ON-TREATMENT COMPARISON BETWEEN CORRECTIVE HIS BUNDLE PACING AND BIVENTRICULAR PACING FOR CARDIAC RESYNCHRONIZATION:

A SECONDARY ANALYSIS OF HIS-SYNC

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STRUCTURED ABSTRACT

Background. The His-SYNC pilot trial was the first randomized comparison between His bundle pacing in lieu of an LV lead for cardiac resynchronization therapy (His-CRT) and biventricular pacing (BiV-CRT), but was limited by high rates of crossover.

Objective. To evaluate the results of the HIS SYNC pilot trial utilizing treatment-received (TR) and per-protocol (PP) analyses.

Methods. The His-SYNC pilot was a multicenter, prospective, single-blinded, randomized, controlled trial comparing His-CRT versus BiV-CRT in patients meeting standard indications for CRT (e.g., NYHA II-IV patients with QRS>120 ms). Crossovers were required based on prespecified criteria. The primary endpoints analyzed included improvement in QRS duration, LVEF, and freedom from cardiovascular (CV) hospitalization and mortality.

Results. Among 41 patients enrolled (64±13 yrs, 38% female, LVEF 28%, QRS 168±18 ms), 21 were randomized to His-CRT and 20 to BiV-CRT. Crossover occurred in 48% of His-CRT and 26% of BiV-CRT. The most common reason for crossover from His-CRT was inability to correct QRS due to nonspecific intraventricular conduction delay (IVCD=5). Patients treated with His-CRT demonstrated greater QRS narrowing compared to BiV (125±22 ms vs. 164±25 ms [TR], $p<0.001$;124±19 ms vs. 162±24 ms [PP], $p<0.001$). A trend towards higher echocardiographic response was also observed (80 vs. 57% [TR], $p=0.14$; 91% vs. 54% [PP], $p=0.078$). No significant differences in CV hospitalization or mortality were observed.

Conclusions. Patients receiving His-CRT on-treatment demonstrated superior electrical resynchronization and a trend toward higher echocardiographic response than BiV-CRT. Larger prospective studies may be justifiable with refinements in patient selection and implantation techniques to minimize crossovers.

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INTRODUCTION

Cardiac resynchronization therapy (CRT) has an established role in the treatment of patients with heart failure and electromechanical dyssynchrony with wide QRS duration.[1-3] As an adjunct to guideline-directed medical therapy, CRT has been consistently shown to improve quality of life, NYHA status, and LV remodeling with improvements in ejection fraction and reduction in LV dimensions and volumes.[4] Mortality reduction was demonstrated in the CARE HF trial with CRT pacing alone.[2] Despite these benefits, non-response to CRT remains high, estimated between 30-40%.[5, 6] A possible limitation to conventional CRT is that electrical synchronization via biventricular pacing (BiV) is achieved through non-physiological means, via fusion of an epicardial LV wavefront with an endocardial wavefront from the right ventricular apex.

His bundle pacing (HBP) has been to shown to be a viable bailout option for CRT and more recently has been evaluated for feasibility as a first-line strategy.[7-12] Capture of the native conduction system can achieve complete restoration of normal physiologic His Purkinje conduction, which may more favorably promote remodeling compared to BiV. Recent data suggests that the underlying pathophysiology of left bundle branch block (LBBB) patterns is attributable to focal disease located proximally in the left conduction system, which provides a mechanistic explanation for QRS correction when proximal pacing circumvents a site of distal conduction block with a sufficient pacing stimulus.[13] Although there has been growing enthusiasm for HBP as a means to electrically correct wide QRS complexes and electrical cardiac resynchronization, only a single study reported outcomes comparing BiV-CRT versus HBP in lieu of an LV lead for CRT (His-CRT) in a crossover study design.

The His Bundle Pacing versus Coronary Sinus Pacing for Cardiac Resynchronization Therapy (His-SYNC) pilot trial was an investigator-initiated, prospective, randomized, controlled clinical trial that aimed to assess the feasibility and efficacy of His-CRT as a first-line strategy for CRT compared to BiV pacing (BiV-CRT) with regard to both electrocardiographic and echocardiographic response. By intention-to-treat analysis, His-CRT did not demonstrate improvements in electrocardiographic or echocardiographic parameters as compared to BiV-CRT.[14] Interpretation of these results, however, was confounded by high rates of crossover which were mandated by protocol when CRT could not be achieved by the allocated treatment. We present secondary on-treatment analysis of His-SYNC to examine the direct effect of treatment completed and to describe reasons for crossover.

METHODS

The study was conducted at 7 centers and the University of Chicago served as the Study Coordinating Site (NCT0270045). Approval by the local institutional review board (IRB) was obtained at each participating center prior to enrollment, and all patients provided written informed consent. Patients were blinded to their treatment-allocation (His-CRT or BiV-CRT) in this two parallel-arm study. Enrollment began in May 2016 and ended in June 2018. All data were sent to the core laboratory (UChicago) for analysis. An interim analysis was performed midway (01/2018) through enrollment to assess for safety, and no significant differences were noted.

Eligible patients with heart failure (HF) greater than 18 years of age meeting American Heart Association (AHA)-American College of Cardiology (ACC)-Heart Rhythm Society (HRS)

meeting Class 1 or Class II guideline indications for CRT were considered for inclusion.[15] Exclusion criteria included existing CRT device, pregnancy, or inability of the patient to provide consent for themselves either due to medical or psychiatric comorbidity. Subjects were not compensated for participation.

Study Procedures

The implant procedure was performed as per standard technique for cardiac implantable electronic devices. Patients were centrally randomized to assignment to His-CRT or traditional coronary sinus lead for biventricular pacing. HBP was performed utilizing the Medtronic SelectSecure Model 3830 lead (Medtronic, Minneapolis, MN, USA). Delivery of the lead was performed utilizing either the fixed curve Model C315His catheter (Medtronic, Minneapolis, MN, USA) or the deflectable Model C304 sheath (Medtronic, Minneapolis, MN, USA), per the operator preference. His bundle mapping and lead fixation at the time of implant was performed as described previously.[10]

Briefly, His bundle mapping was performed using standard fluoroscopic views to assess septal orientation in LAO and anterosuperior orientation in RAO. The sheath was positioned across the tricuspid annulus and the helix of the lead is introduced beyond the sheath to assess local electrograms guided by the atrial-ventricular ratio. The His potential was mapped with clockwise rotation of the sheath to direct inferoposteriorly toward the septum and clockwise to direct anterosuperiorly away from the septum. Pacing was performed with unipolar and bipolar configuration to assess for QRS narrowing at sites with stable His potential recording.

Patients allocated to left ventricular (LV) lead for BiV-CRT underwent coronary sinus (CS) cannulation and LV lead placement per routine implant procedure.[16] LV lead, type, and vendor (e.g., Abbott, Biotronik, Boston Scientific, Medtronic, or MicroPort) were left to the discretion of the implanting physician. Intraprocedurally, operators were encouraged to target a posterolateral or lateral branch of the CS in regions with long electrical delay as assessed by surface QRS to LV sense (QLV) timing. Placement of the LV lead into the anterior interventricular vein or middle cardiac vein was discouraged. In order to facilitate optimal lead placement, arterial access for levo-phase CS angiography or LV septal mapping to characterize site of bundle-branch block was also permitted at the discretion of the implanting physician. Crossover was encouraged in patients randomized to BiV when LV lead could not be placed due to difficult cannulation of the CS, limited CS branch targets, or phrenic nerve capture resulted in diaphragmatic stimulation during BiV. V-V interval timing was adjusted by the implanting physician to optimize QRS narrowing.

Crossover was mandated in patients randomized to His-CRT if the paced QRS width did not narrow by at least 20% or to a QRS width of ≤ 130 ms (due to data lack of benefit for BiV at QRS widths below this cut-off),[17] or if fixation of the HBP lead could not be performed with adequate stability or pacing output (≤ 5 V @ 1.0 ms). QRS correction with either nonselective or selective capture was accepted, as described in a recent working group recommendations statement.[18] Corrected QRS width was measured from the onset of the intrinsicoid R-wave noted in V1 or V2, as described based on data regarding His engagement from intracardiac left-sided recordings.[13] An example of patient meeting successful QRS correction is shown in **Figure 1**.

Patients were followed with an incision check at approximately 2 weeks, and routine clinical evaluation at 1, 3, 6, and 12 months. Patients underwent device interrogation in-person or

remotely at each of the available timepoints. Reported device measurements included lead sensing (mV), pacing capture threshold (V), pulse width (ms), and impedance (ohms). In patients with multipoint pacing enabled (n=2), measurements utilizing the lowest LV bipole stimulation output were utilized for comparison.

Study Endpoints

The primary endpoints included measures of electrocardiographic (i.e., change in QRS width) and echocardiographic (i.e., change in LVEF) parameters at 6 months. Time to first cardiovascular (CV) hospitalization or all-cause mortality at 12 months was also examined. Patient-level ECG and echocardiographic files were sent to the UChicago core laboratory for adjudication and re-assessment.

QRS widths were measured using electronic calipers (Cardio Calipers, Iconico, Philadelphia, PA, USA). Patients with baseline bundle branch block morphology were categorized according to the classification set forth in the ACC/AHA/HRS guidelines.[19] Patients with LBBB pattern that did not meet the Strauss criteria[20] (i.e., QRS width ≥130 ms in women, ≥140 in men, QS or rS in leads V1 and V2, and mid-QRS notching or slurring in 2 of leads V1, V2, V5, V6, I, and aVL) were categorized as intraventricular conduction delay (IVCD).

Echocardiographic assessment was performed by two readers blinded to the type of device received. Baseline and follow-up (6-month) transthoracic echocardiography were subsequently analyzed offline using the Excelera software platform (Philips Healthcare, Andover, MA, USA). Left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volumes (LVESV) were calculated using the disk summation method from

measurements 4-chamber and 2-chamber views with LVEF calculated using the standard formula (i.e., LVEF= [LVEDV-LVESV]/LVEDV). Echocardiographic response was defined as an LVEF improvement by ≥5% from baseline.[21]

Secondary outcomes included incidence of CV hospitalization alone and incidence of significant ventricular arrhythmia (i.e., ventricular tachycardia [VT] or ventricular fibrillation [VF] requiring device therapy) during 12 months of follow-up. Quality of life was also assessed utilizing the Kansas City Cardiomyopathy (KCCQ) questionnaire, which was administered at baseline, 6, and 12 months, along with assessment of New York Heart Association (NYHA) function class. Latest available KCCQ data at 6 or 12 months were used for analysis. Data regarding endpoints of interest were collected and stored prospectively a remote database (REDCap, Vanderbilt University, Nashville, TN, USA).

Procedure-related complications were reported, including those that were implant-related (i.e., pneumothorax, perforation, pericardial effusion, implant site hematoma, implant site infection) and lead-related (i.e., lead dislodgement, lead fracture, or inability to pace due to high threshold or phrenic capture) during follow-up.

Statistical Analysis

For baseline and clinical characteristics, continuous variables were expressed as means ± standard deviations or medians with interquartile ranges and compared with either independent t-tests, Wilcoxon signed-rank tests, or Mann-Whitney U tests depending upon normality. The sample size was estimated based on the primary endpoint of echocardiographic response to test the hypothesis that an absolute 10% greater improvement in LVEF would be observed with His-

CRT compared to BiV, with a significance level (α) = 0.05 and a power of 0.8. Categorical variables were expressed as relative counts and percentages and compared with Chi-square tests of association or Fisher's exact tests, as appropriate. Kaplan–Meier curves were generated to describe time to CV hospitalizations and mortality, and then tested using log-rank tests. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and STATA MP version 15 (College Station, TX, USA).

RESULTS

Study Population

A total of 41 patients were enrolled, 21 were initially randomized to His-CRT and 20 to BiV, with 1 patient withdrawal prior to device implantation in the BiV arm. The average duration of follow-up was 12.2 months, with 1 patient lost to follow-up during the study period. Overall, the mean age was 64.6±12.6 years, 38% were female, 63% were Caucasian, 65% demonstrated a history of coronary artery disease, 33% had a history of paroxysmal or persistent atrial fibrillation (AF), and 48% had a history of chronic kidney disease. Patients were maintained on guideline-directed medical therapy with 98% on beta-blockade and 75% on either angiotensin-converting enzyme inhibitor (ACE-I), angiotensin II receptor blocker (ARB), or combination with neprilysin inhibitor.

Among the 21 patients that were randomized to His-CRT, 11 patients received successful HBP implantation with correction of QRS. Among 20 randomized to BiV, one patient withdrew prior to implantation, and 14 patient received successful LV lead implantation. High rates of

crossover were noted in both arms (10/21 [48%] of patients assigned to His-CRT and 5/19 [26%] of BiV-CRT), and was not significantly different between the two arms (p=0.20). Analysis according to treatment-received (TR) consisted of 16 His-CRT and 24 BiV-CRT patients, and per-protocol (PP) analysis included 11 His-CRT and 14 BiV-CRT patients. (**Figure 2**) No significant differences were noted in His-CRT versus BiV-CRT based on baseline demographics when analyzed as-treated (**Table 1**). The mean procedural time 2.9±1.3 hours for His-CRT and 2.4±1.2 hours for BiV-CRT (p=0.25). Patients that necessitated crossover had significantly longer procedural times than those that were implanted per-protocol (3.3±1.6 vs 2.3±0.9 hours, p=.04).

Reasons for Crossovers

Five patients that crossed over to BiV from His-CRT had IVCD (not meeting Strauss criteria) that could not be corrected with narrowing by at least 20% and to a QRS width ≤ 130 msec. (**Figure 3)** Three patients demonstrated incomplete QRS narrowing with persistent width >130 ms. In 2 patients, the His bundle could not be mapped. Intraprocedural examples of patients demonstrating QRS narrowing and no correction are shown (**Supplemental Figure 1**). Left-septal recordings were available for a subset of patients (n=14), and corrective His bundle pacing was most likely in patients with either left intrahisian or block of proximal left bundle branch. HBP failed to correct any patient with intact Purkinje activation noted on left septal mapping consistent with IVCD. One patient randomized to His-CRT crossed-over to BiV, and the CS could not be cannulated; the patient then underwent surgical LV lead placement guided by epicardial LV electroanatomic mapping to a region of long delay.

In those that crossed over from BiV to His-CRT, suboptimal venous branch targets were present (n=2), technical inability to cannulate the coronary sinus or target branch (n=2), and vascular occlusion necessitating venoplasty (n=1). **Figure 4** shows an example of a patient with atretic CS anatomy without favorable targets who underwent successful His-CRT after cross-over.

Primary Endpoints by On-Treatment Analysis

Overall, the average QRS width was 168±18 ms (35 left bundle branch block [LBBB] pattern, 2 right bundle branch block [RBBB], and 3 who were chronically right ventricular [RV]-paced). Among patients with LBBB pattern at baseline, 71% met the Strauss criteria for LBBB. Patients undergoing His-CRT according to treatment received demonstrated greater electrical resynchronization than patients assigned to BiV-CRT. QRS width narrowed from baseline in His-CRT from 174±18 ms to 125±22 ms (p<0.001), versus 165±17 ms to 164±30 ms for BiV-CRT (p=0.82). QRS duration was significantly shorter in those that received His-CRT compared to those that received BiV-CRT (125±22 ms vs. 164±30 ms; p<0.001).

There were no significant differences in LV volumes or LVEF at baseline in patients based on treatment-received. At a median follow-up of 6.2 months, the LVEF improved significantly in both arms relative to baseline. Patients receiving His-CRT demonstrated a median increase in LVEF from 28.3% (23.0-34.3%) to 34.6% (30.8-45.0%) (p<0.001). Patients that received BiV-CRT demonstrated a median increase in LVEF from 27.7% (23.6-30.7%) to 32.0% (30.9-40.1%) (p<0.001). Pre and post QRS widths and LVEF are shown by group in **Figure 5.** In analysis by treatment-received, median change in LVEF was numerically higher for

His-CRT compared BiV-CRT, but this difference was not statistically significant (+7.2% [5.0-16.3%] vs. +5.9 [1.5-11.3%], *p*=0.17). A trend toward higher rates of echocardiographic response (80% vs. 57%, p=0.14) was similarly observed. Decline in LVESV% was similar between both groups with a mean -22%±24% for those receiving His-CRT and -19%±14% (*p*=0.62). Electrocardiographic and echocardiographic changes over the study are summarized in **Figure 6.**

Overall event rates were low during the study period, with a total of 6 CV hospitalizations (3 due to HF hospitalization, 2 peri-procedural, and 1 for AF requiring cardioversion). Two patients demonstrated VT/VF requiring device therapy in follow-up, one of which resulted in pulseless electrical activity and death (BiV-CRT crossed over to His-CRT). One other death occurred outside the hospital for which device interrogation data was unavailable (His-CRT). There were no significant differences between patients receiving His-CRT versus BiV with respect to the composite of time to CV hospitalization or all-cause mortality.

Primary Endpoints by Per-Protocol Analysis

When analyzing patients receiving treatment per-protocol allocation, His-CRT was superior to BiV for electrical resynchronization (124±19 ms vs. 162±24 ms; *p*<0.001). No significant difference in median LVEF improvement was observed between groups (median increase in LVEF +11.8% His-CRT versus +5.2% BiV, *p*=0.11) although numerically higher response was observed with His-CRT compared to as-treated analysis (**Supplemental Figures 2 and 3)**. A stronger trend towards echocardiographic response was found in patients receiving

His-CRT in per-protocol comparison (91% versus 54%, p=0.078). Only one patient that completed His-CRT per protocol did not demonstrate an improvement in EF. No difference in reduction in LVESV% was seen with -22%±25% improvement with His-CRT versus -19%±17% with BiV (p=0.75).

Secondary Endpoints

Median NYHA class at baseline was comparable between patients treated with His-CRT (median NYHA class 3 [2.25-3.0]) versus BiV-CRT (median NYHA class 2.75 [2.25-3.0]) (p = 0.66). Improvement by ≥1 functional class was similar between the two groups at 6-months (53% His-CRT versus 39% BiV, p=0.41) and at 12 months (25% His-CRT versus 31% BiV, p=0.89). No patients declined by ≥1 functional grade at 6 months in either group. At 12 months, 1 patient declined by a single functional grade in the His-CRT group and none in the BiV group (p=1.0). Median total KCCQ score at baseline was 101 points (78-112 points). Rise in KCCQ was noted for both patients receiving His-CRT (median +16 points [+8-25 points]) and BiV (median +10 points [+2-16 points]), and was not significantly different between the two groups (p=0.22). No differences in VT/VF were observed during follow-up with two events occurring in those with His-CRT, and none in patients receiving BiV-CRT (p = 0.16).

Adverse Events

A total of four periprocedural complications occurred. One patient with severe peripheral vascular disease and prolonged procedure (patient who received BiV-CRT after crossover) sustained a transient ischemic attack with aphasia which resolved in follow-up. Two patients

developed atrial lead micro-dislodgement associated with pericardial effusion (2 BiV-CRT, one of whom had crossed-over). One hematoma in a patient receiving His-CRT patient required evacuation without additional sequelae. No infectious complications were observed.

Device Parameters

Device parameters at baseline and follow-up are noted in **Table 2** according to the treatment received. No significant differences were found in right atrial (RA) or right ventricular (RV) lead measurements of sensing, threshold, or impedance. QLV was reported in 20 of 24 patients receiving BiV across both arms (mean 131±29 ms; mean QLV ratio 0.80±0.19). With respect to resynchronization pacing, HBP was associated with higher pacing output to achieve QRS correction (2.75 V versus 0.85 V, p=0.002) and pacing pulse width (1 ms versus 0.5 ms, p<0.001) at baseline and in follow-up. No significant change was found in His lead output or pulse-width at baseline when comparing baseline to 6 (2 V at 1 ms, p=0.63 versus baseline) or 12 months (2.5 V at 1 ms, p=0.99 versus baseline). Two patients treated with His-CRT were observed to have higher correction thresholds with loss of QRS correction in follow-up. In both cases, the His lead was maintained and the configuration of the pacing vector was changed from His-tip to His-ring to His-tip to RV coil configuration, which reduced in correction threshold (2.25V @ 1.0 ms and 3.75 @1.0 ms). [22] No dislodgements of His or LV leads were seen during the 12-month study period in either group.

DISCUSSION

The major findings of this secondary analysis of HIS SYNC are:

1) His-CRT was superior to BiV-CRT for electrical resynchronization, as measured by QRS narrowing.
2) Echocardiographic response was numerically but not statistically higher in patients receiving His-CRT versus BiV-CRT.
3) Inclusion of IVCD accounted for the majority of crossovers in patients allocated to His-CRT.

The His-SYNC pilot trial represents an investigator-initiated collaboration to prospectively assess the feasibility of His-CRT in comparison to BiV-CRT. Prior work has demonstrated the utility of His-CRT as bailout strategy for failed attempt at traditional CRT and a single prospective investigation utilized Y-adapted His and LV leads to compare outcomes in a crossover design.[9] To the best of our knowledge, the His-SYNC pilot trial is the first randomized trial to compare His pacing in lieu of an LV lead with BiV for CRT in clinical practice. Further, it represents the first study in the field that prospectively compares two modalities to achieve CRT, but intention-to-treat analysis was confounded by a high rate of crossover. To examine the physiologic effects of His-CRT, we performed secondary analysis based on on-treatment principles. Per-protocol analysis provides an assessment of the efficacy of His-CRT in an optimal setting.

Importantly, His-SYNC compared echocardiographic response between two methods to achieve CRT rather than medical therapy. In contrast to the intention-to-treat analysis, in which patients assigned to His-CRT demonstrated lower baseline EF at baseline, the present analyses

showed well-matched groups, with no differences in LV volumes, LVEF, or baseline demographics by treatment-received. COMPANION and CARE-HF were the initial landmark trials to demonstrate mortality benefit in patients undergoing CRT with BiV compared to medical therapy.[1, 2] Improvements in LVEF has been inconsistently correlated with the magnitude of QRS narrowing[23], although when dichotomized, increases in paced QRS duration[24] and duration over 200 ms[25] may predict poor response to BiV-CRT. While there was no significant improvement in QRS duration in patients randomized to BiV-CRT in this pilot study, LVEF improvements were observed and long mean QLV timing reflect optimized LV lead positions. Importantly, reductions in mortality and LV volume indices have been demonstrated in pivotal trials with relatively modest EF improvements. In CARE-HF, differences in mean EF between patients that received CRT compared with medical therapy were 3.7% at 3 months and 6.9% at 18 months. Similarly, differences in mean LVEF in MADIT CRT at 1 year between patients treated with ICD only versus ICD with CRT were 8% (3% vs 11%).[3]

The echocardiographic response for patients receiving His-CRT (median +7.2 [TR] and median +11.8 [PP]) is consistent with positive response with His-CRT, but did not reach the estimated 10% difference between groups. (**Supplemental Figure 4**) In the present study, differences in medians of approximately 7% were observed in the per-protocol analysis in favor of His-CRT over BiV-CRT (p=0.078). Indeed, when examining response by initial ECG pattern, all but one patient who received His-CRT with LBBB pattern fulfilling Strauss criteria at baseline demonstrated echocardiographic response. These findings, however, should only be interpreted as hypothesis-generating due to the as-treated comparison. When combined with previous data, these observations justify the need for larger prospective studies designed to test

noninferiority and superiority of this novel technique for cardiac resynchronization. The present work also helps to inform the power and sample size calculations for future studies.

Pre-specified criteria in the study protocol mandated crossover, and rates were particularly high in patients originally randomized to His-CRT. In this regard, this pilot study should be interpreted as a comparison between two strategies. The main reason for crossover from BiV to His-CRT, which was higher than prior studies (26%), were primarily due to unfavorable cardiac venous anatomy. One contributing factor was that LV leads were not placed in anterior interventricular or middle cardiac veins, as these locations have been associated with modest responses to CRT. In addition, operators were conscious of maximizing electrical delay of implanted leads, as QLV was >95 ms in 85% of patients receiving BiV (mean QLV 131±29 ms; mean QLV/QRS duration ratio 0.80±0.19).

Analysis of the baseline ECGs in patients that required crossover to BiV from His-CRT revealed that 50% of patients exhibited nonspecific IVCD. The inclusion criteria for this pilot trial was a broad population based on current guidelines for traditional BiV-CRT. Subsequent to the design of His-SYNC, we have recently demonstrated that IVCD patients with intact Purkinje activation based on intracardiac mapping exhibit 0% predictive value for corrective His bundle pacing.[13]

Limitations

This pilot study with small sample size was underpowered to detect differences less than 10% between groups and the possibility of a type II error cannot be excluded. The criteria for LBBB definitions have been shown to clearly impact the outcomes of CRT studies and electrophysiologic definitions are essential to stratify patients that are most likely to benefit from

resychronization.[26] Implantations tools have not evolved substantially since 2010 with introduction of the C315His sheath. Longer helices, deflectable sheaths with septal orientation, and variable curves to accommodate variable patient anatomy are likely to improve His correction rates and stability of thresholds.

Future Directions

The present results from this pilot study strongly suggest that His-CRT is not suitable for an unselected CRT population. With crossover rates approaching 50% from His-CRT, further investigation with the same study protocol is not warranted. The findings of this pilot study inform the methodology of the planned HIS SYNC II trial, where refinement in patient selection to exclude those with IVCD may reduce crossovers substantially. Future studies that evaluate His-CRT should target patients with a LBBB pattern that reflects complete conduction block that can be circumvented by His bundle pacing,[27] and identify surface ECG characteristics that can consistently identify these patients. These mechanistic insights were discovered during the same time period in which the present trial was conducted. Additionally, advances in sheath and lead technology are necessary to improve implantation success as current delivery tools do not adequately address patient variability in heart orientation and chamber dimensions. In addition, new approaches are being developed to engage the conduction system, including a novel intraseptal fixation technique which captures the left bundle branch and may improve the ability to correct distal block in the left bundle with lower thresholds.[28] This technique expands options available for physiologic pacing in patients whom corrective His bundle pacing is not achievable, but will require further prospective evaluation and validation.

CONCLUSIONS

In this first randomized pilot trial of His-CRT versus BiV for CRT in clinical practice, His-CRT demonstrated superior electrical resynchronization than BiV-CRT in on-treatment analysis, with a trend towards greater echocardiographic improvement which did not reach significance. These secondary analyses should be interpreted as hypothesis-generating, and larger prospective studies with refinements in patient selection and implantation techniques may be justifiable to test for differential clinical outcomes between CRT modalities.

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FIGURE LEGENDS

Figure 1: Typical LBBB pattern (QRS width 195ms, top) with successful QRS correction (bottom) from nonselective His capture resulting in QRS narrowing to 125 ms measured utilizing the onset of the intrinsicoid R-wave in V2.

Figure 2: Flow chart of patients in study.

Figure 3: Examples of 3 patients with IVCD that necessitated crossed over from His bundle pacing to biventricular pacing due to inability to correct QRS. All patients had QRS >130ms but did not meet Strauss criteria for LBBB. A) 66 yo male with NICM, EF 34%, QRS 157 ms that improved to 41% with biventricular pacing at 6 months. B) 52 yo female with NICM, EF 20%, QRS 177 ms that improved to 30% with biventricular pacing at 5 months. C) 77 yo male with ICM EF 28% QRS 161 with mild improvement to 31% at 8 months with biventricular pacing.

Figure 4: Example of a patient randomized to biventricular pacing that crossed over to His bundle pacing. A) Unfavorable anatomy is demonstrated by coronary sinus venography with atretic coronary sinus and unfavorable lateral vein targets. B) Baseline typical LBBB pattern is seen with QRS width of 170ms. C) Postimplant chest radiograph demonstrating 3-lead system with ICD in RV septum, His bundle lead, and atrial lead. D) 12-lead ECG postimplant shows successful resynchronization with His bundle pacing resulting in a final QRS duration of 120 ms. This patient demonstrated an echocardiographic super-response to His CRT from 35% to 53% in 5 months.

Figure 5: Pre and post QRS widths by individual patient in patients receiving His bundle pacing for CRT (His-CRT) versus biventricular pacing (BiV-CRT) shown in the top panel. Change in LVEF before and after pacing is shown in lower panel.

Figure 6: Change in QRS duration before and after pacing with BiV-CRT versus His-CRT, rate of echocardiographic response, and median change in LVEF before and after therapy.

TABLES

Table 1. Demographic, electrocardiographic, and echocardiographic characteristics at baseline of patients by assignment group.

Table 2. Device parameters in follow-up in by treatment received (His-CRT or BiV)

TABLE 1: Baseline demographic, electrocardiographic, and echocardiographic characteristics of patients by treatment received

Characteristic	His-CRT (*n*=16)	BiV-CRT (*n*=24)	*p*-value
Sex	7 (43.8%)	8 (33.3%)	0.51
Age	63.4 ± 13.3	65.5 ± 12.4	0.61
Height (cm)	167.3 ± 11.9	171.2 ± 11.6	0.31
Weight (kg)	84.0 (74.9-88.5)	83.5 (77.6-96.0)	0.81
BMI	28.8 (26.4-33.2)	29.7 (26.2-31.3)	0.99
Race			
Caucasian	10 (62.5%)	15 (62.5%)	1
African-American	5 (31.2%)	7 (29.2%)	1
Hispanic	1 (6.2%)	1 (4.2%)	1
Other	0 (0.0%)	1 (4.2%)	1
Medication Use			
BB	15 (93.8%)	24 (100%)	0.40
ACE-I	4 (25.0%)	7 (29.2%)	1
ARB	4 (25.0%)	6 (25.0%)	1
ARB/Neprilysin Inhibitor	4 (25.0%)	5 (20.8%)	1
Amiodarone	1 (6.3%)	7 (29.2%)	0.11
Digoxin	0 (0.0%)	6 (25.0%)	0.06
Spironolactone	7 (43.8%)	7 (29.2%)	0.34
Comorbidities			
HTN	11 (68.8%)	19 (79.2%)	0.48
CAD	8 (50.0%)	15 (62.5%)	0.43
History of CABG	2 (12.5%)	5 (20.8%)	0.68
COPD	4 (25.0%)	6 (25.0%)	1
DM2	8 (50.0%)	11 (45.8%)	0.80
CKD	8 (50.0%)	11 (45.8%)	0.80
ESRD	1 (6.67%)	2 (8.3%)	1
NYHA Class	3.0 (2.25-3.0)	2.75 (2.25-3.0)	0.66
Electrocardiographic			
PR	183 (166-199)	192 (162-244)	0.32
QRS	174 ± 18	165 ± 17	0.12
QTc	485 ± 41	479 ± 44	0.65
Echocardiographic characteristics			
LVEDV	184 (163-241)	215 (171-271)	0.29
LVESV	130 (110-180)	157 (116-195)	0.34
LVEF	28.0 (23.0-34.0)	27.7 (23.6-30.7)	0.81

Key: Angiotensin-converting enzyme inhibitor, ACE-I; Angiotensin II receptor blocker, ARB; Beta-blocker, BB; Body mass index, BMI; Coronary artery disease (>70% stenosis of any vessel), CAD; Coronary-artery bypass graft, CABG; Chronic kidney disease, CKD; Chronic obstructive pulmonary disease, COPD; Diabetes mellitus Type 2, DM2; End-stage renal disease, ESRD; Left ventricular end-diastolic volume, LVEDV; Left ventricular end-systolic volume, LVESV; Left ventricular ejection fraction, LVEF; New York Heart Association, NYHA; PR interval, PR; QRS duration, QRS; Corrected QT interval, QTc

TABLE 2: Device Parameters in Follow-up in by on-treatment group (His-CRT or BiV)

Parameter	**His-CRT (*n*=16)**	**BiV (*n*=24)**	***p*-value**
Implant measurements			
RA lead sensing (mV)	2.00 (1.50-3.80)	1.75 (1.25-3.50)	0.457
RA lead capture threshold (V)	0.75 (0.60-1.25)	0.70 (0.50-1.00)	0.134
RA lead pulse width (ms)	0.40 (0.40-0.50)	0.50 (0.40-0.50)	0.384
RA lead impedance (ohms)	475 (399-726)	494 (399-600)	0.641
RV lead sensing (mV)	10.25 (9.40-14.80)	12.00 (7.30-15.10)	0.910
RV lead threshold (V)	0.50 (0.50-0.75)	0.50 (0.50-1.00)	0.241
RV lead pulse width (ms)	0.40 (0.40-0.50)	0.40 (0.40-0.50)	0.746
RV lead impedance (ohms)	513 (475-608)	492.50 (428-555)	0.334
HIS or LV threshold (V)*	**2.75 (1.25-3.38)**	**0.85 (0.73-1.31)**	**0.002**
HIS or LV pulse width (ms)	**1.00 (1.00-1.00)**	**0.50 (0.40-0.65)**	**<0.001**
His or LV impedance (ohms)	**433 (340-481)**	**540 (497-680)**	**0.001**
6 Month Follow-Up			
RA lead sensing (mV)	3.55 (2.50-4.60)	2.40 (1.95-3.55)	0.111
RA lead capture threshold (V)	0.75 (0.50-0.80)	0.66 (0.55-0.81)	0.721
RA lead pulse width (ms)	0.40 (0.40-0.40)	0.40 (0.40-0.40)	0.684
RA lead impedance (ohms)	485 (456-513)	456 (380-513)	0.345
RV lead sensing (mV)	13.65 (9.13-16.88)	12.50 (11.30-20.00)	0.275
RV lead threshold (V)	0.50 (0.50-0.75)	0.75 (0.50-1.00)	0.184
RV lead pulse width (ms)	0.40 (0.40-0.40)	0.40 (0.40-0.40)	0.647
RV lead impedance (ohms)	456 (399-551)	428 (380-513)	0.361
HIS or LV threshold (V)*	**2.00 (1.00-3.25)**	**0.94 (0.75-1.25)**	**0.004**
HIS or LV pulse width (ms)	**1.00 (1.00-1.00)**	**0.40 (0.40-0.50)**	**<0.001**
His or LV impedance (ohms)	**295 (284-390)**	**615 (456-703)**	**<0.001**

* Threshold for QRS correction is reported for His bundle pacing