increased. The correlation between SF and QRS shortening reinforces the potential for HPCSP pacing to correct both mechanical and electrical asynchrony.

Subject to more studies, SF – an echocardiographic parameter that can be measured quickly and easily – could become an efficient tool to ascertain in the Electrophysiology Laboratory whether HPCSP properly corrected mechanical dyssynchrony and to predict echocardiographic response in a specific patient. Patients with 0 mm of baseline SF were not responders in our series; moreover, HPCSP did not induce

mechanical asynchrony in these patients and the LVEF remained stable at 6-month follow-up. Our data suggest that patients without baseline SF will not achieve sufficient LVEF increase to be considered responders to the therapy. In these patients, physiological pacing may prevent LVEF worsening.

Patients who did not present echocardiographic response to HPCSP had a mean delta SF of 1.1 mm (vs. mean delta SF of 2.5 mm in responders). The common feature of non-responders was de novo AV block or an RV pacing upgrade. Sairaku et al[28] showed that reverse remodeling is unlikely to occur in patients with AV block and LV systolic dysfunction, compared to those with preexisting CRT indications, even when they have a favorable clinical response to CRT.

4.2 | Echocardiographic response to physiological pacing

In this CRT cohort, 64% of patients were echocardiographic responders (36% non-responders) at 6-month follow-up, which is comparable to the response obtained with biventricular CRT[29,30] and with the physiological pacing series.[6,7,17,31] Our study included 27% of ischemic patients; echocardiographic response was observed in 71% of nonischemic patients and 43% of the ischemic patients.

In the search for a resynchronizing solution for all patients –and the most suitable for each one– HPCSP showed good results, correcting dyssynchrony, improving LVEF at 6 months, and achieving significant change in the degree of MR. At 6-month follow-up, 26% of patients were superresponders. Although randomized studies are lacking, our results concur with previous studies to configure HPCSP as an alternative to biventricular CRT –perhaps not replacing it, but as a promising new tool.

Biventricular CRT does not work in all patients, just as HPCSP will not always work; randomized studies are needed to establish the characteristics of exactly which patient will benefit the most from each technique. In summary, our data show that HPCSP improved dyssynchrony and LVEF. Dyssynchrony correction is a predictor of echocardiographic response.

4.3 | Limitations

The obtained results were derived from a retrospective analysis of prospectively collected data with a low sample size (the first 30 patients implanted in our center); patients were not randomized and echocardiographers who performed the SF measurements were not blinded. First cases in the series could have worse thresholds as a result of being part of the learning curve of the implanters (two electrophysiologists with more than 15 years of experience implanting cardiac devices). The long-term evolution of pacing thresholds in HBP are unknown and need to be carefully monitored.

A powered prospective randomized study comparing HPCSP with conventional biventricular CRT in terms of echocardiographic and clinical response is an essential next step. A randomized trial to compare both CRT approaches is underway in our centre (ClinicalTrials.gov Identifier: NCT04054895).

5 | CONCLUSIONS

HPCSP improved acute intraventricular dyssynchrony in patients with an indication for CRT and obtained 64% echocardiographic responders at 6-month follow-up. SF correction correlated with LVEF increase at 6-month follow-up. Dyssynchrony improvement assessed with SF correction predicted echocardiographic response.

ACKNOWLEDGEMENTS

The authors thank Neus Portella, Carolina Sanroman, and Eulalia Ventura for administrative support; Elaine Lilly for manuscript editing; Rebeca Domingo, Alba Cano, Sara Hevia, Marta Carrasco, and Clara Diago for their work in the resynchronization clinic; David Sanz and Jose Alcolea for their logistical support in the Cardiac Imaging Section. And special thanks to Dr Roderick Tung, Dr Gaurav Upadhyay, and Dalise Shatz for their help in implementing the LBBP program in our center. MPL and the *Devices Team of Hospital Clinic* have received the "Grant of the Catalan Society of Cardiology, 2019": *Resynchronization therapy with hisian pacing*. MPL is funded by the *Research Grant Josep Font 2019*, Hospital Clínic de Barcelona.

DISCLOSURES OF INTERESTS

Dr Pujol Lopez has received speaker honoraria from Medtronic. Dr Tolosana has received honoraria as a lecturer and consultant for Abbott, Boston Scientific, and Medtronic. Dr Mont has received unrestricted research grants, fellowship program support, and honoraria as a lecturer and consultant from Abbott, Biotronik, Boston Scientific, Livanova, and Medtronic and is stockholder of Galgo Medical and Corify. Dr Roca has received honoraria as a lecturer and consultant for Abbott and Biosense Webster. Dr Sitges has received consultant fees and speaker honoraria from Abbott, Medtronic, General Electric, and Edwards Lifesciences.

ORCID

Margarida Pujol-López MD https://orcid.org/0000-0002-4523-6469
Eduard Guasch MDPhD https://orcid.org/0000-0003-4238-5319
Lluís Mont MDPhD https://orcid.org/0000-0002-8115-5906

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How to cite this article: Pujol-López, Margarida, Jiménez Arjona, Rafael, Guasch, Eduard, et al. Septal Flash Correction with His-Purkinje Pacing Predicts Echocardiographic Response in Resynchronization Therapy. *Pacing Clin Electrophysiol*. 2022;45:374–383. https://doi.org/10.1111/pace.14445