Gadolinium Cardiovascular Magnetic Resonance Predicts Reversible Myocardial Dysfunction and Remodeling in Patients With Heart Failure Undergoing β-Blocker Therapy

David Bello, MD; Dipan J. Shah, MD; George M. Farah, MD; Silvia Di Luzio, MD; Michele Parker, MS; Maryl R. Johnson, MD; William G. Cotts, MD; Francis J. Klocke, MD; Robert O. Bonow, MD; Robert M. Judd, PhD; Mihai Gheorghiade, MD; Raymond J. Kim, MD

Background—In some patients with heart failure, β-blockers can improve left ventricular (LV) function and reduce morbidity and mortality. We hypothesized that gadolinium-enhanced cardiovascular magnetic resonance imaging (CMR) can predict reversible myocardial dysfunction and remodeling in heart failure patients treated with β-blockers.

Methods and Results—Forty-five patients with chronic heart failure underwent CMR. Contrast imaging using gadolinium was performed to obtain high-resolution spatial maps of myocardial scarring and viability. Cine imaging was performed to assess LV function and morphology and was repeated in 35 patients after 6 months of β-blockade. Gadolinium CMR demonstrated scarring in 30 of 45 patients (67%). Scarring was found in 100% of patients with ischemic cardiomyopathy (28 of 28) but in only 12% with nonischemic cardiomyopathy (2 of 17). In the 35 patients who were maintained on β-blockers and had a second study, there was an inverse relation between the extent of scarring at baseline and the likelihood of contractile improvement 6 months later ($P<0.001$). For instance, contractility improved in 56% (674 of 1207) of regions with no scarring but in only 3% with >75% scarring (8 of 232). Multivariate analysis showed that the amount of dysfunctional but viable myocardium by CMR was an independent predictor of the change in ejection fraction ($P=0.01$), mean wall motion score ($P=0.0007$), LV end-diastolic volume index ($P=0.007$), and LV end-systolic volume index ($P\leq0.0001$).

Conclusions—For heart failure patients treated with β-blockers, gadolinium-enhanced CMR predicts the response in LV function and remodeling. **(*Circulation*. 2003;108:1945-1953.)**

Key Words: heart failure ■ receptors, adrenergic, beta ■ cardiomyopathy ■ magnetic resonance imaging

Large randomized studies have demonstrated that β-blockers improve survival in patients with heart failure.[1–3] Published clinical guidelines now recommend that β-blockers should be prescribed to all patients with stable heart failure caused by left ventricular (LV) systolic dysfunction unless they have a contraindication.[4] Not all patients, however, respond uniformly to this therapy. For example, those without sustained improvement in LV function may not have improved survival.[5,6] The possibility has been raised that patients with the most advanced disease may have less capacity to respond to β-blockers, presumably because there is less viable myocardium.[7,8] This issue has important clinical implications, because β-blockers, like all medications, can have deleterious effects in particular individuals.

Gadolinium-enhanced cardiovascular magnetic resonance imaging (CMR) is a new technique that can visualize both transmural and subendocardial scarring caused by previous myocardial infarction.[9,10] Recent studies have demonstrated the use of this technique to distinguish between scar and viable myocardium in patients with chronic coronary artery disease and to predict reversible myocardial dysfunction in those undergoing coronary revascularization.[9,11] In the present study, we performed gadolinium-enhanced CMR in patients with chronic heart failure in whom coronary revascularization was not anticipated. Our goal was to obtain high-resolution spatial maps of myocardial scarring and viability in these patients at baseline and, with the addition of cine CMR, to precisely assess changes in LV function and remodeling after 6 months of β-blocker therapy. We hypothesized that gadolinium-enhanced CMR can predict reversible myocardial dysfunction and remodeling in patients with chronic heart failure treated with β-blockers.

Received January 9, 2003; de novo received May 16, 2003; revision received July 21, 2003; accepted July 21, 2003.

From the Feinberg Cardiovascular Research Institute, Division of Cardiology, Northwestern University, Chicago, Ill (D.B., G.M.F., S.D.L., M.R.J., W.G.C., F.J.K., R.O.B., M.G.); and Duke Cardiovascular Magnetic Resonance Center, Division of Cardiology, Duke University, Durham, NC (D.J.S., M.P., R.M.J., R.J.K.).

Cine images for Figures 1 and 4 are available in the online-only Data Supplement at http://www.circulationaha.org.

Correspondence to Raymond J. Kim, MD, Duke Cardiovascular MRI Center, DUMC-3934, Durham, NC 27710. E-mail raymond.kim@dcmrc.mc.duke.edu

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000095029.57483.60**

Methods

Population and Protocol

Forty-five consecutive patients were prospectively enrolled from Northwestern Memorial and Lakeside-VA hospitals. All patients had symptoms of heart failure for ≥2 months and an LV ejection fraction ≤35% on either contrast ventriculography or echocardiography despite conventional therapy. Patients were excluded if they had primary valvular disease; had constrictive, restrictive, or hypertrophic cardiomyopathy; had myocarditis; received or were likely to receive a cardiac transplant; had been treated with β-blockers or drugs with β-blocking properties such as amiodarone within 2 months before enrollment; or had contraindications to CMR (eg, a pacemaker). Patients were also excluded if they had had acute myocardial infarction or coronary revascularization within 2 months before enrollment or if revascularization was anticipated.

The selection and titration of β-blockers was performed in a dedicated heart failure clinic. All patients received a standard heart failure regimen including an ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB). ACEI (or ARB) was started ≥2 months before the study period, with initial titration to full therapeutic or tolerated doses occurring at least 6 weeks earlier. Other than β-blockers, no new cardioactive medications were initiated during this study, although dosages of medications already in use were allowed to change as clinically indicated. CMR was repeated 6±1 months after initiation of β-blockers in 35 patients. Of the remaining 10 patients, 4 were lost to follow-up, 3 did not tolerate β-blockers, 2 had pacemaker/implantable cardioverter-defibrillator implantation, and 1 underwent PTCA. The cause of heart failure was considered to be ischemic if there was >50% stenosis of a major epicardial vessel on angiography, a history of enzymatically proven myocardial infarction, or evidence of ischemia on nuclear stress testing. All other patients were classified as having nonischemic cardiomyopathy. All participants gave written informed consent to the protocol.

CMR Imaging

Images were acquired on a 1.5-T Siemens Sonata using a phased-array coil during repeated breath-holds (≈8 seconds). Steady-state free precession cine images were acquired in multiple short-axis (every 1 cm throughout the entire LV) and 2 to 3 long-axis planes. Gadolinium (gadoteridol, 0.1 to 0.15 mmol/kg) was administered intravenously, and contrast-enhanced images were acquired after 10 minutes with a segmented inversion-recovery technique[10] in the identical planes.

Analysis

The CMR scans were placed in random order after the identity markers were removed. The cine and gadolinium-enhanced images were evaluated separately by the consensus of 2 observers who were unaware of the results of the other modality. Hyperenhanced tissue on the gadolinium-enhanced images was assumed to represent scarred myocardium.[9,11]

Global Parameters

The myocardial borders were planimetered on all the short-axis cine images to determine LV volumes, ejection fraction, and mass (assuming density=1.05 g/cm^3).

Segmental Model

Regional parameters were assessed in a 72-segment model.[11] Only 6 short-axis slices per patient were analyzed, which introduces the possibility of sampling error with regard to the segmental data. Segmental wall thickening was graded as follows: 0, normal; 1, mild or moderate hypokinesia; 2, severe hypokinesia; 3, akinesia; and 4, dyskinesia.[11] Segmental gadolinium enhancement was graded as follows: 0, 0% hyperenhanced; 1, 1% to 25% hyperenhanced; 2, 26% to 50% hyperenhanced; 3, 51% to 75% hyperenhanced; and 4, 76% to 100% hyperenhanced.[11]

Regional Versus Global Dysfunction

Earlier studies suggested that LV dysfunction caused by nonischemic cardiomyopathy is primarily global rather than regional as in ischemic cardiomyopathy and that this characteristic could be used to distinguish between these disorders.[12] To determine whether the contraction pattern on cine CMR could establish the cause of the heart failure in our cohort, patients were labeled as having regional or global dysfunction. Regional dysfunction was defined when the maximum minus the minimum wall motion score for a given patient was ≥3. For example, patients with normal contractility in one region would need to have another region with akinesia or dyskinesia.

ECG

Q waves were determined by Minnesota codes 1-1-1 to 1-2-8 and left bundle-branch block by code 7-1-1.[13]

Statistical Analysis

Continuous data were expressed as mean±SD. Comparison between groups were made by use of 2 sample *t* tests for continuous data and χ^2 tests for discrete data. Changes between baseline and end-of-study measurements were assessed by paired *t* tests. McNemar's test with Bonferroni correction was used to compare the diagnostic accuracy of techniques for the detection of ischemic cardiomyopathy. For myocardial regions, both the χ^2 test for trend and a logistic regression model with a repeated-measures variable for the patient to adjust for the nonindependence of the segmental data (S-PLUS 2000, nonlinear mixed-effects models[14]) were used to assess the relation between the transmural extent of hyperenhancement and changes in contractility. Initial univariate linear regression analysis was performed to assess the relation between clinical and CMR variables (Table 3) and changes in LV function and morphology. Both forward and backward stepwise linear regression analyses were then used to identify predictive multivariate models. All statistical tests were 2-tailed. A value of $P<0.05$ was regarded as significant.

Results

Baseline Characteristics

Characteristics of the study population are summarized in Table 1. Because recruitment was predominantly from a VA hospital, all the patients were male. Heart failure was considered ischemic in 28 patients (62%) and nonischemic in 17 (38%). Among the 28 considered ischemic, 24 had significant multivessel disease on coronary angiography. The remaining 4 who did not undergo angiography had had recent nuclear stress testing demonstrating ischemia; 2 of these also had a history of enzymatically proven myocardial infarction. Among the 17 considered nonischemic, 16 had angiography demonstrating normal coronaries. The remaining patient who did not have angiography was 23 years old and had no risk factors for CAD. Among the 13 patients with Q waves and ischemic disease, 10 met standard European Society of Cardiology/American College of Cardiology criteria[15] for myocardial infarction. None of the 3 patients with Q waves and nonischemic disease met these criteria. Regional as opposed to global dysfunction was found in 49% of patients, with no significant difference in rate found between the ischemic and nonischemic groups. Myocardial scarring (hyperenhancement) was seen in 67% of patients, including 100% of those with ischemic cardiomyopathy and 12% with nonischemic cardiomyopathy.

Patients Completing 6 Months of β-Blockade

Comparisons between patients completing and those not completing 6 months of β-blocker therapy demonstrated no

TABLE 1. Baseline Values

Characteristic	Entire Group (n=45)	Ischemic (n=28)	Nonischemic (n=17)	*P*
Age, y	63±14	67±11	56±17	**0.02**
NYHA functional class				
I	7 (16)	3 (11)	4 (24)	...
II	27 (60)	17 (61)	10 (59)	...
III	10 (22)	8 (29)	2 (12)	...
IV	1 (2)	0	1 (6)	...
Mean	2.1±0.7	2.2±0.6	2.0±0.8	0.40
Diabetes	12 (27)	9 (32)	3 (18)	0.29
Hypertension	25 (56)	16 (57)	9 (53)	0.78
History of myocardial infarction	14 (31)	14 (50)	0	...
History of revascularization	12 (27)	12 (43)	0	...
LV ejection fraction	26±11	24±10	31±12	**0.02**
Mean wall motion score	1.9±0.7	2.0±0.6	1.7±0.8	0.10
Regional dysfunction	22 (49)	13 (46)	9 (53)	0.67
Q wave	16 (36)	13 (46)	3 (18)	**0.05**
Left bundle-branch block	8 (18)	5 (18)	3 (18)	1.0000*
Hyperenhancement	30 (67)	28 (100)	2 (12)	**<0.0001***

Values are given as number (percent) or mean±SD. All numbers in boldface indicate *P* values ≤0.05.

*Fisher exact test (2 tailed).

significant difference in age, NYHA class, rate of ischemic or nonischemic cardiomyopathy, hypertension, diabetes, previous myocardial infarction, previous revascularization, or heart failure medications at baseline. The clinical features for the 35 patients completing β-blocker therapy are summarized in Table 2. With β-blocker therapy, there was a significant decrease in heart rate and diastolic blood pressure but not in systolic blood pressure. Contractile function improved with LV ejection fraction, increasing by 11±10 U. Likewise, all indexes of remodeling showed significant improvement. Cardiac index, however, did not change (2.48±0.82 versus 2.47±0.65, $P=0.96$). When patients with ischemic cardiomyopathy were compared with those with nonischemic cardiomyopathy, no significant differences between groups were observed at baseline except for younger age, higher ejection fraction, and reduced rate of myocardial hyperenhancement in those with nonischemic disease. After β-blocker therapy, all indexes of contractile function and remodeling showed greater absolute improvement in the nonischemic group; however, the differences in improvement did not reach statistical significance.

Relation Between Viability and Improved Contractility and Remodeling

Figure 1 demonstrates representative images in 1 patient before and after β-blocker therapy. Note that hyperenhanced (scarred) myocardium does not improve after β-blocker therapy, whereas nonhyperenhanced (viable) myocardium does improve.

A total of 2278 matched segments were analyzed. At baseline, 1875 segments (82%) had abnormal contractility, whereas 723 segments (32%) had some areas of scarring. After β-blocker therapy, 763 of 1875 segments (41%) improved in contractility, including 38% of segments with mild or moderate hypokinesia, 48% of segments with severe hypokinesia, and 35% of segments with akinesia or dyskinesia.

When all dysfunctional segments were considered, the transmural extent of hyperenhancement at baseline was inversely related to the likelihood of improvement in contractility after β-blocker therapy (Figure 2A; $P<0.0001$). Thus, contractility improved in 56% of segments (674 of 1207) with no hyperenhancement but in only 3% of segments (8 of 232) with >75% hyperenhancement. This inverse relationship remained significant ($P<0.001$) when the data were reanalyzed with a separate parameter for "patient" to account for the nonindependence of segments. When the cause of heart failure was considered, a large difference in the rate of hyperenhancement was noted. Whereas 45±25% of segments from patients with ischemic cardiomyopathy had hyperenhancement, only 5±11% from patients with nonischemic cardiomyopathy had hyperenhancement ($P<0.0001$). Given this low rate of hyperenhancement in nonischemic patients, these segments were pooled and compared separately (Figure 2B). The highest rate of functional improvement was observed in segments from nonischemic patients.

Figure 3 demonstrates that an increasing volume of dysfunctional but viable myocardium at baseline was correlated with greater improvement in ejection fraction and mean wall motion score and greater reduction in LV end-diastolic volume index and LV end-systolic volume index after β-blocker therapy. The volume of dysfunctional but viable

TABLE 2. Patients Completing 6 Months of β-Blockade

Characteristic	Entire Group (n=35)	Ischemic (n=23)	Nonischemic (n=12)	*P*
Age, y	64±12	67±11	59±13	**0.05**
NYHA functional class				
I	5 (14)	2 (9)	3 (25)	...
II	20 (57)	13 (57)	7 (58)	...
III	9 (26)	8 (35)	1 (8)	...
IV	1 (3)	0	1 (8)	...
Mean	2.2±0.7	2.3±0.6	2.0±0.9	0.31
Diabetes	8 (23)	6 (26)	2 (17)	0.53
Hypertension	22 (63)	14 (61)	8 (67)	0.74
History of myocardial infarction	13 (37)	13 (57)	0	...
History of revascularization	10 (29)	10 (43)	0	...
Medications				
ACEI or ARB	35 (100)	23 (100)	12 (100)	1.00*
Digoxin	31 (89)	21 (91)	10 (83)	0.59*
Diuretic	25 (71)	16 (70)	9 (75)	1.00*
β-Blocker final dose, mg/d				
Carvedilol (n=33)	44±15	43±14	47±15	0.42
Metoprolol (n=2)	125±35	125±35	NA	...
Heart rate, bpm				
Baseline	75±14	76±15	74±12	0.68
Change after BBT	−11±16	−13±16	−8±18	0.39
P vs baseline	**0.0003**	**0.0008**	0.16	
Systolic blood pressure, mm Hg				
Baseline	122±16	122±17	122±15	0.95
Change after BBT	−2±15	−4±15	2±15	0.31
P vs baseline	0.51	0.27	0.67	
Diastolic blood pressure, mm Hg				
Baseline	72±12	71±13	73±8	0.67
Change after BBT	−6±13	−8±14	−1±12	0.17
P vs baseline	**0.02**	**0.01**	0.74	
LV ejection fraction, %				
Baseline	26±12	23±10	33±11	**0.01**
Change after BBT	11±10	10±10	12±11	0.45
P vs baseline	**<0.0001**	**<0.0001**	**0.003**	
Mean wall motion score				
Baseline	1.9±0.8	2.0±0.7	1.6±0.8	0.11
Change after BBT	−0.5±0.7	−0.4±0.6	−0.7±0.9	0.15
P vs baseline	**0.0003**	**0.008**	**0.02**	
LV end-diastolic volume index, mL/m^2				
Baseline	124±51	133±56	108±36	0.18
Change after BBT	−10±21	−7±20	−14±24	0.36
P vs baseline	**0.009**	0.08	0.06	
LV end-systolic volume index, mL/m^2				
Baseline	91±48	101±52	73±34	0.11
Change after BBT	−16±20	−14±19	−20±22	0.37
P vs baseline	**<0.0001**	**0.002**	**0.008**	
LV mass index, g/m^2				
Baseline	95±33	96±35	93±29	0.81
Change after BBT	−8±14	−6±14	−11±12	0.34
P vs baseline	**0.002**	0.06	**0.01**	
Regional dysfunction				
Baseline	18 (51)	12 (52)	6 (50)	0.90
Change after BBT	16 (46)	14 (61)	2 (17)	0.34
P vs baseline	0.41	0.16	0.046	
Hyperenhancement	25 (71)	23 (100)	2 (17)	**<0.0001***

BBT indicates β-blocker therapy. All numbers in boldface represent *P* values ≤0.05.
*Fisher exact test (2 tailed).

TABLE 3. Predictors of Improved LV Function and Remodeling

	Change in Ejection Fraction				Change in LV EDVI†		Change in LV ESVI†	
	Univariate		Multivariate*		Univariate		Univariate	
Variable	Coefficient±SE	*P*	Coefficient±SE	*P*	Coefficient±SE	*P*	Coefficient±SE	*P*
Clinical predictors								
Age	−0.10±0.14	0.48	...	...	−0.02±0.30	0.93	−0.0001±0.3	0.99
NYHA functional class	−3.44±2.42	0.17	...	...	−0.87±5.17	0.87	1.71±4.88	0.73
Diabetes	1.67±4.13	0.69	...	...	−1.58±8.57	0.85	−2.42±8.10	0.77
Hypertension	8.99±3.24	**0.009**	6.42±2.03	**0.004**	−2.08±7.44	0.78	−8.04±6.91	0.25
Myocardial infarction history	−7.16±3.37	**0.04**	...	...	3.59±7.43	0.63	9.12±6.87	0.19
Revascularization history	−5.43±3.73	0.15	...	...	5.51±7.91	0.49	9.15±7.37	0.22
Digoxin	−0.83±5.46	0.88	...	...	2.54±11.3	0.82	2.94±10.7	0.78
Diuretic	2.62±3.82	0.50	...	...	−10.6±7.75	0.18	−10.7±7.31	0.15
ACE or ARB (dose change)	0.04±0.05	0.46	...	...	0.02±0.11	0.85	−0.001±0.10	0.99
ACE or ARB (final dose)‡	−0.02±0.04	0.57	...	...	0.12±0.08	0.11	0.11±0.07	0.13
Ischemic cardiomyopathy	−2.78±3.63	0.45	...	...	6.96±7.49	0.36	6.43±7.09	0.37
Carvedilol dose, mg/d*	0.39±0.09	**0.0003**	0.31±0.07	**0.0002**	−0.21±0.26	0.42	−0.45±0.24	0.07
Heart rate	0.18±0.13	0.16	0.20±0.07	**0.01**	−0.14±0.27	0.61	−0.23±0.25	0.36
Diastolic blood pressure	0.19±0.15	0.21	...	...	0.17±0.32	0.60	−0.07±0.30	0.82
Systolic blood pressure	0.12±0.11	0.25	...	...	0.13±0.23	0.56	−0.03±0.21	0.88
Q wave	−2.83±3.56	0.43	...	...	10.4±8.04	0.21	9.26±7.63	0.23
Left bundle-branch block	−4.43±4.54	0.34	...	...	3.93±9.53	0.68	5.19±8.99	0.57
CMR predictors								
LV ejection fraction	−0.17±0.15	0.26	...	...	0.48±0.31	0.13	0.63±0.28	**0.03**
Mean wall motion score	2.53±2.32	0.29	...	...	−8.47±4.68	0.08	−10.1±4.29	**0.02**
LV mass index	0.02±0.05	0.68	...	...	−0.11±0.11	0.35	−0.11±0.10	0.28
LV EDVI	−0.02±0.03	0.55	...	...	−0.17±0.07	**0.01**	−0.14±0.06	**0.04**
LV ESVI	−0.02±0.04	0.59	−0.05±0.02	**0.02**	−0.16±0.07	**0.03**	−0.14±0.07	**0.04**
Percent LV dysfunctional but viable (hyperenhancement ≤25%)	0.19±0.05	**0.0003**	0.10±0.04	**0.01**	−0.31±0.11	**0.007**	−0.42±0.09	**<0.0001**

EDVI indicates end-diastolic volume index; ESVI, end-systolic volume index. Boldface as in Table 2.

*For the 33 patients treated with carvedilol.

†Multivariate analysis demonstrated that percent LV dysfunctional but viable was the only independent significant predictor of the change in LV EDVI ($P=0.007$) and LV ESVI ($P<0.0001$).

‡Normalized to maximum daily recommended dose.

myocardium was not associated with the change in LV mass ($r=-0.23$, $P=0.22$).

Clinical and CMR Predictors of Improved Ventricular Function and Remodeling

According to univariate analysis, carvedilol dose, history of myocardial infarction, and hypertension were clinical predictors of the change in LV ejection fraction after β-blocker therapy (Table 3). The only imaging predictor was the amount of dysfunctional but viable myocardium. There were no clinical variables that predicted changes in LV volumes or mass.

According to multivariate analysis, the amount of dysfunctional but viable myocardium was an independent predictor of the change in LV ejection fraction ($P=0.01$), mean wall motion score ($P=0.0007$), LV end-diastolic volume index ($P=0.007$), and LV end-systolic volume index ($P<0.0001$). For the volume indexes, there were no other independent predictors.

Although all patients were on ACEI or ARB, 8 patients had their ACEI or ARB doses changed during the study period. Neither the change in dose of ACEI or ARB nor final total dose was predictive of change in LV systolic function or remodeling.

Discussion

Reversible Dysfunction and Remodeling

Several studies have demonstrated that LV ejection fraction can improve in heart failure patients after long-term β-blocker therapy.[6,16,17] However, not all patients have improved ejection fraction. With "improvement" defined as an increase in ejection fraction by 5 U, ≈30% to 50% of patients will not have improvement.[16,18] Likewise, in the present study, 43% of the patients did not have improvement. The ejection fraction response is important because this characteristic is associated with clinical outcome.[6,17] For example, Bristow et al[6] found that 6 months of carvedilol therapy

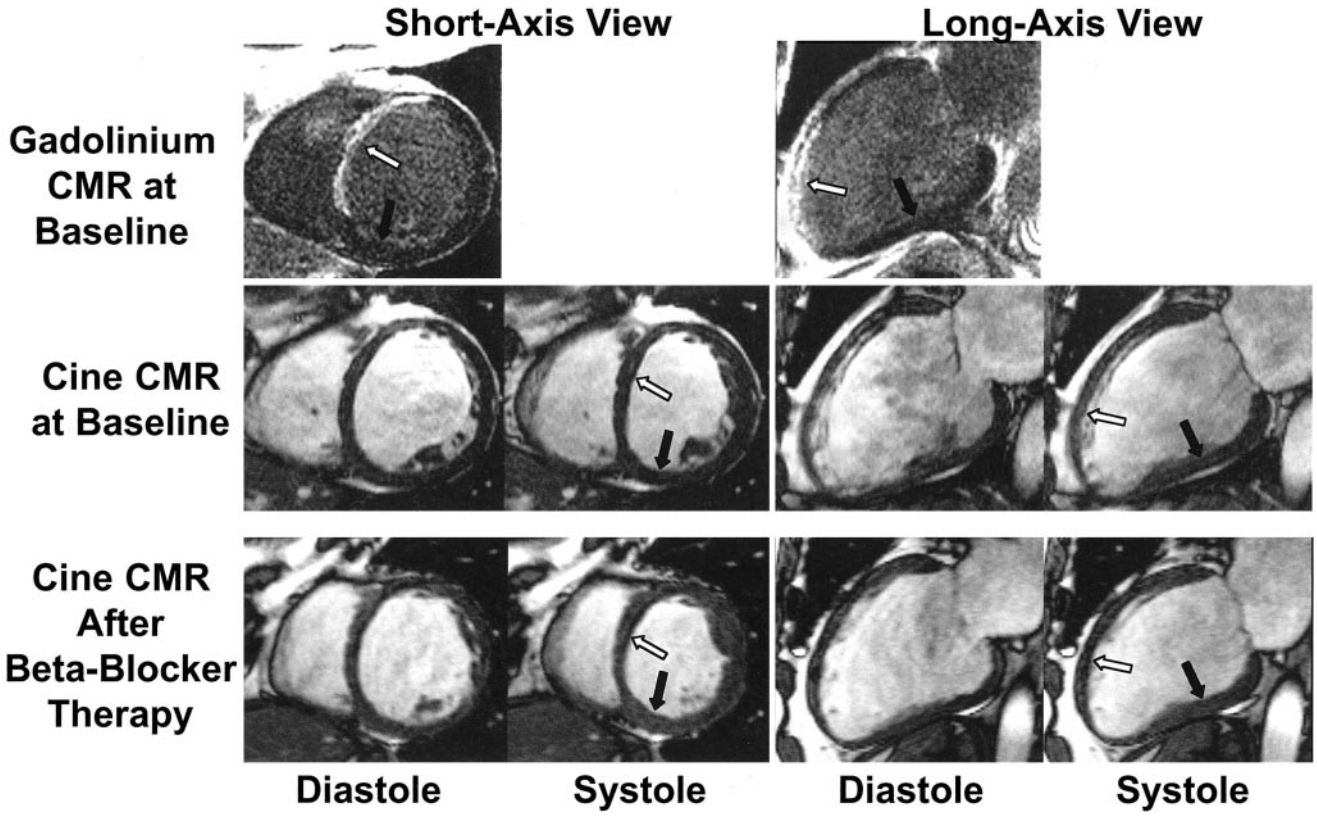

Figure 1. Representative images in 1 patient before and 6 months after β-blocker therapy. Hyperenhanced myocardium (white arrows) does not improve after β-blocker therapy, whereas nonhyperenhanced regions (black arrows) do improve. Also see Data Supplement.

produced a dose-related response in LV function that was associated with a near mirror-image dose-related response in survival. Lechat et al[5] found from their analysis of the Cardiac Insufficiency Bisoprolol Study that improvement in LV function after 5 months of therapy was significantly correlated with further survival. Interestingly, they also found that prognosis may actually worsen with β-blockade in some patients. They observed in patients without improved LV function that the prognosis was worse in the treated group than in the placebo group, even with the appropriate heart rate reduction.

The present study demonstrates that improvement (or, conversely, lack of improvement) in LV function can be predicted by gadolinium CMR. For example, on a regional basis, there was a direct inverse relationship between the transmural extent of scarring by CMR at baseline and the likelihood of contractile improvement after β-blockade. Likewise, on a per-patient basis, the CMR index of the amount of dysfunctional but viable myocardium was an independent predictor of the change in LV ejection fraction and global mean wall motion score.

In the present study, improvement in LV ejection fraction and global mean wall motion score occurred with reversal of cardiac remodeling, including a large reduction in the LV end-systolic volume. This result is consistent with previous studies that have demonstrated that long-term improvement

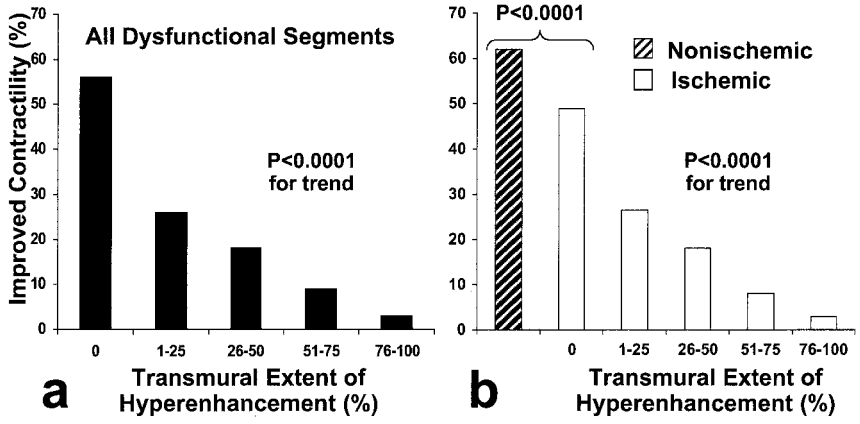

Figure 2. Relation between transmural extent of scarring (hyperenhancement) at baseline and likelihood for improved contractility after β-blocker therapy. Data are shown for all dysfunctional segments (a) and when patients with ischemic cardiomyopathy are separated from those with nonischemic cardiomyopathy (b).

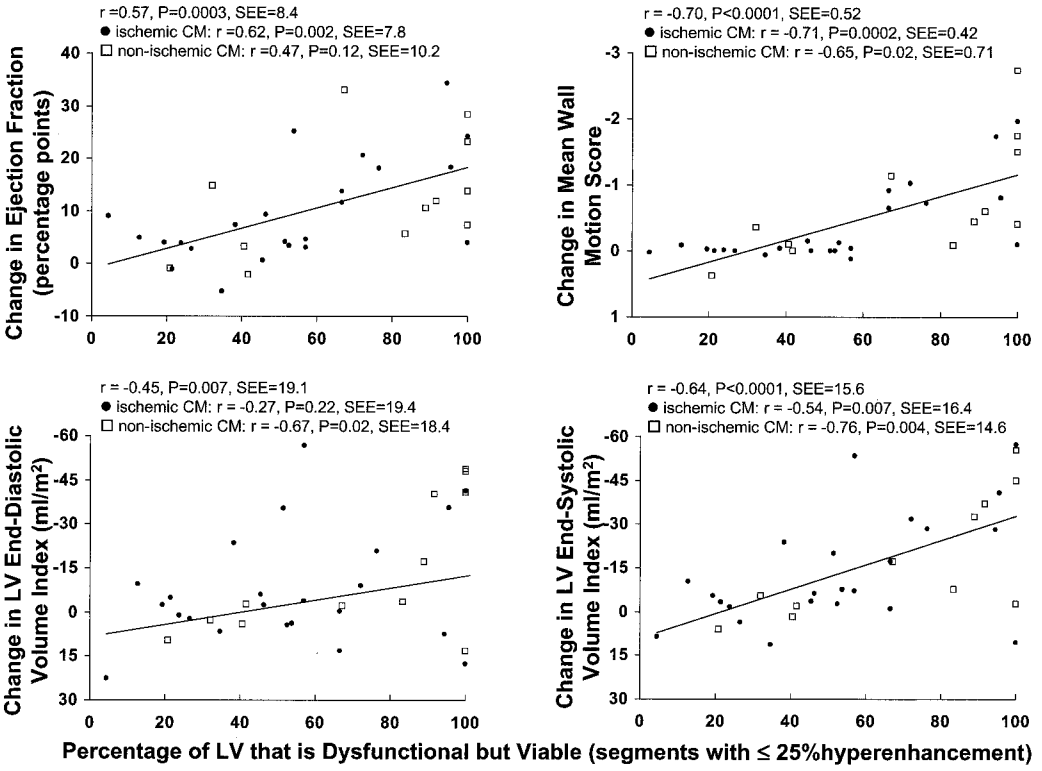

Figure 3. Relation between percentage of left ventricle that is dysfunctional but viable at baseline and changes in ventricular function and morphology after β-blocker therapy.

in LV ejection fraction occurs with reduction in LV chamber volumes and regression of LV mass.[19] These results indicate that increased LV ejection fraction is not simply a result of heart rate reduction with increased ventricular volumes but is probably a result of direct effects of β-blocker therapy on intrinsic systolic function.[20] Previous studies have not sought to identify characteristics that could predict beneficial changes in remodeling. The present study is the first to demonstrate that reverse remodeling can be predicted by an assessment of dysfunctional but viable myocardium.

The mechanism of β-blocker–induced improvement in intrinsic systolic function is unclear. Potential mechanisms include restoration of maladaptive adrenergic signaling, improved myocardial energetics, and favorable changes in expression of myocardial genes that regulate contractility and hypertrophy.[18,20] All potential mechanisms, however, have an inherent assumption: that is, that a sufficient number of viable myocytes exist that can respond to the β-blocker therapy and that dysfunctional regions by and large represent viable myocardium and not scar tissue. In the present study, we observed that essentially none of the regions that were >75% scarred by CMR had improved contractility after β-blocker therapy. Likewise, on a per-patient basis, we observed that patients with a small volume of dysfunctional but viable myocardium were far less likely than those with a large volume to have improved LV ejection fraction regardless of the baseline ejection fraction. Recent experimental studies have shown similar findings. For example, Yaoita et al[21] demonstrated that carvedilol attenuates ventricular remodeling and improves ejection fraction in a heart failure model caused by coronary stenosis but not caused by permanent coronary occlusion. They concluded that carvedilol provides potent cardioprotection for compromised ischemic but viable myocardium rather than for infarcted myocardium. With scientific progress, the paradigm of heart failure has changed appropriately from one of irreversible, progressive pump failure to one of reversible neurohumoral imbalance.[20] The results of the present study, however, indicate that there is an element of irreversibility that is important to consider clinically with regard to changes in ventricular function and remodeling. These regions that have been irreversibly damaged can be identified by gadolinium CMR.

Ischemic Versus Nonischemic Cardiomyopathy

Patients with nonischemic cardiomyopathy generally have greater improvement in ventricular function in response to β-blocker therapy than patients with ischemic cardiomyopathy.[22] Indeed, when Packer et al[22] performed a meta-analysis of 19 randomized controlled trials, they found a striking inverse relation between the magnitude of functional improvement in each trial and the proportion of patients with ischemic disease. Some studies, however, have not demonstrated a difference in response to β-blockade.[16] Many variables may be responsible for this discordance in findings, including the dose and type of β-blocker used, the severity of heart failure symptoms, and the manner in which ischemic or nonischemic disease is defined. The results of the present study suggest an additional source of variance. The level of myocardial viability that is present in any given individual, regardless of the cause of heart failure, may affect the

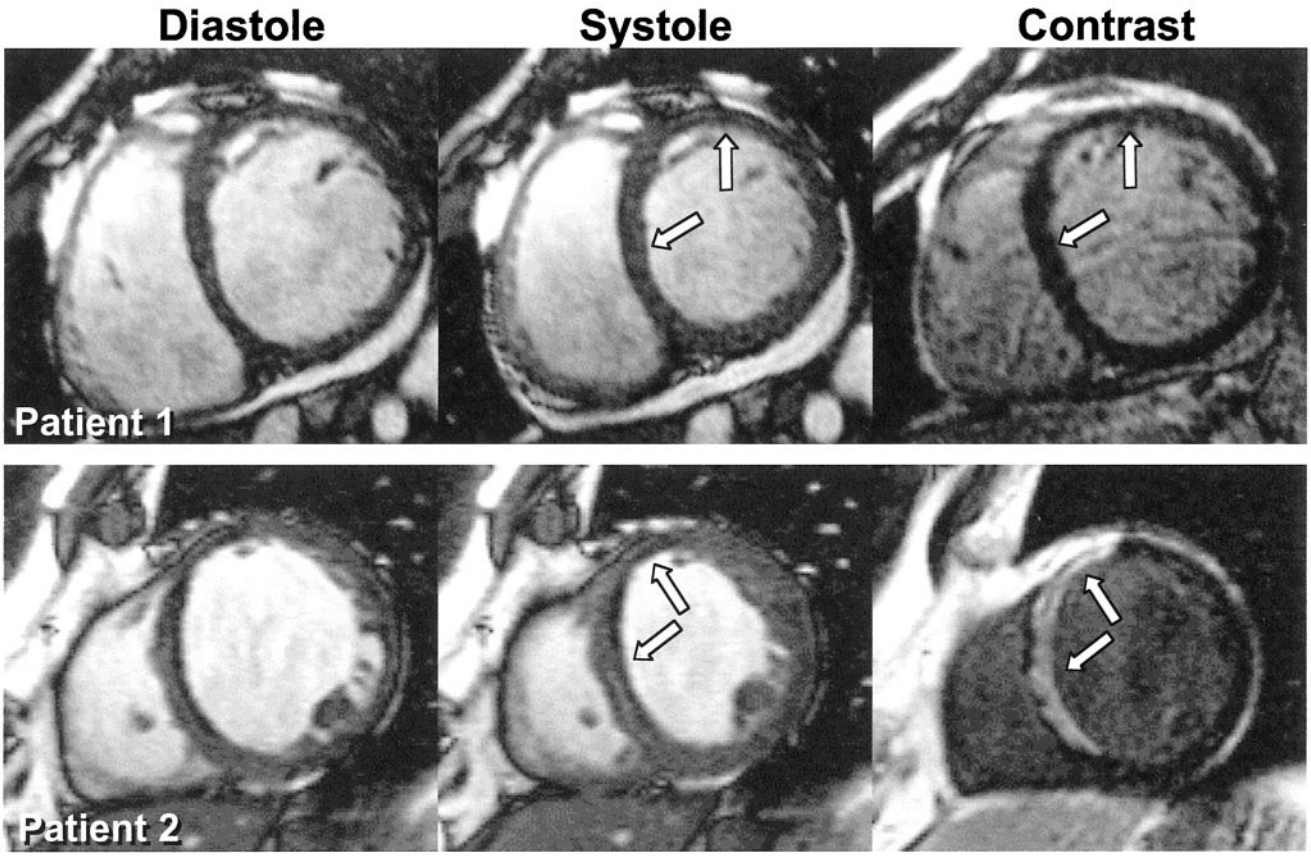

Figure 4. Regional dysfunction (arrows) in a patient with nonischemic cardiomyopathy (patient 1) and a patient with ischemic cardiomyopathy (patient 2). Only patient with ischemic disease has myocardial hyperenhancement. Also see Data Supplement.

response that occurs after β-blocker therapy. In the present study, we stratified myocardial regions on the basis of the transmural extent of scarring. After accounting for baseline differences in scarring, we observed that dysfunctional regions from patients with nonischemic cardiomyopathy were more likely to improve in contractility than regions from patients with ischemic cardiomyopathy. Although end-stage ischemic and nonischemic cardiomyopathy may exhibit common features, this finding suggests that there may be important pathophysiological differences.

In the present study, all patients with ischemic cardiomyopathy had evidence of myocardial scarring. This finding is consistent with necropsy studies that have demonstrated that virtually all patients with congestive heart failure and significant coronary artery disease have gross myocardial scarring at autopsy, even in those without clinical history of myocardial infarction, angina, or Q waves.[23] Conversely, we observed in patients with nonischemic cardiomyopathy that scarring was uncommon, occurring in only 12% of patients. This finding is also consistent with previous studies. Roberts et al[24] found grossly visible scars at cardiac necropsy in 14% of patients with idiopathic dilated cardiomyopathy. Uretsky et al[25] evaluated chronic heart failure patients at autopsy and found old infarcts or scarring in 12% of patients without coronary artery disease. A number of mechanisms may be responsible for myocardial infarction in patients without coronary artery disease, including coronary vasospasm, thrombosis with spontaneous lysis superimposed on minimal atherosclerosis, or coronary emboli. Regardless of the mechanism, myocardial infarction in the absence of coronary artery disease is rare, and our findings suggest that gadolinium CMR may be useful in distinguishing ischemic from nonischemic cardiomyopathy noninvasively. Figure 4 shows cine and contrast views in 2 patients from the present study. Although both patients have regional as opposed to global dysfunction, only the patient with ischemic disease has evidence of myocardial scarring. Data from Table 1 allow calculation of the sensitivity, specificity, and accuracy of 3 noninvasive methods in determining the ischemic cause of heart failure. The presence of Q waves on 12-lead ECG was moderately specific (82%) but not sensitive (46%). The presence of regional dysfunction on cine CMR was neither sensitive (46%) nor specific (47%). The presence of hyperenhancement or scarring on gadolinium CMR was both sensitive (100%) and specific (88%), with a diagnostic accuracy (96%) that was significantly higher than that of Q waves or regional dysfunction ($P<0.05$ for both comparisons).

Clinical Implications

This study demonstrates that myocardial viability in patients with systolic dysfunction is an important factor in determining LV contractile response and remodeling to β-blocker therapy. It should be noted, however, that all patients received

a standard heart failure therapy regimen that included ACEI or ARB. Thus, one should not assume that the beneficial changes found at 6-month follow-up were solely a result of β-blockade. Nevertheless, our results show that regions with transmural scarring by gadolinium CMR are irreversibly damaged and thus do not experience functional improvement from β-blockade. These findings should be interpreted with the knowledge that data so far, although compelling, are insufficient to promote the use of LV dimensions and ejection fraction as a surrogate for mortality in patients with heart failure. For instance, even if resting contractile function does not improve, β-blockers may have antiarrhythmic activity that can reduce sudden cardiac death. Moreover, there is no longer any doubt that β-blockers reduce mortality in class II through IV heart failure.[1–3] Nonetheless, our findings raise questions regarding the efficacy of these agents in patients with predominantly nonviable myocardium. Further study will be necessary to determine whether heterogeneity of response in terms of contractile improvement and remodeling translates into differences in survival and whether assessment of myocardial viability by CMR will be useful in predicting long-term outcome.

Acknowledgments

This study was supported in part by an American College of Cardiology/Merck award (Dr Bello) and National Institutes of Health grants R01-HL-63268 (Dr Judd) and R01-HL-64726 (Dr Kim).

References

1. The Cardiac Insufficiency Bisoprolol Study II: a randomised trial. *Lancet*. 1999;353:9–13.
2. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure. *Lancet*. 1999; 353:2001–2007.
3. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651–1658.
4. Hunt HA, Baker DW, Chin MH, et al. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult. *Circulation*. 2001;104:2996–3007.
5. Lechat P, Escolano S, Golmard JL, et al. Prognostic value of bisoprolol-induced hemodynamic effects in heart failure during the Cardiac Insufficiency BIsoprolol Study. *Circulation*. 1997;96:2197–2205.
6. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation*. 1996;94:2807–2816.
7. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med*. 2001;344:1659–1667.
8. Cleland JG, Pennell DJ, Ray SG, et al. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure: the CHRISTMAS trial. *Lancet*. 2003;362:14–21.
9. Wu E, Judd RM, Vargas JD, et al. Visualisation of presence, location, and transmural extent of healed Q-wave and non-Q-wave myocardial infarction. *Lancet*. 2001;357:21–28.
10. Simonetti OP, Kim RJ, Fieno DS, et al. An improved MR imaging technique for the visualization of myocardial infarction. *Radiology*. 2001; 218:215–223.
11. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med*. 2000;343:1445–1453.
12. Corya B, Feigenbaum H, Rasmussen S, et al. Echocardiographic features of congestive cardiomyopathy compared with normal subjects and patients with coronary artery disease. *Circulation*. 1974;49:1153–1159.
13. Rose GA, World Health Organization. Cardiovascular survey methods. Monograph series (World Health Organization); Geneva: World Health Organization; 1982:178.
14. *S-PLUS 2000 Guide to Statistics: Volume 1*. Seattle, Wash: Data Analysis Products Division, Mathsoft; 1999.
15. Myocardial infarction redefined: a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J*. 2000; 21:1502–1513.
16. Bristow MR, O'Connell JB, Gilbert EM, et al. Dose-response of chronic β-blocker treatment in heart failure from either idiopathic dilated or ischemic cardiomyopathy. Bucindolol Investigators. *Circulation*. 1994; 89:1632–1642.
17. Lechat P, Packer M, Chalon S, et al. Clinical effects of β-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation*. 1998;98:1184–1191.
18. Lowes BD, Gilbert EM, Abraham WT, et al. Myocardial gene expression in dilated cardiomyopathy treated with beta-blocking agents. *N Engl J Med*. 2002;346:1357–1365.
19. Hall SA, Cigarroa CG, Marcoux L, et al. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. *J Am Coll Cardiol*. 1995;25:1154–1161.
20. Eichhorn EJ, Bristow MR. Medical therapy can improve the biological properties of the chronically failing heart: a new era in the treatment of heart failure. *Circulation*. 1996;94:2285–2296.
21. Yaoita H, Sakabe A, Maehara K, et al. Different effects of carvedilol, metoprolol, and propranolol on left ventricular remodeling after coronary stenosis or after permanent coronary occlusion in rats. *Circulation*. 2002; 105:975–980.
22. Packer M, Antonopoulos GV, Berlin JA, et al. Comparative effects of carvedilol and metoprolol on left ventricular ejection fraction in heart failure: results of a meta-analysis. *Am Heart J*. 2001;141:899–907.
23. Schuster EH, Bulkley BH. Ischemic cardiomyopathy: a clinicopathologic study of fourteen patients. *Am Heart J*. 1980;100:506–512.
24. Roberts WC, Siegel RJ, McManus BM. Idiopathic dilated cardiomyopathy: analysis of 152 necropsy patients. *Am J Cardiol*. 1987;60: 1340–1355.
25. Uretsky BF, Thygesen K, Armstrong PW, et al. Acute coronary findings at autopsy in heart failure patients with sudden death: results from the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial. *Circulation*. 2000;102:611–616.

Gadolinium Cardiovascular Magnetic Resonance Predicts Reversible Myocardial Dysfunction and Remodeling in Patients With Heart Failure Undergoing β-Blocker Therapy

David Bello, Dipan J. Shah, George M. Farah, Silvia Di Luzio, Michele Parker, Maryl R. Johnson, William G. Cotts, Francis J. Klocke, Robert O. Bonow, Robert M. Judd, Mihai Gheorghiade and Raymond J. Kim

Circulation. 2003;108:1945-1953; originally published online October 13, 2003;
doi: 10.1161/01.CIR.0000095029.57483.60
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539