**The University of Queensland, School of Medicine,**

**Cardiovascular Research Imaging Centre**

**CRT-OPT- A randomized trial of benefit and cost-effectiveness of Cardiac Resynchronization Therapy (CRT) optimization in heart failure**

**Study Protocol**

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**AIM**

The aimis to determine whether sequential optimization of cardiac resynchronization therapy (CRT) can improve outcome in advanced chronic heart failure (CHF). The efficacy of this strategy will be established by assessment of functional capacity using measurement of 6-minute walk test distance (6MWT), B-type natriuretic peptide (BNP), echocardiographic measures and quality of life (QoL, based on a disease specific questionnaire: Minnesota Living with Heart Failure questionnaire, MLHFQ, and the multi-attribute utility indices: EQ-5D and Assessment of Quality of Life (AQoL). The cost- effectiveness of the strategy will also be assessed, relative to non-optimization. The **hypotheses** are that optimization of atrioventricular delay (AVD) setting will lead to (1) improved exercise capacity (2) improved BNP, LV structure and QoL over the ensuing 6 months, and be (3) cost-effective.

**BACKGROUND**

Chronic heart failure (CHF) affects over 300,000 Australians with another 30,000 new cases diagnosed each year, and accounts for 43,000 hospitalizations and 2,200 deaths annually [1]. The management of CHF costs Australia $1 billion annually [2]. Although cardiac resynchronization therapy (CRT) is limited to CHF patients with specific indications [3], it is conservatively estimated that >1,000 devices are implanted each year in Australia, at a cost of $20 million. CRT is accepted as a class I indication based on its efficacy in improving functional capacity and survival in landmark clinical trials such as CARE-HF and the COMPANION trials [4, 5]. Integral in the protocol of these landmark trials was not just CRT implantation but the subsequent optimization of the CRT pacemaker settings post-implant. **Despite the integral role of optimization in these trials, survey data suggests that only 13% of patients implanted with CRT undergo systematic optimization by any method.** Although optimization algorithms have been incorporated in some CRT pacemakers, there is no compelling evidence that they have resolved the need for optimization. **Echocardiography accounts for 2 in every 3 optimizations** performed [6].

**Comprehensive AV delay optimization**

Comprehensive and tailored CRT optimization will optimize the AVD. It is physiologically intuitive that AV delay optimization will be efficacious and on this basis routine AV delay optimization was included in many of the landmark clinical trials [4, 5]. The evidence for this practice is however lacking from comprehensive multi-centre randomized trials [7]. In addition, the **optimization process is consuming of time (usually ~1 hour), equipment (echocardiograph, pacing programmer), and expertise (cardiologist and technician)**. As the ventricle remodels over time, physiology will change, and **the need for re-optimization is likely to date every 3-6 months** [8]. Also **no economic analysis has been performed to date**. Our study will aim to resolve these questions.

**Preliminary data.**

Our group has extensive experience with echo and CRT. Preliminary work by our group [TS/TM] includes a two-stage double-blind randomized controlled trial study involving 59 patients (age 65±10, 75% male), who had all recently undergone successful CRT implantation (ACTRN12612000805875) [9]. The first stage compared 6 month response between 30 individuals who were randomized to resting echocardiographic optimization of CRT [AVD plus VVD] and 29 who did not. In the second stage, a subset of 37 patients from the original cohort were randomized (double blind) to either resting echocardiographic optimization (n=20) or exercise echocardiographic optimization (n=17) and followed for a further 6 months. Patients undergoing rest optimization demonstrated improvement in almost all variables and significantly in contrast to those without optimization. In a linear regression model, the only significant predictor of BNP improvement was whether an individual underwent resting optimization or not (β=0.38, p=0.04). **In those undergoing resting optimization, the degree of change in AV delay was correlated with improvement in LV end-diastolic volume (r=0.33, p<0.01).** We concluded that echocardiographic optimization of CRT at rest was superior to no optimization or optimization on exercise.

**This study represents the next step of this work, using a multicentre design to study functional capacity, quality of life and economic analysis of CRT optimization.**

**RESEARCH PLAN**

1. **Study design.**

This is a multicentre, randomized, double-blind, cross-over trial to evaluate the utility of echocardiographic optimization of the AV delay in symptomatic (Functional Class [FC] III) CHF patients who have had CRT implanted.

**Sites include: Baker IDI Heart and Diabetes Institute / The Alfred Hospital, Melbourne VIC**

**Royal Hobart Hospital, Hobart, TAS**

**Sunshine Coast University Hospital, Birtinya, QLD**

**Heartwest (Williamstown, St Albans, Niddeire, Hoppers Crossing), VIC**

1. **Study Population.**

Inclusion criteria:

* History of implanted CRT device
* Able to perform a 6-minute walk test
* No more than moderate valvular heart disease (NB: Functional mitral regurgitation is acceptable).

Exclusion criteria:

* Life expectancy <1 year
* In atrial fibrillation
* Prosthetic mitral valve replacement.

The investigators will ensure the patient is stable, on stable (and optimal) medical therapy each visit, and with functional impairment (by 6 minute walk and VO2 if possible) equivalent to FCIII. The baseline history will include co-morbidities (diabetes, COPD, hypertension etc.), current medication.

1. **Data Acquisition.**

Each participant will have 3 visits.

**Visit 1**

Consent will obtained and the patient screened. If suitable the following data will be gathered: Clinical - Medical History;

AE/SAE Assessment;

Blood test, including electrolytes, FBC and BNP;

6 minute walk;

Echocardiography;

Naughton EST protocol;

Medication Compliance (pill count/check printed prescriptions);

QoL Questionnaires (EQ5D, AQoL and MLHFQ);

CRT optimization will then be performed as detailed below.

1. **CRT Optimization & Randomization.**

Optimization will be performed by the investigating physician, a sonographer and a pacing technician. Consenting individuals will be screened, and then undergo baseline testing and randomization, using a computerized protocol with a 1:1 ratio of either optimization or no optimization (visit 1). Only the study nurse and pacing technician will be aware of whether the patient is to be optimized or not, the patient and investigating physician will both be blinded. In this way double-blinding will be maintained for the duration of the study.

**Visit 2**

After 3 months, patients will be called back for an identical visit to baseline. After clinical assessment, optimization settings will be re-evaluated. The study nurse will then instruct the pacing technician to either program these settings or not based on the previous randomization.

**Visit 3**

A final visit, with identical testing, will occur after a further 3 months (6 months from randomization).

1. **Endpoints.**

Endpoints will be selected to assess improvements in patient function, symptoms and well established markers of prognosis;

|  |  |
| --- | --- |
| ***Primary*** | * Functional capacity as defined by 6-MWT distance. |
| ***Secondary*** | * Naughton EST treadmill protocol | |
|  | * QoL questionnaires: EQ5D, AQoL and MLHFQ |
|  | * Percentage days alive and out of hospital score |
|  | * B-type natriuretic peptide |
|  | * Left ventricular volumes/function[2D/3D]/strain analysis |
|  | * Incremental cost effectiveness ratio for CRT optimization (vs   non-optimization) from a health care payer’s perspective |

**6. Cost effectiveness.**

The information gathered in this study will permit the development of a Markov model to study cost-effectiveness. Requisite parameters will relate to transition probabilities (e.g. frequency of CHF admission, new AF, lead revision), utilities (derived from EQ5D and AQoL before and after treatment in each group) and cost (based on patient self-report) including medication and pathology costs, days of hospitalization, specialist appointments and costs of imaging.

**7. Power calculations.** In our preliminary data, baseline 6MW was 384m, and there was a 30m increment post-optimization [9]. This matches our meta-analysis, where 5 of 6 studies showed an improvement from 11-75m [10]. A study of **100 patients per group** would allow us to identify an 8% improvement of 6MW (SD of 80) at a p=0.05, and cluster-adjusted power of 80% (assuming intra- class correlation 0.01). This will also provide 80% power to show an 8% change in exercise capacity (baseline 3.0±0.7 METS [11]).

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VISIT ORDER

\*\*Patients will need to be identified prior to implant to ensure device based optimization occurs at time of implant.

Consent will obtained and the patient screened. If suitable the following data will be gathered:

1. Clinical - Medical History; QRS duration/EF/NYHA/meds pre-implant.
2. AE/SAE Assessment; Review of admissions, days in hospital.
3. Medication Compliance (pill count/check printed prescriptions);
4. QoL Questionnaires (EQ5D, AQoL and MLHFQ);
5. Blood test, including electrolytes, FBC and BNP; Height, weight, HR, BP.
6. Pacing check. Print out of check. Record % of BiV pacing.
7. Echocardiography. GE echo machine. Measures to include LVEF, GLS, 3D, atrial volumes, E/E’, measures of RV function (RV S’, RV free wall 2D strain).
8. AVD optimization – Iterative method as CARE-HF protocol. Including measure of MV VTI x5. Measure of DFT x 5. Check absence of diastolic MR.
9. 6 minute walk;
10. Wait 15 minutes
11. Naughton EST protocol;
12. Randomization, programming of settings. END.