Cardiac Resynchronization Therapy—All You Need To Know, 2006

"In at least 25% of patients with heart failure, some form of ventricular conduction delay will complicate the course of their disease," according to David A. Kass, MD, Division of Cardiology, Johns Hopkins University School of Medicine.

Dr. Kass noted that all rhythm disturbances create electrical "dissonance" in electrical activation and mechanical contraction between and/or within ventricles, reducing pump efficiency and lowering ejection fraction.

These intra- and interventricular conduction delays are associated with increased all-cause mortality and sudden cardiac death (SCD). "Conduction delays can lead to changes in molecular signaling, functional myocardial work area, calcium handling, and conduction dynamics," Dr. Kass said. "What starts as simply an electrical delay quickly becomes far worse."

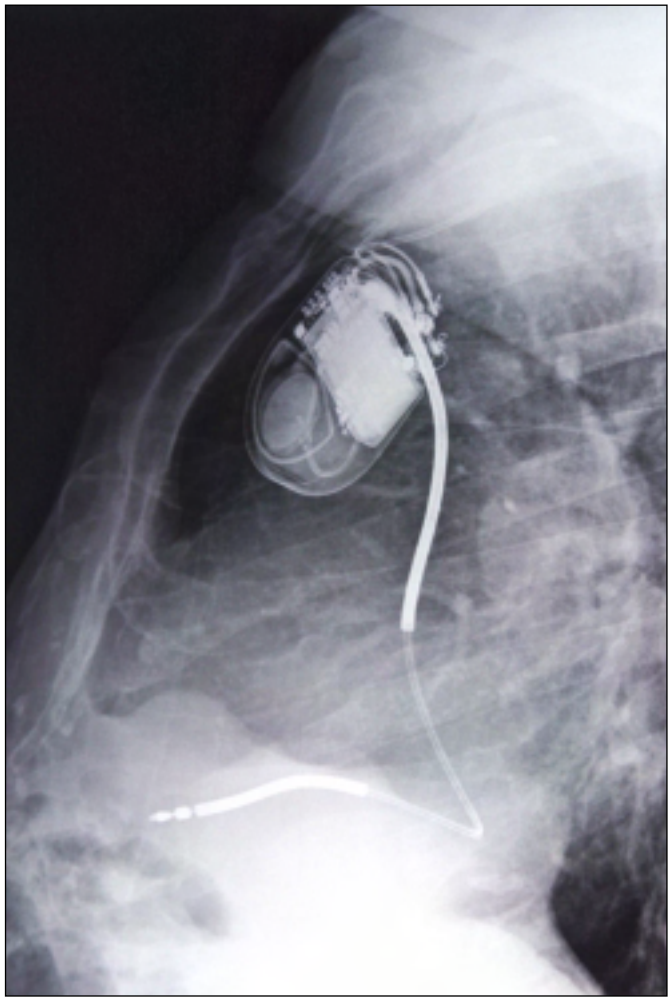
Recent genomics studies with mice point to one of the reasons cardiac dyssynchrony can be so dangerous: ventricular matrix remodeling begins very quickly after onset of ventricular pacing contraction abnormalities. "This is not a situation where pathological changes take years to develop and create problems," observed Dr. Kass. "What the animal studies tell us is that from the moment asynchrony begins the heart begins to compensate and remodel."

Enter cardiac resynchronization therapy (CRT). Dr. Kass noted that the evidence to date "confirms that CRT works well to enhance systolic function at a reduced energy cost and oxygen demand. CRT is like tuning up a car," he said. "It doesn't repair worn or failing parts—but it helps them to work at their maximum efficiency, and for longer than they might otherwise."

Evidence from Clinical Trials

Dr. William T. Abraham, Division of Cardiovascular Medicine, Ohio State University, discussed the data. "The weight of evidence supporting CRT is substantial," he said. "More than four thousand patients have been collectively studied in CRT trials to date. Across the board we have seen consistent improvement in functional cardiac status and increased exercise capacity after CRT. There is also compelling evidence supporting CRT's association with left ventricular regression ("reverse remodeling"), reduced left ventricular volumes and dimensions, and increased ejection fractions."

"The InSync Trial was among the earliest studies that supported long-term clinical benefits of CRT in advanced heart failure," Dr. Abraham said. A series of trials followed, including the MUSTIC, MIRACLE, and MIRACLE ICD trials. "All of these studies consistently demonstrated statistically significant improvements associated with CRT in quality of life, heart failure staging, and exercise tolerance, along with left ventricular reverse remodeling," said Dr. Abraham. "Some of the studies also suggested reductions in morbidity and mortality."



Dr. Abraham noted that a particularly engaging research question is the role of CRT in milder forms of heart failure. Should CRT be utilized earlier, in patients with less severe disease? "The REVERSE trial is looking at this question right now. We should have data within the next 3 to 4 years," Dr. Abraham said. Meanwhile, the PROSPECT trial may offer preliminary data in the next few months on the role of diagnostic imaging as a tool for patient selection for CRT, according to Dr. Abraham.

Cardiac Imaging and CRT: Potential and Promise

Cardiac imaging data from PROSPECT and other studies is eagerly anticipated, said Jeroen J. Bax, MD, Department of Cardiology, Leiden University Medical Center, The Netherlands. While imaging modalities are not yet included in the ACC/AHA CRT guidelines, they are a critical element in the evolution of CRT protocols.

Dr. Bax noted that despite firm evidence of CRT's efficacy in a majority of patients, between 25 and 30 percent who receive CRT are what he termed "nonresponders." This phenomenon, Dr. Bax said, "has generally been attributed to poor patient selection. To avoid unnecessary medical expenses as well as procedure risks, we must reduce the number of nonresponders. So how do we do a better job of patient selection when considering CRT?" At least one answer, Dr. Bax contends, lies in bringing some form of cardiac imaging to the patient selection criteria.

"Many investigators as well as working cardiologists recognize that imaging must play a role," Dr. Bax said. Several studies have noted that an important predictor of non-response to CRT is dyssynchrony within the left ventricle (interventricular dyssynchrony). However, a wide QRS complex may not be the single hallmark of substantial left ventricular dyssynchrony. "This point is supported by recent studies that demonstrate poor prediction of success when only QRS duration is used," Dr. Bax said. "ECG alone is not enough to weed out responders from nonresponders."

Dr. Bax described research done by his group using tissue Doppler imaging (TDI) to evaluate left ventricular dyssynchrony. (The investigators defined left ventricular dyssynchrony as an electromechanical delay seen on TDI between the septum and lateral wall of >60 ms.) "We demonstrated that improved identification of responders using TDI in concert with ECG was possible before implantation of a CRT system," according to Dr. Bax. "A wide QRS may not, by itself, adequately reflect left ventricular dyssynchrony. Indeed, some patients with a wide QRS may not have substantial LV dyssynchrony. More research is needed—but if the data ultimately supports imaging modalities among CRT criteria, we may improve patient selection and response."

CRT: Cost-Effective or Too Costly?

With CRT gaining ground as a treatment modality, Mark A. Hlatky, MD, Professor of Health Research and Policy, Stanford University, discussed the technique's cost-effectiveness.

Introduction of new medical technologies is a major reason that health care costs continue to rise, Dr. Hlatky observed. "The initial cost of implanting a CRT device exceeds $30,000, but the total cost may be even higher depending on its effect on the overall cost of treatment in any given patient. There may be additional costs of treating device complications—and still more costs if the patient is a non-responder."

But CRT may be worth its price tag if it consistently offers significant improvements in survival and quality of life. Dr. Hlatky described cost-effectiveness analysis (CEA), a mathematical tool applied in health care analyses. "CEA calculates dollars spent per number of quality-adjusted life-years (QALY) added by any given medical treatment," Dr. Hlatky explained. Citing a paper that estimated the cost-effectiveness of CRT at more than $100,000 per life-year gained (Nichol et al. *Ann Intern Med*. 2004); Dr. Hlatky noted that "this is not an advantage if compared to the standard benchmark of $50,000 per life-year gained."

But the Nichol analysis also showed that the cost-effectiveness of CRT is "very sensitive to variations in clinical efficacy," suggesting that improved patient selection to optimize CRT outcomes will confer both clinical and economic importance. "As our patients do better with CRT, its cost will drop."

"The overall weight of evidence suggests that CRT improves functional status and quality of life," Dr. Hlatky said. "And CEA is a helpful instrument to tell us we're on the right track financially as well. But as with so many arenas of medicine, more studies are needed."