Cardiac Resynchronization Therapy: The MGH Experience

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Cardiac resynchronization therapy (CRT) has gained acceptance as a useful form of device therapy for patients with refractory congestive heart failure. Despite recent technical advances, a significant number of patients continue to remain unresponsive to this form of therapy. This article provides an overview of CRT, highlights several unresolved issues and describes ongoing research efforts to address some of these important questions.

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Cardiac resynchronization therapy (CRT) has gained widespread acceptance as a safe and efficacious therapeutic measure for congestive heart failure (CHF) associated with a wide QRS complex and ventricular dyssynchrony.^{1–3} Several prospective randomized studies have demonstrated that CRT is associated with a significant improvement both in hemodynamics and in functional status of patients with CHF.^{3–6} CRT exerts its physiological impact via synchronizing ventricular contraction, which in turn results in improved pumping efficiency, improved left ventricular filling, and a reduction in the extent of the mitral regurgitation.⁷ Over time, there is positive remodeling of the heart with a reduction in the left ventricular volumes and an improvement in the ejection fraction.^{8,9} This in turn results in long-term clinical benefits such as improved quality of life, increased exercise capacity, reduction in hospitalization for heart failure, and overall mortality.^{2,3,6,10,11}

Despite its obvious benefits, there remain several unresolved issues, with the most important one being that up to one-third of patients treated with CRT do not derive any detectable benefit.^{12–14} Given the high prevalence, morbidity and mortality of CHF, and the substantial cost to society both from CHF as a disease and from CRT as a therapy, the importance of maximizing the response of all patients to CRT is evident. Other important issues include extending CRT benefits to a wider subset of patients (i.e., subjects with a narrow QRS, less symp-

tomatic subjects such as Class I and II NYHA), optimizing selection of LV pacing site, postprocedural device programming, and patient follow-up. This review provides an overview of CRT, highlights unresolved issues, and describes ongoing research at our institution directed at addressing some of these important questions.

HEART FAILURE: ELECTRICAL ACTIVATION AND MECHANICAL DYSSYNCHRONY

After meeting the criteria of compromised LV function and medically refractory HF (NYHA $\geq$ 3), patient selection is still driven by the presence of a wide QRS on the surface EKG.^{2,3} It is known that the presence of an intraventricular conduction defect, although a surrogate for mechanical ventricular dyssynchrony, is not predictive of acute and long-term response to CRT.^{15,16} The imprecision of the surface EKG in predicting response is explained by the complexity and multiple levels of electrical and mechanical dyssynchrony in the myopathic heart. This dyssynchrony can exist at multiple levels and can be interatrial, atrioventricular, interventricular, intraventricular, and intramural.^{8,17,18} Most studies have emphasized the importance of mechanical LV intraventricular dyssynchrony as the major contributing factor to progressive heart failure and predictor of response

to CRT. Nevertheless, the contribution of the other levels of dyssynchrony should not be underestimated in patients with cardiomyopathy, especially in the nonresponder population.

Simplistic approaches examining the QRS axis, morphology, and duration from the surface EKG have not been able to accurately predict the electrical activation pattern of the ventricles.^{19,20} Typically, a left bundle branch block is associated with an activation pattern which ascends from the apex up along the lateral and posterolateral portion of the left ventricle, to the base.²⁰ This spread of electrical activity correlates well with mechanical activation, and constitutes the basis for the conventional implantation strategy of positioning the LV leads in a lateral location, at the site of latest activation.^{21,22} However, there remains a high level of heterogeneity in the left ventricular activation pattern resulting from the varied levels of intraventricular conduction defects involving either the left or right bundles or fascicles. The presence of a scar in patients with ischemic heart disease further exacerbates the extent of in-homogeneity in the ventricular activation pattern.²³ A paced LV impulse from within a scar may result in an erratic and delayed spread of the activation wave front.

This complex interaction between variability in the selection of the final pacing site (dictated by the presence of a suitable venous branch),²⁴ the inconsistency of the left ventricular activation pattern,^{19,23} and shifts in the electrical and mechanical activation pattern due to right ventricular pacing, may account for the high percentage of nonresponders to CRT.

DETERMINANTS OF RESPONSE

Response to CRT is dependent on selection of the appropriate patient, pacing the correct site and ensuring optimal device programming, and follow-up of the patients. Response can be measured acutely by examining the immediate hemodynamic impact, subacutely by quantifying the extent of remodeling and its impact on functional measures (QOL, walk test, and peak oxygen uptake), and in the long-term by reduction in hospitalization, cardiac events, and total mortality.^{2,3,6}

A substantial percentage of patients receiving CRT, do not necessarily derive any significant benefit from the procedure. This can be attributed to preprocedural selection criteria, intraprocedural determinants such as lead position, and postprocedural factors such as programming parameters

and quality of follow-up care. Unfortunately, simple measures such as baseline QRS and postpacing QRS shortening have not translated into acute or chronic hemodynamic benefit.¹⁶

ECHOCARDIOGRAPHIC ASSESSMENT

A variety of echocardiographic measures are used to improve our understanding of the anatomical and functional aspects of the cardiac substrate. A combination of M-mode, two-dimensional and three-dimensional echocardiography (2-DE and 3-DE) and tissue Doppler imaging (TDI) provide complementary information regarding the level of baseline dyssynchrony as well as acute response and evidence of favorable remodeling to CRT. At MGH we have used echocardiography to measure the acute hemodynamic response to CRT via Doppler velocity profiles of mitral regurgitation obtained from an apical four-chamber view with CRT turned off and then remeasured with CRT turned on, with 10 minutes allowed for hemodynamic stabilization in each mode. Left ventricular $+dP/dt_{max}$ (mmHg/s) is measured as the maximal slope of the upstroke of the mitral regurgitation (MR) jet, representing LV systolic contraction.²⁵ LV synchrony for patient-selection purposes is quantified by the maximum time difference (MTD) to peak systolic velocity between septal, inferior, anterior, and lateral walls as measured by myocardial tissue Doppler Echocardiography (Figs. 1a and b).

Currently, ultrasound TDI is the most widely accepted tool to assess ventricular dyssynchrony.^{9,26} There, however, remains a lack of standardization in accepted TDI measures, as well as several limitations to this technology.²⁷ TDI is still predominantly a two-dimensional technique and the requirement for high frame rates limits resolution and image quality. Also, on account of its angle dependence, TDI allows only specific views of the cardiac anatomy. More recently, live three-dimensional ultrasound has allowed for simultaneous imaging of all the cardiac segments in a cardiac cycle, with new segmental wall volume techniques potentially providing a better understanding of the extent of cardiac dyssynchrony during the same cardiac cycle (Fig. 2). Some of the new ultrasound systems can perform both two-dimensional TDI and live three-dimensional imaging, thereby providing a unique opportunity to assess both techniques independently and comparatively. At MGH, we currently perform both TDI and live three-dimensional

Figure 1. (a) Tissue Doppler imaging measuring the time to peak systolic tissue velocity in a patient pre-CRT. The arrow shows dyssynchrony at the mid-ventricular level with earlier activation of the mid-lateral wall compared to other segments. (b) Tissue Doppler imaging of the same patient showing synchronized activation of all the segments after CRT.

ultrasound in candidate-CRT patients before and after treatment for investigational purposes.

Selecting the Pacing Site

Electrical and Radiographic RV-LV Distance.

Heart failure is a complex condition, which requires individualized therapy. Baseline predictors of responsiveness to CRT are useful, but CRT re-

sponse also relates to selection of optimal sites for the LV and RV pacing leads. Intraprocedural aspects of lead placement, including lead position and proximity to scar tissue play an important role in determining the response to CRT. Current lead implantation strategies are anatomically driven, with the posterolateral or lateral vein considered optimal targets for LV lead placement.^{21,22} Despite this, there is evidence that the

Figure 2. Three-dimensional echocardiogram plotting volumetric changes in a patient post-CRT. The images show endocardial definition of the left ventricle, a segmental map, and a plot depicting the volumetric changes of each segment.

electrical activation pattern is different amongst patients with similar left bundle branch configurations, suggesting that a standard anatomical site may not be reflective of the site with maximal electrical delay or mechanical dyssynchrony in all patients.²⁰ There is also a paucity of information on whether choosing a site based on electrical delay has the same clinical implications in different cardiac substrates (i.e., ischemic vs. nonischemic cardiomyopathy).

Our recent work has shown that pacing from a site with more delayed electrical activation is beneficial and that a left ventricular lead electrical de-

lay greater than half the width of the baseline QRS (Fig. 3a) is associated with a favorable acute hemodynamic response (measured as percentage change in $+dP/dt$, (Fig. 3b) and an improved long-term outcome. While positioning the LV lead, the extent of electrical delay is measured in multiple branches (if the anatomy permits) and usually at more than one position along the same coronary vein. Although our approach is still anatomical, with a preference for a postero-lateral or lateral vein, if there is more than one venous tributary in the region of interest, the site with greater LV electrical delay is the one selected.

Figure 3. (a) Measurement of the left ventricular lead electrical delay (LVLED) is demonstrated. $LVLED = (\text{distance between A and B} / \text{QRS duration}) \times 100\%$. A: onset of QRS; B: Onset of Sensing on LV lead; LVLED: left ventricular lead electrical delay; C: end of QRS. (b) Figure shows that the LV lead electrical delay was longer in acute hemodynamic responders. Acute hemodynamic responders to CRT have been classified as those with a percentage change in $dP/dt \geq 25\%$. NICM-R: Non-ischemic cardiomyopathy-responders; NR: nonresponders; CMCAD: Ischemic cardiomyopathy.

Another important aspect of LV lead placement relates to physical separation between the two pacing electrodes. Given that CRT is intended to improve ventricular synchrony by coordinating LV and RV contraction, we tested the hypothesis that maximal RV to LV electrode separation may positively impact the acute hemodynamic effects of CRT. Our study showed that increased radiographic separation in the dorsal/ventral axis, on a lateral CXR was associated with a beneficial acute hemodynamic response to CRT.²⁵ Attempts are made to obtain maximum electrical and

physical separation between the LV and RV leads, with repositioning of the RV lead along the septum to accommodate for a suboptimal (i.e., anterolateral) LV lead position. The impact of this approach on long-term outcome is currently being evaluated.

Venous Mapping

The importance of detailed venous angiography during LV lead implantation cannot be overemphasized. Coronary venous angiography gives us the lay of the land and a better understanding of cardiac substrate and the different venous branches available for LV lead placement. As our understanding of CRT has evolved, it has become clear that one size does not fit all. Having a venous map helps us individualize our approach, by selecting the most suitable lead for the appropriate branch anatomy. Although placing an LV lead blindly without angiography may occasionally save time, more often it prolongs the procedural time. Additionally, the blind approach also may lead to the acceptance of a suboptimal LV lead location which could have been improved with knowledge of the patient's coronary venous anatomy.

Recently, we have highlighted the need for a segmental classification, to map the coronary veins and tributaries in relation to the left ventricular wall in a manner comparable to that of echocardiography and left ventricular angiography.²⁴ This stresses the need for an organized practical approach to coronary sinus angiography (similar to that of coronary arteriography), with careful attention being ascribed to the tributaries of main venous branches and emphasis on their course and dimensions to facilitate LV lead placement.

Recent developments in rotational contrast venography (Allura FD 10) enable multiangle visualization of the coronary venous anatomy. Using this technology, coronary sinus angiograms can be obtained, in a 4-second isocentric rotation of the imaging camera over a 110° arc. The rotational images can then be reviewed over a full range of angles, providing the implanting physician with detailed information of the origin, course, and tortuosity of each branch. Currently, our efforts have been directed at real-time reconstruction of three-dimensional models of the venous tree (Fig. 4) to give more information regarding the

Figure 4. Rotational venous angiogram, with still frame's in RAO 30° LV: lateral vein, MV: middle cardiac vein, GV: great cardiac vein and AV: anterior cardiac vein. Alongside are three-dimensional reconstructed images of the coronary venous tree.

size of the coronary sinus, its main branches and second-order tributaries.²⁸ This information should prove useful both to define an individual patients' coronary venous anatomy and to tailor an LV lead implant strategy targeting the myocardial segment of interest.

Electron beam computed tomography (EBCT) and multidetector row CT (MDCT) enable three-dimensional reconstruction of tomographic images of the beating heart. This noninvasive modality provides a detailed definition of the coronary venous anatomy, thereby facilitating the identification of the venous tributary, prediction of technical difficulty, and enabling better selection of appropriate implanting system and type of LV lead. As of yet, this technique has not been tested prospectively. Some of the potential limitations are the additional x-ray exposure, need for extra contrast, and limitations of the technique to visualize second- and third-order tributaries in sufficient detail.²⁴ The role of magnetic resonance imaging is actively being evaluated in its ability to more precisely quantify dyssynchrony and better select patients.²⁹ Currently, work at the MRI level is focusing on the development of novel methods to characterize myocardial fiber architecture (Fig. 5) and ultra structure and three-dimensional imaging of myocardial strain.³⁰ Transmural variation of myocardial fiber orientation and its relation to LV site pacing and the consequent impact on LV remodeling is just one of the many potential questions waiting to be addressed.

Image Integration

One of the biggest limitations with current imaging modalities is the inability of a single technique to address the anatomic, mechanical, electrical, and structural issues associated with CRT (i.e., extent of scar and phrenic nerve location). Real-time integration of coronary venous (segmental) branch location with echocardiographic, CT, or MRI-guided measurements of LV segmental dyssynchrony, along with improvement in LV lead technology will significantly influence

Figure 5. Diffusion Tensor Imaging (MRI) of an ex-vivo canine LV specimen. Each line is the 1st eigenvector of diffusion, color-coded by helix angle. The transmural variation in fiber orientation can be clearly seen. Courtesy of T. Reese and V. Wedeen.

our approach to treating patients with heart failure and ventricular dyssynchrony.

There are data from small retrospective studies, which have shown that pacing over the site with maximal discordance may have a better outcome.^{22,31} Current use of intraprocedural echocardiography to demonstrate the most delayed segment to guide LV lead placement is cumbersome and challenging. Hence, preprocedural evaluation of mechanical dyssynchrony and intraprocedural integration with venous mapping may be a useful strategy, but still needs to be tested prospectively.

Recently we have attempted to integrate mechanical information from 3-DE with the anatomical data obtained from 3-DE reconstruction of the rotational venogram (Fig. 6). This form of integration provides information pertaining to the segment with mechanical dyssynchrony and details of the coronary venous tributaries in close proximity.

Implantation Strategies

Suitable LV lead implantation can be obtained using the conventional transvenous or surgical transthoracic approach.³² The latter is usually a

bailout strategy, in case of failure to access the coronary sinus or obtain an optimal LV lead position (i.e., high pacing thresholds or suboptimal anatomical site).³³ Improvement in delivery systems and lead technology now enable stable lead placement in venous branches, which were previously technically challenging. LV lead implantation could also be performed via a transeptal puncture in some patients. This could potentially be a more commonly used bailout strategy in the future, but currently remains technically challenging and investigational. Despite providing access to multiple endocardial LV sites, there remains a high risk of embolic complications and the need for long-term anticoagulation.

The use of remote magnetic navigation is another new modality for LV lead placement. This is a vector-based approach for guiding the angioplasty wire through the coronary veins to the region of interest. Although this technique provides more stability to the guide wire, in our limited experience, tracking the LV lead over tortuous and acutely angulated veins, has some of the same problems as seen with the conventional approach. The potential benefits of the remote navigation system are the possibility of implantation without a guiding catheter, faster procedure, and limited fluoroscopy exposure. This technique is currently being evaluated prospectively in comparison to the usual transvenous approach.

Predicting and Improving Response

Periprocedural Factors

Several variables pertaining to patient selection and optimal LV lead placement have been examined for their ability to predict CRT response. We know that selecting the right patient but pacing the wrong site may be as much a contributor to non-responsiveness to CRT as selecting an inappropriate patient but pacing an anatomically appropriate site. To be able to integrate this information, we recently constructed a simple 4-point response score inclusive of: (i) baseline contractility (dP/dt) measured from the mitral regurgitant jet, (ii) baseline LV dyssynchrony, measured by tissue Doppler imaging as the maximum time difference (MTD) between peak systolic velocity of anterior, septal, lateral, and inferior walls, (iii) horizontal distance between the LV-RV leads in the lateral CXR, and (iv) the extent of electrical delay at the site of LV pacing.³⁴ The score was generated assigning

Figure 6. Integrated image derived from three-dimensional echocardiography and reconstructed venous angiogram. The integrated image can be visualized in multiple planes, to identify segment of dyssynchrony and determine proximity of a suitable venous branch.

1 point for each LV–RV distance >10cm, LV lead electrical delay >50% of the QRS duration, baseline $dP/dt < 600$ mmHg/s and MTD >100 ms. There was a significant correlation between the response score and hemodynamic response to CRT and long-term outcome. This score was generated retrospectively, and its value in predicting response still needs to be tested prospectively. This however, emphasizes the point that response to CRT is a composite of preprocedural and intra-procedural variables.

Postprocedural Factors

The advent of V–V optimization, and the ability to change the ventricular activation wave fronts from the RV and LV pacing³⁵ electrode may further help to reduce the number of nonresponders.³⁶ RV–LV optimization can change the extent of fusion of depolarizing wave fronts advancing from the LV and RV lead. Despite the benefits of RV–LV optimization, this strategy is limited by the constraints of the selected LV and RV pacing sites. Greater electrical separation of the pacing leads will result in greater flexibility in altering ventricular activation pattern when modifying RV–LV timing. Close electrical and physical proximity of the RV and LV leads would limit RV–LV optimization, as only small changes in electrical activation patterns of the ventricles would result when altering the timing of leads in closely neighboring sites.

The programming sequence is individualized, but involves demonstrating left ventricular capture, ensuring near 100% pacing, adjusting the AV interval to optimize LV filling, followed by optimizing the RV–LV time to minimize intraventricular and interventricular dyssynchrony. Selecting the right patient, positioning the LV lead thoughtfully and programming the device to optimize hemodynamics can result in favorable LV remodeling and significantly reduce the percent of nonresponders.

Unresolved Issues

Although CRT has proven to be an efficient adjunctive therapy for patients with heart failure, there are still several important unresolved issues. There is still some uncertainty regarding the role of CRT in patients with chronic atrial fibrillation and/or right bundle branch block. Patients with AF and severe cardiomyopathy already lack an atrial

kick, and CRT-induced reduction in ventricular dyssynchrony has been shown to be beneficial in small studies.³⁷ It is important to ensure adequate nodal blockade to ensure nearly 100% ventricular pacing in these patients in order to obtain full benefit from biventricular pacing. The data on RBBB are less convincing and the role of CRT in this patient subset has not been prospectively examined. Again small subsets of patients in the MIRACLE and CONTAK-CD with RBBB appeared to do as well as patients with LBBB,³⁸ although a more sophisticated evaluation demonstrated benefit only in patients with RBBB who demonstrated intraventricular asynchrony.³⁹

No data are available as to whether CRT is beneficial in patients with moderate to severe pulmonary hypertension. Recent work from our group has shown that subjects with a right ventricular systolic pressure > 50 mmHg have a worse prognosis compared to those with lower pulmonary pressures (unpublished). However there were subjects with significant pulmonary hypertension who did well after CRT implantation, thereby raising the issue of whether a subset of these patients can benefit from CRT. After having shown that CRT is effective in patients with severe heart failure and a wide QRS, there have been recent efforts to assess if this therapy is useful in patients who do not meet these conventional criteria. It has been demonstrated that a significant number of patients with heart failure and a normal QRS duration, may have mechanical dyssynchrony, and could potentially benefit from CRT.⁴⁰ The 'RethinQ Study' is prospectively examining this question in a large multicenter study.

The MADIT-II study showed that there was a high probability for hospitalization for heart failure in patients with mild heart failure (NYHA Class I or II, with $LVEF \leq 0.30$ and $QRS \geq 130$ ms) over a 20-month follow-up.⁴¹ Our work with the MADIT-II study group showed that heart failure progression was associated with a high incidence of appropriate ICD therapy for ventricular tachycardia/ventricular fibrillation and death, suggesting that earlier intervention maybe useful.⁴² The ongoing 'MADIT-CRT' study is specifically addressing this question of whether prophylactic CRT in combination with a defibrillator can prevent the progression of heart failure and reduce all-cause mortality in subjects with only mild clinical heart failure but with reduced LV systolic function and a wide QRS.

Figure 7. Figure represents the multiple levels of interaction required to facilitate care of the CRT patient. EP: Electrophysiology service; HF: Heart failure service; Echo: Echocardiography service; Cards: Primary cardiologist taking care of the patient.

Beyond the LV Lead

HF disease management programs have been shown to be successful, with short-term costs being translated into long-term gains through improved outcomes, i.e., reduced overall mortality, hospitalizations, and medical care cost. The burgeoning heart failure population and increasing number of patients receiving CRT devices has created a need for a dedicated CRT program to manage this population of ailing patients. Most patients eligible to receive CRT devices are very ill and require a multidisciplinary approach involving the primary cardiologist, the electrophysiologist (EP), and heart failure (HF) specialist, with echocardiography support (Fig. 7). This care requires a fair deal of communication and interaction amongst the involved caregivers, including the referring cardiologist and primary care physician. Unfortunately the current state of medical care provided to this patient population is disjointed and not well coordinated in most hospitals. There is no structured cross-talk between the EP, HF service and the primary cardiologist or internist. Patient response when discussed is usually anecdotal and on a case-by-case basis.

The current postprocedure care lacks attention to incorporating information from the heart failure diagnostics (Table 1) or maximizing the benefit patients may derive from device optimization. An integrated approach facilitating optimal patient selection, CRT device optimization and careful titration of the medical therapy in the postimplantation

Table 1. Heart Failure Diagnostics

Activity Graph

- Heart rate trends
 - Mean, maximum, minimum
 - Night/day
- Heart rate variability
 - SDANN
 - Footprint
- Sinus node dysfunction
- Therapy delivery
 - Percent biventricular pacing
 - LV–RV timing
 - AV conduction histogram
 - ICD shocks
 - Antitachycardia pacing
- Arrhythmia detection
 - Atrial flutter
 - Atrial fibrillation
 - Nonsustained ventricular tachycardia
- Transthoracic impedance
- Intracardiac pressures
- Cardiac output

period is critical for maximizing the response of this patient group. A CRT clinic combining the expertise of the electrophysiology and heart failure service along with support from the echocardiography division could provide this multidisciplinary integrated care program. Additionally, CRT is expensive and ensuring its effectiveness in the entire patient population receiving this therapy would serve to enhance cost-effectiveness. Such a multidisciplinary effort would provide the opportunity to implement optimization protocols in a structured manner, thereby helping to convert nonresponders, maximize device benefit (even in initial responders), and integrate echocardiography and device diagnostic information into the clinical care of these patients. This closed circuit provides feedback to the implanting physician regarding the impact of the LV and RV lead site in a particular cardiac substrate and impact on clinical outcome, improving both patient selection and implantation strategies. A need for this integrated service is long overdue and several centers including ours have begun moving in that direction.

REFERENCES

1. Abraham WT. Cardiac resynchronization therapy: A review of clinical trials and criteria for identifying the appropriate patient. *Rev Cardiovasc Med* 2003;4:S30–S37.

2. Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure: A meta-analysis of randomized controlled trials. *JAMA* 2003;289:730-740.
3. Bristow MR, Saxon LA, Boehmer J, et al. Comparison of medical therapy P, defibrillation in heart failure I. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-2150.
4. Nelson GS, Berger RD, Fetters BJ, et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation* 2000;102:3053-3059.
5. Auricchio A, Kloss M, Trautmann SI, et al. Exercise performance following cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *Am J Cardiol* 2002;89:198-203.
6. Gras D, Leclercq C, Tang AS, et al. Cardiac resynchronization therapy in advanced heart failure the multicenter In-Sync clinical study. *Eur J Heart Fail* 2002;4:311-320.
7. Breithardt OA, Sinha AM, Schwammenthal E, et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. *J Am Coll Cardiol* 2003;41:765-770.
8. Cazeau S, Bordachar P, Jauvert G, et al. Echocardiographic modeling of cardiac dyssynchrony before and during multisite stimulation: A prospective study. *Pacing Clin Electrophysiol* 2003;26(1 Pt 2):137-143.
9. Yu CM, Fung WH, Lin H, et al. Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. *Am J Cardiol* 2003;91:684-688.
10. Abraham WT, Hayes DL. Cardiac resynchronization therapy for heart failure. *Circulation* 2003;108:2596-2603.
11. Auricchio A, Stellbrink C, Sack S, et al. Pacing therapies in congestive heart failure study G. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002;39:2026-2033.
12. Reuter S, Garrigue S, Barold SS, et al. Comparison of characteristics in responders versus nonresponders with biventricular pacing for drug-resistant congestive heart failure. *Am J Cardiol* 2002;89:346-350.
13. Pitzalis MV, Iacoviello M, Romito R, et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. *J Am Coll Cardiol* 2002;40:1615-1622.
14. Kass DA. Ventricular resynchronization: Pathophysiology and identification of responders. *Rev Cardiovasc Med* 2003;4(Suppl. 2):13.
15. Fauchier L, Marie O, Casset-Senon D, et al. Reliability of QRS duration and morphology on surface electrocardiogram to identify ventricular dyssynchrony in patients with idiopathic dilated cardiomyopathy. *A J Cardiol* 2003;92:341-344.
16. Molhoek SG, Vane L, Bootsma M, et al. QRS duration and shortening to predict clinical response to cardiac resynchronization therapy in patients with end-stage heart failure. *Pacing Clin Electrophysiol* 2004;27:308-313.
17. Auricchio A, Abraham WT. Cardiac resynchronization therapy: Current state of the art: cost versus benefit. *Circulation* 2004;109:300-307.
18. Daubert JC, Pavin D, Jauvert G, et al. Intra- and interatrial conduction delay: Implications for cardiac pacing. *Pacing Clin Electrophysiol* 2004;27:507-525.
19. Fung JW, Yu CM, Yip G, et al. Variable left ventricular activation pattern in patients with heart failure and left bundle branch block. *Heart* 2004;90:17-19.
20. Auricchio A, Fantoni C, Regoli F, et al. Characterization of left ventricular activation in patients with heart failure and left bundle-branch block. *Circulation* 2004;109:1133-1139.
21. Butter C, Auricchio A, Stellbrink C, et al. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. *Circulation* 2001;104:3026-3029.
22. Ansalone G, Giannantoni P, Ricci R, et al. Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing. *J Am Coll Cardiol* 2002;39:489-499.
23. Lambiase PD, Rinaldi A, Hauck J, et al. Non-contact left ventricular endocardial mapping in cardiac resynchronization therapy. *Heart* 2004;90:44-51.
24. Singh JP, Houser S, Heist EK, et al. The coronary venous anatomy: A segmental approach to aid cardiac resynchronization therapy. *J Am Coll Cardiol* 2005;46:68-74.
25. Heist EK, Fan D, Mela T, et al. Radiographic left ventricular-right ventricular interlead distance predicts the acute hemodynamic response to cardiac resynchronization therapy. *Am J Cardiol* 2005;96:685-690.
26. Bax JJ, Bleeker GB, Marwick TH, et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2004;44:1834-1840.
27. Yu CM, Abraham WT, Bax J, et al. Predictors of response to cardiac resynchronization therapy (PROSPECT)-study design. *Am Heart J* 2005;149:600-605.
28. Mansour M, Reddy VY, Singh J, et al. Three-dimensional reconstruction of the coronary sinus using rotational angiography. *J Cardiovasc Electrophysiol* 2005;16:675-676.
29. Zwanenburg JJ, Gotte MJ, Kuijper JP, et al. Timing of cardiac contraction in humans mapped by high-temporal-resolution MRI tagging: early onset and late peak of shortening in lateral wall. *Am J Physiol Heart Circ Physiol* 2004;286:H1872-H1880.
30. MGH Program in Cardiovascular Magnetic Resonance. Available at <http://www.nmr.mgh.harvard.edu/cardiovasc>.
31. Dohi K, Suffoletto M, Ganz L, et al. Utility of echocardiographic tissue synchronization imaging to redirect left ventricular lead placement for improved cardiac resynchronization therapy. *Pacing Clin Electrophysiol* 2005;28:461-465.
32. Koos R, Sinha AM, Markus K, et al. Comparison of left ventricular lead placement via the coronary venous approach versus lateral thoracotomy in patients receiving cardiac resynchronization therapy. *Am J Cardiol* 2004;94:59-63.
33. Puglisi A, Lunati M, Marullo AG, et al. Limited thoracotomy as a second choice alternative to transvenous implant for cardiac resynchronization therapy delivery. *Eur Heart J* 2004;25:1063-1069.
34. Heist EK, Taub C, Fan D, et al. Novel response score predicts acute hemodynamic response to cardiac resynchronization therapy (Abstract). *Heart Rhythm* 2005;2:582.
35. Sogaard P, Egeblad H, Pedersen AK, et al. Sequential versus simultaneous biventricular resynchronization for severe heart failure: evaluation by tissue Doppler imaging. *Circulation* 2002;106:2078-2084.
36. van Gelder BM, Bracke FA, Meijer A, et al. Effect of optimizing the VV interval on left ventricular contractility in cardiac resynchronization therapy. *Am J Cardiol* 2004;93:1500-1503.
37. Molhoek SG, Bax JJ, Bleeker GB, et al. Comparison of response to cardiac resynchronization therapy in patients with sinus rhythm versus chronic atrial fibrillation. *Am J Cardiol* 2004;94:1506-1509.
38. Egoavil CA, Ho RT, Greenspon AJ, et al. Cardiac resynchronization therapy in patients with right bundle branch block:

Analysis of pooled data from the MIRACLE and Contak CD trials. *Heart Rhythm* 2005;2:611–615.

39. Schuster P, Faerstrand S, Ohm OJ. Color Doppler tissue velocity imaging can disclose systolic left ventricular asynchrony independent of the QRS morphology in patients with severe heart failure. *Pacing Clin Electrophysiol* 2004;27:460–467.
40. Achilli A, Sassara M, Ficili S, et al. Long-term effectiveness of cardiac resynchronization therapy in patients with refrac-

tory heart failure and "narrow" QRS.[see comment]. *J Am Coll Cardiol* 2003;42:2117–2124.

41. Moss AJ, Zareba W, Hall WJ. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877–883.
42. Singh JP, Hall WJ, McNitt S, et al. Factors influencing appropriate firing of the implanted defibrillator for ventricular tachycardia/fibrillation: Findings from MADIT-II. *J Am Coll Cardiol* 2005 (in press).

Michel Mirowski, 1980s

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