CARDIAC RESYNCHRONIZATION: A CORNERSTONE IN THE FOUNDATION OF DEVICE THERAPY FOR HEART FAILURE*

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Accepted goals of heart failure treatment include: 1) improvement in symptom status, 2) prevention of disease progression, and 3) reduction in morbidity and mortality (1). Complex pharmacologic therapies achieve these goals for many, but not all, patients with heart failure. For patients who remain symptomatic despite receiving “optimal” medical therapy, novel adjunctive therapies are needed. Technological advancements are permitting the exploration of the so-called device therapies for heart failure. One such device incorporates biventricular stimulation to resynchronize cardiac contraction. The study by Stellbrink et al. (2) in this issue of the Journal is consistent with other emerging data finding that chronic resynchronization therapy may achieve several treatment goals in heart failure including symptom reduction and slowing of heart failure progression (2–5).

See pages 1957 and 1966

Cardiac resynchronization therapy is only applicable to a subset of heart failure patients, namely those with myocardial conduction system delay. Myocardial conduction system delay, manifest as bundle branch block, impacts 20% to 30% of New York Heart Association (NYHA) functional class III–IV heart failure patients and consists predominately of left bundle branch block (6–9). The presence of bundle branch block introduces contractile inefficiency and dyssynchrony, causing further diminishment of ventricular function (9,10). When left ventricular (LV) conduction delay is superimposed upon ventricular dysfunction, it appears to be a marker of disease severity, predicting an increased risk of both heart failure progression and susceptibility to ventricular arrhythmias (11–15). Cardiac resynchronization attempts to correct the deleterious effects of dyssynchrony. The question remains whether this approach satisfies some or all heart failure treatment goals.

The echocardiographic data provided by Stellbrink et al. (2) are derived from a subset of patients enrolled in one of the first clinical studies of resynchronization therapy in Europe, the Pacing Therapies in Congestive Heart Failure (PATH-CHF) trial (2). Because of rapid advances in device and lead technology, this trial differs from studies subsequently performed in Europe and the U.S., particularly in relation to duration of follow-up and implant tools and techniques. The PATH-CHF trial enrolled 42 patients with advanced NYHA functional class III or IV heart failure due predominately to nonischemic etiologies. Primary end points of the study were measures of functional capacity. The PATH-CHF trial had a unique design, common to two clinical trials of resynchronization therapy performed in Europe (16). At the time of device implantation, subsequent programmed parameters were determined on the basis of acute hemodynamic data measuring aortic pulse pressure and +dP/dt. Hemodynamics obtained in sinus rhythm were compared with right, left and simultaneous biventricular stimulation performed at variable atrioventricular intervals. Specifically, the hemodynamic data were acquired, analyzed off-line and used to determine whether resynchronization was chronically provided by right ventricular, LV or simultaneous biventricular stimulation. Patients enrolled in PATH-CHF had LV stimulation provided from an epicardial LV lead placed via a limited thoracotomy. Patients also received two separate pacemakers and two endocardial right atrial leads to allow for independent programming of right and left ventricle. In contrast, all U.S. trials completed to date provided resynchronization by simultaneous biventricular stimulation (5). Patients were then paced for six months, at which time echocardiography was performed and compared to baseline.

The primary end points of the PATH-CHF trial were positive, but they are not reported in the study by Stellbrink et al. (2), and have only been published in abstract form (17–19). The investigators do report that NYHA functional class significantly improved over six months of resynchronization therapy. The echocardiographic data demonstrate improvements in LV volumes and dimensions, well-validated measures of LV reverse remodeling. Neither LV fractional shortening, mass, sphericity index nor heart rate changed with therapy. There are no data evaluating the effect of therapy on measures of diastolic function or right heart function. Of interest, the beneficial effects of resynchronization on LV volume and dimension did not correlate with either acute hemodynamic or NYHA functional class benefit. Also, there were patients who had progressive ventricular enlargement on therapy but had improvement in acute hemodynamic parameters and/or improvement in functional class. This suggests that the well-described acute hemodynamic benefit of LV or biventricular stimulation may be uncoupled from the potential for a reverse ventricular remodeling effect (20,21). It further suggests that functional benefit can be seen in patients who do not attain reverse remodeling. Accordingly, hemodynamic parameters

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may not be useful in determining the full potential of the therapy to improve both symptom status and ventricular remodeling.

Neither the study by Stellbrink et al. (2) nor a similar study by Touiza et al. (22) in this issue of the Journal was designed to answer whether chronic pacing of one ventricle was equivalent to chronic simultaneous stimulation of both ventricles. In the Stellbrink et al. (2) report, the site(s) of stimulation was determined by the location that produced the most favorable acute hemodynamic profile. In the Touiza et al. (22) study, the stimulation site(s) was determined simply by physician preference, which in part was influenced by individual patient anatomic characteristics that dictated the practicalities of pacer lead placement. A prospective, randomized trial will be needed to determine whether single or biventricular stimulation is important in achieving the treatment goals of chronic resynchronization therapy.

Among other limitations of the Stellbrink et al. (2) study is that the majority of patients had heart failure due to idiopathic cardiomyopathy. The study results may not apply to patients with an ischemic etiology for heart failure, characterized by more regional myocardial dysfunction. As there were changes in heart failure medications throughout the study interval, this may have influenced LV volumes and dimensions at six months independent of resynchronization. Further, as only 60% of patients were receiving beta-blockers, it is difficult to say whether chronic resynchronization is positively or adversely affected by chronic beta-blockade. The Stellbrink et al. (2) study also attempted to define a subgroup of “responders” to resynchronization (as defined by a ≥15% decrease in LV end systolic volume compared to baseline) and to determine whether baseline characteristics of such patients were different from nonresponders.” The “responders” group, however, included patients whose LV end systolic volumes were stable following resynchronization therapy and may themselves have different baseline characteristics than true responders. Little can therefore be said of this subgroup analysis.

Finally, although it is clear that the natural history of heart failure is characterized by progressive myocardial remodeling, studies of beta-blocker therapy that include a control group find that some echocardiographic measures of progression or regression of remodeling may not be detected for up to 18 months. The study by Stellbrink et al. (2) may be too short to understand the full impact (if any) of chronic resynchronization therapy on myocardial remodeling (23).

Ever since the PATH–CHF study was initiated, device technology has rapidly evolved. In the U.S., a resynchronization device has recently gained regulatory approval and a resynchronization ICD is on the cusp of approval. Devices are now available, on clinical protocol, that can be programmed to achieve resynchronization with LV or biventricular stimulation, provide early diagnosis and treatment of atrial arrhythmias, and offer real-time hemodynamic data. All leads can now be implanted with a transvenous approach, thus avoiding thoracotomy. Left ventricular stimulation is now achieved reliably and safely using a coronary sinus branch vein (3,22,24–25). This is important as it reduces the inherent operative morbidity and mortality of thoracotomy in order to place the LV epicardial lead. One patient died of postthoracotomy complications in the Stellbrink et al. (2) study. The addition of defibrillation capability to the device adds little to device size or operative risk (25). Thus, technological advancements have rapidly improved the safety and simplicity of LV lead placement.

Resynchronization devices may be simple and safe, but does chronic resynchronization therapy fulfill its promise to act as an adjunct to pharmacologic agents in the management of heart failure patients with myocardial conduction delay and achieve some or all of the goals of heart failure treatment? In this calendar year, the results of the first controlled clinical trials of resynchronization therapies providing six months of follow-up have been published or presented (2,3,22,24–25). The data are consistent across these studies, demonstrating the therapy’s effectiveness at improving heart failure symptoms and stabilizing or reducing LV volumes and dimensions. Clinical trials initiated in 1999 are evaluating the ability of chronic resynchronization therapy (with or without an ICD), compared to standard medical therapies, to improve all-cause mortality and hospitalization (4,26).

Those of us involved in the clinical studies of cardiac resynchronization already appreciate that these devices promote optimal medical management of the heart failure patient. Improvements in systolic blood pressure resulting from resynchronization therapy allow for upward titration of vasodilating drugs (22,25). The atrial rate support feature is also very useful in this era of increasing use of beta-receptor blocking agents. Although extremely attractive theoretically, the mortality benefit of the defibrillating capability is yet to be determined.

Why have technical devices been developed for cardiac diseases? Simply put, because the need was there. The first implantable pacemakers were devised by Chardack, Wilson, and Greatbach in 1960 to treat heart block because medications were unable to correct this problem. The need was there. The first ICD was proposed in 1966 by Mirowski when a close friend experienced sudden death. Medications were not preventing sudden death. The need was there. Many heart failure patients still experience debilitating symptoms and die prematurely despite “optimal” medical therapy. The need for adjunctive therapy is here. The development of resynchronization therapy is addressing this need. The development of resynchronization therapy is a unique cooperation of electrophysiologists and heart failure pharmacotherapists that is only in its infancy. As Henry Ford observed, “Coming together is a beginning; keeping together is progress; working together is success.” The need is here and success is our goal. We commend the early work of Stellbrink et al. (2) for providing a rationale to establish.
resynchronization as a legitimate adjunctive therapy in the management of heart failure.

**REFERENCES**