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Optimizing Response to Cardiac Resynchronization Therapy for Patients with Heart Failure.

by

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A THESIS

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List of Abbreviations

6MWT	6-minute walk test
ACE	angiotensin converting enzyme
Ang	angiotensin
ANP	atrial natriuretic peptide
ARB	angiotensin receptor blockers
AV	atrio-ventricular
BP	blood pressure
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCB	calcium channel blockers
CCS	Canadian Cardiovascular Society
CI	confidence interval
CM	cardiomyopathy
CMR	cardiac magnetic resonance
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CRT	cardiac resynchronization therapy
CS	coronary sinus
DCM	dilated cardiomyopathy
ECG	electrocardiogram
Echo	echocardiography
EF	ejection fraction
Gd	gadolinium
HF	heart failure
HR	high resolution
HR	heart rate
ICD	implantable cardioverter defibrillator
IHD	ischemic heart disease
LBBB	left bundle branch block
LE	late enhancement
LGE	late gadolinium enhancement
LV	left ventricular
LVEDV	left ventricular end diastolic volume
LVEF	left ventricular ejection fraction
LVESV	left ventricular end systolic volume
MAP	mean arterial pressure
MEC	mechano-electric coupling
MI	myocardial infarction
MLWHF	Minnesota Living with Heart Failure
MRI	magnetic resonance imaging
MUGA	multi gated acquisition
NT BNP	N-terminal brain natriuretic peptide
NYHA	New York Heart Association

PET	positron emission tomography
PND	paroxysmal nocturnal dyspnea
PVCs	premature ventricular complexes
QoL	quality of life
RAAS	renin-angiotensin-aldosterone system
RCT	randomized controlled trials
REF	reduced ejection fraction
RV	right ventricle
SA	sinoatrial
SAS	Specific Activity Scale
SF	Short Form
SNS	sympathetic nervous system
SPECT	single photon emission computed tomography
SV	stroke volume
SVRI	stroke volume resistance index
VAD	ventricular assist device

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Chapter One: **Introduction**

Background:

Heart failure (HF) is a serious health care challenge, with considerable morbidity and mortality. The Heart and Stroke Foundation reports 1 in 5 Canadians will develop this condition[1]. Despite optimal pharmacological management, the prognosis is poor for patients with HF. Cardiac resynchronization therapy (CRT) is an established therapeutic option for symptomatic, drug refractory HF patients with reduced left ventricular ejection fraction (LVEF) less than 35% and evidence of left ventricular (LV) conduction delay (QRS width ≥120 ms), with a left bundle branch block (LBBB)[2]. The mechanism behind CRT includes restoration of coordinated ventricular contraction through biventricular pacing and also restoration of the atrioventricular (AV) delay to improve LV filling and thus reduce mitral regurgitation[3]. The resulting benefit is improvement in LVEF and cardiac output.

More than 100 clinical studies and numerous randomized controlled trials (RCTs) have evaluated the clinical efficacy of CRT in HF. This device therapy has been shown to improve functional capacity, cardiac remodeling, and most importantly, improves morbidity and mortality[4]. Although, approximately 30% of patients do not derive an appreciable response, based on clinical or physiological outcomes. This is an unsolved gap in resynchronization device therapy. Three areas of research are needed including better patient selection for CRT, better understanding of the link between favourable LV remodeling and survival and lastly methods to enhance likelihood of response to CRT. These areas are addressed in projects 1, 2 and 3.

1.1 Enhanced CRT Patient Selection:

Project 1: PREDICT-Predicting Resynchronization Efficacy via Direct and Indirect Technique

Assessment of LV dyssynchrony by various techniques has been the focus of several studies to predict CRT responders, but accurate identification and correlation to response has been challenging. Other potential predictors outside of the current patient selection criteria for CRT have also been investigated, including various patient characteristics, biomarkers and biochemical indices. Although, their reliability to predict CRT response significantly have not been found. CRT has a high initial cost compared to medical therapy alone, and as in other surgical procedures, there are perioperative risks associated with device implantation. Given that the procedure is expensive with an inherent risk of complications, investigating non-invasive novel predictors of CRT response is an important research area and the rationale for the first research study of the thesis.

Hypothesis #1: Increased cardiac reserve is an independent predictor of CRT response in addition to current guidelines.

Aim #1: To determine if the augmentation in pulse pressure with exercise (reflecting cardiac reserve) can be used to reliably predict subsequent LV remodeling response to CRT and thus improve CRT candidate selection.

1.2 A simple method to enhance likelihood of response to CRT:

Project 2: VOLTAGES- Voltage Output from the Left Ventricle To Assess Gradient and Estimate Scar

Improving the CRT response rate requires CRT implantation considerations as well. Implanting the LV lead is more challenging than the other [right ventricle, RV, and atrial] leads, and optimizing pacing is a means to improve CRT response. Optimizing timing parameters, and the location of the LV lead have been the focus of several research studies. It has been established

that placing the LV lead in a region without scar tissue is required for effective pacing of the ventricle and favourable reverse remodeling. Cardiac magnetic resonance (CMR) imaging is the gold standard to identify scar. Nevertheless, it is costly to perform CMR imaging on every CRT candidate. As well, during implantation of the LV lead, knowing whether the lead is in an area of scar in real time would be most useful. As such, the second research study focuses on using a high resolution (HR) electrocardiogram (ECG) machine to identify myocardial scar peri-operatively for implant optimization.

Hypotheses #2: Differences in voltage gradients using a HR ECG can differentiate areas of scar and non-scar.

Aim #2: To determine if a HR ECG can identify regions of scar during CRT implantation to guide optimal LV lead positioning.

1.3 Better understanding of the relationship of remodeling and survival:

Project 3: Reverse Remodeling and the Relationship to Survival in Adult Heart Failure Patients Who Have Undergone Cardiac Resynchronization Therapy – A Systematic Review and Meta-analysis

A meta-analysis on randomized controlled trials investigating CRT response was also completed, to determine whether a common marker of CRT response (reduced left ventricular end systolic volume, LVESV), does indeed correlate with mortality benefit. Several definitions of CRT response have been used in the literature, but the main focus of defining response to therapy should be hard clinical end points of reduced hospitalization readmission/mortality benefit. Surrogate markers are often used that reflect physiologic improvements in cardiac function, but these should be correlated with patient specific important definitions of improvement including reduced mortality and morbidity. The final study looked at correlating physiologic markers of CRT response to mortality and whether CRT response was similar in ischemic and non-ischemic patients.

Hypothesis #3: Cumulative evidence of the literature demonstrates cardiac reverse remodeling, assessed by echocardiographic parameters, is associated with improved long term outcomes (morbidity and mortality). As well, the mechanism whereby CRT improves survival may be different in ischemic and non-ischemic patients.

Aim #3: To summarize the cumulative evidence of LV reverse remodeling and its relationship to survival to investigate its use as a reliable prognostic marker of CRT benefit.

1.4 Literature Search:

A literature search from databases including PubMed, Embase-Ovid and Google Scholar were used to present relevant background information for the research studies, as well as to provide supporting evidence in the manuscripts. The citations in this thesis are from peer reviewed papers, relevant cardiovascular society guidelines, cardiology textbooks and credible websites. Information was also gathered from expert opinion in the field.

1.5 Format of thesis:

Optimizing CRT response include pre-operative, intra-operative and post-operative considerations. This thesis attempts to investigate novel strategies at each of these stages to improve CRT delivery and response rate. The chapters of the thesis are structured with the relevant background information to all studies at the beginning, followed by each individual study in a manuscript format. Finally, a conclusion summarizing the findings, clinical significance and future direction pertaining to all studies are presented. It is also hoped readers will gain insight into the mechanism of CRT and that the information in this thesis may assist in clinical practice.

Chapter Two: **Heart Failure**

2.1 Background:

HF is a type of cardiovascular syndrome affecting an estimated 500 000 Canadians, with 50 000 new cases each year [5]. People with HF exhibit various characteristic symptoms and pathophysiology, but the common overarching definition of HF is that it is a clinical syndrome that develops from a damaged heart causing an inability of the heart to pump blood sufficiently to meet the (metabolic) needs of the body[6]. According to the Canadian Cardiovascular Society (CCS) HF Guidelines, the diagnosis of HF is made when symptoms and signs of congestion and reduced perfusion are found from any condition that reduces the efficiency of the heart muscle[7]. Systemic responses to cardiac dysfunction, including characteristic patterns of hemodynamic, neural, hormonal and renal responses, are important in defining the pathophysiology and clinical manifestations of HF.

HF is a serious condition. It is the leading cause of hospitalization in people older than 65 [8] with the average annual mortality rate of 33%[9] in Canada. The five year survival rate is also quite low, at approximately 50%[5]. Furthermore, HF is increasing in prevalence [10] in part due to the development of therapies for heart attacks and other cardiac conditions allowing patients to survive longer. As people with damaged hearts are living longer, they become more susceptible to HF. Men have a higher relative incidence of HF, but the overall prevalence is similar between both sexes since women have a longer life expectancy and survive longer after being diagnosed with the condition[11]. HF is also a significant economic burden worldwide, estimated at $108 billion per year [12]. In Canada specifically, the annual healthcare costs associated with HF is estimated to be $1.18 billion[12].As HF is a common, costly and fatal disease, understanding the syndrome and factors associated with varying response to therapies is vital.

2.2 Heart Failure Etiology:

Any condition that leads to cardiac structural damage or dysfunction can lead to the development of HF. As such, there is a range of underlying HF causes which influence the particular pathology and clinical presentation of the condition. The exact mechanism of HF may be difficult to pinpoint since compensatory mechanisms (discussed below) can maintain blood pressure and perfusion after the initial injury to the heart, masking the condition until it progresses further.

In North America, coronary artery disease (CAD) is the most common cause of HF in both men and women followed by hypertension, which may coexist with CAD[5]. Cardiomyopathy is also another common cause of HF. Other causes include: valvular heart disease, congenital heart disease, cardiac arrhythmias (including atrial fibrillation) and infection.

CAD is responsible for HF in up to 75% of patients [13]. The disease is defined as a build-up of plaque (made up mostly of calcium deposits, cholesterol, fatty acids, inflammatory cells and fibrous connective tissue[14]) in the inner, elastic layer of coronary artery walls. This results in narrowing and hardening of the arteries, which reduces blood flow to myocardial cells and thus causes cell starvation due to a shortage of oxygen and nutrients to these cells (known as myocardial ischemia). Ischemia causes an immediate loss of contractility in the affected myocardium due to weakened myocytes from the lack of oxygen. If there is severe blockage of the arterial lumen, which usually occurs from rupture of the plaque causing a blood clot, cell death (or necrosis) of downstream myocardial cells results[15]. This is known as a myocardial infarction (MI). Fibrous scar tissue replaces the damaged, necrotic cardiac tissue, which can cause conduction disturbances in the heart.

2.3 Symptoms of HF:

HF is frequently associated with shortness of breath (dyspnea), fatigue and edema, which are known as the "cardinal triad" of symptoms according to the CCS HF guidelines [7].

Dyspnea is caused mainly from pulmonary congestion with accumulation of interstitial or alveolar fluid. Other factors contributing to dyspnea on exertion include: reductions in pulmonary compliance, increased airway resistance, respiratory muscle and/or diaphragm fatigue and anemia[5]. In the early stages of HF, dyspnea may only occur during exertion, but as the disease progresses dyspnea can be observed with less activity and even during rest.

Orthopnea (dyspnea while lying down) is usually a later manifestation of HF than dyspnea with exertion[5]. It results from the redistribution of fluid from the splanchnic circulation and lower extremities into the central circulation when lying down, which causes an increase in pulmonary capillary pressure (causing dyspnea). Nocturnal cough can occur due to this redistribution of blood. Orthopnea is usually relieved by sitting upright or sleeping with additional pillows.

Paroxysmal nocturnal dyspnea (PND) refers to acute episodes of severe shortness of breath and coughing that usually occurs at night and wakes up a person. PND may be manifested by coughing or wheezing, possibly because of increased pressure in the bronchial arteries leading to airway compression, along with interstitial pulmonary edema leading to increased airway resistance[5].

Fatigue is mostly attributed to the low cardiac output found in HF. Skeletal muscle abnormalities and other non-cardiac comorbidities (such as anemia) contribute to fatigue as well. LV systolic dysfunction causes blood to pool in the vessels of the lungs and excess fluid to leak in the alveoli/interstitium resulting in pulmonary edema. Excess fluid accumulation in the legs

(from sodium and water retention by the kidneys as one of the mechanisms) causes pitting edema. This is shown as swelling in the ankles and the feet.

Other symptoms that can be exhibited in patients with HF include:

- Gastrointestinal Symptoms: related to edema of the bowel wall and/or congested liver
- Cerebral symptoms: such as confusion, disorientation, sleep/mood disturbances and may be observed in patients with severe HF, particularly elderly patients (with cerebral artery disease)
- Nocturia: common in people with HF

The New York Heart Association (NYHA) Functional classification is based on the limitation of physical activity assessed by HF symptoms such as dyspnea, fatigue, and/or angina during activity [16]. This classification is commonly used and clinically useful since it correlates with quality of life and survival [17]. NYHA class is also used to assess pharmacological and cardiac device therapy efficacy. Although, the limitation to this classification is that assigning a patient to a particular class is subjective and not standardized and the reproducibility is unclear [16]. Table 1 describes the four NYHA categories.

Table 1: NYHA Functional capacity

NYHA Class:	**Symptoms:**
I (mild)	No limitation of ordinary physical activity (no symptoms), but cardiac disease present.
II (mild)	Ordinary activity causes mild symptoms, but comfortable at rest.
III (moderate)	Less than ordinary activity (such as walking 20-100 m) cause marked limitation (symptoms). Comfortable only at rest.
IV (advanced)	Unable to do physical activity without discomfort. Symptoms may be present at rest. Mostly patients who are bedbound.

The Specific Activity Scale (SAS) also categorizes the degree of cardiovascular disease severity to monitor a patient's status over time and also to assess response to therapy. This interview

based scale, classifies the functional capacity of patients based on their ability to perform well defined specific activities, each with a corresponding metabolic equivalent. It has been found to be more reproducible and valid than the NYHA, although is more time consuming to administer. A summary of the criteria for the SAS functional class is shown in Figure 1.

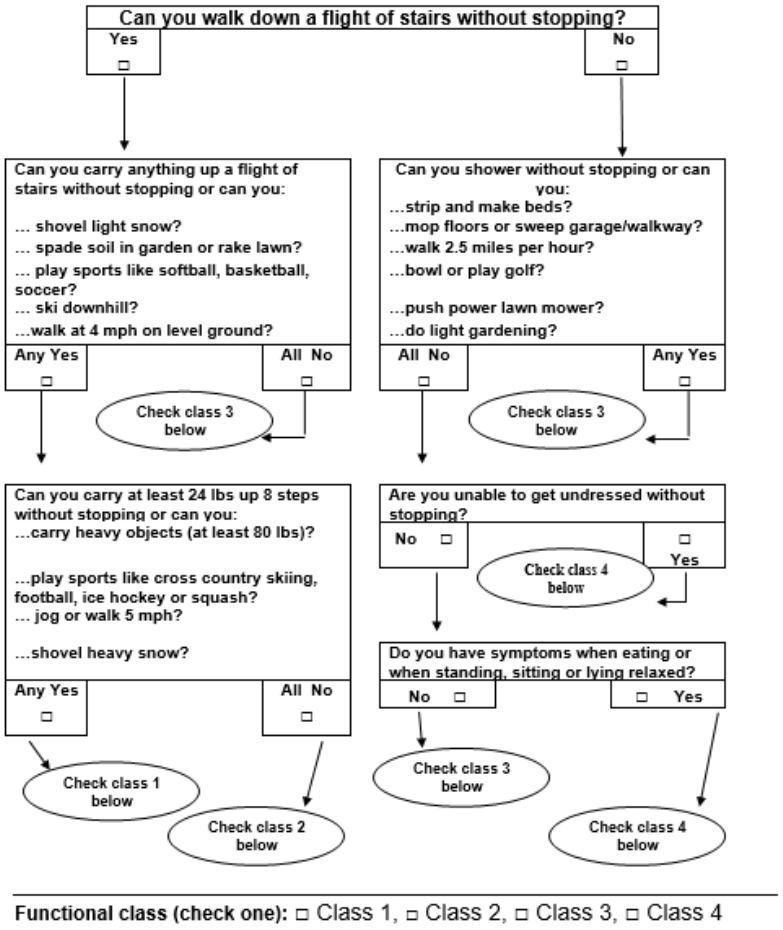

Figure 1: ***Pathway to determine SAS class***

Another measure of functional/exercise capacity includes the 6-minute walk test (6MWT), which simply requires the patient to walk as far as possible in six minutes and then the distance travelled is recorded. The specific timing of six minutes is used as it has been shown to give reproducible results, it is easy to administer versus longer timed tests[18] and more sensitive to differences versus shorter timed tests[19]. The 6MWT has been shown to predict HF hospitalization and long term mortality rates in patients with LV dysfunction (of varying

severity)[20]. The utility of the 6MWT to assess the effectiveness of HF interventions is uncertain; some studies have found it useful, not all[17].

Quality of Life (QoL) questionnaires assess a patient's own perspective of their functional health and well-being with a disease and/or treatment. The components of quality of life assessed include physical, emotional, social and mental. The two QOL questionnaires widely used in HF clinical trials include the Minnesota Living with Heart Failure (MLWHF) and the Short Form (SF) 36 Health Survey. These questionnaires can be helpful in evaluating a patient's health status, but does not reliably predict improved survival[17,21].

2.3.1 Signs of HF:

- Increased heart rate or palpitations: to compensate for the reduced cardiac output in HF
- Rales or crackles: sign of pulmonary edema and audible with a stethoscope in the lung base and throughout the whole lung field in severe HF
- Laterally displaced apex beat: sign of an enlarged heart in people with LV dysfunction
- Abnormal heart sounds (S3 and/or S4): three or four heart sounds instead of the normal two and is a marker of increased intra-cardiac pressure or compliance (S4)
- Heart murmurs: commonly from aortic stenosis or mitral regurgitation and may indicate the presence of valvular heart disease
- Increased jugular venous pressure (JVP): marker of fluid overload

2.4 Pathophysiology of HF:

In the early stages of HF, various compensatory mechanisms try to prevent reduction in cardiac function (and thus maintain tissue perfusion). The initial mechanism is frequently increased heart rate and contractility often resulting in near normal cardiac output[22]. With chronic HF, in addition to the disease process progressing, the compensatory responses become

maladaptive resulting in reduction in cardiac output. The pathological mechanisms of HF are not confined to the heart muscle. It is a multisystem disorder including abnormalities of cardiac, skeletal muscle and renal function. Compensatory mechanisms to try to restore cardiac output include neurohormonal activation, the Frank-Starling mechanism and ventricular remodeling[23].

2.4.1 Neurohormonal compensation:

During the early acute stages of HF, neurohormonal activation plays an important role in maintaining cardiac output. Although, in the long-term, these neurohormonal mechanisms [specifically sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) activation] further deteriorate cardiac function. HF drug therapies aim to counteract these systems.

Initially, when the cardiac output falls abnormally low, the SNS is stimulated (within seconds) to increase heart rate and myocardial contractility, which increases the stroke volume. The SNS also increases the peripheral vasoconstriction, increasing peripheral resistance. Mean arterial pressure (MAP) is thus augmented as it is a product of the peripheral resistance and cardiac output. SNS activation is triggered by sensory baroreceptors within the vasculature that respond, in the case of HF, to low cardiac output and blood pressure (BP). The subsequent release of norepinephrine from sympathetic nerves and epinephrine from the adrenal medulla acts on the heart, kidneys and vasculature to improve cardiac output[5]. The three receptors these catecholamines act on include: $\beta 1$, $\beta 2$ and $\alpha 1$ receptors[23] (as well as $\alpha 2$ receptors, but likely via down regulation). Continuous activation of the SNS has deleterious effects that eventually worsen cardiac performance. In the long term, the ability of the myocardium to respond to chronic high concentration of catecholamines is weakened, as well there are abnormalities in baroreceptor function. Overstimulation of the receptors also causes myocardial toxicity, which

results in decreased EF, arrhythmias and tachycardia[23]. Moreover, there is a reduction in heart rate variability in chronic HF due to sympathetic modulation of the sinus node, which may serve as a prognostic marker in patients with HF [24].

Activation of RAAS promotes release of norepinephrine and sodium reabsorption [23] causing vasoconstriction and fluid retention respectively. The kidneys secrete renin in response to sympathetic activation as well as due to reduced renal blood flow from a decrease in MAP. Renin then acts on angiotensinogen in the liver to make angiotensin I (Ang I). Circulating Ang I is converted by angiotensin-converting enzyme (ACE) in the lungs to angiotensin II (Ang II). Ang II has multiple effects; it enhances sympathetic activity via release of noradrenaline from sympathetic nerve terminals (increasing vasoconstriction)[5] and stimulates the release of aldosterone. Aldosterone is synthesized in the adrenal cortex and increases the reabsorption of sodium in the kidney, causing water reabsorption.

Continued progression of HF eventually leads to a critical reduction in blood flow to all vital organ systems. In terminal HF, the body maximizes all of its vasoconstrictive mechanisms in an attempt to redirect blood flow to these critical organs, adding to the (hemodynamic) load of the failing heart; thus, ventricular function progressively deteriorates. The end result is progressive ventricular dysfunction and possibly death[23].

2.4.2 Frank-Starling mechanism:

In the early stages of HF, the Frank–Starling mechanism plays an important compensatory role. Normally, as preload increases, LV end diastolic pressure increases, which causes a stretch in the myocardium and an increased cardiac output. This process is known as the Frank-Starling mechanism. The stretching of the muscle fibres with increasing preload augments cardiac muscle contraction by increasing the calcium sensitivity of the myofibrils (specifically

the sensitivity of troponin for binding calcium increases and there is an increased release of calcium from the sarcoplasmic reticulum). This causes a greater number of actin-myosin cross-bridges to form within the muscle fibers and an increase in force of myocardial contraction and thus increased cardiac output. The Frank-Starling mechanism is important to enable the myocardium to automatically accommodate for an increase in venous return.

In HF, this mechanism fails, as the ventricle is overloaded with blood to the point where myocardial contraction becomes less efficient. This is due to reduced ability to cross-link actin and myosin filaments in over-stretched myocytes. In a person with systolic dysfunction, the heart is unable to contract efficiently resulting in a lower stroke volume (less blood is pumped out per beat) and an increase in left ventricular end diastolic volume, LVEDV (preload). Initially, this increase in preload leads to a compensatory rise in cardiac output, although it is less than that in the normal heart. As HF increases, stroke volume only increases slightly for the associated increase in LVEDV. Eventually, the heart muscle decompensates (i.e. the compensatory mechanism is exhausted). At this point, increasing LVEDV and LVEDP lead to pulmonary congestion with a depressed cardiac output[23].

2.4.3 Natriuretic Peptides:

There are three important natriuretic peptides with similar structure that exert a wide range of effects on the heart, kidneys and the central nervous system (CNS). Atrial natriuretic peptide (ANP) is released from the atria in response to stretch, leading to vasodilatation and increased sodium excretion. Similar to ANP, brain natriuretic peptide (BNP) is also released from the heart, predominantly from the ventricles with increased stretch[25]. These hormones act directly on blood vessels to cause vasodilation, salt and water excretion and to inhibit secretion of renin, aldosterone, and vasopressin. As these natriuretic peptides are important mediators with increased concentration in the circulation in patients with HF, these peptides can be used to monitor disease

progression[20]. For example, raised plasma concentrations of N-terminal BNP (NT-BNP) is thought to be one of the first signs of HF and an independent predictor of mortality in patients with chronic HF[25]. C-type natriuretic peptide has limited effects on vasodilatation and is released from the CNS (predominantly) and vascular endothelium.

2.4.4 Ventricular Remodeling:

Another abnormality associated with HF is ventricular remodeling, which is an alteration in ventricular size or structure that occurs gradually over many months in response to cardiac injury. Remodeling is initially an adaptive mechanism to myocardial injury, abnormal hemodynamic load and wall stress, but eventually it worsens cardiac function and is associated with mortality [17]. The most common pattern of remodeling is a progressive spherical dilatation of the ventricles with wall thinning[5]. At a histological level, remodeling involves myocyte hypertrophy, apoptosis, myofibroblast proliferation and increased interstitial fibrosis[26]. The result is an enlarged globular heart with reduced systolic function, mitral/tricuspid regurgitation and often intraventricular conduction abnormalities such as bundle branch block[5]. The remodeling process post-MI for example includes the necrotic region being replaced with fibrotic scar tissue, where the infarct zone is thinned and elongated[26]. The LV volume increases initially to maintain cardiac output, but eventually LV spherical dilation occurs with myocyte hypertrophy of non-infarcted surrounding areas and interstitial fibrosis.

LV remodeling can be assessed by measuring LV volumes and LVEF by echocardiography (echo), magnetic resonance imaging (MRI) or nuclear imaging. LV volume measurement at a single time-point and over time have been demonstrated to predict clinical outcomes in patients with HF[26]. *Reverse* remodeling on the other hand has been observed with HF treatments, including with angiotensin converting enzyme (ACE) inhibitors, beta blockers

and cardiac resynchronization therapy (CRT) [27]. As such, the *change* in LV volumes and LVEF with drug or device therapies can also be useful in evaluating these interventions as well as for clinical management. Reduction in LV end systolic volume (LVESV) appears to be the most useful measure of reverse remodeling[27].

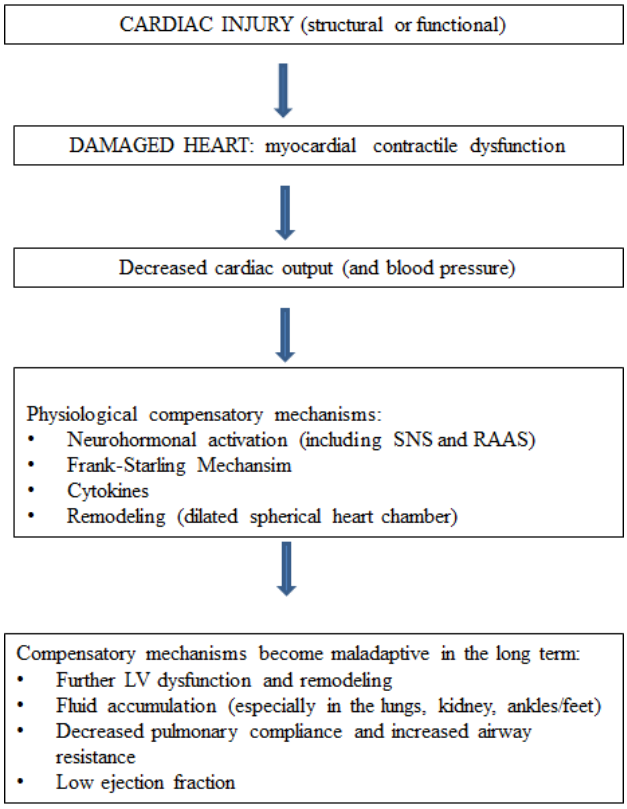

Figure 2: *Mechanism of the Progression of HF*

2.5 Types of Heart Failure:

There are two broad types of HF: systolic and diastolic HF; they can be present together or alone[25].

Systolic HF is defined as the impaired ability of the ventricles to contract and pump blood. It is the more common type of HF and results predominantly from loss of functional myocardium as occurs in ischemic disease[23]. The consequence of LV systolic dysfunction is

reduced cardiac output. Ventricular end-diastolic pressure and volumes increase since the ventricle is unable to adequately empty. This results in increased pressure in the pulmonary vasculature causing fluid to leak into the lung interstitium causing pulmonary edema. On the right side of the heart, the increased pressure is transmitted to the systemic venous circulation and systemic capillaries causing fluid leakage into the tissues, resulting in peripheral edema.

Diastolic HF is the clinical syndrome from impaired ventricular relaxation and used to describe a subgroup of patients with HF and preserved EF[22]. It is typically associated with increased stiffness in the ventricular walls and reduced LV compliance[22]. Ischemia can cause diastolic HF. Myocardial relaxation is an ATP-dependent process and reduction in ATP concentration, as occurs in ischemia, can lead to slowed ventricular relaxation. Hypertrophy or fibrosis reduces LV compliance, which can also delay LV filling and increase LV end-diastolic pressure.

2.6 Diagnosis of Heart Failure:

The CCS HF Management Guidelines suggest the diagnosis of chronic HF to be made when "symptoms and physical signs of congestion and reduced tissue perfusion are documented in the setting of abnormal systolic and/or diastolic cardiac function"[7]. A thorough history and physical examination should be initially performed in those suspected of the condition to rule in or out HF and screen for disorders/genetic factors that might cause or progress HF. NYHA class should also be assessed to determine the severity of symptoms and functional capacity. Further investigation includes measuring NT-pro BNP, a 12-lead ECG and an echo test. An ECG should be performed to assess heart rhythm/rate and QRS duration/morphology for conduction disturbances. An echo is useful to assess systolic and diastolic function, examine cardiac structure (ventricular mass, shape and size), pericardial or valvular disease (such as stenosis) and wall motion abnormalities[23]. If echo images are suboptimal, radionuclide angiography is an

alternative option to assess cardiac function and volumes. This might be the case in patients who are obese or with emphysema[28].

Coronary angiography (to assess coronary anatomy) is recommended for patients with angina or positive non-invasive tests and who might be potential candidates for revascularization[7]. CMR may be useful for prognostic utility as well as identify inflammatory and infiltrative disorders[7] . A chest x-ray is useful to determine the size of the heart and the presence of pulmonary congestion or pleural effusions. Finally, laboratory examination can be helpful to identify signs of end-organ dysfunction of the liver or kidney, as well as electrolyte imbalances and neurohormonal activation. Atypical presentations of HF are found in women, obese patients and the elderly, which can make the diagnosis of HF complex.

2.7 Therapies for Heart Failure:

The treatment of HF includes lifestyle modification, as well as medical therapies. Lifestyle modifications include weight reduction, exercise, as well as smoking and alcohol cessation. Many of the pharmacological therapies are designed to counteract the deleterious effects of the compensatory mechanisms previously discussed. The prognosis of chronic HF has improved in the past decade in part due to developments in drug therapy, including ACE inhibitors, beta blockers and aldosterone antagonists[29]. Electrical device therapy also significantly improves symptoms, quality of life and long term prognosis in select candidates.

For patients who have HF with preserved EF (which constitute approximately 50% of HF patients[30]), it is recommended to first control the risk factors, as ACE inhibitors and angiotensin receptor blockers (ARBs) have been shown to have neutral or very little benefit[7]. Since hypertension and myocardial ischemia are risk factors/potential causes of HF, they should be controlled based on relevant guidelines. As well, diuretics are recommended to be used to control

symptoms of congestion and peripheral edema. If heart rate control is needed, beta blockers and rate lowering calcium channel blockers (CCBs) can be used.

Pharmacological therapy for patients with HF and reduced EF (<40%) is an important component of the HF management.

Despite optimal medical therapy, symptoms and progression of HF may continue. Additional device therapy may improve survival and benefit select HF patients. An implantable cardioverter defibrillator (ICD) is a battery powered electrical impulse generator that are implanted in patients who are at risk of sudden cardiac death due to cardiac arrhythmias (specifically ventricular fibrillation and ventricular tachycardia). The device is programmed to deliver a brief electrical impulse to correct the fatal arrhythmic disturbance. ICD therapy is recommended for patients with HF-REF, with a history of "hemodynamically significant or sustained ventricular arrhythmias" or NYHA II-III with EF<35% or in patients with a previous MI with EF<30%.[7]

CRT aims to coordinate the contraction of the ventricles by simultaneously pacing the two left and right chambers, allowing for more efficient pumping of the heart. CRT is recommended for select patients with NYHA class II to ambulatory class IV HF despite optimal medical therapy, EF<35%, in sinus rhythm with prolonged QRS duration and left bundle branch block (LBBB). The mechanism of CRT and the recommended candidates are discussed in Chapter 2.

Other surgical management therapies for HF patients include coronary revascularization, surgical ventricular remodeling, ventricular assist device (VAD) and heart transplantation. Surgical ventricular remodeling attempts to surgically restore the normal geometry of the ventricle for pumping efficiency. VAD is a mechanical pump that is used to help maintain blood flow to vital organs. In end stage HF, heart transplantation might be the only option, whereby the severely damaged, failing heart is replaced with a new, functional organ.

Chapter Three: **Cardiac Resynchronization Therapy**

3.1 Background:

There have been many advances in the pharmacologic treatment of HF, however there are still many patients, who despite optimal medical management, have severe symptoms, along with an overall poor prognosis [31]. CRT is a biventricular pacing device treatment, which has established morbidity and mortality benefit in addition to either optimal medical therapy or ICD in select patients with systolic HF[32].

CRT uses low voltage stimulation or pacing to stimulate synchronized contraction of the ventricles for improved pumping efficiency and thus improved cardiac function. This cardiac device system involves three leads: one in the right atrium for atrial pacing, one within the right ventricle near the septum and one in the coronary veins to pace the left ventricle. The lead that stimulates and paces the left ventricle, known as the LV lead, is placed through the coronary sinus and into a branching cardiac vein (posterolateral, mid-lateral or lateral branch of the anterior interventricular vein) and is the lead unique to CRT systems.

The major therapeutic benefit of CRT is "LV synchronization" or resynchronizing the activation and contraction of the LV with itself for improved contractile function, allowing for increased ejection fraction and stroke volume. Pacing the LV for coordinated contraction allows for improved LV function (including improved LV filling) without increasing myocardial energy demand[33], indicating improved myocardial efficiency. The goal of CRT is to optimize atrioventricular timing, prolong LV filling and coordinate RV and LV contraction by minimizing inter-and intraventricular mechanical delay (relieving electromechanical dyssynchrony). Interventricular delay is the discordance of right and left ventricular contraction and is association

with dyssynchrony (discussed in a later section). It can be measured by Doppler echocardiography comparing the timing of ECG Q wave to onset of left ventricular outflow tract with Q to onset of right ventricular outflow tract. Intraventricular mechanical delay is the difference in timing of segments of the left ventricle (ie septal and posterior wall). This is due to either premature or late contraction of wall segments due to delayed electrical conduction. It can be measured by various methods using tissue Doppler echocardiography. The long term goals are for these aforementioned acute changes to result in structural and functional reverse remodeling and improved symptoms and survival[34].

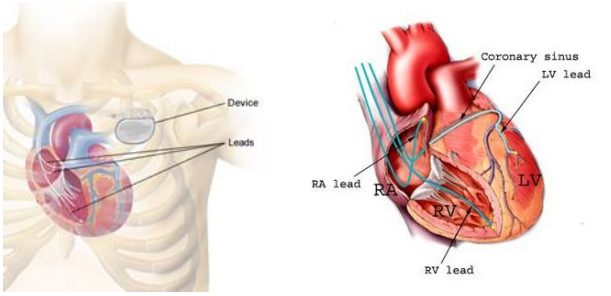

Figure 3: *CRT device: Pulse generator and three leads, or insulated wires, which plug into a clear plastic epoxy connector at top of the pulse generator*[35]

3.2 Types of CRT systems:

Most CRT systems incorporate defibrillation capability as well, so that the lifesaving rescue function of ICD therapy is available should the patient require it[25]. This device, commonly known as CRT-D, is designed as an ICD with a built in CRT, which does not make the device larger, but requires more ports to accommodate three leads. The lead in the right ventricle is the one that delivers the defibrillation energy. CRT devices may not include the defibrillator in which case they are designed similar to a conventional pacemaker, but instead allow three leads to plug into the clear epoxy connector. These devices are often referred to as CRT-P and can only deliver

low voltage stimulation. Common to both CRT-D and CRT-P systems is a pulse generator and three leads (which are plugged into a clear, plastic connector on top of the generator)[25].

3.3 CRT Mechanism:

Several mechanisms are thought to be responsible for the benefit seen in response to CRT in patients with heart failure. These mechanisms include electrical and mechanical resynchronization, reduction in mitral regurgitation and LV reverse remodeling.

i. Electrical and mechanical resynchronization: Dilatation of the LV and associated fibrosis are often found in HF patients and frequently induces intracardiac conduction delays resulting in dyssynchronous LV motion. This often results in the LBBB pattern seen on the surface ECG. Biventricular pacing benefits patients with drug refractory, advanced HF and prolonged QRS durations (>120 ms) by improving cardiac electrical synchrony. The QRS width on surface ECG is a simple method often used as a surrogate for mechanical dyssynchrony. There are three types of dyssynchrony that may impair cardiac function by affecting the systolic and diastolic properties of the heart. Prolongation of the AV conduction time leading to AV dyssynchrony is common in patients with HF**.** The delay in the onset of ventricular systole following ventricular filling gives rise to mitral regurgitation. This results in a lower LV preload, and decreased cardiac output. Interventricular dyssynchrony, defined previously, is usually a result of right or left bundle branch block, and often leads to septal contraction which is out of phase with one of the ventricular free walls. Intraventricular dyssynchrony occurs when there is heterogeneity in the timing of mechanical events between different segments of the LV. As a consequence, the ventricle expends a great deal of energy changing its shape but not ejecting blood.

This dyssynchrony commonly extends to the papillary muscles resulting in mitral regurgitation. However, a proportion of patients with a prolonged QRS duration (up to a third) do not exhibit inter or intraventricular dyssynchrony, which may be in part why up to a third of HF patients with prolonged QRS duration selected for CRT do not derive benefit.

ii. Reduction in mitral regurgitation: As mentioned earlier, prolongation of the AV interval can cause MR. Thus, CRT pacing with short AV intervals can reduce MR. Coordinating LV contraction by CRT increases the maximal rate of LV systolic pressure rise (dP/dt) and thus the trans-mitral pressure gradient. CRT reduces the severity of MR by decreasing the effective regurgitant orifice area. This effect is related to an improvement in LV systolic function.

iii. LV Reverse Remodeling: Biventricular pacing has been shown to have a beneficial effect on LV remodeling. CRT enhances ventricular ejection efficiency due to coordinated contraction, reduces MR, which unload both ventricles and initiate reverse remodeling. Data from several randomized trials (including PATH-CHF, MIRACLE, CONTAK-CD, and Vigor-CHF) consistently showed that CRT can induce reverse remodeling in most patients.

CARE-HF[31] investigators postulate that the morbidity and mortality benefit of CRT found (independent of defibrillation) is due to restoring ventricular synchrony, which in turn improves LV function. This reduces mitral regurgitation, which causes increased perfusion pressure, decreases cardiac filling and subsequently reverses LV remodeling. This cascade of events is experienced by patients as improved symptoms, quality of life and a lower risk of hospitalization and death.

A study by Cho et al. [34] looked at whether there is cellular processes involved in the improvement in myocardial function with CRT or if it is mainly the mechanical wall motion changes that improve pump function in HF patients with dyssynchrony. This theory came about from comparing CRT responders and non-responders and finding that myocardial gene expression of proteins involved in the pathophysiology of HF (natriuretic peptides, calcium handling proteins and β-receptors) was restored more so in responders[36]. As well, Cho et al. found decreases in circulating biomarkers of extracellular matrix remodeling in responders[37]. These changes suggest reversal of molecular changes found in HF might be a contributory mechanism involved in long-term improvement in LV function and survival with CRT.

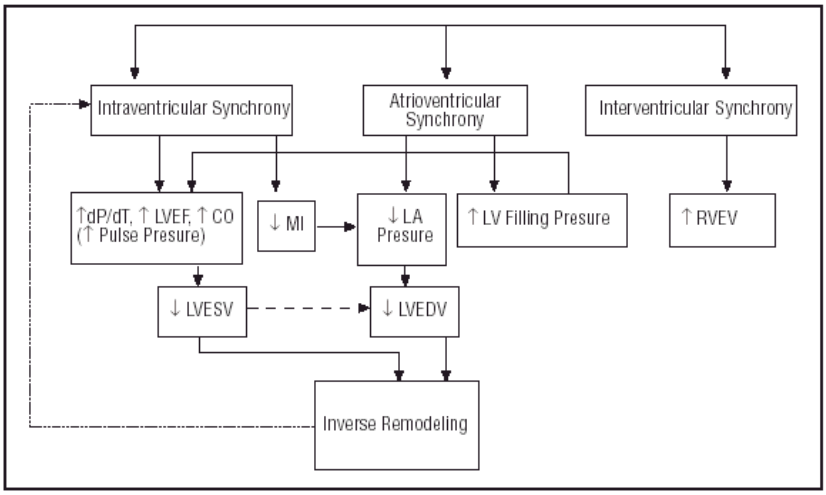

Figure 4: *Proposed Mechanism of CRT: CRT improves mechanical synchrony, resulting in efficient systole. Ejection fraction (EF) and cardiac output (CO) are improved. The end effect of reverse remodeling will add to improved cardiac synchrony and decrease mitral regurgitation*[38]

3.4 Patient Selection:

Not all patients with systolic HF are ideal candidates for CRT. There have been many research studies in various patient populations since the inception of CRT in 1994 to determine who would benefit from resynchronization therapy[27]. Although this matter is not fully resolved, there is high quality evidence, based on significant trials, for specific recommendations on the

prescription of CRT[2]. Due to limited health care resources, the expense of device implantation and the invasiveness of the implant procedure, identification of the characteristics of the patients most likely to benefit from CRT are imperative.

The most recent CCS Guidelines on the use of CRT stress the importance of ensuring adequate medical therapy is implemented before device therapy consideration[2]. Thereafter, QRS duration, LVEF and NYHA functional class assessment is recommended to determine appropriate candidates for CRT. Specifically, patients in sinus rhythm with drug refractory HF, in NYHA II to IV, a low left ventricular ejection fraction (LVEF ≤ 0.35) and a QRS duration of $\geq$ 130 ms[1] because of LBBB, are candidates for CRT[2]. These recommendations are based on the inclusion criteria of the most recent landmark CRT trials and the characteristics of patients who derived CRT benefit enrolled in these large multicentre trials[2]. The RCTs that have compared the effect of CRT in addition to either optimal medical therapy alone or ICD therapy in patients with HF. Evidence from RCTs compared to observational studies has the advantage of separating the therapeutic response of CRT from the natural course of the underlying disease (in this case HF condition) minimizing confounding effects. In other words, since eligible patients are randomly assigned to either group, the differences in outcomes between CRT and the control group would be due to the treatment, CRT, and not confounded by the differences in baseline characteristics in RCTs[2].

[1] Long QRS duration usually indicates dyssynchronized LV contraction
[2] Although the limitations of RCTs include selection bias, if the selected study sample is not representative of the patient population

3.4.1 Evidence for CRT in less symptomatic patients:

MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy) and RAFT (Resynchronization/Defibrillation for Ambulatory Heat Failure Trial) are the two large studies that provide the most conclusive evidence for the addition of CRT to ICD therapy in a less symptomatic population (NYHA class I and II) [2]. In MADIT-CRT, the patients enrolled were limited to those with NYHA I-II symptoms, with the majority of patients in NYHA class II (approximately 80% in both CRT-D and ICD alone groups). In this less symptomatic group, it was found that there was a significant lower risk of the primary end-point (which was all-cause death or nonfatal HF events) compared to ICD alone (17% vs 25%; p=0.001)[39]. The reduction in this primary end-point was primarily due to the reduced risk of nonfatal HF events alone in the CRT-D group (14% vs 23%; p<0.001)[39]. In RAFT, patients enrolled ranged from NYHA II-III, with 80% in NYHA II. Of those with less symptomatic HF (NYHA class II), a lower risk of death or hospitalization for HF was noted in the CRT-D intervention group (27% vs 35% with ICD alone; p=0.001)[40]. The risk of death from *any cause* in NYHA II group was also lower (15% vs 21%; p=0.006)[40]. In addition, in the 4 studies that assessed CRT added to ICD in less symptomatic patients, there was an overall 20% reduction in the risk of death (p=0.02)[2].

A systematic review and meta-analysis of CRT in patients with NYHA I and II was also conducted[41]. This review reported those without HF symptoms (i.e. NYHA class I) did not have a significant reduction in risk of death/hospitalization. Although the review found those with mild symptoms (i.e. NYHA class II) did have a significant reduction in death/hospitalization[2]. Even though the collective evidence on less symptomatic HF patients suggests CRT in addition to ICD

treatment is beneficial in terms of clinical outcomes[3], most of the patients enrolled in the aforementioned studies are in NYHA class II, with only a small proportion in NYHA class I. The evidence from the systematic review combined with significant data favouring CRT-D vs ICD alone from individual trials (namely MADIT-CRT and RAFT), suggest the prescription of CRT in NYHA class II, with there not being sufficient evidence to indicate CRT for asymptomatic HF patients (NYHA class I).

3.4.2 Evidence for CRT in symptomatic patients:

The usual study enrollment criteria includes patients in NYHA functional class III or IV[42], which guide CRT recommendations. The systematic review and meta-analysis of CRT by Wells et al. showed a non-significant reduction in the risk of death (14% reduction; p=0.17), although CRT-P has been shown to be significantly beneficial from this review[32]. As such, the combined results favour CRT use in the highly symptomatic population (NYHA class III and ambulatory class IV). Although, there is lack of evidence to recommend CRT-D in patients with chronic, non-ambulatory NYHA class IV symptoms[2] as they were not largely represented in the landmark CRT trials.

3.4.3 Other considerations when selecting patients for CRT:

Similarly, clinical trial inclusion/exclusion criteria and subgroup analyses from multicenter studies provide evidence for the effects of sex, QRS duration, type of intraventricular conduction delay (LBBB versus right bundle) and AF on CRT benefit.

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[3] Significant LV reverse remodelling benefit was also found in MADIT-CRT and REVERSE trials [39,112]

3.5 Benefits of CRT:

Beneficial effects of CRT include improvement in HF symptoms, exercise capacity, LV systolic performance, reduced mitral regurgitation, increased cardiac output, quality of life, and survival[33,27,43]. Combined evidence from 5 studies[32] on the efficacy of CRT-P found a 27% significant relative risk reduction in all-cause mortality. CRT-D was found to have a significant relative risk reduction of 17% in mortality when collective data from 7 studies[32] were pooled.

To highlight some of the earlier reported benefits of CRT, even temporary CRT was found to increase LV stroke volume and reduces pulmonary capillary wedge pressure (Leclerc et al). Auricchio et al group showed that CRT increases LV dP/dt. The Multisite Stimulation in Cardiomyopathies (MUSTIC) study in 2001, which was the first randomized controlled cross-over trial in resynchronization therapy, found that CRT dramatically reduced HF hospitalizations and improved NYHA class, as well as quality of life, exercise distance, and peak oxygen uptake[44]. Finally, more recently, the Cardiac Resynchronization in Heart Failure (CARE-HF) trial indicated that CRT-P led to a 36% relative reduction in total mortality compared with medical therapy and was associated with a reduction in NYHA class from 3.06 at baseline to 2.1 at 90 days post-implantation[31]. The comparison of medical therapy, pacing, and defibrillation in heart failure, studied in the COMPANION trial, revealed that the addition of a defibrillator to a CRT device (CRT-D) also resulted in additional survival benefits compared with CRT-P[45]. With respect to quality of life, the COMPANION study showed an improvement of 9.3% with CRT-D, 8.8% with CRT-P and 3.7% with medical therapy alone.

Other, more recent, large multicenter randomized trials (REVERSE and MADIT-CRT) have shown significant improvements in LV size and function, LVEF, RV function, left atrial size and mitral regurgitation severity in patients treated with CRT versus ICD alone. These

findings were found consistently in all studied subgroups, although patients with QRS duration≥ 150 ms, LBBB, non-ischemic etiology and female patients derived greatest improvement in LV volumes[18]. The extent of reverse remodeling was concordant with and predictive of death or HF events and thus suggest a convincing mechanism by which CRT therapy improves outcomes

3.6 Risks of CRT:

CRT implantation can be complex, with added complexity upgrading a patient with an existing device to CRT. The complication rate with de nova CRT implant is up to 6.4% [48]. Excess adverse events have been attributed to LV lead dislodgement and implant failure (<1.2%). There is also an increased chance of multiple surgeries due to pulse generator replacements and lead revisions, which are higher in CRT than non-CRT procedures[49]. There is also the small risk of dissection or perforation of the coronary sinus; although rare, could lead to substantial morbidity and even mortality. Although, in tertiary centres, the success rate for placement of a cardiac resynchronization device is high (implantation success rate was 97.5%, with an optimal location of the LV lead achieved in 90% of patients) and the procedure is safe[50]. Follow-up of the CRT device and battery life are similar to that of contemporary dual-chamber pacemakers and ICD devices[51],

3.7 Concept of Response:

Despite the established benefit of CRT, approximately one third of selected patients do not appear to respond to this intervention, emphasizing the need for better selection criteria for this device system [52]. Several hundred papers have attempted to address this issue by exploring methods to improve patient selection and outcomes[31,53]. However, obtaining a true estimate of non-responder rate is a complicated issue because precisely defining response itself is problematic as inconsistent criteria have been used to define a positive response [54].

Table 2: Various Published Definitions of Response[47]

Definition:	Cut Off
Clinical Variables:	
NYHA functional class	≥ 1 class reduction
6MWD	≥ 50 m increase
Both NYHA and 6 MWD	≥ 1 class reduction and ≥ 25% increase 6MWD
VO_2 max	≥ 10% increase
All-cause mortality	Any event
HF hospitalization	Any event
MLWHF	≥ 10 score increase
Quality of Life	≥ 10 or 15 score increase
Echocardiographic Variables:	
LVEF	0.05 increase (absolute)
LVESV	10 or 15% *relative* reduction
LVEDV	15% reduction

The definition of benefit or response to CRT varies widely between studies and include clinical, echocardiographic or combined criterion[54] However, there is poor agreement or correlation between the different response criteria. Even the agreement between echocardiographic and clinical criteria for defining a positive response to CRT is only slightly better than that expected by chance alone[54]. This inconsistency in the definition of response to CRT severely limits the ability to generalize results over multiple studies and a standard needs to be developed. A common definition of response to CRT should be clinically relevant, an important treatment benefit to the individual patient and ultimately associated with improved quality of life and/or prolonged survival[27]. Another complexity discussed by Foley et al, 2009, is the discordance between symptomatic and prognostic benefit from CRT in that they are not necessarily correlated[27] , which is also the case to other HF treatments. Yu et al[55], also found similar findings in symptomatic or clinical response (NYHA class, 6MWD, quality of life) 3 to 6 months post CRT in both survivors and non-survivors, emphasizing symptomatic improvement does not necessarily reflect survival benefit (i.e. prognosis). This discordance causes challenges in studying CRT efficacy in terms of deciding on the relative importance of measures of response. Should patient selection be based on symptomatic relief or survival benefit (often

assessed by a surrogate marker such as LV reverse remodeling)? Are patients who are considered non-responders based on lack of remodeling, but who derive symptomatic benefit, truly non-responders to CRT? These questions raise important issues in the study of CRT response and clinical practice. As suggested by Yu et al[55], the answers may lie in a consensus to define a clinically meaningful composite score to reliably measure response to CRT. A clinical composite score is a measure of response which could consider factors such as reduction in LVESV, NYHA, hospitalization and death, in a weighted manner. A composite measure "may be the best overall choice for defining response in future CRT trials"[54] .

Nevertheless, although the actual nonresponder rate may be difficult to estimate, it is clear there are a substantial number of apparently suitable patients, based on current guidelines, who do not respond; thus necessitating a focus on determining novel predictors of CRT response.

Ultimately, a final objective in selecting patients should be to prolong survival and/or alleviate symptoms and improve quality of life.

3.8 Predictors of Response to CRT:

Lack of response to CRT may be due to several factors including comorbid conditions that have progressed HF beyond CRT efficacy, failure to achieve adequate mechanical synchrony (which may be due to sub-optimal LV lead positioning), and an absence of dyssynchrony. Mullens et al, 2009[56], summarized the common issues related to suboptimal CRT response, which included suboptimal AV timing, arrhythmia, anemia and suboptimal LV lead position. Figure 5 details the potential causes of reduced CRT response[22].

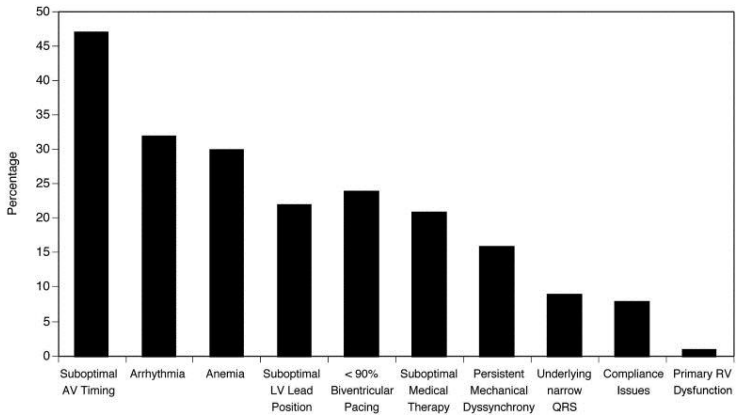


Figure 5: *Potential Causes of Sub-Optimal CRT Response*[7]

3.8.1 LV Dyssynchrony:

Different predictors of response to CRT have been proposed. One of the widely studied and used predictors (of reverse remodeling with CRT) is the presence of LV dyssynchrony[57]. Traditionally, a widened QRS complex has been used to select those patients with substantial LV dyssynchrony, but recent studies have shown that QRS duration is only a weak marker of LV dyssynchrony, thus suggesting a low predictive value for response to CRT [58]. Imaging based measures of mechanical dyssynchrony have also not predicted response well[59]. Even failure of response to CRT despite the presence of LV dyssynchrony has been demonstrated[52] and improvement in dyssynchrony after initiation of CRT only weakly predicts chronic response[60]. Thus there is still not a universal agreement with correlating amount of dyssynchrony and CRT therapy.

3.8.2 Patient Characteristics: HF Etiology and Type:

Patient characteristics, such as the underlying cause and type of HF have been reported to relate to the outcome of CRT. Specifically, it has been found that ischemic HF is a potential predictor for non-response. As such, response to CRT may be related to the extent of viable myocardium and inversely related to the extent and location of scar tissue.

3.8.3 LV Pacing Lead:

The optimal site of LV lead placement has also been studied as a potential predictor of response to CRT[61,62,63]. One theory is that greater reverse remodelling occurs with pacing at the site of late mechanical activation[64]. Echocardiogram with TDI has been used to select regions of latest activation in the LV [65]. LV–RV interlead distance has also been shown to predict (hemodynamic) response to CRT as measured by a rise in dp/dt; thus may be used to improve the success rate at the time of lead implantation[66]. MADIT-CRT found no difference in clinical outcome based on lead position other than LV leads in the apical region. Thus, pacing from a non-apical LV epicardial region is recommended[52]. Although, Wilton et al found there is no significant association between the different locations of LV implant and death[67].

The LV lead is usually the most challenging lead to be placed. Implantation requires cannulation of the coronary sinus opening (the os) and then advancing the LV lead through this cannula into the coronary sinus (CS). A successful implant typically involves placement of the LV lead in a posterolateral or anterolateral coronary vein with good lead stability, adequate thresholds and without phrenic nerve stimulation.

i) Anatomical Considerations: Coronary Venous Anatomy

To begin with, there is much anatomic variation in os location among individuals, even those without HF or cardiac conditions. As well, the CS opening may be hard to locate in patients with dilated hearts, which includes many HF patients or those with atrial fibrillation as the right atrium may be enlarged with folds obscuring the os[5]. Further difficulty is due to the fact that the os is often partially covered by the varying size valve of the CS, the Thebesian valve, which is situated at the base of the inferior vena cava. This valve may or

may not be present. The coronary venous anatomy of patients differs widely, so it is important that the individual patient's veins are studied before implantation of the device.

ii) Phrenic nerve stimulation:

Phrenic nerve stimulation is a complication of LV lead implants and may produce diaphragmatic stimulation. This issue occurs when the LV lead is positioned in such a way that output pulses stimulate the phrenic nerve[7]. To test if this has occurred during implantation, the LV lead is paced at high outputs to see if phrenic nerve stimulation is possible. Post operative attempts to "program around" this problem usually do not work.[66]

iii) Scar:

Scar burden can be assessed by nuclear scans [either single photon emission computed tomography (SPECT) or positron emission tomography (PET)], although they are not routinely done. Scar assessment is more commonly done by multi gated acquisition scan (MUGA), echocardiography and late enhancement cardiovascular magnetic resonance (LE CMR), the gold standard technique for imaging of myocardial scar[68].

Several studies suggest scar tissue in the posterolateral wall, as assessed by contrast-enhanced MRI, result in non-response to CRT [69]. Pacing the left ventricle in nonviable or scarred myocardium may result in less effective LV pacing (due to interfering with electrical capture), as a consequence, failure of LV resynchronization and lack of CRT response. As well, the placement of the lead at areas of LV scarring can lead to worsening of HF due to unopposed RV pacing or worsening of ventricular tachycardia[70]. Hemodynamic studies have also demonstrated that smaller dP/dt measures are found in paced areas of myocardial scar[71].

Scar burden and its location have been implicated in several studies to explain poor clinical and echocardiographic response outcomes in ischemic cardiomyopathy[47]. Poor CRT response in ischemic heart disease has been associated to LV lead implantation in myocardial scar and also to total scar burden[52]. Thus, identification of myocardial viability and scar burden in the left ventricular region, as well as avoidance of scar tissue for LV lead implantation, are recommended for procedural consideration prior to implantation.

iv) LV Lead dislodgement:

Failure to capture is defined as when a pacing spike is seen on the ECG but there is no evidence of resulting depolarization. The most common reason for this is the dislodgement of the LV pacing wire from the epicardium[72], which occurs approximately 5% of the time[73]. The LV lead does not have a usual fixation method and relies on anchorage within the vein by lead tip design[7]. For this reason and also during removal of implanting tools (the catheter and the sheath) during the procedure, LV dislodgement can occur.

v) Left ventricular lead stability:

Choice of lead depends on the anatomy of the venous branch. If the branch is very large and possible dislodgement is a concern, a lead with a curled or sigmoid shape may be chosen[9]. Lead design should be carefully considered to maintain stable position of the LV lead. The LV lead is much more limited in its possible placement locations and there might only be one viable location for the LV lead in a given patient[66]. Improper lead placement can hamper capture and in such cases, the lead may require surgical revision. Therefore, information about coronary venous anatomy and scar location/extent prior to implantation is essential.

There is a novel quadripolar LV lead that claim to be able to pace at a preferred site with lead stability[74]. A quadripolar LV lead has 4 electrodes along the distal end and can pace the LV wall at several locations and through multiple vectors along the lead. Suboptimal pacing sites, such as areas of scar or sites at risk of phrenic nerve stimulation) can possibly be avoided with the new quadripolar lead. As well, more optimal sites, such as pacing at the most delayed mechanical/electrical activated region could be achieved. Lead stability is reported not to be compromised due to placing the tip of this lead in a distal part of the vein for lead security and the other electrodes placed near the optimal pacing site. Furthermore, quadripolar LV leads are able to pace the LV with more electrodes, allowing for multisite pacing and reducing the pressure of one optimal position. Recent trials have shown benefit over conventional bipolar leads, although future studies are required to assess the acute hemodynamic response and the long term outcomes of these leads[74].

3.8.4 Medical Reasons:

Finally, medical reasons can also explain lack of response to CRT. These include suboptimal drug therapy for HF, significant mitral regurgitation, other comorbidities (obesity, anemia, severe COPD, chronic renal failure) and end-stage HF (restrictive pattern on echo, RV enlargement). Surgical correction of mitral regurgitation and coronary revascularization in patients with ischemic cardiomyopathy should be considered in this case. Some patients are too ill, frail and/or have extensive comorbidities to tolerate the CRT procedure and derive benefit[2].

Chapter Four: **Myocardial Scar and CRT**

4.1 Background:

Myocardial scar is fibrous tissue that has replaced normal tissue destroyed by cardiac disease. The scarring can disrupt the electrical conduction system of the heart and affect nearby myocytes. In patients with ischemic cardiomyopathy, the response to CRT may be related to the location and/or extent of myocardial scar tissue. Ypenburg et al. found that the total (overall) scar at baseline was correlated with changes in LVEF, LVEDV and LVESV after CRT (i.e. with LV reverse remodeling). As well, the number of viable segments was also correlated with LV reverse remodeling. Extensive scar tissue in the region of the LV lead also do not respond to CRT. The basic definition of "myocardial ischemia" is a greater myocardial tissue oxygen demand than supply[1]. In the normal heart, an increase in myocardial tension, contractility or heart rate results in an increase in oxygen demand that is matched by an increase in coronary artery blood flow and oxygen delivery. In coronary artery disease, there is a narrowing of the arteries supplying the heart (due to plaque buildup) and consequently reduced oxygenated blood flow to the heart, which is the most common cause of myocardial ischemia. Coronary artery disease is the cause of HF in up to 75% of patients in industrialized countries[1].

During short term ischemic episodes, the heart`s defense mechanism tries to resolve the imbalance of oxygen demand and supply by downregulating myocardial contractile function and increasing the rate of glycolysis (anaerobic energy production). In doing so, there in an increase in sarcolemma glucose transport and intracellular acidosis results from a build up of the glycolytic breakdown products which further inhibits contraction[5].

The inner myocardial layers of the LV are more vulnerable to blood flow reduction, so mild ischemia is usually confined to the inner layer subendocardium[3]. This is due to the higher systolic

wall stress in this layer compared to the mid and epicardial layers and so there is a greater metabolic demand in the subendocardium[2]. As the coronary obstruction becomes more severe, the ischemia proceeds from sub-endocardium outwards to the sub-epicardium until the full myocardial wall is affected.

4.2 Locating Myocardial Scar:

Myocardial scar burden and the identification of potential viable myocardium are important indicators of cardiac function. Thus, the location of dysfunctional or scarred myocardium is a key prognostic indicator. Myocardial infarct size can be measured using delayed contrast-enhanced CMR and has been shown to correlate well with histological measurements in both the acute and chronic settings. Furthermore, contrast enhanced CMR offers distinct advantages over other imaging modalities because it does not rely on the recovery of wall motion abnormalities to identify viability and are able to accurately depict smaller sub-endocardial infarctions.

Late gadolinium enhancement cardiovascular magnetic resonance imaging (LGE-CMR) is reliable and reproducible in identifying myocardial scar tissue[i] and is know as the gold standard to identify scar burden. The amount and extent of transmural myocardial scar tissue on LGE-CMR has been shown to predict overall mortality in patients with coronary artery disease, independent of LVEF. Gadolinium (Gd) is an elemental contrast agent that is bound to a large carrier molecule and thus unable to enter into the intracellular space, allowing the Gd contrast to remain extracellularly[75]. LGE is based on the difference in volume distribution of Gd from the delayed washout of contrast material in infarcted myocardium due to leakage into the interstitial space caused by microvascular damage. Either the myocardial cell membrane is disrupted (as in acute myocardial infarction due to cellular necrosis) or extracellular space increases (as in scar tissue secondary to chronic myocardial infarction due to collagen deposit) resulting in an increased distribution of Gd enhancement. CMR also provides detailed information on cardiac

morphology, function, and stress myocardial perfusion, in addition to an evaluation of acute and chronic tissue injury. Thus CMR is highly recommended for select patients with HF.

Non-invasive imaging techniques are recommended in HF patients to guide treatment decisions. Transthoracic echo is the "first line" tool to assess cardiac structure and function[14]. Echo provides readily accessible measurements of LV volumes, EF and mitral regurgitation which is not only informative to assess HF severity, but also CRT appropriateness. Echo is a non-invasive, widely available and relatively quick/less costly (than CMR), which makes it a popular imaging tool for CRT. An electrocardiogram (ECG) of ischemia is different depending on whether the ischemic area affects mainly the sub-endocardium or the sub-epicardium. In case of subendocardial ischemia ST depression appears with different intensity according to the degree and in case of sub-epicardial or transmural ischemia ST elevation occurs. Severe and prolonged ischemia produces a region of necrosis spanning the entire thickness of the myocardial wall. Such *transmural* infarcts usually cause ST segment elevation. The cellular modifications generated by acute ischemia are responsible for changes in the ST segment, which makes ST segment changes an early marker of ischemia.

4.3 Viable myocardium and CRT response:

The findings in Ypenburg et al's paper "Extent of Viability to Predict Response to CRT in Ischemic HF Patients"[4], reports response to CRT is directly related to the extent of viable myocardium. The presence of scar tissue and total scar score shows an *inverse* relation to CRT response. Having a total scar score of more than 14 appeared to be predictive of nonresponse. Thus, additional criteria are needed to identify patients who are likely to benefit from CRT than the standard LV function and QRS duration criteria. Ischemic cause of HF is also identified as a predictor of nonresponse. This data suggests that a certain extent of viability is needed to permit response to CRT.

Chapter Five: **Excitation Contraction Coupling**

5.1 Electro-Mechanical Coupling:

Contraction of the heart muscle requires initiation of action potentials with a change in membrane potential (voltage) across the cardiac cell membranes by movement of ions. The cardiac electrical conduction system coordinates myocyte mechanical/contractile activity. The details of the electrical and mechanical coupling of the heart will be discussed in this chapter.

In the normal heart, electrical activation originates from the sinoatrial (SA) node, located in the wall of the RA, lateral to the superior vena cava opening[76]. The SA node is composed of a fibrous tissue matrix with (pacemaker) cells that automatically depolarize, initiating action potentials at a regular rate. These spontaneous depolarizations are the most rapid within the normal heart, thus functioning as the dominant pacemaker[76]. The rate of action potentials of the nodal cells depends on various conditions, such as metabolic needs, atrial stretch, as well as neural and humoral activation[77]. At rest, the rate is usually 60 to 100 beats per minute. Both adrenergic and cholinergic nerve terminations influence sinus node activity. Binding of neurotransmitters to adrenergic and cholinergic receptors stimulate the sympathetic and parasympathetic system respectively. Once the action potential has started in the sinus node, it spreads through both atria to reach the atrioventricular (AV) junction. The “Bachmann bundle” or anterior interatrial band, is a large muscle bundle that connects the RA and the LA enabling conduction of the electrical impulse from the right to the left atrium[78]. The other three conduction tracts that make up the atrial conduction system are known as the anterior, middle and posterior tracts, which run from the SA to AV node[79]. In the normal heart, propagation of the action potential from the SA node through the atria takes approximately 100 ms.

The annulus fibrosus electrically isolates the atrial and ventricular myocardium. It is composed of central fibrous rings that surrounds the atrioventricular orifice[76]. The collagen proteins in the right and left rings are impermeable to electrical conduction. As such, the atrioventricular (AV) node is the only physiologic electrical connection between the atria and ventricles. It lies at the inferior posterior section of the interatrial septum near the opening of the coronary sinus, and conducts the normal electrical impulse from the atria to the ventricles[80]. The AV node delays ventricular activation by approximately 120 ms, which is functionally important to ensure the atria eject blood properly into the ventricles prior to ventricular contraction. The AV delay allows for optimal ventricular filling and protects the ventricles from abnormally fast rate response in the event of atrial arrhythmias[81]. Another important property unique to the AV node to prevent rapid conduction through the ventricles is "decremental conduction"[80]. This is where the more frequently the AV node is stimulated (e.g. during rapid atrial arrhythmias such as atrial fibrillation and atrial flutter) the slower it conducts[82]. The AV node's normal intrinsic firing rate without stimulation (i.e. from the SA node) is 40-60 times/minute[83]. As such, loss of the conduction system before the AV node should still result in pacing of the ventricles by the, albeit slower, pacemaker ability of the AV node.

From the AV node the electrical impulse reaches the bundle of His which transmits the impulse to the apex via the bundle branches. The Purkinje fibers are at the end of the heart's conduction system, and provide electrical conduction to the ventricles, causing the ventricular myocytes to contract at a paced interval[81]. The bundle of His branches into the left and the right bundle branches, which run along the interventricular septum. The right bundle proceeds on the right side of the interventricular septum (intramyocardially) as a thin, unbranched extension of the bundle of His. The left bundle branch further divides into the left anterior and the left posterior fascicles. The left anterior subdivision is longer and thinner than the posterior one,

which makes it more vulnerable to damage[80]. These bundles and fascicles give rise to the Purkinje fibers (located sub-endocardially in the lower third of the septum and in the anterior free wall[84]. These fibers then stimulate the ventricular muscle. It takes about 30-40ms for the impulse to travel from the bundle of His to the ventricular muscle. The electrical conduction is transmitted faster in the Purkinje system since their cells are longer and have a higher content of gap junctions. During normal excitation of the Purkinje system, a high degree of electrical coordination between distant regions of the myocardium occur due to the fast propagation over the long fibers of the Purkinje system and due to the wide distribution of Purkinje-myocardial junctions[84]. As such, the Purkinje fibers play an important role in the synchronization of electrical myocardial activity. These junctions located subendocardially in both the RV and LV are the only sites where the Purkinje system and myocytes are electrically coupled and result in the earliest activated and contracting regions of the ventricles[81]. See Figure 6 for the electrical conduction system of the heart.

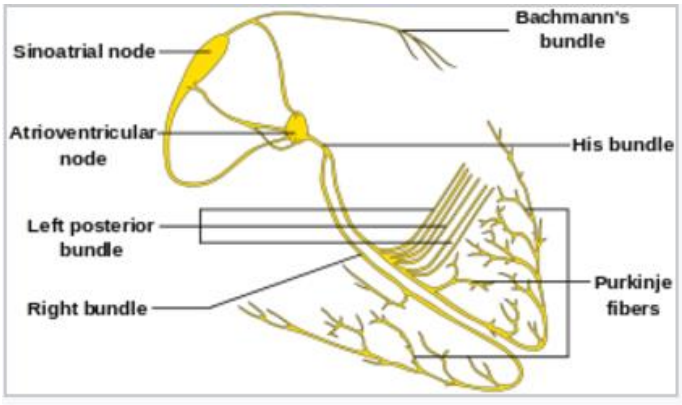


Figure 6: ***Electrical conduction system of the heart.***

In the normal heart, the first site of endocardial ventricular activation is usually in the LV at the interventricular septum or anterior region. The activation then begins in the RV endocardium (at the site of exit of the right bundle branch) within approximately 10 ms.

Thereafter, the depolarization wavefronts proceed simultaneously in the LV and RV, mainly in the direction from apex to base and from septum to lateral wall in both ventricles[81]. Overall, the postero-lateral/basal region of the LV is the last part of the heart to be depolarized. Simultaneous depolarization occurs from the endocardium to the epicardium. The duration of total ventricular electrical activation is 50 to 80ms in the normal heart[81].

Electro-mechanical coupling or excitation-contraction coupling represents the process by which an electrical action potential leads to contraction of cardiac muscle cells. This is achieved by converting a chemical signal into mechanical energy via the action of contractile proteins. Calcium is the crucial mediator that couples electrical excitation to physical contraction by movement in and out of the myocyte's cytosol during each action potential[85]. All cardiomyocytes (including pacemaker cells) are electrically coupled through gap junctions. An action potential in one cell will cause all neighbouring cells to depolarize, allowing the heart chambers to act as a unit, allowing synchronous contraction. Depolarization triggers calcium influx through voltage gated, L-type calcium channels (open/activated at depolarized membrane potentials)[85]. The influx of calcium from these channels activates ryanodine receptors to change conformation and release stored calcium from the sarcoplasmic reticulum (a process known as "calcium induced calcium release")[85]. Large levels of intracellular Ca^{2+} act on tropomyosin complexes to induce myocyte contraction.

Some time is needed for calcium released from the sarcoplasmic reticulum to be transported and bind to the contractile proteins, which gives rise to a time delay between depolarization and the onset of contraction. The entire electromechanical delay amounts to approximately 30 ms[86]. This delay can be observed as the interval between the R-wave of the ECG (ventricular depolarization) and the rise in LV pressure (ventricular contraction). In the normal heart, activation of the ventricular wall occurs by rapid impulse conduction up to the sub-

endocardium. From there, the impulses are conducted through the slower conducting myocardium. Accordingly, during normal sinus rhythm in the normal heart (i.e. without conduction abnormalities) electrical activation is relatively synchronous. Activation occurs earliest in the LV septal endocardium and latest in the epicardium of the LV lateral wall[76]. Although it may be assumed the mechanical activation proceeds in a similar sequence to the electrical activation, a more synchronous contraction than electrical activation occurs. This may be due to the difference in electromechanical delay between endocardium and epicardium (compensating for the electrical activation delay between the endo- and epicardium)[81]. Synchronous contraction is important for efficient pumping of blood out of the heart.

5.2 Clinical significance:

Disorders of the electrical conduction system of the heart are separated into different categories based on the location of the cellular damage. These include LBBB, which occurs in approximately one third of patients with HF due to (maladaptive) cardiac remodeling, which can affect the conduction system[84]. Cardiac remodeling commonly refers to persistent changes in the properties of myocardium in response to abnormal external stresses to the heart. The left intraventricular conduction system in LBBB is either blocked or delayed resulting in abnormal (slow) electrical activation within the LV due to slow conduction through the myocardium itself. In patients with LBBB, the RV is the first endocardial ventricular activation, and then spreads slowly to the left side of the septum (trans-septal conduction), followed by LV endocardial activation. Total LV endocardial activation time in patients with LBBB is much longer than in patients without conductions delays[87]. Longer QRS duration in LBBB has been related to electrical interventricular and LV intraventricular dyssynchrony, and is a recommended criterion for CRT due to CRT's mechanism of improving inter and intraventriular coordination.

Pathological AV conduction occurs in more than half of patients with HF[81]. When the normal physiologic, synchronous electrical activation is lost, a conduction delay and asynchronous activation pattern occurs. The conduction delay results from the electrical impulse being conducted through the myocardium, which has slower conduction properties than the specialized conduction system. Ventricular pacing alters the normal sequence of electrical activation. Asynchronous electrical activation also leads to asynchronous and dis-coordinate contraction. Not only is the onset of contraction different but also the normal pattern of contraction (regions of the ventricular wall are out of phase)[81]. Local differences in wall motion and deformation during asynchronous electrical activation are reflected in local differences in myocardial work. The asynchronous activation of the ventricles usually leads to inter- and intraventricular asynchrony.

5.3 Ventricular Dyssynchrony:

Normal cardiac contraction consists of synchronized contraction of the atria and then both ventricles. Electrical conduction is normally rapidly spread with excitation-contraction coupling being efficient in the ventricles[29]. Cardiac excitation-contraction coupling is the process where myocyte electrical depolarization activates coordinated movement of calcium in the cell to bring about contraction. Myocardial dysfunction and remodeling disturbs the normal electrical and mechanical functioning of the heart, often resulting in dyssynchrony, which results in further pumping dysfunction. Dyssynchrony is exhibited in many patients with HF, either in the mechanical form (pumping dysfunction), electrical (conduction disorder) or both. Mechanical ventricular dyssynchrony is a difference in timing of ventricular contractions. It can involve the right and left ventricles beating out of synchrony (interventricular dyssynchrony) or it can involve the LV alone, where the chamber does not contract as a unified whole (intraventricular dyssynchrony). In myocardial ischemia, impaired regional contractility and wall motion

abnormalities frequently produce mechanical dyssynchrony without disturbing electrical conduction[88]. Mechanical dyssynchrony is assessed with imaging techniques such as echocardiography, tissue Doppler or MRI[25].

In electrical dyssynchrony, abnormal conduction in damaged myocardium impairs the velocity and direction of electrical propagation. Abnormal ventricular depolarization, manifested as QRS prolongation, generates regions of both early and delayed ventricular contraction. [89]. The primary marker for LV electrical dyssynchrony is a QRS duration of 120 ms or greater and is an independent predictor of mortality in HF patients [88]

All forms of ventricular dyssynchrony impair the heart's ability to pump blood and lead to reduced cardiac output.

5.4 Mechano-Electric Coupling:

The heart is also intrinsically regulated, including feedback from its mechanical state to ion channel function, electrical conduction, and calcium–myofilament interactions. This essential aspect of intra-cardiac regulation, is known as Mechano-Electric Coupling (MEC)[90].

It is now established that mechanical stress/strain within the heart alters the electrophysiology and influences the behaviour of the electrical wavefronts in the heart during the cardiac cycle. Alteration in the volume within the cardiac chambers, the atria and ventricles alters the degree of stretch on the cardiac fibres. This has been shown to affect the timing of electrical recovery (i.e. repolarization) following activation in a wide variety of laboratory models and humans[90].

MEC is important in cardiac diseases (ie. contributing to the electrophysiological effects of non-uniform contraction). This stretch induced homogenization of repolarization may be an important intrinsic mechanism for protecting against repolarization heterogeneity across the heart.

With normal physiological activity in the normal heart, the effect of LV pressure on repolarization differs between early and late activated regions, leading to decreased dispersion of

repolarization. Whereas, in cardiac pathologies, where regional deformation of repolarization is altered in the ventricles, the temporal relation of local action potential phase to mechanical activity or ventricular pressure is shifted, leading to increased dispersion of repolarization. Focusing attention on MEC, not just the feed forward mechanism of cardiac excitation and contraction, stabilization of electrophysiological disturbances may occur. A decrease in the risk for ventricular tachyarrhythmias with CRT has been shown[91]. The electrical benefits of CRT (mechanically targeted therapy) may represent an improved temporal relation between local electrical activity, mechanical load, and contractile function[90]. Combined with emerging understanding of cardiac stretch activated channels as pharmacological targets, *mechanical* heart rhythm management is a potential area for MEC based anti-arrhythmic treatments with the target to normalize repolarization timing.

Effects of CRT:

In LBBB, activation spreads from the right bundle branch to the RV wall and after trans-septal conduction, activation spreads to the LV from the septum to the LV lateral wall[76]. Resynchronization of asynchronous hearts occurs when two activation wave fronts, originating from opposite walls, merge in the middle[6]. This can be achieved by stimulating the RV and LV wall almost simultaneously through biventricular pacing. The merging wave fronts of contraction during biventricular pacing have been observed in normal canine hearts using MRI[6].

This stimulation also improves the coordination of contraction. The more uniform distribution of cardiac contraction during CRT also leads to a higher efficiency of the entire LV.

The improved pump function that results reduces neurohormonal activation, evident by reduction in plasma BNP levels[6]. Furthermore, the improved contractility and pump efficiency reduces mechanical ventricular stretch. These two effects may explain the decrease of end-diastolic and end-systolic LV volumes over time (referred to as reverse remodeling). Such reverse remodeling

indicates a structural improvement in the myocardium. Yu et al.[92] showed the improved (increasing) reverse remodeling effect of resynchronization over time by measuring the time course of LV cavity volume and LV dP/dT during the first 3 months of CRT onset. As this study showed significant differences from baseline in reverse remodeling at the 3 month time period, this follow up time period was used in the PREDICT research study to investigate CRT reverse remodeling (response to CRT).

Chapter Six: **Predicting Resynchronization Efficacy via Direct and Indirect Cardiac Techniques (PREDICT)**

6.1 Introduction:

CRT, in addition to pharmacological therapy, is an important therapeutic option in select, drug refractory patients with congestive HF. CRT is recommended for patients with sinus rhythm, NYHA class II - IV, LVEF≤35%, QRS≥130 ms if LBBB and the absence of severe chronic kidney disease (creatinine < 200 mmol/L or GFR>30mL/min/m^2). A meta-analysis of 14 RCTs data illustrated the established benefit of CRT, concluding a greater likelihood of improvement by at least one NYHA class, with improvements in 6MWD and quality of life. RCTs have also shown that the addition of CRT to standard treatment not only improves symptoms, but also improvement in LV reverse remodeling[93]. CRT most importantly is associated with a reduced rate of hospitalization and all-cause mortality.

Despite many patients responding favourably to CRT, up to 30% of patients do not respond to the device therapy, irrespective of selecting candidates based on current guidelines. The main reasons attributed to non-response include improper patient selection, suboptimal lead placement and/or device programming. Several studies have investigated patient factors to help identify benefit to CRT over the past decade[94] . Age, sex, presence of atrial fibrillation, type of intraventricular conduction delay and certain co-morbidities have been associated with CRT response[2]. A number of other variables have been studied to determine additional predictors of resynchronization efficacy including echocardiographic measures of dyssynchrony[59], QRS morphology[31] and right bundle branch block[95]. Although, these measures do not show strong evidence to support their use in patient selection beyond current indications. Due to the invasiveness of the CRT procedure and high health care costs associated with implantation[48],

identifying appropriate candidates is crucial. A simple, non-invasive method to assess cardiac reserve would be highly beneficial to assist in predicting benefit to CRT. An augmentation in cardiac index after a 6 minute hall walk test, pre-CRT, has been shown to predict subsequent benefit to CRT[16]. Thus the utility of augmentation of hemodynamic measurements of cardiac performance with exercise (reflecting cardiac reserve) to improve prediction of responders to CRT was examined.

Several studies have revealed poor CRT response based on myocardial scar burden and pacing the LV lead in regions of scar[52,96,97]. This would limit resynchronization efficacy as tissue fibrosis may severely impair myocardial contractility and conduction properties[98,99]. An extension of this concept is that a positive response to CRT requires intact or viable myocardium, whether ischemic or non-ischemic heart disease is present. The stimulated cardiac tissue should be viable for proper conduction and myocardial contractility. Advanced fibrosis (infarcted myocardium) has been shown to affect CRT response and can be assessed prior to CRT implant via CMR, MUGA or echocardiography. But what about the remaining cardiac tissue? Prior studies have shown the detection of viable myocardium assessed by determining contractile reserve inherent to the myocardium is advantageous for optimal CRT function[100,69,101]. These studies used stress echocardiography (dobutamine[69,101] or bicycle exercise testing[100]) to demonstrate preserved contractile reserve was related to improved CRT benefit. Cardiac reserve can be evaluated by echocardiography or nuclear imaging when the heart is stressed, pharmacologically or by exercise. Although, this would be technically challenging in clinical practice, requiring the use of radiation (in the case of nuclear imaging) and involves costly resources. Cardiac reserve can also be measured by Swan-Ganz catheters and arterial lines, but they are invasive methods that would not be practical to routinely obtain.

6.2 Objective:

To assess if indirect measurements of cardiac reserve during exercise will improve prediction of clinical benefit and reverse remodeling two to six months post CRT.

Primary hypothesis: Indirect measurements of cardiac reserve with exercise will reliably predict response to CRT and thus can be used to select candidates for device therapy, in addition to current guidelines.

6.3 Methods:

The study design was a prospective, observational study. Fifty patients with NYHA class II to IV, LVEF$\leq$35% and wide QRS complex duration greater than 120 ms were prospectively enrolled between 2011 and 2014. Subjects were studied prior to CRT and at a follow up period (either three or six months post CRT). Functional class (based on NYHA and SAS class), B-type natriuretic peptide (pro-BNP), 6MWD, BP and echo measurements (including LVEF and LVESV) were assessed at each visit. Continuous BP measurements were obtained by photoplethysmography using the Nexfin device.

Clinical responders were pre-defined as survivors who had $\geq$ 1 improvement in NYHA or SAS class or a $\geq$ 25% increase in hall walk distance during the follow-up (3 or 6 months post-op) compared with the baseline values. The follow up period was pre-determined to allow sufficient time for LV remodeling. Favourable *LV reverse remodeling* was pre-defined as $\geq$ 15% relative reduction in LVESV or an absolute increased in LVEF of 0.05 at follow-up compared with baseline, as assessed by echocardiography.

6.3.1 Study protocol:

Pre-CRT (baseline) testing involved assessing hemodynamics parameters at rest and post exercise (6MWT). The same testing was performed at the follow up period, post CRT visit. See

Figure 7 for the summary of the study protocol. Enrollment, study testing, and analysis was completed by the graduate student and principal investigator with assistance from members of the research team. The study was approved by the University of Calgary Research Ethics Board.

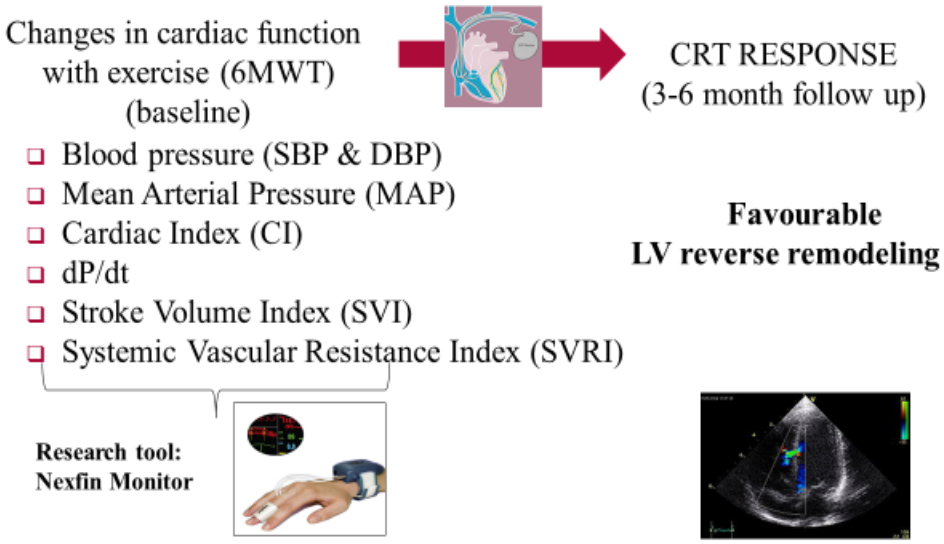


Figure 7: ***Summary of PREDICT Study Protocol***

6.3.2 Nexfin:

The Nexfin device (produced by the Netherlands company: BMEYE) non-invasively measures cardiac output and other hemodynamic parameters based on finger arterial pulse waveform analysis using an inflatable finger cuff with an embedded photoelectric plethysmograph. This is the Finapres methodology. Measures of systolic, diastolic and MAP are assessed on a beat-to beat basis, providing an estimate of cardiac output. The Nexfin monitor has been shown to provide accurate measurements[102]. The advantage of this technique is that it presents a portable method to record continuous measurements during rest and exercise.

The measurements obtained through Nexfin include:

- Heart rate (HR)
- Systolic blood pressure

- Diastolic blood pressure
- Mean arterial pressure (MAP)
- Cardiac Index (CI)
- dP/dt
- Stroke volume index (SVI)
- Stroke Volume Resistance Index (SVRI)

Continuous measurements were obtained on each patient by having the Nexfin wheeled beside the patient in a cart during the 6MWT. The device was monitored during the walk test to ensure proper functioning. 5 to 6 measurements were averaged pre and post 6MWT (exercise) to obtain a more accurate assessment of hemodynamic parameters for each study subject. These measurements were obtained while the patient was standing for both pre and post walk. If the patient was experiencing frequent premature ventricular complexes (PVCs), 8 to 10 measurements were used in the analysis.

6.3.3 6 Minute Walk Test:

The walking test was conducted in an enclosed corridor with the Nexfin monitor still hooked up to the patient. The corridor was not heavily transited and free of obstacles and distractions. It was divided into marked 1 meter sections to allow easy measurement of the distance walked. Patients were instructed to walk from one end of the hallway to the other end for six minutes, covering as much distance as possible. Patients were instructed to terminate the walk prior to six minutes if severe shortness of breath, muscular pain, dizziness or angina symptoms developed. The walk test will assess study subject's functional capacity (by determining their walk distance and symptomatic limitations), as well as test their cardiac reserve by stressing the heart. A treadmill or dobutamine stress test was not appropriate given these patients underwent CRT surgery within 24 hours of pre-implant PREDICT study testing. Pre- and post walk hemodynamic parameters (using the Nexfin device) were measured with the patient sitting down.

6.3.4 Study Population:

The study participants included patients with heart failure undergoing CRT implantation who consented to participate in the PREDICT study.

Inclusion Criteria:

1. Candidate for CRT based on current guidelines.
2. Adequate echocardiograph images to measure the LV end systolic and diastolic volumes.
3. Ability to undergo a 6MWT & mild to moderately limited by HF symptoms.
4. Ability to independently comprehend & complete the quality of life questionnaires.
5. Intact AV conduction.
6. Stable atrial rhythm (i.e. no history of chronic atrial fibrillation as the benefit of CRT in this population is variable).
7. Able and willing to comply with the required follow-up schedule.

Exclusion Criteria:

1. Unable or unwilling to provide informed consent.
2. Medical condition other than heart failure likely to cause death within 6 months.
3. Cardiac transplant planned within 4 months.

6.3.5 Cardiac Reserve:

The traditional definition of cardiac reserve is calculated as the cardiac output during stress minus cardiac output at rest. Cardiac reserve will be assessed non-invasively through hemodynamic measurements of cardiac performance during exercise (6MWT). Cardiac reserve will be determined by the difference in hemodynamic parameters (CO, SV, PP) pre and post walk test.

6.3.6 Echocardiography:

Echo measurements were completed in the core lab by a qualified technician and analyzed by the principle investigator and graduate student. Biplane LVESV and LVESD were calculated from apical two and four-chamber views. As per clinical practice, contrast was used when required. Basic data (volumes, valvular assessment and tissue Doppler) was collected on all patients. In a multivariate analysis, among a number of clinical and echocardiographic parameters, only a reduction in LVESV was an independent predictor of all-cause or cardiovascular mortality. As such, LVESV reduction (i.e. reverse remodeling) is the primary outcome used to assess CRT response.

6.3.7 Statistical analysis:

Continuous variables were expressed as mean ± SD. Categorical data were summarized as frequencies and percentages. Differences in baseline characteristics between responders and non-responders were analyzed using unpaired Student t tests (continuous variables) and Fisher exact tests (dichotomous variables) as appropriate. Adjusted odds ratios (ORs) with their corresponding 95% Cis were reported. For all tests, *p* less than 0.05 was considered statistically significant.

6.4 Results:

Table 3: **Baseline Characteristics and Stratified based on Favourable Reverse Remodeling**

Augmentation in Hemodynamic Parameters with Exercise (6MWT)	Overall Baseline Value (n=47)	CRT Response (LV reverse remodeling) n=32	CRT Non-Response (no LV reverse remodeling) n=15	*P* value
Age, mean	64 ± 9	69 (± 2)	67 (± 4)	0.608
Gender: n (%) Male Female	 38 (87) 6 (13)	 17 (69%) 12 (31%)	 15 (92%) 1 (8%)	 0.018
Ischemic HF, n (%) Non-Ischemic HF, n (%)	19 (42) 26 (58)	9 (31%) 20 (69%)	11 (67%) 5 (33%)	0.069
NYHA class:n(%) II III IV	 8 (18) 30 (67) 7 (16)	 7 (24%) 22 (76%) 0 (0%)	 6 (33%) 9 (59%) 1 (8%)	0.273
QRS duration (ms)	159 ±29	165 (± 10)	146 (± 10)	0.186
6 Minute Walk Test (6MWT)	315 (±10)	296 (± 28)	344 (± 30)	0.258
Baseline NT-BNP	6.87(±0.36)	6.86 (±0.37)	6.93 (±0.37)	0.901
LVEDV (mL)	221 (± 23)	208 (±26)	250 (±19)	0.235
LVESV (mL)	163 ± 72	157(±24)	182 (±16)	0.419
LVEF (%)	27.1± 6	27.0 (±2)	27.4 (±2)	0.899
Δ PP	12.0 (±2.7)	14.9 (±3.2)	5.9 (±4.4)	0.115
Increase in PP (≥ 5 mm Hg)	73%	84%	50%	0.018
Δ SVI	3.12 (±1.9)	1.40 (±1.9)	6.77 (±4.3)	0.187
Δ SVRI	-225 (±214)	113 (±268)	-946 (±277)	0.019
Δ MAP	12.4 (±2.8)	16.4 (±3.0)	3.9 (±5.3)	0.035
Δ dp/dt	426 (±90)	330 (±92)	631 (±200)	0.122
Δ CI	0.94 (±0.14)	0.85 (±0.15)	1.13 (±0.29)	0.344

Table 4: Hemodynamic Parameters Stratified based on Clinical Response (NYHA)

Augmentation in Hemodynamic Parameters with Exercise (6MWT)	CRT Clinical Response (improvement by ≥ 1 NYHA class) n=31	No CRT Clinical Response (no improvement in NYHA class) n=16	*p* value
Δ PP	12.7 (± 2.5)	10.8 (± 6.3)	0.736
Increase in PP (≥ 5 mm Hg)	78%	63%	0.310
Δ SVI	1.54 (± 2.2)	6.19 (±3.4)	0.246
Δ SVRI	43.2 (± 238)	-744 (± 405)	0.080
Δ MAP	15.5 (± 3.4)	6.38 (± 4.4)	0.119
Δ dp/dt	499 (± 96)	285 (± 189)	0.266
Δ CI	0.77 (± 0.2)	1.28 (± 0.2)	0.334

Table 5: Hemodynamic Parameters Stratified based on Clinical Response (SAS)

Augmentation in Hemodynamic Parameters with Exercise (6MWT)	CRT Clinical Response (improvement by ≥ 1 SAS class) n=29	No CRT Clinical Response (no improvement in SAS class) n=18	*p* value
Δ PP	11.2 (± 2.1)	13.3 (± 6.2)	0.715
Increase in PP (≥ 5 mm Hg)	79%	63%	0.321
Δ SVI	2.12 (± 2.4)	4.72 (±3.2)	0.509
Δ SVRI	-127 (± 249)	-382 (± 393)	0.567
Δ MAP	10.3 (± 3.1)	15.9 (± 5.3)	0.332
Δ dp/dt	425 (± 83)	428 (± 198)	0.986
Δ CI	0.78 (± 0.2)	1.21 (± 0.2)	0.124

Table 6: Diagnostic accuracy (Pulse Pressure and LV remodeling)

	% (CI)
Sensitivity	88% (61.7-98.4)
Specificity	50% (21.1 – 78.9)
Positive Predictive Value (PPV)	70% (45.7 – 88.1)
Negative Predictive Value (NPV)	75% (34.9-96.8)

The 68% with favourable LV remodeling had a median change in pulse pressure post 6MWT of 14.9 mmHg while those without remodeling had a 5.90 mmHg change (p = 0.115). The 68% of patients with LV remodeling were more likely to have a $\geq$ 5mm Hg increase in pulse pressure (84%). A 5mm Hg or larger augmentation of pulse pressure post exercise categorized patients who went on to have favorable LV remodeling with an accuracy of 88% (negative predictive value of 75%). There was a significant increase in SVRI in remodelers (113 dyn*s/cm*m^2) with exercise versus non-remodelers (-946 dyn*s/cm*m^2) as well. There was also a significant augmentation in MAP with exercise in remodelers as well (16.4 mmHg versus 3.9 mm Hg). Augmentation in pulse pressure was associated with a 3.1 fold (p=0.044) higher odds of response to CRT, adjusted for age, sex and ischemic etiology. CI, SVI and dp/dt did not show a significant change in responders versus non-responders.

6.5 Discussion:

Assessing cardiac reserve may be a useful factor to predict CRT response. The arterial pulse pressure can give rapid and useful information about cardiac output. Muscular exercise significantly stresses the cardiovascular system. During exercise, two factors need to cooperate to augment cardiac performance: increased venous return and sympathetic nerve tone together with reciprocal reduced vagal activity. Increased venous return acts by way of the Frank-Starling mechanism with greater diastolic filling contributing to more vigorous systolic contraction. Enhanced sympathetic nerve activity, not only causes acceleration of the heart (rate) but also increased myocardial contractility. The power of contraction is augmented and contraction is more rapid, which shortens the systole period to allow for an important increased duration of diastole filling. As a result of these various adjustments, the extent of cardiac performance can be

adjusted with exercise. A capacity to augment myocardial performance would be required based on the mechanism of CRT. CRT provides electrical-mechanical stimulation, but assessing that the heart be able to cope (based on reserve) is vital.

An augmentation of pulse pressure reflecting cardiac reserve was significantly associated to CRT response. As well, since SVRI and MAP significantly increased in responders versus non-responders, this may shed light further into the mechanism of CRT, in that CRT may benefit patients by affecting systemic resistance rather than contractility.

6.6 Limitations:

The cut off point for remodeling has yet to be determined. The follow up period may not have been enough time to assess remodeling or clinical benefit. As such, those defined as non-responders may have had *delayed* response to CRT. As well, pulse pressure approximates cardiac output. It is affected by several patient factors including rate of systolic ejection, as well as the caliber and dispensability of peripheral arteries. Finally, the Nexfin device's precision to measure CI, SVI, SVRI and dp/dt have been validated in small studies, but not in this studied specific patient population (advanced HF patients), and the accuracy of this device may not be generalizable to this population. The accuracy of the blood pressure measurements was validated by recording multiple measurements per patient for the initial 10 patients and comparing it manual and automatic BP recordings.

6.7 Conclusion:

Measuring the change in pulse pressure after a 6-MWT may provide a simple and reliable method of predicting benefit from CRT. From the MADIT-CRT trial, a response score based on seven factors associated with reduction in LVEDV one year after CRT-D implantation included:

female sex, nonischemic origin, LBBB, QRS≥ 150 ms, prior hospitalization for HF, LVEDV≥ 125 mL/m^2 and LA volume <40 mL/m^2. The response score was found to correlate with 13 percent increase in clinical benefit per one point increment in the response score (with CRT-D versus defibrillator). The current investigation of cardiac reserve highlights the utility of another factor associated with reduction in echocardiographic response and would be useful to incorporate as an additional factor in patient selection for CRT. The data also highlights that the mechanism of CRT may lie in affecting the systemic vascular resistance and requires further research to investigate this area. Also noted from this study is the variability of response to CRT, emphasizing careful, individualized assessment of CRT appropriateness, based on current guidelines, quality evidence of factors associated with favourable response and clinical judgment.

Chapter Seven: **Voltage Output from the Left Ventricle To Assess Gradient and Estimate Scar (VOLTAGES)**

7.1 Introduction:

CRT reduces both morbidity and mortality in select patients with HF who despite optimal medical therapy remain symptomatic with LV dysfunction. However, a significant proportion of patients fail to achieve benefit from CRT. The position of the LV lead is an important factor in achieving response to CRT[12]. Optimizing implantation of the LV pacing site includes consideration of scar burden, individual venous anatomy and pacing parameters. Despite the utility of CRT, approximately one third of patients do not respond to this intervention. Thus optimizing response is needed.

7.2 Implantation of the LV Lead:

The LV lead is often the most challenging lead to place[25]. A successful implant has been shown to involve the placement of the LV lead in a postero-lateral or lateral coronary vein with good lead stability, adequate pacing thresholds and without phrenic nerve stimulation[103]. The left phrenic nerve is located along the lateral wall of the heart and stimulation causes diaphragmatic contraction, wherein the lead would require repositioning. Even with the LV lead positioned at the lateral/posterolateral wall, optimal placement varies between patients due anatomic variation in coronary venous anatomy, differences in underlying heart disease and site of maximal electrical/mechanical delay[104]. Identifying an optimal pacing site is challenging and should be patient specific taking into consideration evidence-based optimal LV lead locations[105], individual patient anatomy, pacing parameters (i.e. timing the delays between the RV and LV activation so

the paced wavefronts meet near the ventricular septum[25]), maximizing RV and LV lead distances, and scar burden.

7.3 Scar Burden and Placement:

LV lead placement in the presence of scar affects LV pacing and limits benefit from CRT. Finding a site that is free of scar appears to be essential for effective CRT delivery[106].

Contrast enhanced CMR reliably identifies location and extent of scar, which can assist in guiding LV lead placement. Patients with greater scar burden are less likely to show a clinical response to CRT[107]. Even presence of scar in the posterior-lateral LV position, a region typically targeted for LV lead placement, also has been shown to reduce rates of clinical response and reverse remodeling[107]. Despite these findings that an LV lead with the tip in an area of scar is less likely to effectively pace the LV[108], pre-implant CMR is not a practical option given the expense, and inability to perform in patients with an existing ICD or pacemaker.

The purpose of this study is to determine if a simple ECG measure (voltage gradient) can be used to identify an LV pacing site that is free of significant transmural scar. Pacing the LV in scarred myocardium may result in less effective LV pacing and, as a consequence, failure of LV resynchronization and lack of response to CRT[69].

7.4 Study Hypotheses:

The first hypothesis is that the electrical pulse measured on the skin surface will be similar to that delivered by the LV pacing lead in regions without scar (i.e. no electrical gradient), while the electrical pulse measured on the skin surface will be smaller to that delivered by the LV pacing lead in regions with scar (i.e. large electrical gradient).This concept is summarized below.

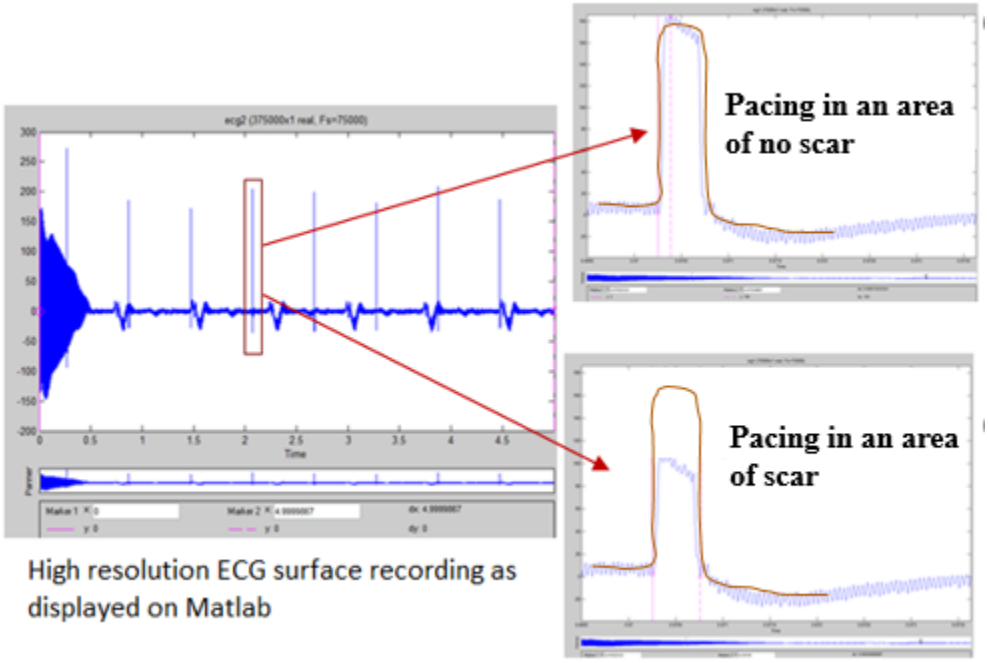


Figure 8: ***Voltage gradient in areas of scar versus no scar in the left ventricle:*** *The pacing parameters (represented by the orange line) set by the implanter compared to the pacing output in Matlab (represented by the blue line). In a region of no scar, we hypothesize the pacing output will have the same amplitude as the input set by the implanter. In regions of no scar, we hypothesize the pacing output will have a reduced amplitude.*

Clinical Implication: If the *voltage gradient to identify scar hypothesis* is shown to be true, then assessment of the voltage gradient will provide a simple, practical method of identifying more optimal LV pacing sites intra-operatively, with a resultant increase in the likelihood of response to CRT.

The second aim of the study is to detect loss of biventricular capture. We hypothesize that a HR ECG can be used to detect failure of biventricular capture, through individual identification of pacing stimuli from the RV and LV versus immediate versus delayed capture of the myocardium. This concept is summarized in **Figure 9.**

LV lead dislodgement is a common complication of CRT[72], occurring approximately 5% of the time[73]. Most LV leads rely on bends or cants in the lead body for stability within the CS[7], resulting in a higher rate of lead dislodgement as compared with standard pacing leads used in the RA and RV. Since pacing from the LV and RV are often simultaneous, or nearly so, it can be difficult to diagnose LV lead non-capture related to LV lead dislodgement. Thus, a specialized programmer and highly trained personnel are required to assess the CRT system. A reliable, simple and widely available method to diagnose non-capture would be of great clinical value.

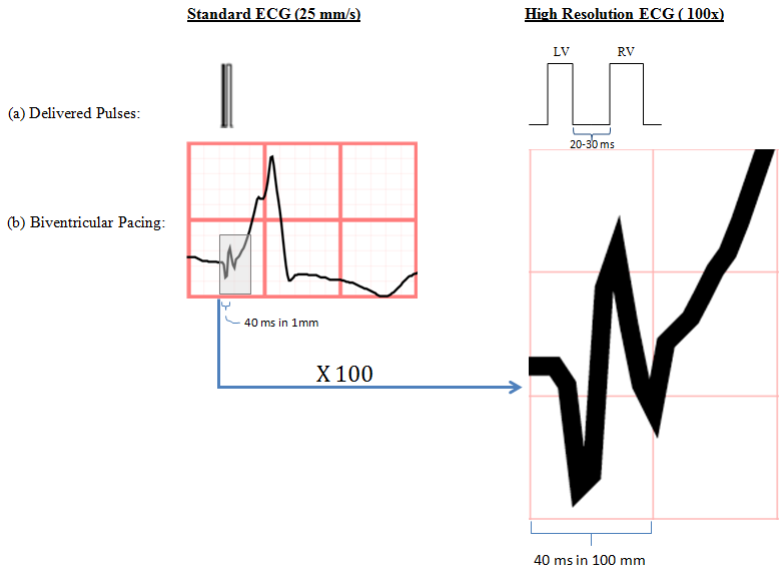


Figure 9: ***Standard versus HR ECG tracings in CRT (biventricular) pacing***

Clinical implication: If the *detecting loss of biventricular capture hypothesis* is shown to be true, then patients can be diagnosed more easily and efficiently of LV lead dislodgement and non-capture.

The wide availability of a 12-lead ECG makes it an appealing screening tool and may be used to evaluate the burden of myocardial scar and biventricular capture. The aims of this study

are to investigate the utility of a new HR ECG system (GE Medical) to identify myocardial scar and LV lead non-capture.

The specific questions are:

a) For a given (known) pacing stimulus, does the amplitude and duration of the recorded pacing spike on the surface ECG correlate with the amount of local scar as measured using CMR?

b) Can a HR ECG be used for detection of LV lead dislodgement (non-capture)?

7.5 Methods:

To investigate our hypotheses, a HR ECG will be used to measure the surface voltage recordings at a frequency of 75 000 Hz compared to the standard ECG of 2 000 Hz during CRT implantation. This will provide more detailed information on the electrical potentials generated by the heart as the electrical signals are recorded at a higher rate.

7.5.1 Patients and study protocol-

A cohort of 20 patients with ischemic heart disease scheduled for CRT implantation from 2012 to 2014 were prospectively enrolled in this observational study. Selection for CRT device implantation were based on current standard guideline criteria, including advanced HF (NYHA class II-IV), EF< 35% and QRS duration $\geq$120 ms.

7.5.2 Study subjects:

A group of 20 patients met the eligibility criteria and were enrolled in the study. 2 patients were later removed from analysis due to protocol deviations (LV lead unable to be placed in one study

subject and unable to obtain data in second patient). The study was approved by the University of Calgary Research Ethics Board.

INCLUSION CRITERIA:

(a) HF due to ischemic heart disease.

(b) Appropriate candidate for CRT device therapy, including symptomatic, drug-refractory HF (NYHA class II to IV), QRS duration ≥120 ms, and LVEF ≤ 0.35.

(c) Prior CMR for scar assessment.

(d) Ability to independently comprehend the study.

(e) Able and willing to comply with the required follow-up schedule.

(f) Males or females of any age group.

Exclusion Criteria:

(a) Unable or unwilling to provide informed consent.

(b) Inability to place the RV and LV lead.

(c) Patient has had a large intercurrent MI or an episode of myocarditis since initial defibrillator implant and previous CMR.

7.5.3 CMR Assessment Pre-CRT-

Each patient received a CMR pre-CRT to determine the extent and location of scar burden. CMR reports were prepared by experienced radiologists blinded to all other data. Infarcted myocardial tissue was defined as transmural with ≥ 50% hyper-enhancement of the LV wall thickness, otherwise it was defined as non-transmural. A standard 17 segment model was used to identify

areas of scar tissue of the LV (see figure 10 below). Scoring was appointed as 0=absence of hyperenhancement (ie no scar), 1=hyperenhancement of 1-50% of LV wall thickness (non-transmural scar), 2= hyperenhancement of ≥50% (transmural scar).

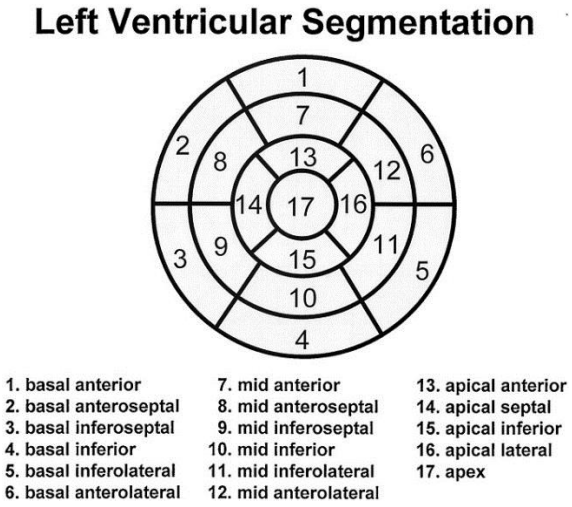


Figure 10: 17 segment LV model

7.5.4 High resolution ECG data acquisition and analysis-

ECG sampling with the HR system was conducted on each study participant during CRT implant to compare voltage input (delivered energy from the LV lead) and surface output (voltage recording from the ECG). Clinically relevant voltage inputs (2.0 to 4.0 volts) were used with a pacing duration between 0.4-0.8ms. The sampling was attempted in at least three different LV locations to assess areas of scar and viable tissue. Areas to evaluate capture included:

1) main body, 2) anterior / great cardiac vein, 3) middle cardiac/ inferior vein and 4) lateral or posterior-lateral vein (figure 11).

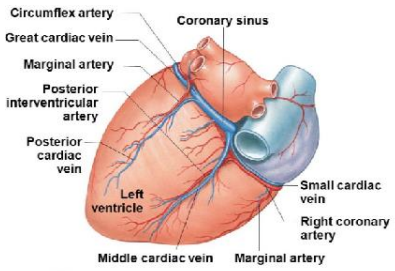


Figure 11: Coronary Veins draining the Heart

The ECG voltage gradients (difference in input and output of the LV pacing spike voltage amplitude) in areas of scar and non-scar were compared to elucidate any correlations of ECG measurements to scar burden. Delivered energy from the LV lead (voltage and duration of the pacing spike) versus surface measured energy at various pacing sites with versus without scar will be compared. Analyses was performed blinded to all clinical and CMR data. Data collection included the developed Grigori software from GE, and was analyzed using Matlab software to open the HR ECG data and measure the voltage gradients of the pacing spike.

7.5.5 Statistical Analysis-

Voltage recordings from the HR ECG were measured using the Matlab software. The amplitude of the LV pacing spike was measured (in Volts, V) and the average from the ECG leads was used. Since each lead of the ECG "sees" a different area of activity of the heart, assessment of voltage gradient in areas of scar/non-scar had to be measured using an average of all leads, such that a confounding variable of voltage differences based on ECG lead location to scar was minimized. As well, since voltage gradients vary by patient, absolute value analysis was restricted to intra-patient comparison.

Figure 12 depicts the HR ECG surface recording from one location of the LV in a study subject, where the LV lead pacing parameters were 5V for 0.4ms. Whether pacing produced capture of

the myocardium was determined, and the amplitude and duration of the pacing spike were measured in Matlab.

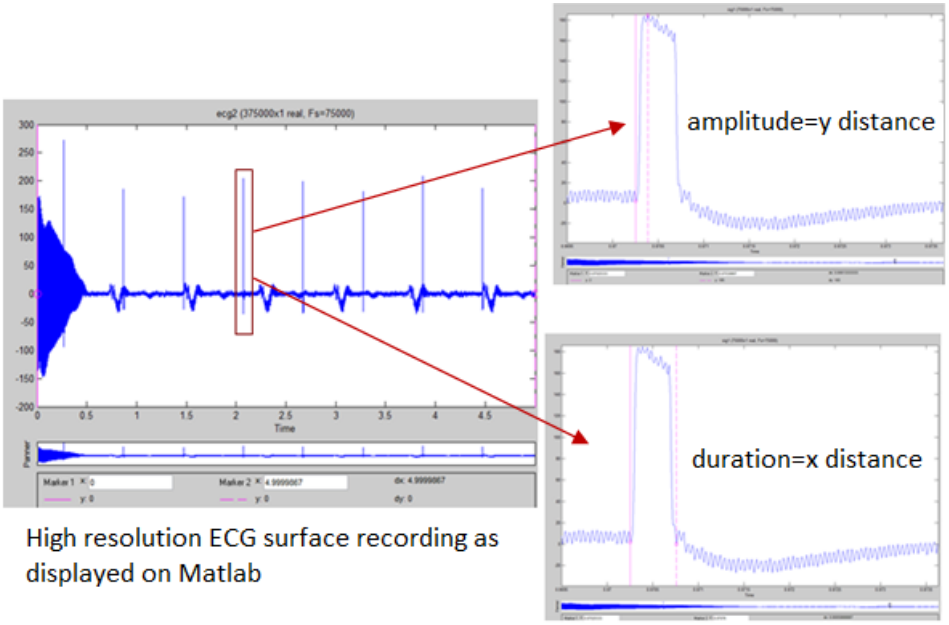


Figure 12: ***Non-capture in one location of the LV. The surface pacing spike amplitude and duration were measured in Matlab and compared to the input parameters in areas of scar and non-scar.***

The average voltage gradient in regions with and without scar was compared with each patient and using a paired t-test. All p-values < 0.05 will be considered significant. The ability of the HR ECG to detect LV non-capture was evaluated using standard diagnostic test parameters (sensitivity, specificity, accuracy). Statistical analyses was performed within the lab by the graduate student and principal investigator.

7.6 Results:

Baseline characteristics are listed in Table 7. Device implantation was successful in all patients, except 1 and one patient was withdrawn from the study due to a protocol deviation. One patient died within a year.

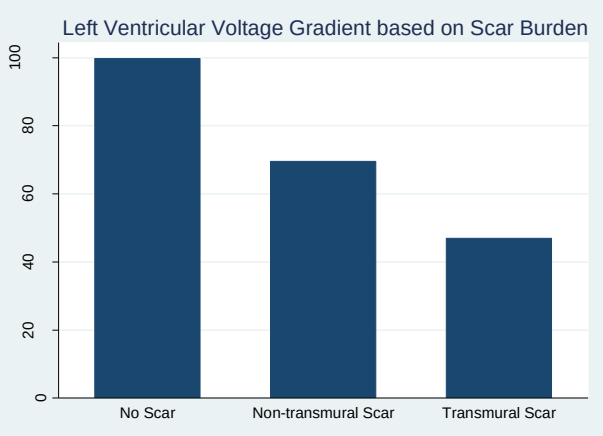
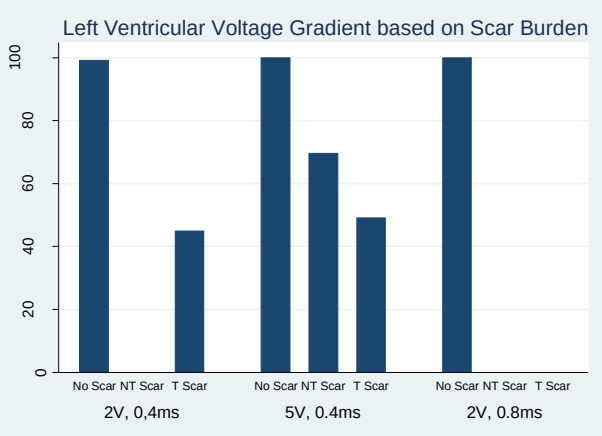
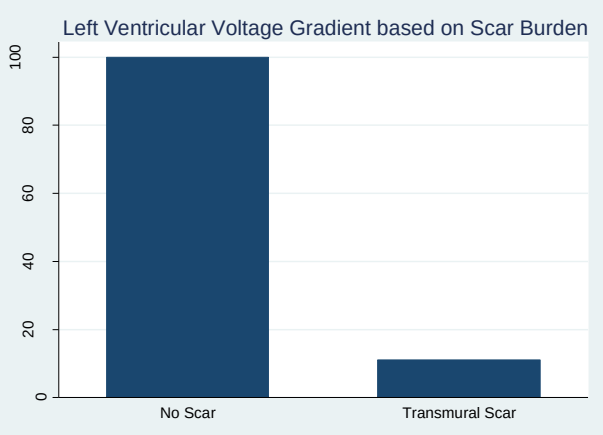
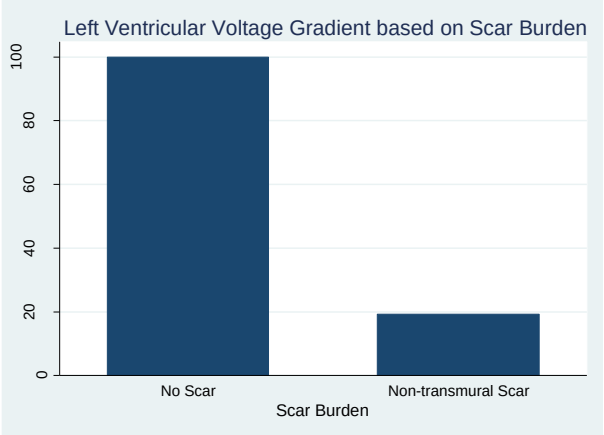
Table 7: Patient Characteristics

Variable	Patients (n=20)
Age (yrs)	74
Male/Female	17 (94%)/ 1(6%)[1]
NYHA class	II: 12 (67%); III: 6 (33%)
QRS duration (ms)	174.8
LBBB (% of subjects)	100
LV ejection fraction (%)	22.8
LV end-systolic volume (ml)	264.8
LV end-diastolic volume (ml)	338.6

1. Two Protocol Deviations, thus total of 18.

Voltage gradients were calculated based on the HR ECG surface voltage recordings at specific LV pacing parameters. Since ECG voltage recordings vary by patient, recordings were standardized to percentages of maximum amplitudes per patient and then compared based on scar burden within each patient and all study subjects (see Table 8 and 9).

Table 8: Examples of Intra-patient Variations in Voltage Gradients based on Presence of LV Scar

STUDY PATIENT	Voltage Gradients based on Presence of Scar	Voltage Gradients based on Presence of Scar and Pacing Parameters
1		
6, 9	 **(study subject #6)**	 **(study subject #9)**

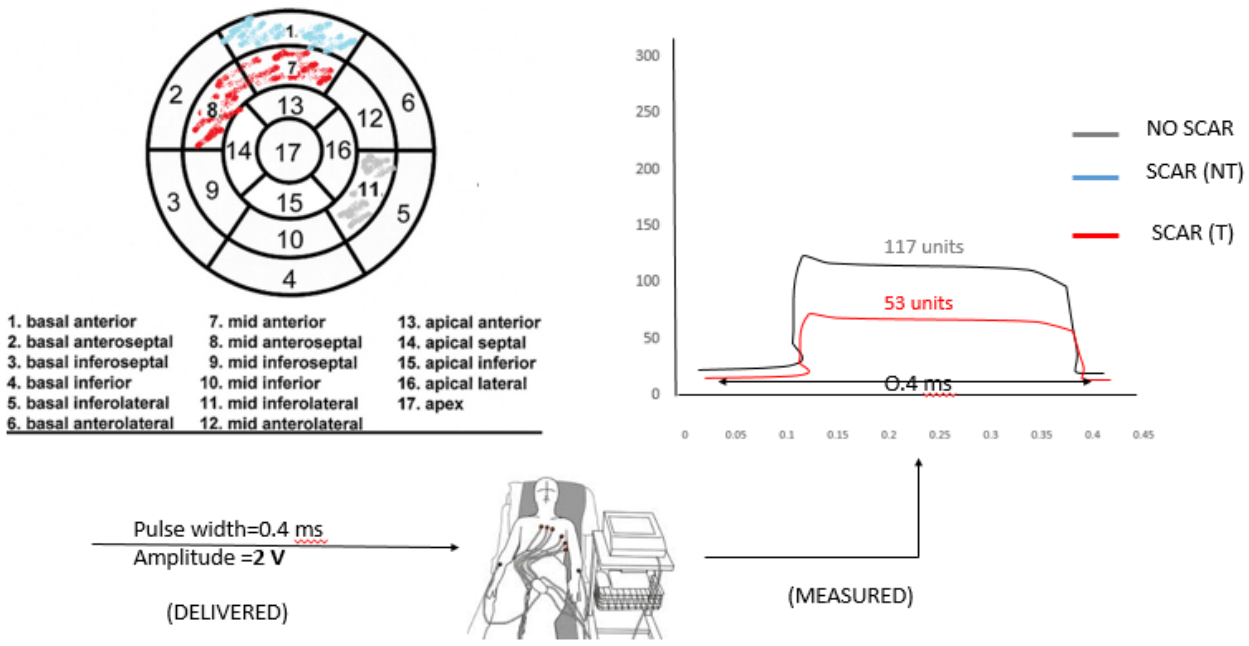


Figure 13: *Depiction of Change in Voltage Gradient in an Individual Patient based on Scar (voltage duration was consistently the same, only amplitude changed in different regions)*

Table 9: **T-test of the Relationship of Voltage Gradient and Regions of Scar**

	Median (IQR) of Voltage Gradient (% of max amplitude)	**95% Confidence Interval (CI)**	***P* value**
Scar*	67 (34, 92)	43 - 78	< 0.02
No Scar	100 (72, 100)	71 - 99	Reference

* Scar = transmural or non-transmural

Analysis of the pacing spike from the HR ECG did not reveal distinction of separate RV and LV pacing amplitudes to identify non-capture/LV dislodgement. There was a pattern of negative polarity of the pacing spike amplitude, which was associated with non-capture. The sensitivity and specificity were calculated using Stata, and reported in Table 10. Different modes of pacing were used (integrative bipolar, unipolar, true bipolar), which affected the polarity. As such, only true bipolar measurements were used to minimize confounding results.

Table 10: **LV Capture Testing based on Polarity of Pacing Amplitude**

Detection of Non-Capture based on the Polarity of the Pacing Amplitude*	**%**	**95% Confidence Interval (CI)**
Sensitivity	92	64-99
Specificity	47	33-77

*Identification of LV myocardial non-capture based on a negative polarity amplitude with LV pacing mode of true bipolar.

Discussion:

Voltage data collection during CRT implantation can help assess CRT function and assist in intra- operative modifications for optimal lead placement and thus device effectiveness. ECG analysis should be done during implantation for instant verification of proper ventricular capture. A HR ECG may be used to assess areas of scar, which should be avoided for LV lead placement, as it is found to produce a diminished CRT response[109]. Large multicenter studies have shown that lateral or posterolateral LV lead positions result in better outcomes (morbidity and mortality) with apical positions associated with worst outcomes[104]. Although even the preferred LV lead sites are sub-optimal when they consist of areas of scar [109], with reported reduced rates of clinical

response and reverse remodelling[60]. Thus attention should be placed on identifying areas of LV scar for optimal lead placement.

A surface ECG measures electrical activity between 2 poles on the body. The pathway of energy traveling through the heart (or vector) varies depending on whether the heart is unpaced or paced (RV, LV or biventricularly). In an unpaced, normal heart, the main depolarization vector moves from atrium down to the ventricles. This gives a positive R wave in lead I, where lead I depicts mostly right sided activity. CRT devices, and other cardiac devices, provides electrical stimulation to the heart that travels in a specific direction. CRT or biventricular pacing creates a main vector that originates midway from the RV and LV regions and travels upwards. This affects ECG morphology, resulting in an isoelectric/negative R wave (in lead I). The electrical energy gets translated to the ECG tracing depending on the depolarization front (i.e. the energy of the waveform) moving towards the positive pole (positive inflection) or away from the positive pole (negative deflection). As such, capture assessment can be determined from the morphology changes of the QRS. Briefly, a step down approach can be used to determine the threshold for capture where pulse amplitude and duration are programmed (usually for each ventricle separately) and gradually degradation of the voltage until capture is lost, which identifies the capture threshold. In a unipolar LV lead, the lead paces by forming an electrical circuit from LV tip to RV ring or coil (depending on the device and type of lead). During step-down capture testing of a tied output CRT device, the premise is similar in that the transition, with degradation of voltage, will identify capture loss with significant changes in morphology of QRS reflecting a transition from biventricular to single chamber ventricular pacing (i.e. biventricular to RV or LV pacing only, depending on which ventricle's capture threshold is reached first). This requires proper ECG analysis and ability to interpret the (changes in) morphology patterns in a timely

manner. A quick, simple method of identifying non-capture (or lead dislodgement) would thus be useful to identify non-capture and possible lead dislodgement.

7.6.1 High Resolution ECG to Identify Scar-

The results of this study demonstrate a consistent correlation of LV scar tissue with voltage gradient (table 9). In areas of non-transmural and transmural scar, the surface voltage recorded on the high resolution is much more dampened (from the pacing delivered voltage) than non-scar regions. Furthermore, regions with similar scar burden (no scar, non-transmural or transmural scar based on hyperenhancement from CMR pre-CRT) with the same pacing parameters in individual study patients, have statistically similar surface recordings. These results could be due to scarred, dysfunctional myocardial tissue that exhibits delayed conduction around the LV pacing site, which affects transmission of the voltage signal along necrotic/damaged myocytes. Presence of scar in the posterior–lateral LV, the region typically targeted for LV lead placement, was shown to reduce rates of clinical response and reverse remodelling of the LV in several trials[52]. An LV lead with its tip in such an area of scar is less likely to effectively pace the LV. Despite these findings, pre-implant contrast enhanced CMR remains uncommon practice due to the expense and the inability to perform this test on patients with an existing pacemaker/defibrillator. As such, the results of this pilot study which correlate higher voltage gradient with scar tissue presence warrant exploring further using a HR ECG intra-operatively to identify optimal placement of the LV lead.

7.6.2 High Resolution ECG to Detect Non-capture-

Interestingly, similar capture rates were found in regions of non-scar and scar. Ypenburg et al found similar sensing and pacing thresholds in both patients with and without scar, suggesting

that ineffectual CRT in patients with scar underlying the lead tip may not be due to complete lack of ability to stimulate the myocardium [110]. It may be that the electrical stimulation is not translated *as effectively* to mechanical stimulation of the ventricles which causes non-response. As well, it has been shown the dP/dt is reduced when the LV is paced in an area of scar[111] . The relationship between electrical and mechanical stimulation of the LV may be related to areas of slow conduction that are likely to exist in regions of scar, which will affect the timing and contraction of mechanical activation of the paced myocardial segment. It is possible that delivery of pacing to an area of scarred myocardium will result in delayed propagation of contraction throughout the LV with resulting limited ventricular performance.

LV non-capture is one of the causes of CRT nonresponse. The secondary observation of this study was that there was a difference in polarity in the surface recording (amplitude) in regions of capture versus non-capture. When the LV pacing lead was unable to capture the myocardium, the surface pacing amplitude was often negative polarity. The sensitivity for this relationship was high at 92.3%, but the specificity was weak. A confounding factor was that the mode of LV pacing was not consistently reported; as such, the pacing mode may not have been always true bipolar and thus may have affected the results.

The polarity change with non-capture could be due to similar reasons the QRS waveform exhibits differentiating polarity with RV, LV or biventricular pacing. Non-capture or LV dislodgement results in either RV or loss of biventricular pacing, which changes the direction of the waveform, therein changing the direction of polarity. This may be more apparent with the HR ECG due to the sampling frequency. Further testing, ensuring the same mode of LV pacing, is warranted.

7.7 Conclusion:

Using a HR ECG is quite promising as a means to increase CRT response rates and this technique requires further study. Impaired myocardium, such as scarred tissue, impedes the electrical/mechanical conduction, that may be producing the decreased surface voltage recording. This concept can be used to identify regions of non-viable myocardium, to avoid these regions when placing the LV lead. As well, the HR ECG was able to show differential polarity based on capture that should be explored further, as it may be used to easily determine non-capture or LV dislodgement. In addition to identifying and avoiding regions of scar, other factors that need to be considered for optimal pacing include: evidence supporting posterolateral and lateral positions, regions of maximal delay, electrical dyssynchrony and programming parameters (rate, mode, and AV delay).

7.8 **Future direction:**

Given the QRS complex of a surface ECG is characteristic of depolarization (ventricular contraction) from the electrical energy of a pacing output in cardiac devices, the QRS morphology could also be used to assess scar. This is based on the postulation electrical energy would take longer to radiate out across the ventricles in scarred regions with resultant wider QRS complex. This could assist optimizing lead placement and is a potential future direction with the HR ECG. As well, since the HR ECG is able to provide more detailed information about the pacing spike and QRS morphology (how positive or negative it is), the relative change in morphology of paced activity between visits can provide useful information of changes in device performance (lead dislodgement/other potential problems).

Chapter Eight: **Reverse Remodeling and the Relationship to Survival in Adult Heart Failure Patients Who Have Undergone Cardiac Resynchronization Therapy:** ***A Systematic Review and Meta-analysis***

8.1 Abstract:

Importance: CRT is associated with reduced morbidity and mortality among HF patients, echocardiographic response to CRT has yet to be reported in a meta-analysis.

Objective: To summarize the current literature on echocardiographic response to CRT and explore the relationship between echocardiographic response and clinical response to CRT.

Evidence Review: We searched electronic databases (MEDLINE, EMBASE, PubMed, CENTRAL, Web of Science, and the Cochrane Database from 1950 until Oct 10, 2013) and included articles bibliographies for RCTs reporting on echocardiographic response to CRT among HF patients. Echocardiographic response to CRT was summarized using a random effects meta-analysis.

Findings: Among 8232 citations identified, 16 studies enrolling 2714 patients were included. Echocardiographic response to CRT was quantified using changes in LVEF and LVESV in the CRT groups relative to the control groups. Patients who underwent CRT had an absolute pooled increase in LVEF of 3.44% [12, studies, 95% confidence interval (CI) -1.24 to 8.12, I^2 100.0%, p-value <0.001] and an absolute pooled reduction in LVESV of 15.82 ml (10 studies, 95%CI 6.71 to 24.93, I^2 99.3%, p-value <0.001) compared to patients who did not receive CRT. Using meta-regression there was a positive association between the percentage of patients with ischemic heart disease (IHD) in the study and the magnitude of increase in LVEF and LVESV (LVEF b_1 0.15, 95%CI 0.02 to 0.27, p-value 0.029; LVESV b_1 0.47, 95%CI -0.01 to 0.95, p-value 0.054). The pooled risk ratio of death was found to be 0.71 (7 studies, 95%CI 0.52 to 0.97, I^2 19.3%, p-

value 0.283). Using meta-regression greater magnitudes of increase in LVEF and reduction in LVESV were both shown to be associated with decreased risk of death (LVEF b_1 -0.07, 95%CI -0.17 to 0.02, p-value 0.098; LVESV b_1 -0.03, 95%CI -0.08 to 0.02, p-value 0.139).

Conclusions and Relevance: CRT appears to produce an increase in LVEF and a decrease in LVESV in HF patients; It appears the greater magnitudes of increase in LVEF and reduction in LVESV are associated with lower risk of death and these echocardiographic changes could be used as surrogate markers of better clinical outcome.

8.2 Introduction

HF is an important health care issue, affecting an estimated 500,000 Canadians, with 50,000 new patients diagnosed each year.[1] Although there have been many advances in the treatment of HF, there remain many patients who, despite optimal medical management, have severe symptoms and an overall poor prognosis.[2] CRT is designed to pace both the right and left ventricles simultaneously for improved pumping efficiency and thus improved cardiac function. It is currently indicated for patients with symptomatic, drug-refractory HF who have reduced LVEF and prolonged QRS durations.[3] The beneficial effects of CRT include improvement in symptoms, exercise tolerance, quality of life, as well as a reduction in morbidity and mortality. [4-7]

Despite the established benefit of CRT on average, approximately one third of patients do not appear to benefit.[8] Many investigations have attempted to address this issue by exploring methods to improve patient selection and outcomes.[6,8] Although, one challenge is that the definition of CRT response varies amongst studies and there is poor agreement between the different response criteria.[9] As such, there is a need for a clinically relevant and consistent

definition of response to CRT to allow for the ability to generalize results over multiple studies to properly evaluate CRT patient selection and improve outcomes.

Given the life-threatening nature of HF, an effective treatment should reduce risk of mortality and hospitalizations. Previous meta-analyses by Wells and colleagues, McAlister and colleagues and Bradley and colleagues have shown CRT is beneficial in reducing all-cause mortality when compared with optimal medical therapy or an ICD. [7,10,11] There has also been an individual patient data meta-analysis performed by Cleland and colleagues, however this analysis was not systematic in nature and did not include all available studies on this topic to date.[12] Although these reviews reported a mortality benefit with CRT in randomized controlled trials, the cumulative evidence of echocardiographic response across HF patient populations has yet to be reported in a systematic review. LV reverse remodeling (measured by a reduction in LVESV and/or increase in LVEF) has been proposed as a promising surrogate of clinical long-term outcome in patients receiving CRT therapy.[13] However, it is currently unclear whether LV reverse remodeling (herein referred to echocardiographic response) is predictive of improved long-term clinical outcome from large populations of HF patients.[14]

Given the current efforts investigating predictors of response to CRT for improved patient selection, as well as the need in clinical practice for a surrogate end point of long term prognosis post CRT, the current meta-analysis summarizing the effect of CRT on echocardiographic response and mortality/hospitalization and the relationship between them is needed.[6,8] Thus the objectives of this systematic review and meta-analysis are to: (1) summarize the current evidence regarding the echocardiographic response to CRT devices in adult HF patients compared to medical therapy and ICD therapy, (2) summarize the current evidence of clinical

(mortality/hospitalization) response to CRT compared to medical therapy and ICD therapy, and (3) investigate if a relationship exists between echocardiographic and clinical responses to CRT using data from randomized trials.

8.3 Materials and Methods

Inclusion, analysis of articles, and reporting of their results were outlined *a priori* in a protocol developed according to the recommendation from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (See PRISMA checklist included in Appendix 1).[15]

8.3.1 Search Strategy

Two investigators (J.H., S.M.) created the search strategy. Searches were conducted in the following databases: MEDLINE, PubMed, EMBASE, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews. Searches were conducted without language restrictions from the databases first available dates until October 10, 2013, with the exception of PubMed which was searched for only the 3 months prior to the search date to capture any new and relevant studies that have yet to be indexed in MEDLINE. References of included articles were hand searched for relevant citations and experts in the field were contacted to ensure that all relevant studies had been captured.

Using a combination of Medical Subject Headings (MeSH) terms and key words we created three search themes: cardiac resynchronization therapy, heart failure, and outcomes. Individual terms within each theme were combined with the Boolean operator OR and the three themes were combined with the Boolean operator AND (See Table 11 for the MEDLINE search strategy).

8.3.2 Study Selection

Two reviewers (J.H., S.M.) independently screened all titles and abstracts, reviewed

potentially relevant citations in full, and decided on study inclusion. We used the following inclusion criteria: (1) study design was a randomized trial of CRT versus another standard HF therapy, (2) study patients were adult (≥ 18 years of age) HF patients with NYHA Class II-IV[16], QRS interval ≥ 120ms, and EF ≤ 35%, (3) physiologic outcomes of interest (specifically LV reverse remodeling, EF, LVEDV, and LVESV) were reported in the study. The following exclusion criteria were used: (1) non-original research, (2) non-randomized study design, (3) study included pediatric patients (<18 years of age), (4) animal studies, (5) studies where patient baseline characteristics were not reported. Agreement between reviewers was quantified using the kappa statistic.[17] Disagreements were resolved by consensus or third party arbitration.

8.3.3 Data Extraction

The same two reviewers (J.H., S.M.) extracted data independently and in duplicate. All data was extracted into a pre-designed database. Data extracted included: (1) baseline patient demographics including age, sex, QRS duration, EF, LVESV, NYHA class, and number of patients in atrial fibrillation or with IHD; (2) study level data including study country, number of patients included in the study, number of patients in each randomization arm, and type of CRT device implanted; (3) any patient important outcomes including but not limited to the number of physiologic responders and non responders to CRT, number of clinical responders and non responders to CRT, the extent of LV reverse remodeling assessed by LVESV, EF and LVEDV, and number of deaths and long term hospitalizations; and (4) author definitions of patient important outcomes.

8.3.4 Risk of Bias Assessment

The same two reviewers (J.H., S.M.) also evaluated the methodological quality of each included study independently and in duplicate using the Cochrane Collaboration's tool for

assessing risk of bias in randomized controlled trials.[18] This tool assesses selection bias, performance bias, detection bias, attrition bias, and reporting bias by assessing six different sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.[18] This tool uses a three point ordinal scale (low/high/unclear) to assess whether in the study in question each source of bias has the potential to introduce a low or high amount of bias into the study or if there was not enough information reported to assess the selected source of bias. We also assessed other important study characteristics including the number of patients with ischemic heart disease in each study and the author's definitions of the selected outcomes.

8.3.5 Analysis

Dichotomous results, including mortality and hospitalizations, were calculated as risk ratios. Continuous measures including ejection fraction and left ventricle end systolic volume were calculated as the difference in means between baseline and follow-up within CRT and control groups within individual studies (representing the change in these measures over the course of the study) and then a difference of differences was calculated between the CRT and control groups (representing the difference in these changes between the CRT and control group). Where appropriate these risk ratios or difference of changes were pooled using the random effects model proposed by DerSimonian and Laird.[19]

Inter-study heterogeneity was assessed by calculating Cochrane's Q homogeneity[20] and I squared inconsistency statistics.[21] Using the guidelines suggested by Higgins and colleagues we considered an I^2 statistic of >25% as a low degree of heterogeneity, >50% as moderate heterogeneity, and >75% as high heterogeneity[22]. For the pooling of the difference of the changes in LVEF and LVESV, results were stratified by control group therapy. In order to explore

sources of heterogeneity meta-regressions of the differences of changes in LVEF and LVESV and the percentage of patients with IHD in each study were performed. As meta-regression is an underpowered analysis, a p-value < 0.10 was considered significant.

In order to assess if the risk of death varied according to echocardiographic response to CRT a meta-regression of the log risk ratio of death and the difference of differences in ejection fraction and left ventricle end systolic volume was also performed. Publication bias was assessed using funnel plots[23] and Egger's test of small study effects.[24] All analyses were performed using Stata version 12.0 (Stata Corp., College Station, TX, USA).

8.4 Results:

8.4.1 Study Selection and Characteristics

Among 8232 unique citations identified, 16 studies enrolling 2714 patients met the inclusion criteria and were included in the systematic review (Figure 14). [5,25-39] Agreement between reviewers was moderate ($\kappa = 0.524$ 95% CI 0.420 to 0.629).

Among the 16 studies, 13 were randomized controlled trials[5,25,26,28,29,31-36,38,39] and 3 were randomized cross-over trials[27,30,37]. Of the randomized controlled trials, five used standard medical therapy as a control,[31,32,34,36,37] three used ICD therapy as a control,[25,28,39] and five used left ventricle pacing only as a control. [26,29,33,35,38] One study used two control groups (left ventricle pacing and sequential biventricular pacing), in order to maintain consistency only data from the left ventricle pacing group was used as control data.[33] One trial consisted of a randomized and non-randomized arm, to maintain consistency with our inclusion criteria only data from the randomized arm of the trial was collected and analyzed.[28] Of the randomized cross-over trials two used standard medical therapy as a control[27,30] and one used left ventricle only pacing as a control.[37] Fourteen were studies of general heart failure patients[5,25-29,31,33-39] while two

were studies of heart failure patients undergoing coronary artery bypass grafting (CABG).[30,32] Follow up length varied from 4.5 to 18 months with the majority of studies having a follow up length of 6 months. Additional data concerning patients with IHD enrolled in the CARE-HF study[5] was collected from a separate publication.[40] The characteristics of included studies are shown in Table 12.

8.4.2 Risk of Bias Assessment

As many of the studies had previously published protocols or other study publications, study methodological quality was not always clearly or completely reported and these other publications were consulted in order to completely assess study characteristics.[41-44] The methodology of the included studies was largely hard to assess as many of the publications did not report on aspects necessary to assess the biases included in the Cochrane Collaboration's tool (Table 13); i.e. only four of the sixteen studies had reporting which was adequate enough to assess both random sequence generation and allocation concealment.[28-30,33] Blinding of participants and personnel and outcome assessment was also unable to be assessed in seven of the studies.[27,28,31,34-36,38] The majority of studies had complete outcome data reporting[25,26,28-30,33,37,39] and no studies exhibited selective reporting. The number of patients with ischemic heart disease was reported in 12 studied and the percent of included patients with ischemic heart disease ranged from 20 – 100% (Table 12). [5,25-28,31,33,34,37-39]

8.4.3 Echocardiographic Response to CRT

Four studies gave a definition of echocardiographic response to CRT and reported the number of patients fulfilling the response criteria at follow up.[26,28,31,33] None of these studies gave the same definition for echocardiographic response to CRT, which precluded calculating a pooled incidence of echocardiographic response to CRT. The definitions given ranged from a minimum

increase in LVEF from 10% to 25% and a reduction in LVESV at follow up from 15% to 20% or combination of both. Echocardiographic response to CRT varied by given definition and ranged from 42 – 59% (Table 14).

Echocardiographic response to CRT in terms of the difference of the changes in baseline and outcome LVEF in the CRT and control groups could be calculated in 12 studies.[25,26,28-30,32-37,39] In all but two of these 12 studies the CRT group had a greater increase in LVEF than the control group; both of these studies were comparisons of CRT to left ventricle pacing.[29,37] The pooled difference of the change in baseline and outcome LVEF in the CRT and control groups is shown in Figure 15. The overall pooled result was 3.44% [95% confidence interval (CI) -1.24 to 8.12, I^2 100.0%, p-value <0.001]; that is overall in comparison to the control groups the CRT groups had a greater change in ejection fraction from baseline by 3.44% however this result was not significant as the 95%CI contains zero.

As shown in the I^2 (100.0%) and Cochrane's Q p-value (<0.001) from this analysis there was a high amount of heterogeneity present in this estimate. As such we stratified by control group therapy (ICD therapy, left ventricle pacing, and standard medical therapy). In the studies using standard medical therapy as their control group the pooled difference of the change in baseline and outcome LVEF in the CRT and control groups was 6.56% (95%CI -2.28 to 15.39, I^2 100.0%, p-value <0.001), for the studies using ICD therapy as their control the pooled difference was 2.00% (95%CI -0.12 to 4.13, I^2 90.9%, p-value <0.001), and in studies using left ventricle pacing as their control group the pooled difference was 1.44% (95%CI 0.17 to 2.70, I^2 95.2%, p-value <0.001). These analyses show that in the studies comparing CRT to LV pacing there was a significant increase in LVEF in the CRT group but in the studies comparing CRT to ICD and standard medical therapy the increase in LVEF in the CRT group was non-significant. These

analyses are also all associated with high heterogeneity indicating that control group therapy does not completely explain the heterogeneity found in the pooled analyses.

Echocardiographic response to CRT in terms of the difference of the reduction in LVESV from baseline in the CRT and control groups could be calculated in 10 studies.[25,28-30,32-34,36,37,39] In all but three of these 10 studies the CRT group had a greater decrease in LVESV than the control group. The pooled difference between the reduction in LVESV from baseline in the CRT and control groups is shown in Figure 16. The overall pooled result was 15.82ml (95%CI 6.71 to 24.93, I^2 99.3%, p-value <0.001); that is overall in comparison to the control groups the CRT groups had a greater reduction in LVESV from baseline by 15.82ml.

As shown in the I^2 (99.3%) and Cochrane's Q p-value (<0.001) from this analysis there was a high amount of heterogeneity present in this estimate. As such we stratified by control group therapy (ICD therapy, left ventricle pacing, and standard medical therapy) also shown in Figure 16. In the studies using standard medical therapy as their control group the pooled difference of the reduction in LVESV from baseline between the CRT and control groups was 25.99ml (95%CI 7.67 to 44.32, I^2 99.3%, p-value <0.001), for the studies using ICD therapy as their control the pooled difference was 11.31ml (95%CI -2.07 to 24.70, I^2 84.5%, p-value 0.002), and in studies using left ventricle pacing as their control group the pooled difference was 6.08ml (95%CI -2.71 to 14.87, I^2 97.2%, p-value <0.001). These analyses show a reduction in LVESV in studies of CRT compared to standard medical therapy but in studies comparing CRT to ICD therapy or LV pacing there was not a significant difference in the reduction in LVESV between the CRT and these control groups. These analyses are also all associated with high heterogeneity indicating that the studies may vary on another study level factor aside from control group therapy.

In order to assess if echocardiographic response to CRT varied on the percentage of patients with ischemic heart disease in each study, we performed meta-regressions of the difference in the change of LVEF and LVESV between the CRT and control groups on the percentage of patients with ischemic heart disease in each study. Ten studies afforded the data to perform the meta-regression of the difference in the change in LVEF on the percentage of patients with IHD enrolled in the study;[25,26,28-30,32-34,37,39] while nine studies afforded the appropriate data for the meta-regression of the difference in the change in LVESV on the percentage of patients with IHD enrolled in the study.[25,28-30,32-34,37,39] The results of these meta-regressions are shown in Figure 17. Here it can be seen that a greater increase in LVEF and a greater reduction in LVESV in the CRT group as compared to the control group have a positive linear association with the percentage of patients with IHD at the study level.

The results of the meta-regression of the difference in the change in LVEF on percent IHD show that for every percentage point increase in IHD there is a 0.15% increase in the difference of the change in LVEF from baseline between the CRT and control groups favoring the CRT groups. In other words at the study level as the percentage of patients with IHD increases so does the LVEF response to CRT. The p-value for this regression was significant at 0.029. The results of the meta-regression of the difference in the reduction in LVESV on percent IHD show that for every percentage point increase in IHD there is a 0.47ml increase in the difference of the reduction in LVESV from baseline between the CRT and control groups favoring the CRT groups. In other words at the study level as the percentage of patients with IHD increases so does the LVESV response to CRT. The p-value for this regression was also significant at 0.054.

8.4.4 Clinical Response to CRT

Seven of the included studies afforded the data needed to calculate the risk ratio of death for those receiving CRT.[5,25,29,31,32,35,39] All studies with the exception of two produced a point estimate showing CRT treatment was protective against death.[25,29] Upon pooling using random effects meta-analysis a pooled log risk ratio of -0.34 (95%CI -0.66 to -0.03, I^2 19.3%, p-value 0.283) was obtained (Figure 18). Exponentiated this gives a risk ratio of 0.71 (95%CI 0.52 to 0.97); meaning that those treated with CRT have 0.71 times the risk of death compared to those not treated with CRT indicating that CRT treatment is protective against death. The result was homogenous across all studies as indicated by the low I^2 and non-significant Cochrane's Q p-value.

Seven of the included studies presented data on hospitalizations in the CRT and control groups.[5,26,28,29,31,32,39] One study[29] reported hospitalizations as a rate per person-month at risk and another[39] only reported data on all cause hospitalizations; however the remaining five reported data such that a risk ratio of heart failure related hospitalization between the CRT and control groups could be calculated. All studies produced a point estimate showing CRT treatment was protective against heart failure hospitalization. Upon pooling using random effects meta-analysis a pooled log risk ratio of -0.44 (95%CI -0.61 to -0.28, I^2 1.1%, p-value 0.400) was obtained (Figure 19). Exponentiated this gives a risk ratio of 0.64 (95%CI 0.55 to 0.76); meaning that those treated with CRT have 0.64 times the risk of heart failure related hospitalization compared to those not treated with CRT indicating that CRT treatment is protective against heart failure hospitalization. The result was homogenous across all studies as indicated by the low I^2 and non-significant Cochrane's Q p-value.

8.4.5 Association Between Echocardiographic and Clinical Responses to CRT

In order to assess if echocardiographic response to CRT was associated with clinical response to CRT we performed meta-regressions of the log risk ratio of death on the difference in the change of LVEF and LVESV between the CRT and control groups in each study. Five studies afforded the appropriate data for the LVEF meta-regression[25,29,32,35,39] and four studies for the LVESV meta-regression.[25,29,32,39] The results of these meta-regressions are shown in Figure 20. Here it can be seen that the log risk ratio of death has a negative linear association with a greater increase in LVEF and a greater reduction in LVESV in the CRT group as compared to the control group at the study level.

The results of the meta-regression of the log risk ratio of death on the difference in the change in LVEF show that for every percentage point increase in the change in LVEF between the CRT and control groups there is a decrease in the log risk ratio of death of 0.07 favoring the CRT group. In other words at the study level as CRT group shows a larger response to CRT in terms of increased LVEF the risk ratio of death between the CRT and control group decreases or CRT seems to become more protective against death with a larger echocardiographic response. The p-value for this regression was significant at 0.098. The results of the meta-regression of the log risk ratio of death on the difference in the change in LVESV show that for every milliliter increase in the reduction of LVESV between the CRT and control groups there is a decrease in the log risk ratio of death of 0.03 favoring the CRT group. In other words at the study level as the CRT group shows a larger response to CRT in terms of decreased LVESV the risk ratio of death between the CRT and control group decreases. The p-value for this regression was non-significant at 0.139. There was not sufficient data to perform meta-regressions of the log risk ratio of heart failure hospitalizations on the difference of the change in LVEF or LVESV between

the CRT and control groups.

8.4.6 Assessment of Small Study Effects

In order to assess for publication bias by means of missing studies and/or small study effects we produced funnel plots and performed Egger's tests of small study effects using our primary outcomes of the difference in the change in LVEF and LVESV from baseline between the CRT and control groups (Figure 21). Upon visual inspection of the funnel plots it can be seen that there may be several small studies with estimates of large differences between the changes in LVEF and LVESV between the CRT and control groups missing. There may also be a few small studies with estimates of difference in LVESV between 0 and 20 missing as well. However, when performing the Egger's test of small study effects a non-significant p-value for testing the null hypothesis of no small study effects is obtained for both primary outcomes of the difference in the change in LVEF (intercept -12.35, 95%CI -74.12 to 49.43, p-value 0.666) and LVESV (intercept -2.30, 95%CI -17.43 to 12.84, p-value 0.735) indicating that our study is not subject to publication bias via small study effects.

8.5 Discussion:

The pooled evidence from RCTs comparing the effect of CRT over either optimal medical therapy or ICD therapy in patients with moderate to advanced HF, prolonged QRS, and EF<35% show an incremental benefit of CRT in terms of both LV remodeling parameters and clinical outcomes. Summarizing the current evidence from randomized trials has the added advantage over observational studies of separating the therapeutic response to CRT from the natural course of the underlying disease.

To our knowledge this is the first meta-analysis to pool echocardiographic response to CRT versus alternate therapies. Overall, with CRT treatment, there was an incremental increase

in EF of 3.44%. The lack of a significant relative increase in EF may be explained by the inclusion of LV pacing control groups[26,29,33,35,37] in the pooled estimate. CRT biventricular pacing compared to LV only pacing has been shown to confer similar benefits,[41,45] so it was not unexpected the only two studies with a not-significant relative increase in EF came from the LV pacing control group.[29,37] The wide confidence interval of the overall relative change in LVEF related to the inclusion of two RCTs which included only patients undergoing CRT and CABG as co-interventions.[30,32] The greater increase in EF post CRT in CABG patients suggests CABG plus CRT affords even more LV reverse remodeling benefit. The high amount of heterogeneity, even despite stratifying by control group therapies, could be due to differential subgroup effects. Although the populations included many similar patient demographics, the proportion with ischemic heart disease varied substantially from 20 to 100%, which could explain the differing echo response from CRT.

In general, when CRT was added to treatment, there was a significant reduction of LVESV of 15.82 ml. Again, the magnitude of the overall result may be influenced by the inclusion of the CABG co-intervention studies,[30,32] emphasizing that CRT in CABG patients is associated with a greater physiologic response that needs to be further explored in future studies. Nevertheless, the cumulative evidence shows a relative reduction in LVESV compared to medical therapy alone particularly and overall, thus an increased LV reverse remodeling from CRT. Similar to the pooled results of the effect of CRT on EF, there was much variance in the study effects with LVESV, even when stratified by control therapy, further supporting that there are subgroup factors effecting physiologic response to CRT which need to be explored. From the pooled results of the echocardiographic response to CRT, not only does it show CRT is favourable over other treatments in terms of LV function, but also that LV reverse remodeling is

one mechanism of action of CRT.

Overall, CRT was shown to be protective against both death and hospitalizations. These results were consistent amongst the studies independent of control therapy, confirming what has been found in prior studies examining clinical response from CRT in HF patients.[7,10,11]

The most clinically relevant finding of this review was the significant association observed between echocardiographic response and clinical outcomes in CRT patients. The more extensive LV reverse remodeling was shown to be related to reduction in risk of death in a dose response type relationship, at the study level. This is the first meta-analysis to demonstrate an association between echocardiographic and clinical outcomes, and serves as hypothesis generating, yet potentially clinically useful, at this point. Echocardiographic measurements may be useful as a surrogate marker in clinical practice for long-term prognosis. An analysis of patient level data to test this hypothesis is needed.

Previous studies evaluating the effects of CRT have used other various response measures, for example NYHA functional class or 6 minute walk distance.[46,47] Although, the limitation to doing so is that these clinical parameters are subjectively assessed by physicians and thus may not serve as reliable endpoints to evaluate. Echocardiography has the advantages of being widely available, reproducible and now perhaps linked to long term prognosis. As such, echo assessment is a conceptually attractive measure of CRT response.

The heterogeneity in the magnitude of echocardiographic response to CRT found amongst studies was explored by assessing if response was affected by HF etiology. The randomized trials included in our meta-analysis were of mixed patient population, with similar baseline characteristics, although the proportion of ischemic patients varied between the studies, which could account for the differences in echocardiographic response between studies. As well,

previous studies have suggested a relationship between HF etiology and LV reverse remodeling after CRT.[4,48]

The findings from our meta-analysis showed as the proportion of ischemic patients in the study populations increased an incremental increase in echocardiographic response to CRT was seen. This suggests ischemic HF patients may derive more remodeling benefit, which might relate to the difference in clinical course of the disease than non-ischemic HF. Interestingly, our findings showed the clinical benefit of CRT (both reduction in risk of death and hospitalization), were similar amongst the studies, which included varied proportion of ischemic and non-ischemic patients. Data from recent clinical trials have also showed that among patients with HF, IHD and non-IHD patients gained similar clinical benefit from CRT, but varying degrees of reverse remodeling. [40,49,50] This could suggest that the mechanism of response to CRT may be different in ischemic and non-ischemic patients. Patients with ischemic HF may benefit from CRT other than improved LVEF and LVESV, such as by arrhythmia suppression.[51]

Although, further subgroup analysis with individual patient level data would be needed to appropriately examine effect of CRT therapy in these two distinct etiology groups.

Our findings suggest that CRT confers remodeling benefit, as well as reduction in hospitalization and death. Furthermore, it may be useful for physicians to assess short term echocardiography indices of LV reverse remodeling to predict long term benefit to CRT. Analysis of patient level data is required to determine a clear association between echocardiographic and clinical response and to warrant emphasis, in clinical practice, to prognosticate patients based on echocardiographic findings.

The demonstrated differences in echocardiographic response, yet similar clinical response to CRT amongst studies of varying ischemic population suggest there may be etiology specific

factors that affect the physiologic mechanism of response to CRT delivery. As well, CRT responders are commonly classified based on the predefined echocardiographic criteria of a reduction in LVESV of 15% and increase in LVEF of 5%.[6,52] Since the degree of echocardiographic response is shown to vary by HF etiology, this commonly employed definition of CRT responders may not be appropriate across all patient populations. A research priority should be to explore the effect of CRT in ischemic versus non-ischemic patients.

There are some limitations to our meta-analysis. First, the randomized trials included had varying follow up times ranging from 4.5 to 18 months. This is important because the shorter duration follow up may not have captured all the echocardiographic and clinical outcomes, altering the estimate of the effect of CRT. Secondly, some randomized trials that met our inclusion criteria, did not report the actual values of the outcomes of interest, rather illustrated the results graphically. This reduced the sample size in our meta-analyses. Contacting authors to obtain the required information would strengthen our statistical analyses.

Finally, the absence of patient level data limits our ability to further examine subgroup effects of CRT on echocardiographic and clinical outcomes. As well, with using aggregate data from trials of CRT the association of echocardiographic response to clinical outcome could subject to the ecological fallacy, thus the insistence for a randomized trial with individual patient data to elucidate the relationship.

8.6 Conclusion:

This meta-analysis showed that CRT is associated with significant echocardiographic and clinical benefit and there is an association between the two measures of response. This data demonstrates that patients with moderate to advanced drug refractory HF, prolonged QRS and low ejection fraction clearly benefit from CRT. As well, echocardiographic response indices

(LVESV and LVEF) may be a reliable definition of CRT response to use in the short term due to its availability, reproducibility and possible association to clinical outcome. As such, echocardiographic measurements post CRT could be used for patient counseling purposes. .

Randomized trials evaluating the relationship of echocardiographic response and mortality benefit to CRT are needed. As well, given varying degrees of LV reverse remodeling among studies and the relationship between ischemic heart disease and remodeling indices, a priority should be for appropriate examination of subgroups, focusing on HF etiology.

8.7 TABLES-Systematic Review and Meta-Analysis:

Table 11: MEDLINE Search Strategy

Themes (combined with Boolean operator "AND")	**Cardiac Resynchronization Therapy**	**Heart Failure**	**Outcomes**
MeSH Terms (combined with Boolean operator "OR")	cardiac resynchronization therapy; cardiac pacing, artificial	heart failure; heart failure, diastolic; heart failure, systolic; myocardial ischemia; cardiomyopathy, dilated; coronary artery disease; ventricular dysfunction	ventricular remodeling; echocardiography
Keywords (combined with Boolean operator "OR")	cardiac resync*; biventricular pacing	non-ischemic heart failure; non ischemic heart failure; ischemic cardiomyopathy; ischemic heart failure; systolic dysfunction	echocardiogra*; outcome*; left ventricular remodeling; LV remodeling; reverse remodeling; echo* responders

Table 12**:** Characteristics of Studies included in the Systematic Review

Study, Year	Trial Name	Country	Study Design	Control Group	Follow Up Duration	Patients (n)	No. IHD	Patient Age*
Abraham et al., 2004[25]	MIRACLE ICD II	United States	Randomized Controlled Trial	ICD	6 months	186	106	CRT: 63 (12.8) Control: 63.1 (12.1)
Boriani et al., 2010[26] (Leclercq et al., 2005 also used to assess study characteristics[41])	B-LEFT	Europe (multi-country)	Randomized Parallel-Design Trial	LV pacing	6 months	176	92	66 (9)
Butter et al., 2006[27] (Stellbrink et al., 2000 also used to assess study characteristics[42])	PATH-CHF II (subgroup analysis)	Germany and The Netherlands	Randomized Cross-Over Trial	Inactive CRT Implant	12 months	29	34	58 (8)
Diab et al., 2011[28]	N/A	England	Randomized Controlled Trial	ICD	6 months	70	58	CRT: 67 (7) Control: 65 (13)
Gasparini et al., 2006[29]	BELIEVE	Italy, France, and Spain	Randomized Controlled Pilot Trial	LV pacing	12 months	74	N/R	66.7 (7.4)
Goscinska-Bis et al., 2008[30]	N/A	Poland	Randomized Cross-Over Trial	Inactive CRT Implant	12 months	23	N/R	64.7 (7)
Piepoli et al., 2008[31]	N/A	Italy	Randomized Controlled Trial	Standard Medical Therapy	12 months	89	52	CRT: 71.2 (1.0) Control: 73.0 (1.3)
Pokushalov et al., 2010[32]	N/A	N/R	Randomized Controlled Trial	Standard Medical Therapy	18 months	178	178	62.8 (7)
Rao et al., 2007[33] (De Lurgio et al., 2005 also used to assess study characteristics[43])	DECREASE-HF	N/R	Randomized Controlled Trial	LV pacing	6 months	306	195	CRT: 66.2 (10.6) Control: 67.4 (9.6)
Saxon et al., 2002[34]	VIGOR-HF	N/R	Randomized Controlled Trial	Inactive CRT Implant	4.5 months	53	11	58 (14)
Sedlacek et al., 2010[35]	N/A	Czech Republic	Randomized Controlled Trial	LV Pacing	12 months	40	N/R	CRT: 59.56 (6.83) Control: 62.05 (12.13)
St. John Sutton et al., 2003[36]	MIRACLE	United States	Randomized Controlled Trial	Standard Medical Therapy	6 months	323	N/R	CRT: 63.9 (11.0) Control: 64.8 (11.4)
Thibault et al., 2011[37]	GREATER-EARTH	Canada	Randomized Cross Over Trial	LV Pacing	12 months	121	62	60.9 (8.8)
Valzania et al., 2008[38]	N/A	N/R	Randomized Controlled Trial	LV Pacing	3 months	22	7	CRT: median 66 (IQR 63-75) Control: median 61 (IQR 59-67)

Cleland et al., 2005[5] and Wikstrom et al., 2009[40]	CARE-HF	Europe (multi-country)	Randomized Controlled Trial	Standard Medical Therapy	18 months	813	339	CRT: median 67 (IQR 60-73) Control: median 66 (IQR 59-72)
Young et al., 2003[39]	MIRACLE-ICD	United States	Randomized Controlled Trial	ICD	6 months	369	257	CRT: 66.6 (11.3) Control: 67.6 (9.2)

*mean (SD) unless otherwise indicated
IHD (ischemic heart disease), AF (atrial fibrillation), ICD (implantable cardioverter defibrillator), CRT (cardiac resynchronization therapy), LV (left ventricle), N/R (not reported), IQR (interquartile range), NIHD (non-ischemic heart disease)

Table 13: Risk of bias assessment of included studies

Study, Year	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Abraham et al., 2004[25]	Unclear	Low	Low	Low	Low	Low
Boriani et al., 2010[26] **(Leclercq et al., 2005 also used to assess study characteristics**[41]**)**	Unclear	Unclear	Low	Low	Low	Low
Butter et al., 2006[27] **(Stellbrink et al., 2000 also used to assess study characteristics**[42]**)**	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Diab et al., 2011[28]	Low	Low	High	Unclear	Low	Low
Gasparini et al., 2006[29]	Low	Low	High	High	Low	Low
Goscinska-Bis et al., 2008[30]	High	High	High	High	Low	Low
Piepoli et al., 2008[31]	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Pokushalov et al., 2010[32]	Low	Low	High	High	Unclear	Low
Rao et al., 2007[33] **(De Lurgio et al., 2005 also used to assess study characteristics**[43]**)**	Unclear	Unclear	Low	Low	Low	Low
Saxon et al., 2002[34]	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Sedlacek et al., 2010[35]	Unclear	Unclear	Unclear	Unclear	Unclear	Low

St. John Sutton et al., 2003[36]	Unclear	Unclear	Unclear	Unclear	High	Low
Thibault et al., 2011[37] **(Thibault et al., 2011 also used to assess study characteristics**[44]**)**	Unclear	Unclear	Low	Low	Low	Low
Valzania et al., 2008[38]	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Cleland et al., 2005[5] **and Wikstrom et al., 2009**[40]	Unclear	Unclear	High	Low	Unclear	Low
Young et al., 2003[39]	Unclear	Unclear	Low	Low	Low	Low

Risk of bias assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials[18] where low indicates the given characteristic had a low potential for introducing risk of bias in the study, high indicates the given characteristic had a high potential for introducing risk of bias in the study, and unclear indicated that there was not enough information present to assess the given characteristic. In some cases study methodology had been reported previously in protocols or earlier publications and these additional publications needed to be consulted to assess certain study characteristics.

Table 14: Reported incidence of echocardiographic response to CRT

Study, Year	**Definition of echocardiographic response to CRT**	**Number of CRT patients meeting criteria at follow up**	**Total patients in CRT group**	**Number of control patients meeting criteria at follow up**	**Total patients in control group**
Boriani et al., 2010	≥ 10% decrease in LVESV at follow up	49	90	46	86
Diab et al., 2011	≥ 15% increase in LVEF at follow up	12	24	3	22
Piepoli et al., 2008	Patient was alive at 12 months with a ≥ 20% increase in LVEF and/or a ≥ 15% decrease in LVESV	26	44	N/R	45
Rao et al., 2007	≥ 10% increase in LVEF at follow up	42	101	25	101

CRT (cardiac resynchronization therapy), LVESV (left ventricle end systolic volume), LVEF (left ventricle ejection fraction)

8.8 Figures-Systematic Review and Meta-Analysis

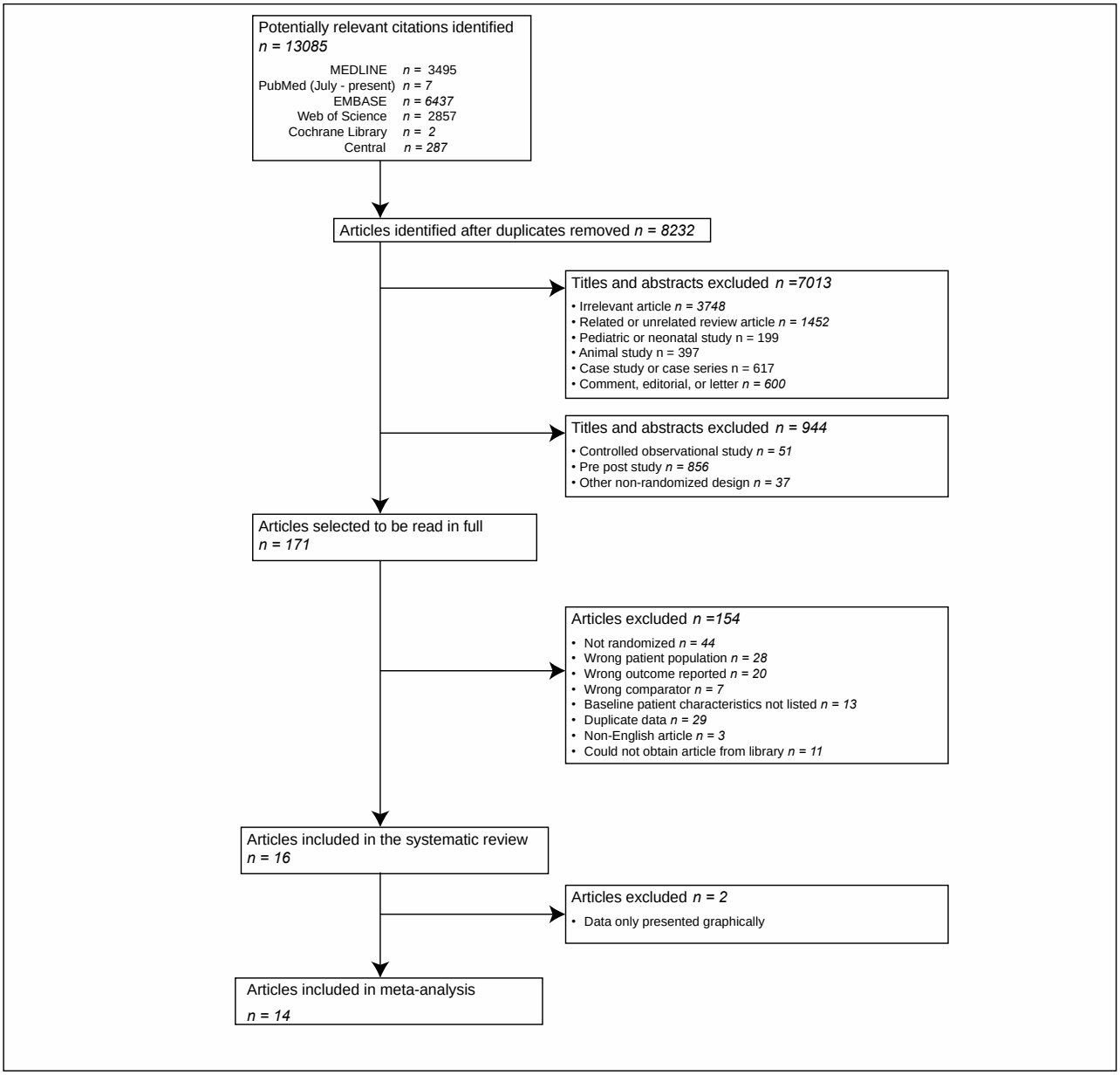


Figure 14: Flow chart of steps in systematic review

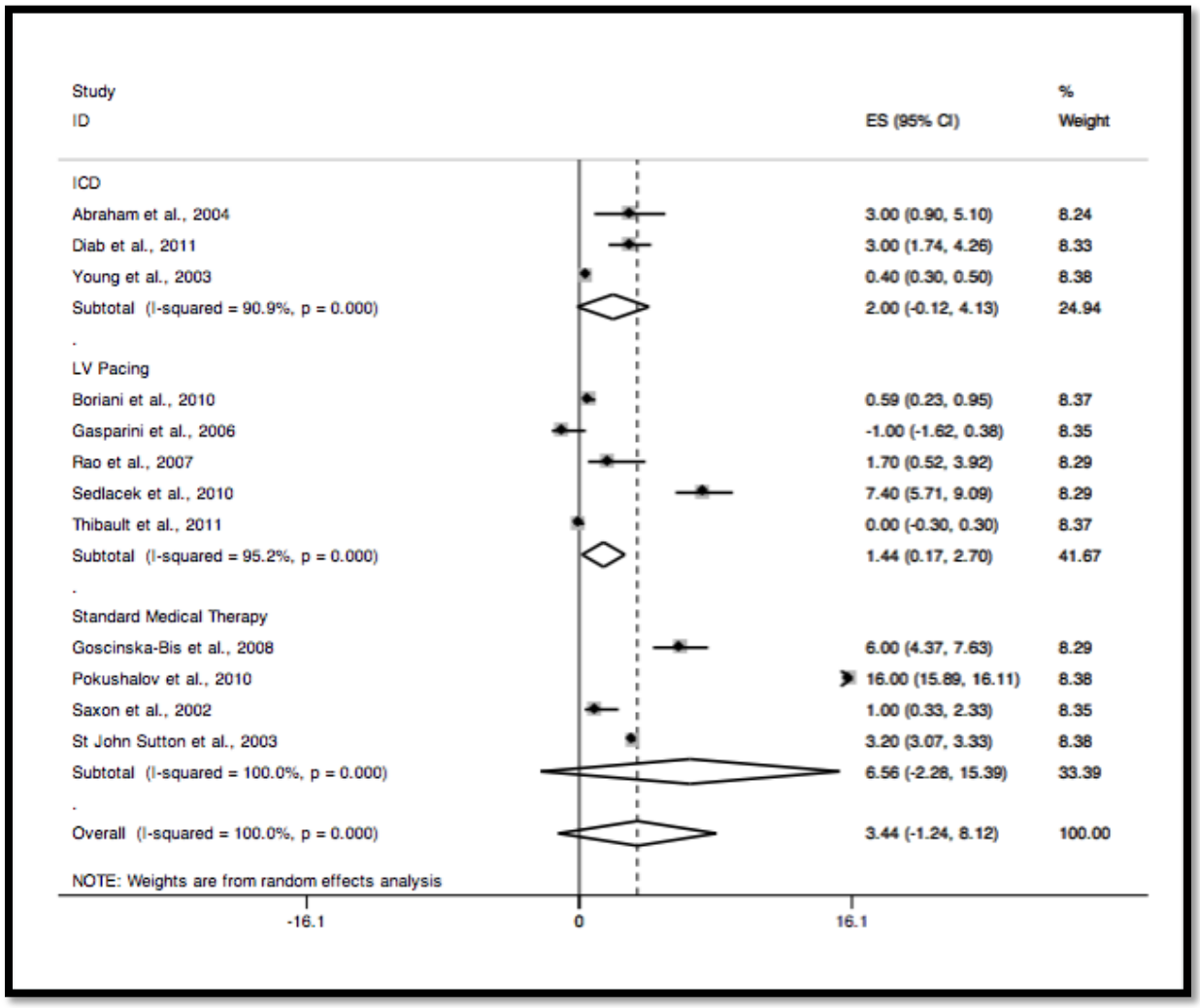


Figure 15: Forest plot of a random effects meta-analysis of the difference of the change in baseline and outcome left ventricular ejection fraction between the CRT and control groups grouped by control group therapy. Numbers are reported in percentages where positive numbers indicate a greater increase in left ventricular ejection fraction in the CRT group as compared to the control group.

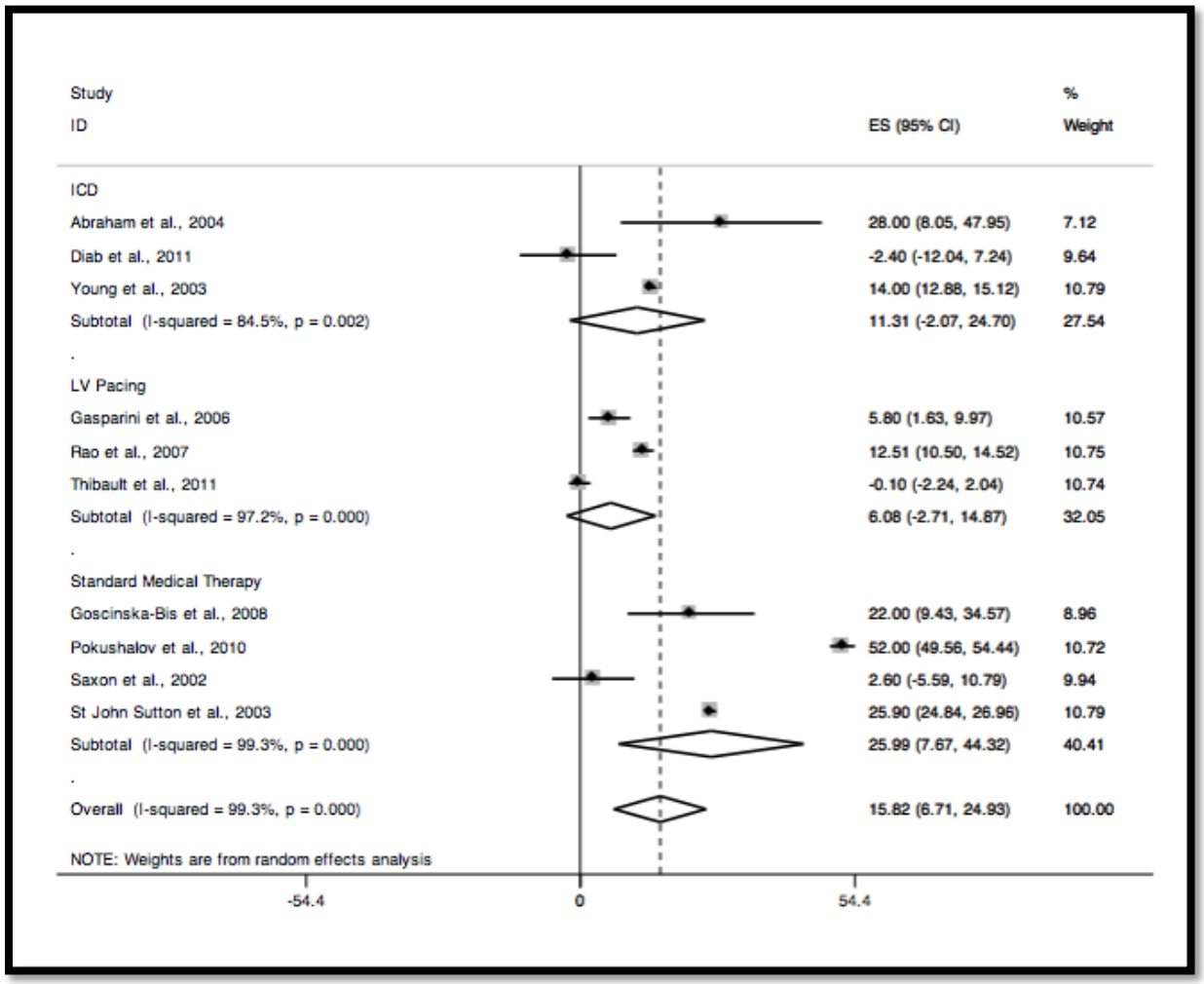


Figure 16: Forest plot of a random effects meta-analysis of the difference of the change in baseline and outcome left ventricular end systolic volume between the CRT and control groups grouped by control group therapy. Numbers are reported in milliliters where positive numbers indicate a greater reduction in left ventricular end systolic volume in the CRT group as compared to the control group.

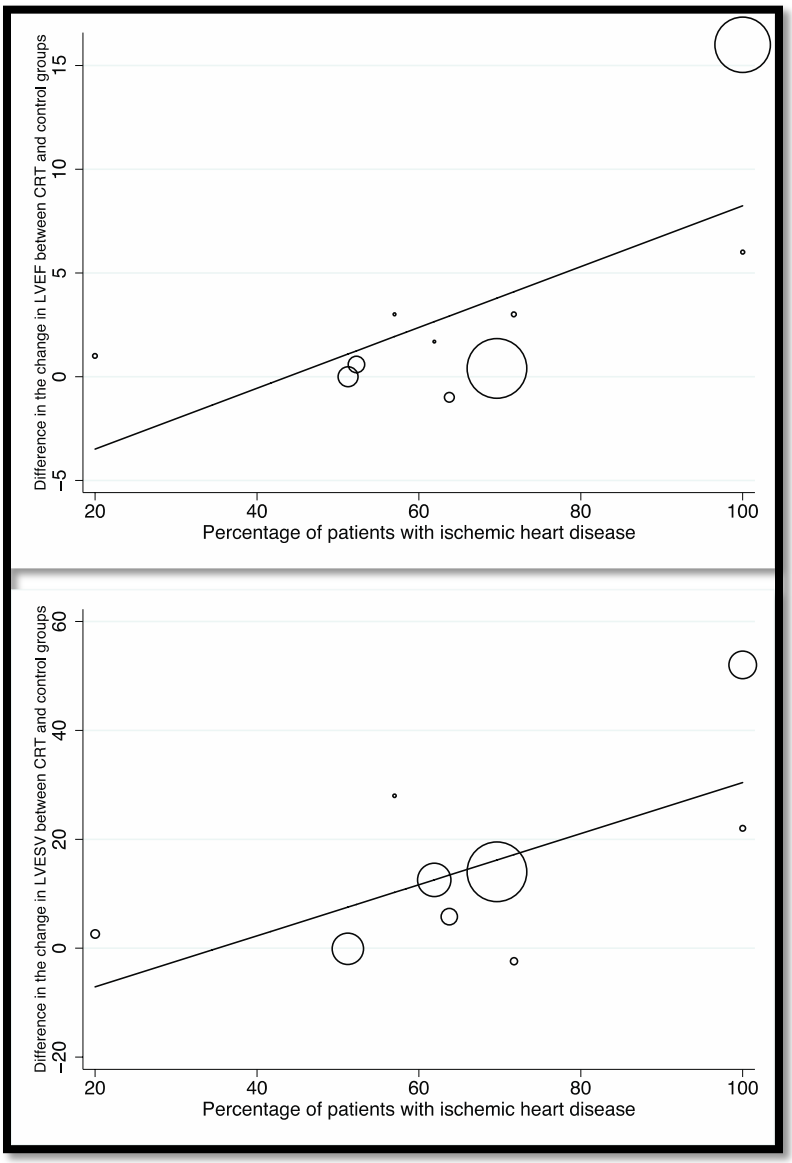


Figure 17: Results of meta-regressions of the difference in the change in left ventricular ejection fraction (LVEF) and left ventricular end systolic volume (LVESV) on the proportion of patients with ischemic heart disease in each study. LVEF is given in percentages where positive numbers indicate a greater increase in LVEF in the CRT group as compared to the control group. LVESV is given in milliliters where positive numbers indicate a greater reduction in LVESV in the CRT group as compared to the control group.

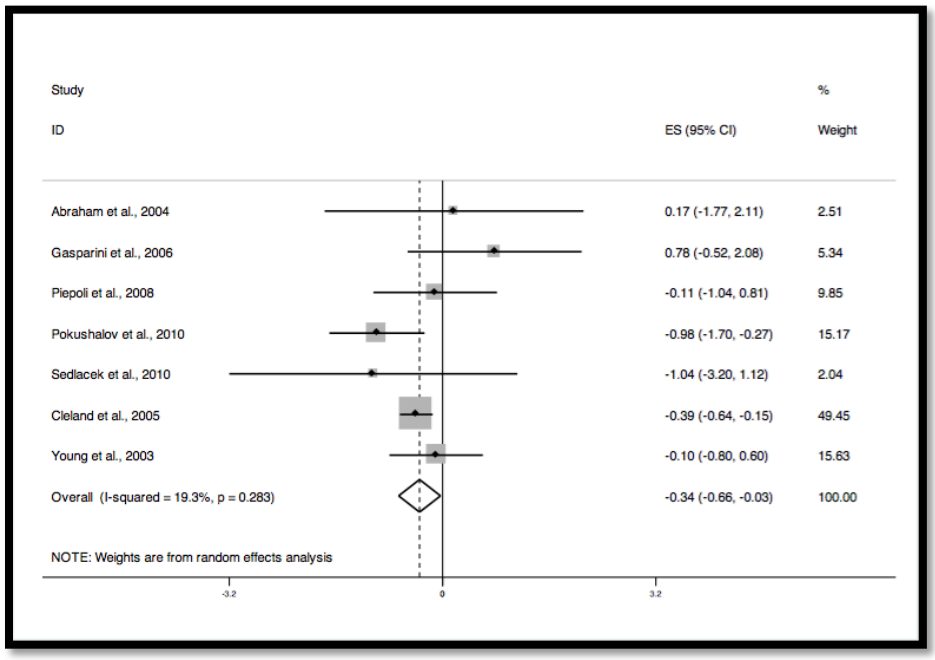


Figure 18: Forest plot of a random effects meta-analysis of the log risk ratio of death between the CRT and control groups. Negative numbers show CRT treatment being protective against death.

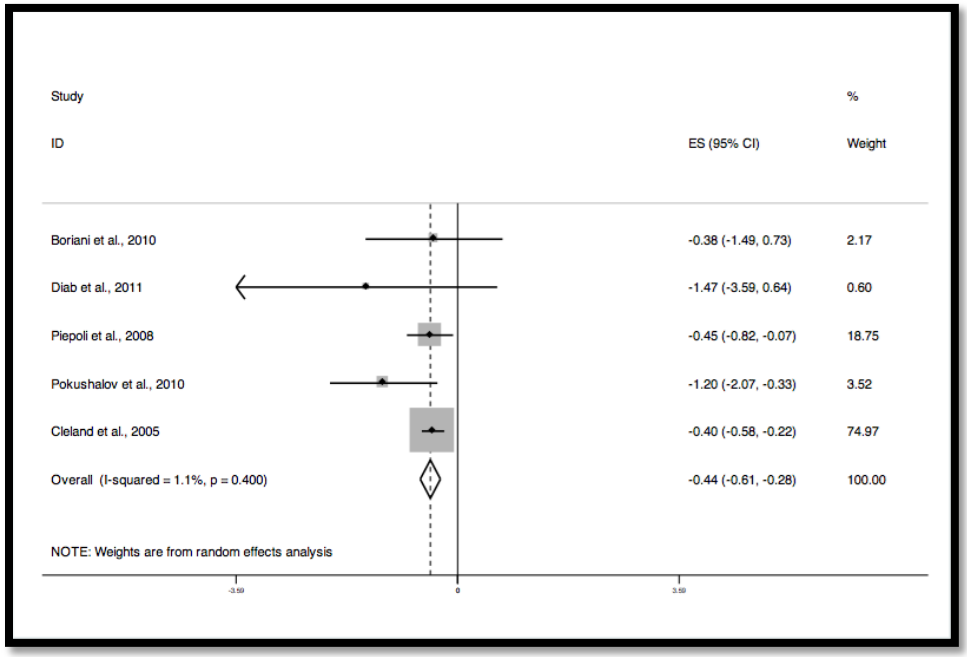


Figure 19: Forest plot of a random effects meta-analysis of the log risk ratio of hospitalization due to heart failure between the CRT and control groups. Negative numbers show CRT treatment being protective against heart failure hospitalization.

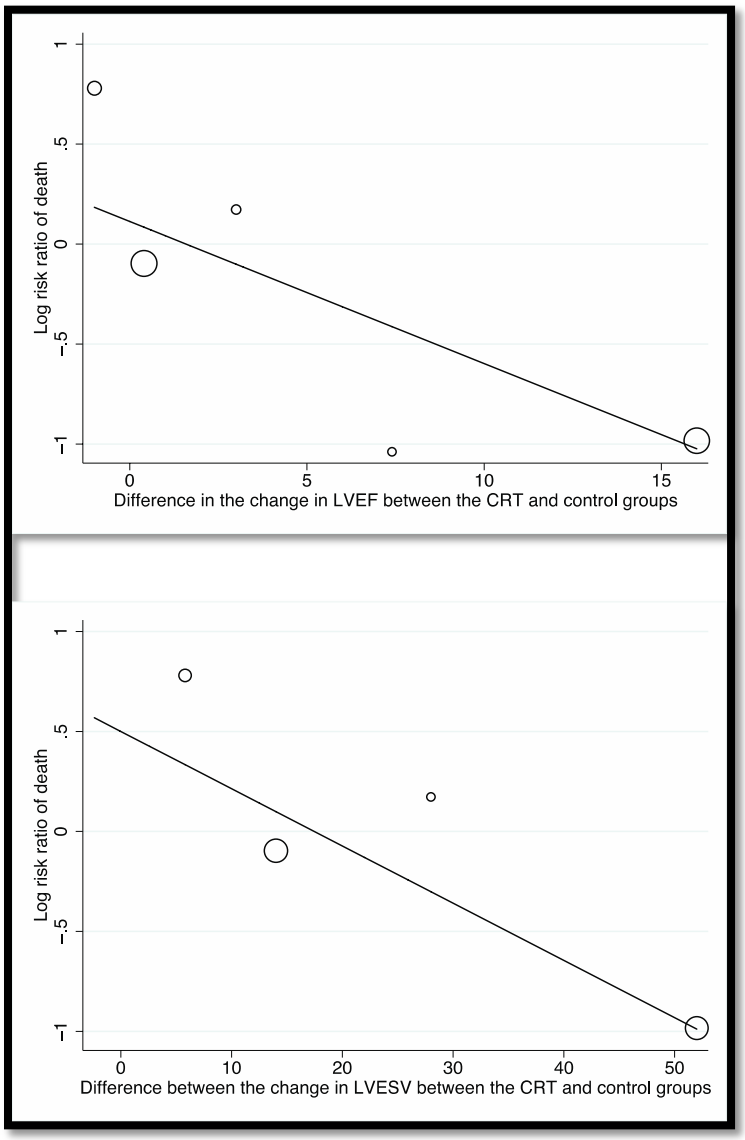


Figure 20: Results of meta-regressions of the log risk ratio of death on the difference in the change in left ventricular ejection fraction (LVEF) and left ventricular end systolic volume (LVESV) between the CRT and control groups. LVEF is given in percentages where positive numbers indicate a greater increase in LVEF in the CRT group as compared to the control group. LVESV is given in milliliters where positive numbers indicate a greater reduction in LVESV in the CRT group as compared to the control group. Negative log risk ratios indicate that CRT treatment is protective against death.

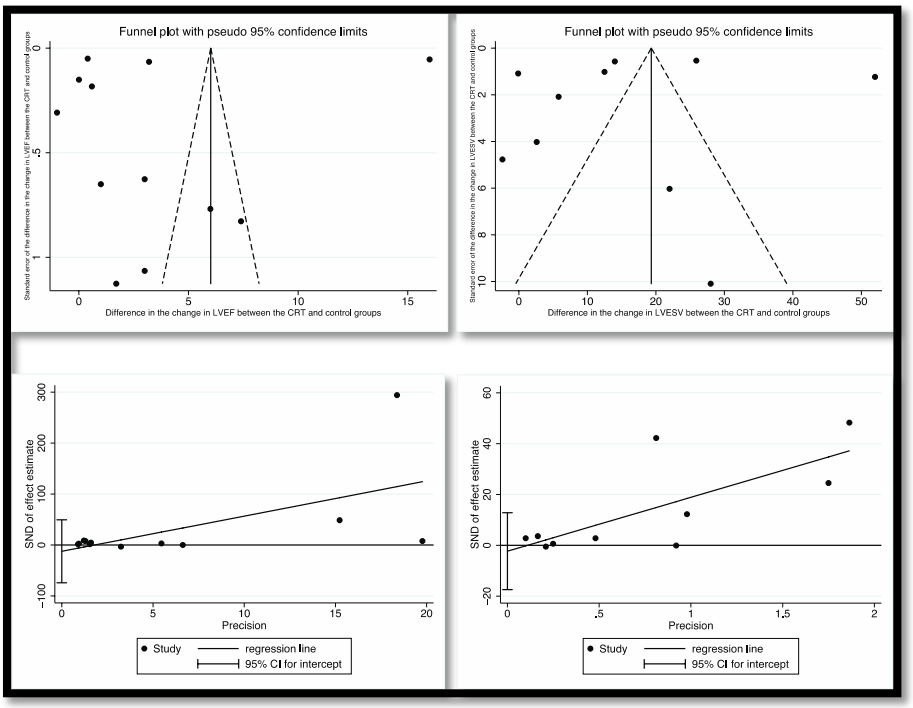


Figure 21: Assessment of small study effects using the difference in the change in LVEF from baseline between the CRT and control groups and the difference in the change in LVESV from baseline between the CRT and control groups. Visual inspection of the funnel plots indicates there may be many small and large studies missing that have estimates of large differences of the changes in LVEF and LVESV from baseline between the CRT and control groups. However Egger's test for small study effects gives a non-significant p-value when testing the null hypothesis of no small study effects.

Chapter Nine: **Conclusion**

The overarching theme from the three studies is that optimizing CRT response is a delicate balance of pre-implant, operative and post-implant considerations. A single measure is not sufficient to reliably predict CRT outcome in the complex syndrome of heart failure and requires a multimodal approach. Selection criteria for device therapy is largely based on randomized controlled trials (including: MADIT CRT, REVERSE, RAFT, MIRACLE, CARE-HF, COMPANION, CONTAK CD). Although, there is still a lack of response in up to 30% of patients based on current guidelines. As such, consideration of non-invasive hemodynamic parameters, such as cardiac reserve, assessed by difference in pulse pressure with exercise, may improve response rate. The augmentation in pulse pressure with exercise pre-CRT was shown to be an independent marker associated with LV reverse remodeling to CRT. As such, cardiac reserve may be an additional important tool in identifying appropriate CRT candidates. In addition, interestingly, the mechanism of CRT response may include affecting systemic vascular resistance since the change in SVRI and MAP found in responders versus non-responders with exercise increased significantly. Further research to study the exact mechanism of CRT is needed.

Even with the optimal candidate, there are implantation challenges that may limit the benefit, notably implanting the LV lead in a site devoid of scar tissue. Accurately identifying and avoiding areas of scar tissue are imperative for CRT response. CMR pre-operatively can determine scar burden, but it is expensive to routinely do for every CRT candidate. Using a HR ECG machine peri-operatively has been shown by the Voltages study to identify scar tissue in regions of LV lead implantation. Areas of scar have a significantly increased voltage gradient than areas of non-scar, most likely due to decreased electrical conduction in areas of fibrosis.

Assessing voltage gradients perioperatively using a high resolution can thus optimize lead placement.

Finally, post implant considerations are essential for optimal CRT response. The meta-analysis of RCTs investigating LVESV response to CRT confirms the established benefit of resynchronization therapy. As well, LVESV is shown to correlated to the important outcome of mortality and as such is an appropriate marker to prognosticate patients. Although, there is significant heterogeneity, especially in ischemic versus non-ischemic patients, yet both HF etiology groups have been shown to similarly respond to CRT in terms of mortality benefit. Thus, another mechanism may be contributing to the mortality benefit in non-ischemic patients, as they have reduced mortality with CRT, yet lack the LV reverse remodeling reflected by decreased LVESV changes. Another important point is that the definition of response to CRT is not standardized. Most important is to increase quality of life, and reduce mortality. Possibly, non-responders that have been reported in non-RCT trials would have deteriorated further faster had they not have CRT, even though they do not meet the pre-defined response criteria.

Also, patient factors are an important consideration not to be overlooked. Other "reserves" in patients should be assessed, including reserves in terms of cognition and overall health to recover from an invasive surgery. As well, factors such as continued optimal pharmacological compliance post surgery are imperative. Variables important in predicting death include dependence on others for the activities of daily living, restricted mobility, poor self rated health, lack of social resources, socioeconomic factors and/or cognitive impairment. There is considerable heterogeneity of the LV electrical activation pattern among CRT candidates, and an individualized approach with patient selection, targeting the LV lead in the region without scar tissue and post post-operative device setting may enhance CRT response.

9.1 Future Direction/Next Steps:

The meta-analysis study showed that ischemic patients may be responding to CRT by a different mechanism than non-ischemic patients. As such, evaluating CRT response based on reverse remodeling, which may not encompass both HF etiology's, may not be appropriate. Future studies would be more applicable and generalizable to potential CRT candidates in the HF population by having a standardized outcome of cardiac related hospitalizations or death. Furthermore, the extent of reverse remodeling has been shown to change with time, so a follow up period of similar timeframe is important in future studies. Given this realization, it would be valuable to use the Nexfin device pre-operatively (or even manual blood pressure pre and post 6 minute walk test) to assess augmentation in pulse pressure. These measurements should be compared to the incidence of hospitalization/death during a narrow window follow up period of 6 months. Finally after trouble shooting the HR ECG equipment to resolve the problem of intermittent functioning, it would be useful to further investigate this potentially valuable ECG device to identify scar tissue intra-operatively in a larger sample size.

CRT has consistently shown to improve long term outcomes in select drug refractory patients, thus future studies related to optimal response to device therapy would be beneficial for patients with HF.

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