Cardiac Resynchronization—A Heart Failure Perspective

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Over the past 15–20 years the development of new heart failure pharmacologic therapy has lowered mortality by 30–40% for this serious and prevalent clinical syndrome, within clinical trials conducted in patients with a dilated cardiomyopathy phenotype. However, over the past 5 years progress in the development of additional effective drugs has slowed, in part due to the success of neurohormonal inhibitors, on which background new therapies must be developed. That there is not an absolute ceiling on the development of new heart failure therapies has been convincingly recently demonstrated in electrophysiologic device trials, conducted on the background of maximal neurohormonal inhibition. Two trials, COMPANION and CARE-HF, have demonstrated unambiguously that in advanced heart failure patients with a marker of mechanical intraventricular dyssynchrony, increased QRS duration, cardiac resynchronization therapy in the form of biventricular pacing can improve major clinical outcomes including mortality. In addition, COMPANION also demonstrated that the addition of an ICD further improved mortality reduction, by lowering the incidence of sudden death. These trials indicate that device/drug therapy is at least additive in the treatment of heart failure, and they herald a new era in the multi-modality approach to therapeutics.

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HEART FAILURE PATHOPHYSIOLOGY AND CLINICAL SYNDROME

The incidence of heart failure continues to rise. There are approximately 550,000 new cases of heart failure diagnosed in the United States each year¹ and heart failure accounts for 300,000 deaths² along with 900,000 hospitalizations per year.³ The natural history of heart failure is that approximately 50% of patients diagnosed with heart failure will die in a 5-year period,⁴ and most from progressive pump failure or sudden death.

The development of heart failure involves multiple factors. The initial pathologic insult can be one of several different processes that ultimately have the same endpoints of myocyte and myocardial dysfunction, and pathologic hypertrophy. Coronary artery disease, myocarditis, valvular pathology, hypertension, toxins, and genetic causes are some of the more common causes of myocardial dysfunction. Some of these processes result in obvious acute dysfunction while others are more insidious. Regardless of the initial pathology the ensuing result is myocyte/myocardial dysfunction

and pathologic hypertrophy, in the form of cellular/chamber remodeling that leads to the dilated cardiomyopathy phenotype. Left ventricular systolic dysfunction and the subsequent increase in wall stress leads to activation of several pathologic processes that result in altered gene expression and further myocyte/myocardial dysfunction. As an integral part of the pathologic hypertrophy process, myocyte elongation results in chamber dilatation, which leads to further increases in wall stress. The marked increase in wall stress and other signaling mechanisms lead to the activation of the renin-angiotensin-aldosterone system (RAAS), the adrenergic nervous system, and cytokine production. While these mechanisms are initially compensatory for myocardial performance, in the end they lead to further remodeling and progressive pump dysfunction.⁵

HEART FAILURE PHARMACOLOGIC THERAPY

Therapies that stop or partially reverse these pathologic processes have a favorable effect on the natural history of heart failure. Beta-blockers,

angiotensin-converting enzyme inhibitors (ACE inhibitors) and aldosterone antagonists have all been shown to improve survival and reduce major heart failure morbidity when used appropriately in heart failure patients. Beta-blockers have proved to be effective in preventing or reversing systolic dysfunction and remodeling. Beta-blockers provide multiple mechanisms of action to aid the failing heart. They provide modulation of the adrenergic nervous system, as well as change the beta-receptor pathway dynamics.⁶ Importantly, they have favorable myocardial metabolic effects. Finally, they act to normalize gene expression patterns by reverting from the fetal gene expression.⁷ The aforementioned effects along with others lead to an improvement of systolic function and ejection fraction, reverse remodeling, and improved survival.

ACE inhibitors are important in the medical treatment of systolic dysfunction regardless of symptoms. In multiple randomized studies conducted in patients with various degrees of heart failure, these agents have been shown to improve survival or attenuate the progression of heart failure. ACE inhibitors exert their effects by inhibiting conversion of angiotensin I to angiotensin II. The resultant inhibition of the renin-angiotensin-aldosterone system leads to improved hemodynamics, reverse remodeling, and improved clinical outcomes.⁸ Angiotensin receptor blockers (ARB) are thought to exert their effects in a similar manner as ACE inhibitors. ARBs are not used in preference to ACE inhibitors, but rather are reserved for those patients with side effects or other contraindications to ACE inhibitors.⁹

Aldosterone antagonists evaluated on a background of ACE inhibitors in patients with more advanced heart failure symptoms have shown a substantial mortality benefit. Aldosterone is released from the adrenal gland following stimulation by the RAAS system, and also may be generated in the myocardium. The binding of aldosterone to the mineralocorticoid receptor leads to sodium and water retention along with loss of potassium and magnesium. As an activator of the sympathetic system and an inhibitor of the parasympathetic system, aldosterone promotes the pathologic neurohormonal cycle seen in heart failure. Both spironolactone and eplerenone have proven mortality benefit when added to appropriate medical therapy in selected patients.^{10,11}

The development of the above pharmacologic therapies has led to marked improvement in the natural history of heart failure,¹² with a 30–40%

improvement in survival and similar degrees of reduction in heart failure hospitalizations. However, recent attempts to develop pharmacologic therapies on a background of beta-blockers, ACE inhibitors/ARBs, and aldosterone antagonists have not been very successful. In fact, since 2001, 75% (10/13) Phase III trials testing the effects of drugs against placebo for effects on major heart failure endpoints have been negative, as defined by a statistically significant effect on a primary endpoint. This illustrates the general difficulty of improving on successful pharmacologic therapy,¹³ which now may require approaches beyond existing treatment paradigms.¹²

GENERAL STRATEGIES FOR LOWERING MORTALITY IN CHRONIC HEART FAILURE

Despite the improvement in outcomes with modern pharmacologic therapy as noted above, mortality in advanced (Class III–IV) chronic heart failure remains high, on the order of 15–20% /year. There are two general ways in which heart failure patients die from cardiovascular causes—pump failure deaths and sudden death. The latter is predominately arrhythmic in nature, but ischemic events and other causes also contribute. Figure 1 plots the annual mortality by mode of death versus the total mortality in various heart failure clinical trials in systolic dysfunction patients reported since 1999, where mode of death was adjudicated by an Endpoints Committee. As can be seen in Figure 1, the percentage of patients dying from pump failure is directly and linearly related to annualized mortality, which is a reflection of the degree of heart failure. On the other hand, the relationship of sudden death to total annualized mortality (or to heart failure severity) is less apparent, and in fact, not statistically significant. Because of these differences in the relationships of total mortality: mode of death, at around 15% annual total mortality pump failure mortality begins to exceed sudden death, which was dominant in trials with lower annualized mortality. Although the transfer of these data to NYHA Heart Failure Class is imperfect, a 15% annualized total mortality is around the transition of early class III to late Class III. For example, the Class III patients in the COMPANION trial were late Class III because of the additional requirement of a heart failure hospitalization in the past 12 months, and pump failure constituted 44% of the total number of deaths adjudicated in the optimal pharmacologic

Figure 1. Effect of severity of heart failure on *Sudden* (SD) and *Pump Failure* (PFD) death rates (*y* axis = annualized SD or PFD during trial), in Phase III HF clinical trials since 1999, where mode of death was adjudicated. The annualized mortality rates for SD or PFD were estimated by multiplying the fractional {mode/total} $\times$ the annual total mortality rate in percent.

therapy control group, compared to 23% for sudden death. The annualized mortality rate for non-device, control patients in the COMPANION trial was 8.4% for pump failure death, and 4.4% for sudden death (Figure 1). The data in Figure 1 suggest that if a new survival-improving therapy is to be developed, it will have to lower sudden death in less advanced (Class I–IIIa) heart failure patients, but will need to favorably impact pump failure deaths in advanced (IIIb–IV) patients. Furthermore, an extrapolation of the data in Figure 1, suggests that in ultra-advanced heart failure (where the annualized mortality may exceed 30% and >80% of deaths may be pump failure related), measures targeted specifically at sudden death would be completely ineffective. The data presented in Figure 1 are the fundamental basis for ICDs being more effective in less advanced heart failure patients, and drugs or devices (such as cardiac resynchronization, CRT) being effective in advanced heart failure.

CARDIAC RESYNCHRONIZATION THERAPY, WITH OR WITHOUT ICD

In contrast to the slowing of progress in heart failure drug development, major advances are being made in the development of devices that fa-

vorably affect the natural history of heart failure.^{12,14–18} The biggest success has been registered with the ICD and CRT electrophysiologic devices, both of which were invented^{19,20} and developed by Mirowski, Mower, and colleagues. Both these devices have been shown to be highly effective on a background of contemporary medical therapy that includes beta-blockers, ACE inhibitors/ARBs, and aldosterone antagonists, which makes their clinical results even more impressive.¹² The current status of the use of ICDs in heart failure patients is covered elsewhere in this issue, and this review focuses on CRT as effected by biventricular pacing.

The initial hypothesis regarding CRT, was that improvement in contractile dyssynchrony would result in improved relaxation and contraction dynamics. Early studies sought to answer the question of the effects of CRT on hemodynamics as well as changes on left ventricular ejection fraction in patients with LV systolic dysfunction and intraventricular conduction delay manifested by QRS lengthening. Evaluation of the hemodynamic effects of biventricular or left ventricular pacing in patients with left bundle branch block (LBBB) revealed improvement in dP/dt max, pulse pressure and MVO₂.^{21–24} These observations led to the planning and conduct of The MIRACLE trial,¹⁴ which

evaluated the effects of CRT on NYHA class, quality of life, cardiac structure, and cardiac function. Patients were evaluated at baseline, 3 months, and 6 months. At 6 months, there was a significant improvement in NYHA class, 6-minute walk test, quality of life score, and left ventricular ejection fraction in those patients with CRT versus controls.¹⁴ These results on heart failure surrogate endpoints were confirmed in the COMPANION trial.¹⁶

Based on these favorable results on myocardial function and heart failure surrogate endpoints, trials were initiated to test the hypothesis that CRT would favorably affect major clinical endpoints in patients with intraventricular conduction delay (IVCD) with prolonged QRS duration. It is estimated that approximately 25% of patients with chronic heart failure from systolic dysfunction have such an abnormality, which results in dyssynchronous contraction.²⁵ In these advanced heart failure patients with conduction disturbances, there is altered ventricular filling, increased mitral regurgitation, decreased dP/dt and dyssynchrony.^{26,27} The consequences of these altered dynamics is linked to an increase in one-year all-cause mortality compared to those patients who lacked in particular, a LBBB.²⁵ Moreover, artificially induced left bundle branch block by means of right ventricular apical pacing alone in patients with heart failure is known to result in an overall increase the combined endpoint of hospitalization and mortality.²⁸

In the COMPANION trial,¹⁶ which enrolled 1,520 patients to receive either CRT + optimal pharmacotherapy (OPT), CRT-D + OPT or OPT alone, biventricular pacing with or without the ICD component resulted in evidence of enhanced systolic function, in the form of improvement of systolic blood pressure and no effect on diastolic blood pressure. At 12 months patients with CRT + OPT had a significant improvement in the primary endpoint of death or total hospitalization in comparison to OPT group (CRT vs. OPT RR 19% $p = 0.014$ and patient with CRT-D + OPT had RR 20% versus OPT $p = 0.011$). For the outcome of death or cardiovascular hospitalization CRT + OPT revealed a risk reduction of 25% $p = 0.002$ versus OPT. Similarly, CRT-D + OPT showed a 28% reduction ($p < 0.001$). For the combined endpoint of death or heart failure hospitalization CRT + OPT exhibited a risk reduction of 34% ($p = 0.002$) and CRT-D + OPT had a risk reduction of 40% ($p < 0.001$) versus OPT at 12 months. For the secondary endpoint of all-cause

mortality CRT versus OPT risk reduction of 24% ($p = 0.59$) and CRT-D vs. OPT risk reduction of 36% ($p = 0.003$).¹⁶

The strong trend to a reduction (by 24%, $p = 0.059$) in mortality in the COMPANION trial was extended to a more robust (by 36%), statistically significant ($p < 0.002$) reduction in the CARE-HF trial.¹⁸ In addition, in CARE-HF trial there was a significant difference between patients treated with chronic resynchronization therapy (CRT) versus controls with respect to the primary endpoint of death or unplanned cardiovascular hospitalization, similar to that observed in COMPANION for the same endpoint. CARE-HF also confirmed the MIRACLE trial salutary effects of CRT on LV ejection fraction, and for the first time CRT therapy was shown to be associated with a reduction in BNP levels.¹⁸

Therefore, based on multiple well-designed multicenter studies, CRT has unambiguously been shown to provide efficacy in terms of reduction in mortality, heart failure, and cardiovascular hospitalizations, and improvements^{14,16,18} in functional capacity and quality of life.^{14,16,18} While pharmacologic therapy has clearly provided improved outcomes in chronic heart failure patients, the addition of biventricular pacing to the best medical therapy has shown to be efficacious, tolerable, and safe for New York Heart Association Class III and IV patients.

Patients with chronic heart failure, and a widened QRS, have an increased risk for all-cause mortality, as was previously stated.²⁵ In addition, there is also a substantially increased risk for sudden death.²⁹ Therefore, in the COMPANION trial it was hypothesized that the addition of an ICD to biventricular therapy would provide a significant improvement in the sudden death component for the population of patients with Class III and Class IV heart failure with an IVCD.

The COMPANION trial evaluated the addition of a defibrillator to CRT therapy, and the subsequent effects on mortality compared to pharmacotherapy alone. For deaths classified as sudden, CRT-D was associated with a 56% reduction in mortality ($p = 0.021$) when compared to OPT on time-to-event curves.³⁰ Conversely, CRT alone had no statistically significant effect on deaths classified as sudden. Thus, in the COMPANION trial the addition of an ICD provided additional protection against sudden death, to the extent that the CRT-D arm exhibited a statistically significant ($p = 0.003$)

Figure 2. Comparison of mode of death in COMPANION^{16,30} vs. CARE-HF.¹⁸

reduction in total mortality. In contrast, on time-to-event curves pump failure deaths tended to be reduced to a similar extent by CRT and CRT-D in the COMPANION trial (by respective amounts of 29% and 27%, both $p < 0.20$).^{16,30}

Figure 2 compares the effects of CRT to optimal pharmacologic therapy in the COMPANION^{16,30} and CARE-HF trials,¹⁸ for mode of death as tabulated by crude mortality rates for the entire periods of follow-up. The effects of CRT-D in the COMPANION trial are also given. For CRT, in the COMPANION trial there was a 22% trend toward reduction in pump failure crude mortality, and a statistically significant reduction (by 40%) in CARE-HF. Although there was a trend for an increase in sudden deaths (34%, $p = 0.42$) in the COMPANION trial, there was also a CRT-related decrease in deaths classified as other cardiac/vascular and noncardiovascular, by 40% ($p = 0.020$). In contrast, there was a trend for a reduction in sudden death in CARE-HF (by 23%, $p = 0.14$), but no decrease in deaths classified as other CV or non-CV. In other words, for CRT there are some minor differences between COMPANION and CARE-HF trials for effects on mode of death, but they likely relate to different methodologies in the classification of the mode of death. Considering the aggregate data from these trials, there is no evidence that CRT increases sudden death in chronic heart failure patients. However, there is also no good evidence that CRT reduces sudden death. As shown in Figure 2,

in the COMPANION trial the addition of an ICD to CRT (CRT-D) resulted in the aforementioned large reduction in sudden death, which for crude mortality rates was by 50% compared to optimal pharmacologic therapy, and 63% when compared to CRT.

With health care costs continuing to rise along with the increased prevalence of heart failure there are concerns regarding the costs of various types of health care modalities including CRT and CRT-D. In cost-effectiveness analysis, evaluating cost per quality-adjusted life years gained for CRT (\$19,600) and CRT-D (\$35,200) were less than the standard benchmark of dialysis.³¹

CONTEMPORARY THERAPEUTIC PRINCIPLES IN HEART FAILURE

Table 1 contrasts the effects of proven-effective therapies of chronic heart failure on the various important components of the heart failure clinical syndrome. As can be seen, in patients who are candidates, CRT produces a degree of benefit that is truly impressive, both in terms of the breadth of efficacy as well as degree. In fact, CRT is the only heart failure treatment that produces major beneficial effects across the spectrum of clinical abnormalities afflicting heart failure patients. For this reason, NYHA Class III or IV patients who qualify for CRT by QRS duration should receive it; particularly since it has been shown to be cost-effective.³¹ In terms of how CRT is implemented,

Table 1. Comparison of Various HF Therapies on Clinical Parameters

Effect	Digoxin	ACEI/ARB	Aldosterone Antagonist	β -blocker	CRT
Mortality	0	+	+++	+++	+++
Heart failure hospitalization	+	++	++	++	+++
Functional capacity	++	+	+	0–+	+++
QOL	+	++	+	0	+++
Total	+ 4	+ 6	+ 7	+ 6.5	+ 12
Tolerability (% tolerating therapy)	>90	>90	50–60	60–90	>90 (of a ~ 25% subgroup of Class III-IV)

Ordered classification of efficacy: 0 = no effect; + = mild, barely detectable effect; ++ = moderate effect, easily detectable; +++ major effect, detectable with extremely robust effect sizes and significance levels.

QOL = quality of life.

relative to pharmacologic therapy, since CRT trials have all been conducted on a background of ACE inhibitors/ARBs and β -blockers^{14,18} or these drugs plus spironolactone,¹⁶ pharmacologic therapy should be delivered first, at the target doses of each agent shown to be effective in clinical trials.

A point of some controversy is the role of CRT-ICD devices compared to CRT alone, or the degree of additional benefit conferred by an ICD when added to CRT. There is only one trial that addresses this issue, COMPANION.¹⁶ As stated earlier in the COMPANION trial, the addition of an ICD lowered sudden death risk by 56%,³⁰ which allowed for an additional, 12% lowering of total mortality to the point that this endpoint became statistically significant in the CRT-D group compared to the optimal pharmacologic therapy arm.¹⁶ Regarding the question of which COMPANION patients were benefited by the addition of an ICD in terms of improved mortality reduction, in general it was the patients with less advanced heart failure (Class III) or LV dysfunction (lower LVEF, lower systolic blood pressure),³² where sudden death is a bigger issue relative to pump failure death. So, for the present, the recommendation would be to consider a CRT-D device in patients in whom an ICD is also indicated, and consider CRT alone for Class IV patients or patients who do not wish to undergo defibrillator therapy.

CONCLUSION

In conclusion, CRT provides multiple beneficial effects including improvement of functional capacity, symptoms, and quality of life. Multiple studies have shown an improvement in morbidity that relates to the reversal of contractile dysfunc-

tion/remodeling. The CRT arm of the COMPANION study demonstrated a trend for, and CARE-HF a statistically significant reduction in, pump failure deaths, while the addition of and ICD to CRT in the COMPANION trial lowered sudden death incidence. While biventricular pacing has been an invaluable addition to the armamentarium in the treatment of heart failure there are multiple facets to this therapy that require further investigation. Some of these are: (1) what are the long-term (>6 months) myocardial functional and structural benefits and what are the mechanisms involved; (2) what are the specific aspects of the effected structural, electrical, and molecular remodeling; (3) most importantly, better methods of identification of patients who will derive symptomatic benefit from this therapy; (4) continued improvement in implantation techniques and tools in order to decrease procedure times will aid patients and implanting physicians; and lastly, how can cost-effectiveness be improved to the extent that this therapy can become more generally available. All of these issues will be addressed by clinical trials or mechanistic studies that are either under way, or in the planning phase.

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Michel Mirowski with Anna in France

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