

**CARDIAC RESYNCHRONIZATION THERAPY IN  
NARROW QRS HEART FAILURE PATIENTS**

A THESIS

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## Abstract

**Introduction:** Cardiac resynchronization therapy (CRT) is a well-established treatment for heart failure (HF) patients with a wide ( $>120$  msec) QRS complex. Despite not meeting current guidelines, some narrow QRS HF patients with mechanical dyssynchrony receive CRT. The effects of CRT on cardiac function, HF symptoms, and outcomes are not clearly known in these patients. **Methods:** All consecutive CRT recipients between 2003 – 2008 with ejection fraction (EF)  $\leq 35\%$  and New York Heart Association (NYHA) class III or IV were studied. There were 146 and 492 patients with narrow and wide QRS complex, respectively. Eighty-five narrow QRS patients in sinus rhythm with suitable images were matched by age and gender to wide QRS patients for a multi-plane tissue tracking and speckle-tracking echocardiographic analysis.

**Results:** Narrow QRS patients were younger and had less radial dyssynchrony at baseline. Increases in EF of  $3.2 \pm 9\%$  and  $6.8 \pm 9\%$  ( $p < 0.05$ ) were seen in narrow and wide QRS patients, respectively. Wide QRS patients had decreased left ventricular size ( $p < 0.01$ ) and increased longitudinal systolic function ( $p = 0.04$ ), while narrow QRS patients had decreased delayed longitudinal contraction ( $p < 0.01$ ), while tending to decrease longitudinal dyssynchrony ( $p = 0.076$ ) and increase radial strain ( $p = 0.086$ ). Both groups improved diastolic function ( $p < 0.01$ ), and had a similar proportion of patients with improved clinical symptoms ( $p = 0.17$ ). Five-year mortality rates were 40% and 46% in the narrow and wide QRS groups respectively ( $p = 0.234$ ); however, wide QRS patients tended to have a more favorable survival free of cardiovascular hospitalization ( $p = 0.056$ ). **Conclusion:** Narrow QRS HF patients with mechanical dyssynchrony respond favorably to CRT, but to a lesser extent than wide QRS patients.

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## **CHAPTER 1. INTRODUCTION**

Cardiac pacemakers have extensively evolved since their first use in the late 1950s. Advancements in technology have transformed the first model, a bulky external generator, into models that are commonly smaller than the palm of a hand. In addition to the more patient-friendly dimensions, pacemakers are now capable of delivering a wide array of therapies.

Initially, pacemakers were solely used as a safeguard for the conduction system of the heart, providing electrical stimulation to the cardiac myocytes when the patient's intrinsic system was unable to provide adequate heart rate and/or conduction of electrical activity from atrium to ventricle. In addition to pacing, implantable cardioverter defibrillators (ICDs) were developed to protect recipients from arrhythmias such as ventricular tachycardia and ventricular fibrillation; conditions that could ultimately lead to sudden cardiac death (Zipes & Wellens, 1998). Dual-chamber pacing devices with leads in the right atrium (RA) and right ventricle (RV) were commonly implanted, with 2.25 million patients receiving atrioventricular sequential pacemakers and 415,780 receiving ICDs between 1990 and 2002 (Maisel et al., 2006).

Beginning in the late 1990s the technique of adding a third lead, introduced through the cardiac venous system of the left ventricle (LV), was tested (Bakker et al., 1994; Cazeau, Ritter, & Bakdach, 1994; Daubert et al., 1998; Rosenthal, Qureshi, & Pitts Crick, 1995). Positioning a LV lead, either posteriorly or laterally, allows for biventricular pacing of the heart. The initial hypothesis was that restoration of a more native ventricular activation pattern and ability to optimize atrioventricular delay would increase systolic performance of patients with heart failure (HF) (Strickberger et al., 2005). Biventricular pacemakers earned the name cardiac resynchronization therapy

(CRT) devices as they were also found to decrease the electromechanical interventricular and intraventricular conduction delays seen in many HF patients, resulting in more synchronous contractions (Strickberger et al., 2005).

Large clinical trials have reported success of CRT in specific HF patient populations (Abraham et al., 2002; Bristow et al., 2004; Cazeau et al., 2001; Cleland et al., 2005). Patients with lower ejection fractions (EF) and greater conduction system delay, quantified by QRS prolongation on a surface electrocardiogram (ECG), have traditionally achieved the greatest benefit. Results from these large clinical trials of CRT led to the recommendation of CRT as a Class I treatment for HF patients with an EF  $\leq$  35%, QRS  $\geq$  120 milliseconds (msec), in sinus rhythm, and New York Heart Association (NYHA) class III or ambulatory class IV HF symptoms on optimal recommended medical therapy (Epstein et al., 2008; Strickberger et al., 2005).

Much of the current literature on CRT in narrow QRS HF patients reports improvements in systolic function and LV reverse-remodeling, often times similar to the results achieved by wide QRS patients. In addition, reductions in NYHA classification and gains in aerobic capacity argue for CRT use in this subset of HF patients. However, small sample sizes, short durations of follow-up, and potential selection bias of patients evaluated has resulted in uncertainty within the cardiology community regarding the benefits of CRT in this patient population (Holzmeister, Hurlimann, Steffel, & Ruschitzka, 2009).

An extensive amount of clinical data on a relatively large consecutive patient population, coupled with the ability for an in-depth echocardiographic (ECHO) analysis, will allow this study to significantly add to the current literature. Previous findings

suggest the need for a longer duration of follow-up, as well as an all-encompassing imaging analysis to better understand the efficacy of CRT in narrow QRS HF patients (Achilli et al., 2003; Beshai et al., 2007). Specifically, the following hypotheses will be addressed:

1. Baseline demographic, clinical, and ECHO measures will be similar between narrow and wide QRS patients.
2. Narrow QRS HF patients receiving CRT improve longitudinal, radial, and global systolic function and LV synchrony, but not to the degree of similar wide QRS patients.
3. Five-year mortality and cardiovascular (CV) hospitalization rates, and subjective evaluation by their cardiologist will show no differences in chronic benefits of CRT between narrow and wide QRS HF patients.

Chapter two will summarize the current literature relating to CRT use in narrow QRS HF patients. A background of HF pathophysiology and disease progression will be established, followed by a brief history of CRT and its recommendations for use. Patient population, brief methods, and subsequent findings regarding clinical, ECHO, and chronic outcomes of previous studies will be reviewed.

Chapter three will detail the methodology of this study. Background information will be provided on the construction of the study center CRT database and clinical data abstraction. Study specific patient inclusion criteria used in an attempt to capture a homogenous patient sample that mimics current literature will be explained. Finally, the

protocols for the use of tissue Doppler imaging (TDI) and speckle-tracking echocardiography (STE) modalities will be presented.

Chapter four will elaborate on the findings of this study, by examining whether narrow and wide QRS HF recipients of CRT differ clinically or in cardiac structure and function at baseline. An ECHO analysis of global and regional cardiac structure and function will be used to compare the efficacy of therapy in the two patient groups. Ultimately, chronic patient benefit from therapy will be determined by comparing mortality, hospitalizations related to CV diagnosis, and subjective physician evaluation of the patient.

Chapter five of this thesis will summarize and discuss the clinical applications of these findings in terms of current success of CRT in narrow QRS patients, patient selection to improve future improvements in CRT in narrow QRS patients, and an argument for adaptation of current CRT implantation guidelines to include selected narrow QRS patients. A currently enrolling international multi-center study of CRT in narrow QRS patients will be discussed along with other areas of future research on the subject.

## **CHAPTER 2. REVIEW OF LITERATURE**

## ***Heart Failure Pathophysiology and Medical Management***

Heart failure is one of the most prevalent and expensive diseases in the United States. There are 5.8 million Americans living with the disease. The one-year mortality rate is 20%. Furthermore, heart failure cost the American health care system an estimated \$39.2 billion in 2010 (American Heart Association, 2010; Lloyd-Jones et al., 2010). A diagnosis of HF is made when the myocardium fails to pump oxygen rich blood at the level needed to perfuse metabolizing tissues. Specific etiologies vary, with the most common forms of HF occurring because of ischemic heart disease, hypertension, and valvular disease (Braunwald, Zipes, & Libby, 2001). Regardless of the starting point for the disease, common hemodynamic and circulatory changes occur, providing short-term relief of symptoms. These short-term compensatory mechanisms are only a quick-fix to a chronic disease, ultimately furthering the progression of HF towards an end-stage resulting in cardiac transplantation or death.

The Frank-Starling mechanism describes how increases in left ventricle end-diastolic volume (LVEDV) and pressure result in acute increases in cardiac output. By lengthening the myocardial fibers at end-diastole, increases LV preload are observed (Brooks, Fahey, White, & Baldwin, 2000). These changes lead to an increase in stroke volume with an accompanying increase in cardiac output. However, the hemodynamic benefit accompanied with increases in LVEDV and pressure is short-lived.

Chronic LV hypertrophy and/or dilation resulting from a compensatory response to an increase in load has many deleterious effects on the entire cardiovascular system (Braunwald et al., 2001). As myocardial sarcomeres are stretched to an optimal length for contractility, the myosin filaments have access to actin receptor sites. Unfortunately,

further stretching beyond this point decreases the amount of tension achieved by mechanical coupling (Brooks et al., 2000). A decrease in tension due to suboptimal actin-myosin coupling translates to a decrease in systolic contractility, as evident in dilated cardiomyopathy. Secondary attempts by the body to maintain a minimal level of cardiac output include systemic vasoconstriction (increased blood pressure), fluid retention, and sympathetic nervous system stimulation (Braunwald et al., 2001). These mechanisms are complex, involving non-cardiac systems such as the renal and adrenergic nervous systems. At this stage, the introduction of optimal medical therapy must occur if the progression of HF is to be slowed (Cowie et al., 1997).

Common pharmaceutical agents prescribed to combat the neurohormal aspect of HF include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-adrenergic receptor-blocking agents (beta blockers), and diuretics (Bristow, 1997; Doughty, Rodgers, Sharpe, & MacMahon, 1997; McGrae McDermott, Feinglass, Sy, & Gheorghide, 1995). The ACE pathway is the dominant mechanism (80%) for generating angiotensin II in a failing heart. ACE inhibitors work by interrupting the renin-angiotensin-aldosterone system. The conversion of angiotensin I to angiotensin II is impeded by an ACE inhibitor, negating the effects of vasoconstriction, cardiac myocyte hypertrophy, and myocyte apoptosis that accompany increased levels of angiotensin II under normal conditions (Braunwald et al., 2001). ARBs differ slightly from ACE inhibitors in that they block the effects of angiotensin II whether it is produced via the ACE or the less prevalent (20%) chymase pathway. Similar pre-load reductions and cardiac output increases are seen between ARBs and ACE inhibitors (Gottlieb et al., 1993; Mazayev et al., 1998). In an attempt to thoroughly

inhibit the renin-angiotensin-aldosterone system, these two drug classes are often used in combination to capitalize on effects targeted at both the ACE and chymase pathways (Braunwald et al., 2001).

Beta blockers have multiple mechanisms of action providing a decrease in HF symptoms. First, a reduction in beta-adrenergic signal transduction results in a decrease in hypertrophic and apoptotic characteristics of cardiac myocytes associated with the cardiotoxic property of norepinephrine exposure (Braunwald et al., 2001). Secondly, a negative chronotropic effect lowers heart rate, increasing the stroke volume in a healthy manner by allowing for more blood flow to fill the ventricles during the increased diastolic period. Thirdly, beta blockers inhibit sympathetic hyperactivity at the renal level, reducing hypertension and limiting the spread of norepinephrine to the heart (Neumann, Ligtenberg, Klein, Koomans, & Blankestijn, 2004). Chronically, beta-blockers increase systolic function after an initial drop in EF is seen. Once the failing heart's intrinsic myocyte dysfunction is remedied by an increase in EF, the compensatory adaptation of a larger LVEDV is no longer needed for increased stroke volume (Bristow, 1997). Consequently, the LV reverse-remodels by decreasing in dimensions closer to those of a healthy heart.

Diuretics decrease water and solute reabsorption by the kidney, resulting in an increased amount of urine production (Braunwald et al., 2001). Different classes include loop, thiazide, potassium-sparing, and spironolactone diuretics. These classes vary in the location of action throughout the kidney, affecting the proximal tubule, the loop of Henle, or the distal convoluted tubule and collecting duct (Braunwald et al., 2001). Furthermore, electrolytes such as sodium, potassium, and chloride are targeted differently

depending on type of diuretic. Regardless of classification, diuretics provide similar benefit to patients with congestive HF by reducing extracellular fluid volume, ventricular filling pressure, and wall stress (Braunwald et al., 2001). By limiting increases in ventricular filling pressure and wall stress, diuretics have the potential to slow LV dilation, hypertrophy, and eventual decrease in myocardial contractility associated with HF (Braunwald et al., 2001).

A considerable portion of HF patients still experience debilitating symptoms even after being treated to maximally tolerated doses of ACE inhibitors, beta blockers, and other common HF drugs (Jessup et al., 2009). After patients have been treated with maximally tolerated doses of medications repeat assessment of EF is appropriate every 6-12 months. If systolic dysfunction continues and patients do not exhibit a major change in clinical status they can be considered for device therapy with CRT (Jessup et al., 2009).

### ***CRT History & Recommendations***

Pacing the LV via a lead in the coronary sinus was first utilized in the mid 1990s, with initial experiments demonstrating success in patients with dilated cardiomyopathy and congestive HF (Bakker et al., 1994; Cazeau et al., 1994; Rosenthal et al., 1995). Cardiac resynchronization therapy was then tested in numerous studies, ranging from single-site cross sectional designs to large multi-center randomized trials (e.g. COMPANION, CARE-HF, MIRACLE, and MUSTIC) (Abraham et al., 2002; Bristow et al., 2004, Cazeau et al., 2001; Cleland et al., 2005). Typical patient populations of these large studies included HF patients with decreased systolic function, conduction system

delay, and activity limiting subjective symptoms. Inclusion criteria were limited to those with an EF  $\leq$  35%, QRS duration  $\geq$  120 msec, and NYHA functional class III or IV symptoms.

The current recommendations for CRT implantation, as governed by American College of Cardiology (ACC), American Heart Association (AHA), and Heart Rhythm Society (HRS), have been developed from the results of these large multi-center trials (Epstein et al., 2008; Strickberger et al., 2005). A Class I indication has been given to CRT devices for patients who have an EF  $\leq$  35%, QRS duration  $>$  120 msec, and NYHA functional class III/IV symptoms. Recently, results of the MADIT-CRT, REVERSE, and RAFT trials have expanded the indications for Boston Scientific CRT-D devices to less symptomatic HF patients, classified as NYHA functional class I and II (Linde et al., 2008; Moss et al., 2009; Reynolds & Gold, 2011; Solomon et al., 2010; St. John Sutton et al., 2009; Tang et al., 2010; S. Wein, Voskoboinik, L. Wein, Billah, & Krum, 2010).

The literature lacks a collection of large multi-center studies of HF patients with a narrow QRS complex ( $\leq$  120 msec), thus the level of evidence to support CRT as a Class I indication for narrow QRS HF patients is not available. However, small, mostly single-center studies have suggested a significant benefit of CRT in patients with narrow QRS and mechanical dyssynchrony. Analysis of the National Cardiovascular Data Registry's Implantable Cardiac-Defibrillator Registry provides estimates of how many CRT recipients have a narrow QRS complex. Of the 45,392 CRT-D implants between January 2006 and June 2008, 12% (5,432) were placed in narrow QRS HF patients (Fein et al., 2010). The demand for CRT in narrow QRS HF patients is partially explained by results of the CONQUEST (Congestive Heart Failure and QRS Duration: Establishing

Prognosis) trial, which reported that more than 42% of the over 3,000 systolic HF patients had a QRS < 120 msec (van Bommel, Delgado, Schalij, & Bax, 2010; Shenkman et al., 2002).

Controversy as to the use of CRT in narrow QRS HF patients is partly fueled by the dissociation of electrical and mechanical dyssynchrony. A study utilizing three-dimensional ECHO technology reported 37% of patients with a narrow QRS had mechanical dyssynchrony, while 38% of those with a wide QRS lacked mechanical dyssynchrony (Kapetanakis et al., 2005). Additionally, severe mechanical dyssynchrony quantified by tissue velocity imaging (TVI) has been observed in 27% of narrow QRS patients with 30% of extremely prolonged (> 150 msec) QRS patients not exhibiting significant mechanical dyssynchrony (Bleeker et al, 2004). This situation is one potential contributing factor to the 25 - 40% non-responder rate of CRT patients (Birnie & Tang, 2006).

Effectiveness of CRT has been defined by many different endpoints, incorporating both objective and subjective measurements. Objective measures of response include the 6-minute walk test for distance (6MWT) and ECHO changes of cardiac structure and function, while subjective clinical responses include changes in NYHA functional classification and quality of life (QOL) questionnaires. The literature investigating CRT in narrow QRS HF patients is a combination of prospective and retrospective study designs. Some studies prospectively enrolled narrow QRS patients with moderate to severe HF symptoms and depressed systolic function ( $EF \leq 35\%$ ) (Beshai et al., 2007; Bleeker et al., 2006; 2005; 2004; Yu et al., 2006). Alternatively, others have retrospectively assessed CRT effects in narrow QRS HF patients that were a

small sample of a larger CRT study (Achilli et al., 2003; Gasparini et al., 2007; Ng et al., 2007; Yu et al., 2004). The EF inclusion criterion for these studies was less stringent, ranging from  $\leq 35\%$  to  $\leq 40\%$ , while clinical classification was the same in that only patients with NYHA class III/IV symptoms were included.

### ***RethinQ***

RethinQ was a double-blind, prospective, multi-center trial enrolling 172 NYHA class III HF patients with  $EF \leq 35\%$ ,  $QRS < 130$  msec, and evidence of mechanical dyssynchrony as measured by ECHO (Beshai et al., 2007). After receiving a CRT device, patients were randomized in a 1:1 ratio with 85 patients receiving CRT therapy and 85 acting as a control group with only the ICD portion of their device turned on. After a 6 month evaluation the control group had the CRT programming of their device turned on.

Presence of mechanical dyssynchrony was determined by both M-Mode and TVI. The opposing posterior and septal walls of the parasternal long-axis were analyzed for time-to-peak displacement using M-Mode ECHO. Significant mechanical dyssynchrony was present when time-to-peak displacement of the posterior and septal walls differed by 130 msec or more. TVI regions of interest were placed at the base of the anteroseptal, posterior, septal, and lateral walls creating tissue velocity curves over time. A difference in time-to-peak systolic velocity  $\geq 65$  msec between the septal & lateral or anteroseptal & posterior walls was defined as significant intraventricular mechanical dyssynchrony. Nearly all (96%) of patients qualified for enrollment based on TVI measurements, while only 4% were eligible because of mechanical dyssynchrony on M-Mode ECHO.

The primary endpoint was the proportion of patients with an increase in peak oxygen consumption  $\geq 1.0$  mL/kg/min at the 6 month evaluation. Secondary efficacy and endpoints included improvement in the QOL score and NYHA class at 6 months. At 6 months, the CRT group (46%) and control group (41%) did not differ in the proportion of patients meeting the primary endpoint ( $p = 0.63$ ). Similar results were also seen between groups in terms of changes in QOL score, 6MWT, and ECHO measurements including EF, LVESV, and LVEDV.

This study is somewhat unique in design in that the control group was narrow QRS patients who did not receive CRT. In most other studies, examining efficacy of CRT in narrow QRS HF patients a control group is composed of wide QRS HF patients (Achilli et al., 2003; Bleeker et al., 2006; 2004; Yu et al., 2006; 2004). Even though the design of RethinQ differs from that proposed in this thesis, the results are important as it is the only prospective multi-center study examining the use of CRT in narrow QRS HF patients.

### ***Clinical Outcomes***

The majority of available studies have reported that narrow QRS HF patients receive clinical benefit from CRT based on reductions in NYHA functional classification, improvements in QOL of scores, and increases in the 6MWT. Significant reductions in NYHA classification were observed in five studies, ranging from  $-0.4$  to  $-0.9$  in narrow QRS sample sizes of 29, 33, 45, 51, and 66 patients (Beshai et al., 2007; Bleeker et al., 2006; Gasparini et al., 2007; Ng et al., 2007; Yu et al., 2006). Results of QOL questionnaires were not as homogenous as changes in NYHA classification. Bleeker et

al. (2006) reported significant improvement ( $39 \pm 18$  to  $25 \pm 17$ ,  $p < 0.001$ ), while two studies reported non-significant changes in QOL scores for narrow QRS HF patients. The 6MTW showed improvements in the narrow QRS groups of patients ranging from 51 – 96 meters with six months or less of follow-up time (Achilli et al., 2003; Bleeker et al., 2006; Gasparini et al., 2007; Yu et al., 2006).

The literature indicates that clinical and functional improvements in response to CRT are often times similar between narrow and wide QRS HF patients, based on 6MWT, NYHA classification, and QOL questionnaire scores. However, in limited instances, wide QRS patients responded more favorably than their narrow QRS counterparts. Additionally, narrow QRS patients never experienced greater increases in these variables as compared to wide QRS patients.

### ***Echocardiographic Outcomes***

Left ventricle size and function are commonly assessed by the Biplane Simpson's method of quantifying EF and measuring either volume (mL) or diameter (mm) of the chamber (Otterstad, Froeland, St. John Sutton, & Holme, 1997). Similar to the clinical evaluation data, there is a consensus across the literature in terms of cardiac structure and function benefits in narrow QRS HF patients treated with CRT. Numerous studies show that both narrow and wide QRS patients significantly and similarly improved EF and LV reverse remodeling post-CRT. Yu et al. conducted the only study to report that narrow ( $-8.6 \pm 14$  cc) and wide ( $-16.1 \pm 18$  cc) QRS patients differ ( $p = 0.02$ ) in the degree to which they reduce LV end-diastolic volume (Yu et al., 2006). However, the wide QRS group did have significantly greater LV end-diastolic ( $194 \pm 82$  cc vs.  $167 \pm 47$  cc,  $p =$

0.04) and end-systolic ( $148 \pm 74$  cc vs.  $122 \pm 42$  cc,  $p = 0.03$ ) volumes at baseline, allowing for a greater potential reduction in response to CRT. If results were reported as percent of volume decrease instead of absolute volume decrease, LV remodeling may have been similar between the groups.

Methods for measuring dyssynchrony vary across the literature, with laboratories using M-Mode, tissue Doppler imaging (TDI), and/or pulsed-Doppler measures of interventricular delay (IVD) (Achilli et al., 2003; Beshai et al., 2007; Bleeker et al., 2006; Yu et al., 2006). Even within studies using TDI to quantify intraventricular dyssynchrony, different applications of the technology were used. Yu et al. placed regions of interest at basal and mid-ventricular levels of six different cardiac walls, for a total of twelve regions of interest (commonly referred to as the “Yu Index”). Analysis performed by Bleeker et al. (2006) differed slightly, using data points from the septal, lateral, inferior, and anterior walls, while ignoring posterior and antero-septal wall data. The primary dyssynchrony measurement presented by Bleeker et al. (2006) was the maximum delay between systolic velocities among the four walls, while Yu et al. (2006) calculated asynchrony by the standard deviation of the time-to-peak systolic velocity of the twelve LV segments.

As dyssynchrony measures of M-Mode, TDI, and IVD are compared collectively, similar reductions in dyssynchrony were observed between narrow and wide QRS patients. Achilli et al. (2003) using the very basic M-Mode measure of LV posterior wall activation delay, saw comparable improvements between patient groups that had similar baseline measurements. Bleeker et al. (2006) reported similar and significant ( $p \leq 0.001$ ) reductions in TDI-measured LV dyssynchrony when pre-CRT values were

compared to both one-day and six-month post-CRT follow-up measures. Finally, IVD measures made by Achilli et al. (2003) were significant ( $p < 0.001$ ), and similar between narrow and wide QRS groups.

Further studies utilized a measure of dyssynchrony as a screening or stratifying tool. Yu et al. (2006) used a cutoff value of 32.6 msec for standard deviation of twelve-segment TVI to reach a predetermined ratio of one-half patients having significant systolic asynchrony while the other half did not have significant asynchrony. Beshai et al. (2007) determined pre-CRT mechanical delay as being a difference in peak systolic velocity  $\geq 65$  msec between the anteroseptal-posterior or septal-lateral opposing walls. These investigators used measures of intraventricular dyssynchrony as a screening tool to determine the number of patients with marked dyssynchrony (Beshai et al., 2007; Yu et al., 2006). A meaningful pre – post comparison of changes in dyssynchrony through CRT use cannot be made because ECHO protocols in most studies only measured EF and LV volume in follow-up and not mechanical dyssynchrony.

### ***Chronic Follow-up***

Few studies have followed patients long enough to report data on mortality and hospitalizations in narrow QRS HF patients. Gasparini et al. (2007) stated two out of 45 narrow QRS patients died of non-cardiac causes, while one patient died suddenly during the follow-up period. In the much larger ( $n = 331$ ) collection of wide QRS patients, eleven deaths were attributed to non-cardiac diagnoses, 35 due to end-stage HF, and five died suddenly. There were no significant differences in mortality rates between narrow and wide QRS patients (4.8% vs. 7.7%,  $p = 0.38$ ). Mortality due to HF did differ

( $p = 0.041$ ) between narrow (0%) and wide (5.2%) groups, but due to the drastic disparity in sample sizes, this comparison may not be valid (Gasparini et al., 2007).

Achilli et al. also made a mortality comparison between the groups, albeit with an even smaller number of patients (narrow = 14, wide = 38) (Achilli et al., 2003). Seven deaths (18.4%) occurred in wide QRS patients, with two attributed to progressive HF. No differences were reported between the groups as 3 patients in the narrow QRS group died (21.4%) with two dying from progressive HF. The mean follow-up duration for this study was  $546 \pm 277$  days, about a third shorter than that of Gasparini et al. (2007).

### ***Summary***

The high prevalence of patients suffering from systolic HF without QRS prolongation is well established. A subset of these patients is receiving CRT although implantation occurs without full scientific backing from governing associations. Instances of CRT benefiting narrow QRS patients through reductions in LV chamber size, increases in systolic function, and reductions in HF symptoms have been shown. However, the lack of long-term follow-up and a comprehensive ECHO analysis pre- and post-CRT in a larger sample size are limitations that will be addressed in this thesis.

## **CHAPTER 3. METHODOLOGY**

### *CRT Database*

A database was constructed containing the 1027 consecutive patients receiving a first-time CRT at the St. Paul Heart Clinic between the years of 2003 and 2008. This database collected demographic, clinical, and basic ECHO information on each patient (Appendices A & B).

A list of eligible patients was developed from device clinic implantation records. The clinic's electronic medical records management system was then searched for each patient. If records were missing, health information services were contacted and record retrieval was attempted from the two hospital systems where all devices were implanted. If a date of death could not be determined from medical records, an online obituary search engine was utilized. Hospitalization dates, lengths of stay, and diagnoses were cross-referenced to those at the two hospital systems for accuracy.

The primary endpoints derived from the CRT database are mortality and cardiovascular (CV) hospitalization rates, while secondary endpoints are subjective clinical response one-year post implant and changes in LV size and function from ECHO analysis. This subjective clinical response was determined by reading physician progress notes at  $12 \pm 2$  months after the implant, and scored as "worse", "no change", "mildly better", or "markedly better". Factors used for determination of the patient response were: HF symptoms, functional capacity, and overall well-being in response to CRT.

Reliability and validity of abstraction were tested by having each completed case report form checked for discrepancies by a second person. Disagreements in data were settled by a third researcher. Also, a total of 25 patients were completely re-abstracted

and the two case report forms checked for accuracy. Case report forms were found to be 89% accurate when completely re-abstracted.

### ***Patient Selection***

In an attempt to limit confounding factors and create sample populations that are more homogenous, inclusion criteria were used to filter the database. When the database was filtered to include only patients with a baseline EF  $\leq$  35% and classified as NYHA functional class III or IV, 146 patients had a narrow QRS ( $\leq$  120 msec) complex, while 492 had a wide QRS ( $>$  120 msec) complex. Of that larger cohort, 85 narrow QRS patients with suitable ECHO images and in normal sinus rhythm were age- and gender-matched to 85 wide QRS patients (not previously RV paced) to be included in the in-depth ECHO analysis of dyssynchrony measurements. The benefits of CRT in wide QRS HF patients are well established, so matching wide to narrow QRS patients served to create a control group.

Patients with a narrow QRS complex do not meet current recommendations for CRT implantation. To support the decision for device implantation in these patients, ECHOs with TDI were performed to assess for mechanical dyssynchrony.

### ***Echocardiography***

Echocardiographic studies were obtained using standard American Society of Echocardiography criteria on the Vivid 7 ultrasound machine (General Electric Co., Milwaukee, WI) and analyzed on the GE EchoPAC PC reading station (version 7.0.0) (Leitman et al., 2004; Schiller et al., 1989). Basic 2-D ECHO images were analyzed for a

visual estimate of EF, LVEDD, LVESD, RV dysfunction, severity of mitral regurgitation (MR), and diastolic filling period (DFP). Both RV dysfunction and severity of MR were score using a semi-quantitative scale of 0 to 6 (0 = none, 1 = trace, 2 = mild, 3 = mild-moderate, 4 = moderate, 5 = moderate-severe, 6 = severe). All ECHO studies were read in a blinded fashion, with no knowledge of the patient's QRS duration. Lead wires of the RV are often visible in ECHO. However, with the possibility of patients being upgraded from an existing ICD to CRT device the knowledge of the ECHO being pre- or post-CRT was nullified.

Studies with TDI available for analysis were used to calculate measures derived from tissue tracking (TT) and TVI modes. In preparation for analysis, cardiac event timings were marked on trans-mitral and -aortic pulsed-wave Doppler flow images. Event timings were automatically transferred within analysis software to the ECG-gated TDI images. The start of a new heartbeat was designated as the closure of the mitral valve.

Tissue-tracking and TVI modes were used to quantify both regional and global systolic function in the longitudinal plane of motion. Apical 4-chamber, 2-chamber, and long-axis views with TDI data were used to determine tissue displacement (TT) and velocity (TVI) throughout the cardiac cycle. Regions of interest (10 mm x 7 mm) were manually placed at the base and mid-ventricle (halfway between base and apex) on the endocardial border of six walls (septal, lateral, inferior, anterior, anteroseptal, and posterior) of the LV. Regions of interest were manipulated so that final location produced the least amount of "noise", or variability in the tissue curves.

TVI was selected and the basal maximum systolic velocity was measured at the septal, lateral, posterior, and antero-septal walls. The maximum systolic velocity was defined as the peak of the velocity curve occurring within the LV ejection period between opening and closing of the aortic valve. Early (E') and active (A') diastolic tissue velocities were considered to be the troughs (most negative value) of the velocity curve in the diastolic period, between opening and closing of the mitral valve.

Analysis mode was then changed from TVI to TT. Using the previously determined cardiac event timings and tissue regions of interest, tissue displacement measurements were made. The magnitude of displacement at aortic valve closure (end-systole) was averaged over the twelve regions of interest to calculate a global systolic contraction score (GSCS). A tissue segment was considered to express delayed onset of activation (DOA) if it displayed paradoxical motion ( $\geq 0.5$  mm) away from the apex/transducer during early systole. Tissue segments achieving maximal longitudinal displacement after aortic valve closure were deemed to have delayed longitudinal contraction (DLC). The duration (msec) of both DOA and DLC were measured. Figure 1 provides a visual explanation of how these measures are shown on an actual TT image.

Ventricular function was analyzed in the radial plane by use of STE. By measuring stable acoustic markers of standard grayscale 2-D ECHO images, STE gives the ability to precisely quantify cardiac motion in the radial plane. These acoustic markers, or "speckles", represent specific fixed points within the myocardium. Tracking these individual speckles frame by frame throughout the cardiac cycle allows motion to be quantified as strain, strain rate, displacement, and velocity. For the purposes of this study, strain (%) variables measured will be peak strain and strain at aortic valve

closure (AVC). Reported strain values are means of all segments of the LV that were tracking properly, giving a global LV measurement similar to that of the GSCS in the longitudinal plane. Figure 2 provides an example STE image where a patient achieves peak strain after AVC.

Basal and mid-ventricular parasternal short-axis views (if available) were manually traced along the endocardial border of the LV. Computer software tracks the endocardial border throughout the entire cardiac cycle. During this process, the LV is divided into six sections: antero-septal, anterior, lateral, posterior, inferior, and septal. Each segment is then closely examined and determined to be tracking properly or not, with poor tracking segments being left out of analysis.

Measurements of intraventricular (within the LV) dyssynchrony were made in the longitudinal and radial planes. The standard deviations of time-to-peak displacement in the longitudinal plane and time-to-peak strain in the radial plane were calculated to give measures of synchrony of systolic contraction. Interventricular (between LV and RV) dyssynchrony was measured by calculating the difference in time between onset of pulsed-Doppler flows of the right and left ventricular outflow tracts in relation to the start of the QRS complex on gated ECG.

### ***Statistical Analysis***

Data was recorded on hard copy case report forms, and then entered into a spreadsheet for storage and management (Microsoft Excel 2000, Microsoft Corporation, Redmond, Washington, USA). Statistical analysis was performed using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, California, USA). Baseline

characteristic data were compared between groups with unpaired t-tests for continuous variables of age, HF duration, ECHO follow-up duration, heart rate, blood pressure, weight, and QRS duration. Baseline variables of counts (sample proportions) were compared between groups with Fischer's Exact Test. Variables analyzed in this manner include HF etiology, NYHA class, CRT device type, lead location, comorbidities, and medications.

Echocardiographic measures of LV size, function, and dyssynchrony are all continuous values, reported as mean  $\pm$  standard deviation. Pre- and post-CRT values were compared within a group using paired t-tests, while comparisons between narrow and wide QRS patients were made with unpaired t-tests. Differences in mortality and CV hospitalization rates were compared between groups using the Kaplan-Meier method, with the Log-Rank test statistic applied to determine significance. Lastly, correlations were made between change in ejection fraction and change in fractional shortening, as well as between baseline radial dyssynchrony and change in LVESD. Significance was determined at an alpha level of 0.05.

## **CHAPTER 4. RESULTS**

### ***Baseline***

Tables 1 and 2 include baseline demographic, clinical, and device related data for the smaller detailed ECHO analysis cohort. Tables 3 and 4 provide the same information for the larger cohort, consisting of all patients with NYHA functional class III/IV and baseline EF  $\leq$  35%. The only significant difference in baseline characteristics between the narrow and wide patients who underwent ECHO analysis was QRS duration ( $104 \pm 12$  msec vs.  $158 \pm 27$  msec,  $p < 0.001$ ). Also, more wide QRS patients tended to be on an ACE inhibitor or ARB (86% vs. 73%,  $p = 0.057$ ). This ECHO cohort sample patient population was age- and gender-matched so no significant differences were expected to be seen with respect to gender or age. The larger cohort of patients also had similar baseline characteristics between groups, with few exceptions. Narrow QRS patients were younger ( $64 \pm 15$  yrs vs.  $72 \pm 11$  yrs,  $p < 0.001$ ), received more CRT-D devices (63% vs. 51%,  $p = 0.011$ ), were upgraded less from AV PM to CRT (5% vs. 20%,  $p < 0.001$ ), and were more likely to be on aldosterone-blocking medication (25% vs. 17%,  $p = 0.029$ ).

### ***Echocardiography***

Echocardiographic measurements of structure and function are presented in Table 5, while those specific to dyssynchrony are described in Table 6. At baseline, narrow and wide QRS patients had similar measures, respectively, of EF ( $25 \pm 6\%$  vs.  $25 \pm 5\%$ ,  $p = 0.552$ ), LVESD ( $5.3 \pm 0.8$  cm vs.  $5.4 \pm 0.9$  cm,  $p = 0.353$ ), GSCS ( $3.8 \pm 1.9$  mm vs.  $4.2 \pm 1.8$  mm,  $p = 0.127$ ), longitudinal dyssynchrony ( $75 \pm 42$  msec vs.  $82 \pm 31$  msec,  $p = 0.233$ ), and severity of MR ( $2 \pm 1.4$  vs.  $2 \pm 1.4$ ,  $p = 0.995$ ). Baseline differences were present as narrow QRS patients had greater DLC ( $86 \pm 49$  msec vs.  $70 \pm 39$  msec,

$p = 0.024$ ), less radial dyssynchrony (standard deviation of time-to-peak strain:  $92 \pm 56$  msec vs.  $120 \pm 54$  msec,  $p = 0.003$ ), and less interventricular delay on pulsed-Doppler ( $19 \pm 20$  msec vs.  $34 \pm 28$  msec,  $p < 0.001$ ).

Increases in EF post-CRT were present in both narrow ( $3.2 \pm 9\%$ ,  $p = 0.002$ ) and wide ( $6.8 \pm 9\%$ ,  $p < 0.001$ ) patients, with the increase being significantly ( $p = 0.012$ ) greater in the wide QRS patients. Wide QRS patients reverse-remodeled significantly, in terms of decreasing both LVEDD ( $-0.39 \pm 0.7$  cm,  $p < 0.001$ ) and LVESD ( $-0.46 \pm 0.9$  cm,  $p < 0.001$ ). Changes in LV chamber size were not significantly different post-CRT in the narrow QRS patients. Longitudinal systolic performance was increased in the wide QRS group as GSCS increased ( $0.5 \pm 2$  mm,  $p = 0.04$ ), albeit not significantly ( $p = 0.825$ ) different from that of narrow QRS patients. Radial strain at aortic valve closure tended to increase in the narrow QRS group ( $p = 0.086$ ), while neither group increased peak radial strain.

In regards to dyssynchrony measures, narrow QRS patients significantly decreased DLC ( $-17 \pm 48$  ms,  $p = 0.009$ ) and tended to decrease the standard deviation of longitudinal time-to-peak displacement ( $-10 \pm 41$  ms,  $p = 0.076$ ). Wide QRS patients significantly decreased interventricular delay ( $-10 \pm 31$  ms,  $p = 0.009$ ).

A beneficial and similar ( $p = 0.857$ ) increase in DFP was achieved by both narrow ( $46 \pm 133$  msec,  $p = 0.004$ ) and wide QRS ( $42 \pm 143$  msec,  $p = 0.009$ ) groups. Finally, severity of MR was decreased in only the wide QRS group ( $-0.6 \pm 1$ ,  $p < 0.001$ ). There were no changes seen in mean maximum systolic velocity, peak radial strain, radial dyssynchrony, or diastolic relaxation measurements in either group.

The validity of visual estimating EF, as opposed to using the Biplane Simpson's method, was shown by incorporating more objective LV dimensional measurements of LVEDD and LVESD. The Pearson's Correlation shown in Figure 3, compares change in fractional shortening  $((LVEDD - LVESD) / LVEDD)$  to change in EF, producing  $R = 0.4619$ ,  $R^2 = 0.2134$ ,  $p < 0.001$ .

### ***Chronic Clinical Follow-up***

Narrow and wide QRS patients had similar clinical outcomes based on one-year post implant subjective response, CV hospitalization rate, and mortality rate of the overall large cohort. The number of patients with mildly or markedly improved clinical symptoms at one year was similar, with 61% of narrow QRS patients and 67% of wide QRS patients meeting these criteria ( $p = 0.166$ ). Kaplan-Meier curves (Figure 4) demonstrate similar ( $p = 0.234$ ) survival at five years in narrow (60%) and wide (54%) QRS patients. Figure 5 depicts a nearly significant ( $p=0.056$ ) difference in favor of wide QRS patients with survival free of CV hospitalization at five years with narrow QRS patients at 25% and wide QRS patients at 29%.

## **CHAPTER 5. DISCUSSION / CONCLUSION**

The purpose of this study was to examine the effects of CRT on HF patients with a narrow QRS complex ( $\leq 120$  msec) and evidence of mechanical dyssynchrony in comparison to a control group of wide QRS complex ( $> 120$  msec) HF patients. We had hypothesized that both groups of HF patients would have similar baseline characteristics, similar long-term mortality and hospitalization rates, with wide QRS patients receiving a greater hemodynamic response to CRT assessed by ECHO. The major findings of this study are: 1) narrow QRS patients are younger at implant, have less DLC, and less radial dyssynchrony at baseline; 2) similar 5-year mortality rates are observed between groups, while narrow QRS patients tended to have a greater 5-year CV hospitalization rate; 3) narrow QRS patients received some hemodynamic improvements, but it was often to a lesser degree than that of the matched wide QRS patients.

Improvements in the primary ECHO measurements of EF, LVEDD, and LVESD were greater in the wide QRS patients. EF was the only primary ECHO measure to improve from baseline in narrow QRS patients, with decreases observed in LVESD and LVEDD that did not reach significance ( $p = 0.128$ ,  $p = 0.191$ , respectively). Changes in secondary ECHO measurements of GSCS, DFP, and interventricular delay were not significantly different between the two groups of HF patients. Lastly, the narrow QRS patients improved from baseline in other secondary ECHO measurements such as strain at AVC, longitudinal dyssynchrony, and DLC but not to a significantly greater degree than wide QRS patients.

The narrow QRS group had a greater proportion ( $p = 0.004$ ) of subjects with  $\Delta EF \leq 0$ , but had a similar proportion of “super-responders” with  $\Delta EF \geq 15\%$  (narrow: 15% vs. wide: 26%,  $p = 0.116$ ). This combination of ECHO based “non-responders” and

“super-responders” shows a greater variation in hemodynamic response to CRT in the narrow QRS group. Although the proportion of “non-responders” was greater in the narrow QRS group, significantly improved systolic function and reduced symptoms of HF are also seen as evident in the 15% “super-responder” rate in this study cohort. However, with larger sample sizes, the data would likely show that “super-responders” are present to a greater degree in wide QRS HF patients as the data was trending towards significance.

Based on this multi-plane analysis, the mechanism of response in global systolic function (EF) may differ between groups. The wide QRS patients achieved greater LV reverse-remodeling, accompanied by an increase in longitudinal contractility. Comparatively, the narrow QRS patients tended to improve in radial strain and longitudinal measures of synchrony. A previous study examined the effects of CRT on longitudinal, radial, and circumferential function and dyssynchrony, but only four out of the 70 subjects had a narrow QRS complex (Kaufman, Kaiser, Burns, Kelly, & Bank, 2010). An analysis with a similar goal, performed on narrow QRS recipients of CRT, could provide insight into differing response mechanisms of CRT depending on QRS duration.

Regardless of differences in systolic response to CRT, both groups of patients observed similar increases in diastolic function. This is important as improvements in diastolic function have previously been shown to reduce signs and symptoms of HF, while increasing exercise capacity in patients with systolic HF (Nishimura & Tajik, 1997). An equal degree of improvement in diastolic function, coupled with the

possibility for significant systolic improvement, results in narrow QRS patients often improving, but to a lesser extent than wide QRS patients in this ECHO analysis.

Conclusions from the five-year survival and survival free of HF hospitalization data must be made with two caveats in mind. First, we do not know what the survival or hospitalization rates would have been in this same group of patients had they not received CRT. Therefore, we do not truly know the direct effect of CRT on long-term outcomes in these patients. Secondly, HF patients with a wide QRS have a worse long-term prognosis when compared to similarly treated narrow QRS HF patients (Kashani & Barold, 2005; Shenkman et al., 2002; Xiao, Roy, Fujimoto, & Gibson, 1996). The two groups of HF patients in this study were well matched at baseline with similar EF, proportion with ischemic etiology, and medication usage, but natural disease prognosis would expect wide QRS patients to have higher rates of mortality and CV hospitalizations.

This data suggests that wide QRS HF patients receive a greater benefit from CRT based on long-term endpoints. The two groups of HF patients had similar ( $p = 0.234$ ) mortality rates, with wide QRS patients having less ( $p = 0.056$ ) incidence of CV hospitalizations. Even though these results are similar between patient groups, the effect of CRT on these groups is not. CRT may be providing greater improvement to the natural HF disease progression in the wide QRS patients by producing similar or even more favorable long-term results. This is likely a change from what would have been seen in these patients if they were only treated with optimal pharmacologic therapy.

It may be reasonable to assume that these are simply not just years free from death or CV hospitalization, but years of an improved functional capacity in most

patients. With 61% of narrow QRS patients receiving mild or significant improvements in HF symptoms, not only were some beneficial hemodynamic responses observed on ECHO analysis, but improvements in everyday life assessed by clinical status were seen. This subjective measure may be less respected in the scientific community due to the variability of classification between physicians and patients self-reporting of symptoms. However, an improvement in HF symptoms is often more valued to a patient than objective measures of LV size and function.

The comparison of demographic, clinical, and ECHO variables between patient groups shows that narrow and wide QRS HF patients receiving CRT are very similar at time of implant. No differences in terms of duration of HF prior to implant, blood pressure, resting heart rate, body weight, and proportions receiving common HF medical therapy reveal that narrow QRS patients' treatment for HF prior to device implantation follows a similar course as wide QRS patients.

### ***Clinical Significance***

The results of this study show some benefit of CRT in narrow QRS HF patients exhibiting mechanical dyssynchrony prior to implantation, but the benefit appears to be less than that in wide QRS patients. In accordance with evidence based cardiology, the results of this current study cannot unequivocally support the use of CRT in narrow QRS HF patients. However, hemodynamic improvements in secondary ECHO measurements and positive subjective clinical response do not rule out the use of CRT in select narrow QRS HF patients.

A patient presenting with coronary artery disease, non-ischemic dilated cardiomyopathy, hypertrophic cardiomyopathy, genetic arrhythmia syndromes, or syncope with inducible sustained ventricular tachycardia in addition to a decreased EF ( $\leq 35\%$ ) will represent a difficult decision regarding device selection, regardless of the patient's QRS duration or NYHA classification. Patients with one of the previously mentioned disease states accompanied by a low EF ( $\leq 35\%$ ) qualify for implantation of an ICD under current guidelines (Epstein et al., 2008). However, the knowledge of electrical system dysfunction associated with worsening HF and the increased rate of infection with multiple device operations would perhaps favor a CRT-D device as a proactive measure although they do not currently qualify for the advanced device because of QRS duration ( $<120$  msec) or NYHA class (I/II).

It is well established that QRS duration lengthens with progression of HF disease and worsening LV function (Kashani & Barold, 2005; Shenkman et al., 2002; Xiao et al., 1996). Even if HF patients are treated appropriately, QRS duration has been shown to increase at a rate of 5 msec per year (Xiao et al., 1996). Additionally, numerous studies have shown that rate of infection increases with subsequent generator change-outs when compared to receiving a first time device (Johansen et al., 2011; Klug et al., 2007; Nery et al., 2010; Poole et al., 2010). The combined knowledge of an impending disease progression, the increased rate of infection with multiple generator change-outs, and results of this current study should be thoroughly considered. Positive results based on  $\Delta$ EF% and some measures of dyssynchrony provide evidence to support implanting a CRT-D device in selected patients with significant mechanical dyssynchrony not meeting recommendations due to QRS duration or NYHA class versus implanting them with an

ICD that they may need revisions in the future due to worsening HF symptoms. This study suggests that there may be a benefit in placing a CRT device in a narrow QRS HF patient with mechanical dyssynchrony requiring a defibrillator, knowing that an improved subjective clinical response and ECHO outcomes may be achieved.

A standard for quantifying a cut-off of mechanical dyssynchrony for increased predictive success rate of CRT must be established for patients lacking QRS prolongation (Beshai et al., 2007). Definitions of significant mechanical dyssynchrony have been proposed for traditional wide QRS patients, such as the standard deviation of time-to-peak velocity of a 12-segment TVI  $> 33$  msec or a maximum delay between peak velocities  $\geq 65$  msec (Bax et al, 2004; Yu et al., 2006; 2002). However, these cut-offs have shown conflicting results as a predictor of reverse-remolding in narrow QRS HF patients receiving CRT (Beshai et al., 2007; Bleeker et al., 2006; Yu et al., 2006). These definitions of significant mechanical dyssynchrony by Bax et al. (2004) and Yu et al. (2006) are based upon longitudinal dyssynchrony. Our data shows that in these groups of narrow and wide QRS HF patients receiving CRT based on clinical evaluation and evidence of mechanical dyssynchrony there are similar baseline measures of longitudinal dyssynchrony, but different measures of radial dyssynchrony, with narrow QRS patients having significantly less. A predictor of reverse-remodeling specific to narrow QRS HF patients may be more successful if additional baseline characteristic including radial strain and dyssynchrony are put into the model.

Endpoints based on EF changes, mortality, and hospitalizations are cornerstones of HF research. However, this study does not allow for the truest comparison of the effect of CRT on narrow QRS HF patients as the control group does not consist of narrow

QRS HF patients not receiving CRT. This type of comparison was utilized in the RethinQ trial, but with only six months of follow-up and 33 out of the 172 (19%) patients experiencing a HF event, the results did not provide the most clinically significant information (Beshai et al., 2007). Our study design was similar to that of numerous studies comparing the effects of CRT in narrow QRS HF patients to a group of wide QRS HF patients (Achilli et al., 2003; Bleeker et al., 2006; 2004; Gasparini et al., 2007; Yu et al., 2006; 2004). Even though it is not the truest of comparisons, it still provides clinically significant results as newer, off-label uses are often compared to the currently accepted standard treatments.

When making inferences to the clinical significance of these results it is important to remember the study setting and patient population. The study center is a large practice in a major metropolitan setting, catering to a diverse patient population. Large clinical trials of CRT have usually excluded patients with chronic obstructive pulmonary disease, uncontrolled hypertension, renal insufficiency, or reduced life expectancy (Abraham et al, 2002; Cazeau et al., 2001). This current study was less exclusive, with the only comorbidity excluded in the ECHO cohort being atrial fibrillation at the time of implant. The beneficial response to CRT in this study may be limited in part due to the prevalence of comorbidities in addition to HF. However, the trade-off of results that are more “real-world” applicable is an advantage when compared to previous CRT “recommendation setting” clinical trials.

### ***Limitations***

The study reported in this thesis is a single-center, retrospective, and non-randomized analysis of existing clinical data. As with all retrospective studies, missing or incomplete data can limit the completeness of the dataset. Every effort was made to obtain missing data, enlisting the assistance of the health information services department, collaborative hospitals, and using an online obituary search engine when a date of death was not present in medical records. However, an important strength of this study is that we included all patients meeting the minimal entrance criteria during the study period with exclusion of patients with atrial fibrillation only done to ensure the technical feasibility of ECHO analysis. This study was designed with less patient selection bias and is more representative of clinical practice than clinical trials.

### ***Future Research***

Multiple studies and analyses of databases have shown that there are many HF patients with a narrow QRS complex on surface ECG (van Bommel et al., 2010; Fein et al., 2010; Shenkman et al., 2002). Few additional therapies are available to these patients once on optimal pharmacological therapy. Fortunately, CRT has shown some promise in improving symptoms of HF and long-term survival of these patients, but further studies are needed to validate results prospectively in a larger patient population. Patient selection will be crucial in improving response rate to CRT, especially in a narrow QRS patient population. Future studies could benefit from increasing the traditional baseline measures of mechanical dyssynchrony of standard deviation time-to-peak longitudinal velocity (or displacement) or maximum delay between opposing walls to include

variables in this study of DOA, DLC, and radial dyssynchrony. By incorporating a multivariate analysis, an algorithm that better predicts response in this specific patient population could be proposed.

A randomized, prospective, parallel, double-blind trial designed to improve upon the limitations of the RethinQ trial is currently enrolling. EchoCRT plans to randomize 1258 patients at approximately 125 sites world-wide in a similar 1:1 randomization design to RethinQ with half the of the narrow QRS (< 130 msec) NYHA class III/IV patients receiving CRT therapy and half receiving only ICD therapy (Holzmeister et al., 2009). Similarly, patients must exhibit mechanical dyssynchrony at baseline. The protocols differ in that RethinQ only evaluated the 172 randomized patients at day 14 and at 6 months, while EchoCRT will follow patients at one month and then every three months until the study is complete (Beshai et al., 2007; Holzmeister et al., 2009). Time to the combined event of death or first HF hospitalization is the primary endpoint, with change in NYHA classification and QOL score at 6-months being secondary endpoints. A future comparison between EchoCRT's long-term mortality and CV hospitalization data to that in this thesis will give insight to the success of CRT in narrow QRS patients in a clinical trial to those treated in a "real-world" cardiology practice.

Finally, a pacemaker compatible with magnetic resonance imaging (MRI) has recently been approved for use by the Food & Drug Administration (Warren & Dougherty, 2011; Wilkoff et al., 2011). This advanced imaging modality has been shown to have an increased capability to quantify regions of LV tissue motion and areas of myocardial viability after an ischemic event when compared to traditional ECHO analysis (Rickers et al., 2005; Shan, Constantine, Sivananthan, & Flamm, 2004).

Prospective clinical trials evaluating the efficacy of CRT via MRI will significantly add to the current literature. The increased diagnostic and prognostic value of MRI has the potential to decrease the current non-responder rate of CRT, as quantification of viable tissue for resynchronization therapy would improve.

Table 1. Baseline clinical and device characteristics of the ECHO cohort.

	Narrow	Wide	p-value
n (M / F)	85 (57 / 28)	85 (57 / 28)	0.999
Age	64 ± 15	66 ± 12	0.402
Ischemic etiology (%)	65	56	0.346
HF duration prior to implant (years)	4 ± 4	4 ± 5	0.630
ECHO follow-up duration (months)	18 ± 12	17 ± 9	0.293
Resting HR (bpm)	72 ± 15	69 ± 14	0.263
SBP (mmHg)	116 ± 17	119 ± 19	0.255
DBP (mmHg)	69 ± 11	69 ± 12	0.931
Body weight (lbs)	186 ± 41	192 ± 46	0.370
QRS duration (msec)	104 ± 12	158 ± 27	<0.001
NYHA class (%)			
III	88	93	0.434
IV	12	7	0.434
CRT Device Type (%)			
CRT-D	65	71	0.512
CRT-P	9	5	0.370
ICD upgrade to CRT-D	25	25	0.999
AV PM upgrade to CRT	0	0	0.999
LV lead location (%)			
Anterior	2	2	0.999
Lateral	45	56	0.167
Posterior	7	4	0.496
Posteriorlateral	44	36	0.434
RV lead location (%)			
Septal	74	68	0.498
Apical	22	28	0.481

Values are mean ± SD for continuous variables and proportional % for categorical variables.

AV PM = atrio-ventricular pacemaker; CRT = cardiac resynchronization therapy; DBP = diastolic blood pressure; ECHO = echocardiogram; HF = heart failure; HR = heart rate; ICD = implantable cardioverter-defibrillator; LV = left ventricle; NYHA = New York Heart Association; RV = right ventricle; SBP = systolic blood pressure.

Table 2. Comorbidities and medications of the ECHO cohort.

	Narrow	Wide	p-value
Comorbidities (%)			
Diabetes	33	36	0.747
Renal insufficiency	28	27	0.999
COPD	27	26	0.999
PVD	15	11	0.494
Obesity	28	34	0.508
Cancer	16	20	0.692
CVA/TIA	22	14	0.233
Coronary Disease MI, PCI, CABG	67	61	0.523
Medications (%)			
ACE inhibitor / ARB	73	86	0.057
Beta blocker	81	85	0.684
Aspirin	69	67	0.869
Digoxin	34	36	0.873
Anti-Arrhythmic	9	8	0.999
Aldosterone blocker	27	19	0.274
Statin	59	68	0.265

Values are % for categorical variables.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker ; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CVA = cerebralvascular accident; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; TIA = transient ischemic attack.

Table 3. Baseline clinical and device characteristics of the larger cohort.

	Narrow	Wide	p-value
n	146	492	
Age	64 ± 15	72 ± 11	<0.001
Ischemic etiology (%)	62	60	0.565
HF duration prior to implant (years)	4 ± 4	4 ± 5	0.708
ECHO follow-up duration (months)	18 ± 13	18 ± 11	0.786
Resting HR (bpm)	73 ± 16	72 ± 14	0.612
SBP (mmHg)	116 ± 20	118 ± 19	0.288
DBP (mmHg)	69 ± 12	69 ± 11	0.821
Body weight (lbs)	189 ± 44	189 ± 46	0.944
QRS duration (msec)	103 ± 12	158 ± 25	<0.001
NYHA class (%)			
III	89	87	0.668
IV	11	13	0.668
CRT Device Type (%)			
CRT-D	63	51	0.011
CRT-P	10	9	0.870
ICD upgrade to CRT-D	22	21	0.728
AV PM upgrade to CRT	5	20	<0.001
LV lead location (%)			
Anterior	1	4	0.133
Lateral	51	57	0.218
Posterior	5	3	0.128
Posteriorlateral	38	34	0.428
RV lead location (%)			
Septal	73	71	0.755
Apical	20	23	0.497

Values are mean ± SD for continuous variables and proportional % for categorical variables.

AV PM = atrio-ventricular pacemaker; CRT = cardiac resynchronization therapy; DBP = diastolic blood pressure; ECHO = echocardiogram; HF = heart failure; HR = heart rate; ICD = implantable cardioverter-defibrillator; LV = left ventricle; NYHA = New York Heart Association; RV = right ventricle; SBP = systolic blood pressure.

Table 4. Comorbidities and medications of the larger cohort

	Narrow	Wide	p-value
<b>Comorbidities (%)</b>			
Diabetes	35	35	0.999
Renal insufficiency	33	40	0.122
COPD	25	22	0.574
PVD	16	16	0.999
Obesity	31	29	0.757
Cancer	17	21	0.409
CVA/TIA	21	22	0.999
Coronary Disease MI, PCI, CABG	65	61	0.383
<b>Medications (%)</b>			
ACE inhibitor / ARB	75	77	0.579
Beta blocker	83	80	0.476
Aspirin	64	60	0.385
Digoxin	36	38	0.697
Anti-Arrhythmic	15	20	0.228
Aldosterone blocker	25	17	0.029
Statin	57	59	0.702

Values are % for categorical variables.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker ; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CVA = cerebralvascular accident; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; TIA = transient ischemic attack.

Table 5. Echocardiographic structure and function measurements.

	Narrow	Wide	p-value
<b>Dimensions</b>			
LVEDD (cm)	6.2 ± 0.8	6.3 ± 0.8	0.358
	-0.10 ± 0.6	-0.39 ± 0.7*	0.008
LVESD (cm)	5.3 ± 0.8	5.4 ± 0.9	0.353
	-0.15 ± 0.8	-0.46 ± 0.9*	0.025
<b>Systolic Function</b>			
EF %	25 ± 6	25 ± 5	0.552
	3.2 ± 9*	6.8 ± 9*	0.012
<b>Longitudinal</b>			
GSCS (mm)	3.8 ± 1.9	4.2 ± 1.8	0.127
	0.4 ± 2	0.5 ± 2*	0.825
Mean max velocity (cm/s)	3.0 ± 1.1	3.1 ± 1.0	0.581
	0.2 ± 1	0.2 ± 1	0.875
<b>Radial</b>			
Basal strain at AVC (%)	15.3 ± 14	18.4 ± 14	0.221
	3.1 ± 17	-2.0 ± 15	0.103
Basal peak strain (%)	22.4 ± 14	24.8 ± 14	0.333
	2.2 ± 16	-1.6 ± 15	0.271
Papillary strain at AVC (%)	10.0 ± 9	10.9 ± 10	0.588
	3.2 ± 14	1.8 ± 14	0.637
Papillary peak strain (%)	15.9 ± 8	18.1 ± 10	0.175
	3.5 ± 13†	0.2 ± 14	0.246
Overall strain at AVC (%)	12.3 ± 10	14.2 ± 9	0.224
	3.1 ± 13†	0.1 ± 11	0.188
Overall peak strain (%)	19.0 ± 10	20.9 ± 10	0.234
	2.4 ± 12	-0.9 ± 11	0.124
<b>Diastolic Function</b>			
Diastolic filling period (msec)	397 ± 135	407 ± 140	0.632
	46 ± 133*	42 ± 143*	0.857
<b>Other</b>			
Right ventricular dysfunction score (0-6)	0.5 ± 1.1	0.5 ± 1.1	0.724
	0.2 ± 1	-0.1 ± 1	0.123
Mitral regurgitation severity score (0-6)	2 ± 1.4	2 ± 1.4	0.995
	0.1 ± 1	-0.6 ± 1*	<0.001

Values are mean ± SD. P-value is comparison between groups. \* indicates within-group significance at p < 0.05 comparing baseline to follow-up, while † indicates within-group trending at p < 0.10 comparing baseline to follow-up. For each variable, the first row is the baseline and the second row is the change post-CRT.

AVC = aortic valve closure; EF = ejection fraction; GSCS = global systolic contraction score; LVEDD = left ventricle end-diastolic dimension; LVESD = left ventricle end-systolic dimension.

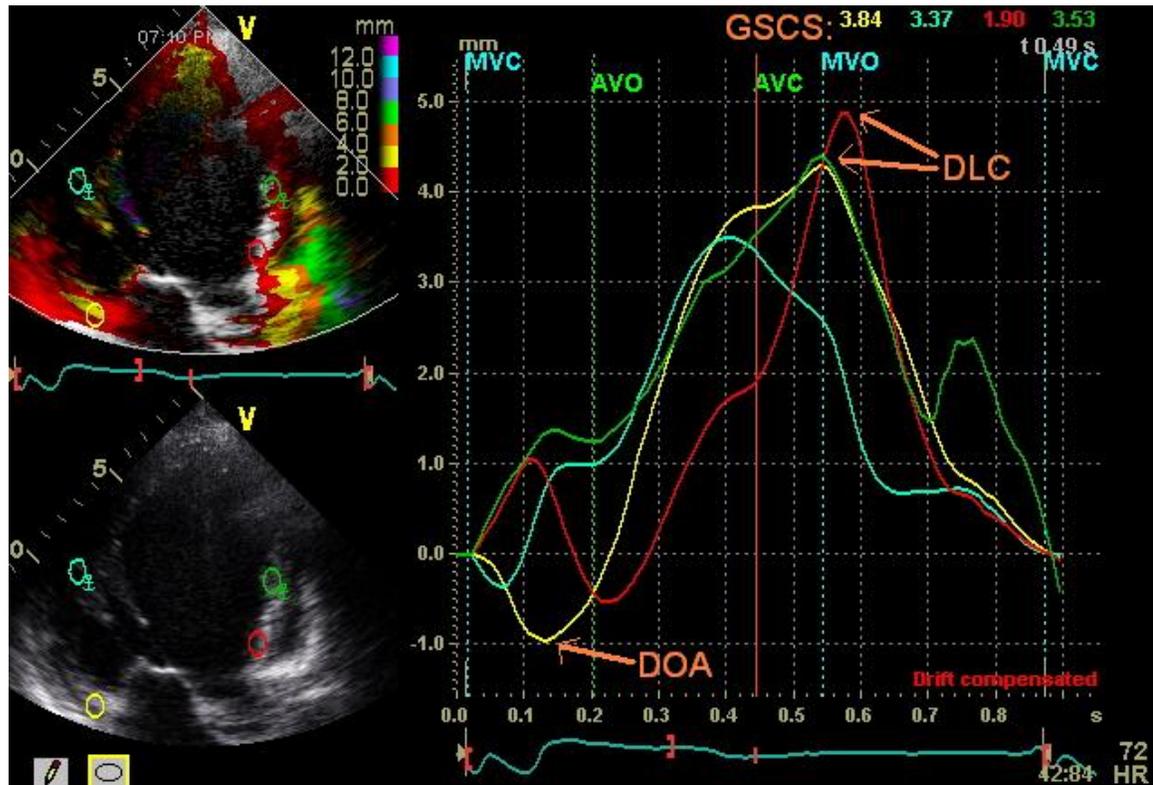
Table 6. Echocardiographic dyssynchrony measurements.

	Narrow	Wide	p-value
<b>Longitudinal</b>			
Delayed onset of activation (msec)	18 ± 19	15 ± 20	0.292
	-3 ± 24	-2 ± 25	0.937
SD time-to-peak (msec)	75 ± 42	82 ± 31	0.233
	-10 ± 41†	-3 ± 43	0.352
Delayed contraction (msec)	86 ± 49	70 ± 39	0.024
	-17 ± 48*	-5 ± 43	0.153
▲ Septal & Lateral max velocities (msec)	54 ± 42	58 ± 48	0.605
	1 ± 54	-2 ± 57	0.807
▲ Ant-sept & Post max velocities (msec)	63 ± 45	56 ± 45	0.359
	-6 ± 53	-3 ± 58	0.785
Subjective dyssynchrony score (0-6)	3 ± 1	3 ± 1	0.999
	-0.2 ± 1†	-0.3 ± 1*	0.611
<b>Radial</b>			
Basal SD time-to-peak (msec)	83 ± 59	97 ± 62	0.207
	-4 ± 77	-3 ± 102	0.947
Papillary SD time-to-peak (msec)	73 ± 57	121 ± 71	<0.001
	-8 ± 78	-23 ± 95†	0.398
Overall SD time-to-peak (msec)	92 ± 56	120 ± 54	0.003
	6 ± 68	-14 ± 82	0.164
<b>Valvular</b>			
IVD (ms)	19 ± 20	34 ± 28	<0.001
	2 ± 24	-10 ± 31*	0.189
<b>Diastolic relaxation</b>			
▲ Septal E' & Lateral E' (msec)	43 ± 34	40 ± 37	0.654
	-6 ± 44	-10 ± 49	0.678

Values are mean ± SD. P-value is comparison between groups. \* indicates within-group significance at  $p < 0.05$  comparing baseline to follow-up, while † indicates within-group trending at  $p < 0.10$  comparing baseline to follow-up.

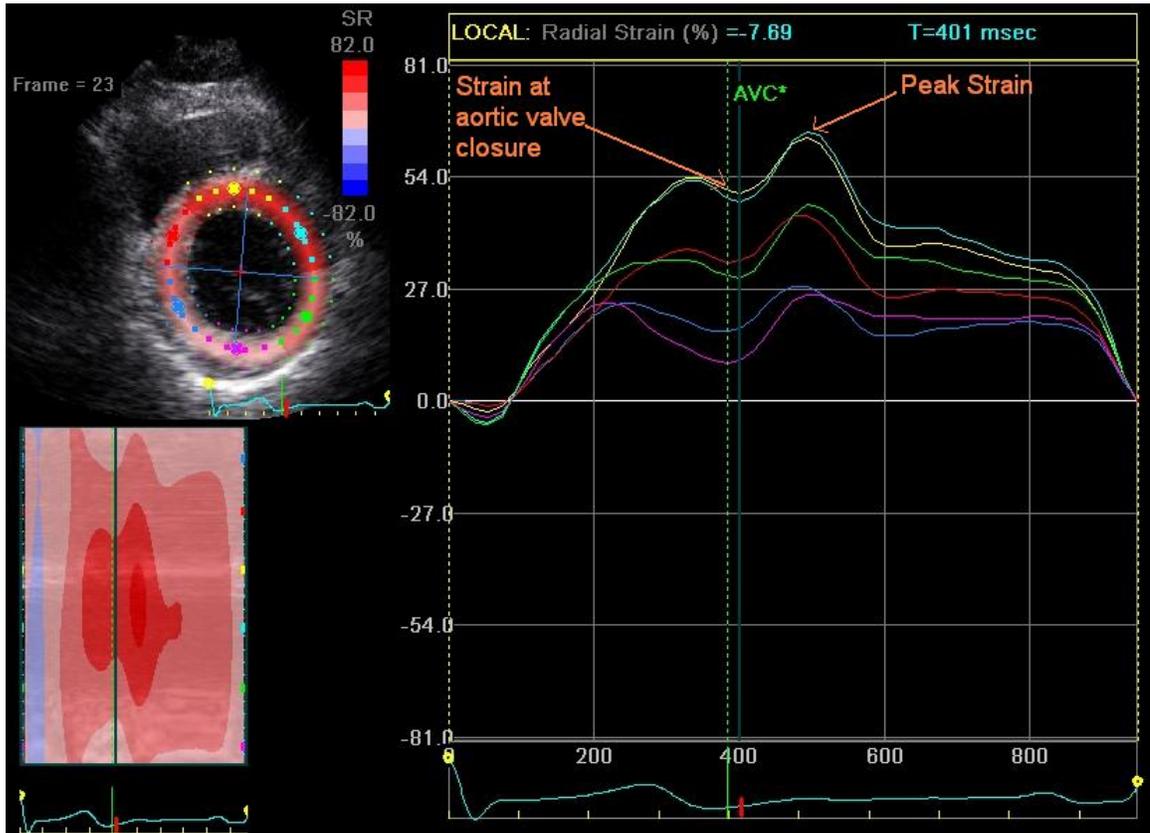
IVD = interventricular delay; SD = standard deviation.

Figure 1. Visual explanation of tissue-tracking dyssynchrony measures.



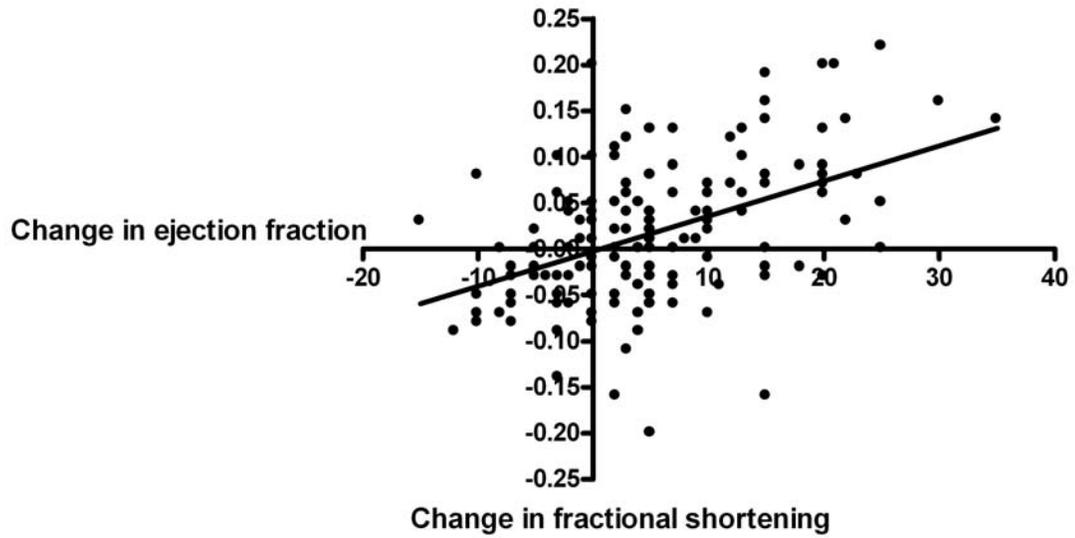
An apical long-axis view using tissue tracking technology. This study displays a segment with delayed onset of activation (DOA), three segments with delayed longitudinal contraction (DLC), and the displacements of tissue segments at aortic valve closure (AVC) used to determine a global systolic contraction score (GSCS).

Figure 2. Visual explanation of speckle-tracking measures.



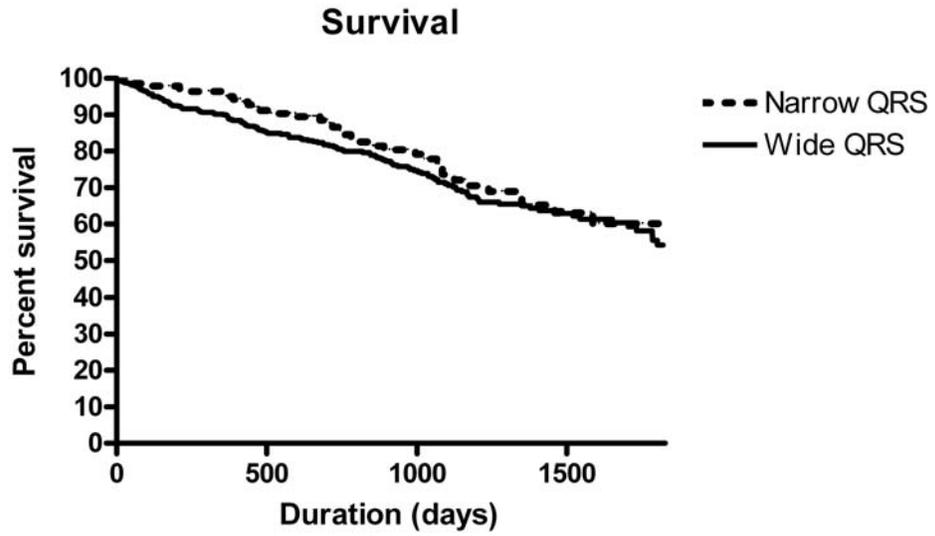
A radial short-axis view is analyzed with speckle-tracking echocardiography. The ventricle is divided into six color-coded segments, with each segment being traced for tissue strain (%) throughout the cardiac cycle. Determination of peak strain and strain at AVC are labeled.

Figure 3. Correlation between change in ejection fraction and change in fractional shortening.



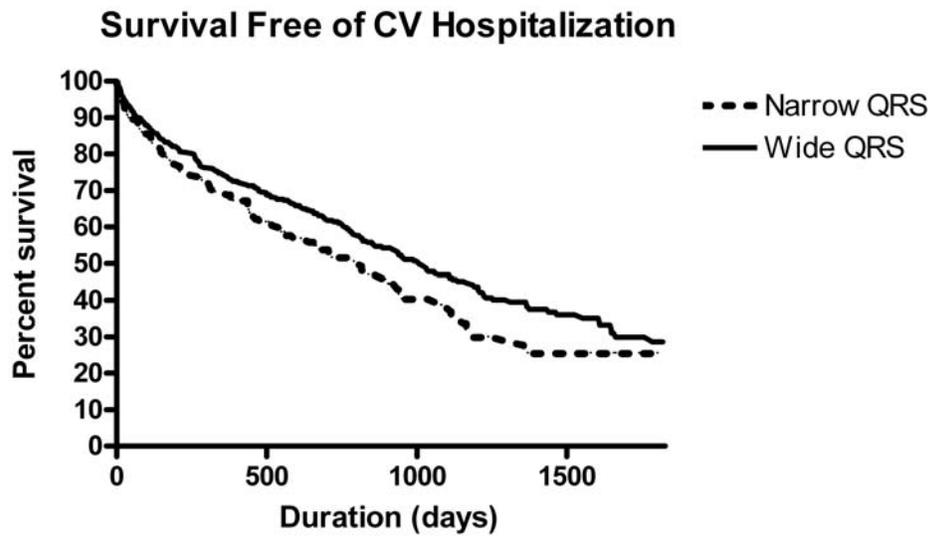
Pearson's Correlation between  $\Delta$  ejection fraction and  $\Delta$  fractional shortening:  
 $R = 0.4619$ ,  $R^2 = 0.2134$ ,  $p < 0.001$ .

Figure 4. Kaplan-Meier analysis of mortality rates.



The five-year survival rate is 60% for narrow QRS patients and 54% for those with a QRS prolongation. Log-rank test statistic  $p = 0.234$ .

Figure 5. Kaplan-Meier analysis of death or CV hospitalization rates.



The five-year survival rate for narrow QRS patients is 25% and 29% for those with a wide QRS complex. Log-rank test statistic  $p = 0.056$ .

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Appendix A: Database abstraction case report form.

St. Paul Heart Clinic CRT Report Card

MsysID:       DOB:   
 Last Name:       Gender:   
 First Name:       Last Edited:   
 Middle Initial:

1. Etiology

Ischemic Heart Disease       Idiopathic/Other  
 Valvular Heart Disease  
 Hypertensive Heart Disease

2. Date of 1st Diagnosis of HF:

3. Comorbidities

Atrial Fibrillation	<input type="checkbox"/> Yes <input type="checkbox"/> No	Cancer	<input type="checkbox"/> Yes <input type="checkbox"/> No
a. Current-sustained?	<input type="checkbox"/> Yes <input type="checkbox"/> No	CVA/TIA	<input type="checkbox"/> Yes <input type="checkbox"/> No
b. Current-paroxysmal?	<input type="checkbox"/> Yes <input type="checkbox"/> No	Smoker	<input type="checkbox"/> Yes <input type="checkbox"/> No
c. Past history?	<input type="checkbox"/> Yes <input type="checkbox"/> No	a. Current?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Diabetes	<input type="checkbox"/> Yes <input type="checkbox"/> No	b. Recent quit (<1 yr)?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Renal Insuff	<input type="checkbox"/> Yes <input type="checkbox"/> No	c. Past history?	<input type="checkbox"/> Yes <input type="checkbox"/> No
COPO/Asthma	<input type="checkbox"/> Yes <input type="checkbox"/> No	Non-Compliance	<input type="checkbox"/> Yes <input type="checkbox"/> No
PVD	<input type="checkbox"/> Yes <input type="checkbox"/> No	CAD, Significant (MI, PCI, CABG)	<input type="checkbox"/> Yes <input type="checkbox"/> No
Obesity	<input type="checkbox"/> Yes <input type="checkbox"/> No	a. CABG	<input type="checkbox"/> Yes <input type="checkbox"/> No
		b. PCI	<input type="checkbox"/> Yes <input type="checkbox"/> No

4. Medications (within 3 mos prior) (Y/N) - If N, choose (R)efusal, (I)ntolerant, (C)ontraindication - update to last vi

ACE/ARB	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="text"/>	ASA	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="text"/>
BB	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="text"/>	Digoxin	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="text"/>
If yes, choose one:	<input type="checkbox"/> Toprol XL		Anti-arrhythmias	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="text"/>
	<input type="checkbox"/> Metoprolol		Aldo blocker	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="text"/>
	<input type="checkbox"/> Coreg		Statin	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="text"/>
	<input type="checkbox"/> Other				

5. CRT Device and Implant

Date of Placement

QRS Duration (msec)

BBB  Left  Other  Right  Paced

Clinical indication for PM or Defib.  Yes  No

Sev. Bradycardia  Yes  No

Symptom. Vtach  Yes  No

Hosp for HF in year prior to CRT  Yes  No

Type

CRT-P

CRT-D

Upgrade from ICD to CRT-D

Upgrade from A-V sequential PM to CRT-P

Upgrade from A-V sequential PM to CRT-D

LV Lead  Anterior  Lateral  Posterior  Posteriolateral

RV Lead  Septal  Apical

SAV delay

PAV delay

V-V timing Offset (msec)

Simultaneous

RV First

LV First

% BIV pacing at 3 mos

% Atrial pacing at 3 mo

Company

Medtronic

BS

St. Jude

Other

6. Clinical response to CRT at 1 yr +/- 6 months

Worse

No change

Mildly Better

Markedly Better

7. Vital Status (choose one)

a. Patient is alive?  Yes  No Date of last contact

b. Patient died?  Yes  No Date of death

c. Patient lost to follow up?  Yes  No Date of last contact

8. Hospitalizations

Date	LOS	Diagnosis
<input type="text"/>	<input type="text"/>	<input type="checkbox"/> CV <input type="checkbox"/> Non-CV
<input type="text"/>	<input type="text"/>	<input type="checkbox"/> CV <input type="checkbox"/> Non-CV
<input type="text"/>	<input type="text"/>	<input type="checkbox"/> CV <input type="checkbox"/> Non-CV
<input type="text"/>	<input type="text"/>	<input type="checkbox"/> CV <input type="checkbox"/> Non-CV
<input type="text"/>	<input type="text"/>	<input type="checkbox"/> CV <input type="checkbox"/> Non-CV
<input type="text"/>	<input type="text"/>	<input type="checkbox"/> CV <input type="checkbox"/> Non-CV
<input type="text"/>	<input type="text"/>	<input type="checkbox"/> CV <input type="checkbox"/> Non-CV
<input type="text"/>	<input type="text"/>	<input type="checkbox"/> CV <input type="checkbox"/> Non-CV
<input type="text"/>	<input type="text"/>	<input type="checkbox"/> CV <input type="checkbox"/> Non-CV

9. Response to CRT

	Pre CRT	1 Yr Post-CRT
Vital Signs		Date: <input type="text"/>
SBP	<input type="text"/>	<input type="text"/>
DBP	<input type="text"/>	<input type="text"/>
HR	<input type="text"/>	<input type="text"/>
Body Weight	<input type="text"/>	<input type="text"/>
Laboratory		Date: <input type="text"/>
Sodium	<input type="text"/>	<input type="text"/>
BUN	<input type="text"/>	<input type="text"/>
Cr	<input type="text"/>	<input type="text"/>

10. NYHA Class

I

II

III

IV

Appendix B: Database ECHO analysis case report form.

**Administrative Information**

Patient ID: \_\_\_\_\_ Reader Initials: \_\_\_\_\_

Date of Reading: \_\_\_\_\_ Date of Study: \_\_\_\_\_

**ECHO Data**

Visually Estimated Ejection Fraction: \_\_\_\_\_%

Heart Rate: \_\_\_\_\_ bpm

Atrial Fibrillation (circle one): YES NO

**PARASTERNAL LONG/SHORT AXIS**

LV end-diastolic width (LVEDW): \_\_\_\_\_ cm

LV end-systolic width (LVESW): \_\_\_\_\_ cm

RVF (circle one):  
0 – Normal  
1 – Slight Decrease  
2 – Mild Decrease  
3 – Mild-Moderate  
4 – Moderate  
5 - Moderate-Severe  
6 – Severe

**Mitral Valve**

Diastolic Filling Period (DFP): \_\_\_\_\_ ms

Mitral Regurgitation (circle one):  
0 – Normal  
1 – Trace  
2 – Mild  
3 – Mild-Moderate  
4 – Moderate  
5 - Moderate-Severe  
6 – Severe

Appendix C: Thesis mechanical dyssynchrony ECHO analysis case report form.

**Administrative Information**

Patient ID: \_\_\_\_\_

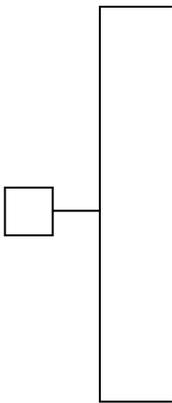
Reader Initials: \_\_\_\_\_

Date of Study: \_\_\_\_\_

Date of Reading: \_\_\_\_\_

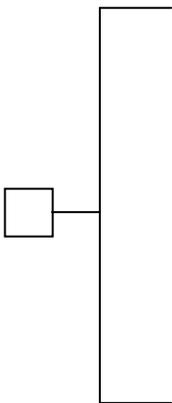
**Speckle-Tracking Echocardiography – Radial Strain**

Loop Saved



TDS	Segment	Strain @ AVC (%)	Peak Strain (%)	Time to Peak (ms)
	Basal Antero-Septal			
	Basal Anterior			
	Basal Lateral			
	Basal Posterior			
	Basal Inferior			
	Basal Septal			

Loop Saved



TDS	Segment	Strain @ AVC (%)	Peak Strain (%)	Time to Peak (ms)
	Mid Antero-Septal			
	Mid Anterior			
	Mid Lateral			
	Mid Posterior			
	Mid Inferior			
	Mid Septal			

**Tissue Tracking – Longitudinal Displacement**

<u>Stored</u>	<b>TDS</b>	<b>Segment</b>	<b>DOA (ms)</b>	<b>SCS (mm)</b>	<b>Time-to-Peak (ms)</b>	<b>DLC (ms)</b>
<input type="checkbox"/>		Basal Septum				
		Mid Septum				
		Basal Lateral				
		Mid Lateral				
<input type="checkbox"/>		Basal Inferior				
		Mid Inferior				
		Basal Anterior				
		Mid Anterior				
<input type="checkbox"/>		Basal Posterior				
		Mid Posterior				
		Basal Antero-Septal				
		Mid Antero-Septal				

**Longitudinal LV Dyssynchrony**

- \_\_\_ Normal
- \_\_\_ Mild
- \_\_\_ Mild-Moderate
- \_\_\_ Moderate
- \_\_\_ Moderate-Severe
- \_\_\_ Severe

**Cardiac Event Timing – Interventricular Delay**

QRS to Aortic Valve Opening: \_\_\_\_\_ ms

QRS to Pulmonic Valve Opening: \_\_\_\_\_ ms

**Tissue Velocity Imaging – Apical 4 Chamber & Apical Long Axis**

Maximum Systolic Velocity:

Basal-Septal \_\_\_\_\_ cm/s      Time-to-Peak \_\_\_\_\_ ms

Basal-Lateral \_\_\_\_\_ cm/s      Time-to-Peak \_\_\_\_\_ ms

Basal-AntSept \_\_\_\_\_ cm/s      Time-to-Peak \_\_\_\_\_ ms

Basal-Posterior \_\_\_\_\_ cm/s      Time-to-Peak \_\_\_\_\_ ms

Diastolic Relaxation:

Basal-Septal E': \_\_\_\_\_ cm/s      Basal-Lateral E': \_\_\_\_\_ cm/s

Time-to: \_\_\_\_\_ ms      Time-to: \_\_\_\_\_ ms

Basal-Septal A': \_\_\_\_\_ cm/s      Basal-Lateral A': \_\_\_\_\_ cm/s

**Data from CRT Database**

Visually Estimated Ejection Fraction: \_\_\_\_\_ %

Heart Rate: \_\_\_\_\_ bpm

Atrial Fibrillation (circle one):      YES NO

LV end-diastolic width (LVEDW): \_\_\_\_\_ cm

LV end-systolic width (LVESW): \_\_\_\_\_ cm

RVF (0-6, normal to severe): \_\_\_\_\_

Diastolic Filling Period (DFP): \_\_\_\_\_ ms

Mitral Regurgitation (0-6, normal to severe): \_\_\_\_\_

Appendix D: Institutional Review Board documents.

## Continuing Review / Request to Close Study Form



- Use this form to request ongoing IRB approval for a study or to request a study be closed.
- Failure to submit a request for continuing review before the expiration of study approval may result in suspension of the study.
- Answer all of the following questions. Use NA where applicable.
- Incomplete or handwritten forms will not be accepted.
- Enclose the IRB review fee.

<b>IRB Study Number:</b> 2562-4E	<b>Investigator:</b> Alan J. Bank, MD
<b>Study Title:</b> Cardiac Resynchronization Therapy: A Retrospective Review of 1000 Consecutive Heart Failure Patients Treated at a Single Center	

<b>I. Initial study approval date:</b> October 2008	<b>Date project began:</b> October 2008
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II. Status of Protocol	
<input checked="" type="checkbox"/> <b>Open and enrolling subjects</b> <i>Include copy of currently approved consent form(s), if applicable.</i>	<b>Closed (check one)</b> <i>Include final study summary</i> <input type="checkbox"/> <b>Completed at this site</b> <input type="checkbox"/> <b>Terminated at this site</b> <small>(study halted before completion)</small> Explain reason for termination:
<b>Closed to enrollment (check one)</b> <input type="checkbox"/> <b>In data collection</b> (subjects remain in follow-up) <i>Include copy of current consent/assent forms, if applicable.</i> <input type="checkbox"/> <b>In data analysis</b> (all subject follow-up completed) <i>Consent/assent forms not required</i>	<b>Other (check one)</b> <i>Include copy of currently approved consent form(s), if applicable.</i> <input type="checkbox"/> <b>Not begun</b> <input type="checkbox"/> <b>On hold</b> <input type="checkbox"/> <b>Other (specify):</b>

III. Study Personnel	
<b>1. Investigator:</b> Alan J. Bank, MD	Practice group: St. Paul Heart Clinic
Mailing address: 225 Smith Avenue North, suite 400	City: St. Paul State: MN Zip: 55102
Phone: 651-292-0616	Fax: 651-233-5088 Pager:
E-mail: abank@stphc.com	Allina Internal Mail Route: 65500
<b>2. List all co-investigator(s), include phone number(s) and email address(es):</b>	

<b>3. Study Coordinator:</b> Ryan Gage    Practice group: St. Paul Heart Clinic			
Mailing address: 225 Smith Avenue North, suite 400	City: St. Paul	State: MN	Zip: 55102
Phone: 651-726-6965	Fax: 651-233-5088	Pager: [REDACTED]	
E-mail: rgage@stphc.com		Allina Internal Mail Route: 65500	
<b>4. Additional study personnel:</b>			
Andrew Bank, Kevin Burns, Spencer Kubo, MD, Inder Anand, MD	Role and practice group: St. Paul Heart Clinic - Bank, Burns & Kubo, VA Medical Center - Anand		
Mailing address: 225 Smith Avenue North, suite 400	City: St. Paul	State: MN	Zip: 55102
Phone: 651-292-0616	Fax: 651-233-5088	Pager: [REDACTED]	
E-mail: [REDACTED]	Allina Internal Zip: 65500		
<b>5. Describe any changes in study personnel not previously reported to the IRB:</b> Josh Parah removed as study coordinator as he resigned from the St. Paul Heart Clinic. Josh was replaced by Ryan Gage. The following were added to the study as study coordinators to assist in data collection: Lauri Eakins Kari Thomas Deanna Rohde, RN Elizabeth (Betty) Schindler, RN Dan Vatterott Mariam Sajady			

#### IV. IRB Review Fee

The following fees are assessed to review a Continuing Review and Request to Close Study

- Continuing Review - \$500
- Request to Close Study - \$300

Check one:

- Review fee is submitted with this application  
 [Internal Transfer of Funds Form](#) is submitted with this application  
 IRB review fees have been waived for this study

#### V. Funding

##### 1. Is this project funded?

Yes  No

If yes, provide current sponsor or funding agency name(s) and grant number if applicable: Boston Scientific

##### 2. Has your relationship with the study sponsor changed in any way since the Yes No NA last continuing review that might require a new conflict of interest disclosure

(e.g. stock purchases, royalty payments, patents, board position, consultant, etc.)?

If yes, please explain: [redacted]

#### VI. Enrollment

Answer all questions. Use NA where applicable.

1. Enrollment Goal (number of subjects approved for this site by the IRB): 1000

2. TOTAL number of subjects enrolled at this site to date: 495 Males: 356 Females: 139

##### 3. Secondary Site Enrollment Information

If this study involves additional Allina sites approved under the Allina Multiple Site Policy, please provide total

subject enrollment for each location.  
4. Provide breakdown of TOTAL number of subjects enrolled in the following categories: [redacted] Mercy & Unity [redacted] United [redacted]  
Phillips Eye Institute [redacted] Vulnerable: [redacted] Minorities (Define race/ethnicity if applicable): [redacted]

**5. Number of subjects enrolled SINCE LAST CONTINUING REVIEW:** 495

**6. Number of subjects withdrawn/discontinued since the last continuing review:** 0

**Specify reason(s) for withdrawal:** na

## **VII. Progress**

**1. Describe study's overall progress and interim findings to date:** Study is progressing as expected. Additional staff have been added to assist with data collection.

**2. Summarize any recent literature findings or other relevant information** (especially information about risks associated with the research).

Attach copy of articles/publications if available: na

**3. Briefly summarize each of the following that have occurred since the time of the last continuing review.**

**Describe any trends identified and actions taken.**

For example, under point a., *do not list all of the serious adverse events already reported*. Instead, discuss the kinds of events subjects have experienced and how explain how common the events are. For example: "Three subjects experienced chest pain while taking the study drug; however, these incidents were most likely attributable underlying health issues and not related to the study drug." Or "Four subjects experienced severe leg swelling after receiving the study device. This event occurred more frequently than expected, so the risk was added to the consent form and the revised consent form was approved by the IRB on April 1, 2005."

- a. Local and non-local **serious** adverse events: na
- b. Local **non-serious** adverse events: na
- c. Unanticipated problems: na
- d. Protocol deviations: na
- e. Complaints made by subjects: na
- f. Problems involving conduct of study: na
- g. Problems involving subject participation: na

**4. Are there any local serious adverse events that were not reported to the IRB?** Yes No

If yes, please explain why the event(s) was/were not previously reported:

na

*In addition, complete and attach a Local Serious Adverse Event Form for each unreported event.*

**5. Describe any unanticipated risks discovered since the last continuing review:** na

**6. Have you submitted all modifications or amendments that have occurred since the last continuing review to the IRB?** Yes No

If no, explain: na

**Enclosed with this form:**

- All current consent/assent forms (if applicable as stated in Section II of this form), or
- A final study summary (for requests for closure)
- Payment of the appropriate fee in the form of a check or a copy of the Internal Transfer of Funds form

Name of Person Completing this Form: Lauri Eakins, CRA	Phone Number: 651-726-6969
Signature of Investigator	Date: