

Electrical Activation Mapping Guided Tailor Made Approach for Cardiac Resynchronization Therapy

1.0 BACKGROUND

Cardiac resynchronization therapy (CRT) is an established therapy for symptomatic heart failure patients despite optimal medical therapy with prolongation of QRS duration on surface electrocardiogram. Several pivotal studies have demonstrated a significant benefit in terms of mortality and morbidity in patients described above.¹⁻⁷ However, there are still 30 to 40% of studied patients being nonresponder to CRT, despite its proven benefit. The responder rate is particular poor in patients with non-LBBB pattern of conduction disturbance⁸⁻¹⁵ with one recent study showing non-LBBB patients has a responder rate of only 38%.¹⁵ The plausible reasons of lack of effect of CRT in these patients include relative less baseline electrical dyssynchrony, a homogenous type of conduction delay without a discrete line of block, lack of electrical ventricular uncoupling and inability to improve or even in some case worsening of electrical dyssynchrony with CRT.¹⁵⁻²¹ The electrical activation response to conventional CRT varies between individual patients may not be predicted by baseline conduction disturbance.^{10,17,19,22} The prevalence of non-LBBB type of conduction disturbance is reported to be as high as 44% in heart failure patients with increase in QRS duration.²³ Hence, a large proportion of heart failure patients with prolonged QRS duration will not benefit from CRT.

The quest to improve CRT responder rate has been subject of intense research interest. Apart from screening for subgroup of heart failure patients with better responder rate to conventional CRT, another possibility is to improve the efficacy of current CRT delivery system. There are two major approaches that have been studied to improve CRT delivery namely selecting the optimal site for LV pacing and alternate method of CRT delivery other than pacing at single epicardial LV site. Study have demonstrated that targeting the LV lead to the site of latest mechanical contraction as determined by strain echocardiogram improved the responder rate.²⁴ Other studies looks into local electrogram guided placement of LV lead to the latest electrically activated segment inside coronary sinus branch.²⁵ Regarding alternate way of CRT delivery, there are interests in using direct His-bundle pacing to overcome the longitudinal conduction delay in the His-Purkinje system. It has been shown that significant narrowing of QRS duration and favorable clinical outcome when compare to conventional CRT can be achieved with direct His-bundle pacing.²⁶ Intuitively, direct-His bundle pacing may provide benefit over pre-excitation of the left ventricle by conventional CRT in patients with right bundle branch block (RBBB) pattern of conduction disturbance. Other potential method to improve CRT outcome is the delivery of multipoint pacing (two LV sites together with one RV site and two RV sites together with one LV site) by recruiting more myocardium to contract simultaneously.²⁷⁻²⁹ Pacing the LV endocardium as compared to epicardium via a coronary access has been shown to improve acute hemodynamic response but however there is no long-term clinical result of endocardial LV pacing comparing to epicardial LV pacing.³⁰

The ability to deliver CRT using different configuration provides opportunity to tailor made resynchronization therapy to heterogenous group of patient in terms of activation delay. This is in contrary to the current concept of a single configuration of CRT deliver suit all patients with widening of QRS duration disregard of pattern of activation delay. Hence the aim of our study is to

investigate whether there is an optimal configuration of CRT delivery that varies between patients with different pattern of activation delay.

Previous study on noninvasive activation pattern has shown that responders showed higher degree of baseline dyssynchrony and greater improvement of dyssynchrony by CRT when compared to nonresponders.¹⁷⁻¹⁹ The optimal configuration of CRT delivery is defined by that result in the greatest improvement of electrical dyssynchrony. The acute change in electrical dyssynchrony indices will be compare between the optimal configuration and the conventional configuration, namely biventricular pacing with single LV lead in posterior or lateral branch of coronary sinus. A significant different between the two configurations would suggest that there indeed is an optimal configuration of CRT delivery and a tailor made strategy is feasible. To prove this concept of tailor made strategy, devices will be implanted to deliver CRT using the optimal configuration determined by noninvasive electrical activation mapping in non-LBBB patients. The medium term improvement of surrogate marker of LV systolic volume will be compared to that of a predefined level of 40%.

Our group has been using echocardiogram to study mechanical dyssynchrony in patients with heart failure and pacing induced LV dysfunction in predicting response to CRT.³¹⁻⁴⁷ However, in subsequent multi-center trial studying 12 different echocardiographic parameters of mechanical dyssynchrony in predicting CRT response, no single echocardiographic measure of dyssynchrony was shown to improve patient selection for CRT.⁴⁸ The results of the study further strengthen the concept that the response to conventional CRT therapy cannot be predicted by baseline dyssynchrony pattern. It is rather the degree of improvement from baseline that will predict response to CRT therapy. The degree of dyssynchrony improvement on the other hand is determined by the interaction of baseline electrical substrate and the activation change brings about by CRT. The electrical substrate is fixed but different configuration of CRT delivery, including different location of LV lead, can produce different changes in activation. In order to study the interaction of electrical substrate and change in activation brings about by CRT, a tool that allows global electrical mapping of both the LV and RV is considered to be important not only to elucidate important information like location of conduction block but also to study the interaction of the left and right ventricle.^{17-19,22}

2.0 STUDY OBJECTIVES

The purpose is to prospectively study the feasibility to optimize configuration of CRT delivery for acute correction of electrical dyssynchrony using a noninvasive mapping of global electrical activation.

Study Hypothesis

Tailor-made configuration of CRT delivery is feasible and able to improve responder rate compare to single method of CRT delivery in candidates with known poor response to CRT.

Primary outcome measure

Responder rate of greater than 10% of LV end systolic volume reduction in patients undergoing tailor-made approach of CRT delivery at 6 months. The responder rate is to compare with pre-defined level of 40% for single method of CRT delivery namely biventricular pacing with LV lead in coronary sinus.

Secondary outcome measures

1. The acute electrical dyssynchrony indices of different methods of CRT delivery.
2. The hemodynamic responses of different methods of CRT delivery.
3. Procedure duration and implantation success rate of the optimal CRT delivery method as determined by the best improvement in electrical dyssynchrony indices.
4. Cine images (PA, LAO 30°, RAO 30°) and Chest X ray (PA view)
5. Peri-operative and 6 months follow-up complications rate:
 - a. Thromboembolic event
 - b. Dislodgement and migration of pacing leads
 - c. Phrenic nerve stimulation
 - d. Others
6. Echocardiogram parameters at baseline and 6 months: left ventricular systolic and diastolic volume, left ventricular ejection fraction, degree of mitral regurgitation, strain imaging.
7. NYHA class, 6 minute hall walk test and quality of life using Minnesota's questionnaire at baseline and 6 months.
8. Electrical parameters including threshold, sensitivity and lead impedance of pacing leads at implant and 6 months follow-up.

3.0 PATIENT SELECTION CRITERIA

Inclusion criteria:

Adult (aged 18 or above) of both sexes

Ischemic or non-ischemic cause of heart failure

QRS duration > 120 ms, non -LBBB type of conduction disturbance

NYHA class III or above

Sinus rhythm

Informed consent by the patient

Already received stable dose of guideline directed medical therapy for at least 3 months

Exclusion criteria

LBBB* patients

Pregnant women

Participation in another study

Patient with contraindication to left ventricle catheterization by a retrograde aortic approach (eg mechanical aortic valve, severe aortic stenosis and aortic dissection)

*The definitions of LBBB (QRS duration \geq 130 ms; QS or rS in lead V1; broad R waves in leads I, aVL, V5, or V6; and absent q waves in leads I, V5, and V6).

4.0 STUDY DESIGN

This is a prospective, single-center, non-randomized study, aiming to demonstrate the feasibility of tailor-made CRT delivery to optimize electrical dyssynchrony correction using noninvasive study of electrical activation in subgroup of patients with poor response to CRT.

Study will be performed in accordance with Declaration of Helsinki.

Recruitment Method

Patients with relative narrow QRS complex and non-LBBB pattern of conduction disturbance who is referred for CRT therapy will be recruited for the study. The clinical care of the patients recruited will not be different to other patients receiving CRT. The study will be carried out in Prince of Wales Hospital, Hong Kong.

5.0 STATISTICAL CONSIDERATION

Hypothesis

The null and alternative hypotheses are as follows:

H0: The responder rate of tailor-made approach \leq 40%

HA: The responder rate of tailor-made approach $>$ 40%

Sample size was calculated employing binomial methods with the following assumptions were used:

Expected responder rate for tailor-made approach =60%

Historical control responder rate =40%

Test significance level (a) = 0.05 (1-sided)

Power= 80%

Based on the above assumptions, the sample size was calculated as 77. Accounting for the attrition of 20%, the total required sample size is 93 patients with device implanted.

Statistical method for additional analysis

All continuous data will be summarized with the number of non-missing data, mean \pm standard deviation, median and range (minimum – maximum). T test will be used for the comparison between the groups. In case the assumption for t test is violated, then the equivalent nonparametric test, such as Wilcoxon rank sum test, Kolmogorov-smirnov test, will be used instead. The normality assumption will be tested by the normality test with the aid of QQ plot.

All categorical data will be tabulated with number of occurrence and percentage. Chi-square test will be used for the comparison between the groups. In case the expected counts in each cell is less than 5, then Fisher's exact test will be used instead.

Procedures for reporting any deviation(s) from the original statistical plan

Any deviations from the statistical analysis plan will be documented.

The treatment of missing, unused or spurious data, including drop-outs and withdrawals.

No imputation techniques will be used.

6.0 PROTOCOL DESCRIPTION

Patient informed consent

The investigator is responsible for obtaining informed consent from each prospective study patient prior to the performance of any study related procedures. After a patient has been provided with the information of the study and given time to think on whether to participating into the study, the patient will be asked to sign and date a consent form. One copy of the signed patient consent form must be handed out to the patient and one must be filed by the investigator in the investigator files. After the patient and the investigator have signed and dated the consent form, the study data collection process may start.

Patients meeting all the inclusion criteria and not meeting any of the exclusion criteria are eligible for the study. Data will be collected at the following study visits:

Enrollment

Noninvasive electrical activation and acute hemodynamic study

Implant

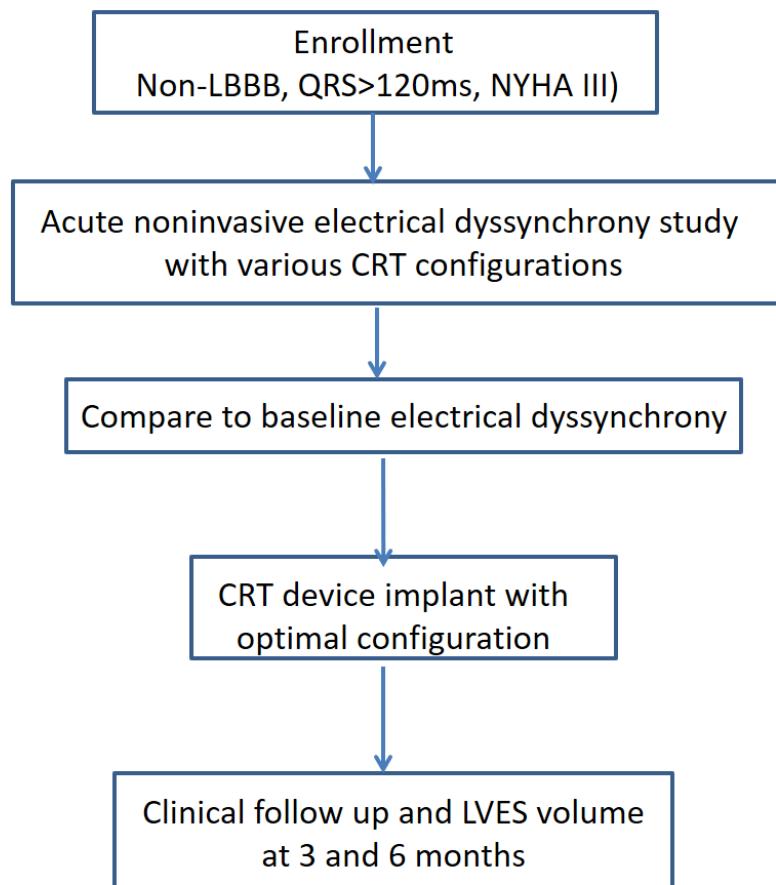
Pre-discharge (PDH) (\leq 72 hours post implant)

Month 3 follow-up visit: 90 ± 14 days post implant

Month 6 follow-up visit: 180 ± 14 days post implant

Table 1. Data collection for each scheduled visit

	Enrollment	Implant *	PDH*	Month 3	Month 6
Patient Informed Consent	x				
Echocardiogram	x		x	x	x
Medical History	x				
Cardiovascular Medication	x	x	x	x	x
NYHA Class	x			x	x
6MHW	x			x	x
SF-36QoL	x			x	x
12-lead electrocardiogram	x	x		x	x
Cine images		x			
Device Interrogation		x	x	x	x
Adverse Event	x	x	x	x	x
Protocol Deviation	x	x	x	x	x

Figure 1. Study Flow Chart

Noninvasive mapping of electrical activation

Ventricular activation maps will be acquired simultaneously with hemodynamic measurements using noninvasive mapping system (ECVUE, Medtronic Inc, USA). A thoracic computed tomographic scan will be acquired with the electrodes attached to the patient. Local ventricular activation times will be defined as the onset of the QRS complex or the pacing spike to the maximal negative slope of each unipolar electrogram.

The following electrical dyssynchrony indices will be derived

- i) Total activation time (TAT) is defined as the time difference between the earliest and latest site of activation on the entire ventricular epicardium (LV and RV);
- ii) RVTAT is defined as the time difference between the earliest and latest site of activation on the RV ventricular epicardium;
- iii) LVTAT is defined as the time difference between the earliest and latest site of activation on the LV ventricular epicardium;
- iv) Ventricular electrical uncoupling (VEU) is defined as mean LV activation time minus mean RV activation time (LVTAT-RVTAT)
- v) Intra-LV electrical dyssynchrony index (ED) is the standard deviation of activation times at 500 sites on the LV epicardium, including the epicardial aspect of the septum.

Placement of electrophysiology catheters for CRT delivery

Pacing leads will be placed in high right atrium, His-bundle region, right ventricular apex, high septal RV, coronary sinus posterior/lateral branch, coronary sinus anterior branch, lateral and septal region of endocardial LV in order to deliver CRT in 8 different configurations as stated below:

- 1) Conventional biventricular pacing with RV lead in right ventricular apex and LV lead in lateral or posterior branch of coronary sinus
- 2) Biventricular pacing with the LV lead in coronary sinus in closest possible proximity to the latest electrical activation region (18 region) if it is different to the site tested in (1)
- 3) Direct His-bundle pacing
 - i) His bundle pacing catheter distal tip as cathode and RV lead proximal pole as anode
 - ii) His bundle pacing catheter distal tip as cathode and proximal pole of LV lead placed in lateral or posterior branch of coronary sinus as anode.
 - iii) His bundle pacing catheter distal tip as cathode and His bundle pacing catheter proximal pole as anode.

In subjects in sinus rhythm

- i) together with RV bipolar pacing with RV lead in RV apex.

In subjects in AF

- i) together with RV bipolar and LV bipolar pacing

4) Multi-point pacing

- i) Triple site pacing with two RV leads in the RV apex and high RV septum and LV lead in posterior or lateral branch of coronary sinus.
- ii) Triple site pacing with RV lead in the RV apex and one LV lead in posterior or lateral branch of coronary sinus and the other LV lead in anterior branch of coronary sinus.
- iii) Triple site pacing with RV lead in RV apex and one quadripolar LV lead in posterior or lateral branch of coronary sinus and pacing at 2 sites simultaneously from the quadripolar lead.

During delivery of CRT the output will be set at twice the capture threshold and pacing impulse will be delivered in VDD mode with an AV delay of 80msec and VV delay at 0msec for all leads in the ventricles.

Acute hemodynamics studies

Invasive LV hemodynamic measurements of LV dP/dt will be recorded using a micromanometer (Radi Medical Systems, St Jude Medical, USA) placed in the LV cavity.

All measurements will be made with an average of 10 second recordings with no occurrence of premature atrial or ventricular beats during the recording and 1 minute interval between changes in pacing settings.

During sinus rhythm and the 7 configurations of CRT pacing as stated above both noninvasive electrical activation map and acute hemodynamic measurement will be recorded for analysis.

Implantation of CRT device**1) Conventional pacing configuration**

The CRT system will be implanted with standard technique for conventional pacing configuration. Only market released CRT devices and leads will be implanted.

2) Epicardial LV pacing in the latest activation site

LV lead will be placed in the LV latest activation site or the site in closest proximity to the latest activation site and if necessary quadripolar or active fixation LV lead will be used to achieve stability.

3) Direct His-bundle pacing

i) In subjects in sinus rhythm

For direct-His bundle pacing, standard techniques will be used to place an LV lead preferably in the posterolateral branch of the coronary sinus system, RV and right atrial lead. His pacing lead (SelectSecure, model 3830, Medtronic Inc, USA) supported using a dedicated delivery sheath (model C315, Medtronic Inc, USA) or a deflectable lead delivery sheath (model C304, Medtronic Inc, USA) to the site showing His bundle signal on the mapping catheter. Multiple position to optimize QRS narrowing and threshold could be tested. The His pacing lead and the LV lead will be connected via a Y-adapter (model 5866-38M, Medtronic Inc, USA). The HBP will be connected to the cathode and the LV tip to the anode of the Y-connector.

ii) In subjects in AF

The same as for subjects in sinus rhythm except the His pacing lead will be connected to the atrial port of the CRT device and LV lead into the LV port of the CRT device without the use of a Y adapter.

4) Multiple point pacing

For multiple point pacing, the septal RV and the bipolar LV leads will be connected to the LV port using a parallel Y-adapter (model 2872, Medtronic Inc, USA) for the 2 RV leads group. Whilst the anterior bipolar and posterior/lateral LV lead will be connected using a parallel Y-adapter (model 2872, Medtronic Inc, USA) for the 2 LV leads group. If simultaneous pacing from 2 sites or the quadripolar LV lead pacing is the optimal configuration, a quadripolar lead will be connected to the LV port.

CRT programming

Para meter	Mandatory Device Setting
Mode	DDD or DDDR
Base Rate	≤ 60 min-1
Max. Sensor Rate/Max. Tracking Rate	140 min-1
Mode Switch	"On" if atrial tachyarrhythmia are suspected
Paced AV Delay	150 ms

Sensed AV Delay	120 ms
V-V Delay	0ms

Adverse Events

Definition

Adverse Event (AE) is defined as any untoward medical occurrence in a patient who participates in a clinical investigation. This definition does not imply that there is a relationship between adverse event and the clinical investigation.

Serious Adverse Event (SAE) is defined as an adverse event that

- a) led to death
- b) led to a serious deterioration in the health of the subject that
 - i. resulted in a life-threatening illness or injury
 - ii. resulted in a permanent impairment of a body structure or a body function
 - iii. required in-patient hospitalization or prolongation of existing hospitalization
 - iv. resulted in medical or surgical intervention to prevent permanent impairment to
- c) led to body structure or a body function to foetal distress, foetal death or a congenital abnormality or birth defect.

List of Anticipated Adverse Events

Possible adverse events (in alphabetical order) associated with the acute noninvasive activation mapping and hemodynamic study, include, but are not limited to the following:

- Air embolism
- Allergic reaction
- Arterial or venous occlusion
- Arterial, venous or cardiac perforation
- Asystole
- Bleeding
- Cardiac tamponade
- Death
- Erosion
- Exacerbation of heart failure
- Infection

- Myocardial damage
- Thromboembolism

Possible adverse events (in alphabetical order) associated with the CRT device implantation, include, but are not limited to the following:

Acceleration of arrhythmias (caused by device)
Angina pectoris
Air embolism
Allergic reaction
Asystole
Bleeding
Cardiac tamponade
Chronic nerve damage
Death
Erosion
Exacerbation of heart failure
Excessive fibrotic tissue growth
Extracardiac stimulation (phrenic nerve, diaphragm, chest wall)
Extrusion
Fluid accumulation
Formation of hematomas or cysts
Histotoxic reaction
Infection
Loss of capture
Myocardial damage
Oversensing / undersensing
Palpitations due to documented arrhythmias
Phrenic nerve stimulation
Pneumothorax
Thromboembolism
Venous occlusion
Venous or cardiac perforation

Adverse Events Recording and Reporting

Safety surveillance and reporting will be done for all patients enrolled in the study. This will be started from the time patient provides with the informed consent until the last study visit has been performed or the patient has died or the patient concludes his participation into the study.

All **Serious Adverse Event** is to be documented and reported to the research ethics committee within 24 hours of notification.

As soon as the final details are available for the AE, the information should be reported on the AE case report form:

- Hospitalization details (if applicable)
- Diagnostic test information (if applicable)
- Treatment given (if applicable)
- Final medical diagnosis and cause
- Patient condition
- Final AE status
- Seriousness of AE based on final medical diagnosis and cause
- Relationship of AE to clinical investigation based on final medical diagnosis and cause

Study Termination

All reasonable efforts should be made to retain the patient in the clinical investigation until completion of the clinical investigation.

If a patient concludes their participation in the study, the future care and management will not be affected, whether it is voluntary or otherwise:

- A patient completes the study (Month 6 follow-up).
- A patient / family member may request to withdraw from the clinical investigation at any time with no effect to the patient's present care.
- A patient dies.
- An investigator may withdraw a patient from the study at any time as according to the best interest to the patient.

Risks associated with Participation in the Clinical Investigation

The risks involved with this study are comparable to those associated with the implant of any CRT.

The additional risks are related to the computerized tomography of the heart with possible complication of contrast injury to kidney and allergic reaction. Other additional risks are related to pre-implantation electrical activation study which involves putting in pacing catheters and pressure monitoring catheters in the body with possible risk of injury to the heart, blood vessel, bleeding, wound complications and infection.

Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this CIP, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups.

Anticipated Benefits

The proposed tailor made method of CRT delivery may improve the outcome inpatient that will be recruited in the study with high incident of non responding to CRT by improving electrical dyssynchrony correction.

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