CARDIAC RESYNCHRONIZATION THERAPY: A REVIEW AND FUTURE DIRECTIONS

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INTRODUCTION

In millennia past, descriptions of congestive heart failure (CHF) often included ancient remedies. The earliest Egyptian papyri translated in the last century reveal a remarkably sophisticated understanding of heart ailments being the prime culprit in conditions of generalized edema (also called dropsy) and CHF.[1] Starting in medieval times and continuing until the late 19th century, treatment for CHF included bloodletting to restore balance among the four humors.[2]

Writings as early as 1250 A.D. described using adjunctive pharmacologic therapy such as cardiac glycoside-containing herbal extracts to treat CHF.[3] Several centuries ago, William Withering, a physician and botanist, wrote about the clinical effects of a foxglove plant extract in treating CHF. As a result, digitalis and its derivatives became one of the earliest medicines used in heart failure therapy.

Rather than bloodletting, medical management of CHF has progressed in the last century to include diuretics to reduce pulmonary congestion; vasodilators of differing stripes; and, in the last 15 years, the initially counterintuitive use of beta-blockers as therapeutic mainstays. Other therapies are directed at treating the underlying cause of CHF, such as revascularization or valve replacement. Ultimate destination therapies include cardiac transplantation or the implantation of mechanical assist devices (e.g., left ventricular assist devices), while new strategies such as immunomodulation or stem cell therapy remain in various stages of investigation.

In the late 1990s, the important role of electrical conduction disease was recognized in a significant number of patients with moderate to severe CHF; these patients demonstrated electrocardiac evidence of ventricular dyssynchrony (VD). Small clinical studies subsequently demonstrated that restoration of ventricular-ventricular synchrony could acutely improve parameters of cardiac performance.[4-6] This concept of electromechanical therapy led to the initial trials of cardiac resynchronization therapy (CRT) as an important adjunctive treatment for patients with moderate to severe CHF. CRT is now a well-established adjunctive therapy for drug-refractory CHF in patients with moderate to severe diminishment in functional capacity.[7-12]

BACKGROUND AND BENEFITS OF CRT

Half of those with moderate to severe CHF (New York Heart Association, or NYHA, class III-IV) have electrocardiographic evidence of significant intraventricular conduction delays, which can worsen left ventricular (LV) systolic function as well as mitral regurgitation.

Early uncontrolled studies have shown that multisite biventricular pacing improves hemodynamics and cardiac performance in both acute and chronic situations. These studies showed an acute rise in contractility, pulse pressure and cardiac output.[4-6] Subsequent studies have shown that chronic therapy can bring about improved functional capacity, reverse remodeling, enhanced ejection fraction, less arrhythmic burden and improved mortality.[7-12]

TECHNICAL ASPECTS

Initial therapeutic strategies targeted patients with NYHA III and IV heart failure despite optimal medical therapy and with normal sinus rhythm. Thus, atrial synchronized biventricular pacing was first accomplished with standard right atrial and right ventricular apical pacing systems followed by placement of epicardial LV leads. Subsequently and presently, atrial-biventricular pacing is accomplished in most patients via retrograde transcoronary sinus placement of LV pacing leads.

As is the case with most complex procedures, LV lead implant success depends on operator experience as well as individual patient anatomy. In a meta-analysis of CRT that included more than 3,200 patients, the acute LV lead implant success rate was seen in approximately 90% of patients.[11] At the Methodist DeBakey Heart Center (MDHC), our physicians have seen a success rate in excess of 95% out of more than 1,000 cases. The advent of over-the-wire pacing leads and multiple forms of guide systems has permitted cannulation of more optimal pacing sites and, in turn, higher success rates.

Perioperative complications in the meta-analysis were low, with a perioperative death rate of 0.4% (13 of 3,245 patients). Infection rates are uniformly low. The incidence of lead dislodgement is generally limited to the LV lead and was reported in 9% of the patients.[11]

In our experience at MDHC, there has been one death resulting from rupture of the coronary sinus despite urgent evacuation of blood from the pericardial space.

MORTALITY BENEFITS OF CRT

It is now well established that CRT with or without associated defibrillator function has significant beneficial effects on patients with moderate to severe heart failure who are on optimal medical therapy. All-cause mortality was significantly reduced by 21% in a meta-analysis, with benefits apparent by three months of therapy after implantation. This was seen in patients with and without associated defibrillator protection (Figure 1).[11]

NON-MORTALITY BENEFITS

CRT has also proven to affect the remodeling of diseased hearts. Not only has this been demonstrated in echocardiographic assessment but also at the cellular level as well. Using paired right-

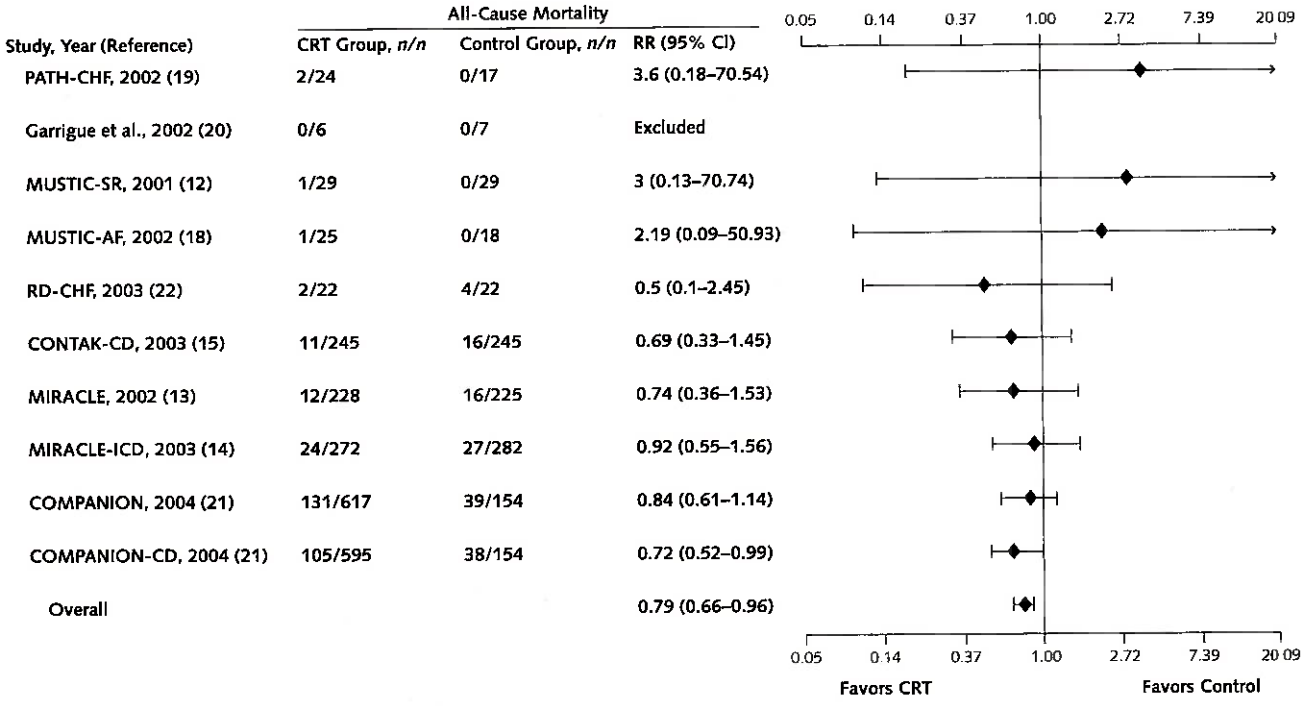

Figure 1. All-cause mortality with cardiac resynchronization therapy (CRT) versus controls.
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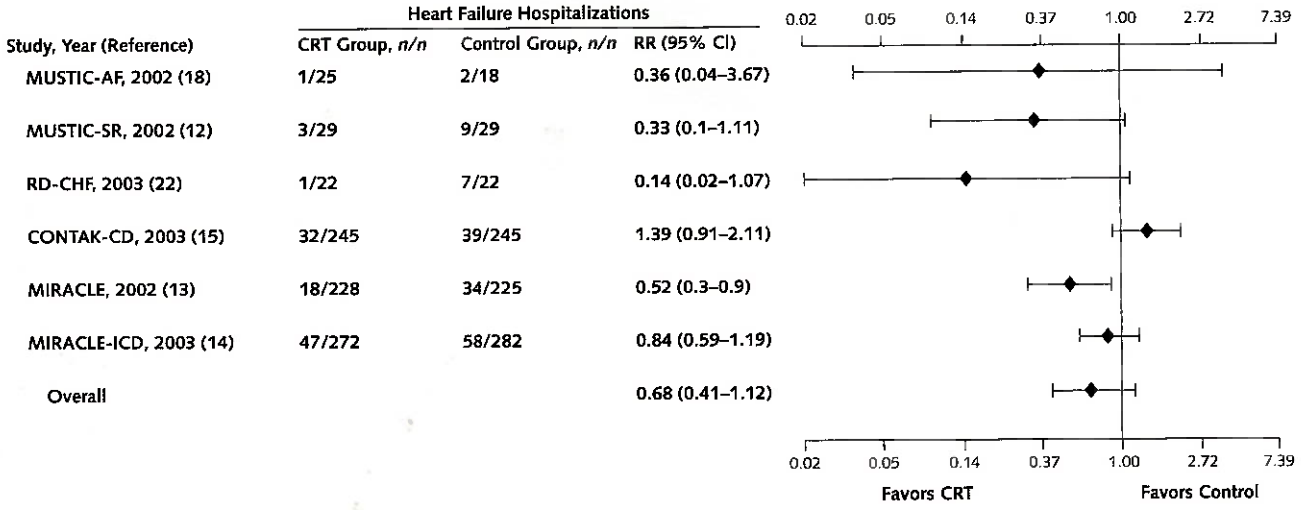

Figure 2. Heart failure hospitalizations with cardiac resynchronization therapy (CRT) versus controls.
Reprinted with permission from McAlister FA, et al. Systematic Review: Cardiac Resynchronization in Patients with Symptomatic Heart Failure. *Ann Intern Med.* 2004;141:381-390.

ventricular biopsy specimens taken at the time of CRT implant and three months later, MDHC physicians have shown statistically significant reductions in myocyte size, myocardial collagen content and tumor necrosis factor-alpha.[13] Echocardiographic evaluations are consistent in demonstrating reduced LV size and mitral regurgitation and improved ejection fractions.

There is also a well-established reduction in hospitalizations for CHF exacerbations (Figure 2) and improved quality of life scores as well.[11] Exercise tolerance as measured by 6-minute walk improved significantly, and there was a reduction in NYHA classification. These benefits have been documented to occur early and persist in excess of 12 months.

OPTIMIZING CRT BENEFIT

Despite the electrocardiographic manifestation of dyssynchrony, current literature suggests only 70-80% of patients receiving CRT devices demonstrate expected improvements. Reasons for nonresponders are multifold and vary from progression of intrinsic disease, progressive cell apoptosis in severe CHF, and suboptimal LV stimulation site to nonoptimized programming of device pacing intervals. Implanters can only control a few of the aforementioned variables and in particular can be limited by individual patient anatomy.

The lateral LV wall is typically, but not always, the most delayed myocardial segment activated, and there are only a limited numbers of branches in which to deliver the pacing lead. Therefore, in general, placement of the LV lead in the most lateral branches is sought. At times, there may be several choices in the lateral LV wall where lead delivery is feasible. Utilization of dyssynchrony markers preoperatively or intraoperatively can often guide optimal branch selection.

Atrioventricular (AV) intervals determine optimum LV programming. Short AV intervals would not appropriately maximize LV filling, and long AV intervals may result in LV systole during atrial contraction as well as diastolic mitral regurgitation. AV delay optimization typically guided by Doppler echocardiography has been validated to improve cardiac output.[18] AV delays should be optimized on a regular basis as reverse remodeling of the LV may lead to variation in the optimum intervals.

Current CRT devices can also vary the timing intervals between right ventricular and left ventricular pacing stimulation. Such ventricular-ventricular (VV) interval programming, with sequential biventricular pacing as opposed to simultaneous biventricular pacing, may further minimize the ventricular dyssynchrony by appropriately "preexciting" that ventricle with the greatest delay in native excitation.[19] The intervals need to be assessed on an individual and ongoing basis as CRT responders will likely exhibit sufficient changes in LV mechanics to warrant reevaluation of optimal timing intervals. While there is no standard determinant of optimum VV interval programming, maximum aortic flow and minimal mechanical dyssynchrony have been used as reasonable endpoints.

Assuring appropriate atrial sensing and maximizing ventricular pacing are more obvious parameters that require careful attention. Hence, in patients with atrial fibrillation, ventricular response rates need to be controlled so that intrinsic AV conduction is minimized and biventricular pacing is maximized. In patients with sinus rhythm, frequent atrial arrhythmias may lead to atrial undersensing or prohibitively rapid ventricular conduction; in both settings, the underlying rhythm may be controlled with medications or catheter-based radiofrequency ablation.

FUTURE DIRECTIONS

Despite the established benefits of CRT, not all patients with moderate to severe CHF are eligible. Current guidelines for CRT indicate that patients should have NYHA functional class III or IV, QRS duration >120 msec, and systolic dysfunction (LVEF < 35%). However, emerging evidence suggests that CRT may be applicable and beneficial to a much broader population, including patients with mild heart failure (NYHA functional class II) as well as patients with QRS duration < 120 msec.

CRT IN NYHA II HEART FAILURE

The hypothesis of a CRT benefit in NYHA functional class II, where symptoms are relatively mild, is to

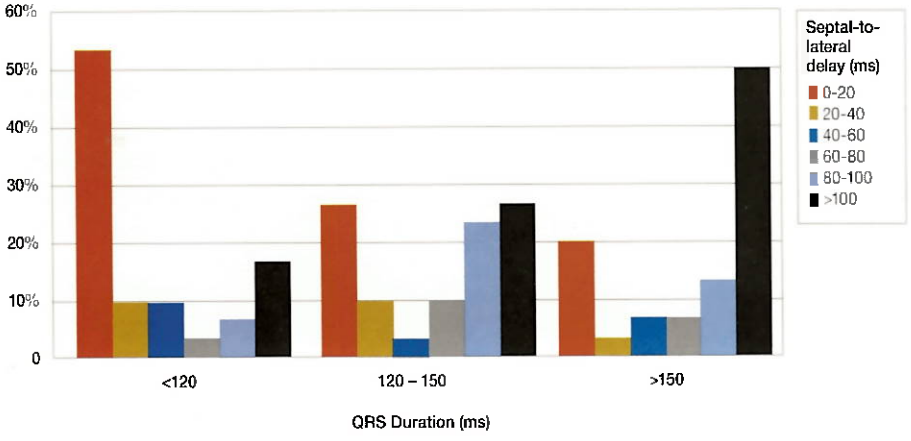

Figure 3. Distribution of septal-to-lateral delay (as marker of left ventricular dyssynchrony) and QRS duration.
Reprinted with permission from Bleeker GB, et al. Relationship between QRS duration and left ventricular Dyssynchrony in patients with end-stage heart failure. *J Cardiovasc Electrophysiol.* 2004;15:544-549.

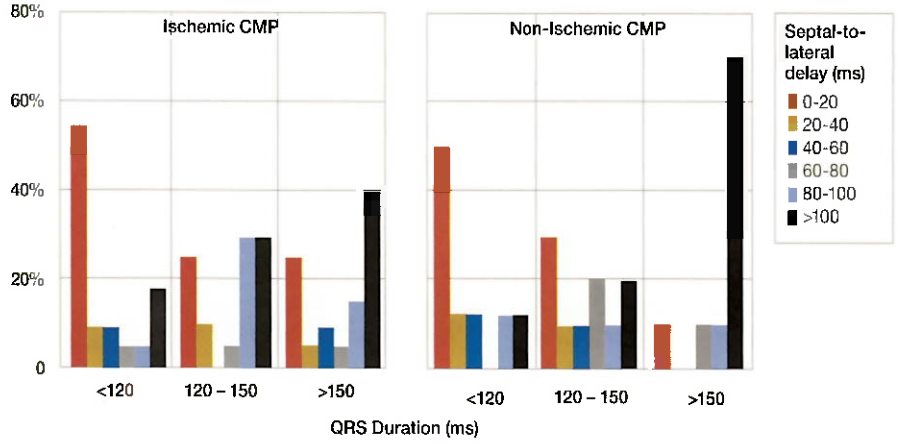

Figure 4. Distribution of septal-to-lateral delay and QRS duration in patients with ischemic versus nonischemic cardiomyopathy (CMP).
Reprinted with permission from Yu CM, et al. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. *Heart.* 2003;89:54-60.

delay disease progression by improving cardiac performance. Several small studies to date have demonstrated improvement in reverse remodeling or in functional class.[14,15]

MDHC participated in the REVERSE, a large multicenter clinical trial that is now in the follow-up stage, to determine the benefits of CRT therapy in patients with low ejection fraction, QRS duration >12 om/sec, and NYHA functional class I or II. A future multicenter study examining resynchronization with defibrillation therapy in NYHA Class II patients will be enrolling in fall 2007. This study will examine the combined endpoints of mortality and morbidity in mild CHF.

CRT IN NARROW QRS COMPLEX HEART FAILURE

The major clinical trials of CRT were performed in patients with electrocardiographic manifestation of dyssynchrony, i.e., wide QRS intervals (>120-150ms). The hypothesis was that a wide QRS interval equates to mechanical dyssynchrony with resultant CRT benefit in these patients. Unfortunately, QRS duration is a poor marker of mechanical dyssynchrony, with up to 30-45% of patients with QRS intervals < 120ms demonstrating mechanical dyssynchrony (Figure 3).[17]

Several small studies have shown CRT benefits in heart failure patients with mechanical dyssynchrony despite narrow QRS (Figure 4).[16,17] Currently, there is no standardized test or definition to evaluate mechanical dyssynchrony. MDHC has participated in a large multicenter study of CRT in narrow QRS. Enrollment in this study is closed, but the potential benefits of CRT in narrow QRS are available at our institution via an investigator-initiated study examining this patient subgroup.

SUMMARY

There have been remarkable advances in CHF treatments since the days when bloodletting seemed to be the definitive therapy. There are now well-established indications for using electro-mechanical CRT to treat moderate to severe CHF in patients on optimal medical therapy. Our goals for the future are to understand potential CRT benefits in the much larger but less-affected group of patients with CHF and to minimize nonresponders by effectively placing LV leads and programming the myriad parameters available.

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