

Left ventricular apical wall motion abnormality is associated with lack of response to cardiac resynchronization therapy in patients with ischemic cardiomyopathy

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BACKGROUND Many patients with appropriate indications fail to respond to cardiac resynchronization therapy (CRT).

OBJECTIVE The purpose of our study was to determine the relationship between CRT response and preimplantation apical wall motion abnormality.

METHODS We analyzed data from 83 patients with ischemic cardiomyopathy who underwent CRT. All patients had New York Heart Association class III or IV symptoms despite maximal medical therapy, left ventricular ejection fraction (LVEF) $\leq 35\%$, and QRS duration ≥ 130 ms or < 130 ms with left ventricular dyssynchrony. CRT responders at 6 months were defined as surviving patients with: (1) no hospitalization for heart failure, and (2) improvement of New York Heart Association classification. Patients underwent echocardiography before and 6 months after implantation to assess changes in regional wall motion and LVEF.

RESULTS At baseline, CRT responders ($n = 39$) and nonre-

sponders ($n = 44$) had similar LVEF ($22.9\% \pm 6.9\%$ vs $23.1\% \pm 8.3\%$), QRS duration (159 ± 43 ms vs 159 ± 36 ms), and medical treatment. CRT nonresponders had a higher prevalence of preimplantation apical wall motion abnormality (68% vs 33% , $P = .003$). Patients with baseline apical wall motion abnormalities ($n = 43$) were less likely than others ($n = 40$) to show improvement in wall motion at 6 months (30% vs 81% , $P < .001$) or clinical response to CRT (31% vs 64% , $P = .003$).

CONCLUSION The presence of a preimplantation apical wall motion abnormality was associated with a lower rate of CRT response in patients with ischemic cardiomyopathy.

KEYWORDS Echocardiography; Wall motion abnormality; CRT response; Ischemic cardiomyopathy

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Cardiac resynchronization therapy (CRT) has proven to be an effective treatment for advanced heart failure (HF) in patients with cardiac dyssynchrony, reducing symptoms within 3 to 6 months of implantation.^{1–4} However, up to one-third of patients fail to respond to CRT.^{3,5,6} Simple methods to identify candidates most likely to benefit from CRT are needed. At present, the best-established parameter is the presence of echocardiographic left ventricular (LV) dyssynchrony.^{7,8} However, several different methods have been proposed for assessment and interpretation of dyssyn-

chrony.⁹ Further, this parameter can be technically difficult to assess in some patients.

It is unclear whether the underlying etiology of cardiomyopathy affects the response rate to CRT.^{10,11} Bleeker et al¹² recently showed that even in the presence of dyssynchrony, patients with posterolateral scar were unlikely to respond to CRT, probably because of ineffective LV pacing. Thus, dyssynchrony alone is insufficient to predict CRT response, especially in some patients with ischemic cardiomyopathy.

Other factors also may play a role in CRT nonresponse in ischemic patients. During biventricular pacing, septal and lateral LV segments are activated first, exposing apical segments to increased wall stress.¹³ We hypothesized that in the presence of apical LV dysfunction, biventricular pacing from the right ventricular (RV) apex and LV lateral wall might be less effective and could potentially worsen apical wall function. The purpose of this study was to determine the relationship between CRT nonresponse and preimplantation LV apical wall motion abnormality.

Supported by a grant from the French Society of Cardiology (Dr. Lellouche), and by American Heart Association, National Affiliate (Grant 0430287N), and National Heart, Lung, and Blood Institute R01HL084261 grants (Dr. Shivkumar). The first two authors contributed equally to this work. **Address reprint requests and correspondence:** Dr. Kalyanam Shivkumar, UCLA Cardiac Arrhythmia Center, Division of Cardiology, Department of Medicine, 47-123 CHS, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, Los Angeles, CA 90095-1679. E-mail address: kshivkumar@mednet.ucla.edu. (Received May 20, 2007; accepted June 20, 2007)

Methods

We retrospectively analyzed data on stable HF patients who were referred to our institution for CRT between January 2003 and June 2005. Inclusion criteria were New York Heart Association (NYHA) functional class III or IV HF symptoms despite optimal medical therapy as defined by current guidelines,¹⁴ left ventricular ejection fraction (LVEF) $\leq 35\%$ (by echocardiography, contrast ventriculography, or radionuclide scanning), and QRS duration ≥ 130 ms or <130 ms with LV intraventricular dyssynchrony (defined as difference of at least 60 ms between the timing of the peak systolic velocities of the septum versus the lateral wall) by tissue Doppler imaging.^{15,16} Patients with ischemic cardiomyopathy, defined as having at least 1 epicardial coronary artery with angiographic diameter stenosis of $\geq 70\%$ ¹⁷ and corresponding wall motion abnormality, were included. Patients with myocardial infarction in the previous 3 months and those with hemodynamic instability requiring inotropic or vasopressor support were excluded. Review of these patient data was approved by our institutional review committee.

Implantation technique

In each patient, the LV lead was implanted via the coronary sinus to achieve permanent epicardial stimulation from a lateral or posterolateral vein. If these veins were not accessible, the LV lead was implanted in a diagonal vein near the lateral LV wall. Leads were also implanted in all patients in the RV apex and right atrium. The lead position was determined during implantation by fluoroscopy in the left anterior oblique and right anterior oblique projections. Final lead position was assessed by postoperative chest radiograph in the anteroposterior and lateral views. All devices were programmed for atrio-biventricular stimulation.

Data collected

The following characteristics were recorded before CRT implantation and 6 months after implantation: clinician-assigned NYHA functional class, echocardiographic parameters including LVEF, left ventricular end-diastolic diameter (LVEDd), and regional wall motion. After 6 months of follow-up, hospitalization for decompensated HF and cardiovascular death also were assessed. QRS duration was determined before implantation, within 24 hours after CRT implantation, and at 6 months of follow-up.

Patients underwent transthoracic echocardiography in the left lateral decubitus position with commercially available systems (General Electric Vingmed Vivid 7, Piscataway, NJ, and Siemens Sequoia, Mountain View, CA). Images were obtained with a 3.5-MHz transducer at a depth of 16 cm in parasternal and apical views (standard long-axis, short-axis, 2-chamber, and 4-chamber images). Standard 2-dimensional and Doppler data triggered to the QRS complex were saved in cine-loop format. LV volumes and LVEF were estimated from apical 2-chamber and 4-chamber images using the biplanar Simpson method. Mitral re-

gurgitation (MR) severity was assigned a semiquantitative score (grade 1 to 4) according to conventional criteria.¹⁸

Dyskinesis was defined as outward movement of a myocardial segment during systole. Akinesis was defined as no movement of a myocardial segment during systole. Hypokinesis was defined as reduced wall motion during systole compared with normal segments. Each myocardial segment was assigned a wall motion score using a 4-point scale: 1, normal; 2, hypokinetic; 3, akinetic; and 4, dyskinetic. Echocardiographic data were collected at baseline and 6 months after CRT implantation. We defined a segment as improved if wall motion score decreased at 6 months and worsened if wall motion score increased at 6 months. A patient was defined as echocardiographically improved or worsened at 6 months based on the summed wall motion score for all myocardial segments. Two independent echocardiographers interpreted the studies.

Definition of response

We used clinical criteria to define CRT response.⁴ At 6 months, patients with a decrease in NYHA functional class by ≥ 1 level, no HF hospitalization, and no cardiovascular death were considered CRT responders. All others were considered nonresponders.

Statistical analysis

Continuous variables are expressed as mean \pm SD. Continuous variables were compared using the unpaired Student *t* test or Mann-Whitney *U* test if necessary. Categorical variables were compared with the Chi-square test or Fisher exact test. Differences between values at baseline and 6 months were tested using the paired Student *t* test for continuous variables and the McNemar test for categorical variables. Univariate analysis of all variables was performed. All tests were 2-tailed, and a *P* value $<.05$ was considered statistically significant.

Results

During the study period, 213 patients were referred to our center for CRT device implantation. Fourteen patients were excluded from study participation because of a QRS duration <130 ms without echocardiographic dyssynchrony, and 8 patients because of hemodynamic instability. Endocardial LV lead implantation was unsuccessful in 15 patients, who were then referred for surgical epicardial lead implantation. Of the remaining 176 patients, 93 did not have ischemic heart disease and were excluded. The study population thus consisted of 83 patients meeting study criteria and undergoing successful endocardial CRT implantation. In this population, 20 (24%) patients had a QRS duration <130 ms with intraventricular dyssynchrony assessed by tissue Doppler (11 of these had a QRS duration <120 ms).

Study population characteristics

The overall population characteristics are summarized in Table 1. The LV lead was placed in a lateral or posterolateral vein in 92% of cases and a diagonal vein leading to the

Table 1 Baseline characteristics of the overall study population (n = 83)

Age (years)	69 ± 10
Male (%)	88
Hypertension (%)	70
Dyslipidemia (%)	63
Smoking (%)	19
Diabetes (%)	24
NYHA class 3/4 (n)	65/18
LVEF (%)	23 ± 7
LVEDd (mm)	63 ± 9
Chronic AF (%)	23
Ventricular pacing pre-CRT (%)	29
Lateral LV lead position (%)	92
Mitral regurgitation (grade 1/2/3/4)	49/21/13/0
QRS duration before implantation (ms)	159 ± 39
ACE-I or ARB (%)	80
β-Blocker (%)	77
Diuretic (%)	80
Digoxin (%)	39
Statin (%)	58

ACE-I = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; LV = left ventricular; LVEDd = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association classification.

lateral wall in all remaining cases. None of the LV leads was placed in an apical position. At 6 months of follow-up, 6 patients had died and 15 patients were hospitalized because of decompensated HF.

Comparison of responders and nonresponders

By the study criteria, 39 patients (47%) were classified as CRT responders and 44 patients (53%) were classified as

nonresponders. Baseline characteristics of responders and nonresponders are shown in Table 2. There were no significant differences between these groups regarding cardiovascular risk factors or HF drug therapy. Baseline echocardiographic parameters were similar in both groups. In responders versus nonresponders, LVEF was 22.9% ± 6.7% vs 23.1% ± 8.3%; MR quantified as grade 1/2/3/4 was seen in 21/10/8/0 vs 28/11/5/0 patients; and LVEDd was 64 ± 8 mm vs 63 ± 10 mm (*P* = NS for all comparisons). Preimplantation QRS duration was also similar, 159 ± 43 ms vs 159 ± 36 ms (*P* = .96). NYHA functional class at baseline was not significantly different in responders and nonresponders. The prevalence of any degree of apical wall motion abnormality at baseline was significantly lower in the responder group compared with the nonresponder group (33% vs 68%, *P* = .003).

Table 3 lists changes from baseline to 6-month follow-up for responders and nonresponders. Compared with baseline, at 6 months responders had a significant increase in LVEF (22.9% ± 6.7% vs 29.8% ± 9.9%, *P* < .001). There was no statistically significant change in QRS duration (159 ± 43 vs 150 ± 18 ms, *P* = .09). In the nonresponder group, no significant changes were observed in LVEF (23.1% ± 8.3% vs 26.0% ± 11.1%, *P* = .08) or QRS duration (159 ± 36 vs 167 ± 24 ms, *P* = .15).

Comparison of patients with and without apical wall motion abnormality

We divided the study population into 2 groups according to the presence of baseline apical wall motion abnormality. As shown in Table 4, patients with preimplantation apical wall motion abnormality (n = 43) had similar baseline charac-

Table 2 Characteristics of patients classified as responders and nonresponders at 6 months

	Responders (n = 39)	Nonresponders (n = 44)	<i>P</i> value
Age (years)	70 ± 11	68 ± 9	.48
Male (%)	87	89	.99
Hypertension (%)	72	68	.81
Dyslipidemia (%)	67	52	.20
Smoking (%)	18	20	.99
Diabetes (%)	30	18	.21
NYHA class 3/4 (n)	30/9	35/9	.77
LVEF (%)	22.9 ± 6.7	23.1 ± 8.3	.93
Baseline apical wall motion abnormality (%)	33	68	.003
LVEDd (mm)	64 ± 8	63 ± 10	.56
Ventricular pacing pre-CRT (%)	38	21	.09
Lateral LV lead position (%)	92	91	.99
Chronic AF (%)	21	25	.79
QRS duration before implantation (ms)	159 ± 43	159 ± 36	.96
Mitral regurgitation (grade 1/2/3/4)	21/10/8/0	28/11/5/0	.49
ACE-I or ARB (%)	87	73	.17
Beta blocker (%)	82	73	.43
Diuretic (%)	79	80	.99
Digoxin (%)	41	39	.82
Statin (%)	62	55	.65

ACE-I = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; LV = left ventricular; LVEDd = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association classification.

Table 3 Comparison of baseline and 6-month follow-up data

	Responders (n = 39)			Nonresponders (n = 44)		
	Baseline	6 months	P value	Baseline	6 months	P value
LVEF (%)	22.9 ± 6.7	29.8 ± 9.9	<.001	23.1 ± 8.3	26.0 ± 11.1	.08
MR quantification	1.6 ± 0.8	1.1 ± 0.4	<.001	1.5 ± 0.7	1.6 ± 0.7	.11
QRS duration (ms)	159 ± 43	150 ± 18	.09	159 ± 36	167 ± 24	.15
NYHA class	3.2 ± 0.4	2.1 ± 0.5	N/A*	3.2 ± 0.4	3.1 ± 0.5	N/A*

LVEF = left ventricular ejection fraction; MR = mitral regurgitation; N/A = not applicable; NS = not significant; NYHA = New York Heart Association classification.

*No P value determined because NYHA class is part of responder definition.

teristics compared with those without apical disease (n = 40), respectively (LVEF 23.8% ± 8.0% vs 22.2% ± 7.1%, P = .38; LVEDd 62 ± 10 mm vs 64 ± 9 mm, P = .38; and NYHA class 3.2 ± 0.4 vs 3.3 ± 0.4, P = .27). There was a significantly lower rate of CRT response (31% vs 64%, P = .003) in patients with apical disease compared with other patients.

At 6-month follow-up, patients with baseline apical wall motion abnormality also showed a lower rate of overall echocardiographic improvement, as defined by summed wall motion score (30% vs 81%, P < .001) and a higher rate of echocardiographic worsening (30% vs 4%, P = .01). In the subgroup of patients with apical disease (n = 43), CRT responders and nonresponders had similar baseline NYHA class (3.2 ± 0.4 vs 3.1 ± 0.4), LVEF (23.3% ± 6.5% vs 23.6% ± 8.7%), LVEDd (62 ± 10 mm vs 62 ± 8 mm), age (66 ± 10 years vs 68 ± 10 years), gender, cardiovascular risk factors, and HF drug therapy (P = NS for all comparisons). Finally, in the subgroup of patients with QRS duration <130 ms (n = 20), patients with apical wall motion abnormality had a significantly lower rate of CRT response compared with patients without apical disease (33% vs 67%, P = .02).

Table 4 Patient characteristics by presence of apical wall motion abnormality

	Apical disease (n = 43)	No apical disease (n = 40)	P value
Baseline LVEF (%)	23.8 ± 8.0	22.2 ± 7.1	.38
Baseline NYHA class	3.2 ± 0.4	3.3 ± 0.4	.27
Baseline LVEDd (mm)	62 ± 10	64 ± 9	.38
CRT response (%)	31	64	.003
Echocardiographic improvement (%)	30	81	<.001
Echocardiographic worsening (%)	30	4	.01

CRT = cardiac resynchronization therapy; LVEDd = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association classification.

Changes in regional wall motion after CRT

We examined the evolution of wall motion abnormalities according to location. Figure 1 shows rates of regional echocardiographic improvement in myocardial segments with abnormal wall motion at baseline: 23%, 50%, 50%, 49%, and 72%, in apical, anterior, lateral, inferior, and septal segments, respectively. Echocardiographic worsening was observed in 26%, 0%, 0%, 6%, and 0% of apical, anterior, lateral, inferior, and septal segments, respectively (Figure 2).

Discussion Major finding

The key finding of our study is that preimplantation apical wall motion abnormality was associated with a lower rate of CRT response in a cohort of patients with ischemic cardiomyopathy.

Since its initial report,¹⁹ CRT has proven to be a safe²⁰ and effective¹⁻³ treatment for patients with refractory HF and cardiac dyssynchrony. A recent study showed that CRT reduces both cardiovascular morbidity and mortality in these patients.² The first randomized trial of CRT included NYHA class III patients with LVEF ≤35% and QRS duration ≥150 ms.¹ Later studies showing the benefits of CRT included patients with either NYHA class IV symptoms²¹ or QRS duration between 120 and 150 ms with echocardiographic LV dyssynchrony.²

However, CRT is not always effective. In the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) study, 43% of patients receiving CRT-ICD did not have improvement in NYHA class.²¹

Given the complexity and expense of LV lead implantation, factors predicting lack of response should be identified. One such predictor is the presence of posterolateral scar tissue, recently demonstrated by Bleeker et al¹² to be associated with CRT nonresponse. These data are consistent with another study raising concern that patients with ischemic heart disease might be less likely to respond to CRT.¹¹

In searching for factors that might predict lack of response to CRT in patients with ischemic cardiomyopathy, we found that the presence of preimplantation apical wall motion abnormality was associated with a lower rate of response. The explanation for these findings is not known,

but one possible mechanism is increased apical wall strain caused by late activation. Indeed, in contrast to both RV and LV univentricular pacing, biventricular pacing causes apical segments to be depolarized last. This has been shown both experimentally¹³ and in a mathematical simulation.²² Wall stress is increased in these segments as a result of both augmented preload from exaggerated early systolic stretch and higher afterload from late contraction when LV pressure is higher.²³ This can alter protein expression²⁴ and result in structural remodeling of the affected ventricular wall.²⁵ Thus, CRT could exaggerate wall motion abnormalities and reduce contractile efficiency in patients with pre-existing apical disease.

Consistent with this hypothesis, we showed that the rate of echocardiographic improvement of apical wall motion was lower compared with other myocardial segments. Moreover, apical segments were more likely to display echocardiographic worsening after CRT.

Limitations

Our study was retrospective and from a single center. The findings should be confirmed in a prospective study with larger sample size before apical disease is considered a predictor of CRT nonresponse. Moreover, data on LV dyssynchrony were not universally available because our study spanned a period before echocardiographic dyssynchrony analysis was routinely performed. However, in some patients the presence of LV dyssynchrony is not clear-cut, especially with a suboptimal tissue Doppler signal. In contrast, apical wall motion abnormality is usually clearly shown by 2-dimensional echocardiography.

The 43% response rate observed in this study was lower than that seen in clinical trials of CRT, perhaps reflecting our ischemic cardiomyopathy study population, different definitions of CRT response, and real-world performance of CRT. Finally, although few patients in our study had posterolateral wall motion abnormalities by echocardiography,

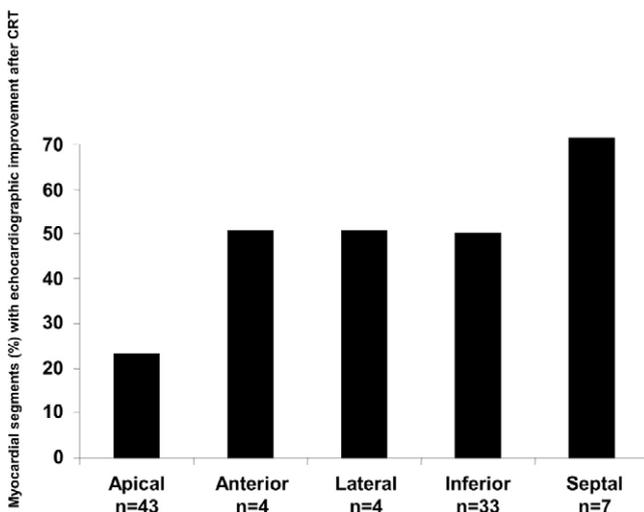


Figure 1 Regional improvement of wall motion. Myocardial segments showing improved wall motion at 6 months compared with baseline, by location.

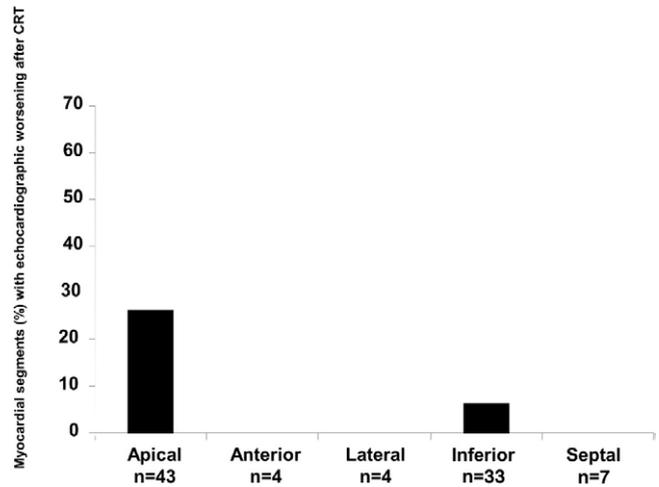


Figure 2 Regional worsening of wall motion. Myocardial segments showing worsening of wall motion at 6 months compared with baseline, by location.

a more sensitive method of scar assessment, such as magnetic resonance imaging, might have shown a higher prevalence of posterolateral scar. To the extent that this varied systematically between those with and without apical wall motion abnormality, the results may have been affected.

Conclusion

In patients with ischemic cardiomyopathy and cardiac dyssynchrony (either prolonged QRS duration or echocardiographic dyssynchrony), the presence of preimplantation apical wall motion abnormality was associated with a lower rate of CRT response. This may be attributable to increased wall stress of late-activated myocardial segments, but the underlying mechanisms require further investigation.

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