Clinical Outcomes After Cardiac Resynchronization Therapy: Importance of Left Ventricular Diastolic Function and Origin of Heart Failure

Alan D. Waggoner, MHS, Aleksandr Rovner, MD, Lisa de las Fuentes, MD, Mitchell N. Faddis, MD, PhD, Marye J. Gleva, MD, Navinder Sawhney, MD, and Víctor G. Dávila-Román, MD, *St Louis, Missouri*

Background: **Cardiac resynchronization therapy (CRT) improves functional outcomes in patients with severe systolic heart failure. Whether the effects of CRT on left ventricular (LV) diastolic function and clinical outcomes are influenced by the cause as either ischemic or nonischemic cardiomyopathy (CM) has not been well established.**

Methods: **A total of 57 patients (age 60 ± 11 years; 25% women; LV ejection fraction 25 ± 5%) were studied before and 4 ± 2 months after CRT by echocardiography. Heart failure cause was ischemic CM in 19 and nonischemic CM in 38. Measurements of LV systolic and diastolic function were determined by 2-dimensional and Doppler echocardiography with Doppler tissue imaging of regional myocardial velocities. Clinical outcome events were assessed at long-term follow-up and included hospitalization for heart failure exacerbation, heart transplantation, or cardiac-related death.**

Results: **There were significant increases in LV ejection fraction, reductions in end-systolic volumes, and improved LV systolic dyssynchrony in both groups. However, significant improvements in LV diastolic function were observed only in the patients with nonischemic CM. Clinical events occurred in 53% of the ischemic group versus 26% of the nonischemic group ($P < .05$) after 20 ± 11 months of CRT. Univariate and multivariate analysis revealed that Doppler-estimated LV filling pressures were predictors of clinical outcome events.**

Conclusions: **After CRT patients with ischemic CM exhibit lack of improvement in LV diastolic function despite favorable effects on LV systolic performance. The Doppler-derived LV filling indices may be an important predictor of long-term clinical outcomes after CRT.** (J Am Soc Echocardiogr 2006;19:307-313.)

Cardiac resynchronization therapy (CRT) improves functional outcomes in 70% to 80% of patients regardless of whether the heart failure (HF) cause is ischemic cardiomyopathy (CM) or nonischemic CM.[1-3] The benefits of CRT, if determined by reductions in left ventricular (LV) volumes and improvement in LV ejection fraction (EF), are less favorable in ischemic CM.[4] Several studies have reported that ischemic CM patients have less improvement in LV dyssynchrony and worse clinical outcomes.[5-8] The effects of CRT on LV diastolic function have not been well established. Pulsed wave Doppler (PWD)-derived LV filling indices are prognostic indicators of clinical outcomes in patients with HF.[9,10] The hypothesis of this study was that among patients with HF treated with CRT, those with ischemic CM have less improvement in LV diastolic function and worse clinical outcomes compared with those who are nonischemic. Measurements of LV systolic and diastolic function were obtained in patients with HF before and after 4 months of CRT by echocardiography; long-term clinical follow-up for cardiac events was obtained.

From the Cardiovascular Imaging and Clinical Research Core Laboratory, Washington University School of Medicine, Cardiovascular Division.

Supported by grants from the American Society of Echocardiography; National Institutes of Health R01HL58878, S10RR14778, K24HL67002; and the Barnes-Jewish Hospital Foundation to the Cardiovascular Imaging and Clinical Research Core Laboratory.

Reprint requests: Alan D. Waggoner, MHS, Cardiovascular Division, Box 8086, Washington University School of Medicine, 660 S Euclid Ave, St Louis, Missouri 63110 (E-mail: *waggonea@msnotes.wustl.edu*).

0894-7317/$32.00

doi:10.1016/j.echo.2005.10.014

METHODS

Patient Characteristics

This was a prospective, single-blinded longitudinal cohort evaluation study. Between June 2001 and September 2004, patients who were scheduled to receive implanta-

tion of a CRT device were asked to participate in the study. Inclusion criteria were New York Heart Association (NYHA) class III or IV and a history of medically refractory HF symptoms despite optimized pharmacologic therapy for at least 3 months, in sinus rhythm with a QRS duration longer than 0.15 seconds, LV enlargement (LV diastolic diameter >6.0 cm), and LVEF less than 35%. The protocol was approved by the human studies committee of Washington University.

All patients had diagnostic cardiac catheterization performed within 1 year before CRT. The results of coronary angiography were reviewed for determination of HF cause. Ischemic CM was determined if significant coronary artery disease (>50% stenosis in at least one major coronary vessel) was present. Functional assessment included NYHA class, HF quality-of-life scores (Minnesota Living with HF Questionnaire), and 6-minute walk distance. Clinical outcome events included hospitalization for HF exacerbation, cardiac transplantation, and cardiac-related death. Cardiac-related death was defined as either caused by worsening HF or witnessed sudden death.

CRT Device Implantation

CRT devices included pacemaker only and pacemaker defibrillators as determined by the implanting physician. Device implantation was performed by a transvenous approach; the LV lead was advanced through the coronary sinus and targeted to the midlateral wall. Alternative LV stimulation sites (ie, anterolateral or posterolateral) were used when a midlateral coronary sinus branch was either absent or unacceptable because of phrenic nerve stimulation or high stimulation threshold. After implantation, the CRT device was programmed off and echocardiography was performed within 24 hours. CRT was then instituted by programming to atrial sensed biventricular pacing. The programmed atrioventricular delay was determined by continuous wave Doppler measurements of aortic time velocity integral as previously reported by our group.[11]

Echocardiography

Heart rate, systolic and diastolic blood pressures, and pulse pressure (systolic − diastolic blood pressure) were obtained at the time of echocardiography. Two-dimensional measurements included LV volumes at end diastole and end systole from the apical 4- and 2-chamber views (method of disks). LVEF was calculated by the biplane method and LV mass was determined by the area-length method and indexed for body surface area.[12] PWD transmitral velocities were obtained at the mitral leaflet tips according to established guidelines.[13] Measurements included the early diastolic (E) and atrial (A) wave inflow velocities, the mitral E/A ratio, and the E-wave deceleration time (DT). Diastolic filling time was determined as the time interval (milliseconds) from the onset of LV inflow to mitral valve closure. Isovolumic relaxation time (IVRT) was measured from the closure of the aortic valve to the onset of mitral inflow.

Doppler tissue imaging (DTI) was performed in the apical 4- and 2-chamber views by placement of a 3-mm sample volume at the lateral, septal, anterior, and inferior mitral annulus for measurements of the systolic (Sm) and early diastolic (Em) velocities. Sm and Em velocities from the 4 sites were averaged to derive the global Sm and global Em.[14] The time intervals of Q wave to peak Sm and Q to peak Em at each site was determined and the maximal difference of Q-Sm or Q-Em between sites were calculated as measures of LV systolic and diastolic dyssynchrony, respectively, as shown in Figure 1. PWD-derived mitral E wave/DTI-derived Em velocity at the septal annulus was calculated to estimate the LV filling pressure.[15] Color M-mode flow propagation (FP) velocity was obtained in the apical 4-chamber view; the ratio of mitral E-wave/FP velocity was also determined as an estimate of LV filling pressure.[13,16] Measurements represent the average of 3 to 5 consecutive cardiac cycles.

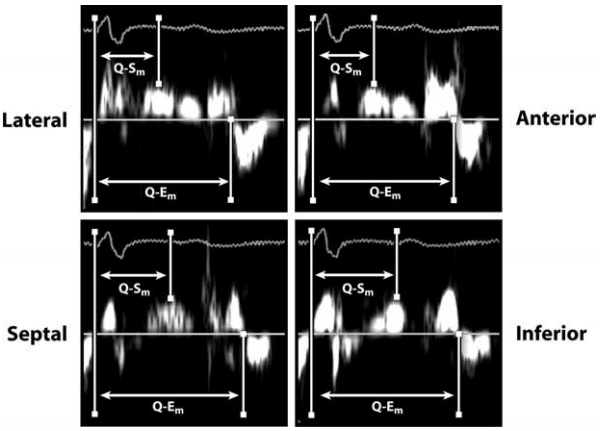

Figure 1 Pulsed DTI measurements of Q-Sm and Q-Em time intervals at the left ventricular (LV) annular sites. The Q-Sm and Q-Em intervals are longer at the septal and inferior sites; maximal differences of 130 ms and 50 ms, respectively. Abbreviations: Q-Em, electrocardiographic QRS onset to onset of LV relaxation; Q-Sm, electrocardiographic QRS onset to peak systolic contraction.

Statistical Analysis

Continuous variables are expressed as the mean ± 1 SD. Comparison of the clinical and echocardiographic variables before and after CRT was performed using paired and unpaired Student *t* test or χ^2 analysis as appropriate. Univariate and multivariate logistic regression analysis was used to determine the predictive value of baseline patient characteristics, and functional and echocardiographic variables for long-term clinical events. Variables that achieved *P* less than .1 by univariate analysis were used in the multivariate analysis by forward stepwise method. Kaplan-Meier survival analysis with log rank compression was used to evaluate the difference in clinical outcome event rates between ischemic and nonischemic groups. Statistical significance was determined as a *P* value of less than .05. Statistical analyses were performed using software (SPSS, Version 11.0, SPSS Inc, Chicago, Ill).

Table 1 Patient characteristics by heart failure origin

	Ischemic cardiomyopathy (n = 19)	Nonischemic cardiomyopathy (n = 38)	*P* value
Age, y	63 ± 11	60 ± 12	NS
Male sex, %	95	66	<0.05
PR interval, s	0.21 ± 0.03	0.20 ± 0.03	NS
QRS interval, s	0.18 ± 0.02	0.18 ± 0.03	NS
Medications			
ACE inhibitor, %	88	97	NS
ARB/β-blocker, %	71	97	NS
Digoxin, %	65	71	NS
Loop-sparing diuretic, %	94	80	NS
Potassium-sparing diuretic, %	65	51	NS

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; β, beta; *NS*, not significant.

Table 2 Functional and hemodynamic measurements by heart failure origin before and after cardiac resynchronization therapy

	Ischemic cardiomyopathy (n = 19)		Nonischemic cardiomyopathy (n = 38)	
	Pre-CRT	4 mo Post-CRT	Pre-CRT	4 mo Post-CRT
NYHA classification	3.3 ± 0.5	2.4 ± 0.6*	3.1 ± .4	2.4 ± .6*
Heart failure score	65 ± 21	43 ± 24†	67 ± 21	42 ± 28*
6-min walk distance, ft	667 ± 303	885 ± 316†	721 ± 278	1041 ± 280*
HR, beats/min	77 ± 11	70 ± 11†	74 ± 13	72 ± 15
SBP, mm Hg	113 ± 12	119 ± 16	110 ± 19	120 ± 18†
DBP, mm Hg	67 ± 8	70 ± 10	66 ± 11	70 ± 9
Pulse pressure, mm Hg	46 ± 11	48 ± 12	44 ± 14	50 ± 15†

CRT, Cardiac resynchronization therapy; *DBP*, diastolic blood pressure; *HR*, heart rate; *NYHA*, New York Heart Association; *SBP*, systolic blood pressure. Pre-CRT and 4 mo post-CRT variables were similar between groups.
*$P \leq .001$, †$P \leq .01$, vs pre-CRT.
Variables are expressed as mean ± SD.

RESULTS

Patient Characteristics

The study population included 19 patients with ischemic CM and 38 patients (67%) with nonischemic CM (Table 1). Age and QRS duration were similar between groups. The ischemic CM group primarily consisted of men. Pharmacologic therapy of α- and/or β-adrenergic blockers was lower in the ischemic CM group but use of diuretic agents was greater. A combined CRT/defibrillator device was implanted in 74% of the ischemic CM and in 84% of the nonischemic CM group. The LV pacing lead was placed in a midlateral or posterior-lateral vein more frequently in the ischemic CM group compared with the nonischemic CM group (89% vs 74%, respectively; $P < .05$). The programmed atrioventricular delay interval was similar between groups (119 ± 26 vs 121 ± 32 milliseconds, P = not significant) and remained unchanged during follow-up.

Functional Outcomes After CRT

Both groups had significant improvement in functional measurements after CRT (Table 2). NYHA improved by at least one class in 75% of the ischemic group compared with 66% of the nonischemic group after CRT. HF scores decreased by more than 10% in two thirds of patients regardless of HF cause; 6-minute walk distance improved by more than 100 ft in 64% of the patients with ischemic CM versus 80% of the nonischemic group.

Hemodynamic and Echocardiographic Measurements

Heart rate decreased significantly after CRT in the ischemic group. Systolic and pulse pressure increased significantly only in the nonischemic group after CRT. The ischemic group had significantly lower LV EF before CRT (Table 3). LV end-systolic volumes decreased and LV EF increased significantly in both groups after CRT; LV end-diastolic volumes decreased significantly only in the nonischemic group. The ischemic group had significantly higher mitral E velocities, higher E/A ratio, and shorter IVRT intervals before CRT. The mitral E/A ratio was greater than 2 more often in the ischemic group compared with the nonischemic group (47% vs 8%, $P < .01$) and DT was less than 160 milliseconds in 58% of the ischemic group versus 26% of the nonischemic group ($P < .05$). Mitral E-wave velocity decreased, and both diastolic filling time and IVRT increased significantly, in both groups after CRT.

Table 3 Two-dimensional Doppler echocardiographic measurements by heart failure origin before and after cardiac resynchronization therapy

	Ischemic cardiomyopathy (n = 19)		Nonischemic cardiomyopathy (n = 38)	
	Pre-CRT	4 mo Post-CRT	Pre-CRT	4 mo Post-CRT
LV EDV, mL	215 ± 64	194 ± 63	241 ± 101	208 ± 95*
LV ESV, mL	168 ± 55	134 ± 53†	181 ± 85	143 ± 86*
LV ejection fraction, %	23 ± 5‖	31 ± 9*	26 ± 5	35 ± 11*
LV mass index, g/m^2	146 ± 32	144 ± 35	161 ± 38	156 ± 42
Mitral E velocity, cm/s	93 ± 32‖	75 ± 29‡	74 ± 32	64 ± 31‡
Mitral E/A ratio	2.2 ± 1.4§	1.7 ± 1.2§	1.1 ± 0.7	0.8 ± 0.3†
Deceleration time, ms	177 ± 83	181 ± 46‖	192 ± 57	220 ± 56‡
Diastolic filling time, ms	356 ± 97	420 ± 113†	353 ± 108	410 ± 129†
IVRT, ms	94 ± 35‖	124 ± 31†	119 ± 29	129 ± 30‡

A, Late filling velocity; *CRT*, cardiac resynchronization therapy; *E*, early filling velocity; *EDV*, end diastolic volume; *ESV*, end systolic volume; *IVRT*, isovolumic relaxation time; *LV*, left ventricular.
*$P \leq .001$, †$P \leq .01$, ‡$P \leq .05$ vs pre-CRT; §$P < .001$, ‖$P \leq .05$ vs nonischemic.
Variables expressed as mean ± SD.

Table 4 Doppler tissue imaging and color M-mode flow propagation velocities by heart failure origin before and after cardiac resynchronization therapy

	Ischemic cardiomyopathy (n = 19)		Nonischemic cardiomyopathy (n = 38)	
	Pre-CRT	4 mo Post-CRT	Pre-CRT	4 mo Post-CRT
Q-Sm difference, ms	66 ± 30	44 ± 26‡	63 ± 24	51 ± 33‡
Sm global, cm/s	5.6 ± 1.4	5.5 ± 1.3	5.5 ± 1.6	6.3 ± 1.5*
Q-Em difference, ms	57 ± 42	49 ± 24	60 ± 28	45 ± 30‡
Em global, cm/s	8.0 ± 1.3	7.0 ± 1.4†	7.3 ± 2.2	7.1 ± 2.1
Mitral E/Em septal	15.1 ± 5.3	13.7 ± 5.8§	13.4 ± 6.8	10.7 ± 5.0*
FP velocity, cm/s	38 ± 8	36 ± 8	35 ± 11	37 ± 10
Mitral E/FP	2.4 ± 0.6	2.0 ± 0.7	2.2 ± 0.7	1.7 ± 0.7†

CRT, Cardiac resynchronization therapy; *E*, early filling velocity; *Em*, Doppler tissue early diastolic velocity; *FP*, color M-mode flow propagation; *Sm*, Doppler tissue systolic velocity. *$P \leq .001$, †$P \leq .01$, ‡$P \leq .05$ vs pre-CRT; §$P \leq .05$ vs. nonischemic.
Variables expressed as mean ± SD.

However, the PWD-derived E/A ratio and DT improved significantly only in the nonischemic group.

The DTI-derived maximal difference in Q-Sm time intervals, as a measurement of systolic dyssynchrony, decreased significantly in both groups after CRT (Table 4). However, Sm global velocity increased significantly only in the nonischemic group. The maximal difference in the Q-Em interval (a measure of diastolic dyssynchrony) decreased significantly only in the nonischemic group after CRT. The Em global velocity decreased significantly in the ischemic group. Mitral E wave/Em septal velocity ratio (ie, LV filling pressures) decreased significantly only in the nonischemic group. The color M-mode FP velocities were unchanged after CRT; mitral E-wave/FP velocity ratio decreased significantly in the nonischemic group, which also suggests decreases in LV filling pressures.

Clinical Outcomes After CRT

At the time of echocardiographic follow-up (mean 4 ± 2 months), the clinical event rates were similar in the ischemic and nonischemic groups (16% vs 11%, respectively); all were a result of hospitalization for HF exacerbation. However, at long-term follow-up (mean 20 ± 11 months), the combined clinical outcome event rate was higher in the ischemic compared with the nonischemic group (53% vs 26%, $P < .05$). The Kaplan-Meier plot of the event rate after CRT in patients with ischemic and nonischemic CM is shown in Figure 2. The curves diverge early with a trend toward statistical significance ($P = .09$).

The pre-CRT demographic, functional, and echocardiographic variables that were assessed by univariate and multivariate analysis for predicting clinical outcome events are shown in Table 5. Variables that remained predictive in the multivariate regression model included mitral DT, IVRT, and E/Em septal ratio.

DISCUSSION

The results of this investigation demonstrate that functional outcomes and echocardiographic measures of LVEF, including DTI-derived measures of LV systolic dyssynchrony, improve after CRT re-

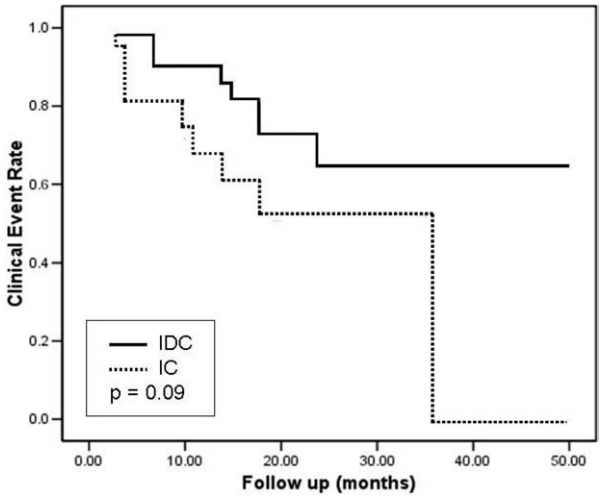

Figure 2 Kaplan-Meier curve of clinical event rate after CRT for ischemic (*IC*) group compared with nonischemic (*IDC*) group.

gardless of HF origin. However, the nonischemic CM group had significant decreases in LV filling pressures (mitral E/A, E/Em, E/FP ratios), significant improvements in the rate of early diastolic filling (ie, DT), and LV diastolic synchrony (ie, Q-Em velocity difference). These results were not observed in the ischemic CM group. At long-term follow-up after CRT, clinical events (ie, hospitalization for HF exacerbation, heart transplant, cardiac-related death) were 2-fold greater in the ischemic group. Doppler indices of diastolic function, including DT, IVRT, and mitral E/Em septal ratio, were predictive of the long-term clinical outcome events.

An improvement in functional outcome measurements at short-term follow-up after CRT (ie, 3-12 months) without regard to HF origin has been previously reported.[1-4,13] In the COMPANION trial, investigators reported a primary end point of death and/or HF exacerbation requiring hospitalization was similar in ischemic and nonischemic groups at 12-month follow-up. Other studies, however, have reported that ischemic CM is associated with a less favorable response to CRT when defined by either functional or clinical outcomes.[6,7,19] This study demonstrated that functional measures improved after CRT in both groups, but was not associated with better clinical outcomes at long-term follow-up in patients with ischemic CM. It has been previously demonstrated that improvements in functional measures do not necessarily translate to improved clinical outcomes in patients with HF receiving pharmacologic and/or resynchronization therapy.[20,21]

The decreases in LV end-systolic volumes, increases in LVEF, and improvements in LV systolic dyssynchrony at early follow-up after CRT are consistent with prior studies.[3-8] The current study demonstrates that the cause of HF is a significant determinant of LV diastolic function after CRT, as assessed by conventional (ie, PWD mitral inflow) and relatively load-independent (ie, DTI Em, color M-mode FP) indices. The decreases in LV early filling velocity (ie, mitral E wave) and increases in diastolic filling time that were observed in both groups are likely a result of decreased end-systolic volumes and improved LV systolic function. Studies from our group have recently reported that improvements in LV diastolic function acutely after CRT and at short-term follow-up are coupled to the response in LV volumes and systolic function.[17,18] However, the ischemic group did not exhibit significant decreases in LV filling pressures (ie, mitral E/A, E/Em septal, or E/FP ratios) after CRT despite improvements in LV systolic function. This may be explained by one or more of the following: (1) presence of relatively restrictive LV filling before CRT (ie, higher mitral E/A ratio and shorter DT interval); (2) lack of significant change in end-diastolic volumes; and (3) lack of improvement in diastolic synchrony, presumably because of the presence of infarcted myocardial segments. Furthermore, LV relaxation as assessed by the DTI-derived global Em velocity worsened in the ischemic group at short-term follow-up.

Doppler-derived parameters of LV filling are important indicators of clinical outcomes in patients with HF and severe LV systolic dysfunction.[9,10,21] The results of this investigation suggest that elevated LV filling pressures, before and after CRT may be an important prognostic marker of adverse outcomes. Furthermore, long-term clinical outcomes after CRT were less favorable in the ischemic group despite the improved echocardiographic measurements of LV systolic performance. The ischemic group did have pre-CRT

Table 5 Univariate and multivariate analysis of variables to predict clinical outcome events after cardiac resynchronization therapy

	Univariate analysis	Multivariate analysis
	P value	*P* value
Heart rate	.06	
LV ejection fraction	.10	
Mitral E velocity	.04	
Deceleration time	.02	<.05
IVRT	.03	<.05
E/Em septal ratio	.01	<.05
E/FP ratio	.05	
6-min Walk	.10	

E, Early filling velocity; *Em*, doppler tissue early diastolic velocity; *FP*, color M-mode flow propagation velocity; *IVRT*, isovolumic relaxation time; *LV*, left ventricular.

characteristics that could have influenced their clinical outcomes including a higher prevalence of male sex, NYHA class IV symptoms, and lower use of β-adrenergic blocker pharmacologic therapy.[22,23] Importantly, the univariate and multivariate analysis revealed Doppler indices of LV filling and estimated LV filling pressures (ie, mitral DT, IVRT, and E/Em septal ratio) before CRT were significant predictors of clinical outcomes.

Study Limitations

This study included a smaller number of patients with ischemic CM compared with nonischemic CM, which likely explains the statistical lack of significance in the Kaplan-Meier analysis. However, patients with ischemic CM had a 2-fold higher event rate that was evident at a longer follow-up interval (mean 20 months) after CRT. Most of the prior reports of clinical outcomes after CRT have been confined to follow-up of 1 year or less. Furthermore, this investigation identified that measurements of LV diastolic function differ in ischemic compared with nonischemic groups prior to and after CRT that were statistically significantly in the univariate and multivariate analysis to predict clinical outcomes.

Conclusions

CRT improves functional outcomes and LV systolic performance with decreases in LV dyssynchrony regardless of ischemic or nonischemic HF cause. The long-term clinical outcomes and improvement in diastolic function are less likely to occur in patients with ischemic CM. Measurements of LV diastolic filling pressures may be a predictor of clinical response after CRT.

REFERENCES

1. Abraham WT, Fisher WG, Smith AL, DeLurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845-53.
2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.
3. Molhoek SG, Bax JJ, van Erven L, Bootsma M, Boersma E, Steendijk P, et al. Comparison of benefits from cardiac resynchronization therapy in patients with ischemic cardiomyopathy versus idiopathic cardiomyopathy. Am J Cardiol 2004;93:860-3.
4. St John Sutton M, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation 2003;107:1985-90.
5. Gasparini M, Mantica M, Galimberti P, Genovese L, Pini D, Faletra R, et al. Is the outcome of cardiac resynchronization therapy related to the underlying etiology? Pacing Clin Electrophysiol 2003;26:175-80.
6. Reuter S, Garrigue S, Barold SS, Jais P, Hocini M, Haissaguerre M, 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.
7. Pitzalis MV, Iacoviello M, Romito R, Guida P, De Tommasi E, Luzzi G, et al. Ventricular asynchrony predicts a better outcome in patients with chronic heart failure receiving cardiac resynchronization therapy. J Am Coll Cardiol 2005;45:65-9.
8. Yu CM, Fung JWH, Zhang Q, Chan CK, Chan YS, Lin H, 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.
9. Xie G-Y, Berk MR, Smith MD, Gurely JC, DeMaria AN. Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure. J Am Coll Cardiol 1994;24:132-9.
10. Hansen A, Haass M, Zugck C, Krueger C, Unnebrink K, Zimmermann R, et al. Prognostic value of Doppler echocardiographic mitral inflow patterns: implications for risk stratification in patients with chronic congestive heart failure. J Am Coll Cardiol 2001;37:1049-55.
11. Sawhney NS, Waggoner AD, Garhwal S, Chawla M, Osborn J, Faddis MN. A randomized trial of atrioventricular delay programming for cardiac resynchronization therapy. Heart Rhythm 2004;1:562-7.
12. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantification of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989;2:358-67.
13. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler quantification task force of the nomenclature and standards committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002;15:167-84.
14. Peterson LR, Waggoner AD, Schechtman KB, Meyer T, Gropler RJ, Klein S, et al. Otherwise healthy obese young women demonstrate concentric left ventricular remodeling and diastolic and systolic dysfunction. J Am Coll Cardiol 2004;43:1399-404.
15. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a simultaneous Doppler-catheterization study. Circulation 2000;102:1788-94.
16. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic application for the study of diastolic function. J Am Coll Cardiol 1998;32:865-75.
17. Waggoner AD, Faddis MN, Gleva MJ, de las Fuentes L, Heuerman S, Davila-Roman VG. Cardiac resynchronization therapy acutely improves diastolic filling. J Am Soc Echocardiogr 2005;18:216-20.
18. Waggoner AD, Faddis MN, Gleva MJ, de las Fuentes L, Davila-Roman VG. Improvements in left ventricular diastolic function after cardiac resynchronization therapy are coupled to response in systolic performance. J Am Coll Cardiol 2005;46:2244-49.
19. Diaz-Infante E, Mont L, Leal J, Garcia-Bolao I, Fernandez-Lozano I, Hernandez-Madrid A, et al. Predictors of lack of

response to resynchronization therapy. Am J Cardiol 2005;95:1436-40.
20. Massie BM. 15 Years of heart failure trials: what have we learned? Lancet 1998;352:S129-33.
21. Penicka M, Bartunek J, De Bruyne B, Vanderheyden M, Goethals M, De Zutter M, et al. Improvement of left ventricular function after cardiac resynchronization therapy is predicted by tissue Doppler imaging. Circulation 2004; 109:978-83.
22. Molhoek SG, Bax JJ, Bleeker GB, Holman ER, Van Erven L, Bootsma M, et al. Long-term follow-up of cardiac resynchronization therapy in patients with end-stage heart failure. J Cardiovasc Electrophysiol 2005;16:1-7.
23. Aranda JM, Woo GW, Conti JB, Schofield RS, Conti CR, Hill JA. Use of cardiac resynchronization therapy to optimize beta-blocker therapy in patients with heart failure and prolonged QRS duration. Am J Cardiol 2005;95:889-91.