Impact of physiological pacing on functional mitral regurgitation in systolic dysfunction: Initial echocardiographic remodeling findings after His bundle pacing

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BACKGROUND Although His bundle pacing (HBP) has been shown to improve left ventricular ejection fraction (LVEF), its impact on mitral regurgitation (MR) remains uncertain.

OBJECTIVES The aim of this study was to evaluate change in functional MR after HBP in patients with left ventricular (LV) systolic dysfunction.

METHODS Paired echocardiograms were retrospectively assessed in patients with reduced LVEF (<50%) undergoing HBP for pacing or resynchronization. The primary outcomes assessed were change in MR, LVEF, LV volumes, and valve geometry pre- and post-HBP. MR reduction was characterized as a decline in ≥1 MR grade post-HBP in patients with ≥grade 3 MR at baseline.

RESULTS Thirty patients were analyzed: age 68 ± 15 years, 73% male, LVEF 32% ± 10%, 38% coronary artery disease, 33% history of atrial fibrillation. Baseline QRS was 162 ± 31 ms: 33% left bundle branch block, 37% right bundle branch block, 17% paced, and 13% narrow QRS. Significant reductions in LV end-systolic volume (122 mL [73–152 mL] to 89 mL [71–122 mL], $P = .006$) and increase in LV ejection fraction (31% [25%–37%] to 39% [30%–49%], $P < .001$) were observed after HBP. Ten patients had grade 3 or 4 MR at baseline, with reduction in MR observed in 7. In patients with at least grade 3 MR at baseline, reduction in LV volumes, improved mitral valve geometry, and greater LV contractility were associated with MR reduction. Greater reduction in paced QRS width was present in MR responders compared to non-MR responders (-40% vs -25%, $P = .04$).

CONCLUSIONS In this initial detailed echocardiographic analysis in patients with LV systolic dysfunction, HBP reduced functional MR through favorable ventricular remodeling.

KEYWORDS Bradyarrhythmia; Cardiac resynchronization therapy; Functional mitral regurgitation; Heart failure; His bundle pacing; Left bundle branch block; Right bundle branch block

(Heart Rhythm O2 2021;2:446–454)

Introduction

Functional mitral regurgitation (MR), or MR in the absence of underlying primary structural or degenerative abnormality of the mitral valve (MV), is commonly observed in patients with left ventricular (LV) dysfunction.[1] The presence of functional MR is associated with an increased risk of morbidity and hospitalization, and severe functional MR has been shown to be independently associated with increased risk of mortality beyond traditional markers such as low LV ejection fraction (LVEF).[2,3] While medical therapy with vasodilators, beta-blocking agents, or antagonists of the renin-angiotensin-aldosterone system remain first-line,[4,5] biventricular pacing as a means to deliver cardiac resynchronization therapy (CRT) also has an established role in treating MR among patients with systolic dysfunction and intraventricular conduction delay, and may reduce the risk of subsequent hospitalization.[4,6,7]

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2666-5018/

https://doi.org/10.1016/j.hroo.2021.07.007

KEY FINDINGS

- Physiological pacing via His bundle pacing (HBP) is associated with improvement in measures of left ventricular (LV) remodeling, including reduction in volume and increased left ventricular ejection fraction.
- Among patients with severe mitral regurgitation (MR) at baseline, HBP was associated with reduction in MR, and this was more common among patients with wide QRS at baseline
- Initial detailed echocardiographic assessment revealed that improvement in mitral valve geometry and LV contractility are possible mechanisms of MR improvement after HBP.

More recently, His bundle pacing (HBP) has emerged as a new strategy to maintain synchrony in patients with narrow QRS, and to achieve resynchronization in patients with wide QRS due to bundle branch block.[8,9] HBP has been associated with improvements in LVEF with reduction in heart failure hospitalization.[10] A recent evidence review committee found that HBP was comparable to biventricular pacing with respect to improvements in measures of LV remodeling (ie, LV end-systolic and end-diastolic volumes) and LVEF relative to right ventricular (RV) pacing.[11] HBP has recently gained an indication (class IIa) for patients with moderate LV dysfunction with an LVEF between 36% and 50% who are expected to require $\geq$40% ventricular pacing.[12]

Despite growing evidence of impact on ejection fraction, the impact of HBP on functional MR has not been systematically analyzed. While biventricular pacing has been demonstrated to improve MR, the impact of HBP on MR and the role for patient selection has not been reported. We sought to characterize the impact of HBP on MR in patients with baseline LV dysfunction, examine possible mechanisms of MR reduction, and identify predictors of improvement.

Methods

Study population

All patients undergoing permanent device implant (dual-chamber, or CRT device implant with or without defibrillator) at the University of Chicago Medical Center from February 2016 to February 2019 were prospectively followed in a registry that was approved by our Institutional Review Board (IRB# 16-0272) for the purpose of safety and clinical outcomes assessment, and adhered to the guidelines of the Helsinki Declaration. All patients provided informed consent prior to device implant. Indications for device placement included need for pacing for standard bradyarrhythmia indications (ie, high-degree atrioventricular [AV] block with expected $\geq$40% ventricular pacing) or resynchronization pacing for patients with heart failure and wide QRS in whom either biventricular pacing was not successful or primary HBP was offered after close discussion of the risks and benefits. Patients were selected for this cohort study if (1) they had EF $<$50% and (2) they underwent implantation with an HBP device (either single-chamber, dual-chamber, or CRT device) with $>$40% pacing, demonstrated baseline LV dysfunction (ie, baseline LVEF $\leq$50%), and in whom complete paired echocardiographic data were available allowing for quantitative assessment of LV volumes and MR. Patients undergoing primary LV septal or left bundle branch pacing were excluded. Patients with history of MV replacement were excluded from analysis, although history of other valve replacement or repair (eg, aortic valve replacement, MV annuloplasty) were included. No patients underwent valve surgery or percutaneous valvuloplasty after implant.

Implant technique and follow-up

Implant procedures were performed according to routine practice for pacemaker or defibrillator devices. The Medtronic SelectSecure Model 3830 lead (Medtronic, Minneapolis, MN) was used in all cases for HBP. The lead was deployed using either the fixed-curve Model C315His catheter (Medtronic) or deflectable Model C304 sheaths (Medtronic), per the operator preference. His bundle mapping and lead fixation at the time of implant was performed as described previously.[8,13] Briefly, the 3830 lead was advanced through to the sheath, which is positioned across the tricuspid annulus (in anterosuperior orientation in right anterior oblique and septal orientation in left anterior oblique). The tip of the 3830 helix was extended slightly beyond the sheath and unipolar electrograms were obtained. These were simultaneously displayed both on the device programmer (Medtronic Encore Programmer; Medtronic) and the electrophysiology recording system (GE CardioLab EP Recording System, Waukesha, WI) at a sweep speed of 100 mm/s. Local electrograms were inspected in order to discern a His potential and atrial-to-ventricular electrogram ratio of at least 1:2 or greater to minimize the risk of atrial oversensing, and the lead was deployed in a region with adequate ventricular sensing with acceptable capture thresholds. After lead deployment, signals were then reassessed in bipolar configuration to ensure stability. Final programming (unipolar vs bipolar) was left to the discretion of the operator with a goal to maintain the narrowest possible QRS configuration. QRS correction with either nonselective or selective capture was accepted, as described in a recent working group statement.[14]

In patients with wide QRS due to bundle branch block, baseline QRS morphology was characterized according to the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines as left bundle branch block (LBBB), right bundle branch block (RBBB), nonspecific intraventricular conduction delay, or predominantly RV paced at baseline. In patients with wide QRS undergoing HBP, pacing output-dependent morphology changes of the paced QRS consistent with loss of His capture at lower output was required at implant to be demonstrated prior to lead fixation. Based on data regarding

His engagement from intracardiac left-sided recordings, the corrected paced QRS duration was measured from the onset of the intrinsicoid R wave noted in V_1 or V_2.[9] Left ventricular activation time (LVAT) was measured as the time between stimulation artifact and the peak of R wave in V_6. QRS durations and LVATs were measured either using the GE CardioLab (GE Healthcare, Chicago, IL) recording system or with measurement of postimplant electrocardiograms (ECGs) using electronic calipers (MUSE, Version 9; GE Healthcare; or Cardio Calipers; Iconico, Philadelphia, PA).

Patients were followed postoperatively with an incision check at approximately 2 weeks and routine clinical evaluation at 3, 6, and 12 months. Device interrogations also were performed either in-office or remotely. Reported device measurements included lead sensing (mV), pacing capture threshold (V), pulse width (ms), and impedance (ohms). At each follow-up visit, 12-lead ECGs were performed during device testing to ensure HBP capture remained present. AV delays were optimized to ensure HBP capture and QRS correction were present. Device outputs were also adjusted to maintain adequate safety margin (double or at least 1.5 V above capture threshold).

Echocardiographic imaging and analysis

Baseline and follow-up transthoracic echocardiogram imaging was performed at a single institution using either an iE33 or EPIQ 7C system (Philips Healthcare, Andover, MA), equipped with an X5-1 phased-array transducer. The images were stored and subsequently analyzed offline using the Excelera software platform (Philips Healthcare). Readers were blinded to QRS change and clinical outcome at the time of retrospective review. A multiparametric assessment of MR severity was performed systematically using the following qualitative and semiquantitative parameters: (1) Color-flow Doppler jet area was evaluated at 50–70 cm/s Nyquist limit, as the ratio of the area of the regurgitant jet in comparison to the LA area. (2) The relative density of the continuous-wave Doppler jet was compared to the density of the anterograde transmitral flow. (3) Pulmonary vein flow S/D ratio was calculated as the ratio of the maximal anterograde systolic and diastolic velocities of the pulmonary vein orifice sampled with pulsed-wave Doppler. (4) Mitral E wave velocity was measured as the maximal velocity of the transmitral anterograde flow sampled with pulsed-wave Doppler at the tip of the mitral leaflets. (5) The vena contracta (VC) averaged from the 4- and 2-chamber (4Ch and 2Ch) views using color-flow Doppler with VC <0.3 cm indicative of mild MR while VC >0.7 cm was indicative of severe MR. MR severity was graded taking into consideration all the aforementioned parameters, using a 4-level ordinal scale (grade 1 = trivial, grade 2 = mild, grade 3 = moderate, or grade 4 = severe) consistent with the American Society of Echocardiography Guidelines.[15] MR response was characterized as an improvement by at least 1 grade in MR after HBP in patients $\geq$grade 3 at baseline.

MV apparatus structures were also evaluated. Annulus area was obtained both in end-diastole and in end-systole by measuring the annulus diameter in the parasternal long-axis and 4Ch views. Tenting height was measured in mid-systole in the 3-chamber (3Ch) view as the distance between the annulus plane and the leaflets' coaptation point with tenting area measured in the same view. Posterior and anterior leaflet angles were measured in mid-systole in 3Ch as the angles between the posterior and anterior leaflets and the annulus plane, respectively. Interpapillary distance was measured in end-diastole and end-systole, in the parasternal short-axis view. LV contractility (dP/dt) was estimated by using continuous-wave Doppler assessment of MR during isovolumetric contraction. Disk summation methodology was used to calculate left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volumes (LVESV) from the 4Ch and 2Ch views dedicated, respectively, for the left ventricle. LVEF was calculated using the standard formula: LVEF = (LVEDV − LVESV)/LVEDV. LV sphericity index was calculated by dividing the major-axis dimension to minor-axis dimension in the 4Ch view.

Endpoints

The primary endpoint was reduction in MR severity after HBP. In addition, echocardiographic parameters of interest included change in LVEF and LV volumes across all patients. In order to explore possible mechanism of improvement of MR among patients with at least moderate MR at baseline, MV geometry (ie, tenting area, coaptation height, leaflet angles, interpapillary muscle distance), LV sphericity, and LV contractility (dP/dt) were also assessed and analyzed between MR responders and nonresponders. Clinical outcomes included time to first cardiovascular (CV) hospitalization or death, where indication for hospitalizations were adjudicated by reviewers blinded to determination of MR response.

Statistical analysis

For baseline clinical characteristics, continuous variables were expressed as means ± standard deviations or medians with interquartile ranges and compared with either Student *t* tests or Mann-Whitney *U* (Wilcoxon) tests, depending upon normality. Categorical variables were expressed as relative counts and percentages and compared with χ^2 tests of association or Fisher exact tests. Paired *t* tests or nonparametric Wilcoxon match-pair sign rank tests were used to compare pre- and post-echo parameters. Pre- and post-MR final grades (on the 4-level ordinal scale) were compared using a McNemar test. Kaplan–Meier curves were generated to describe time to survival in terms of MR responder, and then tested using log-rank tests. Tests were 2-tailed and considered statistically significant with a P value $< .05$. All statistical analyses were conducted using STATA MP version 15 (Stata Corp, College Station, TX).

Table 1 Baseline characteristics

Characteristic	All patients (N = 30)
Age	68 ± 15
Male	22 (73%)
Height (cm)	175 (163–178)
Weight (kg)	82.4 ± 19.3
BMI	26.6 (23.0–28.9)
CAD	11 (38%)
CABG	3 (10%)
Any valve surgery	8 (27%)
Pre NYHA class	
1	7 (23%)
2	6 (20%)
3	13 (43%)
4	4 (13%)
History of any VT	10 (33%)
History of any AF	10 (33%)
Hypertension	23 (77%)
Diabetes mellitus	10 (33%)
CKD	20 (67%)
CKD stage	
1	0 (0%)
2	10 (33%)
3	8 (27%)
4	1 (3%)
End-stage renal disease	1 (3%)
Creatinine	1.10 (1.00–1.40)
LVEDV mean (mL)	164 (125–226)
LVESV mean (mL)	122 (73–152)
LVEF (%)	31 (25–37)
Baseline QRS width (ms)	162 ± 31
Baseline QRS morphology	
LBBB	10 (30%)
RBBB	11 (37%)
RV-paced	5 (17%)
Narrow	4 (13%)
CRT system (defibrillator or pacemaker)	22 (73%)
Dual-chamber pacemaker	8 (27%)

AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CKD = chronic kidney disease; CRT = cardiac resynchronization therapy; LBBB = left bundle branch block LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; RBBB = right bundle branch block; RV = right ventricle; VT = ventricular tachycardia.

Results

Baseline and implant characteristics

During the 3-year study period, 119 patients underwent attempts for HBP, during which His bundle lead placement was successful in 103 (87%). Among patients with baseline LV dysfunction (LVEF <50%), 30 patients with complete paired echocardiographic data were analyzed with mean clinical follow-up of 17 months. Baseline characteristics are presented in Table 1. The mean age was 68 ± 15 years with 73% male, 38% with history of coronary artery disease, 67% with history of chronic kidney disease, and 57% with NYHA grade 3 or 4. At baseline, MR distribution was 23% grade 1 (trivial), 44% grade 2 (mild), 13% grade 3 (moderate), and 20% grade 4 (severe). Overall, median LVEF at baseline was 31% (25%–37%), median LVESV was 122 mL (73–152 mL), and median LVEDV 164 mL (125–226 mL).

With respect to past arrhythmic history, 35% demonstrated history of ventricular tachycardia and 33% demonstrated history of paroxysmal or persistent atrial fibrillation. The majority of patients demonstrated wide QRS patterns at baseline (33% LBBB, 37% RBBB, 17% chronically RV-paced, and 13% narrow QRS). A total of 73% of patients received CRT devices (CRT-D 82%, CRT-P 12%), and 27% received dual-chamber pacemakers. The median threshold of the His lead at the time of implant was 1.50 V (0.7–2.75 V) with a mean pulse width of 0.89 ± 0.32 ms. The mean His lead impedance was 488 ± 134 ohms.

Impact of HBP on MR, LVEF, and QRS

After HBP a significant reduction in mean MR severity was observed at a median 4.7 months. The distribution of MR after HBP was 47% exhibiting grade 1, 30% grade 2, 20% grade 3, and 3% grade 4. Improvement in the proportion of patients exhibiting grade 1 MR after HBP reached significance (23% at baseline to 47% in follow-up, $P = .02$) (Figure 1A). Among patients with at least grade ≥2 MR at baseline, MR reduction was observed in 12 of 23 patients (52%). The majority of patients (n = 8, 35%) declined by 1 ordinal grade and 4 patients (17%) improved by 2. Among patients with grade 3 or 4 MR at baseline, 7 (70%) demonstrated decline in MR after HBP, and 57% of these patients improved by 2 ordinal grades (33% of grade 4 patients at baseline improved to grade 2 and 50% of grade 3 at baseline improved to grade 1 after HBP). Overall, 17 patients (57%) demonstrated no change in MR grade and a single patient had a 1-grade deterioration (who had a narrow QRS at the time of implant). When examined quantitatively, the median vena contracta among all patients was 0.32 cm (0.08–0.48) cm at baseline and decreased to 0.20 cm (0.00–0.34 cm) ($P < .001$) (Figure 1B). A representative example of change in MR and change in ECG of a patient LBBB is shown in Figure 2.

There was significant improvement in LVEF and volumes across the cohort. Median LVEF increased from 31% (25%–37%) to 39% (30%–49%) ($P < .001$) and was associated with an improvement in median LVESV from 122 mL (73–152 mL) to 89 mL (68–122 mL) ($P = .006$). There was a trend towards improvement in median LVEDV, from 164 (125–226 mL) to 143 (123–201 mL), which did not reach significance ($P = .12$). Depiction of major echocardiographic indices pre- and post-HBP are shown in Figure 3.

There was significant reduction in QRS width after HBP (baseline 162 ± 31 ms to 112 ± 15 ms after HBP, $P < .001$) across all patients. Average QRS at baseline by morphology was similar among patients with wide QRS (LBBB 179 ± 21 ms, RBBB 159 ± 20 ms, RV-paced 180 ± 20 ms) and significantly longer than patients with narrow QRS (103 ± 4 ms, $P < .001$ vs wide QRS morphologies). Corrected QRS width in follow-up was significantly reduced among wide QRS patients (LBBB 113 ± 18 ms, RBBB 112 ± 12 ms, RV-paced 114 ± 22 ms) and was comparable in narrow QRS patients (109 ± 13 ms). The mean LVAT after

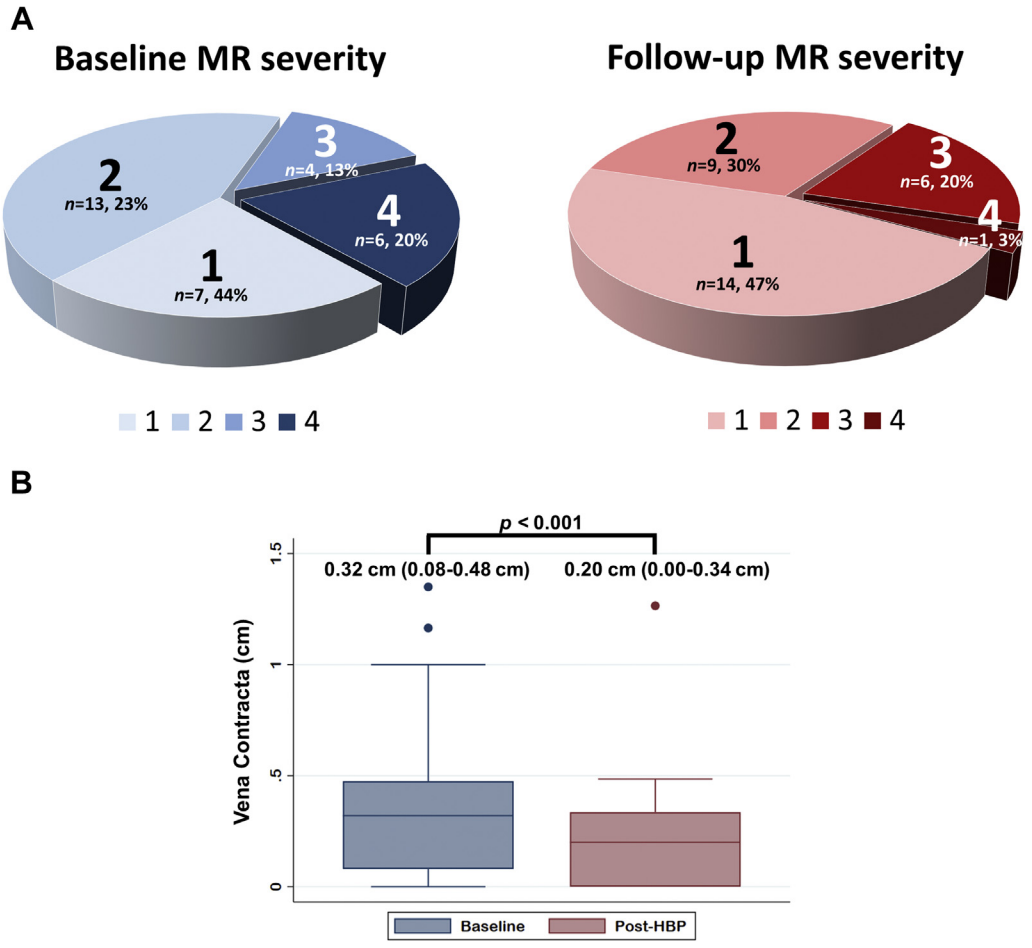

Figure 1 **A:** Distribution of grades of mitral regurgitation at baseline and in follow-up after His bundle pacing (HBP). **B:** Improvement in functional mitral regurgitation as assessed by vena contracta at baseline and in follow-up after HBP. MR = mitral regurgitation (grade 1, trivial; grade 2, mild; grade 3, moderate; grade 4, severe).

implant was 99 ± 20 ms and was similar when stratified by QRS morphology at baseline (LBBB 100 ± 25 ms, RBBB 101 ± 19 ms, RV-paced 99 ± 18 ms, narrow 91 ± 15 ms; $P = .87$). Patients with narrow QRS demonstrated only grade ≤2 MR at baseline and showed no significant change after HBP. Patients with wide QRS all demonstrated comparable MR change after HBP (LBBB -0.4 ± -0.7 grades, RBBB -0.5 ± 0.7 grades, RV-paced -1 ± 1 grade; $P = .35$).

Predictors of MR response with HBP

The baseline demographics of patients who were identified as demonstrating MR response were well matched to patients without reduction in MR, with the exception slightly higher baseline creatinine in MR nonresponders. The vena contracta of patients exhibiting MR response was comparable at baseline with patients that did not improve (median 0.58 cm [0.43–1.17 cm] vs 0.44 cm [0.42–0.98 cm], $P = .43$). There were no significant intergroup differences in baseline LVEF, volumes, or measures of LV geometry among patients with and without MR response at baseline. MR responders demonstrated greater improvement in ordinal MR grade and demonstrated significant reductions in LVESV when compared to nonresponders in follow-up (-44 mL [-108 to +9 mL] vs +10 mL (-8 to +16 mL], $P = .03$). They also demonstrated smaller MV annulus area after HBP (at end-diastole: 8.27 cm^2 [7.43–9.13 cm^2] vs 16.61 cm^2 [10.83–17.66 cm^2], $P = .03$; at end-systole: 6.33 cm^2 [5.60–7.77 cm^2] vs 15.33 cm^2 [8.81–15.45 cm^2], $P = .03$). LVEF change after HBP trended higher among MR responders vs nonresponders, but this did not reach statistical significance (+6% [+5 to +24%] vs -1% [-8% to +10%], $P = .21$) (Supplemental Table).

When evaluating only patients with MR response in order to discern mechanisms of improvement, both measures of reduction in tethering forces and improved closing forces were observed (Table 2). Favorable LV remodeling was observed in MR responders, notably with significant reductions in LVESV (154 mL [99–218 mL] to 109 mL [89–143 mL], $P = .04$); smaller MV annulus area in end-diastole (9.86 cm^2 [8.65–15.90 cm^2] to 8.27 cm^2 [7.43–9.13 cm^2], $P = .04$) and end-systole (8.03 cm^2 [7.48–14.16 cm^2] to 6.33 cm^2 [5.60–7.77 cm^2], $P = .03$). Reduced tenting area, shorter tenting height, and smaller posterior leaflet angle

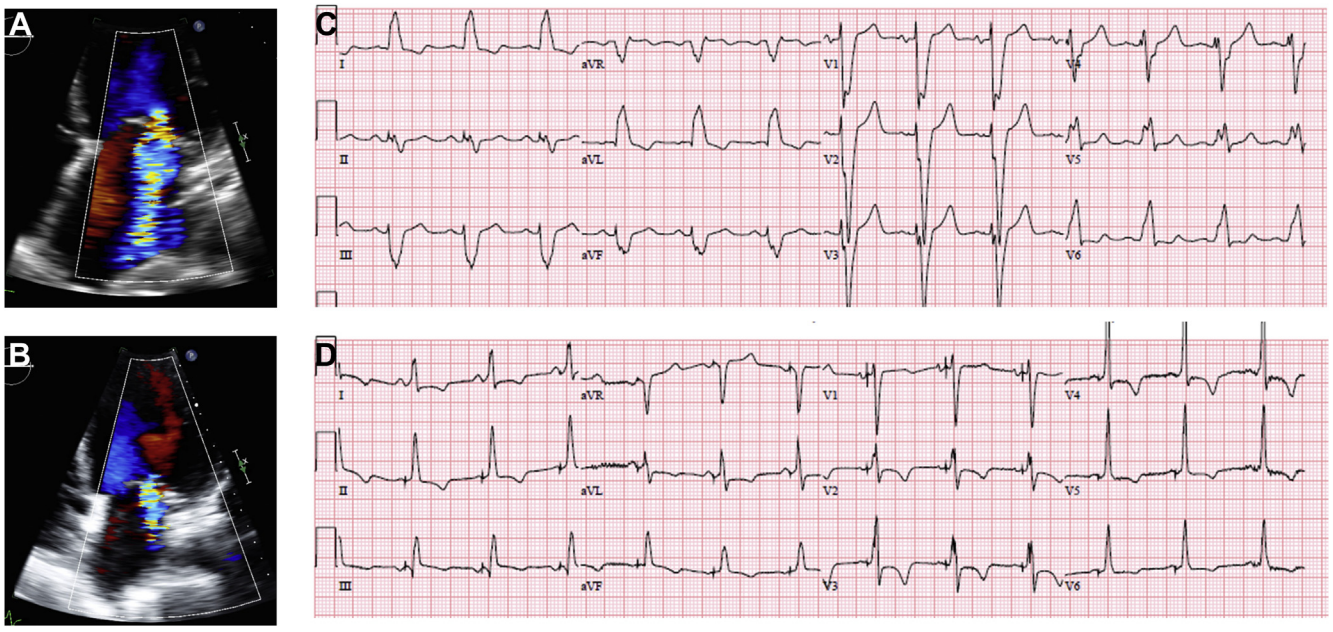

Figure 2 Representative example of change in mitral regurgitation before and after His bundle pacing (HBP) in patient with left bundle branch block (LBBB). A 70-year-old male with left ventricular ejection fraction (LVEF) with severe mitral regurgitation at baseline and LVEF 12% with LBBB pattern (QRS width 197 ms) underwent HBP with QRS correction (corrected QRS width 115 ms) and improvement in mitral regurgitation (MR) to 29% and post-HBP LVEF of 29%. **A:** MR pre-HBP. **B:** MR post-HBP. **C:** Baseline electrocardiogram (ECG). **D:** Follow-up ECG.

was also observed in follow-up among MR responders. No significant improvements in measures of LV geometry or LV contractility were noted in MR nonresponders.

When examining MR response by baseline QRS morphology, patients with MR response demonstrated numerically longer QRS width at baseline, but this did not reach significance (182 ± 26 ms vs 168 ± 28 ms, $P = .46$), possibly owing to small sample size. MR response was observed in 67% of LBBB and chronically RV-paced patients at baseline and 75% of RBBB patients. Nonselective HBP capture with QRS correction was observed in all patients at programmed outputs. Percent QRS correction was significantly greater among patients that achieved an MR response relative to nonresponders (-40% ± 9% vs -25% ± 6%, $P = .04$).

Clinical outcome

Overall clinical outcome was evaluated over a mean follow-up duration of 17 ± 9 months. Two deaths and 12 cardiovascular hospitalizations were noted across all patients during the study period. Heart failure was the cause of cardiovascular hospitalization in 8 of 12 patients (67%); pocket hematoma, atrial flutter, planned premature ventricular complex ablation, and noncardiac chest pain were the remaining causes. When examining outcomes of patients with grade ≥3 MR at baseline, a trend towards reduced rate of CV hospitalization was found among patients demonstrating MR response relative to nonresponders, which did not reach significance ($P = .054$).

Discussion

The primary findings of the current study are the following: (1) In the majority of patients with LV dysfunction and wide QRS, we found that HBP was associated with significant reductions in MR severity, in concert with improvement in EF and reduced LV volumes. (2) Patients with wide QRS were the most likely to show improvement in MR after HBP, and greater degree of QRS narrowing was associated with MR response. (3) MR reduction after HBP appears associated with a combination of favorable LV geometric and annular remodeling along with increased LV contractility.

The present findings focus on the impact of HBP on MR and are in line with physiologic observations and prior data regarding improvement in functional MR with biventricular pacing for CRT. The observation that biventricular pacing was associated with reverse LV remodeling and reduced MR was first shown in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial,[16] in which all patients received CRT devices and were randomized to either CRT-ON or CRT-OFF in a double-blinded fashion. In the study, significant improvements in LV volumes were noted at 6 months that were also associated with significantly decreased functional MR.[17] In addition to the impact CRT has on MR, both severity of baseline MR and persistence of MR after biventricular pacing has been predictive of worse overall survival, increasing the clinical significance of focusing on MR when considering pacing strategies.[18]

Early work in CRT found that the probable mechanisms for MR improvement with biventricular pacing were an acute

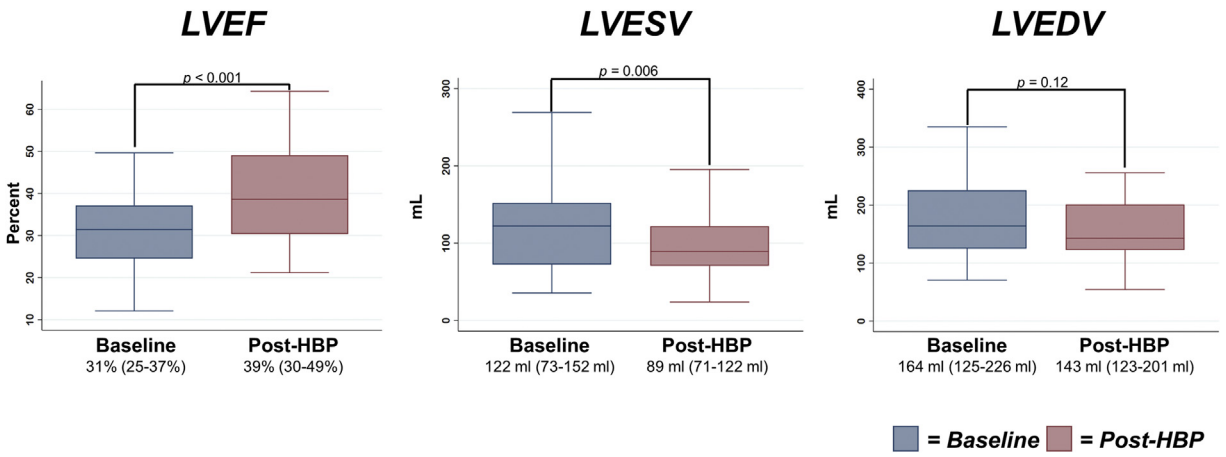

Figure 3 Left ventricular ejection fraction (LVEF) and measures of left ventricular (LV) remodeling at baseline and after His bundle pacing (HBP). LVEDV = LV end-diastolic volume; LVESV = LV end-systolic volume.

rise in LV closing forces[19] together with improved papillary muscle synchrony.[20] Certainly, the presence of scar adjacent to the papillary muscle also has been associated with an increased risk of MR,[21] but it likely does not explain the mechanism of MR for the majority of patients. Building upon observations from canine models, even dramatic LV dysfunction was not associated with development of MR in the absence of LV dilation.[22]

Our present understanding suggests that functional MR in heart failure is due to a complex interplay of closing and tethering forces acting on the valve, and that the primary impact of biventricular pacing appears appear to be improved LV function and favorable ventricular remodeling.[23,24] Similarly, in patients receiving HBP, those patients who were MR responders demonstrated significant improvements in LVESV after therapy, particularly when compared to MR nonresponders. LV closing forces, as measured by instantaneous dP/dT, also were significantly improved for MR responders relative to baseline, and they were concordant with increased LVEF in the same group. Perhaps more

Table 2 Echocardiographic indices of geometry and left ventricular function in mitral regurgitation responders (n = 7) before and after His bundle pacing

Characteristic	Pre-HBP	Post-HBP	*P*
Vena contracta – mean (cm)	0.58 (0.43–1.17)	0.33 (0.05–0.42)	.02*
MR final evaluation			
1	0 (0%)	2 (29%)	.50
2	0 (0%)	2 (29%)	.50
3	2 (29%)	3 (43%)	1
4	5 (71%)	0 (0%)	.062
LVEDV mean (mL)	243 (163–279)	160 (123–228)	.043*
LVESV mean (mL)	160 (122–218)	118 (68–135)	.02*
LVEF (%)	31 (16–36)	40 (24–45)	.03*
dP/dT (mm Hg/s)	391 (233–649)	551 (432–805)	.04*
Pulmonary S/D	0.39 (-0.39 to 0.43)	1.04 (0.26 to 1.20)	.07
MV annulus area – end diastole	9.86 (8.65–15.90)	8.27 (7.43–9.13)	.04*
MV annulus area – end systole	8.03 (7.48–14.16)	6.33 (5.60–7.77)	.03*
Tenting area 3Ch (cm^2)	4.65 (3.7–7.3)	2.7 (2.55–3.6)	.02*
Tenting height 3Ch (cm)	1.93 (1.85–2.71)	1.36 (1.22–1.7)	.02*
Posterior leaflet angle 3Ch	58 ± 11	46 ± 8	.01*
Anterior leaflet angle 3Ch	54 (50–65)	45 (35–60)	.09
Interpapillary distance short axis end diastole (mm)	301 (29–34)	27 (23–37)	.40
Interpapillary distance short axis end systole (mm)	24 ± 11	21 ± 6	.44
LV sphericity index	0.61 (0.55–0.62)	0.57 (0.54–0.59)	.06

*Statistically significant ($P < .05$).

HBP = His bundle pacing; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; MV = mitral valve; S/D = systolic/diastolic; 3Ch = 3-chamber.

importantly, significant alterations in MV and LV chamber geometry were noted after HBP, suggestive of a reduction in tethering forces as a driver of reduced MR. This was noted when MR responders were compared to nonresponders, as well as when examining improvement within MR responders at baseline and in follow-up after HBP.

Importantly, close to one-third of patients receiving conventional biventricular pacing derive no detectable echocardiographic or clinical improvement from therapy, and this number may be higher in patients with non-LBBB patterns.[25] In contrast, HBP was associated with improvement in MR in patients who were chronically paced at baseline and patients with RBBB. While traditional biventricular pacing has an established role in treating patients with pacing-induced cardiomyopathy, it may be deleterious in patients with RBBB, and there may be a unique role for HBP in these patients. Indeed, the rate of MR response was similar among patients with baseline LBBB vs RBBB receiving HBP. Chronically paced patients also appear quite suitable for consideration for HBP upgrade, and prior work has shown improvements in ventricular remodeling now in multiple studies.[26,27]

In patients receiving biventricular pacing, longer QLV and shorter final QRS duration have been associated with an increased likelihood in reduction in MR.[6,28] Among patients receiving HBP, the final QRS width has also been associated with improved clinical outcome.[29] In the present study, degree of QRS narrowing was associated with greater likelihood of MR response among patients with grade 3 or 4 MR at baseline. With respect to patients with narrow QRS, it has been well established that traditional biventricular pacing is associated with worse outcome even among patients with demonstrated mechanical dyssynchrony.[30] In the present analysis, only a minority of patients with narrow QRS received HBP, and none demonstrated greater than mild MR. Future work should evaluate the role for MR improvement in this cohort, particularly as the recent guidelines have adopted a class IIb indication for any patient with AV nodal block, and adoption of the technique increases.[12]

More recently, there has been a rise in percutaneous approaches to address MR, and these have been shown to improve heart failure hospitalization and mortality in patients with moderate-to-severe or severe functional MR and clinical heart failure.[31] Catheter-based treatment with the MitraClip has also been successfully used in CRT nonresponders with significant MR[32] and may have a role in HBP patients with ongoing moderate-to-severe or severe MR. In the present study, the proportion of patients with severe MR declined by 83% after HBP (with 33% declining from grade 4 to grade 2). Whether HBP may have a role in differentiating those patients with functional MR out of proportion to systolic dysfunction to improve patient selection for advanced percutaneous valve procedures remains to be seen. Consistent with the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial, patients with reduction in MR had improved clinical outcomes, although the small number events in the present cohort can only be hypothesis-generating.

Limitations

The present investigation was a subanalysis of a prospective registry performed at a single center with limited sample size and relatively few clinical events. Echocardiographic analyses, while standardized, were performed retrospectively in patients with complete paired echocardiographic sets—which may introduce selection bias and which limits generalizability. Although LV function and dyssynchrony qualitatively improved, quantitative assessment with speckle tracking was not the focus of this analysis. There was a trend toward reduced CV hospitalizations in MR responders, but the small size of the study limits the ability to generalize findings. Lastly, the causal mechanism of MR reduction after HBP cannot be determined in this series, as echocardiographic measures evaluated here are fundamentally associative and it may include the impact of unmeasured confounders.

Conclusion

Among patients with systolic dysfunction, HBP is associated with an improvement in functional MR. Notably, overall improvement degree of MR was observed across patients with heterogeneous etiologies of wide QRS (LBBB, RBBB, paced). Possible mechanisms for improvement in MR after HBP appear to be due to reductions in LV volume and increased contractility, with significant improvements in both MV and LV chamber geometry observed. Degree of QRS correction with HBP was associated with greater likelihood for MR response.

Acknowledgements

The authors wish to thank Pouyan Razminia, MD, who assisted with data collection.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures

Dr Gaurav Upadhyay has been a speaker or consultant for Abbott, Biotronik, Medtronic, and Zoll Medical. Dr Hemal Nayak has been a speaker for Medtronic, Biotronik, and Boston Scientific. Dr Zaid Aziz has been a speaker for Biotronik. Dr Roderick Tung has been a speaker or consultant for Abbott, Biotronik, Boston Scientific, and Medtronic. Drs Davide Genovese, Jonathan Lattell, Michael Henry, Parth Desai, Hannah Wey, Andrew Beaser, Cevher Ozcan, Michael Broman, and Roberto Lang report no relevant disclosures.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

All patients provided informed consent prior to device implant.

Ethics Statement

Patients were prospectively followed in a registry that was approved by the Institutional Review Board (IRB# 16-0272) for the purpose of safety and clinical outcomes assessment and adhered to the guidelines of the Helsinki Declaration.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2021.07.007.

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