PROTOCOL TITLE:
HIS BUNDLE PACING VERSUS CORONARY SINUS PACING FOR CARDIAC RESYNCHRONIZATION THERAPY

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IND OR IDE # NOT APPLICABLE

Contents

STUDY SUMMARY

TITLE	**His-bundle pacing versus coronary sinus pacing for cardiac resynchronization therapy (CRT)**
SHORT TITLE	**The His-Sync Study**
PROTOCOL NUMBER	UofC & Baptist Health Louisville: IRB15-1728 UCLA: IRB#15-000464 NWU: STU00202920 Geisinger: 2017-0339 IU: 1707220499 Rush: 16100902-IRB01 Edward: HIS-SYNCH
METHODOLOGY	Single-blind clinical trial
STUDY DURATION	12 months
STUDY CENTER(S)	Multi-center; also enrolling patients at the University of California Los Angeles (UCLA) Medical Center, Northwestern University (NWU), Geisinger Wyoming Valley Medical Center (Geisinger), Indiana University (IU), Rush University Medical Center (Rush), Edward Hospital (Edward), and Baptist Health Louisville
OBJECTIVES	To compare the effectiveness of his-bundle pacing versus coronary sinus LV lead localization in patients with heart failure.
NUMBER OF SUBJECTS	40 patients total
DIAGNOSIS AND MAIN INCLUSION CRITERIA	Patients with heart failure (HF) eligible for CRT as part of routine standard-of-care based on accepted Class I or Class II indications will be considered for this study. Inclusion criteria include: 1) Left ventricular ejection fraction (LVEF) ≤ 35%, sinus rhythm (SR), left bundle-branch block (LBBB) morphology, and QRS duration ≥ 150 msec, and NYHA Class II, III, or ambulatory Class IV patients on goal-directed medical therapy (GDMT) [Class I] 2) LVEF ≤ 35%, SR with LBBB with QRS 120-149 msec on GDMT [Class IIa] 3) LVEF ≤ 35%, SR with non-LBBB with QRS ≥ 150 msec on GDMT [Class IIa] 4) LVEF ≤ 35%, in AF if medication or AV nodal ablation will allow near 100% pacing [Class IIa] 5) LVEF ≤ 35% undergoing new or replacement device with anticipated >40% ventricular pacing on GDMT

	[Class IIa] 6) LVEF ≤ 30%, ischemic etiology of HF, SR with LBBB ≥ 150 msec and NYHA Class I symptoms on GDMT [Class IIb] 7) LVEF ≤ 35%, SR with non-LBBB with QRS 120-149 msec, NYHA Class III/ambulatory Class IV HF on GDMT [Class IIb] 8) LVEF ≤ 35%, SR with non-LBBB with QRS ≥ 150 msec, NYHA Class II HF on GDMT [Class IIb]
STUDY PRODUCT	His-Bundle lead placement will require use of Medtronic delivery sheath (C315 HIS, Medtronic, Minneapolis, MN) and pacemaker lead (Select Secure 3830, Medtronic, Minneapolis, MN) for patients randomized to His bundle pacing. These are FDA approved for routine clinical use. Coronary sinus LV leads utilized in the study will be FDA approved leads per the discretion of the implanting physician
DURATION OF ADMINISTRATION	Pacing will be delivered throughout the duration of the study, with goal pacing delivery of 95%, as is the standard-of-care for patients receiving CRT
REFERENCE THERAPY	The reference therapy will be the control group; i.e., those patients assigned to CRT with use of a CRT
STATISTICAL METHODOLOGY	Traditional statistical methods will be employed. The student's T-test will be used for continuous comparisons. Fisher's exact or the Chi-square test will be applied for dichotomous variables. Time to endpoint analysis will be performed using the Kaplan-Meier method.

List of Abbreviations

ACE-I	Angiotensin-Converting Enzyme Inhibitor
AF	Atrial Fibrillation
ARB	Angiotensin Receptor Blocker
BB	Beta-Blocker
CRT	Cardiac Resynchronization Therapy
CS	Coronary Sinus
FDA	Food and Drug Administration
GDMT	Goal-directed Medical Therapy
HBP	His Bundle Pacing
HF	Heart Failure
ICD	Implantable cardioverter-defibrillator
IRB	Institutional Review Board
LBBB	Left Bundle-Branch Block
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
NYHA	New York Heart Association
RA	Right atrium
RBBB	Right Bundle-Branch Block
RV	Right Ventricle
SR	Sinus Rhythm
TTE	Transthoracic Echocardiogram
UCMC	University of Chicago Medical Center
UofC	University of Chicago
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

1. INTRODUCTION

A. BACKGROUND AND RATIONALE

Heart failure has been characterized as the singular epidemic of contemporary cardiovascular medicine. At 40 years of age, the lifetime risk of developing heart failure is one in five.[1] The prevalence of heart failure exceeds 5.3 million in the United States, and accrued estimated direct and indirect costs totaling $39.2 billion in 2010.[1,2] During the past two decades, cardiac resynchronization therapy (CRT) has emerged as a safe and efficacious device-based therapy for heart failure patients with severe systolic dysfunction and intraventricular conduction delay.[3-5] CRT is the use of a pacemaker with three electrical leads to coordinate myocardial contraction. Two leads are endocardial, placed in the right atrium (RA) and right ventricle (RV), while a third lead is traditionally placed in a tributary of the coronary sinus overlying the epicardial surface of the left ventricle (LV). CRT exerts its physiological impact via synchronizing ventricular contraction, leading to improved left ventricular filling, and pumping efficiency. Multiple prospective randomized studies have shown that CRT yields long-term clinical benefits, including improved quality of life, increased exercise capacity, reduced heart failure hospitalization and decreased all-cause mortality.[6-11]

Despite dramatic impact and expanding indications, however, there remain significant barriers to realizing the overall potential benefit of CRT. Most notably, up to one-third of patients treated with CRT do not derive *any* detectable clinical or echocardiographic benefit, and indeed, some worsen after resynchronization.[3,12] Intrinsic patient and myocardial substrate characteristics *a priori* may limit response in some patients. Additionally, intraprocedural factors–particularly the location of the left ventricular (LV) lead–may also effect longer term outcome. In particular, recent analysis from MADIT-CRT and other studies showed that an LV lead placed in an anatomically apical region of the heart is associated with a worse clinical outcome.[13,14] Distinct and complementary to anatomical localization, characterization of the LV lead with respect to the heart's electrical activation pattern has been shown to be an important determinant of response.[15-18] Effective integration of anatomical and electrical data in order to guide LV lead placement for CRT is still actively being explored.

More recently, the feasibility of resynchronizing ventricular activation by permanent pacing of the His bundle region has been described, with clear clinical advantages over traditional RV apical pacing.[19-23] This technique is an FDA approved therapy for pacing. The physiologic benefit of permanent His bundle pacing (HBP) is the ability to stimulate the ventricles through the intrinsic His-purkinje system, which results in synchronous electrical and mechanical activation. Furthermore, similar to CRT, reports of hyper-response—typically described as patient functional recovery to an LVEF ≥ 50%, has been reported with HBP after restoration of normal intrinsic conduction.[24-26] Perhaps even more provocatively, in a recent study in which patients were implanted with four leads (RA, RV, CS LV lead, and HBP lead), both modes of resynchronization (HBP and CS) were studied utilizing a cross-over design, and both were found to be associated with similar benefit (with patients acting as their own controls).[27] Indeed, HBP may have theoretical advantages over CRT using a coronary sinus lead, which is associated with limited coronary venous anatomy and complications that include coronary sinus dissection, venous perforation, and the potential for proarrhythmia. While both techniques comprise the standard-of-care for pacing, direct comparison of HBP with traditional

CS lead position for CRT has not yet been investigated, and is the motivation behind the His-SYNC Study.

B. OBJECTIVES

We hypothesize that:

a. In patients with advanced heart failure and evidence of intraventricular conduction delay who meet criteria for CRT, HBP may be safely achieved *and*
b. HBP is associated with similar echocardiographic and clinical outcome as conventional CS pacing during CRT

Specific aims:

Aim 1: To determine the overall rate of successful His-bundle lead placement at the time of implant of CRT. Patients randomized to HBP but who cannot be successfully implanted with a HBP lead will cross-over to traditional CS lead position.

Aim 2: To assess the impact of HBP versus CS pacing on acute and mid-term outcomes. Acute outcomes include incidence of periprocedural complication and change in QRS duration pre-and post-pacing. Mid-term outcomes include echocardiographic response at 6 and 12 months along with a composite clinical outcome of heart failure hospitalization, arrhythmia, and all-cause mortality.

2. STUDY DESIGN

Study design: Single-blind study. Patients will be randomized, at the time of implant, to HBP versus CS pacing, and remain blinded to their treatment allocation. Both treatment options use standard-of-care, FDA-approved devices. The distinction is only in the allocation toward HBP and CS pacing. Treating physicians will be aware of assignment in order to facilitate routine device follow-up. Echocardiographic and electrocardiographic evaluation will also be performed in a blinded manner.

Cross-over is permitted between treatment group allocation if:

- CS lead cannot be placed due to difficult cannulation of the CS, limited branches at the posterolateral or lateral wall, or phrenic nerve capture. These patients may then cross-over to HBP.
- HBP patients may cross-over if lead cannot be positioned with adequate stability and reasonable pacing output or if QRS width does not narrow by at least 20% or to a QRS width of $\leq$ 130 msec.

Implant procedure will be per routine percutaneous access, as is standard for pacemaker and ICDs. All patients will receive an FDA-approved cardiac resynchronization therapy pacemaker or defibrillator device, as per standard of care outlined for the patient. In order to facilitate optimal lead placement, arterial access for levo-phase CS angiography and/or LV septal mapping to characterize site of bundle-branch block may also be performed, at the discretion of the implanting physician per his/her standard practice.

Follow-up will be performed at 2 weeks post-implant for incision check and device interrogation as is standard of care. In addition, routine device and clinical follow-up will be scheduled at 1, 3, 6, and 12 months.

Electrocardiography (i.e., ECG) will be performed pre-implant, prior to hospital discharge, at 3 months, 6 months, and 12 months. Echocardiography will be performed pre-implant, 6 months, and 12 months to evaluate for change in LVEF, chamber dimension, and wall motion with strain imaging as is standard of care in the treatment of patients with advanced heart failure. NYHA functional class and quality of life (utilizing the Kansas City Cardiomyopathy Questionnaire) will be assessed pre-implant and at 6 months.

Duration of study: 12 months

Primary endpoints: A combination of clinical, electrocardiographic, and echocardiographic endpoints will be prospectively studied. These include:

- **Clinical**: Primary clinical endpoint is a composite of heart failure hospitalization, VT/VF, and any-cause mortality at 12 months.
- **Electrocardiographic**: Change in QRS duration between pre-implant and at hospital discharge, 3 months, 6 months, and 12 months will be performed by readers blinded to treatment allocation. Arrhythmia occurrence (i.e., AF, nonsustained VT, VT or VF requiring device therapy) will be documented throughout the study period
- **Echocardiographic**: Change in left ventricular ejection fraction, chamber dimension, and tissue-strain pre-implant, at 6 months, and at 12 months to be performed by readers blinded to treatment allocation

Primary safety endpoint: Procedure-related complications will be assessed prospectively both acutely and throughout the study period, including:

- **Procedure related**: pneumothorax, perforation, pericardial effusion, or hemorrhage
- **System related**: implant site hematoma, implant site infection
- **Lead related**: lead dislodgement, lead fracture, inability to pace due to high threshold, phrenic capture

Randomization scheme: Patients will be allocated to HBP or standard CS lead at time of implant. Patients with LBBB and non-LBBB will be assigned to separate blocks and randomized separately.

3. Subject Selection and Withdrawal

Sites:
Subjects selected for study will be recruited from eight sites: The University of Chicago Medical Center (Chicago, IL), the Ronald Reagan UCLA Medical Center (Los Angeles, CA), Northwestern University's Northwestern Memorial Hospital (Chicago, IL), Geisinger Cardiology of the Geisinger Health System (Wilkes-Barre, PA), Indiana University Krannert Institute of Cardiology (Indianapolis, IN), Rush University Medical Center (Chicago, IL), Edward Elmhurst Healthcare Edward Hospital (Naperville, IL), Baptist Health Louisville (Louisville, KY). Each site will function independently but follow the same treatment protocol. Each site will maintain

their own randomization schedule. The data from the UCLA, NWU, Geisinger, IU, Rush, Edward, and Baptist Health sites will be shared with the University of Chicago at study completion for data analysis only.

Baptist Health Louisville has formally requested the University of Chicago IRB to serve as its own IRB. The following individuals from Baptist Health will be engaged the conduct of this study in Louisville with the following roles:

- John Mandrola, MD – Principle Investigator
- Vicky Swift, APRN – Sub-Investigator
- Teresa Watkins, RN – Research Coordinator
- Kathleen English, RN – Research Coordinator

All of the study team members at Baptist Health have provided their curricula vitae, as well as confirmation of appropriate human subjects protection training.

Eligibility:

Eligible patients will be similar to those previously enrolled in the large randomized controlled trials which guide current indications for CRT. This includes:

- Patients at least 18 years of age
- LV systolic dysfunction with LVEF ≤ 35%
- Evidence of intraventricular conduction delay with QRS duration > 120 msec
- NYHA Class II, III, and ambulatory Class IV heart failure with either ischemic or nonischemic cardiomyopathy and patients with NYHA Class I symptoms and ischemic cardiomyopathy

Inclusion:

Inclusion criteria are identical to those presently accepted by the American Heart Association (AHA)-American College of Cardiology (ACC)-Heart Rhythm Society (HRS) for CRT.[28] These include:

1) Left ventricular ejection fraction (LVEF) ≤ 35%, sinus rhythm (SR), left bundle-branch block (LBBB) morphology, and QRS duration ≥ 150 msec, and NYHA Class II, III, or ambulatory Class IV patients on goal-directed medical therapy (GDMT) [Class I]
2) LVEF ≤ 35%, SR with LBBB with QRS 120-149 msec on GDMT [Class IIa]
3) LVEF ≤ 35%, SR with non-LBBB with QRS ≥ 150 msec on GDMT [Class IIa]
4) LVEF ≤ 35%, in AF if medication or AV nodal ablation will allow near 100% pacing [Class IIa]
5) LVEF ≤ 35% undergoing new or replacement device with anticipated >40% ventricular pacing on GDMT [Class IIa]
6) LVEF ≤ 30%, ischemic etiology of HF, SR with LBBB ≥ 150 msec and NYHA Class I symptoms on GDMT [Class IIb]
7) LVEF ≤ 35%, SR with non-LBBB with QRS 120-149 msec, NYHA Class III/ambulatory Class IV HF on GDMT [Class IIb]
   LVEF ≤ 35%, SR with non-LBBB with QRS ≥ 150 msec, NYHA Class II HF on GDMT [Class IIb]

Exclusion:
Exclusion criteria include:

- Existing CRT device
- Inability of patient capacity to provide consent for themselves either due to medical or psychiatric comorbidity
- Pregnancy
- Participation in other trials
- Difficulty with follow-up

No payments will be made to subjects to participate.

4. STUDY DEVICE

His-bundle lead pacing will be performed with the Medtronic SelectSecure™, Model 3830 lead. Delivery of the lead utilizes a deflectable sheath, the Medtronic SelectSite™, Model C304. Both devices are FDA approved for the purpose of his-bundle pacing. It is the only device available which is presently FDA approved for selective His pacing.

The lead has not been subject to any FDA advisories or recalls. Current lead performance is regularly reported and available at:
http://wwwp.medtronic.com/productperformance/model/3830-selectsecure.html

CS lead and CRT device generator selected for implant will be left to the discretion of the operator. Only FDA approved CS leads and CRT generators will be utilized in the study. There are five present manufacturers of CS leads and CRT generators: Biotronik, Boston Scientific, Medtronic, Sorin, and St. Jude Medical. The University of Chicago utilizes all five vendors, and there is no convincing data to suggest the superiority of any one vendor over the others.

5. STUDY PROCEDURES

Pre-Implant

- Patients will be screened for study
- Pre-implant ECG reviewed (to be performed on day of screening)
- Baseline transthoracic echocardiogram (TTE) reviewed (does *not* need to be performed during inpatient hospitalization; outpatient or outside-hospital TTE report may also be performed)
- Patients who screen-in will be provided Kansas City Cardiomyopathy Questionnaire
- NYHA functional class to be determined by treating physician
- Operating physician will be informed of patient allocation to facilitate planning of procedure

Randomization, Implant, and Periprocedure Care

- RA and RV leads will be positioned per routine
    - Arterial access for CS angiography or LV septal mapping may be performed at the discretion of the implanting physician in order to facilitate optimal lead placement

- 'LV' lead will be positioned in CS or at His-bundle based on allocation assignment
    - The allocation assignment will be based on randomization schedule (developed using random number generator)
    - The study coordinator will keep allocations in a sealed envelope and provide to implanting physician at time of procedure
    - Patients with LBBB and non-LBBB will be randomized separately
    - Each independent site will maintain their own randomization schedule
- If the initial allocated site is unsuccessful, alternative site will be pursued
- Intracardiac EGM information (surface QRS to LV site or QLV), pacing output, and lead position at final site will be recorded
- Predischarge ECG performed
- Predischarge device interrogation will be performed (as per standard of care)

2-Week Incision Check
- As per routine post-device care, all patients will be scheduled for routine postoperative device check at 2 weeks to evaluate incision
- Device interrogation (as per standard of care)

1-Month Visit
- Routine device interrogation
- Routine clinical check

(Note: Week 2 and Month 1 visits may be combined, per treating doctor discretion, for the simple post-op wound and clinical visit)

3-Month Visit
- Routine ECG
- Routine device interrogation
- Routine clinical check

6-Month Visit
- Post-implant TTE
- Routine ECG
- Routine device interrogation
- Routine clinical check
- Administration of Kansas City Cardiomyopathy Questionnaire
- NYHA functional class to be determined by treating physician

12-Month Visit
- Post-implant TTE
- Routine ECG
- Routine device interrogation
- Routine clinical check
- Administration of Kansas City Cardiomyopathy Questionnaire
- NYHA functional class to be determined by treating physician

Contact between study visits

- Patients will be enrolled in remote device monitoring (as all CRT patients are) and device alerts will be monitored per routine
- Any hospitalizations will be flagged for review

Future contact

- Patients will be asked to participate in an extended registry to evaluate longer-term clinical outcome after study completion. We will collect data from subjects' medical record for 2 years following their participation in the study. Data collected will include cardiac imaging results, and other clinical events such as hospitalization and death.

6. Statistical Plan and Considerations

Sample size estimation:
The sample size for this study is a total of 40 subjects (20 HBP and 20 CS lead). The sample size estimate was based on a goal to observe an absolute 10% difference in LVEF between the two groups, leading to a Cohen's *d* statistic of 1. With a significance level (α) = 0.05 and a power of 0.8, at least 17 subjects will be required in each group. A goal of 40 subjects was made to allow for possible dropout during the study period.

Statistical methods:
Patients will be studied based on the final treatment allocation. Crossovers and reasons for crossover will also be recorded. Fisher's exact or the Chi-Square test will be used for categorical variables, and continuous parameters will be compared by the two-tailed unpaired Student's t test and the F test for analysis of variance (ANOVA), as needed. Kaplan-Meier method will be used for computing the event free survival curves. Each implant strategy will be compared within this cohort of patients for its impact on percent change QRS duration, LVEF, and as clinical outcome. Multiple logistic regression and multiple regressions using the Cox proportional hazards model will be performed to determine the independent association of each of the implant variables with LVEF and clinical outcome.

7. Risks and Benefits

Cardiac resynchronization has led to significant improvement in survival and freedom from HF hospitalization for patients with advanced HF and conduction delay. The problem of nonresponse remains high, and the goal of this study is to evaluate a possible means to overcome nonresponse by varying LV lead position. There are risks with both CS lead position and His-bundle pacing which include, but are not limited to, the risk for cardiac perforation, tamponade, lead dislodgement, fracture, and site infection. Early data[27] that two technologies are comparable with respect to risk profile. The benefit of identifying an additional suitable location for LV lead position would be to extend the benefit of CRT to a broader group of patients.

8. Safety and Adverse Events

Safety:
As noted above, periprocedural complications will be logged with respect to procedure, system-related, and lead-related events. Each site's complications will be independently reviewed at the midpoint by the site's primary investigators. Should there be a trend towards increased complication risk, the study will be halted.

Adverse Events:
As noted above, all adverse events associated with devices will be monitored periprocedurally and continuously through the study. The site's PIs will independently review all events at respective sites after randomization of 20 combined subjects in order to make a determination for continuance.

9. Data handling and Record Keeping

Data will be collected on paper by study coordinators and transcribed into an electronic database which will be maintained on-campus locations at UCLA, NWU, Geisinger, IU, Rush, Edward, Baptist Health, and UofC. Data will be managed by the PIs and study coordinators. Access to the data will be limited to site PIs and research coordinators only during the study enrollment period. All patient specific identifiers will be kept separate from the primary research database. The research database will be organized by a unique patient identifier.

10. Study Monitoring, Auditing and Inspecting

All periprocedural complications and adverse events will be reviewed by PIs at study midpoint to ensure there is no significant difference in event rate between the study groups. Should there be significant differences, or if there should be a high overall event-rate out-of-line with the procedural norm for CRT, the study will be halted.

11. Financial Considerations

No renumeration will be provided to subjects.

12. Ethical Considerations

No specific ethical considerations are identified in relation to this study.

13. Conflict of Interest

This is an internally funded study with no external support.

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15. APPENDIXES

A. QUESTIONNAIRE

Kansas City Cardiomyopathy Questionnaire

KCCQ_2006_no sig line.pdf

B. SCHEDULE OF EVENTS (SCHEMA)

	Pre-Implant (Screening)	**Implant & Periprocedure (Day 0)**	**Week 2[d]**	**Month 1[d]**	**Month 3**	**Month 6**	**Month 12**	**Year 2 & Year 3**
Medical Records Review	X							X
Clinical Evaluation	X	X	X	X	X	X	X	
Electrocardiogram	X	X[c]			X	X	X	
Echocardiogram	X					X	X	
Urine Pregnancy Test[a]	X							
Kansas City Cardiomyopathy Questionnaire	X					X	X	
NYHA Functional Class Determination	X					X	X	
Randomization	X[b]							
Device Interrogation		X[c]	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	

[a] Only for women of childbearing potential
[b] Pre-procedure to facilitate planning of procedure
[c] Pre-discharge
[d] Week 2 and Month 1 visits may be combined, per treating doctor discretion