Emerging Role of Cardiac Resynchronization Therapy in Heart Failure

Nazar Luqman,[1] Chun-Li Wang,[2] Ruey J. Sung[3] and Chi-Tai Kuo[2]

Morbidity and mortality due to heart failure remains high in spite of advances in its medical management. During the last decade a new modality has emerged that has now proven to be beneficial in a select group of patients with heart failure. This is the cardiac resynchronization therapy (CRT), which is based on correcting various types of cardiac dyssynchrony that many patients with heart failure have. Though a large number of trials have demonstrated clinical and hemodynamic benefits of CRT, it is only recently that mortality benefits have been shown. The mortality benefit is further improved when CRT is combined with intracardiac defibrillator in selected patients of heart failure. Based on the existing criteria for selection of heart failure patients for CRT (NYHA III or IV, depressed left ventricular ejection fraction < 35% and presence of left bundle branch block with QRS duration > 120 ms), 30-40% patients do not respond favorably. Newer modalities like speckle tracking imaging and three-dimensional echocardiography are being validated to differentiate responder from nonresponder. This is extremely important in view of the high cost of the device. This review article highlights logic behind CRT, criteria for selection of cases, problems of non response, role of combined CRT-defibrillator and other related issues.

Key Words: Biventricular pacing • Cardiac resynchronization therapy • Dyssynchrony • Heart failure • Implantable cardioverter-defibrillator • Left bundle branch block

Despite a growing number of therapeutic options, more than half of patients with heart failure (HF) still die within 5 years of their diagnosis. In recent years, an additional treatment strategy is focused on optimizing heart rhythm management and preventing sudden cardiac death through cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICD) in selected patients of HF. Although further studies are needed to define the optimal use and the cost-effectiveness of these therapies, and the need for more effective ways to guide patient selection, the bulk of the clinical evidence now indicates that for selected patients with HF, the use of CRT, ICD or combined CRT-ICD in addition to optimum pharmacological therapy offers benefit beyond what medical therapy alone can give. It improves quality of life and functional status, reduces the need for hospitalization, and has a significant survival benefit, all of which one seeks to achieve in therapy for HF. This review article highlights logic behind CRT, criteria for selection of cases, problems of non response, role of combined CRT-ICD and other related issues.

Received: February 11, 2008 Accepted: February 25, 2008
[1]Department of Cardiology, RIPAS Hospital, Brunei Darussalam; [2]Department of Cardiology, Chang Gung Memorial Hospital & School of Medicine, Chang Gung University, Taoyuan; [3]Department of Medicine, National Cheng Kung University School of Medicine, Tainan, Taiwan.
Address correspondence and reprint requests to: Dr. Chi-Tai Kuo, Department of Cardiology, Chang Gung Memorial Hospital, No. 5, Fushin Street, Kweishan Township, Taoyuan 33375, Taiwan.
Tel: 886-3-328-1200 ext. 8162; Fax: 886-3-327-1192; E-mail: chitai@adm.cgmh.org.tw

1. CONDUCTION ABNORMALITIES IN HF

The efficiency of heart as a pump is highly dependent upon its synchronized electrical and mechanical function. It is adversely affected if the relationships are adversely between atria and ventricle (atrioventricular dyssynchrony), right and left ventricle (interventricular dyssyn-

chrony) or within the left ventricle affecting its normal sequence of activation (Intraventricular dyssynchrony).[1,2]

1.1. Atrioventricular dyssynchrony

This can result from dysfunction of sinus node or atrioventricular node. It has been variously reported from 31 to 53% in patients with HF.[2,3] The hemodynamic consequences are: (1) reduced diastolic filling due to fusion of E and A waves as a result of prolongation of PR interval; (2) diastolic mitral regurgitation due to fusion of E and A waves and prolonged PR interval leading to delayed closure of mitral valve and hence presence of raised left ventricular end diastolic pressure; and (3) reduced peak dP/dt.[4,5]

1.2. Interventricular dyssynchrony

This occurs predominantly due to left bundle branch block (LBBB) (Table 1). The early right ventricular activation leads to right ventricular ejection during the left ventricular end-diastolic period and the septal motion is paradoxical. Consequently there is reduced left ventricular filling, decreased septal contribution, and increased functional mitral regurgitation, which ultimately decrease forward cardiac output.[6] Interventricular dyssynchrony is the most common cause of ventricular dyssynchrony, affecting 30% to 50% of patients with systolic heart failure and LBBB, as evidenced by a widened QRS interval on surface electrocardiograms.[4,7]

Xiao et al. described a positive correlation between the QRS width and the duration of mitral regurgitation, left ventricular contraction and relaxation times, and negative correlation with the peak rise in left ventricular pressure.[8] The morphology of the QRS complex (typical right bundle branch block, LBBB or nonspecific block) did not have a direct influence on the magnitude of the abnormalities. In another study, 29% of patients with HF had a complete LBBB and 9% had a right bundle branch block.[9] Overall, left axis deviation was seen in 65% of patients with HF. Both prolongation of the PR interval and a wide QRS complex were independent predictors of mortality in various studies of patients with HF. Patients with a wide QRS duration (> 200 milliseconds) had a five times greater mortality risk than those with a narrow QRS duration (< 90 milliseconds).[3,10]

1.3. Intraventricular dyssynchrony

Contractile sequence within the left ventricle is not coordinated, thus left ventricular segments which contract early, do not contribute to the ejection of blood and segments that contract late do so at a higher wall stress, causing the early contracting segments to undergo paradoxical stretch.[6] Consequently, the end result is impaired systolic function, reduced cardiac output, and increased end-systolic volume and wall stress.[11] Additionally, mitral regurgitation worsens in part because of left ventricular remodeling, and pre-systolic regurgitation may occur due to delayed contraction of papillary muscle root attachments.[11] The study by Yu et al. examined the prevalence of mechanical dyssynchrony in HF patients with wide and narrow QRS complexes.[12] This study examined 67 patients with QRS duration > 120 milliseconds (in the form of LBBB or intraventricular conduction delay) and 45 patients with QRS duration ≤ 120 milliseconds. Systolic dyssynchrony was present in 43% of patients with narrow QRS complexes and in 64% with wide QRS complexes. Thus electrocardiography alone may not be adequate enough to demonstrate intraventricular dyssynchrony in patients with HF.

2. PATIENT SELECTIONS FOR CRT

Although the benefits of CRT have been endorsed by most of the guidelines, physicians continue to struggle with the issues of patient selections. Several questions remain to be fully answered, such as the role of CRT alone vs. combined CRT-ICD, the most effective way to measure ventricular dyssynchrony, whether the best and worst responders to CRT can be identified prior to implantation, and what role economics should play in these decisions. CRT is an expensive therapy; device

Table 1. Mechanisms of desynchronization due to left bundle branch block

Decreased septal motion
Earlier filling of right ventricle
Late left ventricular contraction in early diastole
Delay in mitral and aortic closure and worsening of mitral regurgitaion
Paradoxical septal motion towards left ventricle during right ventricular contraction
Increased left ventricular contraction, ejection time and relaxation time
Contraction of right ventricle earlier than left ventricle
Lack of increase of left ventricular ejection fraction on exercise

charges in the United States range from $25,000 to $40,000 and total patient charges can be as high as $100,000.[13] Moreover, a substantial proportion (25% to 30%) of patients who undergo CRT may not respond to therapy.[14] This has, in large part, been attributed to poor patient selection. So far, QRS duration has been the criteria used to select those heart failure patients who may benefit from cardiac resynchronization therapy. A QRS duration > 155 milliseconds, especially if combined with very poor left ventricular contractility, appears to be a reliable predictor of success for CRT.[15] However, QRS duration may not reliably reflect the degree of mechanical dyssynchrony, which has been shown in Doppler echocardiographic studies to predict adverse clinical events and response to CRT, even in patients with relatively narrow QRS intervals. Attempts are being made to quantify left ventricular dyssynchrony, primarily using echocardiographic parameters. For example, a baseline aortic preejection period > 160 milliseconds or a time delay of left ventricular septal to posterior wall contraction of > 180 milliseconds predicted efficacy of CRT.[16,17] Newer strategies apply tissue-Doppler and three-dimensional echocardiography in aiding patient selection.[18] These are currently time-consuming, and are operator dependent. As of now, the guidelines recommend CRT for patients with left ventricular ejection fraction less than 35%, sinus rhythm, and New York Heart Association functional class III or ambulatory class IV symptoms despite optimum medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration of > 120 milliseconds.

3. TECHNICAL ISSUES AND FOLLOW-UP

CRT being a relatively new technique requires a certain level of expertise and a learning curve. There are certain technical aspects and follow-up issues that deserve special consideration in order to achieve optimum results. Most commonly a transvenous-coronary sinus approach is used. The usual steps would be:

- Cephalic and/or subclavian vein access;
- Right ventricular lead placement;
- Engaging coronary sinus through a guide sheath or with help of a catheter;
- Coronary sinus venogram after balloon occlusion in right/lateral anterior oblique projections;
- Access an appropriate left ventricular vein. Use a lead or guide wire to preferably access a lateral vein;
- Check for sensing and pacing parameters, diaphragmatic stimulation and lead stability;
- Place atrial lead;
- Remove the coronary sinus guide sheath; and
- Keep template of right ventricular, left ventricular and biventricular capture complexes for later comparisons.

3.1. Difficulties In coronary sinus engagement

Coronary venous anatomy is highly variable and the procedure can be quite time-consuming and technically demanding, despite the operator's previous implantation experience. Commonly encountered barriers are: (1) abnormally high or posterior location; vertical, tortuous, or S shaped coronary sinus; (2) Thebesian valve impeding the advancement of the sheath; and (3) narrowing or stenosis of coronary sinus from previous surgery, etc. Most of these difficulties can be overcome with certain maneuvers.

3.1.1. Location for left ventricular lead placement

Placement of the left ventricular lead to a location that resynchronizes the electrical and mechanical activation sequence of the left ventricle to provide better coordination during systole is the key to successful cardiac resynchronization therapy. Currently, it is recommended that the left ventricular lead should be positioned at the lateral free wall, which corresponds to the anatomical region of the lateral or posterior-lateral cardiac vein of the coronary sinus.[19-21] In one study, surgical placement of the lead was made and acute hemodynamic effects were studied with multiple left ventricular pacing sites. This study showed best improvements from the midlateral segment in only 27% of patients, and worse in the mid-posterior segment.[22] In PATH-CHF II (Pacing Therapies for Congestive Heart Failure) left ventricular or biventricular pacing were assessed in an acute study. In most of these patients, left ventricular free wall pacing resulted in a larger gain in pulse pressure (9% vs. 5%, $p < 0.001$) and positive dP/dt (12% vs. 5%, $p < 0.001$) when compared with left ventricular anterior wall pacing.[23] However, more data is required to clarify if acute hemodynamic-guided left ventricular pacing site selection is superior to empirical placement of the lead at the left ventricular free wall.

3.1.2. Success for left ventricular lead placement and complications

The MIRACLE (Multicenter Insync Randomized Clinical Evaluation) trial investigators reported an overall success rate of 92% for the implantation of the InSync pacemaker (Medtronic model 8040; using Medtronic LV Attain model 2187 stylet driven left ventricular lead in 98% of implants) in 453 patients.[20] Coronary sinus dissection or perforation occurred in approximately 6% of patients. Other serious complications were complete heart block, hemopericardium and cardiac arrest (together approximately 1.2% of patients). Left ventricular lead dislodgment was noted in 6% of patients during the course of the 6 months follow-up. Other studies have also shown overall implant success rate of more than 85-90%.[20,21]

3.2. Follow-up of patients with cardiac resynchronization devices

Following successful implantation of the cardiac resynchronization device, routine threshold testing is necessary to confirm successful biventricular capture. Use of a template 12-lead electrocardiogram from the time of implant is the most reliable means to confirm biventricular capture. Clinical parameters like functional class, severity of heart failure, need for hospitalization along with echocardiographic parameters of cardiac dyssynchrony and mitral regurgitation are useful tools to track the progress of an individual patient's response to therapy and to the optimized atrioventricular delay programming. Serial adjustments to atrioventricular delay programming may be required.

In individual patients, atrioventricular interval optimization may be necessary to ensure maximum benefit from CRT.[25] This process can be complex and labor intensive. Pacing threshold testing for left ventricular and right ventricular pacing leads has become easier in devices that use separate pacing outputs but can be challenging in those with a common right ventricular/left ventricular pacing channel. Newer generations allow for programming of the right ventricular to left ventricular timing, possibly further increasing complexity to device follow-up.

4. MARKERS OF CARDIAC RESYNCHRONIZATION THERAPY EFFICACY

4.1. ECG markers

It would seem logical that shortening of the QRS duration with biventricular pacing is a simple way to predict clinical improvement, or to identify the optimal pacing sites in the left ventricular epicardial surface. Unfortunately, this is not the case. In some acute studies, hemodynamic improvement occurred with biventricular pacing in the absence of QRS shortening and some patients respond better to left ventricular than to biventricular pacing.[23,26] In one study 73% of the patients showed improvement by biventricular pacing.[27] The only parameter that differed significantly between the responders and non-responders was the QRS duration under biventricular pacing. The responders had a significantly shorter QRS during biventricular pacing than at baseline (154 ± 17 vs. 179 ± 22 milliseconds, $p < 0.05$) compared with the nonresponder (177 ± 26 vs. 176 ± 30 milliseconds).[27] However, in the Multisite Stimulation in Cardiomyopathy (MUSTIC) Study, no significant shortening was noted with biventricular pacing (175 ± 19 vs. 172 ± 22 milliseconds); in spite of significant clinical benefit.[19] Other studies have also reported clinical improvement in the absence of QRS shortening during biventricular pacing.[28-30] In a few patients prolongation of QRS duration has been described during active biventricular pacing.[28-30] Several of these patients showed clinical improvement, although it is not clear how the QRS duration would widen during biventricular pacing.

4.2. Echocardiographic markers

Echocardiography is useful in clinical assessment before and after CRT because it is noninvasive, easily available, and able to quantify the changes of regional or global ventricular function. The appropriate use of echocardiography to assess ventricular dyssynchrony could play a vital role in selecting appropriate patients for CRT (responder selection) and predicting outcome. Several echocardiographic techniques have been used for these purposes, including M-mode, two-dimensional echocardiography, tissue Doppler imaging, tissue synchronization imaging, strain, strain rate, speckle-tracking imaging, and three-dimensional echocardiography, and. These techniques ranged from the assessment of 2 segments by M-mode to all myocardial segments by three-dimensional echocardiography. A summary of the different techniques and criteria to predict a favorable response is provided in Table 2.

Using an M-mode echocardiography, the septal-to-posterior wall motion delay with a cutoff value of 130

Table 2. Echocardiographic predictors of favorable response to cardiac resynchronization therapy

Author	N	Follow-Up	Methods	Criteria	Cut-off	Responders		Sensitivity	Specificity
						Definition	N (%)		
Pitzalis MV[17]	20	1 month	M-mode	Septal-to-posterior wall motion delay	130 ms	↓ LVESV ≧ 15%	12 (60%)	100%	63%
Marcus GM[31]	79	6 months	M-mode	Septal-to-posterior wall motion delay	102 ms	↓ LVESV ≧ 15%	NA	24%	66%
Penicka M[32]	49	6 months	PW-TDI	Inter- and intra-ventricular delay (Ts-onset) of 3 basal LV and 1 basal RV segments	102 ms	↑ relative LVEF ≧ 25%	27 (55%)	96%	71%
Bax JJ[33]	80	12 months	CC-TDI	Septolateral delay of Ts (ejection phase)	60 ms	↓ NYHA≧1 & ↑ 6m-WD ≧ 25%	59 (74%)	92%	92%
Yu CM[34]	54	3 months	CC-TDI	Ts-SD of 6-basal, 6-mid LV segments (ejection phase)	31 ms	↓ LVESV ≧ 15%	31 (57%)	96%	78%
Notabartolo D[35]	49	3 months	CC-TDI	Maximal difference in Ts in 6-basal segments (both ejection and post-systolic phases)	110 ms	↓ LVESV ≧ 15%	29 (59%)	97%	55%
Gorcsan J 3rd[36]	29	Within 2 days	TSI	Septoposterior delay (both ejection and post-systolic phases)	65 ms	↑ LVSV ≧ 25%	15 (52%)	87%	100%
Yu CM[37]	56	3 months	TSI	qualitative	NA	↓ LVESV ≧ 15%	30 (54%)	47%	89%
			Tissue velocity	Ts-SD of 6-basal, 6-mid LV segments (both ejection and post-systolic phases)	34 ms			87%	81%
Dohi K[38]	38	1 day	CC-TDI Strain	Septoposterior delay of peak radial strain	130 ms	↑ LVSV ≧ 25%	21 (55%)	95%	88%
Suffoletto MS[39]	48	1 day	Speckle-tracking radial strain	Time to peak radial strain of 6-mid LV segments	130 ms	↑ LVSV ≧ 15%	32 (67%)	91%	75%
	50	8 months			130 ms	↑ relative LVEF ≧ 15%	38 (76%)	89%	83%
Kapetanakis S[40]	23	10 months	3D echo	SD of time-to-minimal-volume ratio (of the cardiac cycles) in 16 LV segments	NA	Symptomatic improvement	17 (74%)	NA	NA

CC-TDI: color-coded tissue Doppler imaging, EF: ejection fraction, ESV: endsystolic volume, PW-TDI: pulsed wave tissue Doppler imaging, TSI: tissue synchronization imaging; Ts-onset: time to onset of segmental systolic tissue velocity; Ts-SD: standard deviation of time to peak systolic velocity, LV: left ventricular, SV: stroke volume, 3D: three dimensional, 6-m WD: six minutes walking distance.

milliseconds has been proposed as a powerful predictor of reverse remodeling.[17] However, the reproducibility and feasibility of measuring the M-mode dyssynchrony index were poor and this index did not correlate with the extent of clinical improvement.[31]

Tissue Doppler imaging has been widely used in evaluating the regional times and velocities of left ventricular segments and allows comparisons of time delay in relation to the onset of cardiac cycle in different left ventricular segments.[32-35] The segmental tissue velocities can be measured from pulsed-wave tissue Doppler imaging or color-coded tissue Doppler imaging. Color-coded tissue Doppler imaging allows comparisons of electromechanical delay in multiple segments simultaneously

and decreased the influence of the changes in heart rate, respiration and loading conditions.[33-35] The cut-off values of time delay using the tissue Doppler imaging techniques for prediction of responders varied with the number of analyzed segments (2, 4, 6, or 12) and different criteria.[32-35] It has also been demonstrated that the more segments analyzed, the higher the predictive value.[34]

A recently developed technique to quantify left ventricular dyssynchrony is the color coding of time to peak longitudinal velocities, tissue synchronization imaging.[36,37] The color-coding imaging is superimposed on the conventional two-dimensional images to allow qualitative appreciation of the time delays of segmental peak velocities. The qualitative identification of lateral or posterior wall delay is a quick guide to predict a favorable outcome. In the absence of lateral wall delay, however, it is important to quantify the left ventricular dyssynchrony by computing the time delay from several left ventricular segments.[37]

Strain and strain rate analysis allows evaluation of the amplitude and timing of myocardial deformation and decreases the influence of translational motion or tethering of adjacent tissues. This analysis can be derived offline from color-coded tissue Doppler imaging or novel speckle tracking echocardiography.[34,38,39] From a large prospective study comparing the tissue Doppler imaging, and strain rate analysis to assess left ventricular dyssynchrony, tissue Doppler imaging is superior to longitudinal strain or strain rate (derived from tissue velocity) in predicting left ventricular reverse remodeling.[33] However, the value of strain analysis has been appreciated by a recent study using the speckle tracking radial strain to assess intra-ventricular dyssynchrony.[39] The radial strain analysis by speckle tracking can be used to predict immediate response and long-term effect and determine the optimal site for left ventricular lead placement.[39]

Three-dimensional echocardiography has evolved from reconstruction of multiple two-dimensional images to an almost real-time three-dimensional technique. This technique allows us to quantify intra-ventricular dyssynchrony after taking into account all segment of the heart in radial, circumferential and longitudinal directions. It has been validated and was found to be a good tool to assess intra-ventricular dyssynchrony.[40] In one such study a systolic dyssynchrony index was derive from dispersion of time to minimum regional volume for all 16 left ventricular segments through the three-dimensional data set.[40] This index was found to correlate with the severity of left ventricular dysfunction but not with the QRS duration. This index has been proposed as a tool to predict favorable outcome but has not been tested in a large and prospective study. With an increasing number of methods and indices for evaluating left ventricular dyssynchrony, it will be important and valuable to compare several indices in the same study patients and test these indices in predicting clinical outcome and reverse left ventricular remodeling prospectively.

4.4. Clinical markers

Several controlled and uncontrolled studies of CRT for the treatment of advanced congestive HF and wide QRS complexes have been published (Table 3).[19,20,29,41,42] The primary end-points of the biventricular pacing studies include changes in 6 minutes walk distance, New York Heart Association function class, and the effect of CRT on quality of life as assessed by the Minnesota-Living-In-CHF score. Other end-points include myocardial oxygen requirement (VO_2) during exercise testing, and left ventricular ejection fraction. Recently total mortality is also an end-point in some studies.

MUSTIC study enrolled patients with New York Heart Association functional class III congestive HF, left ventricular ejection fraction less than 35%, and QRS width more than 150 milliseconds.[19] Patients in sinus rhythm had a significant increase in the 6 minutes walk distance, increase in peak exercise O_2 consumption, improvement in quality-of-life score, and significantly fewer hospitalizations. More than 80% of patients preferred resynchronization to control ($p < 0.001$). The MIRACLE study was a prospective, randomized, double-blind, controlled trial of biventricular pacing.[20] The study included a total of 453 patients with congestive HF, an ejection fraction of 35% or less, and QRS duration of 130 milliseconds. Patients assigned to CRT experienced an improvement in the distance walked in 6 minutes walk distance (39 vs. 10 meters, $p = 0.005$), functional class ($p = 0.001$), quality of life (-18 vs. -9 points, $p = 0.001$), time on the treadmill during exercise testing (81 vs. 19 seconds, $p = 0.001$) and ejection fraction (4.6 vs. -0.2%, $p < 0.001$). Fewer hospital admissions as well as intravenous diuretics were required in the cardiac resynchronization group. The results from MUSTIC and MIRACLE have been confirmed by a number of other studies, including the PATH-CHF.[20,24,43] A summary of these trials is presented in Table 4.[20,44-46] Whether the type of underlying heart disease

Table 3. Trials related to CRT with and without combined ICD

Studies	Nature of Study	Patients
MUSTIC[19]	Biventricular pacing (Sinus rhythm & atrial fibrillation)	131
MIRACLE[20]	Biventricular pacing	300
MIRACLE ICD[74]	Biventricular pacing + ICD on indication	400
CONTAK-CD[48]	Biventricular pacing + ICD on indication	580
COMPANION[47]	Biventricular pacing	2200
BELIEVE[81]	Biventricular pacing + ICD on indication	75
INSYNC III[48]	Biventricular pacing (Asynchronous LV-RV)	224
CARE-HF[46]	Biventricular pacing (Mortality Study)	800
PAVE[82]	Biventricular pacing, AF post AV junction ablation	650
PATH-CHF II[44]	Biventricular vs. LV vs. RV pacing	64

CRT: cardiac resynchronization therapy, ICD: intracardiac cardioverter defibrillator, LV: left ventricle, RV: right ventricle.

Table 4. CARE-HF: Primary and main secondary endpoints

Endpoint	Medical therapy	Medical therapy + CRT	*p* value
Primary endpoints			
All-cause mortality or unplanned hospitalization for a cardiovascular event (%)	224 (55%)	159 (39%)	< 0.001
Secondary endpoints			
All-cause mortality	120 (30%)	82 (20%)	< 0.002
All-cause mortality or unplanned hospitalization for worsening heart failure (%)	191 (47%)	118 (29%)	< 0.001

CRT: cardiac resynchronization therapy.

has any influence on the clinical success of biventricular pacing has been assessed by several studies. These studies have concluded that the response to biventricular pacing was similar, regardless of whether the cardiomyopathy was of ischemic or nonischemic etiology.[2,13,17,19,20]

5. MORTALITY BENEFITS

In the MUSTIC Study (58 randomized patients), mortality from pump failure was 5%, surprisingly low for this functional class III population.[19] In the InSync trial, an uncontrolled, prospective study in which 68 patients with congestive heart failure had successful implantation of biventricular pacing devices, had a mortality rate of 16.6% at 6 months' follow-up and in the MIRACLE Study, there were 16 deaths in the control group and 12 deaths in the resynchronization group.[20,29]

However, the CARE-HF (Cardiac Resynchronization In Heart Failure) study was the first one that showed a benefit from CRT with respect to survival as a sole endpoint, and also the first one to show benefit and continued improvement over a long follow-up period.[46] Together with the previously published COMPANION (Comparison of Medical, Resynchronization, and Defibrillation) trial, these results demonstrate the unequivocal benefits of CRT and confirm the safety of this therapy.[47] The CARE-HF study enrolled a total of 813 patients at 82 centers in 12 European countries patients in the CRT, demonstrated a highly significant risk reduction in the primary endpoint of death and cardiovascular hospitalization (37% relatively risk reduction, $p < 0.001$) and all-cause mortality (36% relatively risk reduction, $p = 0.002$) compared with the control.[46] CRT also reduced the risk of death from any cause or HF-related hospitalization by 46% ($p < 0.001$) (Table 4). Pooled data from four randomized clinical trials of biventricular pacing (total of 1634 patients) evaluated the effectiveness of CRT in the prevention of death in patients with HF.[48] The pooled data showed that CRT reduced death from progressive HF by 52% relative to controls. Progressive HF mortality was 1.7% for CRT patients and 3.5% for controls. A trend was evident showing that CRT reduced all-cause mortality (odds ratio: 0.77; 95% confidence interval: 0.51-1.18).

6. RESPONDERS AND NON-RESPONDERS

Due to the technical challenges, compounded by lack of consensus on most appropriate selection criteria for patients that will respond as well as optimum location for left ventricular lead placement, a good number of patients do not respond to CRT. The MIRACLE study was one of the landmark trials that established the effectiveness of CRT to improve a broad range of functional and clinical measures in patients with moderate-to-severe HF, ejection fraction $\leqq$ 35%, and an intraventricular conduction delay as measured by a QRS duration $\geqq$ 130 milliseconds.[20] Although a far greater percentage of patients in the CRT group demonstrated improvement than in the control group (67% vs. 39%, respectively), the percentage of non-responders to CRT was a disappointing 32%.

In one study 73% of the patients showed improvement by biventricular pacing.[27] The only parameter that differed significantly between the responders and non-responder was the QRS duration after biventricular pacing. The responders had a significantly shorter QRS duration during biventricular pacing than at baseline (154 ± 17 vs. 179 ± 22 milliseconds, $p < 0.05$) compared with the non-responders (177 ± 26 vs. 176 ± 30 milliseconds).

6.1. Electrical aspects

Strong evidence has emerged that QRS duration on surface electrocardiogram is a poor predictor of clinical response to CRT and may not accurately reflect the presence or absence of ventricular dyssynchrony.[17,49,50] Mechanical dyssynchrony can exist in patients with narrow QRS intervals and may also be noticeably absent in patients with widened QRS complexes.[12,13,51,52] Prolonged QRS duration on surface electrocardiograms may be caused by interventricular, intraventricular and, recently proposed intramural delay.[53] A positive correlation between QRS duration and interventricular conduction delay has been described in patients with dilated cardiomyopathy but relation between QRS duration and intraventricular dyssynchrony is not entirely clear.[54] CRT for interventricular delay probably plays only a secondary role in these patients. A mechanical study using echocardiography suggested that interventricular mechanical delay is unable to predict a favorable response to CRT.[34]

6.2. Mechanical aspects

Non-response to CRT is multi-factorial and may be related to the extent of mechanical dyssynchrony, left ventricular pacing site and cause of congestive HF. Independent predictors for identifying non-responders include prior myocardial infarction, absence of significant mitral regurgitation, and ischemic cardiomyopathy.[19] Echocardiography is particularly useful as it is easily available but lacks a unifying definition of response to CRT; and most cutoff values were derived from l studies with small sample size of 20 to 30 patients.[17,33,36] Both the conventional use of tissue Doppler echocardiography, as well as novel echo applications, such as speckle tracking imaging and three-dimensional echocardiography has been evaluated as potential approaches to specifically measure dyssynchrony in order to screen candidates for CRT.

Tissue Doppler imaging is a special form of Doppler echocardiography to detect the direction and velocity of the contracting or relaxing myocardium. Tissue Doppler imaging is a robust and reproducible echocardiographic tool to detect regional function and timing of cardiac events in the myocardium.[55] Systolic dyssynchrony is present in 43% of HF patients with narrow QRS complexes and in 64% with wide QRS complexes.[12] In other words, in about one-third of HF patients with wide QRS complexes are not associated with significant mechanical dyssynchrony. This observation is consistent with the prevalence of nonresponder rate in clinical trials of CRT. Two more recent reports also observed the presence of intraventricular mechanical delay in HF patients with narrow QRS duration.[56,57] The observation that mechanical dyssynchrony, that demonstrated by tissue Doppler imaging, occurs in HF patients with narrow QRS duration, indicates a potentially beneficial role for CRT in these patients. The dyssynchrony index that assessed intraventricular dyssynchrony of the 12 left ventricular segments by tissue Doppler imaging has been shown to be the strongest predictor of reverse remodeling.[34] The role of three-dimensional echocardiography, though promising, is yet to be defined.

6.3. Left ventricular lead placement

Appropriate placement of left ventricular lead is of paramount importance in achieving optimum synchronization. However, the role of acute hemodynamic-guided placement of left ventricular lead has not been estab-

lished. Implantation of the left ventricular lead at the left ventricular free wall region resulted in the largest gain in hemodynamic status including pulse pressure (10%) and positive dP/dt (21%).[45,58] Up to 30% patients may not have the left ventricular lead implanted in these sites.[19,59] In another study surgical placement of the lead at multiple left ventricular pacing sites, the study showed that the pacing site with the best hemodynamic effect occurred in the midlateral segment but in only 27% of patients. It suggested avoiding the left ventricular mid-posterior segment.[22] In PATH-CHF II study, patients with either left ventricular or biventricular pacing were assessed in an acute study.[23] In most of these patients, left ventricular free wall pacing resulted in a larger gain in pulse pressure (9 vs. 5%, $p < 0.001$) and positive dP/dt (12 vs. 5%, $p < 0.001$) when compared with left ventricular anterior wall pacing.[23] More data is required to clarify if acute hemodynamic-guided left ventricular pacing site selection is superior to empirical placement of the lead at the left ventricular free wall. In a recent study clinical response and mortality was studied in patients who had left ventricular lead placement in different sites for biventricular pacing.[60] A total of 233 consecutive patients were stratified on the basis of whether the lead was placed in the anterior and anterolateral branches (Group 1, n = 66) or in the lateral and posterolateral branches (Group 2, n = 167). Although a higher percentage of Group 2 patients than Group 1 patients had functional improvement, the difference between the 2 groups was not significant (67 vs. 54%, respectively; $p = 0.07$).[60] Despite the difference in degrees of ejection fraction improvement, the rate of mortality was similar between Groups 1 and 2 (13.6 vs. 17.9%, respectively; p = NS). (Table 4) In another study too all intraventricular parameters (septal-to-posterior and septal-to-lateral wall motion delays) were significantly decreased in patients with the electrode implanted in the lateral position than in those patients with the lead in the anterior position ($p = 0.02$ and $p = 0.04$, respectively).[61]

6.4. Device settings issues

The correct setting of the CRT device is another factor governing the success of the therapy. Optimization of the atrioventricular interval is crucial to ensure an optimal time for diastolic filling and abolishing diastolic mitral regurgitation. The optimization of atrioventricular interval can be achieved either by Ishikawa's method or by Ritter's method that are based on Doppler echocardiography.[62,63] Assessment of optimal interventricular pacing interval between the left and right ventricles (V-V interval) may also be important to increase the response rate to CRT. Recent data from Bordachar et al. suggested that optimization of V-V interval was able to reduce further the degree of mechanical dyssynchrony, improve cardiac function, and decrease mitral regurgitation.[64]

Device manufacturers are already devoting considerable attention to second-generation technology. For example, all three of the leading CRT-ICD suppliers have recently introduced advanced left ventricular lead systems designed to make lead implantation easier in patients with difficult anatomy, and second-generation software algorithms are also under development. Advances such as these will positively impact patient care in the years ahead.

7. CARDIAC RESYNCHRONIZATION IN SPECIAL CIRCUMSTANCES

7.1. CRT and atrial fibrillation

During acute testing, Blanc et al. reported improvement in hemodynamic parameters in 6 patients with atrial fibrillation and temporary biventricular pacing.[65] Other study also suggested improvement of various degrees when patients with atrial fibrillation were paced with temporary biventricular leads.[66] The MUSTIC study group showed that if continuous biventricular pacing can be ensured, atrial fibrillation does not appear to preclude effective CRT in patients with severe left ventricular dysfunction and wide QRS complexes.[67] Other uncontrolled studies of patients with chronic atrial fibrillation showed similar results where atrial fibrillation did not preclude benefit from biventricular pacing.[65,68,69] However, in some of these studies, atrioventricular junction ablation was used to control the rate and to allow continuous biventricular pacing. Therefore, the effect of biventricular pacing may be confounded by the rate control and rhythm regularization effect of atrioventricular junction ablation.[66-69]

7.2. CRT in patients with right bundle branch block

For HF patients with right bundle branch block, it is not known if CRT will result in the same extent of bene-

fit as to those with LBBB. Approximately 10% of patients with congestive HF have a wide QRS complex with right bundle branch block pattern on surface electrocardiograms. Patients with right bundle branch block may also have significant conduction delays in the left bundle branch, which may manifest as left or right axis deviation. Preliminary studies in a small number of patients suggest that patients with right bundle branch block tend to benefit more from biventricular and right ventricular stimulation than left ventricular pacing.[42,70] New insight is provided from a recent study where heart failure patients with right bundle branch block were compared to those with LBBB by three dimensional non-contact mapping. Interestingly, patients with right bundle branch block also exhibited significant left ventricular activation delay in addition to that of the right ventricle.[71]

7.3. CRT in patients with narrow QRS

Patients with HF and a QRS duration < 120 msec are not devoid of mechanical dyssynchrony. Several echocardiographic studies have shown that intraventricular mechanical delay was present up to 30-50% of these patients Moreover, echocardiographic and clinical benefits were also observed in these patients receiving CRT.[72,73] Biventricular pacing may also be beneficial in patients with first-degree atrioventricular block and a narrow QRS complex, or in patients with standard indications for pacing (i.e. complete atrioventricular block) in the absence of congestive HF or wide QRS complexes.[73] Conventional ventricular pacing would be anticipated to reduce systolic function and thereby offset benefits from improved chamber filling, whereas biventricular pacing may better maintain electrical and mechanical synchrony in such cases.

7.4. CRT in elderly patients

While age was not exclusion criteria in the clinical trials reported here, special circumstances need to be considered when contemplating CRT for the elderly. There are presently no data as to the utility of CRT in HF other than severe systolic dysfunction. Although little data are available, it is likely that procedural complications, such as coronary sinus perforation or contrast-induced renal toxicity, are increased among elderly persons. Furthermore, comorbidities present in elderly persons may influence the device choice: a CRT pacemaker to improve quality of life or a CRT-ICD pacemaker to improve quality of life and prolong life.

8. COMBINED CRT AND ICD

While CRT can improve hemodynamic and functional status of patients with HF, concerns regarding the risk for sudden death remain. ICD on the other hand can prevent sudden cardiac death but do not address the underlying pathophysiology of HF. These concerns are further substantiated by the results of the COMPANION trial, and the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) data.[47,74,75] A preliminary study involving 511 patients (442 patients with an implantable cardioverter-defibrillator with biventricular pacing capabilities, vs. 69 patients with conventional ICD) suggests that biventricular pacing with defibrillator capabilities may impact survival favorably when compared to a group treated with ICD therapy alone.[76] COMPANION and CARE-HF trials demonstrated CRT-ICD to further reduce the incidence of sudden cardiac death.[46,47] In COMPANION, sudden cardiac death was the cause of death in about 36% of patients on pharmacologic therapy and in about 23% of patients in the group receiving CRT and in CARE-HF, 32% to 35% of deaths were due to sudden cardiac death. COMPANION enrolled 1520 patients with New York Heart Association functional class III/IV symptoms, ejection fraction $\leqq$ 35%, and QRS interval $\geqq$ 120 milliseconds.[47] It was the first trial designed to compare CRT-ICD with CRT alone. Patients enrolled in COMPANION were randomized to 3 arms: optimal medical treatment, optimal medical treatment in combination with CRT, or optimal medical treatment in combination with CRT-ICD. All patients who received a CRT device had a significantly reduced risk of death or hospitalization from any cause. However, combined CRT-ICD fared better, after 16 months of follow-up, demonstrated a 40% reduction in the risk of death or hospitalization from HF and a 36% reduction in the risk of death from any cause. The risk of all-cause mortality alone was also significantly reduced in the combined CRT-ICD group compared with the control (36% relative risk reduction, $p = 0.003$) while those receiving only CRT showed a 24% relatively risk reduction in death vs. control ($p = 0.059$).

Largely on the basis of the results of these 2 trials,

the guidelines now endorse the use of CRT and combined CRT-ICD in HF patients who meet certain criteria (reduced left ventricular ejection fraction, New York Heart Association functional class III/IV HF, and evidence of ventricular dyssynchrony via wide QRS duration).

MIRACLE ICD showed combined CRT-ICD to improve quality of life, functional capacity, and exercise duration in patients already on optimal medical therapy.[77] The MADIT II focused on the influence of CRT in mildly symptomatic New York Heart Association functional class II patients and found that CRT appears to offer important benefits to those with less severe HF with the potential to limit disease progression in these patients.[75] This double-blind, parallel-group, controlled study randomized 186 patients (New York Heart Association functional class II, QRS interval $\geqq$ 130 milliseconds, left ventricular ejection fraction $\leqq$ 35%, and an established indication for an ICD) to the control group (defibrillator activated, CRT off; n = 101) or to the CRT group (ICD activated, CRT on; n = 85). A total of 98 control and 82 patients who received CRT completed the study through the 6-month follow-up. 58% of the patients received CRT were classified as improved, compared with 36% of the controls (p = 0.01). Other combined CRT-ICD trials have also shown favorable results.[78] MADIT-CRT and RHYTHM ICD have enrolled a high-risk patient population that included symptomatic, non-reversible New York Heart Association functional class III/IV HF, left ventricular ejection fraction $\leqq$ 35%, and an approved ICD indication and is investigating a second generation combined CRT-ICD, and Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE), is on the roll.

9. COST CONSIDERATIONS

Considering that the average cost of a CRT device ranges between $25,000 and $40,000 in the United States, with total per-patient charges (namely hospitalization costs) reaching $100,000 in some cases, and a relatively high non-response rate has raised concerns regarding the actual number needed to treat to achieve clinical benefit and the associated cost implications of managing such a large patient population.[15] A recent meta-analysis that evaluated the safety and efficacy of CRT in more than 3200 patients enrolled in 9 trials documented that the patient number needed to treat to prevent one HF hospitalization was 12 and the number needed to treat climbed to 24 in order to prevent one death.[78] Evaluating the cost-effectiveness of CRT vs. standard drug therapy for the management of patients with left ventricular dysfunction and QRS prolongation, another recent meta-analysis was published that used computer simulation to calculate how much each strategy would cost per year of life that it saved.[79,80] The study authors reported that CRT was associated with a median incremental cost per quality-adjusted life-year saved of $107,800, which represented $90,000 more than that reported for drug therapy. The high number needed to treat required achieving benefit coupled with the increased costs of CRT place considerable importance on identifying effective means to differentiate responders from non-responders to the therapy.

10. CONCLUSION

When taken together, the overall evidence in favor of ICD and combined CRT-ICD devices in patients with HF is compelling. Although further studies are needed to further define the optimal use and the cost-effectiveness of these therapies (and the need for more effective ways to guide patient selection is an ongoing concern), the bulk of the clinical evidence now indicates that for selected patients with HF, the use of a combined CRT-ICD device in addition to optimal medical therapy confers a multifunctional benefit beyond what medical therapy alone can offer. This includes an improvement in quality of life and functional status, a reduction in the need for hospitalization, and a significant survival advantage, all of which are goals of optimal HF therapy.

ACKNOWLEDGMENTS

This work was supported in part by Grant NSC 94-2314-B-182A-204 from the National Science Council, Taipei, Taiwan and CMRPG 32004 from Chang Gung Memorial Hospital, Taoyuan, Taiwan.

REFERENCES

1. Bax JJ, Ansalone G, Breithardt OA, et al. Echocardiographic

evaluation of cardiac resynchronization therapy: ready for routine clinical use? A critical appraisal. *J Am Coll Cardiol.* 2004;44:1-9.
2. Shamim W, Francis DP, Yousufuddin M, et al. Intraventricular conduction delay: a prognostic marker in chronic heart failure. *Int J Cardiol.* 1999;70:171-8.
3. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation* 1997;95:2660-7.
4. Grines CL, Bashore TM, Boudoulas H, Olson S, Shafer P, Wooley CF. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. *Circulation* 1989;79: 845-53.
5. Xiao HB, Lee CH, Gibson DG. Effect of left bundle branch block on diastolic function in dilated cardiomyopathy. *Br Heart J* 1991; 66:443-7.
6. Tedrow U, Sweeney MO, Stevenson WG. Physiology of cardiac resynchronization. *Curr Cardiol Rep* 2004;6:189-93.
7. Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Fedele F, Santini M. Biventricular pacing in heart failure: back to basics in the pathophysiology of left bundle branch block to reduce the number of nonresponders. *Am J Cardiol* 2003;91:55F-61F.
8. Xiao HB, Brecker SJ, Gibson DG. Effects of abnormal activation on the time course of the left ventricular pressure pulse in dilated cardiomyopathy. *Br Heart J* 1992;68:403-7.
9. Leclercq C, Cazeau S, Le Breton H, et al. Acute hemodynamic effects of biventricular DDD pacing in patients with end-stage heart failure. *J Am Coll Cardiol* 1998;32:1825-31.
10. Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. *J Am Coll Cardiol.* 2005;46:2183-92.
11. Leclercq C, Hare JM. Ventricular resynchronization: current state of the art. *Circulation.* 2004;109:296-9.
12. Yu CM, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. *Heart* 2003;89: 54-60.
13. Willerson JT, Kereiakes DJ. Cardiac resynchronization therapy: helpful now in selected patients with CHF. *Circulation.* 2004; 109:308-9.
14. Kass DA. Predicting cardiac resynchronization response by QRS duration: the long and short of it. *J Am Coll Cardiol.* 2003;42: 2125-7.
15. Nelson SG, Curry CW, Wyman BT, et al. Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. *Circulation.* 2000;101:2703-9.
16. Sutton MG, Plappert TJ, Hilpitsch KE, et al. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *Circulation.* 2006; 113:266-72.
17. Pitzalis MV, Iacoviello M, Romito R, et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. *J Am Coll Cardiol.* 2002;40:1615-22.
18. Sogaard P, Egeblad H, Kim WY, et al. Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. *J Am Coll Cardiol.* 2002;40:723-30.
19. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344:873-80.
20. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-53.
21. Gras D, Leclercq C, Tang AS, Bucknall C, Luttikhuis HO, Kirstein-Pedersen A. Cardiac resynchronization therapy in advanced heart failure the multicenter InSync clinical study. *Eur J Heart Fail* 2002;4:311-20.
22. Dekker AL, Phelps B, Dijkman B, et al. Epicardial left ventricular lead placement for cardiac resynchronization therapy: optimal pace site selection with pressure-volume loops. *J Thorac Cardiovasc Surg* 2004;127:1641-7.
23. Auricchio A, Stellbrink C, Block M, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. *Circulation* 1999;99:2993-3001.
24. Abraham WT. Rationale and design of a randomized clinical trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with advanced heart failure: the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *J Card Fail* 2000;6:369-80.
25. Gilligan DM, Sargent D, Ponnathpur V, Dan D, Zakaib JS, Ellenbogen KA. Echocardiographic atrioventricular interval optimization in patients with dual-chamber pacemakers and symptomatic left ventricular systolic dysfunction. *Am J Cardiol* 2003; 91:629-31.
26. Nelson GS, Berger RD, Fetics 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;102:3053-9.
27. Alonso C, Leclercq C, Victor F, et al. Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in advanced heart failure. *Am J Cardiol* 1999;84:1417-21.
28. Reuter S, Garrigue S, Bordachar P, et al. Intermediate-term results of biventricular pacing in heart failure: correlation between clinical and hemodynamic data. *Pacing Clin Electrophysiol* 2000;23: 1713-7.
29. Gras D, Mabo P, Tang T, et al. Multisite pacing as a supplemental treatment of congestive heart failure: preliminary results of the Medtronic Inc. InSync study. *Pacing Clin Electrophysiol* 1998; 21:2249-55.
30. Lecoq G, Leclercq C, Leray E, et al. Clinical and electrocardiographic predictors of a positive response to cardiac resynchronization therapy in advanced heart failure. *Eur Heart J.* 2005; 26:1094-100.
31. Marcus G, Rose E, Viloria EM, et al. Septal to posterior wall mo-

tion delay fails to predict reverse remodeling or clinical improvement in patients undergoing cardiac resynchronization therapy. *J Am Coll Cardiol* 2005;46:2208-14.
32. Penicka M, Bartunek J, de Bruyne B, et al. Improvement of left ventricular function after cardiac resynchronization therapy is predicted by tissue Doppler imaging echocardiography. *Circulation* 2004;109:978-83.
33. Bax JJ, Marwick TH, Molhoek SG, et al. Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure before pacemaker implantation. *Am J Cardiol* 2003;92:1238-40.
34. Yu CM, Fung JW, Zhang Q, et al. Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. *Circulation* 2004;110:66-73.
35. Notabartolo D, Merlino JD, Smith AL, et al. Usefulness of the peak velocity difference by tissue Doppler imaging technique as an effective predictor of response to cardiac resynchronization therapy. *Am J Cardiol* 2004;94:817-20.
36. Gorcsan J 3rd, Kanzaki H, Bazaz R, Dohi K, Schwartzman D. Usefulness of echocardiographic tissue synchronization imaging to predict acute response to cardiac resynchronization therapy. *Am J Cardiol* 2004;93:1178-81.
37. Yu CM, Zhang Q, Fung JW, et al. A novel tool to assess systolic asynchrony and identify responders of cardiac resynchronization therapy by tissue synchronization imaging. *J Am Coll Cardiol* 2005;45:677-84.
38. Dohi K, Suffoletto MS, Schwartzman D, Ganz L, Pinsky MR, Gorcsan J, 3rd. Utility of echocardiographic radial strain imaging to quantify left ventricular dyssynchrony and predict acute response to cardiac resynchronization therapy. *Am J Cardiol.* 2005; 96:112-6.
39. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J, 3rd. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation.* 2006; 113:960-8.
40. Kapetanakis S, Kearney MT, Siva A, Gall N, Cooklin M, Monaghan MJ. Real-time three-dimensional echocardiography: a novel technique to quantify global left ventricular mechanical dyssynchrony. *Circulation.* 2005;112:992-1000.
41. Yu CM, Chau E, Sanderson JE, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002; 105: 438-45.
42. Popovic ZB, Grimm RA, Perlic G, et al. Noninvasive assessment of cardiac resynchronization therapy for congestive heart failure using myocardial strain and left ventricular peak power as parameters of myocardial synchrony and function. *J Cardiovasc Electrophysiol* 2002;13:1203-8.
43. Auricchio A, Stellbrink C, Sack S, et al. The Pacing Therapies for Congestive Heart Failure (PATH-CHF) Study: rationale, design and endpoints of a prospective, randomized multicenter study. *Am J Cardiol* 1999;83:130D-5D.
44. Auricchio A, Stellbrink C, Sack S, et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol.* 2002;39:2026-33.
45. Linde C, Leclercq C, Rex S. et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation In Cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol.* 2002;40:111-8.
46. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-49.
47. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* 2004;350:2140-50.
48. 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;289:730-40.
49. Fauchier L, Marie O, Casset-Senon D, Babuty D, Cosnay P, Fauchier JP. Interventricular and intraventricular dyssynchrony in idiopathic dilated cardiomyopathy: a prognostic study with fourier phase analysis of radionuclide angioscintigraphy. *J Am Coll Cardiol.* 2002;40:2022-30.
50. 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; 89:346-50.
51. Bleeker GB, Schalij MJ, Molhoek SG, et al. Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure. *J Cardiovasc Electrophysiol.* 2004; 15:544-9.
52. Turner MS, Bleasdale RA, Vinereanu D, et al. Electrical and mechanical components of dyssynchrony in heart failure patients with normal QRS duration and left bundle-branch block: impact of left and biventricular pacing. *Circulation.* 2004;109:2544-9.
53. Auricchio A, Yu CM. Beyond the measurement of QRS complex toward mechanical dyssynchrony: cardiac resynchronisation therapy in heart failure patients with a normal QRS duration. *Heart* 2004;90:479-81.
54. Rouleau F, Merheb M, Geffroy S, et al. Echocardiographic assessment of the interventricular delay of activation and correlation to the QRS width in dilated cardiomyopathy. *Pacing Clin Electrophysiol* 2001;24:1500-6.
55. Yu CM, Lin H, Ho PC, Yang H. Assessment of left and right ventricular systolic and diastolic synchronicity in normal subjects by tissue Doppler echocardiography and the effects of age and heart rate. *Echocardiography* 2003;20:19-27.
56. Latini R, Masson S, de Angelis N, Anand I. Role of brain natriuretic peptide in the diagnosis and management of heart failure: current concepts. *J Card Fail* 2002;8:288-99.
57. Bleeker GB, Schalij MJ, Molhoek SG, et al. Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure. *J Cardiovasc Electrophysiol* 2004;

15:544-9.
58. Takagi Y, Dumpis Y, Usui A, Maseki T, Watanabe T, Yasuura K. Effects of proximal ventricular septal pacing on hemodynamics and ventricular activation. *Pacing Clin Electrophysiol.* 1999;22: 1777-81.
59. Alonso C, Leclercq C, d'Allonnes FR, et al. Six year experience of transvenous left ventricular lead implantation for permanent biventricular pacing in patients with advanced heart failure: technical aspects. *Heart* 2001;86:405-10.
60. Rossillo A, Verma A, Saad EB, et al. Impact of coronary sinus lead position on biventricular pacing: mortality and echocardiographic evaluation during long-term follow-up. *J Cardiovasc Electrophysiol.* 2004;14:1120-5.
61. Macias A, Gavira JJ, Alegría E, Azcarate PM, Barba J, García-Bolao I. Effect of the left ventricular pacing site on echocardiographic parameters of ventricular dyssynchrony in patients receiving cardiac resynchronization therapy. *Rev Esp Cardiol.* 2004;57:138-45.
62. Ritter P, Padeletti L, Gillio-Meing L, Gaggini G. Determination of the optimal atrioventricular delay in DDD pacing. Comparison between echo and peak endocardial acceleration measurements. *Europace.* 1999;1:126-30.
63. Ishikawa T, Sumita S, Kimura K, et al. Prediction of optimal atrioventricular delay in patients with implanted DDD pacemakers. *Pacing Clin Electrophysiol* 1999;22:1365-71.
64. Bordachar P, Lafitte S, Reuter S, et al. Echocardiographic parameters of ventricular dyssynchrony validation in patients with heart failure using sequential biventricular pacing. *J Am Coll Cardiol* 2004;44:2157-65.
65. Blanc JJ, Etienne Y, Gilard M, et al. Evaluation of different ventricular pacing sites in patients with severe heart failure: results of an acute hemodynamic study. *Circulation* 1997;96:3273-7.
66. Etienne Y, Mansourati J, Gilard M, et al. Evaluation of left ventricular based pacing in patients with congestive heart failure and atrial fibrillation. *Am J Cardiol* 1999;83:1138-40.
67. Leclercq C, Walker S, Linde C, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J.* 2002; 23:1780-7.
68. Leclercq C, Victor F, Alonso C, et al. Comparative effects of permanent biventricular pacing for refractory heart failure in patients with stable sinus rhythm or chronic atrial fibrillation. *Am J Cardiol* 2000;85:1154-6.
69. Rodriguez LM, Smeets JL, Xie B, et al. Improvement in left ventricular function by ablation of atrioventricular nodal conduction in selected patients with lone atrial fibrillation. *Am J Cardiol* 1993;72:1137-41.
70. Garrigue S, Reuter S, Labeque J, et al. Usefulness of biventricular pacing in patients with congestive heart failure and right bundle branch block. *Am J Cardiol* 2001;88:1436-41.
71. Fantoni C, Kawabata M, Massaro R, et al. Right and left ventricular activation sequence in patients with heart failure and right bundle branch block. *J Cardiovasc Electrophysiol* 2005;16:112-9.
72. Achilli A, Sassara M, Ficili S, et al. Long-term effectiveness of cardiac resynchronization therapy in patients with refractory heart failure and "narrow" QRS. *J Am Coll Cardiol* 2003;42: 2117-24.
73. Gasparini M, Mantica M, Galimberti P, et al. Beneficial effects of biventricular pacing in patients with a "narrow" QRS. *Pacing Clin Electrophysiol* 2003;26:169-74.
74. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002;346:877-83.
75. Abraham WT, Young JB, Leon AR, et al. Multicenter InSync ICD II Study Group. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation.* 2004;110: 2864-8.
76. Daoud E, Hummel J, Higgins S, et al. Does ventricular resynchronization therapy influence total survival? *Pacing Clin Electrophysiol* 2001;24:539.
77. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA* 2003;289:2685-94.
78. Goldberger Z, Lampert R. Implantable cardioverter-defibrillators: expanding indications and technologies. *JAMA* 2006;295: 809-18.
79. Nichol G, Kaul P, Huszti E, Bridges JF. Cost-effectiveness of cardiac resynchronization therapy in patients with symptomatic heart failure. *Ann Intern Med.* 2004;141:343-51.
80. Hlatky MA, Massie BM. Cardiac resynchronization for heart failure. *Ann Intern Med.* 2004;141:399-400.
81. Gasparini M, Bocchiardo M, Lunati M, et al. Comparison of 1-year effects of left ventricular and biventricular pacing in patients with heart failure who have ventricular arrhythmias and left bundle-branch block: the Bi vs Left Ventricular Pacing: an International Pilot Evaluation on Heart Failure Patients with Ventricular Arrhythmias (BELIEVE) multicenter prospective randomized pilot study. *Am Heart J.* 2006;152:155.e1-7.
82. Doshi RN, Daoud EG, Fellows C, et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol.* 2005;16:1160-5.