Resynchronization Therapy for Heart Failure

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I. *Introduction*

Heart failure (HF) is a clinical syndrome comprised of symptoms and signs associated with congestion and/or hypoperfusion. It can result from any structural or functional cardiac disorder that impairs the ability of the ventricles to eject blood (systolic dysfunction), to fill properly (diastolic dysfunction), or both. Heart failure is a worldwide pandemic. It afflicts approximately 22 million individuals worldwide and 5 million people in the United States, with 2 million and 550,000, respectively, new cases annually. More than 6% of the population older than 65 years of age have HF, and the incidence and prevalence are increasing. In the United States, HF accounts for approximately 900,000 hospitalizations and represents the single largest expense for Medicare. Heart failure causes or contributes to up to 300,000 deaths per year. The five-year mortality rate is as high as 50% as a result of progressive pump failure or sudden death. Heart failure is associated with large financial expenditures. It is estimated that the annual management of HF costs up to $56 billion in the U.S. The largest expenditure is for the treatment of decompensated HF, accounting for approximately $38 billion per year[1–11].

Two systems of stratifying patients with HF have been developed. The system most commonly employed is the New York Heart Association (NYHA) functional classification, which describes the degree of physical disability imposed on the patient[10]. This system is based on extent of symptoms, is useful to assess prognosis, and is used to determine entry criteria for clinical trials. A new classification was recently introduced that emphasizes both the evolution and progression of the disease (Table 1). This system, developed by the American Heart Association (AHA) and the American College of Cardiology (ACC), recognizes that there are risk factors and structural disorders that lead to the development of HF [1]. The implication of this system is that preventive strategies, including pharmacologic interventions, employed before the development of left ventricular (LV) dysfunction and before the development of HF symptoms may reduce HF progression, morbidity, and mortality in patients otherwise destined to develop HF. In those individuals with established HF, systolic dysfunction with cardiac dilation and an ejection fraction less than or equal to 40% accounts for two-thirds of the cases, and coronary artery disease is the cause in nearly 70% of the cases[12]. Sixty percent of the HF population have NYHA Class II and III symptoms. The annual mortality rate for this group of HF patients is 10%. Pharmacologic therapies have made a major impact in this group. However, despite the benefits of pharmacologic therapy, approximately 20% of HF patients will have moderate to severe symptoms with an annual mortality rate as high as 50%. The modes of death are progressive pump failure or sudden cardiac death. In the MERIT-HF trial, patients with NYHA Class II symptoms were more likely to die suddenly (64%) rather than from progressive pump failure (24%)[12]. Patients with advanced NYHA Class IV HF were more likely to die from progressive pump failure (56%) compared to sudden cardiac death (33%)[12]. It must be emphasized that in absolute terms, the risk of dying suddenly is still greater in patients with advanced HF than in those with less severe HF. Specific pharmacologic therapies slow disease progression from its early stages to the advanced stages. Once symptoms have developed, aggressive multimodality interventions are instituted to alleviate symptoms and improve clinical status and quality of life, especially in those with advanced symptoms. Therapeutic modalities that have been shown to reduce morbidity and mortality from both progressive pump failure and sudden death perspectives should be instituted[1, 11–13].

Table 1. AHA/ACC Guidelines – Stages of Heart Failure

Stage	Description
A	**Patients at high risk of developing HF** because of the presence of conditions that are strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF.
B	**Patients who have developed structural heart disease** that is strongly associated with the development of HF **but who have never shown signs or symptoms of HF.**
C	**Patients who have current or prior symptoms of HF** associated with underlying structural heart disease.
D	**Patients with advanced structural heart disease** and marked symptoms of HF at rest despite maximal medical therapy and **who require specialized interventions.**

Novel therapeutic modalities are needed to act in concert with pharmacotherapy in HF, as optimal pharmacotherapy alone still leaves a substantial portion of HF patients with significant symptoms and a shortened survival. A rapidly evolving adjunctive therapeutic modality involves using implanted electrical devices: cardiac resynchronization with or without implantable cardioverter defibrillators (ICD). This executive summary will focus on the rationale, practicalities, and outcomes thus far established from clinical trials of cardiac resynchronization therapy (CRT), alone or with an ICD (CRT-D), in patients with HF. This summary will attempt to answer the question, "Do symptomatic HF patients with low ejection fraction and QRS prolongation derive an incremental benefit from the addition of CRT or CRT-D to optimal pharmacotherapy?"

II. Mechanisms and Consequences of Mechanical Remodeling in HF

The definition of HF is broad and takes into account multiple aspects of an extraordinarily complex pathophysiologic system (Figure 1). Acute HF describes patients with sudden pulmonary edema and/or severe hypoperfusion. Chronic HF is characterized by symptomatic patients with compensated cardiac dysfunction who experience episodes of decompensation (acute HF). Untreated patients with asymptomatic cardiac dysfunction can progress to chronic HF or sometimes present initially as acute HF. Unfortunately, cardiac dysfunction is inevitably progressive: cardiac dysfunction begets HF, and initial HF begets further HF. The clinical consequences are debilitating symptoms and high rates of morbidity and mortality. Understanding the pathophysiologic events leading to cardiac dysfunction has led to novel therapies that disrupt the maladaptive consequences of cardiac injury and reduce the attendant morbidity and mortality of HF. Two notable examples are the angiotensin-converting enzyme inhibitors (ACE-I) and B-blockers, both of which slow HF progression and contribute to the reversal of maladaptive cardiac remodeling[12, 14].

Myocardial injury, regardless of etiology, is the initiating event leading to cardiac dysfunction and ultimately to the syndrome of HF. A paradigm of events begins with myocardial injury, which triggers molecular events, which in turn translate into cellular responses and culminate in anatomic changes of the heart called remodeling. As a result of remodeling, cardiac performance falls below normal physiologic requirements. This results in peripheral circulatory perturbations that trigger a series of physiologic processes, acutely beneficial but chronically detrimental. Activation of neurohormonal and other mediator pathways ultimately contributes to the symptoms of HF and leads to the various clinical manifestations

of the syndrome of HF. This paradigm should not be considered a simple series of linear events, but rather as a constant interplay of events and responses that detrimentally interact with other ongoing events and responses, the ultimate consequence of which is the progression of cardiac dysfunction.[14]

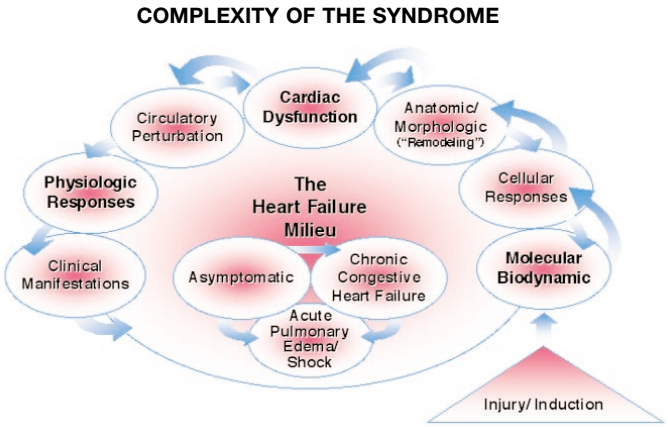

Figure 1. The Facets of Heart Failure
Depiction of the complexity interplay of the various pathophysiologic mechanisms of HF (molecular, cellular, anatomic, and physiologic) with the variable phenotypic expressions of HF (asymptomatic, acute HF, and chronic HF).

Molecular biodynamic changes are triggered by myocardial injury. This injury induces alterations in cellular protein expression and alterations in organelle repair processes that shift myocardial cells toward a fetal phenotype. This process accelerates protein synthesis resulting in myocyte hypertrophy, a key component in myocardial remodeling. The hypertrophied myocyte with a predominance of fetal proteins demonstrates contractile and relaxation disturbances that initiate compensatory cellular responses. Among these cellular responses are quantitative and qualitative changes in adrenoreceptors, changes in transcellular signal transduction, and changes in transcellular calcium transport (Figure 2). Driving these cellular changes are a large host of maladaptive mediators comprised of neurohormones, cytokines, and growth factors that overwhelm the system despite the upregulation of counterregulatory mediators which are antiproliferative and vasodilatory. Maladaptive mediators also promote myocyte apoptosis and loss resulting in fewer contractile units. Cardiac anatomic changes including myocyte hypertrophy, chamber dilation, interstitial fibrosis, and ventricular sphericity (disturbed geometry) are characteristic of cardiac remodeling (Figure 3). Physiologic consequences of remodeling include dilation of the mitral valve annulus and attendant mitral regurgitation, increased wall stress, increased oxygen consumption, and myocardial ischemia even in the absence of epicardial coronary artery disease. All of these factors promote further myocardial injury and the continued progression of cardiac remodeling and cardiac dysfunction[14–21].

Ultimately, cardiac remodeling reduces cardiac performance that falls below a normal physiologic threshold. Inadequate forward cardiac output and tissue perfusion initiate circulatory alterations that are initially beneficial but later prove maladaptive. Baroreceptor dysfunction, reduction in systemic flow to critical organs, and circulatory autoregulation failure result as a misbalance between vasodilatory/antiproliferative mediators versus vasoconstrictive/mitogenic mediators. Maladaptive peripheral responses cooperate to worsen cardiac function. Among these maladaptive peripheral responses are activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. Activation of these neurohormonal systems eventually feeds back to promote the continuation of detrimental molecular changes, cellular responses, cardiac remodeling, and worsening of cardiac performance—and this accelerates the progression of both systolic and diastolic dysfunction. The interplay of these complex processes is consequently manifest as asymptomatic cardiac dysfunction or is overtly manifest as congestive and/or low output states, cardiogenic shock, or sudden death (Figure 4).

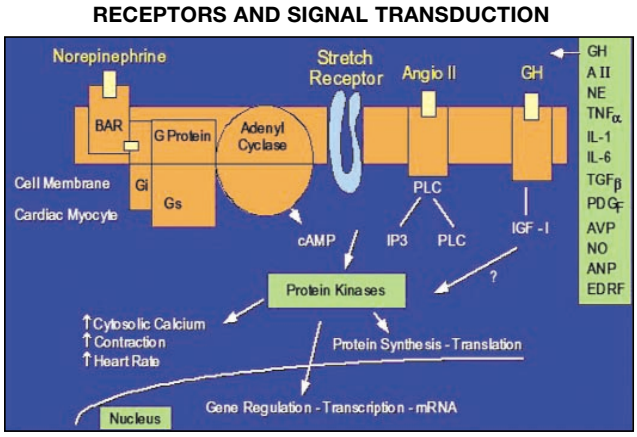

Figure 2. Trophic Factors in Cardiac Remodeling The binding of various neurohormones to receptors on cardiomyocytes over time induces signal transductions that initiate maladaptive trophic pathways leading to cardiac remodeling and diminished cardiac performance.

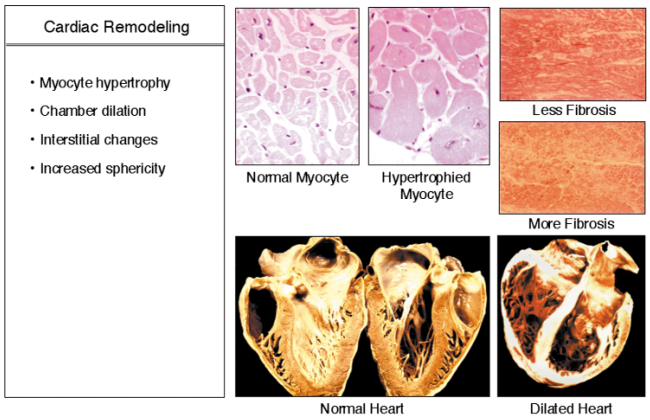

Figure 3. Anatomic and Histologic Basis of Cardiac Remodeling This figure demonstrates the histologic and anatomic changes seen in patients with chronic HF. The resultant disturbed cardiac geometry is referred to as "cardiac remodeling."

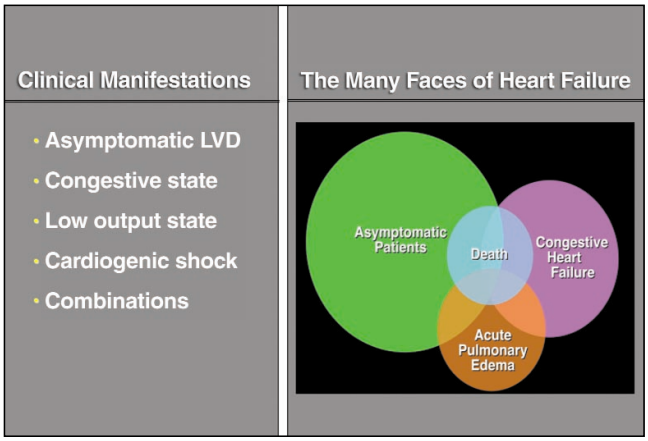

Figure 4. Clinical Manifestations of Heart Failure Heart failure is a syndrome with many possible clinical manifestations. All clinical manifestations can result in death (sudden, or from progressive pump failure).

To summarize, cardiac injury induces molecular biodynamic changes, cellular responses, and anatomic changes that are the hallmark of remodeling. The interplay of cardiac dysfunction and circulatory perturbations leads to maladaptive physiologic responses and ultimately to the clinical manifestations of the HF syndrome. HF is a progressive disorder. Its eventual consequences include debilitating symptoms and high morbidity and mortality rates.

III. Mechanisms and Consequences of Electrical Remodeling in HF

HF is a complex systemic disorder that involves not only changes in the expression of genes that control contraction and excitation but also genes that are involved in neurohormonal regulation, volume regulation, and programmed cell death. As previously described, the inciting event (myocardial infarction, pressure or volume overload, genetic or infiltrative disease of the heart, etc.) has many consequences, one of which is neurohumoral activation, which contributes to myocyte hypertrophy, direct myocyte toxicity, and induction of apoptosis. Neurohormonal activation also leads to increased inotropy by altering the active membrane properties of the myocardial cell, resulting in action potential prolongation and alterations of calcium homeostasis. Long action potentials are labile, associated with increased variability on a beat-to-beat basis. Long action potentials predispose to the development of early or late after-depolarizations that are potentially arrhythmogenic and can lead to polymorphic ventricular tachycardias. Altered cell-to-cell electrical coupling as a result of gap junction remodeling and activation of inflammatory mediators that can alter the cellular interstitium leading to conduction delays and blocks. These conduction disturbances provide the substrate for the development of monomorphic ventricular tachycardia as well as interventricular dyssynchrony. Interventricular dyssynchrony results in a less coordinated sequence of ventricular relaxation and contraction leading to cardiac mechanical inefficiency (Figure 5)[22].

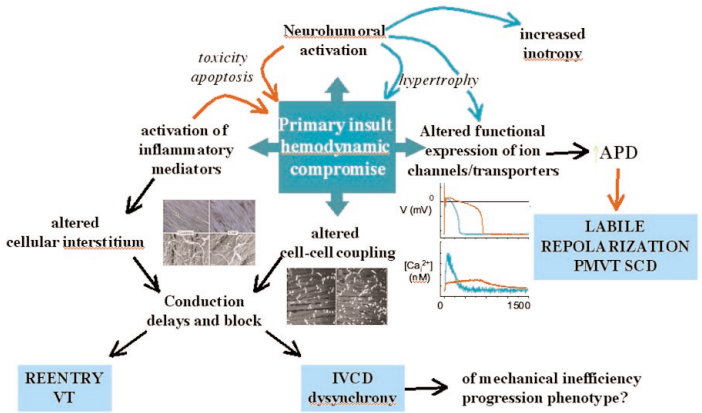

Figure 5. The Electrical Consequences of Heart Failure Heart failure is associated with a number of electrical disturbances, including action potential and repolarization prolongation and conduction delays. These disturbances may result in polymorphous or reentrant ventricular arrhythmias or in diminished cardiac performance.

There are at least two cellular electrophysiologic changes in the failing heart that conspire to produce an arrhythmogenic substrate. These are the prolongation of the action potential and the prolongation of repolarization. The mechanisms leading to action potential duration prolongation are primarily the result of a down-regulation of repolarizing potassium currents and, to some extent, an up-regulation of depolarizing currents—specifically the sodium-calcium exchange channel and changes in activation of the voltage-dependent sodium channel. Arrhythmogenesis is also promoted by the dispersion in action potential duration such that the difference between the longest and the shortest action potential is longer in the failing heart than in the normal heart. This is a rate-dependent phenomenon. At very slow rates,

the dispersion in action potential duration is even more exaggerated in the failing versus the non-failing heart, similar to the effects produced by Class III antiarrhythmics. Furthermore, there are well-described changes in calcium homeostasis that occur in the failing heart, and there are several mechanisms leading to unintended interplay between changes in intracellular calcium and in cell surface signals that affect the action potential[21].

To summarize, prolongation in action potential duration, changes in calcium handling, and cross talk between the two can set up a situation of active depolarization-mediated triggered automaticity of functional reentry in the heart leading to polymorphic ventricular tachycardia as one would encounter with the congenital long QT syndrome. Changes in active membrane properties can also conspire to produce re-entrant monomorphic ventricular tachycardia and conduction delays through prolongation of action potential duration and altered ion channel kinetics. These basic electrophysiologic mechanisms operative in HF help us understand several clinical observations, including the high sudden death rate in HF patients, the propensity for polymorphic VT, and the proarrhythmic complications of antiarrhythmic drugs.

IV. Natural History of HF with QRS Prolongation

Approximately 15% of all HF patients and more than 30% of patients with moderate to severe symptoms have inter- and intraventricular conduction delays with QRS duration greater than 120 ms that may lead to mechanical dyssynchrony of right and left ventricular contraction. Furthermore, prolonged conduction has been associated with adverse outcomes. Data from the Italian Network on Congestive HF Registry involving 150 Italian cardiology centers and enrolling 5,517 outpatients with HF sheds light on the relationship between QRS prolongation and mortality. The group defined complete left bundle branch block (LBBB) by a QRS duration greater than 140 ms and morphologic criteria. In this report, LBBB was associated with an increased one-year mortality from any cause (hazard ratio, 1.70; 95% confidence interval, 1.41–2.05). LBBB was also associated with an increased one-year mortality rate from sudden death (hazard ratio, 1.58; 95% confidence interval, 1.21–2.06). Multivariate analysis showed that this increased risk of death due to LBBB was still significant even after adjusting for age, underlying cardiac disease, other indicators of HF severity, and prescription of angiotensin-converting enzyme inhibitors and beta blockers. A substudy analysis from the Vesnarinone Study (VEST) assessed the relationship between QRS duration and mortality. In this analysis, 3,654 resting, baseline ECGs of patients with NYHA Class II–IV HF were digitally scanned. Age, creatinine, LV ejection fraction (LVEF), heart rate, and QRS duration were found to be independent predictors of mortality ($p<0.0001$). Patients with the wider QRS durations (greater than 200 ms) had a five times greater risk of death than those with the narrowest QRS durations (less than 90 ms). Based on this finding, the authors concluded that the resting ECG is a powerful, accessible, and inexpensive marker of prognosis in dilated cardiomyopathy[22–30].

QRS prolongation has adverse consequences on cardiac performance due to intraventricular dyssynchrony, atrioventricular (AV) dyssynchrony, and interventricular dyssynchrony[31, 32]. Intraventricular dyssynchrony appears to be the most important, and it results in reduced dP/dT max, increased mitral regurgitation duration delays in LV systolic and diastolic events, and reduced diastolic filling times[31–33]. The net result is a disturbance in transseptal pressures and volumes, causing abnormal septal deflections and a reduced septal wall contribution to LV performance. AV dyssynchrony prolongs the isovolumic contraction time (IVCT), thus reducing ventricular diastolic filling times[32]. One consequence of this is an increase in presystolic mitral regurgitation with a reduction in forward cardiac output. The least important factor contributing to diminished cardiac performance in the setting of QRS prolongation is interventricular dyssynchrony. Interventricular dyssynchrony instigates disturbances in ventricular interdependence, resulting in reduced LV filling.

Reversing the adverse consequences of QRS prolongation in HF should seem obvious. CRT should partially or wholly correct intraventricular, AV, and interventricular dyssynchrony and result in improved cardiac performance. The results of previous studies of CRT support the hypothesis that CRT results in improved mechanical and hemodynamic parameters in HF patients with QRS prolongation[34–36]. These observations support the rationale to evaluate the effect of restoring cardiac synchrony with atrial sensed, biventricular/LV stimulation (CRT) and to evaluate the impact of CRT-D in symptomatic HF patients with systolic dysfunction and prolonged QRS duration on symptoms, disease progression, morbidity, and mortality[34–38].

V. Controlled Trials of CRT Alone or Combined with Implantable Cardioverter Defibrillator

Table 2 summarizes the design, inclusion criteria, and results (if available) of the major controlled trials of CRT and CRT-D in HF. In general, most of these trials have similar inclusion criteria: symptomatic NYHA Class II to IV HF, LVEF less than 35%, prolonged QRS durations (>120, >130, or >150 ms), exclusion of patients having pacemaker indications, and stability of medical therapy for HF prior to enrollment. Most commonly, the studies were designed to evaluate the safety and/or efficacy of CRT or CRT-D to no CRT/CRT-D for a period of three to six months. Except for the Post AV Nodal Ablation Evaluation (PAVE) and the Multisite Stimulation in Cardiomyopathy-Atrial Fibrillation (MUSTIC AF) studies, the trials listed have excluded chronic atrial fibrillation. Only the Cardiac Resynchronization in HF (CARE-HF) and Comparison of Medical Therapy Pacing and Defibrillation in HF (COMPANION) trials delineated morbidity and mortality as primary end points. The majority of the completed trials designated functional status, exercise capacity, and quality of life as primary efficacy end points. The following table details the effect of CRT and CRT-D on the various study end points examined[39–55].

Table 2: Controlled Trials of Cardiac Resynchronization Therapy Alone or with an Implantable Cardioverter Defibrillator

Study	Type	Completion Date	Inclusion Criteria	End Points	N*	Results
Pacing Therapies in Congestive Heart Failure (PATH-CHF)	Longitudinal study of CRT with second placebo-control phase; first and third periods are crossover between LV and BiV pacing	1998	NYHA Class III–IV, $QRS_2$120 ms, sinus rate≥55 beats/min, PR≥150 ms	**Peak VO_2, peak VO_2 AT, 6-min walk,** NYHA class, QOL	41	Improved exercise capacity, functional status, and QOL
PATH-CHF II	Crossover randomized trial of no CRT vs. CRT in LV only; 2 groups: QRS 120–150 ms and QRS>150 ms	2001	NYHA Class II–IV, LVEF≤30%, QRS≥120 ms, optimal therapy for HF; ICD patients may be included	**Peak VO_2, peak VO_2 AT, 6-min walk,** QOL, NYHA class, hospitalization	89	Ongoing

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Table 2 *(Continued)*

Study	Type	Completion Date	Inclusion Criteria	End Points	N*	Results
Multisite Stimulation in Cardiomyopathy Sinus Rhythm (MUSTIC SR)	Prospective, randomized, single-blind crossover study of HF	2000	NYHA Class III, LVEF<35%, LVEDD>60 mm, QRS≥150 ms, 6-min walk<450 mm	**6-min walk, peak VO_2, QOL, NYHA class,** hospitalization, patient treatment preference, all-cause mortality, echocardiographic indices	67	Improved 6-min walk, peak VO_2, QOL, and NYHA class; reduced hospitalizations; patients preferred CRT
Multisite Stimulation in Cardiomyopathy Atrial Fibrillation (MUSTIC AF)	Prospective, randomized, single-blind crossover study of HF	2000	NYHA Class >III, LVEF<35%, LVEDD>60 mm, QRS≥200 ms during ventricular pacing, 6-min walk<450 mm	**6-min walk, peak VO_2, QOL, NYHA class,** hospitalization, patient treatment preference, all-cause mortality, echocardiographic indices	64	Improved 6-min walk, peak VO_2, QOL, and NYHA class; reduced hospitalizations; patients preferred CRT
Multicenter InSync Randomized Clinical Evaluation (MIRACLE)	Prospective, randomized, double-blind, parallel, controlled trial; duration, 6 mos.	2001	NYHA Class III–IV, LVEF≤35%, LVEDD≥55 mm, QRS≥130 ms; pts. with pacing indication not allowed; stable optimal medical therapy	**NYHA class, 6-min walk, QOL,** echocardiography indices, peak VO_2, mortality, hospitalization, QRS duration, and neurohormones	453	Improved NYHA class, 6-min walk, QOL, LVEF, ventricular volumes, mitral regurgitation, peak VO_2; reduced hospitalizations
Cardiac Resynchronization in Heart Failure (CARE-HF)	Open-label, randomized, controlled trial of CRT + optimal medical therapy vs. optimal medical therapy alone	2002	NYHA Class III–IV, LVEF≤35%, LVEDD≥30mm/m (height), QRS >50ms or QRS ≥120ms + echocardiographic criteria of dysynchrony; stable optimal medical therapy	**All-cause mortality or unplanned cardiovascular hospitalization;** all-cause mortality, all-cause mortality or hospitalization for HF, NYHA class, QOL, echocardiographic LV function, neurohormone levels, economic impact	800	Ongoing
Post AV Nodal Ablation Evaluation (PAVE)	Randomized trial comparing RV, LV, and BiV pacing (3 groups) in patients with chronic atrial fibrillation	Not Available	NYHA Class I–III, post-AV nodal ablation, 3 mos. of stable medical therapy, capable of 6-min walk but not distance >450 m	**6-min walk, QOL** (benefit from CRT-LV or BiV pacing over RV pacing, which is the current standard of care), echocardiographic indices	652	Ongoing

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Table 2 *(Continued)*

Study	Type	Completion Date	Inclusion Criteria	End Points	N*	Results
Multicenter InSync, Randomized® Clinical Evaluation-Implantable Cardioverter Defibrillator (MIRACLE ICD)	Prospective, randomized, double-blind, parallel, controlled trial evaluating safety and efficacy of CRT in HF patients with ICD indication of 6-mo duration	2002	NYHA Class III–IV, LVEF≤35%, LVEDD≥55 mm, QRS≥130 ms, ICD indication	**QOL, NYHA class, 6-min walk,** peak VO_2, exercise duration, HF composite (death, HF hospitalization, NYHA class, and patient global self-assessment), safety of CRT-D	364	Improved quality of life, NYHA class, and clinical composite end points; CRT-D safe to use
VENTAK CHF/CONTAK CD	Started as a 3-mo crossover between BiV CRT and no CRT; modified to 6-mo parallel, double-blind trial between CRT and no CRT, starting 1 mo after implantation	2001	NYHA Class II–IV, LVEF≤35%, QRS≥120 ms; ICD indication; stable optimal medical therapy	**Composite index: all-cause mortality, HF-related hospitalization, or VT/VF resulting in device therapy;** peak VO_2, QOL, 6-min walk, NYHA class, echocardiographic parameters, and neurohormones	490	Primary end point not met; lead and system effectiveness and safety end points met; improvement in peak VO_2, 6-min walk, QOL, and functional class in NYHA Class III–IV patients
Comparison of Medical Therapy Pacing and Defibrillation in Heart Failure (COMPANION)	Randomized, open-label, 3-arm study to determine whether optimal drug therapy + CRT or drug therapy + CRT-D is superior to drug therapy alone	2002	NYHA Class III–IV, LVEF≤35%, QRS≥120 ms, PR>150 ms, no indication for pacemaker or ICD	**Combined all-cause mortality and all-cause hospitalization,** QOL, functional capacity, peak exercise performance, cardiac morbidity	1120	Stopped early due to reduced all-cause mortality and hospitalization with CRT; reduced all-cause mortality with CRT-D
Pacing for Cardiomyopathy (PACMAN)	Prospective, randomized, parallel, single-blind European study of HF patients with and without ICD indications	Not Available	NYHA Class III, LVEF<35%, LBBB, QRS>150 ms	**6-min walk,** NYHA class, QOL, incidence of ventricular arrhythmias, and hospitalization	328	Ongoing

Adapted with permission from Abraham, William T. Value of biventricular pacing in advanced heart failure, Cardiology Exploration, Cleveland Clinic Foundation, 2002, Volume 5:2-14. Adapted with permission from Barold. Barold SS What is cardiac resynchronization therapy? Am J Med *2001;111:224-232*

**Accrual or accrual goals • Primary end points in bold print*

AT, anaerobic threshold; AV, atrioventricular; BiV, biventricular; CRT, cardiac resynchronization therapy; D, defibrillator; IDC, implantable cardioverter defibrillator; HF, heart failure; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; NYHA, New York Heart Association; QOL, quality of life; RV, right ventricle; VO_2, oxygen uptake; VF, ventricular fibrillation; VT, ventricular tachycardia

A. Study End Points: Coronary Sinus Lead Implant/System Safety (Table 3)

1. MUSTIC

In this trial, there were 131 patients in whom coronary sinus lead implantation was attempted. Success with first attempt was attained in 90% of the cases. In 80% of cases the lateral vein was cannulated. Failure to implant occurred in 7.8% of cases. With respect to electrical performance, the thresholds were at 1.36 + 0.96 volts (V) (0.2–4.5 V), sensing at 13 + 7 millivolts (2.6–30 mV) and impedance 738 ohms (399–1322). The overall implant success rate in this study was 89%. Fifty-eight patients had stable functional leads. The average length of time for successful implant of the total system was 126 + 45 minutes, and for the LV lead placement alone it was 42 + 35 minutes. The average biventricular stimulation threshold at three months post-implant was 2.4 V at 0.5 msec. The late LV lead dislodgment rate was 13%, but all were successfully replaced[45, 54].

Table 3. Safety of Coronary Sinus Lead Implantation

	MUSTIC	CONTAK CD	MIRACLE ICD
N	64	286	421
Successful Implantation • First Attempt • Total	 90% 92%	 87% NA	 NA 88%
Implantation Problems • Failure • Coronary Sinus Trauma • Deaths • Others	 8% NA 0% 4.5%	 13% 2% 0% 15.2%	 12% 4% 0% 38%
Late Complications • Dislodgement • Extracardiac Stimulation • Pocket Infection • Loss of Capture • Deaths • Other	 13.6% 12% 3.4% 0% 0% 3.4%	 6.8% 1.6% 0% 0% 0% 1.8%	 8.6% 3.0% 0% 0% 0% 1.3%
Pacing Thresholds (Ldts) • At Implantation • Chronic	 1.36 ± 0.96 2.4 (3 mo)	 NA 1.8 ± 1.2 (13 mo)	 1.5–1.7 (Model 4189) 1.7–2.3 (Models 218 7/8) NA

NA = Not Available

2. CONTAK CD

This was the first study in the United States to use an over-the-wire (OTW) lead. This lead tracks over a 0.014-inch standard angioplasty guide wire delivered through a guiding sheath placed in the great cardiac vein. In the CONTAK CD trial, 54% of the leads were placed in the lateral vein, 32% in the anterior vein, and 14% in the posterior vein. With respect to procedure and fluoroscopy duration, it is clear that there is a learning curve. Mean procedure time dropped from approximately 220 minutes in operators with a 1 to 3 implant experience to approximately 120 minutes in operators with greater than 15 implant

experience. In addition, mean fluoroscopy time fell from approximately 50 minutes with 1 to 3 implant experience to 35 minutes in operators with greater than 7 implant experience. In the CONTAK CD trial, despite the use of a different LV lead compared to that used in the MUSTIC trial, the initial implant success rate was similar: 87%. After six months of implantation experience, the success rate in one procedure was 91%. Procedure-related adverse events other than implantation failure occurred in 15.2% of attempts. Over a six-month period, 97% of systems were intact. Late complications occurred in 10.2% of patients. Mean chronic LV pacing thresholds in 233 patients were 1.8 + 1.2 V. Mean chronic biventricular sensing R-wave was 9.8 + 4.4 mV[50, 51].

3. MIRACLE ICD

This study included stylet-driven and OTW leads (2187, 2188, and 4189). Of 421 patient implant attempts, successful implantation occurred in 371 (88%) of cases. Adverse events during the implantation occurred both in the successful and in the unsuccessful implants. These included evidence of coronary sinus dissection, heart block, pericardial effusion, ventricular tachycardia, etc. The actuarial probability of being event-free at six months was 85.1% for the 4189 lead and 89.9% for the 2187/2188 leads[49].

In summary, the initial placement of CRT or CRT-D devices via the coronary sinus vein is successful in approximately 90% of first attempts. The success rate and procedure time both improve with experience. The placement of these devices appears safe both acutely and chronically compared to risks associated with standard dual chamber pacemaker implantation. The overall incidence of coronary sinus dissection was 2% to 4% when defined as any evidence of staining in the vascular wall. The incidence of true perforation of the coronary sinus was rare. In the three trials listed in Table 3 (n = 771), there were no reported CRT or CRT-D device-related deaths.

B. Study End Points: Functional Class and Quality of Life

Improvement in clinical status and quality of life by alleviating symptoms is an important goal in the treatment of chronic HF. Trials of CRT or CRT-D have often used NYHA functional class and quality of life as primary end points to assess the impact of CRT on the well-being of the HF patient. Table 2 summarizes the impact of CRT or CRT-D on these parameters in prospective, randomized, controlled trials[38–43, 45–54].

In the PATH CHF study (Table 2), NYHA functional class significantly improved with 63% of patients improving to Class I or II. All improvements persisted after 12 months of therapy. The quality of life scores did not significantly improve. In the MUSTIC SR/AF studies, functional class and quality of life were evaluated at 12 months and compared to baseline. These studies showed CRT resulting in an improvement of NYHA functional class by 25% to 27%, p=0.0001, and quality of life improving by 36%, p=0.0001 (SR) and 32%, p=0.002 (AF)[54,55]. In the MIRACLE trial, which included 453 patients, CRT was associated with improvement in NYHA class (p<0.001). Quality of life as assessed by the Minnesota Living with HF score was better with CRT (−18 points) compared to control (−9, p=0.001). In the MIRACLE ICD trial, at six months NYHA functional class improved in 63% of patients receiving CRT and 47% of patients in whom CRT was off (p=0.028). Quality of life scores had improved by 19 points in the CRT group and by 10 points in the no-CRT arm (p=0.0098). In the CONTAK CD trial, functional class and quality of life at six months was improved in the subgroup of patients with more advanced HF (NYHA functional class III and IV). Seventy-three percent of the patients who received CRT showed an improvement by at least one functional class compared to the no-CRT group (p=0.006). The change in quality of life at six months showed an improvement from baseline of ~10.1 points when compared to control (p=0.017). Although these studies differ in design, whether crossover or parallel, CRT appears to have a favorable effect on functional status and quality of life. This effect, however, seems to be restricted to HF patients with more advanced symptoms—the NYHA functional class III and IV population.

C. Study End Points: Exercise Capacity/VO_2

Exercise intolerance is one of the cardinal symptoms of HF and is an end point that has been evaluated in controlled trials of resynchronization therapy. The studies that are highlighted are the MIRACLE, CONTAK CD, and MIRACLE ICD trials. Table 4 summarizes the demographic and clinical characteristics of the patient populations enrolled in the three trials. Results are shown in Figures 6 to 9. The peak oxygen uptake (VO_2) data, which directly reflects cardiac efficiency and maximal cardiac performance, was very consistent across all three studies for NYHA functional class III–IV patients. The magnitude of improvement with CRT ranged from 1 to 2 ml/kg/min. The six-minute walk test is determined by the same physiologic parameters that determine maximal exercise. The six-minute walk distance improvement ranged from about 20 meters to 40 meters in CRT compared to control patients. Exercise duration is not as objective as the other measures of exercise capacity and is, in fact, subject to greater placebo, training, or familiarity response. However, exercise duration increased by 30 to 60 seconds across the studies in patients receiving CRT. It was concordant with what one would expect from changes in VO_2. The VE/VCO_2 slope provides a more objective measure, as it is not motivation-dependent. It is related to cardiac output and pulmonary blood flow distribution and is a measure of pulmonary dead space and ensuing ventilation-perfusion imbalance. In the MIRACLE trial, there was a reduction in this slope, suggesting a favorable metabolic response with CRT (Figure 9). However, there was no significant difference on VO_2 at the anaerobic threshold with CRT. In conclusion, CRT is associated with significant improvement in exercise capacity, and the improvement was consistent across the studies and concordant among the various measures tested[46, 49, 51].

Table 4. Demographics and Clinical Characteristics of Patients Enrolled in Major Trials Evaluating Exercise Capacity

	CONTAK CD (All Pts)	CONTAK CD (Advanced)	MIRACLE	MIRACLE ICD
N	490	227	453	362
Age (years)	66 ± 11	66 ± 11	65 ± 11	68 ± 10
Gender (% male)	84	78	68	77
NYHA Class (%) (II/III/IV)	33/58/9	-/89/11	-/91/9	-/89/11
LVEF (%)	22 ± 7	21 ± 6	22 ± 6	20 ± 6
Ischemic (%)	69	68	54	68
Peak VO_2 (m//kg/min)	13.5 ± 3.1	12.0 ± 3.0	14.3 ± 3.4	13.5 ± 3.9

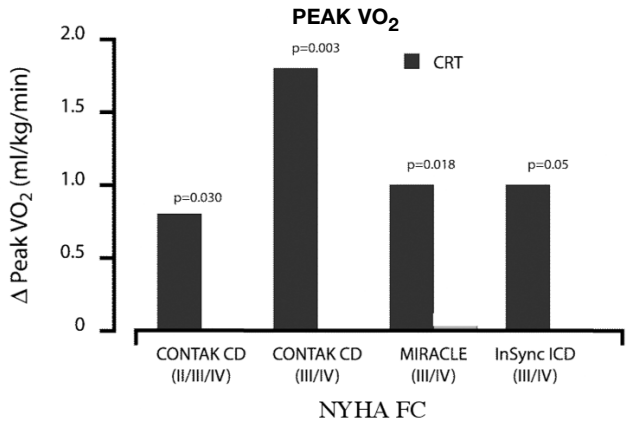


Figure 6. The Effect of CRT on Peak VO_2 Shown are the absolute changes in peak oxygen consumption (VO_2) after six months of CRT.

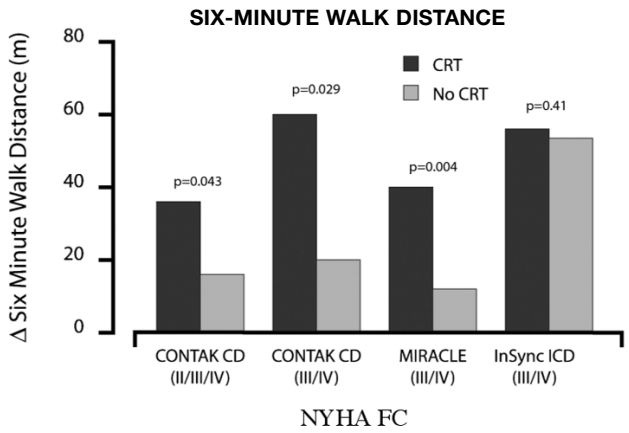


Figure 7. The Effect of CRT on Six-Minute Walk Distance Shown are the absolute changes in a six-minute walk distance after six months of CRT or no CRT compared to baseline in three randomized trials.

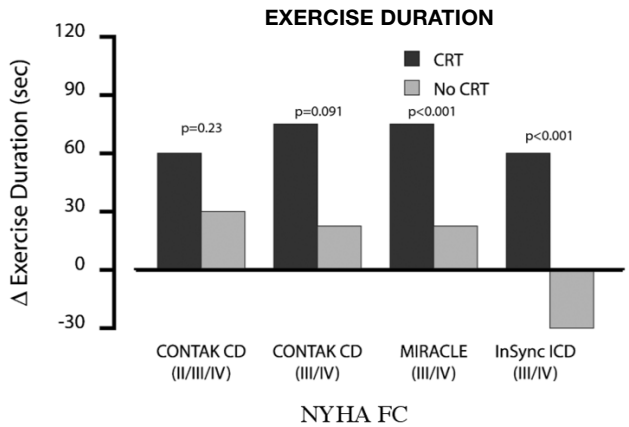


Figure 8. The Effect of CRT on Exercise Duration Shown are the absolute changes in treadmill exercise duration after six months of CRT or no CRT compared to baseline in three randomized trials.

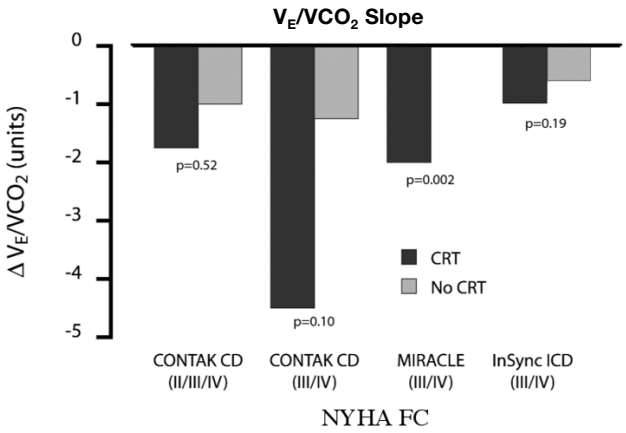


Figure 9. The Effect of CRT on V_E/VCO_2 Slope
Shown are the absolute changes in the V_E/VCO_2 slope after six months of CRT or no CRT compared to baseline in two randomized trials. A significant reduction in the V_E/VCO_2 was only seen in the MIRACLE trial.

D. Study End Points: Measures of Disease Progression

In examining the effect of CRT on measures of disease progression, it must be emphasized that the pertinent parameters were only analyzed as secondary or ancillary end points in the trials performed to date. The echocardiographic assessment of disease progression with CRT can be evaluated by its effect on cardiac structure and function. Anatomic correlates of disease progression include LV dimension, volume and shape, LV mass, and left atrial size. Physiologic correlates consist of measures of systolic function such as LVEF, myocardial performance index, and degree of mitral regurgitation. Measures of diastolic function include Doppler-derived mitral deceleration time (EDT), pulmonary vein systolic/diastolic flow, and the E to A ratio. There have been attempts to evaluate chronic neurohormonal activation with CRT to assess disease progression. The neurohormones measured have included plasma concentrations of norepinephrine, epinephrine, B-type natriuretic peptide, dopamine, and big endothelin. A number of investigators have attempted to evaluate surrogate measures of neurohormonal activation with heart rate variability parameters.

The first trial in the United States to assess the effect of CRT was the VIGOR HF trial, which required implantation of an epicardial lead via a thoracotomy to attain LV stimulation. With three months of continuous biventricular stimulation, left atrial size decreased in 70% of patients. In roughly 80% of patients, significant reductions were noted in LV end systolic and diastolic dimensions and LV end systolic volume. There was no significant effect of CRT on LV end diastolic volume, mass index, sphericity index, and norepinephrine levels. The myocardial performance index was reduced by CRT. The improvement was predominantly due to lengthening of the isovolumic contraction time. In the MIRACLE and MIRACLE ICD trials, six months of CRT significantly reduced LV end diastolic and end systolic volumes, mitral regurgitation, and interventricular mechanical delay while it improved LVEF. In the CONTAK CD trial, CRT resulted in significant reductions of LV diastolic and systolic dimensions, LV end systolic volume, and improvement in LVEF. CRT did not exert any significant effect on neurohormones or heart rate variability. It must be stressed that in these studies, more than 50% of patients were treated with beta-blockers[46, 49, 51, 55–58].

To summarize, over a six-month period, chronic CRT decreased ventricular size and improved most measures of systolic function. In one study, LV mass also decreased[56]. There do not appear to be significant effects on all measures of diastolic function, or sphericity. In addition, a recent study showed that withdrawal of CRT after one month resulted in reversal of its beneficial effects on cardiac structure[31]. These findings suggest that the CRT-induced changes seen on echocardiographic paraments likely reflect partial reverse

remodeling on the myocardium. Whether a longer period of CRT will also affect LV mass and sphericity remains to be studied.

E. Study End Points: Hospitalization/Mortality

It is clear that in patients with systolic HF, prolonged QRS, and moderate to severe symptoms, CRT is associated with improvements in quality of life, functional status, and exercise capacity, as well as improvements in LV structure and function. These improvements may be associated with reduced hospitalization and mortality. Hospitalization and mortality data is reviewed from three controlled, randomized, parallel design studies with six-month follow-up: MIRACLE, MIRACLE ICD, and CONTAK CD trials. In these studies, patients with symptomatic HF of ischemic or non-ischemic etiology and an ejection fraction of less than 35% were randomized. In the CONTAK CD trial, NYHA functional class II–IV were included, while in the MIRACLE and CONTAK CD trials NYHA functional class III and IV patients were enrolled. The QRS duration across these three trials was >120 or >130 ms. All patients were on stable, optimal medical therapy. An indication for a defibrillator was a requirement for inclusion in the MIRACLE ICD and the CONTAK CD trials but was an exclusionary criterion in the MIRACLE trial. The study design across the three trials was similar[46, 49, 51]. All patients had CRT or CRT-D devices implanted and then were randomized to CRT or no CRT for a period of six months. The primary end point in the MIRACLE trial and the MIRACLE ICD trial was a combination of quality of life, six-minute walk distance, and NYHA functional class. The primary end point in CONTAK CD was HF progression defined as a composite of mortality, hospitalization, and VT/VF events. A modified composite included HF events[51].

The recently completed COMPANION trial was prospectively powered to evaluate the effects of CRT versus optimal pharmacologic therapy (OPT) versus CRT-D[52]. The study was terminated after enrolling 1,520 patients in November 2002 due to positive effects of CRT, CRT-D therapies on the primary end point[59].

1. MIRACLE

The MIRACLE trial enrolled 453 patients randomized to CRT versus no CRT. CRT was associated with a 40% reduction in the risk of hospitalization for worsening HF (hazard ratio, 0.60; 95% confidence interval, 0.37–0.96; p=0.03), a 39% reduction in the risk of death or worsening HF requiring hospitalization or intravenous treatment (hazard ratio, 0.61; 95% confidence interval 0.40–0.93; p=0.02), and a 50% reduction in risk of hospitalization for worsening HF (hazard ratio, 0.50; 95% confidence interval, 0.28–0.88; p=.02). Furthermore, the total number of days hospitalized for HF was reduced by 77% in patients receiving CRT compared to control (p=0.012). The average length of stay for worsening HF was reduced by 3.6 days in the CRT arm compared to control (p=0.024). CRT did not reduce mortality, but the study was not sufficiently powered to address this end point[46].

2. MIRACLE ICD

The MIRACLE ICD trial randomized a total of 362 patients to the two treatment arms. In this study, CRT was not associated with a reduction in all-cause mortality, all-cause hospitalization, or HF hospitalization. There was a trend toward reduced risk of death or worsening HF requiring hospitalization in the CRT group compared to control. The trend did not reach statistical significance[49].

3. CONTAK CD

The CONTAK CD trial randomized 490 patients. In this study, the primary end point of reduced HF progression with CRT was not met. In this study, CRT was not associated with a reduction in the combined end points of all-cause mortality and worsening HF requiring hospitalization in the CRT arm compared to no CRT. There was a trend toward reduction in all-cause mortality or worsening HF in the CRT arm compared to no CRT, but this did not reach statistical significance[51].

In summary, three controlled trials had morbidity and mortality evaluated only as secondary or ancillary end points. In these three trials with relatively small sample sizes to adequately examine these end points, CRT was not associated with a reduction in all-cause mortality or all-cause hospitalization (Table 5). Only in the MIRACLE trial was there a reduction in hospitalization for HF and the risk of death or worsening HF requiring hospitalization in the patients receiving CRT. A recent meta-analysis of prospective randomized trials of CRT versus controls found that CRT reduced deaths due to progressive HF by 15% (or 0.49; 95% confidence interval, 0.25–0.93), reduced HF hospitalizations by 29% (or 0.71; 95% confidence interval, 0.53–0.96), and trended toward reduced overall mortality (or 0.77; 95% confidence interval 0.51–1.18)[58].

Table 5. Summary of Morbidity and Mortality End Points

	MIRACLE	MIRACLE ICD	CONTAK CD	COMPANION*
N	453	362	490	1,520
Death and hospitalization	↔	↔	↔	↓
Hospitalization for HF	↓50% p=0.015	↔	↔	↓
Death or worsening HF requiring hospitalization	↓40% p=0.033	↔ + IV meds p=0.07	↔	↓
Death or worsening HF	NA	NA	↔ p=0.10	↓

**preliminary data*

4. COMPANION

The COMPANION trial was designed to prospectively evaluate the effects of CRT on hospitalization and mortality. COMPANION randomized NYHA functional class III and IV HF patients to three treatment arms: optimal pharmacotherapy (OPT), OPT with CRT, and OPT plus CRT-D in a 1:2:2 randomization[52]. All patients were required to have a hospitalization or acute therapy for heart worsening within 12 months prior to enrollment. These preliminary results of this landmark trial establish CRT and CRT-D as important additive therapies, in addition to optimal pharmacologic therapies, in the management of advanced heart failure. The importance of these findings is underscored by the fact that more than 65% of patients enrolled were receiving beta-receptor blocker therapy, and more than 50% were taking spironolactone. The study was stopped in November 2002 after enrolling 1,520 patients, as it met its primary end point. CRT and CRT-D were associated with a 19% reduction in the combined primary end point of all-cause mortality and all cause-hospitalization[59]. Furthermore, CRT-D was associated with 40% reduction in all-cause mortality[59].

5. CARE-HF

CARE-HF, a European trial, aims to randomize 800 patients to optimal medical therapy or optimal medical therapy plus CRT with the primary outcome measure being all-cause mortality or unplanned

cardiovascular hospitalization.[47] The trial is still ongoing but nearing completion.

In conclusion, CRT exerts beneficial effects on several different measures of symptom status. As a result of the early closure of the COMPANION trial, CRT appears to reduce all-cause mortality and all-cause hospitalization. The mortality benefit, however, may be restricted to CRT-D. Details of the findings from this study will be forthcoming and available for further scrutiny. Results of the CARE-HF study are also eagerly awaited for confirmation.

VI. Expanding Indications for Electrical Heart Failure Devices

A. Chronotropic Support

Clinical trials of CRT performed to date have utilized an atrial sensed–biventricular stimulation mode (VDD-biventricular). The goals of this trial design were to establish the independent benefit of biventricular resynchronization. This modality avoids the confounding effects of the potential benefit of providing atrial rate support in this population; it also limited enrollment to patients without a history of sinus node incompetence.

Interestingly, there appears to be a strong physician preference to program on atrial rate support. Data from the CONTAK CD trial of CRT-D indicate that 6–% of patients had atrial rate support programmed on after the study phase of the trial[60].

In those patients with established chronotropic incompetence without overt heart failure, atrial rate support has proven benefit. In heart failure subjects, increased use of drug therapies such as amiodarone or beta-receptor blocking agents increase the risk of developing secondary chronotropic incompetence. Further, atrial rate support will allow patients with bradycardia to receive therapy with rate-slowing drugs[61–64].

B. Atrial Arrhythmia Management

As heart failure severity increases, the incidence of atrial fibrillation increases, impacting up to 50% of patients with NYHA functional class IV symptoms. With the onset of atrial fibrillation, NYHA functional class worsens and risk of thromboembolism increases in the advanced HF population. There is suggestive, but not conclusive, data indicating that atrial fibrillation is a risk factor for increased mortality in heart failure patients. A prospective multicenter trial (AF-CHF trial) recently began enrolling patients. The trial will compare the effects of two management strategies. Patients (n = 1,450) with LVEF less than 35% will be randomized to either ventricular rate control or to therapies aimed at restoring sinus rhythm. The primary end point is total mortality[65–68].

The management of atrial fibrillation can, theoretically, be enhanced with a heart failure device capable of diagnostic, preventative, and therapeutic functions. Although these features are present in market-released pacemakers and/or defibrillators, they have not been tested for safety or efficacy when combined with CRT.

C. Right Heart Hemodynamics/Heart Rate Log Variability

The ability to record short- and long-term right heart hemodynamic data from an implantable device has several potential advantages for the HF patient. These include the ability to improve the current understanding of the hemodynamic alterations that occur in ambulatory HF patients and the hemodynamic responses to therapy. Such data could also provide health care providers with an early warning of hemodynamic deterioration. Appropriate use of this data could profoundly influence health care utilization and patient outcome (Table 6).

Table 6. Implantable Hemodynamic Monitor: Possible Applications

• Improve current understanding of the hemodynamic alterations that occur with heart failure and the hemodynamic response to therapy
• Allow more precise titration and tailoring heart failure and pulmonary vascular disease (PH) therapy
• Provide "early warning" of hemodynamic deterioration
• Aid in the diagnosis of symptomatic events in the outpatient setting (home or clinic)
• Provide method by which to develop, refine, and optimize the use of chronic hemodynamic data for long-term patient management
• Possibly affect the intermediate and long-term morbidity and mortality in patients with heart failure

One implantable device now being tested in clinical trials, the Chronicle Hemodynamic Monitor, measures right heart pressures using a passive fixation lead placed in the right ventricular outflow tract. Data from the recently completed Phase I study demonstrate that right ventricular and pulmonary artery pressures obtained from the device correlate well with simultaneous acute and chronic pulmonary artery catheter-derived pressures. A Phase II trial is in the planning stages to evaluate how use of the hemodynamic data can impact HF management strategies on morbidity and mortality outcomes[69–72].

There is very little published data defining the utility of the use of heart rate variability logs to make therapeutic decisions or to predict HF worsening. Depressed heart rate variability has been independently associated with an increased risk of death from progressive pump dysfunction[73–74].

No device has yet been tested in clinical trials that combines heart rate logs and hemodynamic monitoring with resynchronization therapy.

VII. Technical Issues

A. Operative Considerations

Implantation of a resynchronization device requires a higher level of pre-, intra- and post-operative preparation and care than either standard right-sided pacemaker or ICD implant procedures. Candidates for CRT have advanced HF and, hence, are at higher risk for operative complications. The placement of the coronary sinus lead increased the complexity, duration, and risk of the procedure.

The majority of implanting physicians are utilizing the support of a dedicated anesthesia provider to optimize surgical conditions in order to assure adequate analgesia, anesthesia, and quick recovery while avoiding hemodynamic instability. Many experienced implanting physicians and anesthesia providers avoid general anesthesia or quickly recover the patient after the procedure to avoid prolonged ventilatory support. The majority of procedures are done under monitored anesthesia care (MAC) with conscious sedation.

If general anesthesia is used, a combination of the narcotic remifentanyl and propofol achieves hemodynamic stability, excellent analgesia, anesthesia, and recovery. If MAC is used, remifentanyl and propofol may still be administered as an infusion, but both agents have a narrower therapeutic window than either fentanyl or midazolam[75–77].

B. Techniques to Ensure Implant Safety and Success

Safe and successful implantation of a resynchronization device using a transvenous approach for the right atrial, right ventricular, and left ventricular coronary sinus branch vein lead requires additional skills beyond those used in stylet-driven lead implantation. Familiarity with over-the-wire (OTW) tools and techniques, such as those used in coronary intervention, is essential. Data from clinical trials performed in the U.S., Canada, and Europe indicate that the procedure can be performed with safety and success in more than 87% of patients[45, 46, 49–51].

Due to observations obtained from the COMPANION trial and other clinical trials of resynchronization, it is now recommended that total procedure time be kept under four hours to minimize intra- and post-operative complications. If a resynchronization defibrillator is being placed, consideration can be given to deferring defibrillation threshold testing if the procedure duration is long or a patient's stability is an issue[59].

A second operative table or larger table than is used for right-sided implants is recommended to accommodate the tools needed for the guiding sheath and the OTW tools. Many implanting physicians place the right atrial and right ventricular leads first, to further define right heart anatomy and to protect against heart block when manipulating the coronary sinus guide and lead. A separate venous access site is typically used for the coronary sinus lead to facilitate placement and removal of the guiding sheath. Manipulation of the coronary sinus guide through the vasculature, right heart, and into the coronary veins should be performed with a guide wire or EP electrode catheter, in advance of the guiding sheath, to avoid vascular trauma.

Both LAO and RAO fluoroscopic views facilitate identification of the coronary sinus os and branch veins. Venography performed directly through a guiding catheter using a handheld injection or by use of an occlusive balloon catheter can be used to identify the coronary os and the coronary sinus branch veins (Figure 10). Care should be taken to avoid dissection of the coronary sinus by using scrupulous technique and puffs of contrast to ensure that the guides and catheters are appropriately seated. The ability to store images that can be used as "road maps" is a definite advantage.

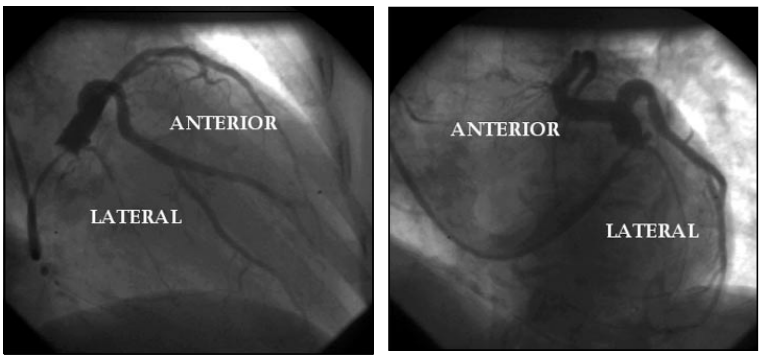


Figure 10. Coronary Sinus Great Vein and Branch Veins
RAO (left panel) and LAO (right panel) radiographic images of the great cardiac vein and branch veins obtained using balloon occlusive venography.

The choice of a stylet-driven or OTW branch vein lead should be based on operator preference and individualized according to the coronary sinus anatomy. The majority of leads now being placed are the OTW leads, as they facilitate the ability to negotiate bends or narrower veins. The wires themselves are useful mapping tools that can help define the anatomy and limit the use of contrast. Large caliber non-tortuous branch veins are ideal for stylet-driven leads.

The risk of lead dislodgment is highest during removal of the guiding sheath, after the lead is in a stable

branch vein position. Placement of a finishing wire, guide wire, or stylet can help to stabilize the lead during this procedure. Avoidance of a lead accumulation or looping in the right atrium is also key to removing the sheath without dislodging the lead.

If technical or anatomic limitations are present that prohibit successful placement of a coronary sinus branch vein lead, many physicians may choose to attempt a second procedure. Alternatively, consideration may be given to a direct epicardial approach for lead placement via thoracoscopy or limited thoracotomy or robotically assisted procedure. The epicardial approach requires a more invasive procedure with associated greater risk and morbidity. The long-term stability of capture thresholds with either an active fixation or steroid eluting epicardial electrode is inferior to that achieved from a coronary sinus branch vein lead[78–79].

C. Technical Aspects of Coronary Sinus Lead Implantation

1. Impact of Atrial and Ventricular Remodeling on Coronary Sinus Anatomy

The anatomic process of remodeling that occurs in heart failure is not limited to the ventricles. As right atrial pressure rises, the atrium dilates in those areas that are not well supported by fibromuscular tissue. These areas include the subeustachian and coronary sinus fossae, located in the inferior aspect or floor of the right atrium. Enlargement of these fossae causes these areas to dilate and deepen, to variable degrees. This in turn alters the shape of the right atrium, which becomes less tubular and more spherical in shape (Figure 11). LV remodeling leads to mitral annular dilation, resulting in changes in the angulation of the coronary sinus. These changes can also impact the location of the coronary sinus os and angulation of the great cardiac vein, making identification and cannulation of the cs and advancement of a wire or guiding sheath extremely challenging in some patients (Figure 12)[80].

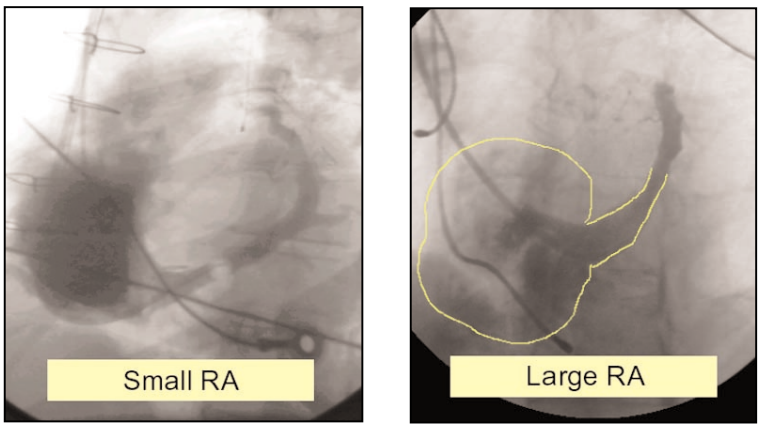


Figure 11. Atrial Remodeling in Heart Failure The left and right panel images are LAO projections. The left panel demonstrates a normal size right atrium. The coronary sinus great vein is also visualized.

The right panel shows incomplete right atrial filling due to marked RA remodeling with contrast injection. The coronary great vein is visualized and takes a vertical course. This coronary sinus OS is displaced upward.

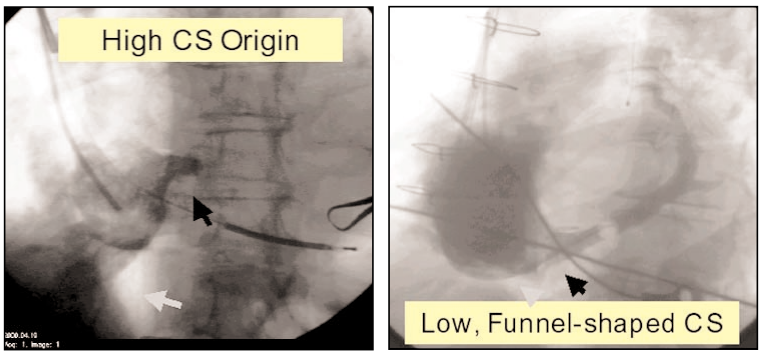
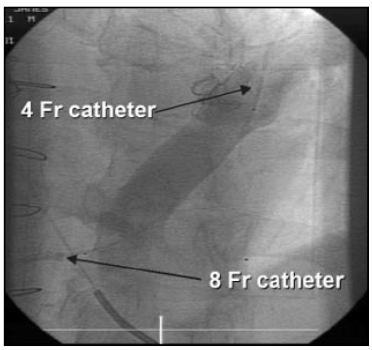


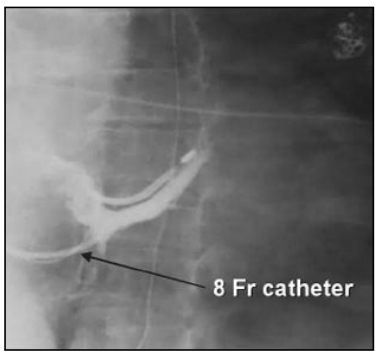
Figure 12. Variations in Coronary Sinus Anatomy in Heart Failure The right and left panels show LAO projections of the coronary sinus during right atrial venography. The left panel demonstrates a high CS origin while the right panel illustrates a low and narrow CS origin.

The presence of remnant valves that can completely or partially occlude the os and great vein also make lead delivery difficult. Care should be exercised to cross these valves with the use of a guide wire and/or venography so that dissection is avoided.

Great cardiac and branch vein dimension is also highly variable (Figure 13). There may be marked differences in branch vein number, diameter, and course, according to whether heart failure is due to non-ischemic or ischemic etiology. Veins that follow the course of occluded arteries may be atretic or tortuous (Figure 14). Soft guide wires and telescoping guiding catheters are available and helpful in negotiating crimps or bends present in tortuous branch veins.

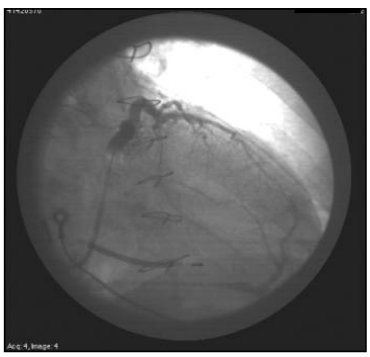


CS diameter 23 mm



CS diameter 7mm

Figure 13. Variations in Coronary Sinus Great Cardiac Vein Diameter in Heart Failure The right and left are panel LAO projections of occlusive venograms of the great cardiac vein. The left panel illustrates a very large caliber vein. The right panel illustrates a small caliber great cardiac vein.



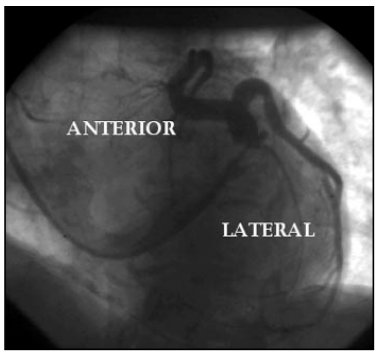


Figure 14. Coronary Sinus Branch Veins – Ischemic Cardiomyopathy The right and left panels are RAO projections demonstrating an occlusive venogram of the coronary sinus distal branch vein anatomy. The branch veins are tortuous and taper markedly in the distal course (left panel).

The right panel demonstrates successful over-the-wire lead placement in this branch vein.

2. Issues Related to Coronary Sinus Epicardial Capture Thresholds

Coronary sinus venous branch vein pacing differs from right ventricular endocardial pacing primarily because the electrode myocardial interface differs. While the epicardium is stimulated directly from the LV electrode, there is a variable degree of distance between the LV electrode, placed in the vein and the epicardium. This distance depends upon the degree of venous/epicardial fat, design of the stimulating electrode, and location of the lead in the vein (Table 8).

First generation resynchronization devices achieve biventricular stimulation with a shared cathode bipolar configuration. The cathode is shared between the LV and RV distal electrodes, and the anode is the proximal ring of the RV lead. This type of parallel circuit increases current flow due to low resistance. However, shared cathodal configurations do not follow simple predictions of impedance according to Ohms law of unparalleled circuits. The shared current flow delivered once the leads are placed in the

header results in a higher capture threshold for both leads, compared to the threshold obtained when they are individually tested in the unipolar mode. The differences range from 22% to 30% higher in the split cathodal bipolar configuration than in the unipolar configuration alone. Another consideration with this type of current delivery is that anodal stimulation of the right ventricle may occur at high voltage outputs. This can result in three separate paced QRS configurations and introduce confusion in determining right and left ventricular capture thresholds (Figure 15)[81].

Table 7. How Is Coronary Sinus Branch Vein Pacing Different?

• LV stimulation is epicardial while RV is endocardial —LV stimulation is through the venous wall —RV stimulation is directly against the endocardium —LV electrode-myocardial interface distance is greater
• Shared cathodal configuration —Bipolar —Unipolar
• Widely split bipole
• Separate output circuits

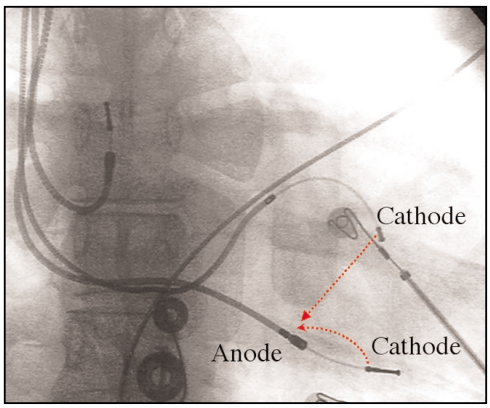


Figure 15. Biventricular Stimulation-Shared Cathode Bipolar (Tip Electrode) This AP image demonstrates an LV branch vein unipolar lead in a lateral coronary sinus vein and an RV bipolar lead in the RV apex.

Biventricular stimulation is achieved using a shared cathodal bipolar configuration.

Current generation resynchronization devices have separate output circuits to stimulate the left and right ventricles independently. Both circuits can be bipolar, and current to each lead can be controlled separately. The impedance is increased compared to the parallel bipolar configuration used now, resulting in the potential for less current flow. However, the two separate outputs also have the potential to increase current flow. Another advantage of this design is that the timing of left and right ventricular stimulation can be varied.

There are several factors that can influence left ventricular branch vein epicardial capture thresholds. An adequate LV capture threshold is generally defined as one that achieves adequate acute R wave sensing

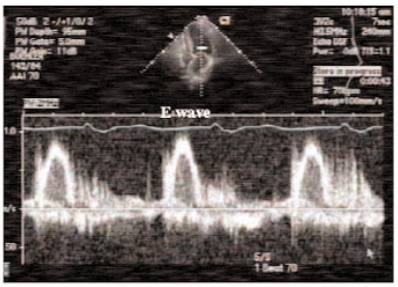
of greater than 5 millivolts and pacing at less than 1.5–2 volts without the presence of phrenic nerve/diaphragmatic stimulation. If diaphragmatic stimulation is not present acutely in the supine patient, at 10 volts and 0.5 msec output, consideration should be given to placing the patient on a wedge or tilting the patient's upper torso to ensure it is not present in an upright position. In dog models, using an OTW lead design, the lowest capture thresholds are found toward the apex versus the base of the left ventricle, where the lead tends to be in closer approximation to the epicardium due to the smaller caliber of the veins distally[81].

VIII. Achieving Resynchronization and Measuring Outcomes

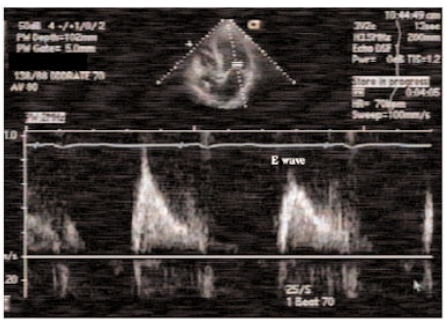
A. Acute Optimization of the AV Interval

While studies have shown that the majority of acute hemodynamic benefit resulting from CRT is independent of the programmed AV interval, left-sided AV timing is an important consideration in the programming of resynchronization devices. Unfortunately, there are no well tested criteria that define the best methods of measuring or assessing the effects of AV interval programming. The most widely used measures are acute hemodynamic measures of forward output and echo/Doppler assessments[82–87].

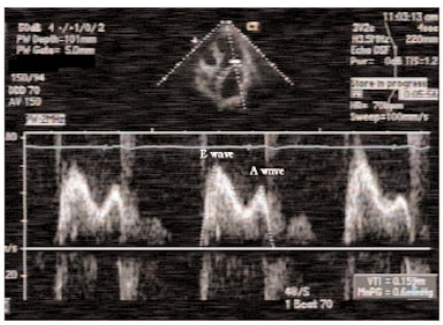
The goals of AV interval programming during CRT are to select the AV interval that optimizes both left ventricular filling and forward stroke volume (Figure 16). In Figure 16, three mitral inflow Doppler profiles are shown. In the top figure, during baseline sinus rhythm with a prolonged PR interval of 240 msec, mitral E and A wave are fused. This is due to atrial contraction beginning in early diastole resulting in atrial contraction becoming superimposed upon the early left ventricular filling phase. This causes curtailed ventricular filling. If atrial relaxation then occurs when left ventricular end-diastolic pressure rises so that it exceeds left atrial pressure, diastolic mitral regurgitation may be observed. The lower left panel illustrates a very short programmed AV interval of 80 msec. In this instance, atrial contraction occurs at the onset of ventricular systole, against a closed mitral valve. Programming the AV interval to 150 msec results in separation of the early filling and atrial contraction, normalizing the filling pattern. Figure 17 demonstrates that forward output, as assessed by aortic valve velocity time interval, also improves at the AV interval that maximizes filling[86].



Baseline PR 240 msec

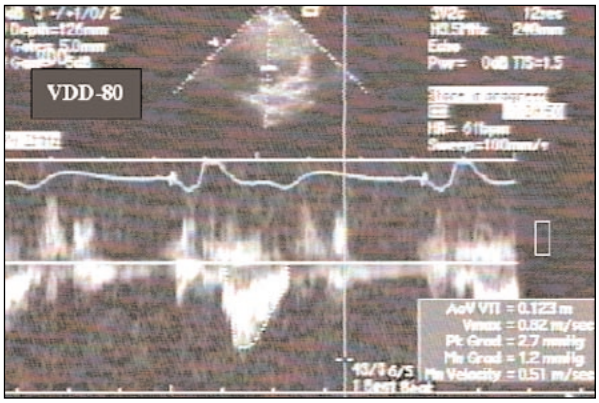


AV Delay = 80 msec

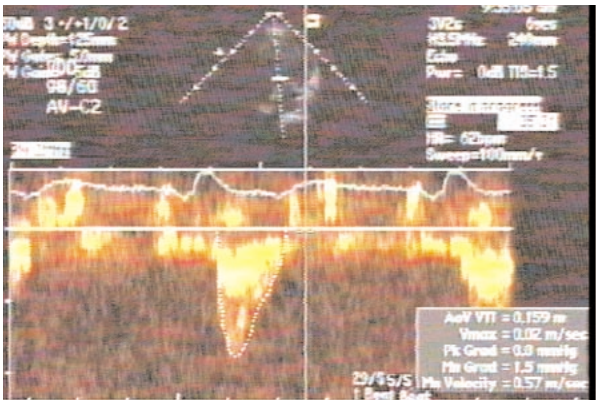


AV Delay = 150 msec

Figure 16. Doppler Profile Mitral Inflow–Effects of Varying AV Interval During Resynchronization Therapy. See text.



VDD with AV delay of 80 msec



VDD with AV delay of 150 ms

Figure 17. Doppler Profile of Aortic Valve Flow of Varying AV Interval During Resynchronization Therapy A surrogate for the stroke volume, velocity time interval (VTI), calculated by Doppler echocardiography of aortic valve flow, is less with very short programmed AV delay (left panel). Forward flow is optimized by extending the programmed AV interval to 150 msec.

Currently, most implanting physicians place the right atrial lead in the right atrial appendage or high right atrium for sensing and pacing. However, timing of mechanical left atrial to left ventricular events during CRT may differ markedly, depending upon whether the atrium is sensed or paced. The presence of discrete atrial conducting pathways, in close relation to the sinus node, facilitates conduction from the right to the left atria during sinus rhythm. Pacing at a distance from these pathways, at a location such as the right atrial appendage, results in a slower conduction through atrial myocardial tissue. This can lead to marked conduction delays to the left atrium. This is a particularly important concern during CRT with intact AV nodal conduction, due to the need to provide the resynchronization therapy in advance of native ventricular depolarization. It is unclear if the benefit of CRT is fully achieved if fusion is present between native conduction with bundle branch block and biventricular stimulation. In addition to these considerations, the optimal AV interval determined for biventricular stimulation may differ from the optimal AV interval needed to achieve resynchronization with LV stimulation alone. The AV interval programming issues become even more complex if the patient is expected to alternate between atrial sensed and paced events[86].

Data from the PATH CHF and PATH II European trials of CRT evaluated acute AV interval optimization by hemodynamic measures. These studies determined the optimal AV interval by assessing pulse pressure and dP/dT measures. There was not complete agreement between these measures on the optimal AV delay. Using maximum pulse pressure as an end point, the data show that programming the AV

interval to correspond to the point of peak atrial pressure is optimal. Using dP/dT as an end point, a programmed AV interval at 50% of the PR interval was optimal in the presence of a QRS duration greater than 150 msec. A programmed AV interval at 70% of the PR interval or even longer produced the greatest increase in dP/dT in those patients with shorter QRS duration and, interestingly, resulted in native and paced QRS fusion[84, 85, 88].

In clinical trials performed in United States, echo/Doppler measures are the most common method used to determine AV interval programming. One Doppler method used in the MIRACLE (Medtronic, Inc.) studies is the Ritter Method or equation. The Ritter equation is complex, but it seeks to maximize transmitral inflow, prolong diastolic filling time, and prevent early closure of the mitral valve. This method does not assess forward output[87].

There are no published data relating Doppler-derived measures to acute hemodynamic measures of pulse pressure or dP/dT.

Use of other technologies such as phonocardiography and noninvasive surrogates for pulse pressure are under investigation.

B. Chronic Optimization of the AV Interval

Currently there are no tested and uniform methods that have been widely adopted for chronic optimization of the AV interval either at rest or with activity. It is unknown if the acute AV interval programmed by whatever method at implantation remains optimal during follow-up.

Data from the MIRACLE trial of CRT with biventricular stimulation performed in the VDD mode used the Ritter formula to optimize AV interval programming. Patients underwent AV interval optimization at pre-discharge and at three and six months of follow-up. An AV delay averaging 100 msec was optimal in the majority of patients and remained stable over time[89].

In a further study, the InSync III of resynchronization, right and left ventricular timing offsets were also studied. Atrial-ventricular interval optimization was performed according to the Ritter method and then fixed. Alterations of V-V timing were performed and forward flow or stroke volume assessed. Interestingly, unlike AV interval programming, there was marked variability in the optimal V-V timing interval over time[89].

There are no chronic data available that provide insight into the best measures or end points for determining the optimal AV interval during activity states. Standard device features such as dynamic AV delay have not been tested with chronic CRT. In the CONTAK CD trial of CRT, the AV interval was programmed short enough to insure complete biventricular capture on treadmill testing, but these values were not correlated with echocardiographic measures[51].

C. Acute Identification of the Optimal LV Stimulation Site

The goal of selecting an optimal left ventricular site for stimulation is to achieve or restore the maximum amount of mechanical and electrical synchrony. There is no accepted method for measuring and comparing the effects of stimulation at various coronary sinus branch vein sites. Measures of the mechanical effects have been assessed using acute hemodynamics and echocardiography, including tissue Doppler analysis, tagged MRI, and nuclear imaging[31, 36, 90, 91].

Electrical resynchronization has been evaluated using ECG measures of QRS duration, analysis of local electrograms and conduction times obtained directly from the LV and RV leads, and anatomical endocardial mapping or epicardial mapping. Echocardiographic tissue Doppler measures, MRI imaging, and phase analysis methods applied to nuclear scans or echocardiograms can provide combined electromechanical data[31, 36, 91, 94].

Interestingly, there appears to be a marked degree of heterogeneity, both electrical and mechanical, among patients with cardiomyopathy and LBBB on surface ECG. In terms of electrical dyssynchrony, the latest activated segment is the LV lateral or posterior lateral wall in the majority, but not in all patients. In most, but not all, the LV anterior septum is an area of lesser delay. In terms of mechanical dyssynchrony, tissue factors such as areas of infarction or fibrosis, which differ markedly between patients, greatly influence the ability to achieve capture at a single target site, simply because it is the area of greatest mechanical delay or strain[91–94].

Studies using dP/dT and pulse pressure as end points show that, in general, most patients achieve maximal benefit from pacing at a lateral, anterolateral, or posterolateral wall site. Pacing in a true anteroseptal branch vein can achieve some benefit but may also worsen hemodynamic measures in up to 20% of patients[94].

A recent study in animals measuring acute hemodynamic and MRI indices of systolic performance showed that mechanical resynchronization can be achieved with LV stimulation alone, which actually worsens electrical dispersion or electrical dyssynchrony. This is consistent with the observation in some clinical trials that QRS narrowing after biventricular stimulation is not required to achieve symptomatic or echocardiographic measures of improvement[46, 91].

D. Alternative Methods of Achieving LV Stimulation

In a minority of patients, a coronary sinus branch vein position cannot be identified due to vein anatomy, or LV tissue characteristics. Alternative methods of obtaining LV stimulation include direct epicardial lead placement using a limited thoracotomy approach or thoracoscopic approach. Hospital stays, operative morbidity, and mortality are higher with this approach. Chronic capture thresholds are also higher, and failure to capture at one year may be observed in up to 20% of patients[78, 79, 95].

Delivery systems are in development for deploying LV epicardial leads via a transcutaneous approach to the epicardial surface[96].

Left ventricular leads have also been placed transvenously, using a transeptal approach to the left ventricle. No long-term efficacy or safety data is available for this technique, which requires long-term anticoagulation. Robotic LV lead placement has also been reported and can be utilized in cases where placement of a coronary sinus branch vein lead is not possible[96–101].

E. How to Measure Clinical Outcome After CRT

The initial investigations of resynchronization therapy demonstrated device system safety and reliability. The other important clinical outcomes of any drug or device therapy studied in heart failure patients include the ability of the therapy to demonstrate improvement in (1) functional status and quality of life, (2) measures of disease progression, (3) morbidity and mortality, and (4) health care utilization and cost.

A variety of surrogate measures of clinical outcomes such as peak oxygen consumption on cardiopulmonary exercise testing, six-minute walk distance, and echocardiographic measures of LV size and function have been widely used to assess the effects of CRT. The roles of other surrogate measures such as brain naturetic peptide (BNP) have not been fully evaluated, but hold promise.

Early analysis of the COMPANION trial data indicates that CRT alone favorably impacts all measures of clinical outcome but does not demonstrate mortality benefit. CRT-D achieves all of the same goals but also favorably impacts mortality. Careful consideration will need to be given, on an individualized basis, as to the most appropriate device for eligible patients[59].

F. How to Assess Disease Progression After CRT

In clinical trials performed to date, echocardiography has been the most widely utilized tool to measure the impact resynchronization on cardiac structure and function. Serial evaluation of ventricular size,

efficiency, mass, shape, systolic and diastolic function, and AV valve regurgitation have all been evaluated.

Several echocardiographic measures, such as left ventricular end systolic volume, and LVEF also correlate with other measures of clinical outcome such as mortality.

Echocardiographic measures of reverse remodeling such as ventricular size, shape, and mass are also important to evaluate. Tissue-Doppler methods have been reported in small numbers of patients, but not in large controlled clinical trials.

A variety of serum markers of the neurohormonal and other mediator pathways' response to HF, such as serum norepinephrine, brain naturetic peptide, and tumor necrosis factors, are being evaluated[40, 46, 49, 55, 56].

Arrhythmia burden is a particularly important marker of disease progression after CRT. This will be an important consideration as LV stimulation alone is evaluated and compared to biventricular stimulation for achieving mechanical resynchronization[93, 94].

G. How to Design CRT Trials: FDA Perspective

The FDA has targeted safety and effectiveness end points for the devices used and for the HF patient population under study with CRT. Thus far, regulatory approval for new devices has required a two-arm randomized controlled study for evaluation of new devices. Device approval has been granted on the basis of improvements in composite end points of HF status that have included quality of life measures, NYHA FC, six-minute walk distance, and cardiopulmonary exercise testing. Secondary end points have included echocardiographic measures and neurohormones. Device end points have included assessment of continuous biventricular stimulation and adequate functioning of the ICD component of the device as well as total system safety.

Preliminary data from the COMPANION provide data on the benefit of CRT on the combined primary end point of all-cause hospitalizations and all-cause mortality and provide important data on the impact of therapy on HF hospitalizations[59].

Future studies will need to further define and expand the most appropriate screening studies to identify patients likely to benefit, and chronic device registries will help to provide data on long-term device system safety.

The Food and Drug Administration has expressed openness to innovative data analysis techniques and trial designs to assess advances in device and lead features or studies designed to assess alternative ways of delivering CRT.

IX. Certification

In the United States, CRT and CRT-D have been market-approved as of September 2001 and May 2002, respectively. However, there is uncertainty and a great deal of controversy regarding the skill set and implant experience that should be required to credential or certify implanting physicians.

As part of the regulatory approval, manufacturers of the devices have designed mandated training programs that include didactic materials and access to experienced implanting physicians for observation and/or proctoring of cases of coronary sinus lead implantation.

At the time of this writing, an update of the North American Society of Pacing and Electrophysiology (NASPE) Guidelines for Implantation of Pacemakers and Defibrillators, which includes resynchronization device credentialing guidelines, are in press[102].

Implanting physicians involved in the clinical trials of the CRT-D were almost exclusively electrophysiologists. This is similar to the implantation of standard ICDs, which remain in the hands of the

electrophysiologist. Many argue that training of more electrophysiologists or certification of non-electrophysiologists is needed to meet the increased demand, due to expanding ICD indications for primary prevention of sudden death. Nonetheless, at the present time, there does not appear to be a clear indication for superceding existing guidelines requiring training in an ACGME-approved electrophysiology fellowship for ICD implantation with or without a coronary sinus lead.

The nationwide ICD implant data cited above contrasts with estimates of the profile of physicians implanting pacemakers, roughly half of whom are not electrophysiologists. These physicians consist primarily of cardiologists and cardiovascular surgeons. In addition, since market approval of the resynchronization device alone, roughly 40% of implanting physicians were non-electrophysiologists.

There are several incremental challenges, which need to be considered by any implanting physician, that distinguish the resynchronization device from a standard pacemaker. Foremost among these are technical considerations. These include prolonged and variable procedure times, issues related to successful cannulation of the coronary sinus os and branch veins, and the ability to recognize and manage the complications of coronary sinus lead placement. These skills cross subspecialty guidelines requiring electrophysiology, coronary interventional, and heart failure management expertise.

The electrophysiologist who is without coronary sinus lead implantation experience, but who implants a minimum of 25 pacemakers and 25 ICDs per year and has experience in cannulation of the coronary sinus during electrophysiology procedures, should observe at least two cases and/or attend a manufacturer's course and receive proctoring from an experienced physician for at least two cases.

The non-electrophysiology physicians who have a volume of at least 35 pacemaker implants per year but no experience in coronary sinus cannulation should attend a manufacturer's course, observe two to five implants, and perform two to five proctored procedures. Additionally, maintaining a volume of at least 35 resynchronization implants per year and a mechanism for tracking outcomes is ideal (Table 9). Independent and device manufacturer-sponsored registries are currently being designed and implemented, which will assist all implanting physicians in tracking outcome data.

Table 8. Suggested Training for Non-EP Physicians

• Attend company course (classroom work; animal lab experience) – 1 day, and
• Observe 2 to 5 procedures – and
• Perform 2 to 5 proctored procedures – and
• Recognize limitations/weaknesses —Appropriate volume (about 35 per year) —Track outcomes

Any physician group needs to be aware of the implications of a failed coronary sinus lead implant procedure. The decision to attempt a second implantation or to refer the patient to another more experienced implanting physician is critical to optimizing the care of the patient. Consideration for the thoracotomy approach to implant the left ventricular lead should be reserved as a last alternative.

As ongoing clinical trial data emerges, further defining eligible patients for resynchronization devices, physician groups such as NASPE may need to consider alternative methods to full fellowship programs

for training and credentialing physicians. These could include training courses or programs that do not result in American Board of Internal Medicine (ABIM) eligibility. Alternatively, device-based training programs that focus on implantable devices with a focus on the heart failure patient and combine training in other treatment modalities for heart failure may need to be considered.

X. Economic Considerations and Impact of Electrical Device Therapy in Heart Failure

Until very recently, billing for resynchronization procedures from both a physician and hospital perspective has been dependent upon use of existing codes and modifiers.

As of January 2003, new physician billing codes (CPT) are available that are specific to placement of a coronary sinus lead (Table 10).

Table 10. New Physician Codes for Resynchronization Therapy—1/03

33224	Insertion of pacing electrode, cardiac venous system, for left ventricular pacing, at time of insertion of pacing cardioverter-defibrillator or pacing cardioverter-defibrillator pulse generator (including revision of pocket, removal, insertion, and/or replacement of generator)
33225	Insertion of pacing electrode, cardiac venous system, for left ventricular pacing, at time of insertion of pacing cardioverter-defibrillator or pacemaker pulse generator (including upgrade to dual-chamber system) (List separately in addition to code for primary procedure)
33226	Repositioning of previously implanted cardiac venous system (left ventricular) electrode (including removal, insertion, and/or replacement of generator)

Language referring to insertion and repositioning of electrodes "14 days after the insertion" has been eliminated.

Beginning October 2002, hospitals will have new ICD-9 procedure codes for resynchronization therapy to ensure compliance and data collection (Table 11). This will allow Medicare to capture charge data that are specific to resynchronization procedures. Resynchronization devices alone (CRT) will continue to be assigned to DRGs 115 and 116. Resynchronization devices with ICD capability (CRT-D) will continue to be assigned to DRGs 514 and 515. There are also new additional heart failure codes that delineate the specific type, kind, and acuity of heart failure[103–105].

While the benefits of CRT have been demonstrated on a variety of end points, the relative cost-effectiveness of the therapy is not yet known. It is clear that there has been a steady increase in the cost of heart failure care; in 1999 this represented $60 billion, or 5% of the U.S. health care costs. Roughly two thirds of this cost is due to the hospital treatment of decompensated heart failure episodes. The majority of these costs are due to length of stay and acute care or intensive care unit stays. Analysis of the COMPANION trial data, demonstrating a marked reduction in all-cause, cardiovascular, and heart failure hospitalization, will help to provide cost-effectiveness data for this therapy.

Table 10. Hospital Codes (DRG) for Resynchronization Therapy

• Beginning October 1, 2002, hospitals should utilize the new ICD-9 procedure codes for resynchronization therapy to ensure compliance and pure data collection
• Diagnosis related groups Resynchronization therapy new codes
• 00.50–Implant of CRT-P system
• 00.51–Implant of CRT-D system
• 00.52–Implant/replace left ventricular coronary venous lead
• 00.53–Implant/replace CRT-P pulse generator only
• 00.54–Implant/replace CRT-D pulse generator only

XI. *Summary*

Based on this review of the studies published and reported to date, CRT benefits patients with advanced HF. CRT improves quality of life, functional status, exercise capacity, and morbidity, and may exert favorable effects on cardiac structure and function without worsening myocardial energetics. [41, 46, 49, 51, 53] Subsequent to the NASPE Expert Consensus Conference on Resynchronization Therapy in HF, the COMPANION study was stopped early and preliminary results reported[59]. The combined primary end point, all-cause mortality and all-cause hospitalization, was met. CRT resulted in a 20% reduction in the risk of all-cause mortality and all-cause hospitalization compared to optimal medical therapy. HF mortality and hospitalization were also reduced. In addition, all-cause mortality was reduced by 40% in the CRT-D arm of the trial. As a result of the completion of the various studies (prior to COMPANION), the AHA/ACC/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices assigned a Class IIa indication for implantation of cardiac resynchronization devices in HF and prolonged QRS[106].

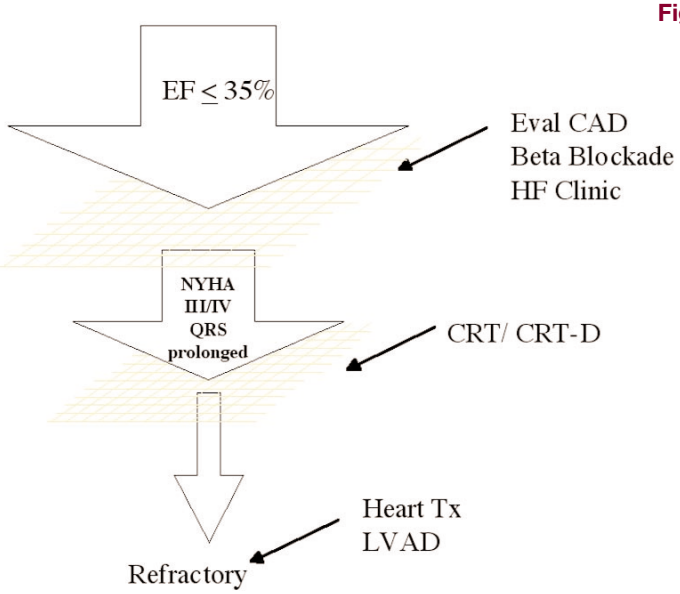
Table 11 summarizes the effect of the various treatment modalities on HF outcomes and the applicability to the HF populations as classified according to NYHA functional class or AHA/ACC Stages[1, 12, 107–115]. Based on current knowledge from reported studies of CRT/CRT-D to date, Figure 18 proposes an algorithm to guide the clinician in determining which population of patients may benefit from intervention and at what point in the disease process it is appropriate to intervene with the various treatment modalities available. Clearly, the approach to the management of HF demands multidisciplinary collaboration between HF specialists, electrophysiologists, surgeons, and allied health professionals.

Although the consensus conference left us with a reasonable algorithm to guide patient management, it also raised a multitude of issues and challenges that we must confront and solve. These issues include long-term benefit concerns, growing complexity of these device therapies, optimization of implantation and programmability, redefining patient populations most likely to benefit, economic impact, and ethical considerations. Indeed, we have only scratched the surface, and a great deal of challenges remain ahead.

Table 11. Summary of Various Treatment Modalities on Outcomes

	β-Blockade	HF Clinic	CRT	ICD	CRT-D	Tx-LVAD
Symptoms	↓	↓	↓	no Δ	↓	↓
Exercise Duration	no Δ	↑	↑	no Δ	↑	?
LV Function	↑	?	↑	no Δ	↑	↑↑
Hospitalizations	↓	↓	↓	↑	no Δ	↑
Survival	↑	↑	?	(↑) (isch)	↑	↑
Cost	$	0	$$	$$$	$$$	$$$$$
Number of Patients Studied (in RCT)	10^4		10^3			10^2
Applicability (AHA-ACC/NYHA)	B-D/I–IV		C-D/III–IV			D/IV

Figure 18. Tiered Therapy for Heart Therapy



APPENDIX

List of Acronyms or Device Names

CARE-HF	Cardiac Resynchronization in Heart Failure
CHRONICLE (IHM)	*CHRONICLE® not an acronym:* Implantable Hemodynamic Monitor
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Congestive Heart Failure
CONTAK-CD	*Not an acronym: name of the device*
InSYNC	*Not an acronym: name of the device and/or study*
MERIT-HF	Metoprolol CR/XL randomized intervention trial in congestive heart failure
MIRACLE	Multicenter InSync Randomized Clinical Evaluation
MIRACLE-ICD	Multi-center InSync Randomized Clinical Evaluation in Patients Requiring an ICD
MUSTIC-SR	Multisite Stimulation in Cardiomyopathy in Patients in Sinus Rhythm
MUSTIC-AF	Multisite Stimulation in Cardiomyopathy in Patients with Atrial Fibrillation
PACMAN	Pacing for Cardiomyopathy, *a European study*
PATH-CHF	Pacing Therapies for Congestive Heart Failure
PAVE	Post AV Nodal Ablation Evaluation
VENTAK-CHF	*Not an acronym: name of the device*
VIGOR-CHF	*Not an acronym: name of the device*

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