Baseline Scintigraphic Abnormalities by Myocardial Perfusion Imaging Predict Echocardiographic Response to Cardiac Resynchronization Therapy in Nonischemic Cardiomyopathy

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ABSTRACT

Background: Significant myocardial scar in the posterolateral left ventricle (LV) has been associated with a diminished response to cardiac resynchronization therapy (CRT) in patients with coronary artery disease, but the effects of resting perfusion abnormalities in nonischemic cardiomyopathy (NICM) are yet to be described.

Hypothesis: We sought to characterize the effect of myocardial perfusion abnormalities upon echocardiographic outcomes of CRT in patients with NICM.

Methods: Twenty-one patients (mean age 64.4 ± 13.3 ; 71.4% male; mean left ventricular ejection fraction [LVEF] $20.2 \pm 6.9\%$) with NICM who underwent CRT implantation and Thallium-201 single positron emission computed tomography (SPECT) myocardial perfusion imaging (MPI) were included. MPI studies were read quantitatively, assigning each of 17 myocardial segments a perfusion score (0–4) and cumulatively generating a summed perfusion score (SPS). The LV lead position was determined by chest radiography. Echocardiograms were performed both before and after (median 12 mo) CRT in 15 patients.

Results: Echocardiographic response, defined as $\geq 15\%$ relative increase in LVEF, was documented in 8 (53.3%) of 15 patients. All patients (5/5) with an $SP \leq 6$ responded to CRT, whereas only 30.0% (3/10) with an $SPS > 6$ responded (odds ratio 3.33 [95% confidence interval {CI} 1.29–8.59]; $p = 0.01$). All nonresponders had inferior perfusion defects. Defect density adjacent to the LV lead tip had little demonstrable effect upon CRT efficacy.

Conclusions: The presence of significant myocardial perfusion defects negatively influences echocardiographic response to CRT in NICM. These findings warrant prospective confirmation and histopathological correlation with explanted hearts.

Key words: cardiac resynchronization therapy, dilated cardiomyopathy, myocardial perfusion imaging, echocardiography

Introduction

Cardiac resynchronization therapy (CRT) has rapidly become an integral treatment modality in patients with drug-refractory congestive heart failure (HF). Several large-scale clinical studies, including the COMPARISON of Medical Therapy, Pacing, AND Defibrillation in Heart Failure (COMPANION) trial and the Cardiac Resynchronization in Heart Failure (CARE-HF) trial, have established CRT's efficacy in reducing mortality and morbidity in patients with a left ventricular ejection fraction (LVEF) $\leq 35\%$, New York Heart Association III–IV HF symptoms, and a wide QRS complex (> 120 ms).^{1,2} However, in these studies, 20%–30% of patients do not respond to CRT, an experience that is also borne out in clinical practice.^{3,4} Given the significant expense and potential risks of CRT, it is important to discern a priori who will respond to this therapy.

Recent studies suggest that scar in the vicinity of the coronary venous lead may hinder CRT-induced reverse remodeling.⁵ Presumably, effective CRT requires electrical capture and mechanical contraction of viable, non-scarred myocardium near the left ventricle (LV) lead.⁶ Myocardial

perfusion imaging (MPI) may assist in identifying such areas by localizing and quantifying myocardial scar. A recent analysis of patients with ischemic cardiomyopathy (ICM) implanted with CRT devices in our laboratory demonstrated that global scar burden, extent of dense scar, and density of scar tissue at the site of LV pacing all portend a lack of echocardiographic response to CRT, suggesting that once a threshold of scar burden is surpassed, CRT becomes ineffective.⁷ Data from other centers also suggest that patients with extensive nonviable myocardium, as determined by MPI, have a diminished clinical response to CRT and do not undergo reverse remodeling.⁸

Nonischemic cardiomyopathy (NICM) is characterized by patchy areas of fibrosis, unlike the confluent lesions corresponding to vascular distributions that characterize ICM, particularly in the setting of prior transmural infarcts. Nevertheless, MPI does demonstrate perfusion abnormalities in NICM,⁹ and these nonuniform perfusion abnormalities do correspond to myocardial fibrosis on endomyocardial biopsy and correlate with severity of LV dysfunction.¹⁰ While patients with NICM included in major prospective CRT

studies experienced a similar response rate as their ischemic counterparts,¹¹ it is unclear whether scar impedes response to CRT in NICM. The finding of demonstrable perfusion defects on MPI in a NICM patient may identify the presence of end-stage disease that is no longer amenable to CRT.

Methods

Patient Population

A database of all patients implanted with CRT-defibrillators (CRT-D) at the University of Pittsburgh Medical Center between 2000–2005 was searched for patients who had undergone MPI. Patients with NICM were selected for analysis of all outpatient and inpatient clinical records. All subjects had documented coronary angiograms demonstrating no stenosis of >50% in any major epicardial coronary artery, performed in the setting of a known cardiomyopathy.

Myocardial Perfusion Imaging

Myocardial perfusion imaging was performed according to standard clinical protocols of the Nuclear Cardiology laboratory at the University of Pittsburgh Medical Center (an Intersocietal Commission for the Accreditation of Nuclear Medicine Laboratories-certified laboratory), with the specific protocol chosen by the ordering physician. Rest and redistribution images were obtained using thallium-201.

Myocardial perfusion imaging studies were interpreted by a core group of cardiologists, utilizing a 17-segment polar map scoring system.¹² Briefly, each of the 17 total myocardial segments is scored normal (0), possibly abnormal (i), mildly abnormal (ii), moderately abnormal (iii), or without uptake of radiotracer (iv). The sum of all segments with abnormal uptake after redistribution or abnormal uptake at rest in those who did not undergo 24-hour imaging yielded the summed perfusion score (SPS), a number between 0 (i.e., a normal scan) and 68 (i.e., 17 segments × maximum score of 4).

Figure 1: (A) Anatomic classification of LV lead tip sites, as viewed in the 45° left anterior oblique projection. (B) The corresponding 17-segment polar map utilized in SPECT MPI interpretation. Equivalent anatomic distributions are color-coded.

Device Implantation

The CRT implantation was performed by electrophysiology staff physicians. All LV leads were placed percutaneously under fluoroscopic guidance. Lateral or posterolateral cardiac veins were preferentially targeted, with alternative positions dictated by anatomy. Contrast venography was performed at the discretion of the implanting physician.

In order to correlate the results of MPI with LV lead placement, the left anterior oblique fluoroscopic image was divided into five sectors, as illustrated in Figure 1. In this scheme, the “posterior” lead position corresponds to “inferior” segments in single-photon emission computed tomography (SPECT) nomenclature. “Posterolateral” leads are located in the “inferolateral” SPECT distribution. The “lateral” lead position comprises both inferolateral and anterolateral SPECT segments. Anterolateral and anterior leads correlate with the identically-named SPECT segments. Lead placement was established by examination of frontal and lateral chest radiographs by a single experienced electrophysiologist who was blinded to outcomes and operative notes. Location was categorized as anterior, anterolateral, lateral, posterolateral, or posterior, as well as basal, midventricular, or apical.

Follow-up

Device follow-up was left to the discretion of the electrophysiology staff. Maximizing biventricular pacing viaprogramming an atrioventricular delay shorter than the intrinsic PR interval, with a goal of at least 95% pacing, as well as ensuring adequate safety margins for pacing thresholds, were given maximum priority.

Transthoracic echocardiography was performed in standard parasternal, apical, and subcostal views and interpreted by a core group of staff cardiologists. The LVEF was determined visually, and mitral regurgitant severity was graded primarily using Doppler color mapping.¹³ Left ventricular end-diastolic diameter (LVEDD) was measured in the parasternal long-axis view immediately before mitral valve closure, and left ventricular end-systolic diameter (LVESD) was measured in this view immediately prior to mitral valve opening.¹⁴ These techniques are most consistent with prevailing community clinical care. A positive LVEF response was defined as a proportional improvement by at least 15% of the baseline value (i.e., $[LVEF_{\text{post}} - LVEF_{\text{pre}}] / LVEF_{\text{pre}}$). A relative LVEF improvement of 10%–20% has been used in the literature to denote a positive response to CRT. For example, in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, the mean response was a 15% improvement in LVEF at 6 months.¹¹

Statistical Analysis

All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 10.1, software (Chicago, Ill., USA). Discrete variables were compared using chi-squared analysis, or in the event of few (i.e., <5) data points, Fisher's exact test. Continuous variables were analyzed via analysis of variance. The Mann-Whitney U test was used when comparing medians. Pearson's correlation was performed to study the linear correlation of variables. A p -value ≤ 0.05 was considered statistically significant. All values are expressed as means ± 1 standard deviation (SD) unless otherwise noted.

Results

Patient Population

One hundred twenty-seven patients who received a CRT-D device at the University of Pittsburgh Medical Center between 2000–2005 also underwent MPI as a part of their clinical care for heart failure. Twenty-one had NICM, and echocardiographic data were available for 15 of these patients (Figure 2). Eight had a significant echocardiographic response, yielding a 53.3% response rate, which

Figure 2: A total of 666 patients were implanted with a CRT-D device at the University of Pittsburgh Medical Center-Presbyterian between 2000 and 2005. From this patient pool, 127 underwent MPI at our institution, of whom 21 had NICM. Echocardiographic follow-up was complete in 15 of these patients. **Abbreviations:** CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy defibrillators; MPI = myocardial perfusion imaging; NICM = nonischemic cardiomyopathy; TTE = transthoracic echocardiography; UPMC = University of Pittsburgh Medical Center.

is somewhat less than that described in prevailing CRT experience. Table 1 illustrates the clinical characteristics of these patients. Outcome data are depicted in Table 2. From these data, it is apparent that LVEF improvement was associated with evidence of reverse remodeling; both LVEDD and mitral regurgitant severity decreased significantly in LVEF responders. Of note, more than one quarter of all patients receiving CRT-D were upgraded from either a non-CRT pacemaker or a non-CRT implantable cardioverter-defibrillator, precluding the use of cardiac magnetic resonance imaging in for assessment of myocardial viability.

Global Myocardial Perfusion Abnormalities and Cardiac Resynchronization Therapy Outcomes

Summed Perfusion Score: The extent of global resting perfusion defects, using the summed perfusion score (SPS) as a quantifiable surrogate, predicted echocardiographic response to CRT. An SPS cut-off of >6 was the most specific value for identifying nonresponders; all patients with less extensive perfusion abnormalities responded to CRT (Table 3) (Figure 3). The hazard ratio for nonresponse in those patients with a higher SPS was 3.33 (95% confidence interval [CI] 1.29–8.59; $p = 0.01$). While some patients (30%) with an $\text{SPS} > 6$ had a positive relative LVEF response associated with absolute LVEF increases of 15%–27%, the most robust absolute LVEF increases were seen in patients with an $\text{SPS} \leq 6$ (lower limit of absolute LVEF increase 32%). The SPS cut-off of 6 was determined through analysis of the receiver operating characteristic curves of LVEF versus SPS (data not shown).

Inferior Perfusion Defect

All patients with an $\text{SPS} > 6$ had perfusion defects in the inferior segments. These 10 patients had adverse echocardiographic findings at baseline and poor response to CRT (non-response hazard ratio [HR] 3.33; 95% CI 1.29–8.59; $p = 0.01$). Quantitative inferior defect severity (i.e., summed perfusion scores of all inferior segments) was inversely related to pre-CRT LVEF ($r = -0.56$, $p = 0.03$).

Post-CRT echocardiographic findings demonstrated improved LV function and evidence of reverse remodeling in patients with no inferior defects. The presence of any inferior defect also predicted a lack of LVEF response. While this finding is partly attributable to baseline differences, both the absolute ($36.2 \pm 5.1\%$ versus $5.0 \pm 10.9\%$) and relative ($142.7 \pm 52.3\%$ versus $26.4 \pm 54.4\%$) LVEF changes were significantly greater ($p = 0.00004$ and $p = 0.002$, respectively) in the cohort with no inferior perfusion abnormalities.

TABLE 1: Comparison of baseline patient characteristics. Numbers in parentheses are percentages of patients with data available. [†]No hibernating myocardium was seen on the redistribution images. *One patient did not have radiographs available to determine LV lead placement. P-values refer to comparison between EF responders and non-responders

	All with echo follow-up (n = 15)	EF responders (n = 8)	EF non-responders (n = 7)	p-value
Demographics				
Age (y)	60.9 ± 12.8	61.5 ± 11.3	60.3 ± 15.2	0.86
Male gender	11 (73.3)	4 (50.0)	7 (100)	0.08
NYHA Class	3.1 ± 0.4	3.0 ± 0.3	3.3 ± 0.4	0.23
Upgrade from pacemaker/ICD	1/1 (6.7/6.7)	0/0 (0/0)	1/1 (14.3/14.3)	0.27
Mean Time from CRT to follow-up TTE (months)	15.4 ± 13.8	20.9 ± 16.1	9.1 ± 7.5	0.10
Median Time from CRT to follow-up TTE (months)	11.0	13.0	9.0	0.10
ECG data				
LBBB on ECG	10 (71.4)	6 (85.7)	4 (57.1)	0.42
PR interval (ms)	187 ± 49	199 ± 39	174 ± 60	0.45
QRS at baseline (ms)	162 ± 27	163 ± 31	160 ± 26	0.84
Heart failure medications				
ACE-I or ARB	13 (86.7)	7 (87.5)	6 (85.7)	1.0
β-blockers	10 (66.7)	6 (75.0)	4 (57.1)	0.61
Digoxin	11 (73.3)	5 (62.5)	6 (85.7)	0.57
Loop diuretic	13 (86.7)	6 (75.0)	7 (100.0)	0.47
Spironolactone	6 (40.0)	3 (37.5)	3 (42.9)	1.0
SPECT imaging				
Rest scan	14* (93.3)	7 (87.5)	7* (100)	1.0
Rest, 24-hour redistribution scans	1 [†] (6.7)	1 [†] (12.5)	0 (0)	1.0
Global SPS	10.5 ± 8.5	8.3 ± 9.5	13.0 ± 7.0	0.30
Inferior defect present	10 (66.7)	3 (37.5)	7 (100)	0.03
Inferior defect burden	5.1 ± 4.3	3.4 ± 5.2	7.0 ± 2.0	0.11
Lateral defect present	4 (26.7)	1 (12.5)	3 (42.9)	0.28
Lateral defect burden	0.5 ± 0.8	0.3 ± 0.7	0.7 ± 1.0	0.30
Inferolateral defect present	5 (33.3)	2 (25)	3 (42.9)	0.61
Apical defect present	7 (46.7)	3 (37.5)	3 (42.9)	0.62
Septal defect present	4 (26.7)	1 (12.5)	3 (42.9)	0.28
Anterior defect present	5 (33.3)	2 (25)	3 (42.9)	0.61
Defect density adjacent to LV lead	0.49 ± 0.66	0.30 ± 0.56*	0.70 ± 0.75	0.26
Any defect adjacent to LV lead	7 (46.7)	2 (28.6)*	5 (71.4)	0.07
CRT				
Anterior lead	0 (0)	0 (0)	0 (0)	NA
Anterolateral lead	5 (33.3)	2 (28.6)	3 (42.9)	0.58
Lateral lead	7 (46.7)	4 (57.1)	3 (42.9)	0.59
Posterolateral lead	2 (13.3)	1 (14.3)	1 (14.3)	1.0
Posterior lead	0 (0)	0 (0)	0 (0)	NA
LV sensed R-waves (mV)	10.0 ± 7.4	9.2 ± 4.7	11.1 ± 10.7	0.68
% RA paced	5.0 ± 7.8	6.5 ± 8.7	3.2 ± 6.8	0.47
% RV-paced	93.6 ± 11.8	98.4 ± 1.6	88.1 ± 16.1	0.10
%LV-paced	93.5 ± 11.9	98.4 ± 1.6	88.0 ± 16.2	0.09

Abbreviations: CRT = cardiac resynchronization therapy; ECG = electrocardiogram; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LV = left ventricle; NYHA = New York Heart Association; RA = right atrium; RV = right ventricle; TTE = transthoracic echocardiogram.

TABLE 2: Echocardiographic and clinical outcomes. Numbers in parentheses are percentages of patients with data available. p-values refer to comparisons between responders and non-responders

	All with echo follow-up (n = 15)	EF responders (n = 8)	EF non-responders (n = 7)	p-value
Pre-CRT echocardiogram				
LVEF (%)	21.5 ± 7.5	24.1 ± 7.4	18.4 ± 6.8	0.15
LVESD (cm)	5.40 ± 0.99	4.96 ± 0.90	5.84 ± 0.95	0.17
LVEDD (cm)	6.22 ± 0.97	5.96 ± 0.81	6.48 ± 1.14	0.43
MR (graded 0–4)	1.5 ± 1.1	1.5 ± 1.2	1.6 ± 1.1	0.90
Post-CRT echocardiogram				
LVEF (%)	36.9 ± 22.3	54.1 ± 15.0	17.1 ± 7.1	<0.001
LVESD (cm)	5.09 ± 1.75	3.83 ± 1.16	6.34 ± 1.27	0.002
LVEDD (cm)	6.24 ± 1.50	5.23 ± 0.82	7.24 ± 1.34	0.005
MR (graded 0–4)	1.4 ± 1.0	0.71 ± 0.64	2.0 ± 1.0	0.014
Echocardiographic outcomes				
LVEF change (absolute %)	15.4 ± 17.8	30.0 ± 10.0	−1.3 ± 3.2	<0.001
LVEF change (relative %)	65.1 ± 76.9	127.9 ± 15.1	−6.6 ± 12.8	<0.001
LVESD change (cm)	−0.21 ± 0.89	−0.70 ± 0.37	0.18 ± 1.02	0.15
Relative LVESD change (%)	−6.0 ± 15.1	−13.6 ± 8.2	1.6 ± 17.6	0.17
LVEDD change (cm)	−0.27 ± 0.95	−0.94 ± 0.84	0.40 ± 0.46	0.014
Relative LVEDD change (%)	−6.2 ± 15.2	−15.3 ± 13.9	5.2 ± 7.1	0.033
MR change	−0.3 ± 0.8	−0.8 ± 0.8	+0.3 ± 0.3	0.012
Clinical outcomes				
Death	2 (13.3)	0 (0)	2 (28.6)	0.20
Transplant/VAD	2 (13.3)	0 (0)	2 (28.6)	0.02
Death/OHT/VAD	4 (26.6)	0 (0)	4 (57.1)	0.026

Abbreviations: CRT = cardiac resynchronization therapy; EF = ejection fraction; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end systolic diameter; MR = mitral regurgitation; OHT = orthotopic heart transplant; VAD = ventricular assist device.

Left Ventricular Lead Position and Local Perfusion Abnormalities

The burden of perfusion abnormalities in the anatomic vicinity of the coronary venous lead was determined by comparing the radiographic lead position with the perfusion scores of adjoining myocardial segments by SPECT. As previously described, frontal and lateral radiographs were used to place the LV lead tip in one of the 17 myocardial segments on the SPECT polar map (Figure 1). The mean perfusion score of all myocardial segments anatomically contiguous with the segment corresponding to the LV lead tip was termed the mean defect density. It was calculated by summing the scores of the segment where the LV lead tip was located and of its contiguous segments and dividing by the total number of those segments.

There was no significant correlation between echocardiographic response and quantitative defect density adjacent to the LV lead tip. Qualitatively, the presence of any perfusion

abnormality in this vicinity did portend adverse outcomes. However, the lack of quantitative correlation between defect density and CRT response suggests that the presence of any perfusion abnormalities in the vicinity of the LV lead merely reflects the higher global SPS in these patients, not a direct effect upon CRT response.

Discussion

Cardiac resynchronization therapy has emerged as an important tool in improving quality-of-life and longevity in patients with moderate and severe HF symptoms, LVEF ≤35%, and a QRS duration >120 ms. However, at present, one-third of patients who meet these clinical criteria and receive a CRT device do not benefit. Given this experience, as well as the significant expense and not-inconsequential risk involved with implantation, it is imperative that we better discern those individuals who will derive benefit from this intervention. In ICM, perfusion abnormalities

TABLE 3: Comparison of patients with normal resting perfusion or minor defects (i.e., SPS 0–6) versus patients with significant perfusion abnormalities (i.e., SPS >6). Numbers in parentheses refer to percentages of patients. Absolute change refers to post-CRT values minus pre-CRT values, whereas relative change refers to the absolute change divided by the baseline pre-CRT value. The LVESD and LVEDD response refers to a $\geq 10\%$ relative decrease in these measurements post-CRT compared with pre-CRT values

	SPS 0–6 (n = 5)	SPS >6 (n = 10)	p-value
MPI findings			
Apical defect	1 (20)	6 (60)	0.28
Septal defect	0 (0)	4 (40)	0.23
Anterior defect	1 (20)	4 (40)	0.60
Lateral defect	0 (0)	4 (40)	0.23
Inferior defect	0 (0)	10 (100)	<0.001
Inferior perfusion score	0 $\pm$ 0	7.6 $\pm$ 2.8	<0.001
Number of abnormal segments (maximum of 17)	1.0 $\pm$ 1.4	6.0 $\pm$ 2.2	<0.001
Number of abnormal anatomic segments (maximum of 7)	0.4 $\pm$ 0.6	2.8 $\pm$ 1.1	<0.001
Number of segments with perfusion score 1–3	1.0 $\pm$ 1.4	4.9 $\pm$ 2.6	0.009
Number of segments with perfusion score of 4	0	1.1 $\pm$ 1.3	0.08
Pre-CRT echocardiogram			
LVEF (%)	27.20 $\pm$ 7.12	18.60 $\pm$ 6.11	0.030
LVESD (cm)	4.53 $\pm$ 0.96	5.77 $\pm$ 0.78	0.06
LVEDD (cm)	5.65 $\pm$ 0.67	6.51 $\pm$ 0.94	0.14
MR (graded 0–4)	1.7 $\pm$ 1.4	1.4 $\pm$ 1.0	0.70
Post-CRT echocardiogram			
LVEF (%)	63.40 $\pm$ 6.23	23.60 $\pm$ 13.09	<0.001
LVESD (cm)	3.38 $\pm$ 0.97	5.77 $\pm$ 1.52	0.014
LVEDD (cm)	5.03 $\pm$ 0.98	6.72 $\pm$ 1.41	0.05
MR (graded 0–4)	1.0 $\pm$ 0.7	1.5 $\pm$ 1.2	0.44
CRT outcomes			
Absolute LVEF change (%)	36.20 $\pm$ 5.07	5.00 $\pm$ 10.88	<0.001
Relative LVEF change (%)	142.67 $\pm$ 52.32	26.34 $\pm$ 54.41	0.002
LVEF responders	5 (100)	3 (33.3)	0.019
LVESD change (cm)	–0.95 $\pm$ 0.21	0 $\pm$ 0.90	0.20
Relative LVESD change (%)	–19.11 $\pm$ 6.07	–1.67 $\pm$ 14.81	0.17
LVESD responders	2 (100)	2 (28.6)	0.17
LVEDD change (cm)	–0.90 $\pm$ 1.11	–0 $\pm$ 0.81	0.19
Relative LVEDD change (%)	–15.22 $\pm$ 18.48	–1.68 $\pm$ 12.63	0.23
LVEDD responders	2 (66.7)	1 (14.3)	0.18
MR change (grade)	–0.9 $\pm$ 1.0	0 $\pm$ 0.5	0.08

Abbreviations: CRT = cardiac resynchronization therapy; EF = ejection fraction; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end systolic diameter; MR = mitral regurgitation.

Figure 3: Global perfusion abnormalities predict LVEF change with CRT. The vertical lines indicate the SPS cut-off of 6 that best delineates responders and nonresponders. The mean LVEF changes with error bars are depicted for patients on either side of this value. The mean absolute LVEF change was $36.2 \pm 5.1\%$ for the SPS 0–6 group versus $5.0 \pm 10.9\%$ in the SPS >6 group ($p = 0.00004$). The relative LVEF changes were $142.7 \pm 52.3\%$ and $26.4 \pm 54.4\%$, respectively ($p = 0.002$). The horizontal line in the right graph represents the 15% relative LVEF increase that indicates echocardiographic response to CRT. Abbreviations: CRT = cardiac resynchronization therapy; LVEF = left ventricular ejection fraction.

as assessed by MPI, both in terms of global burden and density adjacent to the LV lead, predict lack of CRT response.⁹ We hypothesized that a similar relationship exists in NICM.

In this cohort of patients with NICM who underwent CRT-D implantation, we observed an echocardiographic response rate of 53.3%, which is somewhat less than that seen in other published reports. Most CRT nonresponders in this population were found to have significant resting perfusion abnormalities, with a large proportion of these defects located in the inferior segments. However, quantitative perfusion defect density adjacent to the LV lead tip was not associated with echocardiographic outcomes.

The finding that normal or relatively normal perfusion scans predict response to CRT in NICM is not unexpected. Because perfusion abnormalities do reflect myocardial fibrosis,¹⁵ hearts with no such defects likely represent an earlier stage or less severe form of cardiomyopathy. As such, one would expect that CRT would be able to halt, if not reverse, the cardiomyopathic process.

A significant difference between ICM and NICM lies in the severity of perfusion defects that affect CRT response rates (Table 3). Whereas the most severe defects (i.e., segments with a perfusion score of 4) drove nonresponse in ICM, in this NICM population,⁹ nonresponse was driven primarily by segments with modest abnormalities (i.e., segments with a perfusion score of 1–3). This is in keeping

with the hypothesis that infarcts are the cause of resting defects in ICM, whereas patchy fibrosis causes perfusion abnormalities in NICM.

Another difference between ICM and NICM patients is the effect of perfusion defects in the vicinity in the vicinity of the LV lead tip. This difference may relate to the patchy nature of fibrosis in NICM, which contrasts with the dense scar in ICM that should more readily impede local electrical capture and thus prevent reverse remodeling. While a trend toward nonresponse was seen in patients with any defects adjacent to the LV lead in the present analysis, the lack of correlation between local defect density and CRT response suggests that this finding reflects the overall greater likelihood of any scar being in the vicinity of the LV lead tip in those patients with higher global defect burden, rather than a specific effect of local perfusion defects.

The inverse relationship between inferior defects and CRT response may reflect true causality, an epiphenomenon, or a chance finding. Inferior defects are perhaps an artifact signaling the presence of a more dilated heart that has crossed a threshold beyond the reach of CRT. If this were the case, the presence of inferior perfusion abnormalities would be a useful surrogate for “end-stage” NICM not amenable to CRT and would add prognostic value.

Based upon our findings, MPI may be useful as an adjunct in selecting those patients who will most likely benefit from CRT. In particular, this costly and invasive therapeutic modality should potentially be withheld from those NICM patients with more extensive perfusion defects, particularly those located in the inferior segments. Such a limitation may be especially useful when considering CRT in an elderly and/or frail patient, or in a patient with borderline clinical indications for CRT.

Several questions are raised by our findings. One involves the role of perfusion defects and mechanical dyssynchrony in NICM. It is currently unclear whether underlying dyssynchrony may be ameliorated when there is significant scar burden at or near the site of maximum dyssynchrony in ICM patients. There is a published case report that suggests scar tissue may prevent resynchronization despite adequate LV lead thresholds,⁶ raising the possibility of a disconnect between electrical and mechanical capture that elicits cardiac resynchronization. A second question is whether dyssynchrony is reversible in an area of significant perfusion defects, reflecting presumably inert scar tissue? Finally, additional pathohistologic correlations in patients who undergo both MPI and heart transplantation would significantly advance our current understanding of whether resting perfusion defects identified on MPI in NICM represent scar versus artifact, as well as how true histologic scar influences response to CRT.

Study Limitations

This study suffers from the inherent shortcomings involved in retrospective analysis. The study sample size is small, owing to the infrequency with which NICM patients undergo MPI. However, we did include all patients with NICM implanted with a CRT-D device within the past 6 years who underwent MPI at our institution, and no differences in baseline demographic, MPI, or echocardiographic characteristics were noted between those with and without complete echocardiographic follow-up (data not shown). Echocardiographic interpretation was not strictly quantitative, yet all studies were read by a core group of cardiologists at a single institution, minimizing inter-observer variability. Furthermore, most community institutions, as well as many academic centers, do not routinely apply quantitative techniques to echocardiographic interpretation because of their cumbersome nature. Few LVEF changes were of borderline magnitude (i.e., most were either large increases or unchanged), making interobserver variability less likely to have accounted for observed changes.

Myocardial perfusion imaging has less spatial resolution than cardiac magnetic resonance imaging, but more universal familiarity with nuclear imaging in the cardiology community offsets this shortcoming. Furthermore, a significant proportion of patients were ineligible for magnetic resonance imaging because of an indwelling pacemaker or implantable cardioverter-defibrillator.

Conclusions

In this analysis of patients with NICM undergoing CRT-D implantation, perfusion abnormalities by SPECT MPI significantly impacted echocardiographic response. Specifically, all nonresponders had an abnormal scan, while most responders had normal perfusion. The presence of any defect in the inferior segments predicted diminished response to CRT, whereas defect density near the LV lead tip did not influence outcomes. These findings suggest that in NICM, CRT may best be reserved for those patients with normal myocardial perfusion.

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