Left Ventricular Versus Biventricular for Cardiac Resynchronization Therapy
Comparable But Not Equal

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The primary mechanism of benefit associated with cardiac resynchronization therapy (CRT) is attributed to improvement in left ventricular (LV) function resulting from restoration of LV contractile synchrony. The vast majority of implanted CRT-capable devices are programmed to provide the therapy by simultaneous pacing of the right ventricle and LV (biventricular stimulation). This mode of CRT delivery has been the mode best tested in large-scale clinical trials that have demonstrated improvement in functional, anatomic, and event-driven outcomes. The reasons for the more thorough evaluation of biventricular stimulation compared with LV stimulation alone are largely practical in nature. Early studies of CRT systems were designed to demonstrate the safety and efficacy of CRT. Long-term transvenous epicardial LV stimulation was not an established therapy, and LV lead performance was unknown. Biventricular stimulation allowed backup pacing and sensing if the LV lead failed. Additionally, all bradycardia pacing and defibrillating lead timing and therapy delivery are determined by right ventricular lead–based sensing. These considerations necessitated the presence of a right ventricular lead in long-term studies of CRT. There was also the early short-term observation that short-term stimulation results in similar mechanical synchrony with LV or biventricular stimulation, but electric dispersion appears to be increased with LV stimulation. This finding raised concern that LV stimulation alone could create a more favorable milieu for the occurrence of ventricular proarrhythmia.

The left ventricular versus simultaneous biventricular pacing in patients with heart failure and a QRS complex greater or equal to 120 milliseconds study (GREATER-EARTH) investigators report 6-month data collected in 103 patients prospectively randomized in a double-blind multicenter crossover trial of LV versus biventricular CRT. Consistent with other long-term studies (Table), LV stimulation was not reported to be superior to biventricular stimulation for CRT, although it appears to be safe and effective. A novel finding of the study is that patients not responding to either LV or biventricular stimulation have the potential to improve (31% and 17% of nonresponders, respectively) if stimulated in the other mode. The GREATER-EARTH trial enrolled a very well medically treated group of patients with LV dysfunction, advanced symptom class heart failure, and QRS delay. The investigators report a >94% and 99% use of β-receptor blocker and angiotensin-converting enzyme inhibitor or receptor blocker therapy before initiating CRT in all study patients. This was due to the study requirement of a 2- to 8-week medication stabilization period after implantation and before randomization. This requirement differentiates this trial and helps ensure that the findings are a true assessment of CRT and not of other confounding factors, such as functional or structural improvement resulting from medical therapy or exercise training effect. The functional and anatomic end points used in GREATER-EARTH are similar to those used in other long-term studies comparing LV and biventricular CRT and show similar magnitude of improvements. Unlike one other trial that also studied LV or biventricular stimulation delivered for 6 months that reported a greater reduction in LV end-diastolic volumes with biventricular CRT, the GREATER-EARTH trial indicates similar reductions in LV volumes regardless of CRT mode. There also was no difference in the incidence of sustained atrial or ventricular arrhythmias according to CRT mode in the GREATER-EARTH trial. However, these data cannot be considered definitive, relative to arrhythmia risk, because the follow-up was limited to 6 months and there was no assessment of mortality or hospitalization.

The well-conducted GREATER-EARTH trial has significance because it provides some rationale for initiating a programming change to an alternative mode for a CRT device recipient who does not demonstrate clinical improvement. The data also provide indirect support for changing modes in a CRT recipient who demonstrates clinical worsening of heart failure status, a very significant clinical issue associated with long-term CRT device therapy. It is unclear whether LV CRT offers any advantage to the future development of CRT LV leads or devices beyond biventricular CRT. For the foreseeable future, sensing and treating bradyarrhythmias and tachyarrhythmias will require a right ventricular lead. The investment in clinical science required to establish the epicardial transvenous LV lead for these purposes is unlikely to occur. Current transvenous LV lead development is directed more toward solving clinical issues like high capture thresholds and phrenic nerve stimulation as part of a biventricular system. There may a greater...
interest in LV CRT with stimulation technologies that do not require a transvenous lead such as ultrasound-mediated pacing because leadless CRT may offer distinct advantages by reducing lead-related complications and may offer a more site-specific option to placement of the LV lead.13

It should be noted that the total number of patients studied with LV CRT over a nearly 10-year interval and with no more than 6 to 12 months of follow-up is $\leq 500$. In addition, unlike the confluence of consistent data from 2 large-scale clinical trials on biventricular CRT, no study that has evaluated LV CRT has been powered to assess hospitalization and mortality outcomes.2–6 This is important because the mechanisms of mortality benefit with biventricular CRT may extend beyond the establishment of mechanical synchrony with LV stimulation and may be right ventricular lead dependent. Therefore, the major impact of the GREATER-EARTH trial is that it provides clinicians with some confidence that reprogramming a CRT device to LV only, in cases in which the response to therapy is suboptimal or has attenuated over time, is a reasonable and safe option.13

Disclosures
Dr Saxon has received research grants from and also serves as consultant to or on the advisory board for St Jude Medical, Medtronic Inc, and Boston Scientific Corp.

References

**Table. Clinical Studies of Left Ventricular Versus Biventricular Stimulation for Cardiac Resynchronization Therapy**

<table>
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BiV indicates biventricular; arrhythmias; LV, left ventricular; CRT, cardiac resynchronization therapy; B-LEFT, Biventricular Versus Left Unipolar Pacing With ICD Back-Up in Heart Failure Patients; DECREASE HF, a randomized trial comparing simultaneous biventricular pacing, sequential biventricular pacing, and left ventricular pacing; and BELIEVE, Bi vs Left Ventricular Pacing: An International Pilot Evaluation on Heart Failure Patients With Ventricular Arrhythmias.
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